Volcanic environments and thyroid disruption – A review focused on As, Hg, and Co

Article *in* The Science of The Total Environment · July 2025

DOI: 10.1016/j.scitotenv.2025.180018

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Review

Volcanic environments and thyroid disruption – A review focused on As, Hg, and Co

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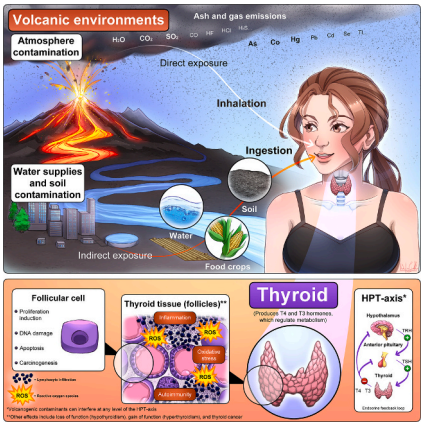
HIGHLIGHTS

- The incidence of thyroid cancer and hypothyroidism is increased in volcanic areas.
- Data on hypothyroidism incidence in volcanic areas is lacking.
- There is no data on thyroid disruption in areas with non-eruptive active volcanism.
- As, Hg, and Co – present in volcanic environments – disrupt thyroid metabolism.
- The toxic effects of As, Hg, and Co on the thyroid are understudied.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Ouyang Wei

Keywords:
Endocrine disruption
Thyroid cancer
Hypothyroidism
Potentially toxic elements (PTEs)
Arsenic

ABSTRACT

The purpose of this review is to explore the link between volcanic environments and thyroid disruption, with focus on the role played by As, Hg, and Co. Volcanoes are the most well-known source of natural pollution, enriching the environment in hazardous elements. It is estimated that about 10 % of world population lives near active volcanoes (Brown et al., 2015). There is evidence supporting a link between living in volcanic environments and thyroid cancer, but it is likely that other types of thyroid disruption are also exacerbated in the populations inhabiting volcanic areas. Arsenic (As) and mercury (Hg) are elements with toxic properties that are present in volcanic environments. Cobalt (Co), which is also present in these environments, is part of the essential

Abbreviations: TH, Thyroid hormones; T4, Thyroxine; TT4, Total thyroxine; T3, Triiodothyronine; TT3, Total triiodothyronine; HPT-axis, Hypothalamus-pituitary-thyroid axis; TRH, Thyrotropin-releasing hormone; TSH, Thyroid-stimulating hormone; TPO, Thyroperoxidase; DUOX, Dual oxidases; Tg, Thyroglobulin; PTEs, Potentially toxic elements; As, Arsenic; Co, Cobalt; Hg, Mercury; GPx, Glutathione peroxidases; TrxR, Thioredoxin reductases; DIO, Iodothyronine deiodinases; Redox, Oxidation-reduction; ROS, Reactive oxygen species.

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https://doi.org/10.1016/j.scitotenv.2025.180018
Received 16 April 2025; Received in revised form 12 June 2025; Accepted 30 June 2025
Available online 7 July 2025

Cobalt
Mercury
Volcanism

cobalamin vitamin (B_{12}). However, exposure to non-cobalamin Co can pose health risks. The effects of these three elements on the thyroid are understudied. A review of 125 publications retrieved from the Web of Science, PubMed, and Scopus databases, covering year 1955 to present, was performed. The known molecular mechanisms underlying thyroid disruption by these elements are discussed. It was found that thyroid cancer incidence, but also that of hypothyroidism are heightened in populations living in volcanic environments, particularly in Iceland, Hawaii, and Italy. Knowledge gaps regarding (i) thyroid disruption in areas with non-eruptive active volcanism, (ii) the toxic effects of As, Hg, and Co on the thyroid, and (iii) the incidence of hypothyroidism and other thyroid pathologies in volcanic environments are highlighted. The need to monitor the population of volcanic areas in terms of health is accentuated.

1. Introduction

Anthropogenic pollution is a well-recognized problem responsible for harmful effects both towards health, such as increasing the risk and/or severity of diseases, and the environment, causing ecosystem changes with repercussions leading to biodiversity loss (Olawoyin, 2018; Häder et al., 2020; Yun et al., 2022; Eastwood et al., 2023) – yet, it is not the only source of environmental pollution. Albeit a controversial term, "natural pollution" (or "non-anthropogenic pollution") refers to the introduction of harmful materials, called pollutants, into the environment by natural sources. Pollutants of natural origin include sea salt particles, ozone formed by photochemical processes, substances from wildfire emissions, volcanic dust, among others (Löhr et al., 2005; Longo et al., 2010; Linhares et al., 2015b; Malandrino et al., 2016; Camarinho et al., 2021; Georgakopoulou et al., 2024). Volcanically active areas represent a very relevant source of natural pollution. Volcanic manifestations are responsible for enriching the environment – soil, water, and atmosphere – in hazardous elements, namely through soil diffusion and degassing, ash and gas emissions, as well as other events like pyroclastic and mud flows (Zielinski, 2002; Zuskin et al., 2007; Calabrese et al., 2015; Pickarski et al., 2023; Torres et al., 2023). Nevertheless, humans have been settling and living in the vicinity of volcanoes throughout history, attracted by the unique landscapes they are associated with, the fertility of their soils, or provision of geothermal resources (Schmincke, 2004; Ruiz et al., 2018; Fiantis et al., 2019). It is estimated that approximately 800 million people – about 10 % of the global population – live within 100 km of an active volcano (Brown et al., 2015), sometimes unaware of the silent dangers associated with their activity (Doocy et al., 2013; Freire et al., 2019; Navarro-Sempere et al., 2023). Gases released by volcanic activity include water vapor (H_2O), carbon dioxide (CO_2), sulfur dioxide (SO_2), carbon monoxide (CO), hydrogen (H_2), hydrogen sulfide (H_2S), hydrogen chloride (HCl), hydrogen fluoride (HF), methane (CH_4), and others in fewer amounts (Baillie et al., 2018; Camarinho et al., 2022; Cruz et al., 2025). Volcanic activity is also associated with the emission of high amounts of radon (^{222}Rn), an odorless gas estimated to be the second leading cause of lung cancer. Chronic exposure to ^{222}Rn, which enters and remains trapped inside poorly ventilated houses through soil diffuse degassing, is linked to situations of pre-carcinogenesis, particularly in inhabitants of hydrothermal areas (Linhares et al., 2018). In addition, elemental enrichment is often associated with volcanic environments, including aluminum (Al), arsenic (As), bromine (Br), barium (Ba), bismuth (Bi), calcium (Ca), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), gallium (Ga), potassium (K), lithium (Li), magnesium (Mg), mercury (Hg), sodium (Na), nickel (Ni), lead (Pb), sulfur (S), selenium (Se), tin (Sn), strontium (Sr), titanium (Ti), thallium (Tl), vanadium (V), and zinc (Zn) (Calabrese et al., 2015; Baillie et al., 2018; Ma et al., 2019; Torres et al., 2023), some of which are highly toxic to living organisms (As, Cd, Hg, Pb, Cr) (Tchounwou et al., 2012; Parelho et al., 2014; de Carvalho Machado and Dinis-Oliveira, 2023).

Faced with the words "active volcanism", one is naturally drawn to think of eruptive activity, which cause greater worry due to the immediate damage caused by explosions and other destructive events (landslides, debris avalanches, volcanic ashfall *etc.*); however, non-eruptive volcanic activity is also threatening yet by far less studied, particularly when regarding its impacts on human health. One of the differences between eruptive and non-eruptive active volcanism lies in the nature of the threats they pose: whereas in places with eruptive volcanism the threat is spontaneous and potentially destructive in the immediate future, in areas with non-eruptive active volcanism the threat is persistent because it is based on over-time exposures. As a result, the potential health hazards associated with areas with non-eruptive active volcanism are more tolerated, underestimated, and understudied. Non-eruptive volcanic activity can be manifested with secondary phenomena like fumaroles, geysers, and hot springs (known as hydrothermal unrest) (Sandri et al., 2017). Worldwide volcanoes are responsible for the emission of large amounts of CO_2 and gaseous elemental mercury (Hg^0). Globally, between 2005 and 2015, volcanic CO_2 flux reached 51.3 $\pm$ 5.7 Tg CO_2 y^{-1} (11.7×10^{11} mol CO_2 y^{-1}) for non-eruptive degassing, and 1.8 $\pm$ 0.9 Tg y^{-1} for eruptive degassing (Fischer et al., 2019). Mercury emission rates from Mount Etna volcano, located in Sicily, Italy, between 2004 and 2006 were in the range of 1.1–10 t y^{-1} (with an average of 5.4 t y^{-1}), which made it so the activity of this volcano alone accounted for roughly 7 % of global non-eruptive Hg emissions from continuously degassing volcanoes (Bagnato et al., 2007). In the Azores archipelago, Portugal, the hydrothermal areas of Furnas volcano – a non-eruptive active volcano – can emit over 1000 tons of CO_2 (1000 t d^{-1}) (Viveiros et al., 2010; Andrade et al., 2014), and about 9.6×10^{-5} t d^{-1} of Hg^0 (measured in a study area of 0.04 km^2 inside the volcano crater) (Bagnato et al., 2018). On studies conducted in this hydrothermal area, at a histological level, it was found that wild mice chronically exposed to the non-eruptive volcanic activity in Furnas exhibit peribronchiolar inflammation, structural alterations consistent with asthma and chronic bronchitis, and epithelial alterations that could develop into other respiratory pathologies (Camarinho et al., 2019). In addition, Hg deposits can form in the lungs, spinal cord and brain tissues of mice living under the abovementioned conditions, leading to several tissue alterations due to mercurial toxicity (Camarinho et al., 2021; Navarro-Sempere et al., 2021, 2023, 2025).

Many other studies have covered the association between acute and long-term human exposure to volcanogenic pollutants in general and the onset/exacerbation of disease, namely when it comes to the respiratory system, eyes and skin, and even psychological effects, with the added possibility of other diseases, such as thyroid disorders (Arnbjörnsson et al., 1986; Hansell et al., 2006; Zuskin et al., 2007; Longo et al., 2010; Linhares et al., 2015b; Latina et al., 2013; Shabani, 2021; Stewart et al., 2021).

The thyroid is a butterfly-shaped organ of the endocrine system which plays a pivotal role in metabolism. Tied to the production of thyroid hormones (TH) – thyroxine (T4), and triiodothyronine (T3), thyroid function impacts everything from nervous system development, linear growth, thermogenesis, the hepatic metabolism of nutrients, and fluid balance, as well as exerting influence on the cardiovascular system. The functional units of the thyroid are cuboidal cells known as thyrocytes (or thyroid follicular cells), which are organized in spherical structures (called follicles) composed of a simple cuboidal epithelium, inside of which the colloid is stored. C cells (also known as parafollicular cells), which produce the calcitonin hormone to decrease blood calcium

levels when necessary, can be found in the spaces between thyroid follicles (Cote et al., 2015) (Fig. 1). Thyroid function is controlled *via* the endocrine feedback loop in the hypothalamus-pituitary-thyroid axis (HPT-axis, Fig. 2), in which TH production is regulated by negative feedback according to their concentration in the bloodstream. The hypothalamus secretes thyrotropin-releasing hormone (TRH) to promote the synthesis and secretion of thyrotropin (thyroid-stimulating hormone, TSH) by the anterior pituitary, which then acts on the thyroid to stimulate the biosynthesis and secretion of TH (Ortiga-Carvalho et al., 2016). TSH stimulates the uptake of iodide from the bloodstream *via* the sodium-iodide symporter upon binding to receptors on thyrocytes. Iodide is then oxidized into iodine by thyroperoxidase (TPO) and hydrogen peroxide (H_2O_2) generated by dual oxidases (DUOX), so that it can be incorporated into thyroglobulin (Tg) – the precursor of TH, which is stored in the colloid (Leemans et al., 2019).

Potentially toxic elements (PTEs) are metals and metalloids associated to environmental pollution, which can be harmful towards living organisms, therefore impacting ecosystems and human health (Nieder and Benbi, 2023; Boahen et al., 2024). Endocrine disruption by environmental chemicals and PTEs interferes with several of the organism's systems, leading to "adverse developmental, reproductive, neurological, and immune effects in humans, abnormal growth patterns and neurodevelopmental delays in children" (Monneret, 2017). Endocrine disruptors, are exogenous substances that can act as hormones in the endocrine system, therefore causing changes in the physiological function of endogenous hormones (Yilmaz et al., 2020). Concerning the thyroid, it is documented that PTEs, which are more abundant in volcanic environments, can mimic the chemical structure of T4 and T3, interfering with the production of TSH. Disruption of the communication along the HPT-axis by PTEs can happen at any level; in some cases, direct damage to thyrocytes can also be implicated (Kashiwagi et al., 2009; Al-Maathidy et al., 2019; Fiore et al., 2019; Babić Leko et al., 2021; Coelho et al., 2024). The outcomes of endocrine disruption involving the thyroid range from potentially lethal thyroid cancer to sub-lethal hypo- and hyperthyroidism, and even thyroid autoimmune disorders (Pearce, 2024). The main route of exposure and absorption of contaminants from volcanic environments is through inhalation (Bernardo et al., 2019; Mueller et al., 2020). Exposure is also possible *via* the ingestion of plants grown in volcanic soils or the ingestion of volcanic soil itself (Baillie et al., 2018; Candeias et al., 2022), as well as drinking water from nearby sources (Nuvolone et al., 2023). As mentioned before, arsenic (As), mercury (Hg), and cobalt (Co) are three abundant elements in volcanic environments. Both As, a metalloid, and Hg, a heavy metal, have no physiological role in the body – they are highly toxic to living organisms (de Carvalho Machado and Dinis-Oliveira, 2023). On the other hand, Co is part of the essential cobalamin vitamin (also known as B_{12}), which is required for many biochemical and physiological functions – deficiencies in this vitamin are critical and lead to disease (Tchounwou et al., 2012). Being a crucial component in the synthesis of cobalamin – which is produced by microbes in the gut of ruminants, but not by humans, who obtain this

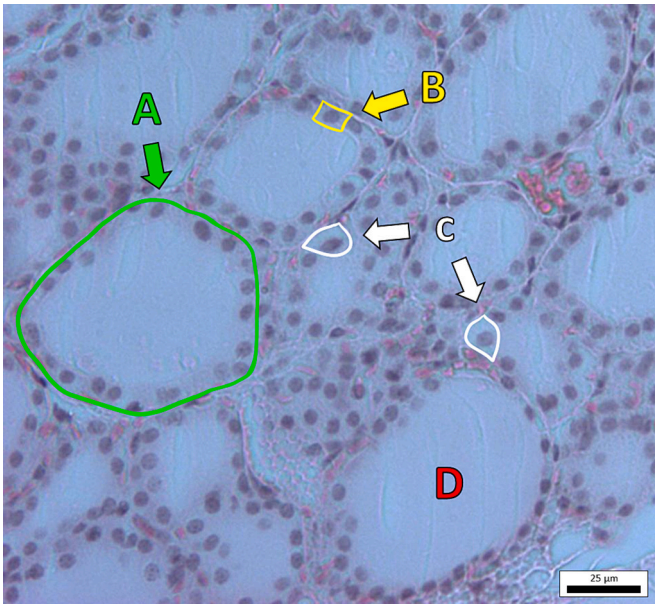

Fig. 1. Histological section of the thyroid tissue of wild mice (*Mus musculus* Linnaeus, 1758). **Labels:** A = follicle; B = thyrocyte (or thyroid follicular cell); C = C cell (or parafollicular cell); D = colloid. Photomicrograph by N. M. P. Coelho; scale bar = 25 µm.

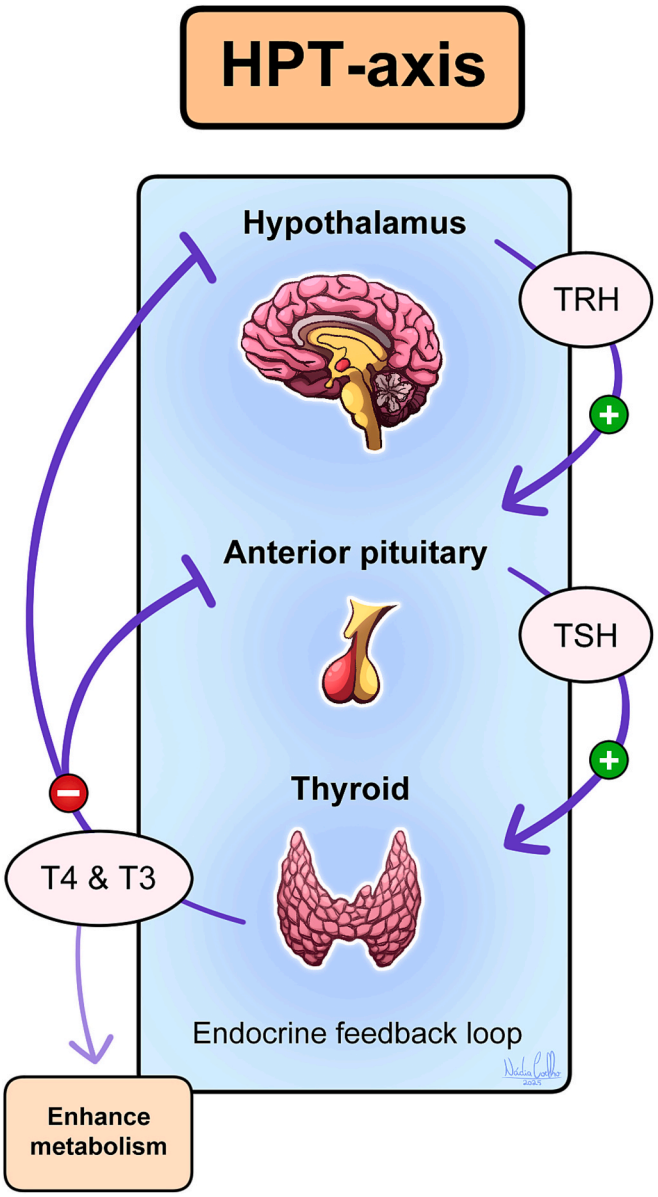

Fig. 2. Hypothalamus-pituitary-thyroid axis (HPT-axis). The endocrine feedback loop in the HPT-axis regulates thyroid function by controlling thyroid hormone (TH) production *via* negative feedback, according to the concentration of thyroxine (tetraiodothyronine, T4) and triiodothyronine (T3) in the bloodstream. The hypothalamus secretes thyrotropin-releasing hormone (TRH) to promote the synthesis and secretion of thyrotropin (thyroid-stimulating hormone, TSH) by the anterior pituitary, which then acts on the thyroid to stimulate the biosynthesis and secretion of TH.

vitamin through diet (González-Montaña et al., 2020) –, Co is indirectly essential for humans; however, it does not serve any other physiological role in the body. In fact, exposure to high levels of Co can pose health threats if absorbed in excess or through inadequate routes (Leyssens et al., 2017). Cobalt metallostasis is needed at the upper-end of the tolerable range, so that toxicity derived of aberrant reactivity, as well as mismetalation, can be prevented. A well-known example of Co toxicity is contact dermatitis, though, in severe cases, it can also be involved in mechanisms of neurotoxicity, pneumonia, and increase the risk of lung cancer onset *via* inhalation (Osman et al., 2021).

The term "thyroid disruption" encompasses any adverse thyroid outcomes from exposure to PTEs, including cancer, hypothyroidism, and hyperthyroidism (Calsolaro et al., 2017; Noyes et al., 2019). There are published articles suggesting a link between living in volcanic environments and thyroid disruption, with a marked emphasis on thyroid cancer (Pellegriti et al., 2009; Malandrino et al., 2016; Putri et al., 2022). Previous research in Italy showed that thyroid cancer incidence doubled in the volcanic area of Sicily when compared to a non-volcanic area (18.5 *vs.* 9.6/105 inhabitants in the volcanic and the control areas, respectively) (Duntas, 2016; Malandrino et al., 2016). Still, it is plausible that other types of thyroid disruption may also be exacerbated in populations living in volcanic environments, which are also deserving of greater interest. Several studies have addressed the toxic effects of As, Hg, and Co on the thyroid, suggesting they often promote the development of thyroid cancer and hypothyroidism. Even with this evidence, the disruptive effects of As, Hg and Co upon the thyroid seem to be understudied in comparison to other elements; hence, it is appropriate to address their role in the emergence of thyroid disruption. Therefore, the purpose of this review is to deepen and update the knowledge regarding the link between chronic exposure at volcanic environments and thyroid disruption, with specific focus on the role played by the elements As, Hg, and Co.

2. Methodology

2.1. Search strategy

To ensure adequate coverage, three databases – Web of Science (Clarivate), PubMed, and Scopus – were used to find the publications relevant for this review (Shea et al., 2017). In Web of Science, the search was performed using the following combinations of keywords: "Volcan*" (Topic) and "Hypothyroi*" (Topic); "Volcan*" (Topic) and "Thyroid Cancer"; "Heavy metal*" (Topic) and "Hypothyroi*"; "Heavy metal*" (Topic) and "Thyroid cancer" (Topic); "Arsenic" (Topic) and "Hypothyroi*"; "Arsenic" (Topic) and "Thyroid cancer" (Topic); "Cobalt" (Topic) and "Hypothyroi*"; "Cobalt" (Topic) and "Thyroid cancer" (Topic); "Mercury" (Topic) and "Hypothyroi*"; "Mercury" (Topic) and "Thyroid cancer" (Topic). The same combinations were searched in PubMed, with "All Fields" selected for each word. A similar approach was used in Scopus, with "Article title, Abstract, Keywords" selected for each word. The search was limited to primarily hypothyroidism and thyroid cancer.

Only publications written in English were considered. A specific publication time window was not defined, which implies that the search included all of the publications included in these databases until the final search day (17th of May 2025). The first work found was published in 1955. Finally, only peer-reviewed publications were included for data extraction. Whenever available, data extraction included the study population, study duration, addressed exposures, and exposure outcomes.

2.2. Eligibility criteria

Publications involving humans were eligible if they (i) directly addressed thyroid disruption, (ii) addressed human environmental exposures to contaminants commonly associated with volcanic environments. On the other hand, publications involving humans were excluded if they (i) only addressed congenital thyroid disruption, (ii) lacked sufficient information on thyroid disruption, (iii) did not address any sort of environmental routes of exposure.

In vitro and *in vivo* studies with animal models were included for mechanistic insights on the action of contaminants on the thyroid, which were eligible if (i) directly addressed the thyroid, (ii) addressed cell and/or animal models exposures to contaminants commonly associated with volcanic environments. By contrast, *in vitro* and *in vivo* studies with animal models were excluded if (i) mechanistic insights on the action of contaminants on the thyroid were lacking or insufficient.

2.3. Publication selection

The flowchart in Fig. 3 describes the process and number of publications obtained in each step of this review's publication selection.

3. Results and discussion

A total of 125 publications were selected for this review. Some publications were included in multiple tables, given their scope fell within more than one of the categories (*i.e.*, combination of topic keywords) used during the study selection. The final number of publications per category is as follows: 36 regarding the relationship between volcanic environments and thyroid disruption (Table 1); 41 regarding the role played by As (Table 2), 28 regarding the role played by Hg (Table 3), and 39 regarding the role played by Co (Table 4) in thyroid disruption. All references were organized by chronological order for discussion.

It is important to note that the epidemiological publications reviewed are mostly ecological or regional comparisons, which cannot prove causation and may be subject to confounders – especially when it comes to factors such as socioeconomic and dietary differences. Individual exposure data (blood levels of As, Hg, Co and their connection to altered thyroid function markers, for example) was not available in these studies, hence linking outcomes to specific contaminants is largely inferential. Moreover, most *in vivo* studies used doses higher than typical environmental exposure, and often in combination with iodine-deficiency models (*i.e.*, presenting a hypothyroid status before exposure to the studied PTEs), which may limit direct extrapolation to human populations.

3.1. Volcanic environments and thyroid disruption

The vast majority of included publications suggested a link between living in volcanic environments and the emergence of thyroid disruption. Still, the connection is not completely clear, given that (i) there was some discrepancy in the findings of dedicated studies, (ii) most research was done in specific areas (namely, the volcanic environment of Sicily, Italy), and (iii) several knowledge gaps are yet to be addressed. However, the subject has been gaining more traction as of late, with more and more publications exploring and supporting this notion. In terms of thyroid outcomes, it seems that the incidence of primarily thyroid cancer, but also hypothyroidism, is heightened in populations of volcanic areas.

Of the publications included in this review, the first suggesting a possible connection between volcanic environments and thyroid disruption was the work of Kung et al. (1981). After searching in available cancer registries for cases of thyroid cancer in volcanic areas, the authors noted that thyroid cancer incidence was outstandingly high in Iceland and Hawaii, where there are active volcanoes producing large amounts of lava. By contrast, it was later suggested by Arnbjörnsson et al. (1986) that living in environments with volcanic activity had no connection with thyroid disruption, namely when it came to explaining a high incidence of thyroid cancer in the population. In this study, conducted in Iceland, where several volcanoes with diverse types of

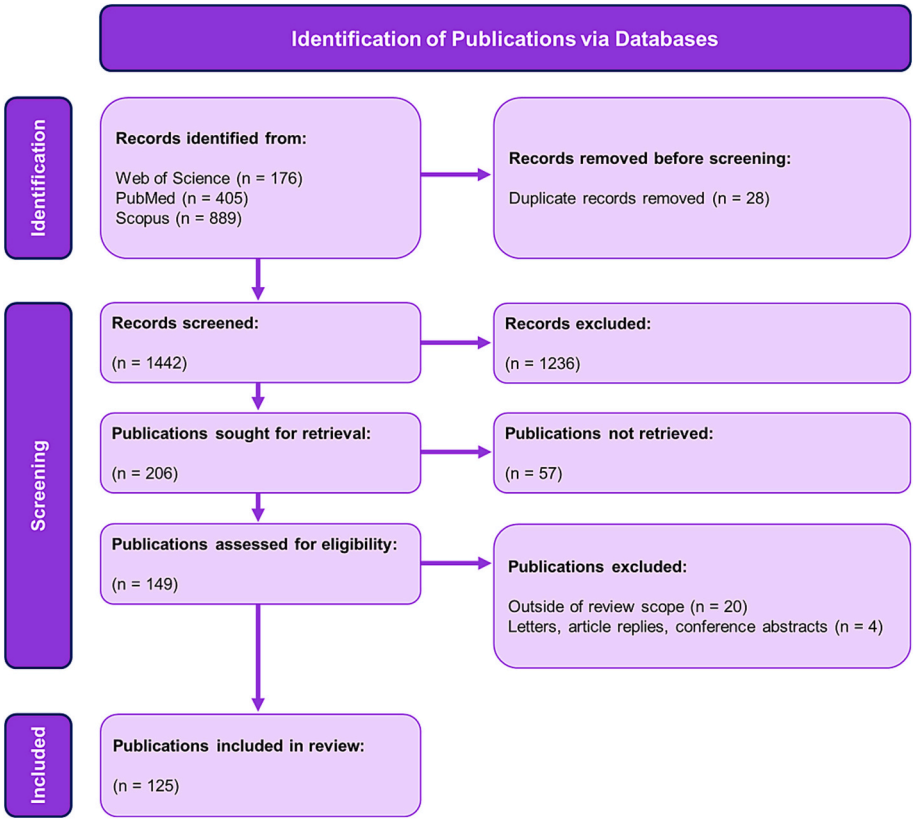

Fig. 3. Flowchart of this review's publication selection process.

eruptions (from effusive to explosive eruptions that produce massive plumes of ash), stated that the high incidence of thyroid cancer in the island was likely fundamentally due to genetic factors and the population's high intake of iodine from seafood. A study developed by Spitz et al. (1988) in the United States aimed to summarize descriptive epidemiological findings for newly-diagnosed thyroid cancer patients reported to the Surveillance, Epidemiology, and End Results (SEER) program during 1973–1981. It was found that New Mexico Hispanic men and Chinese, Japanese, Hawaiian, and Filipino men and women had significantly higher thyroid cancer rates (with weighted rate ratios ranging from 1.56 to 3.17). In particular, thyroid cancer rates for Hawaii residents were elevated regardless of ethnic group, which suggested a role of volcanic environments in thyroid cancer. Over the following years, the vast majority of published research suggests a clear association between exposure to volcanic environments and the occurrence of thyroid disruption, with a pronounced emphasis on thyroid cancer (Duntas and Doumas, 2009; Pellegriti et al., 2009; Agate et al., 2012; Floor and Román-Ross, 2012; Kristbjornsdottir and Rafnsson, 2012; Latina et al., 2013; Malandrino et al., 2013a; Malandrino et al., 2013b; Arena et al., 2014; Marcello et al., 2014; Russo et al., 2015; Duntas, 2016; Malandrino et al., 2016; Russo et al., 2017; Tavarelli et al., 2017; Nettore et al., 2018; Boffetta et al., 2020; Kim et al., 2020b; Malandrino et al., 2020; Bitonti and Mazza, 2024; Gianì et al., 2021b; Kruger et al., 2022; Paz-Ibarra et al., 2024; Shen et al., 2024; Street et al., 2024). Most evidence supporting this link arises from studies conducted on Sicily, Italy, where Mount Etna volcano is located – the most active stratovolcano in the world, characterized by explosive eruptions, minor lava flows and the emission of ash plumes (Pellegriti et al., 2009; Latina et al., 2013; Malandrino et al., 2013a; Malandrino et al., 2013b; Arena et al., 2014; Russo et al., 2015; Malandrino et al., 2016; Russo et al., 2017; Tavarelli et al., 2017; Boffetta et al., 2020; Bitonti and Mazza, 2024). Studies reporting a connection between volcanic environments and thyroid disruption on other parts of the world include the review articles of Duntas and Doumas (2009), Duntas (2016), Vigneri et al. (2017), Malandrino et al. (2020), Gianì et al. (2021b), and Kruger et al. (2022), with particular incidence on the areas situated along the "Rings of Fire" (or Circum-Pacific Belt), which holds 75 % of all active volcanoes on Earth and accounts for 90 % of all earthquakes. Of the studies dealing with thyroid cancer included in this review, there were no original research articles covering areas where there is non-eruptive active volcanism, although chronic exposure to these environments has been linked to situations of pre-carcinogenesis, higher incidence rates of cancer, and several other adverse health effects (Amaral et al., 2006; Rodrigues et al., 2012; Linhares et al., 2015b; Rodrigues and Garcia, 2015; Linhares et al., 2017; Linhares et al., 2018; Putri et al., 2022). Therefore, it is evident that a major knowledge gap exists on thyroid disruption, particularly regarding thyroid cancer, in populations living in areas with non-eruptive active volcanism. Moreover, ionizing radiation is considered one of the most relevant factors in increasing the risk for thyroid cancer (Bogović Crnčić et al., 2020). Considering the high amounts of ^{222}Rn emitted in these areas of hydrothermal unrest, the need for further research within this scope is highlighted.

3.1.1. *Thyroid cancer*

"Thyroid cancer", representing the most frequent endocrine tumors, is an umbrella term that includes various thyroid disorders of neoplastic origin with often distinct clinical manifestations and symptoms (Gimm, 2001; Lee et al., 2023). Such disorders are categorized as either differentiated thyroid cancer – including well-differentiated tumors, poorly differentiated tumors, and undifferentiated tumors – or medullary thyroid cancer, which develops in the thyroid's C cells. While well-differentiated tumors, like papillary thyroid cancer and follicular thyroid cancer, are the most common and can be cured with available treatments, patients with poorly differentiated and undifferentiated tumors – both types being classed as anaplastic thyroid cancer – have a much lower chance of recovery, given the highly aggressive nature and

Table 1
List of articles included in this systematic review regarding the effects of exposure to volcanic environments on the thyroid. Information regarding study design, addressed exposure, and key findings is presented. **In vitro* or *in vivo* study with animal models. **Only exposures related to volcanic environments and/or elements commonly associated with them were considered. ***The key findings display information specifically regarding the link between the features of volcanic environments and the thyroid.

Study	Design	Exposure**	Key findings***
Volcanoes and Carcinoma of the Thyroid: A Possible Association (Kung et al., 1981)	Searching in available cancer registries for thyroid cancer incidences in volcanic areas.	Human exposure to volcanic environments.	Thyroid cancer incidence is outstandingly high in Iceland and Hawaii, where there are active volcanoes producing large amounts of lava.
Thyroid Cancer Incidence in Relation to Volcanic Activity (Arnbjörnsson et al., 1986)	From the period of 1955–1982, data from the Icelandic Cancer Registry was obtained for the country's population. Information regarding gender and tumor histotype was considered. The age-standardized incidence rate for the world population (ASR_w) was calculated.	Human exposure to the volcanic environment of Iceland.	No connection was found between the high incidence of thyroid cancer in Iceland and the volcanic activity in the country.
Ethnic Patterns of Thyroid Cancer Incidence in the United States, 1973–1981 (Spitz et al., 1988)	Summarizing descriptive epidemiological findings for 7696 patients with newly diagnosed thyroid cancer reported to the Surveillance, Epidemiology, and End Results (SEER) program during 1973–1981.	Human exposure to volcanic environments.	New Mexico Hispanic men and Chinese, Japanese, Hawaiian, and Filipino men and women had significantly higher thyroid cancer rates (with weighted rate ratios ranging from 1.56 to 3.17). Thyroid cancer rates for Hawaii residents were elevated regardless of ethnic group, suggesting a role of volcanic environments in this pathology.
Fluoride and Environmental Health: A Review (Ozsvath, 2009)	Searching for articles in which connections between fluoride (F^-) and environmental health are reported.	Human exposure to F^- in several contexts.	Chronic ingestion of F^- – which is present in volcanic environments – at high doses can impair thyroid function.
The 'Rings of Fire' and Thyroid Cancer (Duntas and Doumas, 2009)	Searching in scientific databases for articles in which connections between volcanoes and the incidence of thyroid cancer are reported.	Human exposure to volcanic environments.	The high prevalence of thyroid cancer around the "Rings of Fire" suggests the role that exposure to volcanic environments plays in thyroid pathogenesis, due to the many ways in which these environments are enriched in heavy metals and other elements.
Papillary Thyroid Cancer Incidence in the Volcanic Area of Sicily (Pellegriti et al., 2009)	All incident thyroid cancers in Sicily, Italy, from 2002 to 2004 were included in a register-based epidemiological survey. The age-standardized incidence rate for the world population (ASR_w) was calculated. The association of thyroid cancer incidence rate with sex, age, tumor histotype, and various environmental factors was evaluated by modeling the variation of the ASR_w.	Human exposure to the volcanic environment of Sicily, Italy.	Papillary thyroid cancer has a higher incidence in Catania province, Italy, due to the inhabitants' chronic exposure to a volcanic environment.
New and Old Knowledge on Differentiated Thyroid Cancer Epidemiology and Risk Factors (Agate et al., 2012)	Searching in scientific databases for articles in which a link between distinct factors and the incidence of differentiated thyroid cancer is reported.	Human exposure to volcanic environments.	The incidence of differentiated thyroid cancer is explained by the complex interaction between genetic and environmental factors, in which volcanic environments may or may not play a role.
Selenium in Volcanic Environments: A Review (Floor and Román-Ross, 2012)	Searching in scientific databases for articles in which connections between selenium (Se) and volcanic environments are reported.	Human exposure to volcanogenic Se.	Se concentrations are relatively high in volcanic environments. The impact of exposure to volcanic-derived selenium (Se) on the thyroid remains unclear. There are registry records of thyroid cancer in the volcanic area of Sicily, Italy, among individuals with both high and low serum Se levels.
Incidence of Cancer Among Residents of High Temperature Geothermal Areas in Iceland: A Census Based Study 1981 to 2010 (Kristbjornsdottir and Rafnsson, 2012)	As part of an observational cohort study, based on data from the 1981 National Census in Iceland, the population of a high-temperature geothermal area (35,707 person years was compared with the population of a cold, non-geothermal area (571,509 person years). The hazard ratio (HR) and 95 % confidence intervals (CI) for cancer incidence were estimated in Cox-model, adjusted for age, gender, education and housing.	Human exposure to a high-temperature geothermal area of Iceland.	In the high-temperature geothermal area, the HRs for thyroid cancer, including of other cancers, were increased, although the 95 % CIs included unity.
Changes in the Incidence of Thyroid Cancer Between 1991 and 2005 in Italy: A Geographical Analysis (Lise et al., 2012)	Data from the Anonymous Cancer Registry of the Italian Association of Cancer Registries (ATRIUM) from 1991 to 2005 was included in the study. Age-standardized incidence rates (ASR) were computed for all histological subtypes of thyroid cancer according to cancer registries. Papillary thyroid cancer was analyzed *via* estimated annual percent change and joinpoint regression analysis.	Human exposure to volcanic soil.	Although an association between the incidence of papillary thyroid cancer and the presence of volcanic soil has been suggested, it seems unlikely to account for the rapidly increasing incidence of papillary thyroid cancer in Italy.

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Table 1 (*continued*)

Study	Design	Exposure**	Key findings***
Hashimoto's Thyroiditis: Similar and Dissimilar Characteristics in Neighboring Areas. Possible Implications for the Epidemiology of Thyroid Cancer (Latina et al., 2013)	In the form of a retrospective cohort study, a review of the clinical records of Catania and Messina patients from 1995 to 2005 at the Thyroid Clinic of the Endocrine Division was performed to compare presentation and yearly changes of Hashimoto's thyroiditis. Yearly changes of the number of new Hashimoto's thyroiditis patients, age at presentation, female-to-male ratio, thyroid size and nodule (s), functional status (euthyroidism, hypothyroidism, transient hyperthyroidism, Hashitoxicosis), and serum thyroid antibodies (TPOAb and TgAb) status were assessed. Linear correlation was used to test for trend of changes of each index over the years.	Human exposure to the volcanic environment of Sicily, Italy.	Although they are neighboring provinces, the incidence of thyroid cancer and Hashimoto's thyroiditis differed between Catania and Messina: in Catania, thyroid cancer incidence was higher, and Hashimoto's thyroiditis was lower. Thyroid cancer and hypothyroidism, namely Hashimoto's thyroiditis, could be influenced by distinct environmental factors. In terms of Hashimoto's thyroiditis patients' thyroid functional status, there were differences in the rates of subclinical and overt hypothyroidism: in Messina, most hypothyroidism patients presented subclinical hypothyroidism.
Papillary Thyroid Microcarcinomas: A Comparative Study of the Characteristics and Risk Factors at Presentation in two Cancer Registries (Malandrino et al., 2013a)	All incident cases of papillary thyroid microcarcinomas recorded in 2002–2006 in the Sicilian Regional Registry for Thyroid Cancer (SRRTC) were included in a retrospective, observational study. Information regarding histotype, age at diagnosis, gender, extent of surgery, tumor size, extrathyroid extension, multifocality, and TNM category was considered. The obtained data was compared with that from Surveillance Epidemiology and End Results (SEER) in the United States.	Human exposure to the volcanic environment of Sicily, Italy.	Papillary thyroid microcarcinoma incidence is twice as high in Sicily, compared with the United States. Within Sicily, the incidence of papillary thyroid microcarcinoma is twice as high in the volcanic area, suggesting the role of volcanic environments in the appearance of this disease.
Descriptive Epidemiology of Human Thyroid Cancer: Experience from a Regional Registry and the "Volcanic Factor" (Malandrino et al., 2013b)	Searching in different cancer registries for data regarding epidemiology of human thyroid cancer, with focus on the population of Sicily, Italy.	Human exposure to the volcanic environment of Sicily, Italy, with emphasis on the chemicals in drinking water.	There were 2.3 times more cases of thyroid cancer in the Catania province (a volcanic area of Mount Etna, Sicily, Italy): $ASR_w = 31.7/10^5$ in females and $6.4/10^5$ in males *vs.* 14.1 in females and 3.0 in males in the rest of Sicily. It is suggested that volcanogenic carcinogens may promote papillary thyroid cancer.
Determination of Total Vanadium and Vanadium(V) in Groundwater from Mt. Etna and Estimate of Daily Intake of Vanadium(V) Through Drinking Water (Arena et al., 2014)	Water was sampled monthly at 21 sites from the area of Mount Etna, Sicily, Italy, in 2011. Total vanadium (V) was determined by inductively coupled plasma mass spectrometry (ICP-MS) and speciation by ion chromatography-ICP-MS (IC-ICP-MS). The daily intake of V(V) of adults and children through drinking water was estimated.	Human exposure to the volcanic environment of Sicily, Italy, with emphasis on V in drinking water.	High concentrations of V in the drinking water of volcanic areas could be associated with pathological conditions like thyroid cancer.
The Influence of the Environment on the Development of Thyroid Tumors: A New Appraisal (Marcello et al., 2014)	Searching in scientific databases for articles in which connections between environmental factors and thyroid tumors are reported.	Human exposure to volcanic environments.	Living in a volcanic area may promote differentiated thyroid cancer.
Several Site-specific Cancers are Increased in the Volcanic Area in Sicily (Russo et al., 2015)	Cancer registries from 2003 to 2007 covering 82 % of the population of Sicily (72,197 incidence cases) were analyzed in the study to compare the incidence of 34 site-specific types of cancer in the area around the Mount Etna volcano (where thyroid cancer incidence is very high) with adjacent non-volcanic areas. Differences in crude incidence ratios (IRR) between the two areas were calculated.	Human exposure to the volcanic environment of Sicily, Italy.	Much like thyroid cancer, other types of cancers, like that of the stomach and prostate, show high incidence in the volcanic area of Sicily, Italy. Results suggest the role of exposure to volcanic environments in the appearance of multiple types of cancers.
Volcanic Environments: "Biomonitoring" their Links to Thyroid Cancer (Duntas, 2016)	Searching in scientific databases for articles in which connections between volcanic areas and thyroid cancer are reported.	Human exposure to volcanic environments.	Given the non-anthropogenic pollution that characterizes volcanic environments, more and more evidence supports the role of volcanic areas in the pathogenesis of thyroid cancer.
The Impact of Recent Volcanic Ash Depositions on Herbivores in Patagonia: A Review (Flueck, 2016)*	Searching in scientific databases for articles in which connections between volcanic events and effects on livestock are reported.	Herbivore exposure to volcanic ash in Patagonia.	Herbivores exposed to volcanic tephra developed conditions like fluorosis, anemia, and hypothyroidism, among others.
Increased Thyroid Cancer Incidence in a Basaltic Volcanic Area is Associated with Non-Anthropogenic Pollution and Biocontamination (Malandrino et al., 2016)	Thyroid cancer epidemiology from 2002 to 2006 in Mount Etna, an active volcanic area from Sicily, Italy, was obtained from the Sicilian Regional Registry for Thyroid Cancer (SRRTC). 27 trace elements were measured by quadrupole mass spectrometry (QMS) in the drinking water and lichens (to characterize environmental pollution), and the urine of residents (to characterize biocontamination). Thyroid cancer incidence and trace metal concentration were compared between residents of the volcanic area considered	Human exposure to the volcanic environment of Sicily, Italy, with emphasis on trace elements in drinking water.	There is a complex non-anthropogenic biocontamination with many trace elements, such as cadmium (Cd), mercury (Hg), manganese (Mn), palladium (Pd), thallium (Tl), uranium (U), vanadium (V), and tungsten (W), in Sicily, an active volcanic area where thyroid cancer incidence is increased. The mentioned elements were increased in concentration values higher than two-fold in the urine of residents of the volcanic area, in comparison to that of the individuals from the control area. The combination of the increased

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Table 1 (*continued*)

Study	Design	Exposure**	Key findings***
	(Catania province) and in adjacent non-volcanic control areas.		concentrations of trace elements in volcanic areas is associated with thyroid cancer.
Intake of Boron, Cadmium, and Molybdenum Enhances Rat Thyroid Cell Transformation (Luca et al., 2017)*	28 9-weeks old female Wistar rats prone to developing thyroid tumors by low-iodine diet (hence, becoming hypothyroid) and methimazole treatment received *ad libitum* drinking water supplemented with boron (B), cadmium (Cd), and molybdenum (Mo) at concentrations in the range double to that found in the urine samples of residents of the Mount Etna volcanic area, Sicily, Italy. 24 h urine samples were collected from the rats at 1-, 5- and 10-months old and evaluated in terms of element concentration. At 5- and 10-months old, the rats were euthanized and their thyroid was analyzed in terms of histopathology, and element concentration. Results were compared between the test and control groups.	Female Wistar rats exposure to B, Cd, and Mo in drinking water.	Slightly increased environmental concentrations of B, Cd, and Mo, which can be found in volcanic environments, display a combined toxic effect by accelerating the appearance of transformation marks in the thyroid gland of hypothyroid rats.
Thyroid Cancer in the Pediatric Age in Sicily: Influence of the Volcanic Environment (Russo et al., 2017)	Data regarding all incident pediatric (0–19 years old) thyroid cancers in Sicily, Italy, between 2002 and 2009 was obtained from the Sicilian Regional Register for Thyroid Cancer (SRRTC) and analyzed for the area of residence. Information regarding age at presentation, gender, tumor histotype, and tumor characteristics was considered. Such data was compared to that of adults. Both the pediatric and adult data obtained for Sicily were compared to that from Surveillance Epidemiology and End Results (SEER). The age-standardized incidence rate for the world population (ASR_w) was calculated.	Human children exposure to the volcanic environment of Sicily, Italy.	Thyroid cancer incidence is markedly increased in children inhabiting the volcanic environment of Sicily, Italy, suggesting a short-term effect of unidentified carcinogens of volcanic origin.
Anaplastic Thyroid Cancer in Sicily: The Role of Environmental Characteristics (Tavarelli et al., 2017)	Data from the Sicilian Regional Register for Thyroid Cancers (SRRTC) from 2002 to 2009 was included in the study. Information regarding individuals' age, gender, anaplastic thyroid cancer incidence, tumor size and histotype, extrathyroidal extension, stage, and coexistence with pre-existing differentiated thyroid cancer was evaluated in different areas of Sicily, Italy, then compared with data from Surveillance Epidemiology and End Results (SEER) in the United States. Poisson regression analysis was performed to compare the incidence of thyroid cancer in the different geographical areas considered.	Human exposure to the volcanic environment of Sicily, Italy.	The incidence of anaplastic thyroid cancer doesn't seem to be directly associated with environmental factors. However, differentiated thyroid cancer incidence in the volcanic area of Sicily, Italy, was doubled in relation to the rest of the island.
Heavy Metals in the Volcanic Environment and Thyroid Cancer (Vigneri et al., 2017)	Searching in scientific databases for articles in which connections between heavy metals and thyroid carcinogenesis are reported.	Human exposure to volcanic environments.	Cell damage resulting from repeated exposure to low concentrations of heavy metals, even when within what are considered "normal" or "safe" limits, like what happens in volcanic areas, can be explained by a potentiation effect resulting from the mixture of different metals acting synergistically.
Nutritional and Environmental Factors in Thyroid Carcinogenesis (Nettore et al., 2018)	Searching in scientific databases for articles in which connections between nutritional and environmental factors and thyroid carcinogenesis are reported.	Human exposure to volcanic environments.	Volcanogenic gas, ash, and lava emissions pollute ground water, vegetables, and animals, thus contaminating humans *via* the food chain. A long stay in volcanic areas seems to be associated with the development of thyroid cancer.
Effect of Low-dose Tungsten on Human Thyroid Stem/Precursor Cells and their Progeny (Gianì et al., 2019)*	36 female patients aged between 30 and 65 years old admitted to surgery for a solitary thyroid nodule (classified TIR 3 at cytology and resulting benign at pathology) donated a small aliquot of their excised thyroid tissue. A small sample of normal-appearing thyroid tissue at least 5 mm distant from the nodule was collected and used for *in vitro* studies. Three different human thyroid cell models were made from the collected thyroid tissue: (1) thyrocytes in primary culture, (2) stem/progenitor thyroid cells (thyrospheres), and (3) thyrocytes differentiated from thyrospheres, indicated as "secondary" thyrocytes. Cells were exposed to sodium tungstate dihydrate	Human thyroid cells exposure to tungsten (W) in salt form.	Chronic exposure to slightly increased W is harmless for mature thyrocytes, but significantly alters the biology of stem/precursor thyroid cells and of their progeny. Moreover, it can be a driver for characteristics of preneoplastic formation.

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Table 1 (*continued*)

Study	Design	Exposure**	Key findings***
	($Na_2WO_4.2H_2O$; Sigma), which was dissolved in deionized water and added to the culture media in a concentration range of 1 nM–1 μM (culture media were replaced every 2–3 days). Cell proliferation, apoptosis, gene transcription, and DNA-repair proteins were analyzed. Western blot analysis, and measurements of *in vitro* cell transformation were performed.		
Exposure to Emissions from Mount Etna (Sicily, Italy) and Incidence of Thyroid Cancer: A Geographic Analysis (Boffetta et al., 2020)	186 municipalities in the area close to Mount Etna, Sicily, Italy, with a total of 1.9 million inhabitants, were included in the study. The angle between the bearing of the municipalities and each direction of the plume was measured. Regression analysis on the incidence rates of thyroid cancer from 2003 to 2016, adjusted for the distance from Mount Etna, population size, and income was performed.	Human exposure to the volcanic environment of Sicily, Italy, with emphasis on volcano emissions.	The plume from Mount Etna seems to play a role in determining the high rates of thyroid cancer in the area.
Geographic Influences in the Global Rise of Thyroid Cancer (Kim et al., 2020b)	Searching in scientific databases for articles in which connections between geographic and environmental factors and thyroid cancer are reported.	Human exposure to volcanic environments.	Residing in volcanic areas seems to increase the risk of thyroid cancer.
Increased Thyroid Cancer Incidence in Volcanic Areas: A Role of Increased Heavy Metals in the Environment? (Malandrino et al., 2020)	Searching in scientific databases for articles in which connections between living in volcanic areas, chronically exposed to slightly increased levels of metals, and the appearance of thyroid cancer are reported.	Human exposure to volcanic environments, with emphasis on heavy metals.	An association between living in volcanic areas and higher incidence of thyroid cancer was observed. Different mechanisms may explain the specific carcinogenic effect of borderline/high environmental levels of metals on the thyroid, namely: (i) hormesis, the nonlinear response to chemicals causing important biological effects at low concentrations, (ii) metal accumulation in the thyroid relative to other tissues, and (iii) the specific effects of a mixture of different metals.
Thyroid Stem Cells but Not Differentiated Thyrocytes Are Sensitive to Slightly Increased Concentrations of Heavy Metals (Gianì et al., 2021a)*	14 female patients aged between 30 and 65 years old admitted to surgery for a solitary thyroid nodule (classified TIR 3 at cytology and resulting benign at pathology) donated a small sample of normal thyroid tissue for *in vitro* analyses. Three different human thyroid cell models were made from the collected thyroid tissue: (1) thyrocytes in primary culture, (2) stem/progenitor thyroid cells (thyrospheres), and (3) thyrocytes differentiated from thyrospheres, indicated as "secondary" thyrocytes. Cells were exposed to the following metals in the form of salt compounds: copper (Cu) used as $CuSO_4$, zinc (Zn) as $ZnCl_2$, mercury (Hg) as $HgCl_2$, palladium (Pd) as $PdCl_2$, and tungsten (W) as Na_2WO_4. Cell proliferation was assessed, and immunoblot analyses were performed.	Human thyroid cells exposure to Cu, Zn, Hg, Pd, and W in salt form.	Stem/precursor thyroid cells are sensitive to small increases in environmental metal concentrations, though differentiated thyrocytes are not.
Heavy Metals in the Environment and Thyroid Cancer (Gianì et al., 2021b)	Searching in scientific databases for articles in which connections between heavy metals and thyroid cancer are reported.	Human exposure to volcanic environments, with emphasis on heavy metals.	Thyroid cancer incidence is doubled in volcanic areas in comparison to non-volcanic areas due to significant heavy metal contamination arising from volcano emissions. Chronic exposure to slightly increased heavy metal concentrations, but still considered within the "normal range", can have significant effects over the thyroid, favoring the disposition for thyroid cancer.
Thyroid Carcinoma: A Review for 25 Years of Environmental Risk Factors Studies (Kruger et al., 2022)	Searching in scientific databases for articles in which connections between environmental factors and thyroid cancer are reported.	Human exposure to volcanogenic pollutants in the environment.	The non-anthropogenic pollution of soil, water, and the environment with heavy metals present in volcanic areas is associated with an increased risk of thyroid cancer.
Assessment of Five Typical Environmental Endocrine Disruptors and Thyroid Cancer Risk: A Meta-analysis (Yang et al., 2023)	Searching in scientific databases for articles in which connections between exposure to environmental endocrine disruptors (EEDs) and thyroid cancer are reported.	Human exposure to EEDs, such as heavy metals.	Exposure to certain EEDs, such as polybrominated diphenyl ethers (PBDEs), phthalates (PAEs), and heavy metals, increases the risk of thyroid cancer.
Spatial Explorative Analysis of Thyroid Cancer in Sicilian Volcanic Areas (Bitonti and Mazza, 2024)	Exploring the spatial distribution of thyroid cancer near Mount Etna, Sicily, Italy, through georeferencing data from the Cancer Registry of Eastern Sicily. Local Moran's I index was used to assess the	Human exposure to the volcanic environment of Sicily, Italy.	The presence of a volcano seems to lead to an increase in thyroid cancer incidence.

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Table 1 (*continued*)

Study	Design	Exposure**	Key findings***
	presence of clusters of higher-risk areas, considering the proximity to the volcano and the non-uniform distribution of the population across the territory.		
Modifiable Risk Factors for Thyroid Cancer: Lifestyle and Residence Environment (Shen et al., 2024)	Searching in scientific databases for articles in which connections between lifestyle and residential environment and thyroid cancer are reported.	Human exposure to volcanic environments.	Populations living in volcanic environments have an increased risk of developing thyroid cancer.
The Impact of Environmental Factors and Contaminants on Thyroid Function and Disease from Fetal to Adult Life: Current Evidence and Future Directions (Street et al., 2024)	Searching in scientific databases for articles reporting the influence of environmental factors on the thyroid.	Human exposure to volcanic environments.	Living in volcanic regions can be a threat to thyroid function, and therefore predisposing for thyroid cancer.
Environmental Factors Related to the Origin and Evolution of Differentiated Thyroid Cancer: A Narrative Review (Paz-Ibarra et al., 2024)	Searching in scientific databases for articles in which connections between environmental factors and differentiated thyroid cancer are reported.	Human exposure to volcanic environments.	Living in a volcanic residence is an environmental risk for thyroid disease.

rapid spread of the tumors (Gimm, 2001; Nabhan et al., 2021; Boucai et al., 2024). In any case, thyroid nodules may or may not be present. The risk and severity of these disorders is dependent on factors like age, gender, exposure to environmental contaminants, exposure to radiation, among others (Bogović Crnčić et al., 2020). A lot of the articles included in this review address thyroid cancer in general, either regarding its incidence as a whole or devoting some focus towards specific types (Arnbjörnsson et al., 1986; Spitz et al., 1988; Duntas and Doumas, 2009; Floor and Román-Ross, 2012; Kristbjornsdottir and Rafnsson, 2012; Latina et al., 2013; Malandrino et al., 2013a; Malandrino et al., 2013b; Arena et al., 2014; Marcello et al., 2014; Russo et al., 2015; Duntas, 2016; Malandrino et al., 2016; Russo et al., 2017; Nettore et al., 2018; Boffetta et al., 2020; Kim et al., 2020b; Malandrino et al., 2020; Gianì et al., 2021b; Kruger et al., 2022; Yang et al., 2023; Bitonti and Mazza, 2024; Paz-Ibarra et al., 2024; Shen et al., 2024). The systematic review of Putri et al. (2022) offers extensive data regarding thyroid cancer incidence on populations inhabiting volcanic environments, also including data on other cancers.

In short, research shows that the incidence of thyroid cancer can double in volcanically active areas compared to non-volcanic ones. A few articles, however, directly assess specific types of thyroid cancer, namely the work of Agate et al. (2012), focused on differentiated thyroid cancer. The incidence of differentiated thyroid cancer is considered, in this case, as a result of "a complex interaction between genetic and environmental factors", in which exposure to volcanic environments may play a part. Under the same category, Pellegriti et al. (2009) and Lise et al. (2012) address papillary thyroid cancer, while the work of Malandrino et al. (2013a) focuses on papillary thyroid microcarcinoma. The available information regarding this type of thyroid cancer can be summarized in a higher incidence of papillary thyroid cancer in the volcanic area of Sicily, Italy, in comparison to non-volcanic areas. Despite these connections, it was concluded that exposure to volcanic environments alone is unlikely to account for the rise in thyroid papillary cancer in the region (Lise et al., 2012). In fact, the emergence of disease is rarely due to a single factor – exceptions include monogenic disorders like cystic fibrosis, hemochromatosis, and hemophilia A (Apgar and Sanders, 2022) –, but a combination of several factors acting synergistically, hence the designation of "multifactorial" disease (Stolk et al., 2008; Fuller, 2018), as it is the case for most cancers (Wu et al., 2018). Findings from another study in Sicily show there were 2.3 times more cases of thyroid cancer in the Catania province (a volcanic area of Mount Etna, Sicily, Italy), with an $ASR_w = 31.7/105$ in females and 6.4/105 in males *vs.* 14.1 in females and 3.0 in males in the rest of Sicily. Because of this, it was suggested that volcanogenic carcinogens may promote papillary thyroid cancer. On the other hand, Tavarelli et al. (2017) address anaplastic thyroid cancer, stating that the incidence of this type does not seem to have any correlation with environmental factors, rather being primarily determined by genetic factors. As such, it was presumed that the high incidence rates of this thyroid disorder in Sicily, Italy, are not caused by living in this volcanic environment. Finally, the work of Russo et al. (2017) was the single one addressing pediatric thyroid cancer. Much like adults, children aged between 0 and 19 years old inhabiting volcanically active areas were also more likely to develop cancer than those inhabiting non-volcanic areas. Taken together, the available body of evidence highlights the importance of categorizing the different types of thyroid cancer occurring in a population and their various underlying risk factors, including the influence of environmental risk factors commonly associated with volcanic environments. Conducting research with this goal is necessary to improve thyroid cancer risk assessment in these areas.

3.1.2. *Hypothyroidism and Hashimoto's thyroiditis*

Besides cancer, another thyroid pathology that is seemingly more prevalent in volcanic environments is hypothyroidism, especially linked to Hashimoto's thyroiditis. Hypothyroidism is a condition in which the thyroid gland is underactive, therefore producing amounts of T4 and T3 below physiological needs, with repercussions affecting the entire organism, often involving unspecific symptoms (such as fatigue, lethargy, intolerance to cold, weight gain, dry skin) (Jansen et al., 2023). Depending on the underlying causes, hypothyroidism can be classified as: primary, when the issue lies in the thyroid's tissues; central, when in the pituitary; or peripheral, when in the hypothalamus. Hypothyroidism can be classified as subclinical when TSH levels are higher than normal, but T4 and T3 levels are within adequate levels, or overt when both TSH and TH levels are abnormal (Chaker et al., 2022). The risk and severity of hypothyroidism depend on factors such as inadequate intake of iodine (deficiency or excess), radiation therapy, certain medications, among others (Zamwar and Muneshwar, 2023). The review of Flueck (2016) aimed to summarize the main impacts of volcanic ash deposition in Patagonia on herbivores. It was found that herbivores exposed to volcanic tephra developed conditions like fluorosis, anemia, and hypothyroidism, among others. The work of Luca et al. (2017) also highlighted the influence of environmental factors in the occurrence of hypothyroidism, particularly exposures associated with volcanic environments. Although little is known about the link between volcanic environments and hypothyroidism, the authors' work revealed that "slightly increased environmental concentrations of B, Cd, and Mo, which can be found in volcanic environments, accelerate the appearance of transformation marks in the thyroid gland of hypothyroid rats". Hashimoto's thyroiditis is an autoimmune disorder in which the immune system targets the thyroid gland, being often associated with hypothyroidism. Lymphocytes infiltrate the thyroid tissue and destroy thyroid cells *via* cell and antibody-mediated immune responses, which ultimately leads to lower production of T4 and T3 by thyrocytes. Some factors that can contribute

Table 2
List of articles included in this systematic review regarding the effects of arsenic (As) exposure on the thyroid. Information regarding study design, addressed exposure, and key findings is presented. *_In vitro_ or _in vivo_ study with animal models. **Only exposures related to As were considered. ***The key findings display information specifically regarding the effects of As on the thyroid.

Study	Design	Exposure**	Key findings***
Study of Distribution and Interaction of Arsenic and Selenium in Rat Thyroid (Glattre et al., 1995)*	78 Wistar weanling rats were pretreated with arsenate (100 mg/L As), selenite (1 mg/L Se), and arsenate (100 mg/L As) plus selenite (1 mg/L Se) added to the drinking water. After 4 weeks, all the animals were sacrificed and serum T3 and T4 were determined by double-antibody radioimmunoassay. Thyroid tissue concentrations of As and Se were determined in female rats by neutron activation analysis, and tissue specimens were examined histopathologically.	Wistar rats exposure to arsenate.	For both male and female rats, the measurements indicated that T4/T3 was lowest in the selenium (Se) group, intermediate in the arsenic (As) group, and highest in the controls. Postmortem examination showed that the thyroid tissue of rats pretreated with As alone exhibited obvious toxic alterations, whereas only minor to no changes were found in the tissues of the groups pretreated with Se or As + Se. Multivariate analyses demonstrated that (i) s-T4 and s-T3 were significantly correlated with sex, (ii) s-T3 was positively correlated with Se pretreatment, and that the T4/T3 ratio was negatively correlated with both As and Se pretreatment.
Cancer Induction by an Organic Arsenic Compound, Dimethylarsinic Acid (Cacodylic Acid), in F344/DuCrj Rats After Pretreatment with Five Carcinogens (Yamamoto et al., 1995)*	A multiorgan bioassay in rats given various doses of dimethylarsinic acid (cacodylic acid or DMA) to evaluate its effects on chemical carcinogenesis. 124 male F344/DuCrj rats were divided randomly into 7 groups. Rats in groups 1–5 were treated sequentially with diethylnitrosamine (100 mg/kg bw, i.p., single dose at the commencement) and *N*-methyl-N-nitrosourea (20 mg/kg bbw, i.p., 4 times, on days 5, 8, 11, and 14). Thereafter, rats received 1,2-dimethylhydrazine (40 mg/kg bw, s.c., 4 times, on days 18, 22, 26, and 30). During the same period, rats were sequentially administered N-butyl-N-(4-hydroxybutyl) nitrosamine (0.05 % in the drinking water, during weeks 1 and 2) and *N*-bis(2-hydroxypropyl)nitrosamine (0.1 % in the drinking water, during weeks 3 and 4; DMBDD treatment). After a 2-week interval, groups 2–5 were given 50, 100, 200, or 400 ppm DMA, respectively, in the drinking water. Groups 6 and 7, which were not given DMBDD treatment, received 100 and 400 ppm DMA during weeks 6–30. All rats were euthanized at the end of week 30 for the multiorgan bioassay.	Male F344/DuCrj rats exposure to DMA.	DMA significantly enhanced the tumor induction in the thyroid of rats, with incidences in group 5 (400 ppm DMA) of 45 %.
Possible Carcinogenic Potential of Dimethylarsinic Acid as Assessed in Rat *In Vivo* Models: A Review (Yamamoto et al., 1997)*	Searching in scientific databases for articles in which connections between exposure to DMA and carcinogenic effects on rats are reported.	Rats exposure to DMA.	DMA promotes the induction of tumors on the thyroid of rats.
Sawmill Chemicals and Carcinogenesis (Huff, 2001)	Searching in scientific databases for articles in which connections between common sawmill chemicals and carcinogenesis are reported.	Rats exposure to DMA.	DMA promotes the induction of tumors on the thyroid of rats.
A Concise Review of the Toxicity and Carcinogenicity of Dimethylarsinic Acid (Kenyon and Hughes, 2001)	Searching in scientific databases for articles in which connections between exposure to DMA and toxic effects are reported.	Rats exposure to DMA.	DMA promotes the induction of tumors on the thyroid of rats. DMA seems to play a role in the carcinogenesis of inorganic As. DMA promotes the induction of tumors on the thyroid of rats.
Recent Advances in Arsenic Carcinogenesis: Modes of Action, Animal Model Systems, and Methylated Arsenic Metabolites (Kitchin, 2001)	Searching in scientific databases for articles in which connections between exposure to As and biological effects are reported.	Rats exposure to DMA.	Possible mechanisms of As carcinogenesis include (i) chromosomal abnormalities, (ii) oxidative stress, (iii) altered DNA repair, (iv) altered DNA methylation patterns, (v) altered growth factors, (vi) enhanced cell proliferation, (vii) promotion/progression, (viii) gene amplification, and (ix) suppression of p53.
Oxidative Stress by Inorganic Arsenic: Modulation by Thyroid Hormones in Rat (Allen and Rana, 2003)*	Rats were divided randomly in 6 groups of 5 rats each. Groups A and B were made hyperthyroid by injecting L-thyroxine (25 mg/100 g bw) intramuscularly on every 4th day for 3 weeks. Groups C and D were made hypothyroidic by injecting, *n*-propylthiourea (2.5 mg/100 g bw) intramuscularly twice a week for 30 days. Groups E and F contained As and saline treated control rats, respectively. Groups A, C, and E were selected for As	Rats exposure to inorganic As (iAs).	As is less toxic in hyperthyroid than in hypothyroid rats. There seems to be a physiological antagonism between As and T4.

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Table 2 (*continued*)

Study	Design	Exposure**	Key findings***
	treatment. Each rat was administered a predetermined sublethal dose, *i.e.*, 4 mg/100 g bw of arsenictrioxide [As(III)] dissolved in saline water through gavage on each alternate day for 30 days. At the end of the experiment, samples of several of the rats' organs were collected and analyzed for the presence of As, the determination of lipid peroxidation, estimation of glutathione content, among others.		
Dimethylarsinic Acid: Results of Chronic Toxicity/Oncogenicity Studies in F344 Rats and in B6C3F1 Mice (Arnold et al., 2006)*	DMA was administered in the diet to B6C3F1 mice (at dose levels of 0, 8, 40, 200, and 500 ppm) and to F344 rats (at dose levels of 0, 2, 10, 40, and 100 ppm) for 2 years, according to US EPA guidelines. Alterations in several organs, such as the formation of carcinomas and other tissue changes, were assessed.	F344 rats and B6C3F1 mice exposure to DMA.	Dose-related increases in the height of the thyroid follicular epithelium were observed in both males and females; however, such changes seemed to reflect an adaptive response of the thyroid to decreased levels of circulating thyroid hormone, rather than an adverse effect. DMA is carcinogenic in rats at relatively high doses, but not in mice. Female rats appear to be more sensitive to the effects of DMA than male rats.
Arsenic as an Endocrine Disruptor: Arsenic Disrupts Retinoic Acid Receptor–and Thyroid Hormone Receptor–Mediated Gene Regulation and Thyroid Hormone–Mediated Amphibian Tail Metamorphosis (Davey et al., 2008)*	Human embryonic NT2 or rat pituitary GH3 cells were treated with 0.01–5 μM sodium arsenite for 24 h, with or without retinoic acid (RA) or thyroid hormones (TH), respectively, to examine effects of As on receptor-mediated gene transcription. An amphibian *ex vivo* tail metamorphosis assay was used to examine whether endocrine disruption by low-dose As could have specific pathophysiologic consequences.	Human embryonic NT2 or rat pituitary GH3 exposure to sodium arsenite, and *ex vivo* amphibian tail cells exposure to As.	Changes in expression of type 1 deiodinase (*DIO1*) were observed at 6 or 24 h of As exposure, indicating a transient superinduction by As at very low doses, and a transient repression by As at higher doses. As alters hormone-signaling by disrupting the normal function of both RA receptor and TH receptor.
Arsenate and Perchlorate Toxicity, Growth Effects, and Thyroid Histopathology in Hypothyroid Zebrafish *Danio rerio* (Liu et al., 2008a)*	Hypothyroidism was induced in zebrafish (*Danio rerio*) *via* exposure to perchlorate, having the toxicity of arsenate in hypothyroid and euthyroid fish been compared. The lethal concentration 50 (LC_{50}) was determined, and histopathology was assessed. The recovery of thyroid histopathological indices following cessation of perchlorate exposure was determined.	*Danio rerio* exposure to perchlorate and arsenate.	Perchlorate can enhance the toxicity of arsenate. Growth rates were significantly retarded, having hypothyroid fish been more sensitive to arsenate. Thyroid histopathology can be recovered from after cessation of perchlorate exposure, but not in terms of colloid area nor growth rate.
Exposure to Arsenic in Urban and Rural Areas and Effects on Thyroid Hormones (Ciarrocca et al., 2012)	Total urinary As and thyroid markers were obtained from 108 non-smoking traffic policemen and 77 subjects working as roadmen in a rural area. 50 subjects were monitored to evaluate airborne exposure to As. Multiple linear regression models were made to determine the association between the studied variables.	Human exposure to airborne As.	A higher exposure to As induces a greater decrease in FT4, and FT3 levels, while inducing an increase in TSH levels.
Arsenic and Human Health Effects: A Review (Abdul et al., 2015)	Searching in scientific databases for articles in which connections between As exposure and human health effects are reported.	Human exposure to As in several contexts.	Exposure to low levels of As in groundwater seemed to be associated with hypothyroidism. Mechanisms of As toxicity on the thyroid include (i) preventing the synthesis of thyroid hormones (TH), and (ii) increasing the proliferation of thyroid follicles.
Association of Hypothyroidism with Low-level Arsenic Exposure in Rural West Texas (Gong et al., 2015)	A total of 723 participants from Project FRONTIER living in rural West Texas were included in the study, based on their history of hypothyroidism diagnosis. As and iodine (I) levels in their groundwater used for drinking and/or cooking were estimated by the inverse distance weighted (IDW) interpolation technique. Logistic regression analysis was performed to estimate the association between groundwater As and cumulative As exposure with hypothyroidism.	Human exposure to As in groundwater.	The prevalence of hypothyroidism in the study population, exposed to a low level of As (2–22 μg/L), was significantly higher than the national prevalence.
Association Between Arsenic Exposure and Thyroid Function: Data from NHANES 2007–2010 (Jain, 2016)	Data from the National Health and Nutrition Examination Survey (NHANES) 2007–2010 from a total of 4126 individuals was included in the study. In 4 smaller subsamples within the available data (iodine-deficient males, iodine-replete males, iodine-deficient females, and iodine-replete females), analyzes were performed in terms of As variables in urine, total As (UAS), arsenobetaine (UAB),	Human exposure to As.	Exposure to As significantly lowered thyroid function, often no matter if individuals were iodine-replete.

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Table 2 (*continued*)

Study	Design	Exposure**	Key findings***
	dimethylarsinic acid (UDMA), and As adjusted for arsenobetaine (UAAS) with TSH, free and total serum thyroxine (FT4, TT4), free and total triiodothyronine (FT3, TT3), and Tg. 96 regression models were generated in the study. The interaction between variables was explored.		
Mechanisms of Arsenic Disruption on Gonadal, Adrenal and Thyroid Endocrine Systems in Humans: A Review (Sun et al., 2016)	Searching in scientific databases for articles in which connections between As exposure and human endocrine-disruption are reported.	Human and animal exposures to As in several contexts.	Different forms of As exhibit distinct mechanisms of toxicity. Toxic mechanisms of As(V) include (i) causing histopathology, (ii) elevating T4 levels. Toxic mechanisms of As(III) include (i) inhibiting thyroperoxidase (TPO) activity, (ii) altering the expression of thyroid hormone receptors, (iii) increasing T4 and T3 levels, (iv) increasing TSH and thyroglobuline levels, (v) decreasing free T4 and T3 levels.
Effects of Combined Exposure to Chronic High-fat Diet and Arsenic on Thyroid Function and Lipid Profile in Male Mouse (Ahangarpour et al., 2018)*	72 male Naval Medical Research Institute mice were divided into six groups and provided with a high-fat diet or low-fat diet while being exposed to 25 or 50 ppm of As in drinking water for 20 weeks. Following 24 h since the last experimental day, blood samples were collected for hormonal and biochemical measurements.	Male Naval Medical Research Institute mice exposure to As.	Exposure to As alone induced hypothyroidism, decreasing the levels of T3 and increasing the levels of TSH, and T4/T3 ratio. Combined exposure to a high-fat diet and As-induced hypothyroidism were concomitant with hypolipidemia, hyperleptinemia, hyperadiponectinemia, induction of oxidative stress, and glutathione sulfhydryl reductase (GSH) level reduction.
A Review of Environmental Epidemiology Studies in Southwestern and Mountain West Rural Minority Populations (Gonzales et al., 2018)	Searching in scientific databases for articles in which connections between environmental factors and the epidemiology of human pathologies are reported. Only environmental epidemiological studies conducted in the Southwest and Mountain West geographical locations of the USA were included.	Human exposure to As in groundwater.	As in groundwater and cumulative exposure to As are strong predictors for hypothyroidism.
The Role of Heavy Metals and Polychlorinated Biphenyls (PCBs) in the Oncogenesis of Head and Neck Tumors and Thyroid Diseases: A Pilot Study (Petrosino et al., 2018)	Hair and blood samples were collected from 20 volunteers with the aim of measuring the concentrations of 14 heavy metals and 12 polychlorinated biphenyls (PCBs). The measured concentrations were compared between individuals based on the presence of head and neck tumors.	Human exposure to PCBs and heavy metals, including As.	Patients with thyroid diseases, particularly carcinomas, tended to present higher As levels in the hair and blood.
Determination of Toxic and Essential Trace Elements in Serum of Healthy and Hypothyroid Respondents by ICP-MS: A Chemometric Approach for Discrimination of Hypothyroidism (Stojsavljević et al., 2018)	Inductively coupled plasma-mass spectrometry (ICP-MS) was used to determine the concentration of 3 toxic (Ni, As, Cd) and 6 essential trace elements (Cr, Mn, Co, Cu, Zn, Se) in blood serum of hypothyroid and euthyroid individuals, with the aim of setting the experimental conditions for accurate determination of a unique profile of these elements in hypothyroidism. Chemometric tools were applied for discrimination of patients with hypothyroidism.	Human exposure to several elements, including As.	Hypothyroid individuals had significantly higher serum As concentrations than euthyroid individuals.
In Search of Key: Protecting Human Health and the Ecosystem from Water Pollution in China (Chen et al., 2019)	A bottom-up inventory analysis hybrid life cycle impact assessment approach was used together with SimaPro 8.4 software to quantify the health and ecological impacts of water pollution in China at a macro level, from environmental and economic perspectives. Among others, direct water pollutant emissions and their potential impacts on China were quantified.	Human exposure to several water pollutants, including As, in China.	Exposure to As from water pollution seems to be associated with thyroid diseases, particularly thyroid cancer.
Evaluation of Trace Metals in Thyroid Tissues: Comparative Analysis with Benign and Malignant Thyroid Diseases (Stojsavljević et al., 2019)	Thyroid tissue samples were collected from healthy individuals and individuals with thyroid diseases, with the aim of establishing the differences in the baseline content of 4 essential (Mn, Cu, Zn, Se) and 4 toxic metals (As, Cd, Pb, U). Metals were quantified by inductively coupled plasma-mass spectrometry (ICP-MS).	Human exposure to several trace metals, including As.	Exposure to As seems to be associated with thyroid diseases, particularly hypothyroidism.
Non-essential Trace Elements Dietary Exposure in French Polynesia: Intake Assessment, Nail Bio Monitoring and Thyroid Cancer Risk (Zidane et al., 2019)	Measurements of the concentrations of 4 non-essential trace elements (Hg, Pb, As, and Cd) were performed in fingernail samples of Polynesians (from 373 healthy controls and 229 individuals with thyroid diseases), with the purpose of investigating the potential	Human exposure to several dietary non-essential trace elements, including As, in French Polynesia.	As was present in some fruits, vegetables, and drinking water samples at appreciable concentrations, and especially high in certain sea products. Each μg/day/kg bw of As exposure increased thyroid cancer risk by 30 % more in patients with

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Table 2 (*continued*)

Study	Design	Exposure**	Key findings***
	association between these and different thyroid cancer risks. A descriptive analysis of Polynesian food was performed. The association between thyroid cancer risk and daily intake levels of non-essential trace elements and with fingernail non-essential trace element levels were assessed.		a history of cancer in first-degree relatives than in those without.
Significance of Arsenic and Lead in Hashimoto's Thyroiditis Demonstrated on Thyroid Tissue, Blood, and Urine Samples (Stojsavljević et al., 2020)	51 female patients of Hashimoto's thyroiditis and 52 healthy females were included in the study. From each participant, thyroid tissue, intravenous blood and urine samples were collected. On each sample, the essential trace elements for thyroid homeostasis and the main threatening toxic trace elements were analyzed by inductively coupled plasma mass spectrometry (ICP-MS).	Human exposure to As.	The antagonistic effect of As and lead (Pb) on the extrusion of essential selenium (Se) likely explains the lack of Se in the thyroid tissue of Hashimoto's thyroiditis patients.
Does Arsenic Exposure Have a Role in Development of Thyroid Disease? (Argha et al., 2021)	Seven patients with thyroid disease were included in the study. Thyroid disease included cases of goiter, Hashimoto's thyroiditis, follicular adenoma, papillary thyroid carcinoma, and adenomatoid goiter. Arsenic exposure of the patients was estimated by inductively coupled plasma mass spectrometry (ICP-MS) of hair and nail samples.	Human exposure to As.	The high concentration of As in the patients' samples suggests that this metal plays a role in the development of thyroid disease.
Environmental Arsenic Exposure and its Toxicological Effect on Thyroid Function: A Systematic Review (Esform et al., 2022)	Searching in scientific databases for articles in which an association between As exposure and effects on thyroid function are reported.	Human, animal, and *in vitro* exposures to As in several contexts.	The concentration of As in serum and urine is associated with thyroid dysfunction. The increase of As levels in serum or urine is associated with a decrease in both T4 and T3 levels, and an increase in TSH levels.
Thyroid Hormones in Relation to Polybrominated Diphenyl Ether and Metals Exposure Among Rural Adult Residents Along the Yangtze River, China (Hu et al., 2021b)	A total of 329 rural adult residents along the Yangtze River, China, were included in the study. The plasma concentration of 8 polybrominated diphenyl ether congeners (PBDEs) and 14 urinary metals to reflect the levels of environmental exposure. Multiple linear regression models were used to evaluate the association between PBDEs, metals and thyroid hormone levels. Bayesian Kernel Machine Regression (BKMR) was used to examine PBDEs and metals mixtures in relation to thyroid hormones (TH).	Human exposure to PBDEs and metals, such as As, along the Yangtze River, China.	Urinary As was inversely associated with FT3. FT3 was significantly negatively associated with As.
Assessment of As Exposure in the Population of Sabalpur Village of Saran District of Bihar with Mitigation Approach (Kumar et al., 2021)	From a total of 520 households in the Sabalpur village, 128 were included in the study for sampling. Handpump water samples from the households were collected in duplicates at each 50–70 m of distance. Hair and nail samples were collected from a volunteer from each household. All samples were analyzed in terms of As concentration using the graphite furnace atomic absorption spectrophotometer (GF-AAS). The health survey covered all 520 households, having a total of 673 individuals been interviewed. Individuals showing symptoms of arsenicosis were interviewed extensively. Geographic Information System (GIS) analysis was performed to map out the data of As concentration in intervals per sample matrix.	Human exposure to As in drinking water.	Thyroid cancer was reported in individuals exposed to As poisoning through groundwater.
A Case-control Study on the Association of Mineral Elements Exposure and Thyroid Tumor and Goiter (Liu et al., 2021)	In a case-control study, individuals with thyroid tumor or goiter ($N = 197$) were matched with a healthy population (N = 197) by age and gender. Serum and urine samples were collected from each individual to determine the concentration of several minerals. Conditional logistic regression was applied to estimate the associations between mineral elements and the risk of thyroid tumor and goiter through single-element models and multiple-element models. Multiple linear regression was used to evaluate relationships between mineral elements and percentage changes of thyroid functions.	Human exposure to several minerals, including As.	Individuals with thyroid diseases had lower As concentrations than healthy individuals.

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Study	Design	Exposure**	Key findings***
Alteration of Trace Elements in Multinodular Goiter, Thyroid Adenoma, and Thyroid Cancer (Stojsavljević et al., 2021)	Blood samples from patients diagnosed with multinodular goiter, thyroid adenoma, and thyroid cancer were examined and compared with control samples using chemometric analysis. The blood concentrations of essential (Mn, Co, Cu, Zn, and Se) and toxic elements (Ni, As, Cd, Pb, and U) were determined by ICP-MS.	Human exposure to several trace elements, including As.	Individuals with multinodular goiter, thyroid adenoma, and thyroid cancer had higher blood As levels than healthy individuals.
Plasma Polybrominated Diphenyl Ethers, Urinary Heavy Metals and the Risk of Thyroid Cancer: A Case-Control Study in China (Zhang et al., 2021)	308 thyroid cancer cases and 308 age- and sex-matched controls were included in a case-control study developed in China. Plasma polybrominated diphenyl ethers (PBDEs) concentrations were determined by gas chromatograph-mass spectrometry (GC–MS), while the concentrations of heavy metals in urine samples were detected by graphite furnace atomic absorption spectrometry (GFAAS) or inductively-coupled plasma optical emission spectrometry (ICP-OES). Conditional logistic regression models were used to explore associations of PBDEs and 4 heavy metals exposures with thyroid cancer risk. A joint-effect interaction term was inserted into the logistic regression models to assess the multiplicative interaction effects of PBDEs-heavy metals on thyroid cancer risk.	Human exposure to several PDBEs and heavy metals, including As.	Exposures to PBDEs, As, and Hg are associated with an increased risk of thyroid cancer.
Carcinogenic Effects of Heavy Metals by Inducing Dysregulation of microRNAs: A Review (Aalami et al., 2022)	Searching in scientific databases for articles in which connections between heavy metals and microRNA dysregulation are reported.	Human, animal, and *in vitro* exposures to heavy metals, including As, in several contexts.	Metals like As, Cd, and Hg are associated with the dysregulation of microRNAs. Exposure to As seems to be related to thyroid carcinogenesis.
Chapter 3 - Arsenic (Fowler et al., 2022)	Searching in literature for works describing As uses, exposures, and effects on humans.	Human exposure to As in several contexts.	Inorganic arsenic (iAs) takes longer to be cleared from the thyroid in comparison to other organs.
Exposure to Multiple Trace Elements and Thyroid Cancer Risk in Chinese Adults: A Case-Control Study (He et al., 2022)	A total of 585 newly-diagnosed thyroid cancer patients and 585 healthy controls were included in the study. 14 urinary elements were measured to explain the fixed-exposure on thyroid cancer risk. Conditional logistic regression models were made to determine the association between the studied variables. Bayesian kernel machine regression (BKMR) was applied to show the tendency of mixed effects. Interaction effects were examined by a Generalized linear model (GLM).	Human exposure to trace elements, including As.	Exposure to As is significantly associated with an increased risk of thyroid cancer.
Comprehending the Role of Endocrine Disruptors in Inducing Epigenetic Toxicity (Kirtana and Seetharaman, 2022)	Searching in scientific databases for articles in which connections between endocrine disruptors and epigenetic toxicity are reported.	Human, animal, and *in vitro* exposures to As.	As exposure disrupts thyroid function.
Endocrine-disrupting Chemicals (EDCs) and Cancer: New Perspectives on an Old Relationship (Modica et al., 2023)	Searching in scientific databases for articles in which connections between exposure to endocrine-disrupting chemicals (EDCs) and cancer are reported.	Human exposure to EDCs, including As, in several contexts.	EDCs such as As, pesticides, tetrachlorodibenzodioxin (TCDD), and polychlorinated biphenyls (PCBs) can cause thyroid cancer, including other thyroid disorders.
Assessment of Five Typical Environmental Endocrine Disruptors and Thyroid Cancer Risk: A Meta-analysis (Yang et al., 2023)	Searching in scientific databases for articles in which connections between exposure to environmental endocrine disruptors (EEDs) and thyroid cancer are reported.	Human exposure to EEDs, such as As.	Exposure to certain EEDs, such as polybrominated diphenyl ethers (PBDEs), phthalates (PAEs), and heavy metals like As, increases the risk of thyroid cancer.
Arsenic-induced Thyroid Hormonal Alterations and Their Putative Influence on Ovarian Follicles in Balb/c Mice (Nandheeswari et al., 2024)*	Female Balb/c mice were given sodium arsenite (0.2 ppm, 2 ppm, and 20 ppm) *via* drinking water for 30 days. Several changes in the mice's thyroid and ovaries were assessed.	Female Balb/c mice exposure to As.	As exposure decreased FT4 and FT3 levels while increasing TSH levels, along with decreasing thyroid follicle size. As significantly reduced the expression of LAMP1 (a lysosomal marker protein), leading to increased lysosomal permeability in the thyroid, resulting in a significant release of cathepsin B. Collectively, these changes led to hypothyroidism.
Prolonged Exposure to $NaAsO_2$ Induces Thyroid Dysfunction and Inflammatory Injury in Sprague-Dawley Rats, Involvement of NLRP3 Inflammasome-mediated Pyroptosis (Fan et al., 2024)*	The toxic effects of sodium arsenite ($NaAsO_2$) exposure at different doses (0, 2.5, 5.0, and 10.0 mg/kg bw) and over different durations (12, 24 and 36 weeks) on thyroid tissue and thyroid hormone levels in Sprague-Dawley rats were investigated.	Sprague-Dawley rats exposure to sodium arsenite.	$NaAsO_2$ exposure can cause accumulation of As in the thyroid tissue of Sprague-Dawley rats. Chronic exposure to $NaAsO_2$ significantly upregulates the expression of NLRP3 inflammasome-related proteins in thyroid tissue, leading to pyroptosis of thyroid cells and subsequent development of thyroid dysfunction, inflammatory injury, epithelial-mesenchymal transition (EMT), and fibrotic changes in the thyroid glands of rats.

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Study	Design	Exposure**	Key findings***
Trace Element Status in Canine Endocrine Diseases (Larrán et al., 2024)*	13 elements (As, Cd, Co, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, Se and Zn) were measured in 40 dogs with hyperadrenocorticism (HAC), 29 dogs with diabetes mellitus (DM), 11 dogs with hypothyroidism (HT), and 30 control dogs using inductively coupled plasma mass spectrometry (ICP-MS). The relationships between trace elements and the 3 endocrinopathies were examined using chemometric procedures.	Dog exposure to trace elements, including As.	Dogs with hypothyroidism had higher As and lower Se levels.
Association Between Toxic Heavy Metals and Noncancerous Thyroid Disease: A Scoping Review (Rafi'i et al., 2025)	Searching in scientific databases for articles in which connections between heavy metals and non-cancerous thyroid diseases are reported.	Human exposure to As in several contexts.	Exposure to As impacts the thyroid in several ways even at low concentrations, such as by (i) causing histological alterations, (ii) increasing the levels of Tg and TSH, while lowering the levels of FT4 and FT3, and (iii) inhibiting thyroid peroxidase (TPO) regulation and activity in a dose-dependent relationship.
Molecular Disturbances and Thyroid Gland Dysfunction in Rats Chronically Exposed to a High Dose of $NaAsO_2$: Insights from Proteomic and Phosphoproteomic Analyses (Xiang et al., 2025)*	The toxic effects of sodium arsenite ($NaAsO_2$) exposure at different doses (0, 2.5, 5.0 and 10.0 mg/kg bw) and over different durations (12, 24 and 36 weeks) on thyroid tissue and thyroid hormone levels in Sprague-Dawley rats were investigated. Proteomic and phosphoproteomic analyses were performed to investigate the molecular mechanisms underlying the effects of chronic $NaAsO_2$ exposure on thyroid function.	Sprague-Dawley rats exposure to sodium arsenite.	$NaAsO_2$ disrupts the synthesis of thyroid hormones (TH) and alters the expression of the TH-synthesizing enzyme dual oxidase 2 (DUOX2). $NaAsO_2$ interfered with several cellular processes, such as causing upregulation of the central carbon metabolism in cancer, and downregulation of glutathione metabolism.
Relationship Between Internal Metal Exposure and Thyroid Cancer Incidence: A Case-control Study Simultaneously Validated by BKMR and WQS Models (Yu et al., 2025)	In a case-control study, the concentrations of 12 metals (Fe, Ni, Cu, Zn, As, Se, Sr, Cd, Cs, Ba, Hg, and Pb) were measured in urine samples of thyroid cancer patients and healthy controls. Weighted quantile sum (WQS) and Bayesian kernel-machine regression (BKMR) analyses were performed.	Human exposure to heavy metals, including As.	Urinary As concentrations were significantly lower in thyroid cancer cases than controls.

to the appearance of Hashimoto's thyroiditis include genetic susceptibility, environmentally modulated X chromosome inactivation patterns or composition of the microbiome. It is also reported that it frequently coexists with thyroid cancer, although the connection between both pathologies hasn't been fully elucidated (Klubo-Gwiezdzinska and Wartofsky, 2022).

The study conducted by Latina et al. (2013), included in this review, offers valuable data on the epidemiology of thyroid cancer and Hashimoto's thyroiditis in neighboring areas of Sicily, Italy: one that is volcanically active (Catania province), and another without volcanic activity (Messina province). Although the non-volcanic area had more hypothyroidism patients than the volcanically-active one, both regions showed a tendency towards an increase in the number of patients through the years (1995–2005). Thyroid cancer incidence would seem to be more associated to volcanic environments than hypothyroidism, given how, similarly to the previously discussed publications, there were many more cancer patients in the volcanically active area in comparison to the non-volcanic area. Therefore, it was suggested that the risk factors contributing to each pathology are distinct. However, bearing in mind that this was the only included study that addressed hypothyroidism, there is yet a considerable lack of corroborating data from other publications in this context, highlighting a second knowledge gap due to the lack of studies addressing exposure to volcanic environments and the emergence of non-cancerous thyroid pathology, specifically, hypothyroidism. Moreover, as previously discussed in regards of distinct types of thyroid cancer, determining which risk factors most influence either thyroid cancer or hypothyroidism remains challenging. This emphasizes once again the importance of categorizing the types of thyroid disruption affecting populations, so that risks and mitigation measures can be better assessed.

3.1.3. *Mechanisms of thyroid disruption by volcanic contaminants*

The addressed reasons why thyroid disorders are notably more prevalent in volcanic environments seem to be tied to the elements that these environments tend to be enriched with. Research demonstrates how the elements of these areas can act as endocrine disruptors, causing adverse effects on multiple organs (Linhares et al., 2013; Plunk and Richards, 2020; Yang et al., 2023), including the thyroid. In fact, it is reported that chronic exposure, even at low (Vigneri et al., 2017) to slightly elevated (Gianì et al., 2021b) doses of volcanogenic contaminants, such as PTEs, can cause significant harm on the thyroid and contribute to thyroid cancer. Vanadium (V) is an example of a toxic element enriching water sources from volcanic environments which is thought to be associated to thyroid cancer (Arena et al., 2014). Still, it is important to keep in mind that other factors may also be involved, such as the existence of iodine-deficient soils, and the presence of other goitrogens (*i.e.*, substances that impact thyroid function, often leading to goiter) in volcanic environments. There is research suggesting that the soils of volcanic environments have low iodine (I) concentrations, which can be a risk factor for the development of iodine-deficiency in animals, including humans (Linhares et al., 2015a; Menon and Skeaff, 2016). Meanwhile, fluoride (F^-) is a well-documented goitrogen that is abundant in volcanic environments, the chronic ingestion of which, at high doses, can impair thyroid function (Ozsvath, 2009). Finally, it's possible that different genetic backgrounds and healthcare access differences also contribute to thyroid disruption in populations inhabiting volcanic areas, therefore making them more susceptible (Panicker, 2011; Agate et al., 2012; Chen and Yeh, 2022).

The review by Gianì et al. (2019) and the *in vitro* study of Gianì et al. (2021a) provide insight into the fate of thyroid cells upon exposure to some volcanogenic contaminants. For instance, it was found that chronic exposure to slightly increased concentrations of tungsten (W) is

Table 3
List of articles included in this systematic review regarding the effects of mercury (Hg) exposure on the thyroid. Information regarding study design, addressed exposure, and key findings is presented. *_In vitro_ or _in vivo_ study with animal models. **Only exposures related to Hg were considered. ***The key findings display information specifically regarding the effects of Hg on the thyroid.

Study	Design	Exposure**	Key findings***
Differential Effects of Methylmercuric Chloride and Mercuric Chloride on the Histochemistry of Rat Thyroid Peroxidase and the Thyroid Peroxidase Activity of Isolated Pig Thyroid Cells (Nishida et al., 1989)*	The interaction of methylmercury chloride (CH_3HgCl) or mercury chloride ($HgCl_2$) with thyroid peroxidase (TPO) was assessed in two experiments. In the first experiment, the thyroids from rats that were given 5.6 mg/kg/day of either CH_3HgCl or $HgCl_2$ for 2 weeks by intubation were observed *via* electron microscopy. In the second experiment, guaiacol oxidation by TPO in isolated and ruptured pig thyroid cells was spectrophotometrically monitored in the presence of either CH_3HgCl or $HgCl_2$.	Rats and pig thyroid cells exposure to CH_3HgCl or $HgCl_2$.	In rats, CH_3HgCl (i) induced the flattening of epithelia, (ii) promoted the formation of large follicles, and (iii) lowered serum TSH levels. Meanwhile, $HgCl_2$ (i) inhibited TPO activity, and (ii) induced the formation of taller epithelia. In pig cells, CH_3HgCl induced a hypothyroid state without affecting TPO. Meanwhile, $HgCl_2$ inhibited TPO activity, inducing a hypertrophic state due to compensation for loss of enzyme activity. Findings suggest differential interaction of organic and inorganic forms of mercurials with the thyroid.
Trace Elements and Thyroid Cancer (Zaichick et al., 1995)	Resected material from 135 patients with thyroid conditions (45 cancer cases and 90 patients with benign nodules) was obtained from operations. The thyroid glands of 65 people who unexpectedly died or committed suicide were used as controls. Instrumental neutron activation analysis was performed for several trace elements. Trace element contents of the International Atomic Energy Agency reference material H-4 (animal muscle) were analyzed simultaneously with the thyroid tissue in order to evaluate the accuracy of the obtained data.	Human exposure to several trace elements, including Hg.	In paranodular tissue, the content of silver (Ag), cobalt (Co), Hg, iodine (I), and rubidium (Rb) was much higher for malignant and benign nodules than they were in controls. Results suggest that heavy metals, like Hg, play a role in the etiology of thyroid cancer.
Preliminary Studies on Thyroid Function in Welders (Zaidi et al., 2001)	A pilot study was performed with 20 male welders and 20 matched healthy controls with no previous occupational exposure to welding. Intravenous blood samples were collected from each individual for serum measurements of TSH, total T3, and total T4.	Human occupational exposure to several heavy metals, including Hg, from welding.	The levels of TSH were significantly increased in welders compared with non-welders. It is suspected that the working environment of welders, in which Hg exposure is common *via* fumes, may play a role in the development of hypothyroidism.
Thyroid Hormones and Methylmercury Toxicity (Soldin et al., 2008)	Searching in scientific databases for articles in which an association between exposure to methylmercury (CH_3Hg) and thyroid hormone homeostasis disruption is reported.	Human, animal, and *in vitro* exposures to methylmercury (CH_3Hg).	It's still unclear whether exposure to CH_3Hg directly alters thyroid hormone homeostasis, yet it seems to be associated with hypothyroidism. There's a possibility that CH_3Hg impacts the function of selenoenzymes, which are crucial for a healthy thyroid.
Some Elements in Thyroid Tissue are Associated with More Advanced Stage of Thyroid Cancer in Korean Women (Chung et al., 2016)	92 Korean women undergoing thyroidectomy were included in the study. Blood and thyroid tissue levels of 4 heavy metals and selenium (Se) were measured. Histopathology, cancer tumor node metastasis stage, and cancer multifocality were assessed.	Human exposure to several elements, including Hg.	The levels of blood Hg are higher in thyroid cancer at stage 1. Other heavy metals, such as cadmium (Cd), selenium (Se), and zinc (Zn), tend to increase in concentration with the progression of thyroid cancer, while Hg concentration decreases.
Increased Thyroid Cancer Incidence in a Basaltic Volcanic Area is Associated with Non-anthropogenic Pollution and Biocontamination (Malandrino et al., 2016)	Thyroid cancer epidemiology from 2002 to 2006 in Mount Etna, an active volcanic area from Sicily, Italy, was obtained from the Sicilian Regional Registry for Thyroid Cancer (SRRTC). 27 trace elements were measured by quadrupole mass spectrometry (QMS) in the drinking water and lichens (to characterize environmental pollution), and the urine of residents (to characterize biocontamination). Thyroid cancer incidence and trace metal concentration were compared between residents of the volcanic area considered (Catania province) and in adjacent non-volcanic control areas.	Human exposure to trace elements, including Hg, in drinking water.	There is a complex non-anthropogenic biocontamination with many trace elements, such as Hg, in Sicily, an active volcanic area where thyroid cancer incidence is increased. The combination of the increased concentrations of trace elements in volcanic areas is associated with thyroid cancer.
The Role of Heavy Metals and Polychlorinated Biphenyls (PCBs) in the Oncogenesis of Head and Neck Tumors and Thyroid Diseases: A Pilot Study (Petrosino et al., 2018)	Hair and blood samples were collected from 20 volunteers with the aim of measuring the concentrations of 14 heavy metals and 12 polychlorinated biphenyls (PCBs). The measured concentrations were compared between individuals based on the presence of head and neck tumors.	Human exposure to PCBs and heavy metals, including Hg.	Patients with thyroid diseases, particularly carcinomas, tended to present higher Hg levels in the hair and blood.
Thyroid Dysfunction: How Concentration of Toxic and Essential Elements Contribute to Risk of Hypothyroidism, Hyperthyroidism, and Thyroid Cancer (Rezaei et al., 2019)	110 newly-diagnosed thyroid disease patients (33 with hypothyroidism, 33 with hyperthyroidism and 11 with thyroid cancer) and 33 healthy individuals living in Birjand City, East of Iran,	Human exposure to several elements, including Hg.	The serum levels of Hg were similar between thyroid disease patients and healthy participants.

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Table 3 (*continued*)

Study	Design	Exposure**	Key findings***
	were included in the study. Blood samples were collected from each individual. The serum levels of 9 trace metals were measured using inductively coupled plasma mass spectrometry (ICP-MS). The correlation between variables was assessed. An unconditional logistic regression analysis was performed to estimate the unadjusted and adjusted odds ratios (ORs). Clustering analysis was performed to investigate the grouping behavior of trace metals.		
Non-essential Trace Elements Dietary Exposure in French Polynesia: Intake Assessment, Nail Bio Monitoring and Thyroid Cancer Risk (Zidane et al., 2019)	Measurements of the concentrations of 4 non-essential trace elements (Hg, Pb, As, and Cd) were performed in fingernail samples of Polynesians (from 373 healthy controls and 229 individuals with thyroid diseases), with the purpose of investigating the potential association between these and different thyroid cancer risks. A descriptive analysis of Polynesian food was performed. The association between thyroid cancer risk and daily intake levels of non-essential trace elements and with fingernail non-essential trace element levels were assessed.	Human exposure to several dietary non-essential trace elements, including Hg, in French Polynesia.	Hg was mostly present in appreciable concentrations in fishery products. Thyroid cancer risk doubled in patients with a history of cancer in first-degree relatives by each μg/day/kg of Hg intake.
Evaluation of the Effects of Chronic Occupational Exposure to Metallic Mercury on the Thyroid Parenchyma and Hormonal Function (Correia et al., 2020)	A cross-sectional study including 55 males occupationally exposed in the past to metallic Hg (14 years after the last exposure) and 55 non-exposed males, matched by age, was conducted in the Hospital das Clínicas, Brazil, from 2016 to 2017. Serum concentrations of TT3 and FT3, TT4 and FT4, TSH, reverse T3 (RT3), selenium and antithyroid antibody titers were obtained. The Hg and iodine (I) concentrations were measured in urine samples. The thyroid parenchyma was evaluated by B-mode ultrasonography with Doppler. Nodules with aspects suspicious for malignancy were submitted to aspiration puncture with a thin needle, and the cytology assessment was classified by the Bethesda system.	Human chronic occupational exposure to metallic Hg.	In comparison to non-exposed individuals, those who had been exposed to metallic Hg had, on average, (i) significantly higher urinary Hg, (ii) higher serum TSH, and (iii) higher proportions of echogenicity alterations. Papillary thyroid carcinomas were documented in three exposed individuals.
Low Doses of Methylmercury Induce the Proliferation of Thyroid Cells *in vitro* Through Modulation of ERK Pathway (Maggisano et al., 2020)*	Human Nthy-ori-3-1 cells were used in the study. Cells were exposed to varying concentrations and exposure times to methylmercury (CH_3Hg) and Hg. Cell cycle and reactive oxygen species (ROS) assays, Western blot analysis, RNA extraction and real-time PCR were performed. The differences exhibited between cells from each experimental condition were assessed.	Human Nthy-ori-3-1 cells exposure to CH_3Hg and Hg.	High concentrations of CH_3Hg are toxic to thyroid cells. Prolonged exposure to low doses of Hg, as may occur from environmental contaminant Hg exposure, promotes thyroid cell proliferation.
Association Between Mercury Exposure and Thyroid Hormone Levels: A Meta-analysis (Hu et al., 2021b)	Searching in scientific databases for articles in which connections between mercury exposure and thyroid hormone levels are reported. The meta-analysis was based on the PECO questions (P = general population; E = 1 μg/L Hg in blood and urine; C = 1 μg/L incremental increase on; and O = variation of thyroid hormone levels).	Human exposure to Hg in several contexts.	Exposure to Hg is significantly associated with an increase in TSH, and free thyroxine (FT4) levels, with a decrease in thyroxine (T4) levels.
A Case-control Study on the Association of Mineral Elements Exposure and Thyroid Tumor and Goiter (Liu et al., 2021)	In a case-control study, individuals with thyroid tumor or goiter (N = 197) were matched with a healthy population (N = 197) by age and gender. Serum and urine samples were collected from each individual to determine the concentration of several minerals. Conditional logistic regression was applied to estimate the associations between mineral elements and the risk of thyroid tumor and goiter through single-element models and multiple-element models. Multiple linear regression was used to evaluate relationships between mineral elements and percentage changes of thyroid functions.	Human exposure to several minerals, including Hg.	Cd, Hg and Tl showed correlations with T4 and FT4, suggesting that certain mineral elements could have potential effects on thyroid function.
Mercury in the Human Thyroid Gland: Potential Implications for Thyroid Cancer, Autoimmune Thyroiditis, and Hypothyroidism (Pamphlett et al., 2021)	115 people aged 1–104 years old, with varied clinicopathological conditions, who had thyroid samples removed during forensic/coronial studies were included in the study. Formalin-fixed paraffin-embedded thyroid tissue	Human exposure to Hg.	Hg in thyroid follicular cells increases with age. The presence of other toxic metals in thyroid cells may enhance Hg toxicity. This metal likely plays a role in thyroid

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Table 3 (*continued*)

Study	Design	Exposure**	Key findings***
	blocks were obtained from each individual. 7 μm sections from the blocks were used to detect intracellular inorganic Hg using autometallography. The presence of Hg was confirmed using laser ablation-inductively coupled plasma mass spectrometry (LA-ICP-MS). 308 thyroid cancer cases and 308 age- and sex-matched controls were included in a case-control study developed in China.		cancer, autoimmune thyroiditis (Hashimoto's thyroiditis), and hypothyroidism.
Plasma Polybrominated Diphenyl Ethers, Urinary Heavy Metals and the Risk of Thyroid Cancer: A Case-control Study in China (Zhang et al., 2021)	Plasma polybrominated diphenyl ethers (PBDEs) concentrations were determined by gas chromatograph-mass spectrometry (GC–MS), while the concentrations of heavy metals in urine samples were detected by graphite furnace atomic absorption spectrometry (GFAAS) or inductively-coupled plasma optical emission spectrometry (ICP-OES). Conditional logistic regression models were used to explore associations of PBDEs and 4 heavy metals exposures with thyroid cancer risk. A joint-effect interaction term was inserted into the logistic regression models to assess the multiplicative interaction effects of PBDEs-heavy metals on thyroid cancer risk.	Human exposure to several PDBEs and heavy metals, including Hg.	Exposures to PBDEs, As, and Hg are associated with an increased risk of thyroid cancer. Joint exposure to PBDEs and Pb or Hg had interaction effects on thyroid cancer risk.
Carcinogenic Effects of Heavy Metals by Inducing Dysregulation of microRNAs: A Review (Aalami et al., 2022)	Searching in scientific databases for articles in which connections between heavy metals and microRNA dysregulation are reported.	Human, animal, and *in vitro* exposures to heavy metals, including As, in several contexts.	Metals like As, Cd, and Hg are associated with the dysregulation of microRNAs. Exposure to Hg seems to be related to thyroid carcinogenesis.
Fish and the Thyroid: A Janus Bifrons Relationship Caused by Pollutants and the Omega-3 Polyunsaturated Fatty Acids (Benvenga et al., 2022)	Searching in scientific databases for articles in which associations between polyunsaturated fatty acids, fish consumption, and thyroid status are reported. Data from the National Health and Nutrition Examination Survey (NHANES) was also used.	Human dietary exposure to Hg.	Exposure to Hg *via* consumption of heavily contaminated fish or recurrent consumption of low-level Hg-contaminated fish can be a driver for thyroid autoimmunity (Hashimoto's thyroiditis), hypothyroidism, and thyroid cancer.
Low-level Environmental Mercury Exposure and Thyroid Cancer Risk Among Residents Living Near National Industrial Complexes in South Korea: A Population-Based Cohort Study (Kim et al., 2022)	A secondary analysis of a prospective cohort study among residents living near industrial complexes in South Korea, recruited during 2003–2011, was performed. Incident thyroid cancer cases were identified from the National Cancer Registry and Statistics Korea. Urinary Hg concentrations were measured using thermal decomposition amalgamation atomic absorption spectrometry (TDA-AAS). Cox proportional hazards regression models were used to estimate the hazard ratio (HR) between Hg exposure and the incidence of thyroid cancer.	Human exposure to Hg derived of industrial complexes in South Korea.	High urinary Hg concentrations are associated with an increased risk of thyroid cancer.
The Importance of Environmental Toxic Substances in Thyroid Cancer (Legakis et al., 2022)	Searching in scientific databases for articles in which an association between environmental toxic substances and thyroid cancer is reported.	Human, animal, and *in vitro* exposures to environmental toxicants, including Hg, in several contexts.	Exposure to Hg shows no association with thyroid cancer.
High Incidence of Thyroid Cancer in Southern Tuscany (Grosseto Province, Italy): Potential Role of Environmental Heavy Metal Pollution (Capezzone et al., 2023)	The number of cases and EU standardized incidence rates of thyroid cancer patients for all the provinces of southeast Tuscany during the period of 2013–2016 was evaluated. The histological records of 226 thyroid cancer patients were analyzed.	Human exposure to environmental heavy metals, including Hg, in Southern Tuscany, Italy.	The high incidence of thyroid cancer in Grosseto province is likely due to heavy metal pollution, in which Hg is included as a relevant contaminant.
Assessment of Five Typical Environmental Endocrine Disruptors and Thyroid Cancer Risk: A Meta-analysis (Yang et al., 2023)	Searching in scientific databases for articles in which connections between exposure to environmental endocrine disruptors (EEDs) and thyroid cancer are reported.	Human exposure to EEDs, such as Hg.	Exposure to certain EEDs, such as polybrominated diphenyl ethers (PBDEs), phthalates (PAEs), and heavy metals like Hg, increases the risk of thyroid cancer.
Elucidating The Link Between Thyroid Cancer and Mercury Exposure: A Review and Meta-analysis (Webster et al., 2024)	Searching in scientific databases for articles using the keywords: "Mercury", "Hg", "Methylmercury", "MeHg", "Thyroid cancer", "Thyroid carcinoma", "Thyroid tumor", "Thyroid nodule", among others. 9 relevant studies containing quantitative data linking Hg exposure to the risk of thyroid cancer were included for the meta-analysis.	Human exposure to Hg in several contexts.	Exposure to Hg is associated with a risk of thyroid cancer, implying a possible predisposing factor.
Evaluation of the Cognitive, Physiological, and Biomarker Effects of Heavy Metal Exposure in Wistar Rats (Mukhi et al., 2024)*	During a 13-week period, 5 groups of rats (6 rats per group, with both males and females) were assessed to study the effects of oral exposure to vanadium (V), mercury (Hg), cadmium (Cd), and arsenic (As). Each rat group was fed a stock solution with one of the metals, prepared at the following concentrations: 16.8 mg/kg V; 3 mg/kg Hg; 8	Rat exposure to V, Hg, Cd, and As.	Rats treated with Cd and Hg showed significantly higher TSH levels than the control group. A significant hypothyroid status with increased TSH and decreased T3 and T4 levels was observed in the Hg-treated groups, with the display of hypothyroidism signs such as increased food intake and weight gain.

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Table 3 (*continued*)

Study	Design	Exposure**	Key findings***
	mg/kg As; 46.6 mg/kg Cd. Physiological, cognitive, and biochemical markers, such as thyroid hormone levels, were assessed.		
Elemental Biomapping of Human Tissues Suggests Toxic Metals such as Mercury Play a Role in the Pathogenesis of Cancer (Pamphlett and Bishop, 2024)	Searching in scientific databases for articles in which elemental biomapping was used to detect toxic metals such as Hg in human cells.	Human exposure to toxic metals, including Hg.	In cases where autometallography showed ^{AMG}TM in the cytoplasm of thyroid follicle epithelial cells, LA-ICP-MSI indicated that Hg was likely to be the cause of most ^{AMG}TM positivity. As such, Hg may play a role in the development of thyroid carcinomas.
The Association Between Metals and Thyroid Cancer in Puerto Rico – A National Health and Nutrition Examination Survey Analysis and Ecological Study (Shaked et al., 2024)	Data from the National Health and Nutrition Examination Survey (NHANES) regarding heavy metal levels and the thyroglobulin antibody (TgAb) as a thyroid cancer marker was included in this study. Additionally, an ecological study was performed using data from the Environmental Protection Agency (EPA) report on Metals from Natural and Anthropogenic Sources in Puerto Rico Soils and data from the Puerto Rico Central Cancer Registry on age-adjusted thyroid cancer incidence rates from 2015 to 2019.	Human exposure, particularly dietary, to Hg.	There was a significant negative association between Hg and TgAb. There were higher thyroid cancer incidence rates and increased metal levels in the soil in the northern parts of Puerto Rico.
Effects of Trace Elements on Endocrine Function and Pathogenesis of Thyroid Diseases – A Literature Review (Bryliński et al., 2025)	Searching in scientific databases for articles in which connections between the studied elements and thyroid diseases are reported.	Human, animal, and *in vitro* exposures to several trace elements, including Hg.	The accumulation of Hg in the thyroid may interfere with hormone secretion and stimulate cancer cell proliferation.
Association Between Toxic Heavy Metals and Noncancerous Thyroid Disease: A Scoping Review (Rafi'i et al., 2025)	Searching in scientific databases for articles in which connections between heavy metals and non-cancerous thyroid diseases are reported.	Human and animal exposures to several toxic metals, including Hg.	There is still discrepancy in the data regarding the association between Hg and thyroid disorders. Several studies report a significant correlation between Hg levels and noncancerous thyroid disease, while others report a nonsignificant association between Hg and noncancerous thyroid disease.
Urinary Trace Elements and Thyroid Nodule Formation in a Longitudinal Cohort of Older Women: Findings from KoGES (Choi et al., 2025)	Cross-sectional and longitudinal analyses were conducted using data from 653 women aged 60 years and older in the Ansung cohort of the Korean Genome and Epidemiology Study (KoGES). Urinary concentrations of 18 elements were analyzed using inductively coupled plasma mass spectrometry (ICP-MS); Hg was analyzed using a Direct Mercury Analyzer (DMA). Logistic regression was used to assess associations between trace element exposure and thyroid nodule prevalence, stratified by nodule size (3.0–4.9 mm, 5.0–9.9 mm, and $\geq$ 10.0 mm).	Human exposure to several trace elements, including Hg.	Hg did not show significant associations with thyroid nodule development.

harmless for mature thyrocytes, but it significantly alters the biology of stem/precursor thyroid cells and of their progeny. Therefore, exposure to W can be a driver for characteristics of preneoplastic formation, which could be translated into situations of pre-carcinogenesis in the thyroid tissue (Gianì et al., 2019). In the same scope of research, it was discovered that stem/precursor thyroid cells are sensitive to small increases of other environmental metal concentrations, like copper (Cu), mercury (Hg), palladium (Pd), and zinc (Zn), though differentiated thyrocytes, again, are not (Gianì et al., 2021a). One of the common molecular mechanisms of PTEs' interference with stem/precursor thyroid cells is the activation of the extracellular signal-regulated kinase (ERK1/2) pathway, resulting in a biphasic increase in proliferation which is typical of hormesis (*i.e.*, low concentrations induce stimulation, whereas high concentrations cause inhibition) (Calabrese et al., 2024; Wan et al., 2024). These findings underline how, even if effects are not immediately noticeable (the existing thyroid tissue is healthy and keeps functioning properly for a while), the continual exposure to slightly increased concentrations of certain elements, even within established "safe limits" matching the natural enrichment in volcanic areas, is damaging to cells and predisposing for thyroid cancer.

Meanwhile, the *in vivo* study with Wistar rat models developed by Luca et al. (2017) offers insight with respect to the combined toxic effect of three elements, which are naturally increased in volcanic environments [boron (B), cadmium (Cd), and molybdenum (Mo)], on thyroid tumorigenesis. The authors showed how the exposure to slightly increased environmental concentrations of B, Cd, and Mo *via* drinking water accelerates the appearance of transformation marks (nuclear aberrations, changes in cell morphology, and papillary structures) in the thyroid gland of hypothyroid rats. This suggests that the pre-existence of hypothyroidism may cause the thyroid to become more sensitive to the combined toxic effect of the mentioned elements, despite the previously reported protective role of B and Mo against genotoxicity. Vigneri et al. (2017) and Gianì et al. (2021b) provide a more extensive review on the effects of several other PTEs on the thyroid.

Cumulatively, the body of published evidence supports the link between living in volcanic environments and increased risk for thyroid disruption, with emphasis on thyroid cancer, specifically differentiated thyroid cancer. Other thyroid pathologies, like hypothyroidism, are still

Table 4
List of articles included in this systematic review regarding the effects of cobalt (Co) exposure on the thyroid. Information regarding study design, addressed exposure, and key findings is presented. *Only exposures related to Co were considered. **The key findings display information specifically regarding the effects of Co on the thyroid.

Study	Design	Exposure*	Key findings**
Hypothyroidism and Thyroid Hyperplasia in Patients Treated with Cobalt (Kriss et al., 1955)	5 patients receiving cobalt (Co) therapy to treat hematological disturbances were followed. Their previous medical history, along with changes during such treatment were described.	Human exposure to Co-60.	Co therapy is associated with thyroid hyperplasia, accompanied with reduction in thyroid function.
Cobalt-induced Hypothyroidism and Polycythemia in Lipoid Nephrosis (Sederholm et al., 1968)	An 11-year-old boy suffering from lipoid nephrosis since the age of 6 ½ years was included in the study for a case report. The boy was followed during his treatments, which included thiosemicarbazone for three weeks, and cobaltous chloride for 4 months to treat the resulting anemia.	Human exposure to cobaltous chloride.	Co therapy induces severe hypothyroidism in children.
Cobalt-60 Therapy of Hodgkin's Disease and the Subsequent Development of Hypothyroidism (Prager et al., 1972)	23 consecutive previously untreated patients with Hodgkin's disease who were treated with radiation therapy were included in the study. Individuals were evaluated for the presence or absence of post-Co-60 therapy hypothyroidism *via* pointed history, physical examination and T4 determination.	Human exposure to Co-60.	Treatment with Co-60 is associated with the development of hypothyroidism.
A 1982–1992 Surveillance Programme on Danish Pottery Painters. Biological Levels and Health Effects Following Exposure to Soluble or Insoluble Cobalt Compounds in Cobalt Blue Dyes (Christensen and Poulsen, 1994)	Searching for articles in scientific databases covering Co-related diseases, and reviewing a surveillance program from 1982 to 1992 on plate painters exposed to Co in two Danish porcelain factories.	Human occupational exposure to Co compounds.	Low-level Co exposure seemed to cause no inhibitory effects on thyroid function, but the ratio between T4 and T3 was increased. This indicates that low-level Co exposure may have an impact on the metabolism of thyroid hormones (TH).
Trace Elements and Thyroid Cancer (Zaichick et al., 1995)	Resected material from 135 patients with thyroid conditions (45 cancer cases and 90 patients with benign nodules) was obtained from operations. The thyroid glands of 65 people who unexpectedly died or committed suicide were used as controls. Instrumental neutron activation analysis was performed for several trace elements. Trace element contents of the International Atomic Energy Agency reference material H-4 (animal muscle) were analyzed simultaneously with the thyroid tissue in order to evaluate the accuracy of the obtained data.	Human exposure to several trace elements, including Co.	In paranodular tissue, the content of silver (Ag), Co, mercury (Hg), iodine (I), and rubidium (Rb) were much higher for malignant and benign nodules than they were in controls. Results suggest that heavy metals, like Co, play a role in the etiology of thyroid cancer.
Thyroid Neoplasia Following Irradiation in Adolescent and Young Adult Survivors of Childhood Cancer (Somerville et al., 2002)	A cohort of 142 survivors of childhood malignancy at risk of developing thyroid abnormalities was included in the study. Thyroid palpation by an endocrinologist or surgeon, serum TSH assay and thyroid ultrasound examination were performed on all subjects. Depending on findings, some subjects proceeded to fine-needle biopsy or surgery (total thyroidectomy).	Human exposure to Co irradiation.	There is a significant risk of thyroid cancer in individuals who were exposed to radiation as part of therapy for childhood cancer. The risk is greater for patients who received scatter (*vs.* direct) irradiation. Nodular changes are normally not apparent for many years, hence the need for lifelong surveillance.
Metals in Perspective: Introduction (Oller and Bates, 2004)	Searching in literature for works in which the effects of Co exposure on health are addressed.	Human exposure to Co in several contexts.	Co prevents uptake of iodine (I) into T4 by inhibiting tyrosine iodinase, resulting in a drop in circulating T4 levels, which may lead to clinical hypothyroidism. With low T4 levels, TSH excretion is increased, resulting in thyroid hormone hyperplasia (goiter). Co intake associated with thyroid pathology has been estimated as 5–10 mg per day (0.07–0.14 mg Co/kg bw per day).
Severe Cobalt Intoxication Due to Prosthesis Wear in Repeated Total Hip Arthroplasty (Oldenburg et al., 2009)	A 55-year-old man with a total hip prosthesis (ceramic femoral head and polyethylene [PE] inlay), whose prosthesis had broken, was included in the study. His medical record, along with subsequent examinations after complaints of multiorgan symptoms, were reviewed.	Human exposure to Co from a hip prosthesis.	Hypothyroidism and other symptoms in the patient, like peripheral neuropathy and cardiomyopathy, seem to have been caused by increased blood Co levels. Most of the patient's symptoms were reversed upon a considerable decrease in blood Co levels.
Absence of Adverse Effect on Thyroid Function and Red Blood Cells in a Population of Workers Exposed to Cobalt Compounds (Lantin et al., 2011)	249 male workers from a Co production department in the North of Belgium were included in a cross-sectional survey, conducted from February 2008 to August 2009. Exposure to Co was measured in urine and blood samples from each participant, including *via* an integrated exposure index. Multiple regression analyses were performed to assess the possible effect of Co exposure on thyroid function and red blood cells.	Human occupational exposure to Co from a Co production department.	There are no observable effects on thyroid function when occupational exposure to Co is kept below the biological limit of occupational exposure (15 μg Co/$g_{creatinine}$ in urine).

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Study	Design	Exposure*	Key findings**
Derivation of a Chronic Oral Reference Dose for Cobalt (Finley et al., 2012)	Searching in literature for works reporting human, animal, and *in vitro* effects of Co exposure. The standard US EPA risk assessment methodology was used to determine a chronic oral reference dose (RfD) for Co.	Human, animal, and *in vitro* exposures to Co.	Co interferes with thyroid metabolism by decreasing I intake. It is suggested that, in the general population, for a lifetime of daily exposure to Co, a chronic oral RfD of 0.03 mg/kg-day would be protective of non-cancer health effects.
Thyroid and Food: A Mediterranean Perspective (Tubili et al., 2012)	Searching in literature for works addressing relationships between diet, foods, and thyroid function.	Human dietary exposure to Co.	Co inhibits iodine intake and interferes with the deiodinase system.
A Review of the Health Hazards Posed by Cobalt (Paustenbach et al., 2013)	Searching in scientific databases for articles in which health hazards posed by Co are reported.	Human exposure to Co in several contexts.	Exposure to excess Co is a cause for reversible hypothyroidism, when at blood or serum levels of ~300 μg/L and higher for a period of over 2 weeks.
Clinical Features, Testing, and Management of Patients with Suspected Prosthetic Hip-Associated Cobalt Toxicity: A Systematic Review of Cases (Devlin et al., 2013)	Searching in scientific databases for articles addressing connections between prosthetic hip implants and cobalt toxicity.	Human exposure to Co from hip implants.	Excess Co exposure from hip prostheses was associated with hypothyroidism in several patients.
Prosthetic Hip-associated Cobalt Toxicity (Pizon et al., 2013)	Searching in medical literature for articles addressing connections between prosthetic hip implants and cobalt toxicity.	Human exposure to Co from hip prostheses.	Hypothyroidism is associated with systemic Co toxicity, derived of hip prostheses.
Systemic Toxicity Related to Metal Hip Prostheses (Bradberry et al., 2014)	Searching in scientific databases for articles addressing connections between prosthetic hip implants and cobalt toxicity.	Human exposure to Co from metal hip prostheses.	Failed hip replacements often result in hypothyroidism due to elevating blood Co levels. The condition may or may not resolve after removal of the prosthesis.
Interpreting Cobalt Blood Concentrations in Hip Implant Patients (Paustenbach et al., 2014)	Searching in scientific databases for articles addressing connections between prosthetic hip implants and cobalt systemic health effects.	Human exposure to Co from hip implants.	Hypothyroidism is often associated with failed hip replacements due to an increase in blood Co levels.
The Association Between Cobalt Deficiency and Endemic Goiter in School-Aged Children (Sanjari et al., 2014)	170 school children aged 9–11 years old in the city of Kerman, Iran, were randomly selected for this cross-sectional study. Serum and urine samples were collected from all individuals. Thyroid function, serum Co levels and urinary I excretion were analyzed. Multiple regression analyses were performed to assess the interaction between the studied variables.	School-aged children exposure to Co.	Low serum Co levels are strongly associated with goiter. Low serum Co levels contributed significantly more to the presence of goiter than low urinary I levels.
Hypothyroidism in Patients Treated with Radiotherapy for Head and Neck Carcinoma: Standardized Long-term Follow-up Study (Alba et al., 2016)	241 patients diagnosed with head and neck carcinoma were included in the study. Factors associated to the population, tumor characteristics, treatment, and occurrence of hypothyroidism were analyzed.	Human exposure to Co from radiotherapy.	Co radiation therapy for the treatment of head and neck carcinomas can induce hypothyroidism, especially if the area receiving radiation includes the thyroid.
Metals (Cobalt, Copper, Lead, Mercury) (Bradberry, 2016)	Searching in literature for works describing Co, Cu, lead (Pb), and Hg health effects.	Human exposure to Co in several contexts.	Co interferes with thyroid metabolism by inhibiting iodine uptake. Exposure to high levels of Co is associated with thyroid toxicity, potentially leading to the development of hypothyroid goiter.
Cobalt Cardiomyopathy: A Critical Reappraisal in Light of a Recent Resurgence (Packer, 2016)	Searching in scientific databases for articles in which a relationship between Co exposure and cardiomyopathy is reported.	Human exposure to Co.	Co can induce reversible hypothyroidism when administered in concentrations of 750–1950 μg/L.
Cobalt Intoxication in a Patient with Hip Prosthesis (Sánchez and Pastó-Cardona, 2016)	A 50-year-old man with history of hip replacement surgeries was included in the study for a case report. The patient's serum Co levels were evaluated, along with his medical records.	Human exposure to Co from a hip prosthesis.	Co toxicity on the thyroid due to failed hip replacements led to hypothyroidism in the patient.
Cobalt Toxicity, an Overlooked Cause of Hypothyroidism (Yu, 2017)	A 64-year-old male with history of revision hip arthroplasty with hearing loss and hypothyroidism was included in the study for a case report. The patient's serum Co levels were evaluated, along with his past medical records.	Human exposure to Co from hip arthroplasty.	Co toxicity on the thyroid can cause destruction thyroiditis and impaired synthesis of thyroid hormones (TH), resulting in hypothyroidism.
Statistical Evaluation of Trace Metals, TSH and T4 in Blood Serum of Thyroid Disease Patients in Comparison with Controls (Hanif et al., 2018)	A population of hypothyroid, hyperthyroid, and healthy individuals was included in the study. The concentrations of several trace metals (Fe, Zn, Cu, Co, Mn, Ni, Cr, Cd, and Pb) and thyroid hormones (TSH and T4) in blood serum samples were measured, with the aim of exploring the imbalances of trace metals in diseased subjects.	Human exposure to several trace metals, including Co.	Co exhibited a significant positive correlation with hypothyroidism. The mean levels of serum Co and T4 were significantly higher in female hypothyroid patients, compared to male hypothyroid patients.
Metallosis Mimicking a Metabolic Disorder: A Case Report (Stepien et al., 2018)	A 58-year-old man suffering from a set of disturbances for 2 years following surgery for the placement of a metal-on-polyethylene hip prosthesis was included in the study. His medical history was described.	Human exposure to Co from a hip prosthesis.	Hypothyroidism is associated with Co toxicity.
Determination of Toxic and Essential Trace Elements in Serum of Healthy and Hypothyroid Respondents by ICP-MS: A Chemometric Approach for Discrimination of Hypothyroidism (Stojsavljević et al., 2018)	Blood serum samples of hypothyroid and healthy individuals were collected. Inductively coupled plasma-mass spectrometry (ICP-MS) was used to determine the serum concentrations of 3 toxic (Ni, As, Cd) and 6 essential trace elements (Cr, Mn, Co, Cu, Zn, Se),	Human exposure to several elements, including Co.	Hypothyroid individuals had significantly higher serum Co concentrations than healthy individuals.

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Table 4 (*continued*)

Study	Design	Exposure*	Key findings**
	with the aim of exploring the differences in trace element profiles between hypothyroid and healthy subjects.		
Thyroid Dysfunction: How Concentration of Toxic and Essential Elements Contribute to Risk of Hypothyroidism, Hyperthyroidism, and Thyroid Cancer (Rezaei et al., 2019)	110 newly-diagnosed thyroid disease patients (33 with hypothyroidism, 33 with hyperthyroidism and 11 with thyroid cancer) and 33 healthy individuals living in Birjand City, East of Iran, were included in the study. Blood samples were collected from each individual. The serum levels of 9 trace metals were measured using inductively coupled plasma mass spectrometry (ICP-MS). The correlation between variables was assessed. An unconditional logistic regression analysis was performed to estimate the unadjusted and adjusted odds ratios (ORs). Clustering analysis was performed to investigate the grouping behavior of trace metals.	Human exposure to several trace metals, including Co.	Low serum levels of Co are associated with the development of hypo- and hyperthyroidism.
Associations Between Essential Microelements Exposure and the Aggressive Clinicopathologic Characteristics of Papillary Thyroid Cancer (Hu et al., 2021a)	608 newly-diagnosed papillary thyroid cancer patients were included in the study. The concentrations of 10 essential microelements were measured in urine samples of all participants. Chi square test and Wilcoxon rank sum test were performed to compare differences between male and female individuals. Multivariate logistic regression was made to assess the associations between essential microelements and the clinicopathologic characteristics of papillary thyroid carcinoma in single- and multi-microelement models.	Human exposure to several essential microelements, including Co.	High levels of Co are associated with decreased risk of capsular invasion. Decreased urinary levels of Co, Fe, and Mo are associated with aggressive papillary thyroid carcinoma clinicopathological characteristics.
A Case-control Study on the Association of Mineral Elements Exposure and Thyroid Tumor and Goiter (Liu et al., 2021)	In a case-control study, individuals with thyroid tumor or goiter (N = 197) were matched with a healthy population (N = 197) by age and gender. Serum and urine samples were collected from each individual to determine the concentration of several minerals. Conditional logistic regression was applied to estimate the associations between mineral elements and the risk of thyroid tumor and goiter through single-element models and multiple-element models. Multiple linear regression was used to evaluate relationships between mineral elements and percentage changes of thyroid functions.	Human exposure to several minerals, including Co.	There were no differences in urinary Co levels between thyroid disease patients and healthy individuals.
Functional and Biochemical Changes in the Thyroid Gland Following Exposure to Therapeutic Doses of External Beam Radiotherapy in the Head-and-Neck Cancer Patients (Randhawa et al., 2021)	45 patients of the head-and-neck cancer, receiving radiotherapy with or without chemotherapy were included in this prospective study. Baseline thyroid function tests and thyroid scans were done, then repeated at the completion of radiotherapy at 3 and 6 months.	Human exposure to Co from radiotherapy.	Hypothyroidism is a significant complication associated with Co-60 teletherapy. Hypothyroidism could be detected within 3 months following the completion of radiotherapy; hence, patients should be monitored for their thyroid function since early.
Alteration of Trace Elements in Multinodular Goiter, Thyroid Adenoma, and Thyroid Cancer (Stojsavljević et al., 2021)	Blood samples from patients diagnosed with multinodular goiter, thyroid adenoma, and thyroid cancer were examined and compared with control samples using chemometric analysis. The blood concentrations of essential (Mn, Co, Cu, Zn, Se) and toxic elements (Ni, As, Cd, Pb, U) were determined by ICP-MS.	Human exposure to several trace elements, including Co.	Individuals with multinodular goiter, thyroid adenoma, and thyroid cancer had lower blood Co levels than healthy individuals.
Prosthetic Hip-associated Cobalt Toxicity: A Systematic Review of Case Series and Case Reports (Crutsen et al., 2022)	Searching in scientific databases for articles addressing connections between prosthetic hip implants and cobalt toxicity.	Human exposure to Co from hip prostheses.	Exposure to Co from hip implants seemed to be associated with hypothyroidism in some patients.
Exposure to Multiple Trace Elements and Thyroid Cancer Risk in Chinese Adults: A Case-Control Study (He et al., 2022)	A total of 585 newly-diagnosed thyroid cancer patients and 585 healthy controls were included in the study. 14 urinary elements were measured to explain the fixed-exposure on thyroid cancer risk. Conditional logistic regression models were made to determine the association between the studied variables. Bayesian kernel machine regression (BKMR) was applied to show the tendency of mixed effects. Interaction effects were examined by a Generalized linear model (GLM).	Human exposure to several trace elements, including Co.	Exposure to Co is associated with a decreased risk of thyroid cancer.

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Study	Design	Exposure*	Key findings**
The Importance of Environmental Toxic Substances in Thyroid Cancer (Legakis et al., 2022)	Searching in scientific databases for articles in which an association between environmental toxic substances and thyroid cancer is reported.	Human exposure to several environmental toxic substances, including Co.	Exposure to Co increases the incidence of thyroid cancer, in combination with molybdenum (Mo) and tin (Sn).
Chapter 9 - Cobalt (Lison, 2022)	Searching in literature for works addressing the toxic properties of Co.	Human exposure to Co.	The thyroid is one of the target organs of Co toxicity. Hypothyroidism is well-documented in patients with hip implants due to elevated Co levels.
The Role of Heavy Metals in Thyroid Cancer: A Meta-analysis (van Gerwen et al., 2022)	Searching in scientific databases for articles in which connections between heavy metals and thyroid cancer are reported.	Human exposure to several heavy metals, including Co.	Low Co blood levels are associated with thyroid cancer.
A Prospective Clinical Study to Assess Primary Hypothyroidism in Head and Neck Cancer Patients Treated with External Beam Radiotherapy (Shewalkar et al., 2023)	200 patients with head and neck cancers, who received external beam radiation using Co-60 or linear accelerator, were included in this prospective study. Thyroid function tests were done in patients after 3 and 6 months of radiotherapy completion.	Human exposure to Co from radiotherapy.	Some patients developed hypothyroidism due to Co-60 therapy. Patients treated with the two-dimensional technique (2-D) had a higher incidence of hypothyroidism than the patients treated with three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT).
Systemic Cobalt Toxicity Secondary to Metal-on-Metal Prosthetic Hip Replacement: A Case Report (Blackmon et al., 2024)	A 58-year-old man with several disturbances following a right metal-on-metal total hip arthroplasty was included in the study. His medical history was described.	Human exposure to Co from a hip prosthesis.	Hypothyroidism seemed to be associated with elevated serum Co levels in the patient.
Effects of Trace Elements on Endocrine Function and Pathogenesis of Thyroid Diseases – A Literature Review (Bryliński et al., 2025)	Searching in scientific databases for articles in which connections between the studied elements and thyroid diseases are reported.	Human exposure to several trace elements, including Co.	Co, I, iron (Fe), manganese (Mn), zinc (Zn), cadmium (Cd), lead (Pb), mercury (Hg), and selenium (Se) are connected with the development of hypothyroidism.
Urinary Trace Elements and Thyroid Nodule Formation in a Longitudinal Cohort of Older Women: Findings from KoGES (Choi et al., 2025)	Cross-sectional and longitudinal analyses were conducted using data from 653 women aged 60 years and older in the Ansung cohort of the Korean Genome and Epidemiology Study (KoGES). Urinary concentrations of 18 elements were analyzed using inductively coupled plasma mass spectrometry (ICP-MS), and mercury was analyzed using a Direct Mercury Analyzer (DMA). Logistic regression was used to assess associations between trace element exposure and thyroid nodule prevalence, stratified by nodule size (3.0–4.9 mm, 5.0–9.9 mm, and ≥ 10.0 mm).	Human exposure to several trace elements, including Co.	Certain trace elements, particularly Mn, copper (Cu), Co, Zn, and uranium (U), may contribute to the formation and growth of thyroid nodules in older women.

very understudied in this context, and the knowledge gap extends to the lack of data on areas with non-eruptive volcanic activity. It is also plausible that hypothyroidism patients are more susceptible to later developing thyroid cancer over prolonged exposure to low doses of volcanogenic contaminants, although molecular insights on the mechanisms that lead to cell transformation and tumorigenesis are yet lacking. The complexity of univocally describing the interaction between volcanic contaminants and thyroid disruption outcomes is compounded by the influence of other risk factors, such as populations' genetic makeup, lifestyle choices, and healthcare access.

3.2. Arsenic (As) and thyroid disruption

Most of the reviewed publications point to a link between arsenic (As) and thyroid disruption. In animal models and humans, exposure to As, especially in the form of dimethylarsinic acid (cacodylic acid, or DMA), seemed to be predominantly associated with outcomes like hypothyroidism and thyroid cancer. Nonetheless, knowledge on the effects of different As forms on the thyroid seems to be lacking.

Arsenic (As) is a well-recognized toxicant found ubiquitously in the environment, whose concentration tends to be increased by anthropogenic sources, such as diverse manufacturing processes and mining activities, and by natural sources from geological formations, as those found in volcanic environments (López et al., 2012; Bia et al., 2015; Ren et al., 2022; Ganie et al., 2023; Murray et al., 2023). This metalloid is found in both inorganic forms – arsenic trioxide (As_2O_3), sodium arsenite ($NaAsO_2$), and arsenic trichloride ($AsCl_3$) are the most common trivalent compounds, and arsenic pentoxide (As_2O_5), arsenic acid (H_3AsO_4), and arsenates (based on AsO_4^{3-}), the most common pentavalent compounds – and organic forms – like arsanilic acid ($C_6H_8AsNO_3$), methylarsonic acid (CH_5AsO_3), dimethylarsinic acid (cacodylic acid, or DMA) ($C_2H_7AsO_2$), and arsenobetaine ($C_5H_{11}AsO_2$); their varying degrees of toxicity constitutes an extra layer of complexity to the interactions and effects of As on the body (IARC, 2012; Camacho et al., 2022). Another factor contributing to that complexity is the various oxidation states that As can take. In general, compounds with As^{3+} [As (III)] are more toxic than those with As^{5+} [As(V)] (Upadhyay et al., 2023). Common routes of exposure to this element include drinking water, inhalation of dust, and the consumption of contaminated food, the latter being most often responsible for continual exposure to As. The most frequent biomarkers used to address human exposure to As involve urine, blood, hair, and nail samples, in which As(III) and As(V) concentrations can be detected (Pellizzari and Clayton, 2006). From a general perspective, the various mechanisms of As toxicity tend to result

in cell injury and cell death (apoptosis). As such, both short and long-term exposure to As are associated with a plethora of adverse health effects, including skin lesions, cognitive impairment, diabetes, anemia, cardiovascular diseases, and various types of cancer (Muzaffar et al., 2023).

Considering its several deleterious effects and the many organs it can target, As toxicity would be expected to also occur in the thyroid. Confirming such hypothesis, all publications included in this review explicitly reported harmful effects on the thyroid resulting from exposure to As, with two exceptions (Liu et al., 2021; Yu et al., 2025). Some assessed the onset and/or exacerbation of thyroid disruption from a general point of view (Glattre et al., 1995; Allen and Rana, 2003; Davey et al., 2008; Sun et al., 2016; Argha et al., 2021; Esform et al., 2022; Stojsavljević et al., 2021; Fowler et al., 2022; Kirtana and Seetharaman, 2022; Modica et al., 2023). Most of the research, however, deals with the emergence of hypothyroidism or hypothyroidism-like effects on exposed individuals (Arnold et al., 2006; Liu et al., 2008a; Ciarrocca et al., 2012; Abdul et al., 2015; Gong et al., 2015; Jain, 2016; Ahangarpour et al., 2018; Gonzales et al., 2018; Stojsavljević et al., 2018; Stojsavljević et al., 2019; Stojsavljević et al., 2020; Hu et al., 2021b; Nandheeswari et al., 2024). Among these, the work of Stojsavljević et al. (2020) specifically addressed Hashimoto's thyroiditis. Thyroid cancer is also reported to arise from As exposure, especially in the form of DMA (Yamamoto et al., 1995; Yamamoto et al., 1997; Huff, 2001; Kenyon and Hughes, 2001; Kitchin, 2001; Arnold et al., 2006; Chen et al., 2019; Petrosino et al., 2018; Zidane et al., 2019; Kumar et al., 2021; Zhang et al., 2021; Aalami et al., 2022; He et al., 2022; Modica et al., 2023; Yang et al., 2023), further corroborating the role of As in the emergence of thyroid disruption.

Abdul et al. (2015) summarize the mechanisms of As toxicity on the thyroid as (i) preventing the synthesis of thyroid hormones (TH), and (ii) increasing the proliferation of thyroid follicles. Meanwhile, Sun et al. (2016) refer to the fact that different forms of As exhibit distinct mechanisms of toxicity. According to the authors' review, toxic mechanisms of As(V) include (i) causing histopathology, (ii) elevating T4 levels, whereas toxic mechanisms of As(III) include (i) inhibiting thyroperoxidase (TPO) activity, (ii) altering the expression of thyroid hormone receptors, (iii) increasing T4 and T3 levels, (iv) increasing TSH and thyroglobuline levels, (v) decreasing free T4 and T3 levels. Finally, Rafi'i et al. (2025) state that exposure to As impacts the thyroid in several ways even at low concentrations, such as (i) by causing histological alterations in its tissues, (ii) increasing the levels of Tg and TSH, while lowering the levels of FT4 and FT3, and (iii) inhibiting thyroid peroxidase (TPO) regulation and activity in a dose-dependent relationship. Another important finding was that inorganic arsenic (iAs) takes longer to be cleared from the thyroid in comparison to other organs, which may exacerbate and facilitate the aforementioned toxicity mechanisms on this organ (Fowler et al., 2022).

3.2.1. *Hypothyroidism and Hashimoto's thyroiditis*

Other than autoimmunity, like in Hashimoto's thyroiditis, the most common origin for hypothyroidism is iodine deficiency, when iodine intake, usually dietary, is insufficient to supply the thyroid with the necessary amount for proper TH synthesis (Markou et al., 2001; Zimmermann and Boelaert, 2015; Chaker et al., 2022). However, the diverse mechanisms of action of endocrine disruptors, ranging from competition with iodine, to the mimics of TH structure and direct damage to the thyroid's tissue, often enable the development of this disorder even when iodine intake is within adequate levels (Niwattisaiwong et al., 2017). For example, nitrate (NO_3^-) is a known thyroid disruptor, which can drive hypothyroidism by inhibiting thyroid iodide uptake upon binding to the sodium-iodide symporter, a membrane glycoprotein located on the surface of thyroid follicles which is responsible for the entrance of iodide from the bloodstream inside thyrocytes, where it is oxidized into active iodine. In fact, Jain (2016) notes that the exposure to As significantly lowers thyroid function, even in individuals who are iodine-replete, emphasizing the impact of endocrine disruptors in overwhelming thyroid capacity. Moreover, the lack of iodine itself seems to boost the endocrine-disrupting activity of some elements (Liu et al., 2008a; Jain, 2016). In terms of exposure, studies denote that both high (Ciarrocca et al., 2012) and low cumulative exposures to As (Gong et al., 2015; Gonzales et al., 2018) are strong predictors for hypothyroidism. Stojsavljević et al. (2018) aimed to explore the unique elemental profile of hypothyroidism patients when compared to euthyroid individuals. The authors found that hypothyroid individuals had significantly higher serum As concentrations than euthyroid individuals. Another study developed by Stojsavljević et al. (2019) also suggested the connection between As and thyroid diseases, particularly hypothyroidism. Hu et al. (2021b) developed a study in China with the intent of assessing human exposure to polybrominated diphenyl ethers (PDBEs) and metals, and its effects on TH. Results showed that (i) urinary As was inversely associated with FT3, and (ii) FT3 was significantly negatively associated with As. In agreement with previously discussed findings, the results of Stojsavljević et al. (2021) also showed that individuals with multinodular goiter, thyroid adenoma, and thyroid cancer had higher blood As levels than healthy individuals. In contrast with the findings of the aforementioned studies, however, in the study of Liu et al. (2021), individuals with thyroid diseases had lower As concentrations than healthy individuals. In the case of Hashimoto's thyroiditis, Stojsavljević et al. (2020) report that the antagonistic effect of As and lead (Pb) on the extrusion of selenium (Se) is likely to explain the lack of Se in the thyroid tissue of patients with this disorder. Se plays a pivotal role in thyroid function and integrity as constituent of selenoproteins, such as glutathione peroxidases (GPx), thioredoxin reductases (TrxR), and iodothyronine deiodinases (DIO), which are involved in TH metabolism, the regulation of oxidation-reduction (redox) state, and maintenance of cellular homeostasis (Steinbrenner et al., 2016). By interfering with Se, both As and Pb contribute to the deregulation of redox reactions, worsening the damage caused by Hashimoto's thyroiditis inflammation (Huwiler et al., 2024). There is a possibility that, much like other PTEs, As can dysregulate microRNAs (miRNAs), as suggested by Aalami et al. (2022). MiRNAs are an important group of molecules involved in controlling gene expression at post-transcriptional level (Jorge et al., 2021). Because of this, the dysregulation of miRNAs may lead to processes of carcinogenesis, therefore causing, among others, thyroid cancer (Nikiforova et al., 2011).

The *in vivo* studies of Allen and Rana (2003), Liu et al. (2008a), and Ahangarpour et al. (2018) explored the link between hypothyroidism and As exposure. Allen and Rana (2003) studied the modulatory effects of TH on As toxicity, using rats as animal models, on lipid peroxidation and oxidative stress. Results suggested that As was less toxic in hyperthyroid than in hypothyroid rats. Moreover, there seemed to be a physiological antagonism between As and T4. It was found that. The work of Liu et al. (2008a) addressed the effect of the arsenate form (AsO_4^{3-}) on the thyroid, including its interaction with perchlorate. *Danio rerio* zebrafish were used as models, divided into two groups: one with euthyroid fish (*i.e.*, with normal thyroid function), and the other with hypothyroid fish (a state achieved *via* the exposure to perchlorate, which is a known thyroid-disrupting chemical). As a pro-oxidant, arsenate generates free radicals, which play a relevant role in the occurrence of oxidative stress-mediated toxicity (Flora and Pachauri, 2013). Oxidative stress, which is often associated with inflammation, happens when there is an imbalance between increased levels of reactive oxygen species (ROS), *versus* low activity of protective antioxidant mechanisms. The consequences of oxidative stress range from direct damage to cells, to damage of proteins and DNA, culminating in the destruction of tissues (Preiser, 2012). In this study, because perchlorate enhanced the toxicity of arsenate, hypothyroid fish were more sensitive to its effects compared to euthyroid fish. The main implications were retarded growth rate and several thyroid histopathologic effects, with a 96-h arsenate exposure at lethal concentration 50 (LC50) of 43 mg/L to hypothyroid fish, and 56 mg/L to euthyroid fish. The authors found that thyroid histopathology

can recover after cessation of perchlorate exposure, but colloid area or growth rate may not, although the extent of recovery depends on the endpoint examined and the duration of exposure (the longer, the harder the recovery). The *in vivo* study of Fan et al. (2024), using Sprague-Dawley rats as models, addresses how exposure to sodium arsenite ($NaAsO_2$) affects the thyroid. The authors investigated the toxic effects of $NaAsO_2$ exposure at different doses (0, 2.5, 5.0, and 10.0 mg/kg bw) and over different durations (12, 24 and 36 weeks) on thyroid tissue and thyroid hormone levels in Sprague-Dawley rats. It was found that $NaAsO_2$ exposure can cause accumulation of As in the thyroid tissue of Sprague-Dawley rats. Chronic exposure to $NaAsO_2$ significantly upregulates the expression of NLRP3 inflammasome-related proteins in thyroid tissue, leading to pyroptosis of thyroid cells and subsequent development of thyroid dysfunction, inflammatory injury, epithelial-mesenchymal transition (EMT), and fibrotic changes in the thyroid glands of rats. Pyroptosis is a form of programmed pro-inflammatory cell death characterized by the flattening of the cytoplasm due to plasma membrane leakage, serving a protective purpose in the host response to infection; however, it can also promote pathogenic inflammation (den Hartigh and Fink, 2018; Yu et al., 2021). The findings of Fan et al. (2024) suggest that exposure to some PTEs, namely As, can mimic infection upon cell entry, to which cells, recognizing it as a pathogen invasion, initiate a programmed cell death that's normally induced by intracellular pathogens. In a subsequent study within the scope and with similar methodology, Xiang et al. (2025) studied the effects of $NaAsO_2$ on the thyroid of Sprague-Dawley rats, implementing proteomic and phosphoproteomic analyses to investigate the molecular mechanisms underlying the effects of chronic $NaAsO_2$ exposure on thyroid function. $NaAsO_2$ disrupts the synthesis of thyroid hormones (TH) and alters the expression of the TH-synthesizing enzyme dual oxidase 2 (DUOX2). $NaAsO_2$ interfered with several cellular processes, such as causing upregulation of the central carbon metabolism in cancer, and downregulation of glutathione metabolism. In the *in vivo* study of Nandheeswari et al. (2024), female Balb/c mice were given sodium arsenite (0.2 ppm, 2 ppm, and 20 ppm) *via* drinking water for 30 days. Results showed that As exposure decreased FT4 and FT3 levels while increasing TSH levels, along with decreasing thyroid follicle size. Moreover, As significantly reduced the expression of LAMP1 (a lysosomal marker protein), leading to increased lysosomal permeability in the thyroid, resulting in a significant release of cathepsin B. Collectively, these changes led to hypothyroidism. Another *in vivo* study, developed by Larrán et al. (2024), assessed the concentration of 13 elements – including As – in groups of dogs with endocrine diseases, namely hyperadrenocorticism, diabetes mellitus, hypothyroidism. Inductively coupled plasma mass spectrometry (ICP-MS) was used to determine the concentration of each element in the dogs' serum, and the relationships between trace elements and the studied endocrinopathies were examined using chemometric procedures. Results showed that dogs with hypothyroidism had higher As and lower Se levels, supporting the role of these elements in this thyroid disruption.

Given the balance of evidence suggesting that diet plays an important role in As toxicity (Milton et al., 2004; da Sacco et al., 2013; Carlin et al., 2016; Sharma and Flora, 2018), Ahangarpour et al. (2018) used mice as models to assess the effect of chronic exposure to As combined with a high-fat diet on the thyroid function and lipid profile. Mice were divided into six groups, according to the diet they were fed (high- or low-fat) and As exposure. The authors found that exposure to As alone induced hypothyroidism-like states in the mice, by reducing the amount of TH. Individually, both As and high-fat diets cause imbalance on redox reactions within the organism, promoting an increased production of ROS, leading to oxidative stress (Flora, 2011; Jomova et al., 2011; Bojková et al., 2021; Kesh et al., 2016; Tan and Norhaizan, 2019; kaur et al., 2024). Therefore, the combination of a high-fat diet and As-induced hypothyroidism drove hypolipidemia, hyperleptinemia, hyperadiponectinemia, and promoted the induction of oxidative stress and the reduction of glutathione sulfhydryl reductase (GSH) in the treated mice groups. In short, data from Liu et al. (2008a) and Ahangarpour et al. (2018) suggest that As exposure can be sufficient to promote hypothyroidism, but its toxicity can be enhanced when other factors are involved.

3.2.2. Thyroid cancer

Cancer is often characterized as a product of cells dividing uncontrollably upon their evasion of endogenous cell cycle control mechanisms, potentially invading and spreading to other parts of the organism (Krieghoff-Henning et al., 2017). However, Brown et al. (2023) propose a broader definition: "cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection". This concept considers the genetic and epigenetic changes that these cells undergo. Cancer emerges when there is some form of genetic damage that compromises the strict regulation of cell division, which can happen endogenously – *via* DNA replication errors or the destabilization of DNA bases by free radicals –, or exogenously – *via* the action of carcinogens, including exposure to ionizing and ultraviolet radiation (Kashyap and Dubey, 2022). Cancers are grouped into types according to their organ or tissue of origin, including molecular characteristics of the cancer cells (Krieghoff-Henning et al., 2017). Cancers commonly associated with exposure to As are those of the skin, lungs, liver, and bladder. While there are still some gaps revolving around the mechanisms of As carcinogenicity, its downstream deleterious effects occur *via* the induction of oxidative stress, alterations to DNA methylation, histone modification, changes in miRNA expression, inhibition of DNA repair, modification of epigenetic regulation of gene expression, and altering protein function (Martinez et al., 2011; Speer et al., 2023). The pilot study of Petrosino et al. (2018) explored the role of some PTEs and polychlorinated biphenyls (PCBs) in the oncogenesis of head and neck tumors and thyroid diseases. The authors found that patients with thyroid diseases, particularly carcinomas, tended to present higher As levels in the hair and blood. Chen et al. (2019) also suggest that exposure to As from water pollution in China seems to be associated with thyroid diseases, particularly thyroid cancer. Zidane et al. (2019) aimed to assess human exposure to several dietary non-essential trace elements in French Polynesia. Their results showed that As was present in some fruits, vegetables, and drinking water samples at appreciable concentrations, and especially high in certain sea products. Each μg/day/kg bw of As exposure increased thyroid cancer risk by 30 % more in patients with a history of cancer in first-degree relatives than in those without. Data from the studies of Kumar et al. (2021), He et al. (2022) and Modica et al. (2023), confirmed that exposure to As can also contribute to the development of thyroid cancer. Finally, in the case-control study of Yu et al. (2025), urinary As concentrations were significantly lower in thyroid cancer cases than controls. Overall, populations exposed to As in some form had higher cancer incidence rates than those non-exposed. Since no *in vitro* or *in vivo* studies were found with animal models providing mechanistic insights on the emergence of thyroid cancer due to As exposure specifically, further research is encouraged to fully unravel its effects.

Glattre et al. (1995) developed an *in vivo* study, with rats as animal models, to investigate the distribution and interaction of As and selenium (Se) in the thyroid. Rats were pretreated with arsenate (100 mg/L As), selenite (1 mg/L Se), and arsenate (100 mg/L As) plus selenite (1 mg/L Se) added to the drinking water. For both male and female rats, measurements indicated that T4/T3 was lowest in the Se group, intermediate in the arsenic (As) group, and highest in the controls. Post-mortem examination showed that the thyroid tissue of rats pretreated with As alone exhibited obvious toxic alterations, whereas only minor to no changes were found in the tissues of the groups pretreated with Se or As + Se. In the study of Yamamoto et al. (1995), a multiorgan bioassay was conducted using rats given various doses of DMA to evaluate its effects on chemical carcinogenesis. The authors found that DMA significantly enhanced the tumor induction in the thyroid of rats, with incidences of 45 % in the group treated with 400 ppm DMA. Other

studies and reviews on the subject discussed these effects, supporting the carcinogenicity of DMA on the thyroid (Yamamoto et al., 1997; Huff, 2001; Kenyon and Hughes, 2001). With this in mind, Kitchin (2001) highlighted possible mechanisms of As carcinogenesis include (i) chromosomal abnormalities, (ii) oxidative stress, (iii) altered DNA repair, (iv) altered DNA methylation patterns, (v) altered growth factors, (vi) enhanced cell proliferation, (vii) promotion/progression, (viii) gene amplification, and (ix) suppression of p53. On the other hand, Arnold et al. (2006) studied the effects of chronic exposure to DMA, using F344 rats and B6C3F1 mice as models. DMA was administered in the diet to B6C3F1 mice (at dose levels of 0, 8, 40, 200, and 500 ppm) and to F344 rats (at dose levels of 0, 2, 10, 40, and 100 ppm) for 2 years, according to US EPA guidelines. Dose-related increases in the height of the thyroid follicular epithelium were observed in both males and females; however, such changes seemed to reflect an adaptive response of the thyroid to decreased levels of circulating thyroid hormone, rather than an adverse effect. DMA was carcinogenic in rats at relatively high doses, but not in mice. The authors also found that female rats were more sensitive to the effects of DMA than male rats. Finally, the *in vitro* study of Davey et al. (2008) explored the effects of As on receptor-mediated gene transcription using human embryonic NT2 cells, rat pituitary GH3 cells, and *ex vivo* amphibian tail cells. Human embryonic NT2 or rat pituitary GH3 cells were treated with 0.01–5 μM sodium arsenite for 24 h, with or without retinoic acid (RA) or thyroid hormones (TH), respectively. Changes in expression of type 1 deiodinase (*DIO1*) were observed at 6 or 24 h of As exposure, indicating a transient superinduction by As at very low doses, and a transient repression by As at higher doses. As such, As altered hormone-signaling by disrupting the normal function of both RA receptor and TH receptor.

In summary, As exposure, especially in the form of DMA, can be a driver for thyroid disruption, primarily leading to outcomes like hypothyroidism and thyroid cancer. Expectedly, the severity of the effects of As exposure is both time- and dose-dependent. However, there is a need for further studies for assessing how different As forms and their varying toxicity potential affect the thyroid.

3.3. Mercury (Hg) and thyroid disruption

Many of the reviewed publications supported a link between mercury (Hg) and thyroid disruption. There was particular emphasis on outcomes like thyroid cancer and hypothyroidism in animal models and humans, namely following exposure to Hg in the form of methylmercury (CH_3Hg). Even so, there were disparities when it comes to serum Hg concentrations between thyroid disease patients and euthyroid individuals: while some studies recorded serum Hg concentrations as significantly higher in thyroid disease patients, others found no notable differences. In any case, knowledge in regards to the effect of different forms of this metal on the thyroid is lacking.

Mercury (Hg) is a rather unique heavy metal, in that its elemental form (Hg^0) presents itself in a liquid state at standard temperature and pressure (Gonzalez-Raymat et al., 1987). Originating from both natural and anthropogenic sources, the concentrations of this ubiquitous metal can be particularly increased due to volcanic activity, gold mining, and industrial processes (Driscoll et al., 2013; Khan and Abbas, 2020; Edwards et al., 2021). The toxic nature of Hg became well-known for the infamous Minamata disease incident, an environmental disaster in which the population of the Minamata city, Japan, 1956, developed severe neurological disorders due to the consumption of fish and shellfish contaminated by methylmercury (CH_3Hg) discharged from a chemical plant. Mercury is nowadays regarded as one of the most hazardous elements on Earth's surface (Yang et al., 2020; Wu et al., 2024). It can be found in inorganic toxic forms, such as mercury chloride ($HgCl_2$) and mercury sulfide (HgS), although its organic forms – like CH_3Hg and dimethylmercury (C_2H_6Hg) – are considerably more toxic than both its elemental and salt forms due to their lipid solubility (Siegler et al., 1999; Liu et al., 2008b; Hong et al., 2012; Perrone et al., 2023). Gaseous elemental mercury (Hg^0) predominantly makes its way into the body *via* inhalation, whereas exposure to other forms of Hg can happen *via* the consumption of contaminated food and water, including in occupational contexts where they are abundant (Park and Zheng, 2012). The main mechanism of Hg toxicity is related to its capability of irreversibly inhibiting selenoproteins, which, beyond being of central importance for proper thyroid function, also serve a major purpose in protecting cells from oxidative stress in general (Steinbrenner et al., 2016; Kang et al., 2024). In addition, Hg compounds may interfere with "intracellular calcium homeostasis, cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and DNA methylation" (Kang et al., 2024). Mercury primarily targets the nervous system and kidneys, although its harmful effects also extend to the digestive and immune systems. Some outcomes of Hg exposure include impaired neurological development, memory loss, nephrotic syndrome, infertility, anemia, among many others (Rice et al., 2014; Vianna et al., 2019; Gao et al., 2022; Kumar et al., 2022).

In view of the systemic health effects associated with Hg, this element is expected to adversely interfere with the thyroid. In fact, exposure to Hg was found to be linked with thyroid disruption, most reportedly thyroid cancer (Zaichick et al., 1995; Chung et al., 2016; Malandrino et al., 2016; Petrosino et al., 2018; Zidane et al., 2019; Correia et al., 2020; Liu et al., 2021; Pamphlett et al., 2021; Zhang et al., 2021; Aalami et al., 2022; Benvenga et al., 2022; Kim et al., 2022; Capezzone et al., 2023; Yang et al., 2023; Webster et al., 2024; Pamphlett and Bishop, 2024). Hg exposure was also found to be associated with hypothyroidism due to the endocrine-disrupting action of this metal (Nishida et al., 1989; Zaidi et al., 2001; Soldin et al., 2008; Hu et al., 2021c; Pamphlett et al., 2021; Benvenga et al., 2022; Mukhi et al., 2024), with emphasis on Hashimoto's thyroiditis (Pamphlett et al., 2021; Benvenga et al., 2022). Nevertheless, Rezaei et al. (2019) and Legakis et al. (2022) contradict most other evidence by suggesting that exposure to Hg might have no connection to thyroid disease. Webster et al. (2024) state that exposure to Hg is associated with a risk of thyroid cancer, implying a possible predisposing factor. This is backed up by Bryliński et al. (2025), suggesting that accumulation of Hg in the thyroid may interfere with hormone secretion and stimulate cancer cell proliferation. Still, Rafi'i et al. (2025) noticed that several publications report a significant correlation between Hg levels and noncancerous thyroid disease, while others report a nonsignificant association between Hg and noncancerous thyroid disease. Collectively, this body of evidence demonstrates that there is still discrepancy in the data regarding the association between Hg and thyroid disruption. Because the role played by Hg on thyroid disruption is not yet fully understood, further investigation is warranted.

3.3.1. Thyroid cancer

Zaichick et al. (1995) studied the amount of select trace elements relevant to the etiology of thyroid cancer. Thyroid samples were collected from resected material of 135 patients who underwent operations. Results showed that in paranodular tissue, the content of silver (Ag), cobalt (Co), Hg, iodine (I), and rubidium (Rb) was much higher for malignant and benign nodules than they were in healthy individuals. These findings suggested that heavy metals, like Hg, play a role in the etiology of thyroid cancer. In another study, developed by Petrosino et al. (2018), hair and blood samples were collected from 20 volunteers – including healthy individuals and head and neck tumor patients – with the aim of measuring the concentrations of 14 heavy metals and 12 polychlorinated biphenyls (PCBs). The measured concentrations were compared between individuals based on the presence of head and neck tumors. The authors found that patients with thyroid diseases, particularly carcinomas, tended to present higher Hg levels in the hair and blood. According to Chung et al. (2016), high blood levels of Hg are connected to thyroid cancer at stage 1. While the concentration of other elements might increase with cancer development, such as cadmium (Cd), selenium (Se), and zinc (Zn), the authors found that the opposite

happened with Hg, meaning its overall concentration may lower as thyroid cancer progresses into later stages. Regarding volcanic environments, in a similar fashion, Malandrino et al. (2016) view the complex interaction between volcanogenic contaminants, including mercurial enrichment, as a likely explanation for the high incidence rates of thyroid cancer in the population of Sicily, Italy. It is worth noting that co-occurring toxic metals in thyroid cells may enhance Hg toxicity, leading not only to cancer, but also hypothyroidism, sometimes coupled with an autoimmune dimension, as it happens in Hashimoto's thyroiditis (Pamphlett et al., 2021; Benvenga et al., 2022). In the study of Zidane et al. (2019), earlier discussed in the context of As exposure, Hg was mostly present in appreciable concentrations in French Polynesian fishery products. Findings showed that, in the study population, thyroid cancer risk doubled in patients with a history of cancer in first-degree relatives by each μg/day/kg of Hg intake. In a cross-sectional study, Correia et al. (2020) aimed to evaluate the association between chronic occupational exposure to metallic Hg and alterations in TH, as well as thyroid gland parenchyma, 14 years after the last exposure. Compared with non-exposed individuals, those who had been exposed to metallic Hg had, on average, (i) significantly higher urinary Hg, (ii) higher serum TSH, and (iii) higher proportions of echogenicity alterations. Moreover, papillary thyroid carcinomas were documented in three exposed individuals. Meanwhile, Kim et al. (2022) report that high urinary Hg concentrations represent an increased risk for thyroid cancer, since thyroid cancer patients display higher urinary Hg concentrations when compared to healthy individuals. Finally, Capezzone et al. (2023) correlate the high incidence of thyroid cancer in Grosseto province, Italy, with PTEs pollution, being Hg one of the abundant contaminants in the area. The ecological study developed by Shaked et al. (2024) in Puerto Rico aimed to explore the association between thyroid cancer incidence and 3 metals (Pb, Cd, and Hg) with known endocrine-disrupting properties and increased metal levels in soil samples in the area. Results showed that there was a significant negative association between Hg and TgAb. Furthermore, there were higher thyroid cancer incidence rates and increased metal levels in the soil in the northern parts of Puerto Rico. On the other hand, Choi et al. (2025) developed a study by performing cross-sectional and longitudinal analyses using data from women aged 60 years and older in the Ansung cohort of the Korean Genome and Epidemiology Study (KoGES). The urinary concentrations of several metals – including Hg – in individuals from the study population were determined. It was found that Hg did not show significant associations with thyroid nodule development.

Despite the above evidence, in the study of Rezaei et al. (2019), the serum levels of Hg proved to be similar between thyroid disease patients and healthy individuals. In addition, Legakis et al. (2022) further suggest that exposures to Hg are not connected to thyroid disease, specifically, thyroid cancer, claiming that there is "no evidence of thyroid carcinogenicity". Blood Hg levels are a good biomarker of short-term high-level exposure, but don't necessarily reflect long-term bioaccumulation patterns and target primarily the detection of Hg in organic forms. Conversely, urinary Hg concentrations are the go-to biomarker for long-term exposure to both elemental and inorganic forms, being a good indicator of Hg body burden (Park and Zheng, 2012). Hair is also considered an appropriate external matrix to assess both environmental and dietary Hg exposures (Esteban-López et al., 2022). Still, properly assessing Hg exposure and the extent of its effects remains a challenge even today (Ye et al., 2016; Esteban-López et al., 2022). On the other hand, while it is true that no *in vitro* nor *in vivo* studies were found in support of the carcinogenic effect of Hg (in metal and salt forms) over thyroid cells, the existing data so far should be enough to raise concern over the matter. Plus, this metal has been known to form deposits in the thyroid and hypothalamus, which may very likely interfere with TH homeostasis (Zhu et al., 2000; Bernhoft, 2012; Pamphlett et al., 2021; Kubicka-Figiel et al., 2024). Hence, more research should be dedicated to better understand the true nature of the interactions between Hg and the thyroid.

Soldin et al. (2008) made a review on the effect of CH_3Hg on the thyroid, hypothesizing that exposure to high levels of CH_3Hg (*i.e.*, cumulative, long-term exposures) could disturb neurodevelopmental processes by selectively affecting TH homeostasis and function. The authors posed that it was still unclear whether exposure to the compound directly altered TH homeostasis, although it seemed to be associated with hypothyroidism. It was proposed that CH_3Hg interferes with selenoproteins, leading to a dysfunctional thyroid. However, Maggisano et al. (2020) confirmed the suspicions of thyroid toxicity by CH_3Hg *via* an *in vitro* study using immortalized, non-tumorigenic thyroid cells (Nthy-ori-3-1) exposed to different concentrations of the compound. Results showed that high concentrations of CH_3Hg are directly toxic to thyroid cells, resulting in cell destruction and carcinogenic effects. Meanwhile, prolonged exposure to low (sub-toxic) doses of Hg, better reflecting environmental Hg exposure, promotes thyroid cell proliferation, namely through the activation of the ERK pathway. Much like other compounds, these results demonstrate how the same compound can prompt different effects depending on the concentration cells are exposed to, which is particularly recurring with PTEs (Damelin et al., 2000; Calabrese and Mattson, 2017; Kim et al., 2020a, 2020b; Moulis et al., 2020; Balali-Mood et al., 2021). In toxicology, this phenomenon is known as hormesis, wherein low doses of a compound have stimulatory activity while high doses have an inhibitory activity (Alì et al., 2021; Calabrese et al., 2024). Meanwhile, the *in vivo* study of Mukhi et al. (2024) evaluated the cognitive, physiological, and biomarker effects of select PTEs exposure – including Hg – in Wistar rats. During a 13-week period, the Hg-treated rat groups (with both males and females) was fed a stock solution prepared with 3 mg/kg Hg. Results showed that rats treated with Cd (46.6 mg/kg Cd) and Hg showed significantly higher TSH levels than the control group. Moreover, a significant hypothyroid status with increased TSH and decreased T3 and T4 levels was observed in the Hg-treated groups, with hypothyroidism signs such as increased food intake and weight gain.

3.3.2. *Hypothyroidism and Hashimoto's thyroiditis*

In a pilot study with welders developed by Zaidi et al. (2001), human occupational exposure to PTEs associated with welding was assessed. A group of 20 male welders was matched with 20 healthy controls with no previous occupational exposure to welding. Intravenous blood samples were collected from each individual for serum measurements of TSH, total T3 (TT3), and total T4 (TT4). Although no differences were found in TT3 and TT4 levels, TSH levels were significantly increased in welders compared with non-welders. As such, it was suggested that the working environment of welders, in which Hg exposure is common *via* fumes, may play a role in the development of hypothyroidism.

Besides the suggested by Soldin et al. (2008) regarding the role of Hg in the development of hypothyroidism, the works of Hu et al. (2021c), Pamphlett et al. (2021), and Benvenga et al. (2022) also shed some light on the matter. The possible mechanisms implicated are strongly related to Hg's oxidative stress-inducing and autoimmunity-promoting characteristics, which could precede the onset of thyroid cancer. Oxidative stress alone can result in the destruction of thyroid cells, therefore leading to a lower production of TH (Chakrabarti et al., 2016). With Hg being capable of directly harming thyroid cells, the tissue's state is only worsened when the body's immune system is activated and directed towards the site of injury. The infiltration of lymphocytes in the thyroid tissue and associated autoimmunity processes further contribute to the generation of ROS, with the ensuing chronic inflammation perpetuating the effects of oxidative stress and, therefore, thyroid tissue damage (Wenzek et al., 2022; Batóg et al., 2023). If the situation continues and ROS begin to target DNA without the activation of apoptosis-related pathways in the affected cells, then it is possible that cancerous progression may occur. In fact, data shows that thyroid cancer is often preceded by benign thyroid disease, such as hypothyroidism and Hashimoto's thyroiditis, meaning that individuals with pre-existing benign thyroid conditions have an increased risk of later developing

thyroid cancer (Hu et al., 2022; Kitahara and Schneider, 2022). Another toxicity mechanism of Hg towards the thyroid might be miRNA dysregulation, as previously discussed in the context of As toxicity (Aalami et al., 2022). While knowledge gaps persist on the extent of Hg impairment over TH metabolism, it is plausible that many thyroid cancer cases occur from exposure to Hg (or other endocrine-disrupting compounds) which were preceded by either undiagnosed or overlooked benign thyroid disease. Whether progression is due to the original condition, the given treatment, the influence of external factors (such as exposure to environmental contaminants), or a multifactorial combination, the need for monitoring benign thyroid disease patients is further reinforced to allow timely intervention before eventual progression into cancer.

Nishida et al. (1989) studied the interaction of methylmercury chloride (CH_3HgCl) and mercury chloride ($HgCl_2$) with thyroid peroxidase (TPO) in two experiments. In the first experiment, the thyroids from rats that were given 5.6 mg/kg/day of either CH_3HgCl or $HgCl_2$ for 2 weeks by intubation were observed *via* electron microscopy. In the second experiment, guaiacol oxidation by TPO in isolated and ruptured pig thyroid cells was spectrophotometrically monitored in the presence of either CH_3HgCl or $HgCl_2$. It was found that, in rats, CH_3HgCl (i) induced the flattening of epithelia, (ii) promoted the formation of large follicles, and (iii) lowered serum TSH levels. Meanwhile, $HgCl_2$ (i) inhibited TPO activity, and (ii) induced the formation of taller epithelia. In pig cells, CH_3HgCl induced a hypothyroid state without affecting TPO. In turn, $HgCl_2$ inhibited TPO activity, inducing a hypertrophic state due to compensation for loss of enzyme activity.

Overall, there is evidence indicating that exposure to Hg disrupts thyroid homeostasis, resulting in thyroid cancer and hypothyroidism, including Hashimoto's thyroiditis. Nonetheless, some studies suggest that Hg is not directly connected to thyroid disease, faced with the similarities between thyroid disease patients and euthyroid individuals in terms of serum Hg concentrations and the lack of data on its carcinogenic effects on the thyroid. Given the genotoxic, oxidative stress-inducing and autoimmunity-promoting traits of Hg, the development of further research within the scope to fill in the existing knowledge gaps is strongly encouraged.

3.4. Cobalt (Co) and thyroid disruption

Publications investigating the link between cobalt (Co) and thyroid disruption were largely about (i) excess Co exposure from failed hip implants, and (ii) the use of Co in radiotherapy for the treatment of certain conditions. A few others explored exposure to Co in different contexts, namely occupational and environmental settings. In essence, excess Co exposure seems to be associated with the development hypothyroidism. Interestingly, Co deficiency appears to also be tied with thyroid disruption, but possibly only when in association with cobalamin. No *in vitro* nor *in vivo* studies were found addressing the effect of Co on the thyroid, making for a major knowledge gap in the topic.

Cobalt (Co) is a metal with a fundamental role in the body as constituent of the essential cobalamin vitamin (B_{12}), which is essential for red blood cell synthesis (erythropoiesis). Cobalamin is also used as a cofactor for enzymes related to DNA, fatty acids, and myelin synthesis, whereby the deficiency in this vitamin can have negative hematologic and neurological consequences (Yamada, 2013; Genchi et al., 2023). Cobalt deficiency can lead to conditions like anorexia, chronic swelling, and detrimental anemia. However, when in excess, this metal can cause symptoms related to vomiting, nausea, diarrhea, bleeding, and low blood pressure, escalating towards heart diseases, thyroid damage, hair loss, bone defects and the inhibition of important enzymes (Genchi et al., 2023). This metal exists in the form of Co^{2+} [Co(II)] which is believed to be the primary toxic form due to its similarity with the calcium ion (Ca^{2+}), essential for several intracellular processes (Simonsen et al., 2012), as well as Co^{3+} [Co(III)] (Barceloux, 1999; Leyssens et al., 2017). Cobalt can be found in the inorganic form as carbonate ($CoCO_3$) or in organic forms like cobalt acetate ($C_4H_6CoO_4$) and cobalt lactate ($C_6H_{10}CoO_6$) (Raths et al., 2023). Besides inhalation through occupational exposure due to mining activities or medical devices, absorption of Co can happen *via* contaminated food and water sources due to its environmental accumulation, which can be increased by the nature of the soils' parent rocks (Barceloux, 1999; Banza Lubaba Nkulu et al., 2018; Poznanović Spahić et al., 2019; Genchi et al., 2023). Naturally, this metal is also present in increased concentrations in volcanic environments (Genchi et al., 2023). In general, Co toxicity results in the reduction of cell viability, increasing cell membrane damage, while also being associated with other oxidative stress-related effects (Rajiv et al., 2016; Chen and Lee, 2024). Moreover, there is data on the carcinogenicity of Co metal and Co sulfate ($CoSO_4$) in experimental animal models (Simonsen et al., 2012). Therefore, a delicate Co balance is needed to maintain its beneficial properties within the organism. It has been defined, *via* a biokinetic model, that adverse health effects are unlikely to happen when blood Co concentrations are under 300 μg/L (100 μg/L with respect to a safety factor of 3) in healthy individuals, and that chronic exposure to acceptable doses is not expected to pose notable health hazards. Nevertheless, it must not be disregarded that hematological and endocrine dysfunctions are the primary health endpoints when Co imbalances occur (Leyssens et al., 2017; Unice et al., 2020).

Many publications focused on the effects of Co in the context of medical procedures, including hip implants, and the treatment of hematological disturbances and Hodgkin's disease. The main thyroid disruption outcome of the aforementioned was hypothyroidism (Kriss et al., 1955; Sederholm et al., 1968; Prager et al., 1972; Somerville et al., 2002; Oldenburg et al., 2009; Devlin et al., 2013; Pizon et al., 2013; Bradberry et al., 2014; Paustenbach et al., 2014; Alba et al., 2016; Sánchez and Pastó-Cardona, 2016; Yu, 2017; Randhawa et al., 2021; Crutsen et al., 2022; Shewalkar et al., 2023; Blackmon et al., 2024). Over time, other types of Co exposure, such as environmental exposures, started to be addressed. Excessive environmental exposure to Co was most often reported to induce hypothyroidism (Christensen and Poulsen, 1994; Oller and Bates, 2004; Lantin et al., 2011; Finley et al., 2012; Tubili et al., 2012; Paustenbach et al., 2013; Sanjari et al., 2014; Bradberry, 2016; Packer, 2016; Yu, 2017; Hanif et al., 2018; Stepien et al., 2018; Stojsavljević et al., 2018; Rezaei et al., 2019; Liu et al., 2021; Lison, 2022; Bryliński et al., 2025; Choi et al., 2025). Some studies also reported connections between Co toxicity and thyroid cancer (Zaichick et al., 1995; Somerville et al., 2002; Hu et al., 2021a; Stojsavljević et al., 2021; He et al., 2022; Legakis et al., 2022; van Gerwen et al., 2022).

3.4.1. Hypothyroidism

Several publications referred to the fact that the therapeutic use of Co – for example, in the form of radioactive Co-60 – often inadvertently resulted in the development of hypothyroidism (Kriss et al., 1955; Sederholm et al., 1968; Prager et al., 1972; Randhawa et al., 2021; Shewalkar et al., 2023). In some works, it was reported that this pathology could be recovered upon cessation of the treatment (Kriss et al., 1955; Sederholm et al., 1968; Prager et al., 1972). A major source of systemic Co toxicity arises from failed hip replacements, especially those based on metal-on-metal (MoM) prosthetics. The emergence of hypothyroidism following failed MoM hip replacements is well-documented, often due to the gradual release of Co into the bloodstream as the prostheses wear out (Oldenburg et al., 2009; Pizon et al., 2013; Bradberry et al., 2014; Paustenbach et al., 2014; Sánchez and Pastó-Cardona, 2016; Yu, 2017; Stepien et al., 2018; Crutsen et al., 2022; Blackmon et al., 2024).

Christensen and Poulsen (1994) focused on the effects of occupational exposure to Co, namely that of plate painters in two Danish porcelain factories. It seemed that low-level Co exposure did not cause inhibitory effects on thyroid function, but the ratio between T4 and T3 was increased. This indicated that low-level Co exposure may have an impact on the metabolism of TH. Oller and Bates (2004) provide some insight into the Co toxicity mechanisms that lead to hypothyroidism,

referring that Co prevents uptake of iodine (I) into T4 by inhibiting tyrosine iodinase, resulting in a drop in circulating T4 levels, which may lead to clinical hypothyroidism. With low T4 levels, TSH excretion is increased, resulting in thyroid hormone hyperplasia (goiter). Paustenbach et al. (2013) suggest that inhalation- and ingestion-related exposures to Co at blood or serum levels of ~300 μg/L and higher for a period of over 2 weeks may originate hypothyroidism, but the condition is reversible upon cessation of the exposure. Packer (2016) equally denotes exposures to Co as causing reversible hypothyroidism in concentrations between 750 and 1950 μg/L. Sanjari et al. (2014) found serum Co levels to be strongly associated with goiter. Additionally, low serum Co levels contributed significantly more to the presence of goiter than low urinary iodine (I) levels. In the study of Hanif et al. (2018), Co was significantly positively correlated with hypothyroidism. The mean levels of serum Co and T4 were significantly higher in female hypothyroid patients, compared to male hypothyroid patients. Similarly, in the study of Stojsavljević et al. (2018), hypothyroid individuals had significantly higher serum Co concentrations than healthy individuals. By contrast, Liu et al. (2021) found that there were no differences in urinary Co levels between thyroid disease patients and healthy individuals.

3.4.2. Thyroid cancer

Findings from the study of Zaichick et al. (1995) showed that, in paranodular tissue, the content of silver (Ag), Co, mercury (Hg), iodine (I), and rubidium (Rb) were much higher for malignant and benign nodules than in healthy individuals. These results suggested that heavy metals, like Hg, play a role in the etiology of thyroid cancer. Somerville et al. (2002) noted that there was a significant risk of thyroid cancer in individuals who were exposed to radiation as part of therapy for childhood cancer. Moreover, the risk was greater for patients who received scatter (*vs.* direct) irradiation. Nodular changes are normally not apparent for many years, hence the need for lifelong surveillance. Legakis et al. (2022) reported that, in combination, molybdenum (Mo), tin (Sn), cobalt (Co), and other metals appear to increase the incidence of thyroid cancer. Regarding Co deficiency, Sanjari et al. (2014) and Rezaei et al. (2019) suggest the association between low serum Co levels with both hypo- and hyperthyroidism, whereas van Gerwen et al. (2022) cover the link between low serum Co levels with thyroid cancer. In contrast to the noticeably harmful effects of Co exposure reported by most of the studies, Lantin et al. (2011) argue that there are no observable effects when exposure is kept below the biological limit of occupational exposure [15 μg Co g(creat)$^{-1}$ in urine]. Hu et al. (2021a) and He et al. (2022) noted a decreased risk of thyroid cancer onset and/or exacerbation upon Co exposure. In contrast, decreased levels of Co in urine were associated with aggressive papillary thyroid carcinoma clinicopathological characteristics (Hu et al., 2021a). Choi et al. (2025) suggest that certain trace elements, particularly Mn, Cu, Co, Zn, and U, may contribute to the formation and growth of thyroid nodules in older women. Considering the aforementioned, it can be surmised that Co may contribute to thyroid disruption at both elevated and diminished concentrations.

Finley et al. (2012) suggest that, in the general population, for a lifetime of daily exposure to Co, a chronic oral reference dose (RfD) of 0.03 mg/kg-day would be protective of non-cancer health effects. Because Co toxicity on the thyroid impairs TH synthesis by preventing the binding of iodine through an unknown mechanism (Sarne, 2016), along with thyrocyte death, exposure to this metal can not only cause hypothyroidism, but also induce destructive thyroiditis (Yu, 2017) – "a condition in which the follicles are destroyed by a relatively acute phase of inflammation in the thyroid gland and thyroid hormones massively leak into the blood" (Uemura et al., 2023). The same outcomes are expected when Co is gradually released by medical devices, like hip prostheses (Stepien et al., 2018). Interestingly, thyroid disruption may follow Co serum levels below normal ranges. Sanjari et al. (2014) note that low serum Co levels were more influential to the appearance of goiter than low urinary iodine levels. Furthermore, Rezaei et al. (2019) refer that low serum Co concentrations can promote hyperthyroidism, although less commonly. Similarly to what was found with hypothyroidism, there is research suggesting how both high and low concentrations of Co may be related to the onset and/or exacerbation of thyroid cancer. However, only a few articles support that link and findings are not consistent (Hu et al., 2021a; He et al., 2022; Legakis et al., 2022; van Gerwen et al., 2022; Bryliński et al., 2025), warranting further investigation.

Generally, Co exposure seems to induce cellular changes consistent with a hypoxic-like response and oxidative stress. Consequently, some genes that can be differentially expressed are involved in Hif-1α signaling, glycolysis, gluconeogenesis, and other energy metabolism-related processes, whereas gene expression alterations associated with oxidative stress tend to be involved in the NRF2-mediated response, protein degradation, and glutathione production (Permenter et al., 2013). In the case of lung cells, upon exposure through inhalation, the toxicity of cobalt oxide (Co_3O_4) is based on the cell particle internalization *via* the *endo*-lysosomal pathway. After that, Trojan-horse mechanism is triggered through which the intracellular release of toxic metal ions follows over long periods of time, involving specific toxicity. This contrasts with toxicity by extracellular dissolution of the particles (Ortega et al., 2014). Because of its oxidative stress-associated effects and targeting of other cell signaling pathways, it could be possible that Co is also involved in carcinogenic processes, yet data is still very much lacking in this regard. Moreover, aside from it being known that Co inhibits the binding of iodine (Sarne, 2016), unfortunately, neither *in vitro* nor *in vivo* studies exploring the relationship between Co and the thyroid were found for this review. Although it is plausible that the effects are like those discussed, there is a considerable knowledge gap regarding the lack of mechanistic insights into how both excess and deficiency of Co impairs thyroid metabolism, specifically, for the potential link to cancer.

All the data gathered in this section further enhances the need of a fine balance of Co concentrations within the organism, as otherwise thyroid function might be compromised. Effects of both high and low Co concentrations upon the thyroid are more linked to the development of hypothyroidism, possibly linked to thyroid cancer, and, less commonly, hyperthyroidism. Hypothyroidism can usually be reversed if excessive Co exposure is ceased. Still, there is a notable knowledge gap regarding mechanistic insights on the relationship between Co and the thyroid, both at high and low concentrations.

4. Major findings and knowledge gaps

Contaminants abundantly occurring in volcanic environments are likely contributors to thyroid disruption. In the context of volcanic environments, areas of non-eruptive volcanic activity are underrepresented.

All the three elements addressed by this review – As, Hg, and Co – are implicated in thyroid disruption in various forms. The toxic effects of As, Hg, and Co on the thyroid are deserving of more attention, as insights into their role in affecting this organ and associated metabolic pathways are considerably lacking.

There is a major knowledge gap regarding the incidence of hypothyroidism and other thyroid pathologies in the population of volcanic areas. Further research within this scope is strongly encouraged, given that As, Hg, Co, and other contaminants of volcanic environments are drivers of thyroid disruption, with emphasis on hypothyroidism.

5. Conclusion

Exposure to volcanogenic contaminants is a cause for concern and potentially leading to several disturbances in the organism. Arsenic (As), mercury (Hg), and cobalt (Co) appear to be drivers of thyroid disruption, elevating the incidence of thyroid cancer, hypothyroidism, and other thyroid pathologies in the population of volcanically active areas.

However, the severity of adverse health outcomes is dependent on the interplay between different compounds, as well as the lifestyle and genetic background of the affected populations. Thus, not every volcanic area resident will experience thyroid issues; outcomes depend on multiple factors including iodine sufficiency, genetic predisposition, and concurrent exposure to other pollutants or stressors.

Despite the natural hazards associated with volcanic environments, a considerable fraction of humanity will always live close to volcanoes and related areas for the richness they provide. Taking into account the findings of this review, further emphasis is put on the need of closely monitoring the health of populations living in volcanic environments. Possible health monitoring measures include regular thyroid function screening and cancer surveillance programs, coupled with environmental contaminant measurements.

CRediT authorship contribution statement

Nádia M.P. Coelho: Writing – original draft, Methodology, Conceptualization. **Filipe Bernardo:** Writing – review & editing, Methodology, Conceptualization. **Armindo S. Rodrigues:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Patrícia Garcia:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that there were no generative AI and AI-associated technologies in the writing process.

Funding

This research was funded by cE3c (DOI 10.54499/UIDB/00329/2020) and IVAR (DOI 10.54499/UIDP/00643/2020) projects from FCT national funds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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