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Systematic Review

Chromium in Water and Carcinogenic Human Health Risk

Maria-Nefeli Georgaki [1,2,*], Marianna Charalambous [3], Nerantzis Kazakis [4], Michael A. Talias [3], Charalampos Georgakis [5], Theodora Papamitsou [2] and Christina Mytiglaki [6]

1 Department of Health Sciences, School of Sciences, European University Cyprus, Nicosia 1516, Cyprus
2 Laboratory of Histology-Embryology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
3 Healthcare Management Program, School of Economics & Management, Open University of Cyprus, Nicosia 2220, Cyprus
4 Laboratory of Engineering Geology and Hydrogeology, School of Geology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
5 Laboratory of Physical Anthropology, Department of History and Ethnology, Democritus University of Thrace, 69100 Komotini, Greece
6 Department of Mineralogy-Petrology-Economic Geology, School of Geology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
* Correspondence: nefgeor@gmail.com

Abstract: Understanding the extent of human health risks with an emphasis on carcinogenesis development attributable to potentially toxic chemicals is critical to effective prevention and mitigation strategies. Chromium (Cr), mainly the hexavalent chromium (Cr (VI)), is a chemical associated with cancer when found in drinking water, making it a major public health issue. This study assessed a possible carcinogenic human health risk among the general population due to exposure to total or hexavalent chromium. We performed a systematic review of the international scientific literature, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol to determine the human risk of cancer mortality and morbidity. In total, 76 articles were checked for eligibility, 13 of which were included in the final systematic review. Only scientific articles from January 2000 to November 2022 published on PubMed were included. Data from both epidemiological ecological studies (Relative Risk and Rate Ratio—RR and Standardized Mortality Rate—SMR) and epidemiological case studies (Lifetime Cancer Risk—LCR, Incremental Lifetime Cancer Risk—ILCR, Cancer Risk—CR, Hazard Quotient—HQ, Hazard Index—HI, Health Risk Assessment—HRA, Disability-Adjusted Life Year—DALY, and Chronic Daily Intake Index—CDI) were included for the overall assessment of carcinogenicity in the general population. According to most articles, there is credible evidence that hexavalent chromium via water is indicated as a major contributor to the global burden of cancer in humans. Some of them emphasize malignant neoplasms in the lung, liver, stomach, and genitourinary system. Although the health index data of the case studies are based on a limited number of samples, they raise concerns about the possibility of an increase in the degree of carcinogenesis. However, there are significant limitations due to the lack of information on the dose and duration of exposure in the target group. Further research involving extensive analysis of the association of the two variables is needed, which depends on more complete information extraction and advanced methodologies.

Keywords: pollution risk; water quality; chromium; drinking water; carcinogenic; cancer

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1. Introduction

In nature, chromium can be found in two forms: trivalent chromium (Cr (III)) in the form of chromium oxides and hydroxides, or hexavalent chromium (Cr (VI)) in the form of chromate salts [1,2]. Depending on the oxidation state in which chromium is detected, both beneficial and harmful effects on human health are observed. While hexavalent chromium is described as poisonous [3], mutagenic [4], strongly soluble, and carcinogenic, trivalent chromium is a necessary trace element for human health [5–7]. The burden of chromium on the environment results from natural processes in the groundwater, due to the interaction of ultramafic rocks and water [8,9]. However, human activities, such as mining, coal burning [1], and the disposal of industrial wastes in water receivers, can cause an increase in chromium concentration. Due to the poor solubility of trivalent chromium, the hexavalent form of chromium, known to be highly mobile and water-soluble, predominates in groundwater.

Onchocke and Sasu [10] developed a technique for the detection of Cr (VI) in groundwater and industrial waste samples. Despite the simplicity of some methods for the determination of hexavalent chromium, such as the determination of the concentration in filtered solutions by colorimetric reaction with 1,5-diphenylcarbazide (DPC), which in acidic conditions forms a purple color, many interferences are created that can lead to overestimating or underestimating its concentration. For this reason, most scientific research is focused on the detection of total chromium in aquatic receivers, with the result that human health toxicity levels from the hazardous form of chromium are not determined.

Determining the source of water contamination is crucial for limiting the human health burden from potentially hazardous elements such as chromium. The impact of mass graves from World Wars I and II on the environment and human health is understudied but can lead to significant concentrations of harmful chemicals in soil and groundwater [11–13]. The enrichment of soil and groundwater depends on various factors such as soil type and proximity to water sources. Global Nest found a significant increase in chromium levels at sites near WWI and WWII mass graves, highlighting the importance of identifying the source of groundwater pollution and maintaining environmental balance to protect human health [14].

Many types of cancer result from exposure to risk factors including potentially hazardous chemicals, making cancer the second most common cause of death in the world [15–17]. Hexavalent chromium is linked to stomach cancer, lung cancer, and Hodgkin's disease, according to the World Health Organization (WHO), and is classified as a highly carcinogenic substance in group A [18–20]. The effect of chromium on the human body varies based on form, dose, and duration of exposure, which can occur through various routes such as water, food, or inhalation. Long-term exposure to hexavalent chromium has the potential to negatively impact health and is dependent on several factors such as gender, age, and body weight [21–23]. The Agency for Toxic Substances and Disease Registry (ATSDR) claims that long-term hexavalent chromium exposure may harm health based on factors such as gender, age, body weight, absorption, amount, and duration of exposure [24]. The toxicity of hexavalent chromium can be limited through reducing conditions in body fluids, including saliva, gastric fluid, and the liver [25,26].

Although the clinical and epidemiological studies of total or hexavalent chromium exposure through the air and food are various [27–31], the scientific studies of total or hexavalent chromium exposure through drinking water and the development or risk of cancer are quite limited. However, many case studies have shown that continuous exposure to chromium, even at low levels, can harm the skin, eyes, respiratory and immunological systems, and cause DNA damage and oxidative stress, leading to the growth of tumors [32]. Epidemiological studies have linked hexavalent chromium to DNA damage, skin diseases, respiratory and immune system problems, and issues with liver and kidney function [3,4,33,34]. One of the most important scientific research projects that have been conducted, Zhang and Li's epidemiological study in a specific Chinese province, was used as a reference point for the effect of chromium on human organisms through ingestion [35]. The study found that high hexavalent chromium levels in drinking water were associated with increased cancer-related deaths in villages near a steel plant, though the study was limited by demographics and a short monitoring period.

Chromium is considered an environmental hazard when found in more than permissible concentrations and is regulated by international, national, and municipal laws. Although hexavalent chromium is a significant groundwater pollutant [36], there is limited information on its permissible levels in drinking water. In the Netherlands, 98% of drinking water supplies have total chromium levels below 2 g/L, with 76% below 1 g/L [37]. In Germany, concentrations below 0.02 to 1 μg/L of total and hexavalent chromium were found in raw and drinking water samples. Specifically, the WHO recommends a guideline value of 50 μg/L for total chromium in drinking water, while the European Union (EU) has set a limit value of 100 μg/L for total chromium in drinking water as part of its Drinking Water Directive. Regarding hexavalent chromium, the WHO has not established a separate guideline value [18,38–40]. Exceptionally, the WHO has set a provisional guideline value of 0.1 μg/L for hexavalent chromium in drinking water, while the maximum discharge limit for hexavalent chromium into the aquatic environment according to the European Union is 0.5 μg/L. Depending on the chromium solubility, environmental receiver or human intake, and toxicity consequences, the United States Environmental Protection Agency (USEPA) has proposed water quality criteria [41,42] with the maximum permitted concentration of total chromium in drinking water at 0.1 mg/L. However, no separate limit has been identified for the harmful hexavalent form of chromium. It is important to note that these guidelines are subject to change and should be regularly reviewed and updated.

This review is a first step that summarizes the existing literature of epidemiologic studies and suggests the next steps in the evaluation of the carcinogenic risk to human health of total Cr or Cr (VI) in drinking water. To date, every review or meta-analysis on chromium has focused on a specific type of cancer, a specific age and occupational group, an experimental animal, or a different route of exposure. Given the different results, conclusions, and interpretations of the older published reviews regarding the association between Cr (VI) exposure and human carcinogenic risk, there is a need to review the current scientific evidence. Thus, the main objective of this research is to conduct a systematic review, using structured mapping, to determine whether there is an increased likelihood or increased risk of morbidity and mortality from various types of cancer in humans due to exposure to water enriched with total or hexavalent chromium. The NIH and NOS criteria were used to critically assess the methodology of each study and identify the risk of bias and potential error such as smoking and dietary factors. A meta-analysis was then performed only on data from ecological studies suitable for quantitative assessment to quantify cancer risk between exposed and unexposed populations. To the best of our knowledge, this review is made for the first time in the existing literature and aims to compel researchers to intensify their research on this topic.

2. Materials and Methods

To assess the risk of carcinogenesis in humans, we performed a systematic review of the international scientific literature using the PRISMA protocol [43]. The protocol describes the research question, review of the literature, search strategy, study categories, study population, exposure, comparison, and outcome specifications (PICOS), as well as details about the risk of bias assessment.

2.1. Research Question

The research question was defined as "What is the relationship between total or hexavalent chromium through drinking water and the risk of developing cancer in the general population?". In PICOS format, in Table 1, the variables of the research question are given.

Table 1. Research question in the form PICOS.

PICOS	
P	General population, without focus on a specific gender, age, or profession
I	Total or hexavalent chromium contamination in drinking water

Table 1. *Cont.*

PICOS	
C	No contamination from hexavalent or total chromium in drinking water
O	Cancer and carcinogenic risk
S	Epidemiological studies

P = Population, I = Intervention, C = Comparator, O = Outcome, S = Study.

2.2. Keywords

To identify enough scientific studies related to the research question, we searched the internet for the main keywords for exposure and disease outcome. For the exposure, the words "chromium" and "contaminated drinking water" were used and, for the outcome, the word "carcinogenic" was used.

Other databases were searched for similar terms and their synonyms (Medical Subject Headings—MeSh Terms). Searching for older systematic reviews investigating the same "exposure and outcome" is also important in identifying keywords used by researchers in these articles. Table 2 shows the exposure and disease outcome keywords used to generate the final study search code.

Table 2. Keywords for searching relevant studies on online databases.

Exposure
chromium, hexavalent chromium, heavy metal, polluted drinking water, contaminated drinking water
Outcome
cancer, carcinogenicity, carcinogenic, tumor

2.3. Inclusion and Exclusion Criteria and Search Databases

A key step of the systematic review is the definition of the inclusion and exclusion criteria on internet search engines. The process of the inclusion and exclusion criteria (Table 3) leads to the determination of the appropriate target population and the selection of the relevant scientific articles.

Table 3. Inclusion and exclusion criteria for the selection of relevant studies with the research question.

Sample	General population, including children, adults, elderly
Species	Person and not animal
Research time	2000–2022
Language	English
Country	Any country
Exposure	Total or hexavalent chromium contamination in drinking water. Studies qualified for inclusion if the water samples included groundwater used for drinking, as well as treated water (filtered, bottled, and tap water).
Type of study	Epidemiological studies (including case reports and case series), except systematic reviews and meta-analyses. Reports, theses, narrative or systematic reviews, conference abstracts, proceedings, and keynote materials were all excluded.

The search for scientific articles was performed on the main database PubMed (https://www.ncbi.nlm.nih.gov/, accessed on 13 March 2022), while Google Scholar (https://scholar.google.com, accessed on 13 March 2022) was used to obtain articles that were not yet archived. Additionally, we looked for potential articles included in the identified studies' reference lists. A citation manager (EndNote) was used to export the potentially eligible studies' citations, and duplicate articles were excluded.

2.4. Final Search Algorithm and Final Number of Articles

After applying the final algorithm to the PubMed database (Table 4) and the appropriate inclusion and exclusion criteria, we identified 76 scientific articles (Figure 1). Data from each study were methodologically assessed with specific methodological scales until inclusion in the systematic review. The risk of bias was assessed as unclear in the case of non-reporting of complete data.

Table 4. Developing a final search algorithm for identifying relevant studies.

(Chromium OR "hexavalent chromium") AND ("contaminated drinking water" OR "polluted drinking water" OR "contaminated potable water" OR "contaminated water" OR "polluted water") AND (carcinogenic OR carcinogenicity OR cancer * OR tumor *) Filters: Full text, English, Humans, from 2000–2022

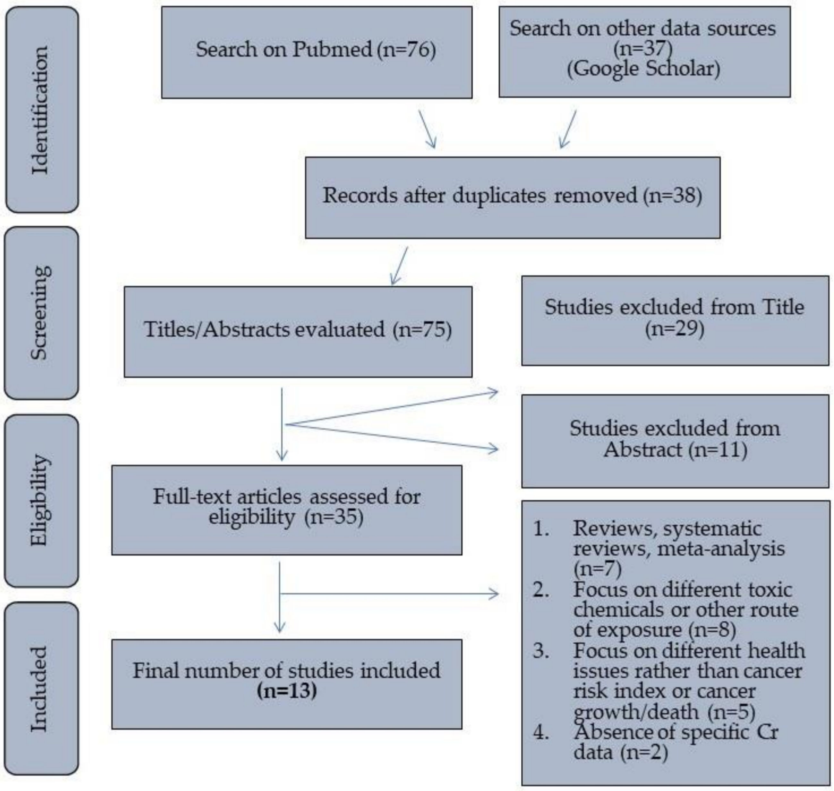

Figure 1. Flow chart of the identification and selection of eligible epidemiological studies investigating the relationship between chromium exposure and carcinogenic risk.

According to Figure 1, 113 studies were identified. Scientific articles (38 of the 113) were removed due to double references in the databases. Based on the title and the abstract, 29 and 11 scientific papers, respectively, were eliminated from our study sample because they focused on a research topic unrelated to our research question or used experimental samples, which were not relevant to the study. Specifically, studies focus primarily on the risk of cancer from arsenic, strontium, or other toxic elements' exposure rather than total or hexavalent chromium. Seven (7) studies were older systematic reviews and meta-analyses of cancer risk assessment for chromium in drinking water and human health or reviews for toxic elements, and other studies did not examine the relationship between hexavalent chromium exposure through drinking water and the development of cancer but focused on other routes of exposure, such as exposure through food and air, or other health effects with a specific sample, such as dermatological diseases.

More studies focused on chronic food exposure to aflatoxin and other various poisonous carcinogen and mutagen substances and hazardous metals, while other studies focused on the mapping of areas with high concentrations of hexavalent chromium in China's groundwater, without specific research on health effects due to human contact with potential toxic metals. Fewer articles focused on determining the concentration of chromium in water samples and cell lines with a specific experimental technique or demonstrated through experimental research that hexavalent chromium induces mutagenesis effects and cytotoxicity in human cells. However, these studies do not extend to samples of polluted environments and affected human populations. Finally, some studies focused mainly on the study of chromium concentration in water, its quality, and the intervention to remove the harmful element. A total of 13 articles were included in this systematic review for further evaluation.

3. Results

3.1. Characteristics of Main Findings

The total number of articles examined in this systematic review covers the years 2000 (January) to 2022 (November). Of the 13 included studies, 10 are epidemiological case studies (case reports or case series) evaluating cancer and non-cancer indices, while the remaining 3 are epidemiological ecological studies evaluating risk effects at a population level and not at the individual level. For each investigation, information was extracted on the study population and size, study site, total or hexavalent chromium concentration in water (surface and groundwater, drinking and tap water), and human health impacts, with emphasis on cancer.

Surface and underground waters, as well as drinking water, were sampled to determine whether they exceeded quality standards, identify the source of contamination, and quantify the level of pollution. According to Directive 98/83/EC of the Council of the European Union of 3 November 1998 (Joint Ministerial Decision Y2/2600/2001), natural and treated water, which is intended for drinking, cooking, or other domestic uses, regardless of whether it comes from a well, distribution network, bottles, or containers, is characterized as water for human consumption. Most of the studies included in the systematic review did not report the origin of the water samples, both for human consumption and recreational water. The included ecological studies were based on age, sex, and calendar years to estimate effect ratios (RR), including SMR and HI.

Data exports from the ecological studies were performed using the accounting package of Microsoft Excel, and then forest plots were created to assess the overall statistical significance of the data and report potential heterogeneity of the individual results. The studies took place in Asia, specifically in China, Iran, Pakistan, India, and Malaysia, in Africa, specifically in Ghana, and, finally, in Europe, specifically in Greece. All study areas were characterized by significant concentrations of ultramafic rocks, enriched with chromium.

From the case studies, information on cancer health risk indices (LCR, ILCR, CR, HQ, HI, HRA, DALY) was extracted. Health risk assessments are tools used to evaluate the potential health effects of exposure to environmental chemical contaminants. These risk indicators are important because they provide a way to quantify the potential health impacts of various factors, such as exposure to environmental contaminants or the burden of disease in a population. The purpose of them is to help inform public health and social awareness by providing a systematic and scientifically supported assessment of health risks.

There are several indicators used to assess these risks, including Relative Risk (RR), which measures the association between exposure and a health outcome, Standardized Mortality Rate (SMR), which compares mortality rates of a population to a reference population, Lifetime Cancer Risk (LCR), which estimates the probability of developing cancer over a lifetime, Incremental Lifetime Cancer Risk (ILCR), which measures the increase in lifetime cancer risk due to exposure, Cancer Risk (CR), which estimates the probability of developing cancer over a specified time period, Hazard Quotient (HQ), which evaluates the potential risk to human health from exposure to a specific chemical, Hazard Index (HI), which measures overall risk from exposure to multiple chemicals, Health Risk Assessment (HRA), which takes into account multiple routes of exposure and both acute and chronic effects, Disability-Adjusted Life Year (DALY), which measures the overall impact of a disease on a population by considering death and reduced quality of life, and Chronic Daily Intake Index (CDI), which measures chronic exposure to a chemical. These indicators provide a comprehensive approach to assess the potential health impacts of exposure to environmental contaminants.

3.2. Characteristics of Participants

The systematic review focused on the general population, regardless of gender, age, and occupation. However, the age and susceptibility of certain groups of the population are believed to be noteworthy for exposure to carcinogenic elements. More specifically, childhood and adolescence are considered, as the likelihood of malignancy in these age groups is based on specific characteristics (e.g., genetics) and the timing of exposure to potentially harmful environmental elements, such as chromium, is difficult to estimate. Children are generally considered more vulnerable to potentially harmful chemicals than adults due to increased exposure rates per unit weight as well as immature metabolism, immunological response, and other developmental factors [44]. Several of the studies included in the review were conducted on a population of children, which introduced significant bias to the overall result.

3.3. Relationship between the Prevalence of Cancer and Chromium Exposure from Drinking Water

The first ecological study [45] presents mortality rates from all cancers, including stomach and lung cancers, for a remarkable population sample in Liaoning Province, China, which was previously studied by Zhang and Li [35]. Researchers in Liaoning Province, China, noticed in 1987 that communities with hexavalent chromium-contaminated drinking water had higher all-cancer death rates, stomach cancer, and lung cancer between 1970 and 1978 than the general population [31]. The effect ratios (RR) and confidence intervals (CI) for death rates from hexavalent chromium-exposed (5) and non-exposed (4) areas were calculated for the period 1970–1978. The age-adjusted rates of stomach and lung cancer were calculated by multiplying the unadjusted rates by the age-adjustment effect ratios for all cancers. The death rate for all cancers was determined to be notably higher in the chromium-exposed area compared to the uncontaminated area (RR 1.13, 95% CI 0.86–1.46) and the entire province (RR 1.23, 95% CI 0.97–1.53). The mortality rate for stomach cancer was higher in exposed areas than in unexposed areas (RR 1.82, 95% CI 1.11–2.91) and across the province (RR 1.69, 95% CI 1.12–2.44). Lung cancer death rates were found to be slightly higher in chromium-contaminated areas than in the rest of the province (RR = 1.15, 95% CI 0.62–2.07) and slightly higher in non-exposed areas. The forest plots (Figure 2) provide results of Rate Ratios obtained from the ecological study (see details in Tables 5–8) [45].

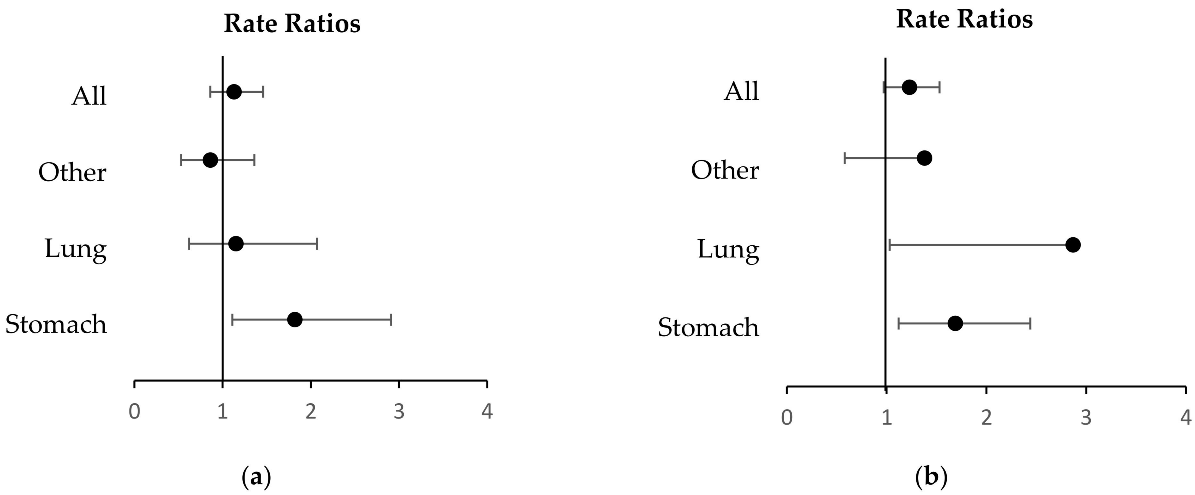

Figure 2. Forest plot with Rate Ratios for comparison: (**a**) study regions with Cr (VI) in drinking water and study regions without Cr (VI) in drinking water; (**b**) study regions with Cr (VI) in drinking water and Liaoning Province. An RR = 1.0 indicates equal rates in the two groups. An RR > 1.0 indicates an increased risk for the group in the numerator. An RR < 1.0 indicates a decreased risk for the group in the numerator.

Table 5. Main characteristics of the selected case studies included in the systematic review.

Reference	Study Location	Population (Sample Size)	Exposure (Water Supply and Other Exposure Measures)	Outcome Measure
[46]	China, Hucan	70 children	1. Human behavior pattern survey data collection. 2. A plastic bottle that had been Lacid-washed contained a total of 20 tap water samples. 3. Two more tap water samples were taken from the school's two different classrooms.	Calculated cancerous and non-cancerous health disorders (HI, HQ, ILCR).
[47]	Iran, Birjand	Total: 235,590 (3–10 years, 11–20 years, and 21–72 years)	Collection of 18 well water samples (72 samples).	1. Calculated cancerous and non-cancerous health disorders (HI, HQ). 2. Calculated Monte Carlo simulation and sensitivity analysis.
[48]	India, Ropar wetland	Children (under 18) and adults (over 18)	Collected 36 groundwater samples (18 samples during each season).	Calculated cancerous and non-cancerous health disorders (CDI, HI, HQ, CR).
[49]	Pakistan, Faisalabad Punjab	3.2 million	1. A total of 48 drinking water samples were collected from tap water and hand pumps. 2. A total of 37 surface water samples were collected from the Chenab River.	Calculated cancerous and non-cancerous health disorders (HQ, CR).
[50]	Asia, Langat River Basin, Malaysia	The Langat River Basin has 1,494,865 households	Collected water samples from each of the four points in the supply chain for drinking water.	1. Calculated cancerous and non-cancerous health disorders (CDI, HI, HQ, CR, LCR). 2. A survey of 402 households with a questionnaire.
[51]	Africa, Ghana, Lake Bosomtwe	Children and adults	Collected 30 water samples from Lake Bosomtwe.	Calculated cancerous and non-cancerous health disorders (HI, HQ, CR).
[52]	Pakistan, Muslim Bagh	20,000 Afghan refugees	The study area produced three different types of water samples: mine, karez, and digged well.	1. Collection of blood samples. 2. Collection of self-reported questionnaire survey. 3. Calculated cancerous and non-cancerous health disorders (CDI, HQ, CR). 4. Calculated indices such as Igeo, EF, and pollution parameters for soil analysis (PLI, PER, Cf, Ei). 5. The indices were calculated using the examined body weight and intake of water from different sources.
[53]	Iran	Total: 83 million (31 provinces divided into 5 regions)	Collected 8000 drinking water samples.	Calculated cancerous and non-cancerous health disorders (CDI, HI, HQ, CR, ILCR) and DALY.
[54]	Iran, Saravan	Iran, Saravan	A total of 89 underground water supplies.	Calculated non-cancerous health disorders (CDI, HQ).
[55]	China, Hanyuan		Collected 96 drinking water samples.	Calculated non-cancerous health disorders (HQ, HI, CR).

GS: Geology Survey of Pakistan, EF: Enrichment factor, Igeo: Geochemical index, PLI: potential loading index, PER: potential ecological risk, Cf: contamination factor, Ei: heavy metal single risk factor, CDI (mg/kg/day): Chronic Dietary intake, HQ: Non-cancer Hazard Quotient, HI: Hazard Index, CR: Cancer Risk, LCR: Carcinogenic Lifetime Cancer Risk, ILCR: Incremental Lifetime Cancer Risk, DALY: Disability-Adjusted Life Year, SMR: Standardized Mortality Ratio, RR: Rate Ratio, RR: Relative Risk, CI: Confidence interval.

Table 6. Main characteristics of the selected ecological studies included in the systematic review.

Reference	Study Location	Population (Sample Size)	Exposure (Water Supply and Other Exposure Measures)	Outcome Measure
[45]	China, Liaoning Province, Jinzhou City	A total of 9 areas (divided to 5 exposed and to 4 unexposed areas)	Collected water samples from 5 exposed areas.	1. Calcualted the mortality rate for estimated person-years at risk using population census data. 2. Calculated SMR and RR for all cancer types, and the CI.
[56]	China, Liaoning Province, Jinzhou City	A total of 4 areas without hexavalent chromium contamination in drinking water.	Information from a previous study for the five areas exposed to hexavalent chromium.	1. Based on data from an earlier study, cancer deaths per person-years at risk 2. Calculated RR. 3. Trends in dose response in villages exposed to hexavalent chromium via water.
[7]	Greece, Oinofyta Municipality	A total of 5842 permanent and legal residents registered in the Municipality's records from 1999 to 2009.	Three sets of hexavalent chromium measurements in water: 1. (2007 November–2008 February) and (2007 November–2008 February)/35 samples >10 g/L (maximum concentration of 156 g/L). 2. (2008 September–2008 December) and (2008 September–2008 December)/3 samples: 41–53 g/L. 3. (2007 Jul–2010 Jul) and (2007 Jul–2010 Jul)/13 samples > 10 g/L (maximum 51 g/L). 4. Recent measurements (July 2009–July 2010) indicated lower levels (0.01–1.53 g/L).	1. Calculated standardized mortality ratios by sex, age, and calendar year (SMR). 2. Calculated adjusting for age and sex and the CI.

SMR: Standardized Mortality Ratio, RR: Rate Ratio, RR: Relative Risk, CI: Confidence interval.

Table 7. Results and conclusions of the selected case studies included in the systematic review.

Reference	Results	Conclusion
[46]	1. The drinking water was safe. 2. Cr ingestion was mostly responsible for the non-cancer risk. 3. HI at the 75th percentile <1.	The cancer health risk of the study population is considered negligible through exposure to chromium in drinking water.
[47]	1. Cr(VI): 0.28 to 132.34 g/L, with an average of 21.306 34.68 g/L. 2. A total of 83.33% of the samples for 15 wells had concentrations < WHO standard, while 16.66% of the samples for 3 wells had concentrations > WHO standard. 3. The 95th percentile total HQ value is greater than 1 (both children and adolescent age groups). 4. Children > Teens > Adults is how chromium's non-carcinogenic risk is distributed among the three age groups in the study area.	The amount of chromium in groundwater for skin contact and drinking contact is the most important variable impacting the risk of non-carcinogenicity in children and adolescents.
[48]	1. Cr > 0.05 mg/L in 50% of samples taken during the summer and all samples taken during the winter. 2. Cr CDIs were higher in children than in adults. 3. Cr CDIs were higher in both children and adults during the winter season. 4. HQ > 1.00 for Cr in the winter season for children (1.99) and adults (1.54). The HQ values for Cr for children (1.03) are greater than 1.00 in the summer season, but less than 1.00 in the winter season.	Study population has a high risk of developing cancer.
[49]	1. The drinking water was deemed of poor quality. 2. The HQ values of chromium in drinking water ((2.13, 3.22) were very close to the threshold limit (HQ > 1) in both adults and children.	Chromium levels in drinking water exceeded the acceptable limit. In adults, chromium posed a high risk of carcinogenicity.
[50]	1. Max concentration of Cr: 12.2×10^{-4} mg/L. 2. Cr in the basin's supply water: 0.37×10^{-3} mg/L. 3. HQ for Cr; Treated water: t: 7.670, p: 8.77×10^{-8} for 2015.River water: t: 16.83, p: 3.81×10^{-34} for 2015, t: 22.41, p: 5.84×10^{-54} for 2020. Tap water: t: 11.64, p: 5×10^{-15} for 2015. Filtration water: t: 9.35, p: 4.12×10^{-12} for 2015. 4. CR for Cr; Treated water: t: 7.670, p: 8.77×10^{-8} for 2015.River water: t:16.83, p: 3.81×10^{-34} for 2015, t: 22.41, p:5.84×10^{-54} for 2020.Tap water: t: 11.64, p: 5×10^{-15}. Filitration water: t: 9.35, p: 4.12×10^{-12}.	1. The level of Cr in the water was within the acceptable range for consumption. 2. No health risks are associated with consuming Cr through household water filtration. 3. The LCR index of Cr ingestion via household filtration water was within the acceptable range.
[51]	1. Cr: 0.0032 mg/L. Dissolved Cr was statistically significant at p: 0.05 (F1.59 = 7.905, $p = 0.007$). 2. Overall chromium: 0.0004 to 0.023 mg/L, with a mean and standard deviation of 0.0032 0.001 mg/L, while all water samples < WHO limit. 3. Cr had a Relative Risk (HI) of 0.27%. 4. The HQ values for oral and dermal Cr exposure in children and adults <1.	The cancer risk estimates were lower than the USEPA's chromium cancer risk range. Cr was determined to be of natural origin by PCA and cluster analysis.

Table 7. *Cont.*

Reference	Results	Conclusion
[52]	1. Only 2% were aware of heavy metals, and about 5% were aware that Cr plants might also pollute the environment in the area. 2. A total of 3% responded that prevalent diseases in the area are due to contaminated water. 3. The Cr in drinking water: 13,530 ppb. 4. The HQ: Cr 5.7–19 in the main group, while the control group's HQ values are Cr 0.0035. The HQ values for all of the metals studied indicate that inhalation is the most common route of exposure for both children and adults, followed by ingestion and dermal contact. 5. Cr's CDI in water: 0.086–0.29. The users of mine water had the highest values and those of open-dug well users had the lowest values. 6. In blood data, the HQ and CDI values of blood samples are within safe limits for various groups.	Significant metal contamination, especially chromium, was detected in the research area's drinking water and soil. Inhalation is the most favorable method of transmission for Cr, which poses a serious risk of cancer in both children and adults.
[53]	1. Cr: 12.1 g/L, < WHO limits. 2. Max Cr: 19.8 g/L (Region 5) and low Cr: 1.4 g/L (Region 1). 3. At the national level, Cr had 16.0% of the HQs. 4. The average ILCR for Cr at the national level was 2.05×10^{-5}. 5. Incidence, mortality, death rate, DALYs, and DALY rate of cancer associated with chromium exposure through drinking water were determined to be 0.11 at the national level (0.09–0.13). Deaths accounted for approximately 96% of the attributable DALY. 6. Chromium concentrations in water are still mostly related to lung and stomach cancer.	The average level of chromium in the study population's drinking water is considerably lower than the national standards established for the purity of that water.
[54]	1. Cr: 0.49 to 20 (g/L), < WHO limits. 2. The mean HQ due to Cr: 0.0143, 0.0186, 0.0143, and 0.0112 for infants, children, teenagers, and adults, respectively. The HQ was lower than allowed.	Ingestion of Cr (drinking water) exposure does not increase the risk of non-carcinogenic health risks.
[55]	1. The Cr (VI) met the standards of Chinese standards for drinking water quality. 2. Adults have a greater risk of carcinogenesis. The Cr(VI) contributes significantly at 10.97%. 3. The contribution of Cr(VI) is relatively significant, with the maximum estimate of the total carcinogenic risk for adults at 93.84%.	There is a risk of hexavalent chromium in the water of the study area. Despite this, the values of the element are within the permissible values for the quality of drinking water.

GS: Geology Survey of Pakistan, EF: Enrichment factor, Igeo: Geochemical index, PLI: potential loading index, PER: potential ecological risk, Cf: contamination factor, Ei: heavy metal single risk factor, CDI (mg/kg/day): Chronic Dietary Intake, HQ: Non-cancer Hazard Quotient, HI: Hazard Index, CR: Cancer Risk, LCR: Carcinogenic Lifetime Cancer Risk, ILCR: Incremental Lifetime Cancer Risk, DALY: Disability-Adjusted Life Year, SMR: Standardized Mortality Ratio, RR: Rate Ratio, RR: Relative Risk, CI: Confidence interval, PCA: Principal component analysis.

Table 8. Results and conclusions of the selected ecological studies included in the systematic review.

Reference	Results	Conclusion
[45]	1. Cr (VI) >20 mg/L. 2. The mortality rate for all cancers (5 study regions with hexavalent chromium in water) was lower than the mortality rate for all cancers (4 combined study regions without hexavalent chromium in water) (RR = 1.13; 95% CI 0.86–1.46). 3. The overall cancer mortality rate was slightly higher in comparison to the province as a whole (1.23; 0.97–1.53). 4. Stomach cancer mortality was significantly higher in regions with contaminated water than in regions without contaminated water (1.82; 1.11–2.91) and across the province (1.82;1.11–2.91) (1.69; 1.12–2.44). 5. Lung cancer mortality was slightly higher in the exposed study regions (1.15; 0.62–2.07), but significantly higher in the province as a whole (1.78; 1.03–2.87). 6. Mortality from other cancers was not increased when compared with either the unexposed study regions (0.86; 0.53–1.36) or the entire province (0.92; 0.58–1.38).	1. Higher cancer mortality rates in exposed areas. 2. Other types of cancer mortality (except stomach and lung cancer) did not increase in the exposed areas. 3. A noteworthy link exists between drinking water exposure to hexavalent chromium and mortality from stomach cancer.
[56]	1. Group B has a higher death rate from stomach cancer and a lower death rate from lung cancer. 2. Lower death rates from stomach cancer in group A, but higher death rates from lung cancer and all other types of cancer. 3. The RR rates between groups B and C were not statistically significant. 4. Death rates for all cancer types were significantly compared between groups A and C. 5. Group B has a higher rate of stomach cancer death and a lower rate of lung cancer death. 6. Trends in dose–response relationships did not show any statistically significant correlations.	Groups A, B, and C have significantly different age-adjusted and unadjusted cancer mortality rates regardless of chromium hexavalent exposure.
[7]	1. The total was 474 deaths (SMR 97.9, 95% CI 89.3–107.1). 2. Cancer-related deaths numbered 118 (SMR 113.6, 95% CI 94.1–136.1). 3. SMR for lung, primary liver, and genital cancer deaths were statistically significant (*p*: 0.047, SMR 145.1, CI 100.5–202.8, *p*: 0.001, SMR 1104.2, CI 405.2–2403.3, *p*: 0.001, SMR 2141.5, CI 54.2–11931.5, *p*: 0.091). 4. For the year 2009, the SMR for all cancer-related deaths was statistically significant (SMR 193, CI 114–304, *p*: 0.015).	High levels of hexavalent chromium in drinking water are considered to be potential human carcinogens.

SMR: Standardized Mortality ratio, RR: Rate Ratio, RR: Relative Risk, CI: Confidence interval.

Comparing the mortality rates in three different regions produced different results for a similar demographic population in China's Liaoning Province [56]. The first group relates to the TangHezi industrial area, where the Jinzhou Alloy Plant factory was located, where hexavalent chromium was not present in the water. Groups B (3 villages) and C (5 villages) are rural areas near the urban-industrial area (group A), with the former not contaminated and the latter contaminated with hexavalent chromium. TangHeZi had a much lower stomach cancer rate and a higher lung cancer rate than agricultural villages, both upgradient and downgradient of the alloy plant. Researchers concluded that the risk of mortality for all cancers is not significantly higher in hexavalent chromium-exposed populations, even though mortality rates in contaminated and non-contaminated areas are similar [56]. For stomach cancer, the B/A ratio is 1.70, 95% CI 1.00, 2.89, $p = 0.05$, while the C/A ratio is 2.07, 95% CI 1.5, 3.44, $p = 0.005$. The B/A ratio for lung cancer is significant (RR = 0.45, 95% CI 0.22, 0.94, $p = 0.03$). There was no evidence of a dose–response relationship between the Cr (VI) concentration in well water either for stomach cancer or for lung cancer. The Forest plot (Figure 3) presents the summary statistics for Relative Risks among the three groups.

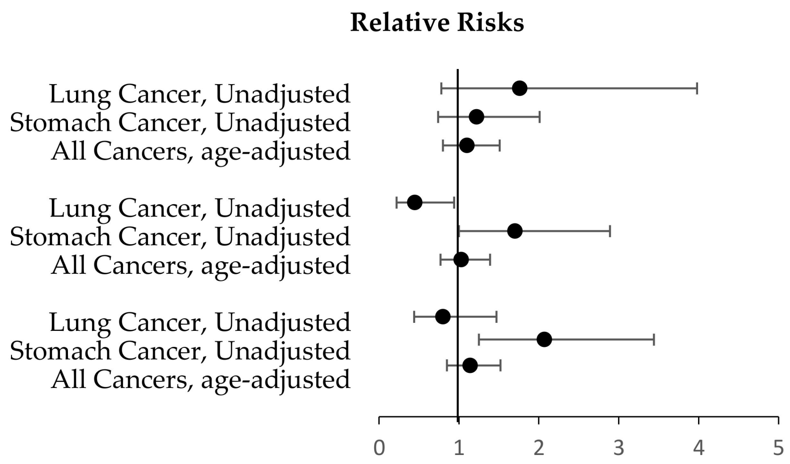

Figure 3. Forest plot with Relative Risks for comparisons of the cancer death rates in an industrial town (Group A), three agricultural villages (Group B), and five agricultural villages (Group C) for each group (RR). An RR = 1.0 indicates identical risk among the two groups. An RR > 1.0 indicates an increased risk for the group in the numerator. An RR < 1.0 indicates a decreased risk for the exposed group.

A similar study in Oinofyta, Greece, from 1999 to 2009, discovered 500 industries that produced industrial waste, and indicated the SMR for various cancers classified by the ICD-9 system in a permanent population (5842) over 11 years [7]. Cancer is responsible for one out of every four deaths, most of which occur between 20 and 39, with no gender differences. Except for 2009 (SMR = 193, 95% CI 114–304, $p = 0.015$), the SMR index for all cancer deaths slightly increased but not statistically (SMR = 114, 95% CI 94–136, $p > 0.05$) (Figures 4–6). SMR is a key marker for liver, lung, and urogenital cancers. Lung cancer, kidney cancer, and other genitourinary organ cancers among women all had statistically significantly higher SMRs. Total cancer, lung cancer, and stomach cancer all had higher mortality rates. Both males and females demonstrated statistically significant SMR for primary liver cancer (Figure 4). High SMR values were noted, but without statistical significance, for several cancer types, including cancers of the lip, oral cavity and pharynx, stomach, female colon, female breast, prostate, and leukemia (Figures 5 and 6). The mortality rate from liver cancer is considered significant in the population exposed to hexavalent chromium in drinking water.

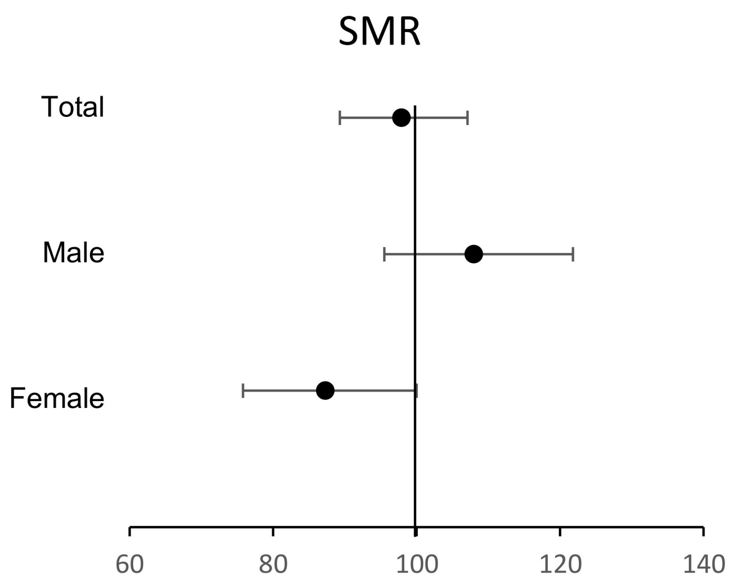

Figure 4. Forest plot of observed total deaths stratified by gender and cancer type (SMR). An SMR < 100 indicates fewer than expected deaths. An SMR = 100 indicates observed deaths equal expected deaths. An SMR > 100 indicates there were excess deaths.

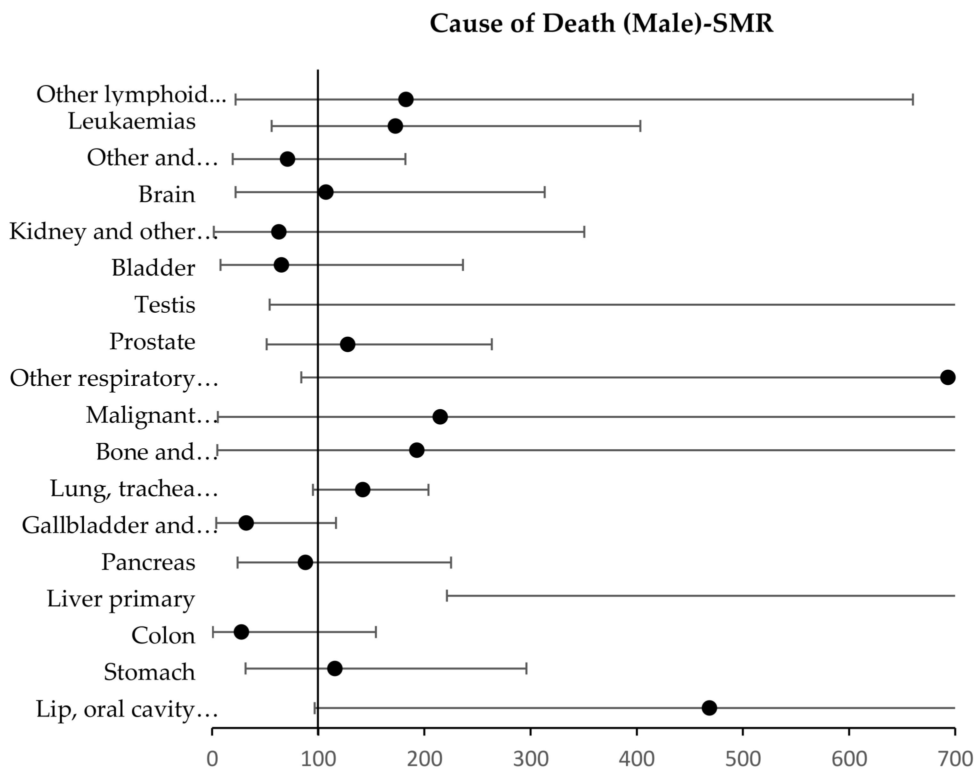

Figure 5. Forest plot of observed male deaths by cancer type (SMR). An SMR < 100 indicates fewer than expected deaths. An SMR = 100 indicates observed deaths equal expected deaths. An SMR > 100 indicates there were excess deaths.

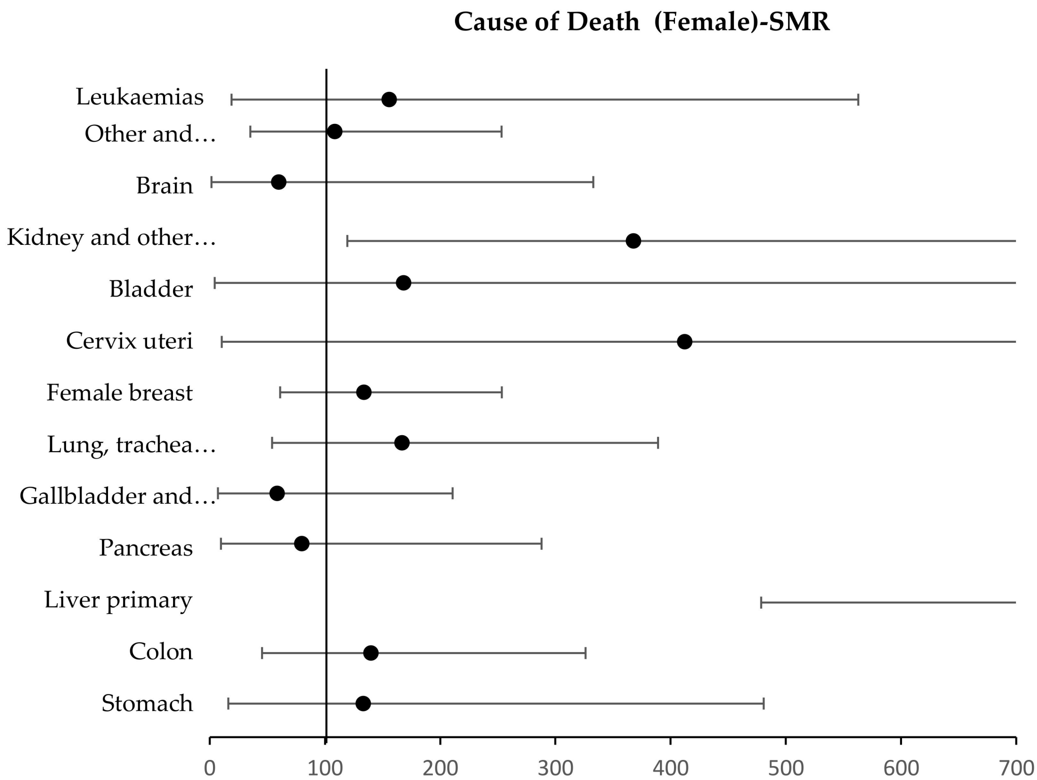

Figure 6. Forest plot of observed female deaths by cancer type (SMR). An SMR < 100 indicates fewer than expected deaths. An SMR = 100 indicates observed deaths equal expected deaths. An SMR > 100 indicates there were excess deaths.

Another study examined the quantification of the cumulative concentration of 12 metals, including chromium, in water and other exposure media (such as food, PM10, soil/dust) in Okanagan, China, in a sample of children [46]. Indices were calculated and assessed for cancer and non-cancer lifetime risk (HQ, HI, ILCR), and the contribution of each route of exposure through different routes is given by the indices (average daily dose via inhalation—ADDinhale, average daily dose via ingestion—ADDingest, and average daily dose via dermal contact—ADDdermal). By measuring the ADD for each of these exposure routes, scientists can better understand the potential health effects of a substance and develop appropriate risk management strategies to protect human health and the environment.

Overall, the quality of the drinking water analyzed was considered safe for the population exposed to it, since the total concentrations of metals were within the acceptable limits defined by the National Drinking Water Quality Standard (GB 5749-2006). GB 5749-2006 is China's National Drinking Water Quality Standard, which is a set of standards that sets permissible limits for various pollutants, including chromium, in drinking water to ensure its safety for human consumption. The drinking water was considered safe for the study population, as the chromium content in the tap water had mean values of 6.67 μg/L, 25%, 6.16 μg/L, 75%, and 7.19 μg/L. The study found that the mean value of chromium content in the tap water was 6.67 μg/L. The values of 25% and 75% indicate the range of chromium content that 25% and 75% of the tap water samples fell within, respectively. Specifically, the statement says that 25% of the tap water samples had a chromium content of 6.16 μg/L or lower, and 75% of the tap water samples had a chromium content of 7.19 μg/L or lower. Although chromium ingestion, via drinking water consumption, was responsible for the overall carcinogenic risk, the contribution to the non-cancer risk index was to a greater extent from chromium inhalation (HI > 1 even at the 25th percentile). However, the overall ILCR was about 100 times above the permissible limit even at the 25th percentile, creating a high concern for potential cancer risks in the study area's children due to exposure through drinking water consumption.

The total chromium concentrations in drinking water supply wells were examined in Birjand, Iran, in children, adolescents, and adults for more than two years [47]. The study focused on how chromium concentration changed over time and space, with samples collected from the south side of the study area exhibiting the highest concentration. The estimated daily intake through ingestion absorption (EDIing) index and the estimated daily intake through dermal absorption (EDIderm) index were quantified, with the first being significantly higher. The USEPA's non-carcinogenic risk assessment indicators (HQ, HI) were also evaluated. For the entire study population, the HQ value for the 95th percentile is greater than 1, whereas the children's population is classified as high risk. In the case of using water for drinking, with a high concentration of chromium, it is necessary to reduce its concentration to the permitted limits.

Similarly, a recent study in the Ropar Wetland, Punjab, India, examined the health risks of toxic metals' exposure, including total chromium, in adults and children in both summer and winter [48]. The CDI was established, which was critical for chromium. Non-carcinogenic health risk indicators (HQ, HI > 1) for adults and children, as well as the CR, were identified. In 50% of the samples collected during the summer season and all the samples collected during the winter season, the chromium concentration was above the allowed limit of 0.05 mg/L. The rise in these indices indicates that rising chromium concentrations in groundwater increases cancer risk, especially in children. One factor could be their low body weight. Furthermore, this susceptible population group is more sensitive in winter (HQ: 1.99 and HI: 10.11).

In the city of Punjab, Faisalabad, Pakistan, researchers assessed the quality of surface and drinking water (Water Quality Index—WQI, Surface Water Quality—SAR, and Magnesium Absorption Ratio—MAR) and estimated the potential risk to human health, both in adults and in children, with an emphasis on carcinogenesis due to exposure to potential toxic elements, including chromium (HQ, HI, ADD, CR) [49]. Chromium values in drinking water ranged between 0.002–0.01 mg/L, while concentrations in surface water ranged between 0.11–0.4 mg/L. Chromium HQ values (2.13, 3.22) were very close to the threshold (HQ > 1) in both adults and corresponding children. In surface water samples, chromium (3.20) had concentrations higher than the threshold established for cancer. Cancer index values were higher for the child population compared to the adult population. The drinking water quality of the study area is considered poor, which is associated with increased human carcinogenesis.

The association between the ingestion of toxic metals, including chromium, through drinking water and potential human carcinogenic risk was extended in the Langat River Basin, Malaysia [50]. Water samples were collected (river water, water treatment plant (WTP), domestic water, (HH), tap water, and filtered water). Human health risk was assessed by calculating the chronic daily chromium intake, non-carcinogenic risk quotient, and carcinogenic risk index, according to chromium ingestion through drinking water (CDI, HQ, LCR). The average chromium concentration was within the maximum permissible limit for drinking water quality, according to the Ministry of Health Malaysia (MOH), World Health Organization (WHO), and European Commission (EC). The mean dissolved chromium concentration in the water supply basin (0.37×10^{-3} +/− 0.21×10^{-3} mg/L) was below the recommended maximum drinking water quality limit (0.5 mg/L). Because the HQ for chromium was significantly below the permissible limit in 2015 and 2020, consuming chromium through residential filtered water does not constitute a health risk. Similarly, the LCR value of chromium ingestion via domestic filtered water was within the safe limit in 2015 and 2020. Although chromium concentrations are within safe limits in the Langat basin, a high concentration of the metal has been found in domestic water (tap water), specifically because the water supply pipeline has been contaminated.

The water quality of Lake Bosomtwe, Ghana, was assessed for the health risk and cancer and non-cancer index for oral and dermal exposure to potential toxic elements, including chromium, in children and adults (ADDingest, ADDdermal, HQ, HI, CR) [51]. Total chromium concentration ranged from <0.0004 to 0.023 mg/L, with a mean and standard deviation of 0.0032 $\pm$ 0.001 mg/L. However, dissolved chromium levels were not detected. All samples of total chromium were under the 0.05 mg/L permissible limit defined by the WHO. The estimated average daily dose via oral consumption (ADDoral) for total chromium for the target groups (ADDoral 3.84 $\times$ 10^{-7} for children, ADDoral 8.22 $\times$ 10^{-7} mg/kg/day for adults) was within their respective RfDoral thresholds (oral reference dose of metal—RfDoral 3.00 $\times$ 10^{-3} mg/L). Similarly, the estimated ADDdermal values for total chromium for the target groups (ADDdermal 1.01 $\times$ 10^{-8} for children, ADDdermal 1.72 $\times$ 10^{-8} mg/kg/day for adults) were within their respective RfDoral thresholds (RfDoral 7.50 $\times$ 10^{-4} mg/L). Research that has already been conducted shows that drinking water enriched with metals has much higher health risks compared with skin contact [57]. The HQ for chromium was rated less than unity (HQ < 1) (non-carcinogenic risk HQ 7.67 $\times$ 10^{-4} for children, HQ 1.64 $\times$ 10^{-3} for adults). The HQ values for all potential exposures, whether oral or dermal, were combined to determine the HI because the population was exposed to a lot of toxic metals. A child's HI value was 0.82 (HI < 1), which indicates that they are unlikely to encounter non-carcinogenic health impacts. The relative risk contributions of chromium to the risk index are 0.27% for children and 0.35% for adults. The cancer risk estimate was within the limits set by the USEPA for cancer (7.67 $\times$ 10^{-4} for children and 1.64 $\times$ 10^{-3} for adults). From the PCA and cluster analysis for the metals, it is not shown that the origin of chromium is due to natural processes.

The degree of carcinogenicity due to exposure to potential hazardous metals including chromium in drinking water was assessed at Iran's national and regional levels [55]. They calculated the carcinogenic and non-carcinogenic indices (HRA, CDI, HQ, DALY, ILCR). The concentration of chromium in drinking water was well below the upper limits (12.1 µg/L), with the highest concentration reaching 19.8 µg/L and the lowest at 0.6 µg/L. The total HQ was determined to be 0.45, the total ILCR 2.05 $\times$ 10^{-5}, and the contribution of Cr exposure to the disease-related burden was 19.3%. The contribution of chromium to the total HQ at the national level was 16.0%. Overall, the burden of disease attributable to exposure to potential toxic metals including chromium through drinking water consumption was poor.

In the city of Saravan, Iran, the content of three potential toxic metals, including chromium, was examined in groundwater samples used for drinking water, irrigation, and industrial purposes [54]. They calculated only the non-cancer index to evaluate human health effects in infants, children, adolescents, and adults (HQ, CDI). Chromium concentration ranged between 0.49 and 20 µg/L, below the WHO guideline of 50 µg/L. The mean serum non-cancer index due to chromium exposure was less than 1 (0.0112–0.0186). Specifically, the mean HQs due to chromium exposure for infants, children, adolescents, and adults were 0.0143, 0.0186, 0.0143, and 0.0112, respectively. All age groups had HQ levels that were below 1. The HQ is insignificant in infants, children, teenagers, and adults, according to the simulation data (CD: 95%). Therefore, chromium exposure through ingested drinking water does not raise the risk of carcinogenic health problems.

Researchers conducted a risk assessment of human health in Hanyuan, China, by collecting drinking water samples and analyzing 10 chemicals, including Cr (VI). Gastrointestinal absorption factors and cancer and non-cancer indices (HQ, HI, CR) were calculated for both adults and children [55]. The researchers concluded that the carcinogenic risk for adults and the cumulative contribution of Cr (VI) exceeded 95%. In contrast to the non-carcinogenic risk, which was determined to be negligible (0.1%), adults are at a higher risk of developing cancer, with a considerable contribution from Cr (VI) at a rate of 10.97%. The concentration of Cr (VI) in drinking water was 0.002 µg, within the limits set by the WHO and China's water sanitation. Even when the drinking water quality complies with established requirements, there is still a possibility for health risks.

Potential causes of disease prevalence in the general population in Pakistan's Baluchistan region were investigated near a chromite mining plant [52]. For toxic metals analysis, samples of drinking water, soil, and human blood were taken from exposed and unexposed populations. The CDI and HQ indices were calculated. The concentration of the four toxic metals in the water samples increased in the following order: Pb, Co = Ni, Cr. The concentration of chromium in drinking water ranged from 1990 to 13,530 ppb, which is significantly above the WHO's limit [18]. It can therefore be concluded that the area's drinking water is unsuitable for human consumption, primarily because of the high percentage of chromium in the studied sample. The assessment of carcinogenic and non-carcinogenic risks to human health demonstrated that both children and adults are at high risk. The group of industrial workers who had direct contact through mining and drank well water had the maximum concentrations of chromium. The lowest concentrations were found in a group of people who lived near the mine and ingested both filtered and unfiltered drinking water. The calculated CDI and HQ values for chromium in children and adults were higher than the health risk levels (less than 1 or equal to 1). The data showed that the drinking water in the area was becoming unsuitable for consumption due to high chromium concentrations. The important thing that was found was that the local population has no consciousness of the risks of toxic metal contamination. Only 2% of the study population knew that hazardous metals, including chromium, could cause environmental pollution, while only 3% knew that the diseases that exist in the area were due to contaminated water.

3.4. Critical Methodological Quality Assessment and Limitations of Systematic Review

The application of critical appraisal guidelines to evaluate the validity of research findings has become a well-established technique in medical science, encouraging the use of evidence-based practice. The systematic review consisted of non-randomized controlled trials and case reports, also known as case studies, while no clinical studies were found during the systematic search. The Newcastle Ottawa Scale (NOS) and the National Institutes of Health Quality Assessment Tool (NIH) were two extensive approaches used to evaluate the methodological quality of the research taken into consideration and included in the final review. In total, the 3 ecological studies were reviewed and evaluated with the NOS scale (Table 9), and the other 10 studies were evaluated with the NIH scale (Table 10) [58].

Table 9. Assessment of methodological quality of non-randomized controlled trials (type: Ecological studies), according to the adapted NOS [46].

References	Selection				Comparability		Outcome		Total Quality Score
	Representativeness of Exposed Cohort	Sample Size	Ascertainment of Exposure	Non Respondents	Adjust for the Most Important Risk Factors	Adjust for Other Risk Factors	Assessment of Outcome	Statistical Test	
[45]	1	1	1	0	1	1	1	1	7
[56]	1	1	1	1	1	0	1	1	7
[7]	1	1	1	0	1	0	1	1	6

Methodological quality classification based on total score: <5, low quality; 5–7, moderate quality; >7, high quality.

Table 10. Assessment of methodological quality of case series/case reports (type: Case studies), according to the adapted NIH quality assessment tool [49].

Reference	NIH Quality Assessment Tool-Criteria									
	Q'1	Q'2	Q'3	Q'4	Q'5	Q'6	Q'7	Q'8	Q'9	Total Quality Score
[46]	1	1	1	1	1	1	1	1	1	9
[47]	1	1	0	0	1	1	1	1	1	7
[48]	1	1	0	0	1	1	1	1	1	7
[49]	1	1	0	0	0	1	1	1	1	6
[50]	0	1	1	1	0	2	0	0	1	8

Table 10. *Cont.*

Reference	NIH Quality Assessment Tool-Criteria									
	Q'1	Q'2	Q'3	Q'4	Q'5	Q'6	Q'7	Q'8	Q'9	Total Quality Score
[51]	1	1	0	0	1	1	1	1	1	7
[52]	1	1	1	1	1	1	1	1	1	9
[53]	1	1	0	1	0	1	0	1	1	6
[54]	1	1	1	1	1	1	1	1	1	9
[55]	1	0	0	0	1	0	1	1	1	5

Question 1: Research question clearly stated, Question 2: Study population clearly defined, Question 3: Participation rate of eligible persons at least 50%, Question 4: Uniform eligibility criteria across all participants, Question 5: Sample size justification, Question 6: Evaluating different levels of exposure, Question 7: Independent variables clearly defined and implemented consistently, Question 8: Were statistical methods well-described and bias considered, Question 9: Were outcome measures clearly defined and results well-described. Methodological quality classification based on total score: Good: 7–9 criteria, Fair: 4–6 criteria, Poor: 0–3 criteria.

The NOS quality scale, suitable for assessing the methodological design of cohort studies and patient-control studies, as well as the modified NOS scale for assessing cross-sectional and ecological studies [59,60], uses a system rating with stars to evaluate three parameters in each study, the study population (selection of populations of each group-selection of study groups), the comparison between the selected groups (comparison of research groups), and the presenting of the and the presenting of the results' health coefficients (exposure or outcome). Studies completing a total score <5 are assessed as low quality, between 5 and 7 are assessed as moderate quality, and >7 as high quality [61]. In this systematic review, the epidemiological ecological studies are characterized by moderate to high methodological quality.

Similar to the NOS scale, the NIH scale approach consists of 10 risk-of-bias questions or limits (except for 4 questions which are unique for cohort studies) for evaluating validity of the case studies. The questions relate to the study of population and groups, sample size, exposure and outcome, levels of exposure and outcome, and adjustment for potential confounders. Studies with scores 0–3 and 4–6 are determined to have high or probably high risk of bias, respectively, and studies with scores 7–9 are determined to have low or probably low risk of bias [62]. Epidemiological case studies are characterized by low to high methodological quality.

Our systematic review includes research studies from around the world and assumes the evaluation of epidemiological factors. It covers a wide range of data sources that indicate a positive correlation between total chromium in drinking water and human carcinogenicity risk, creating a huge risk. However, the systematic review has significant limitations.

Despite conducting a thorough search of well-established databases and careful cross-referencing, the possibility of missing a relevant study cannot be eliminated. Furthermore, the systematic review methodology has limitations such as research search, data selection, and publication biases. The researcher's selection error and personal perception create significant errors, despite the application of thorough methods to analyze the methodological quality of each study included in the review.

Once an epidemiologic study is completed, it is difficult to identify all the variables that may confound the validity of the results. Most epidemiological studies have insufficient data on chromium exposure. Significant data on the hazardous hexavalent form of chromium are lacking, with most studies estimating total chromium. There are significant uncertainties in chromium exposure concentration measurements in water, and valid information on intensity, frequency, duration, and route of exposure is lacking. Individual outcome data, including information on cancer or death from cancer (such as type of primary or metastatic cancer), latency, and risk time, tend to be limited or incomplete. This fact adds significant error to the conclusion since the exposure–outcome relationship may be overestimated or underestimated [63]. A minority of studies have demonstrated the importance of using reliable statistical models to account for confounders.

The results of epidemiological ecological studies at the population level may not represent the corresponding relationship at the individual level [64]. An important limitation is the possibility of misclassification of the patient's cause of death or disease, because the result in both comparison groups may be due to a different cause that is not controlled for separately by the patient. Due to a lack of knowledge, it may be necessary for cancer and non-cancer human health risk indices to make calculated estimations and cautious assumptions. This means that when there are knowledge gaps, human health risk assessments tend to overstate the theoretical risk to protect the public health.

Environmental health risk evaluations also consider the most sensitive (or vulnerable) individuals of the community. This offers a "worst-case scenario" to assist in directing the best choices for reducing the dangers to human health. Human health risk assessment must be considered by the community as considering entire communities or populations. A human health risk assessment emphasizes the type and extent of past, present, and future health risks but does not typically identify specific individuals who have been exposed to a chemical, correlate chemical levels estimated in individuals or groups of people to health outcomes, or diagnose disease, and thus should not be used in place of a discussion with a medical or health practitioner.

4. Discussion

The relationship between total or hexavalent chromium in drinking water and the risk of carcinogenesis in the general population has been the subject of much research. The findings from several studies suggest a significant positive association between the two factors, raising important questions for further research. Despite the evidence of the significant association, consistent with the type of study (ecological, case study) many questions remain unanswered due to limitations in the studies that have been conducted so far.

The high chromium concentrations in the drinking water near the industrial sector of Liaoning Province, China, prompted researchers to conduct a more comprehensive population analysis [45]. The conclusion of a higher overall cancer death rate is in line with previous research, although many questions remain unresolved due to limitations in demographic data (e.g., occupation, residence, age), which are required for more reliable conclusions.

A significant difference was revealed in the studied groups in terms of quality of life [56], which could be explained by the accessibility of health care and nutritional needs. Factors other than the presence of chromium, such as air pollution and smoking, may also contribute to cancer mortality [65,66]. Statistics on TangHeZi show a pattern and scale of cancer mortality associated with higher economic status and other urban impacts, resulting in higher lung cancer rates and lower stomach cancer rates compared with the small rural villages studied here. There were no noteworthy fatalities among the three groups studied. The Relative Risk (RR) compared between the groups should be investigated further to investigate the rural and industrial quality of life and habits to be considered more credible.

Focusing on SMR, different types of cancer (liver, lung, stomach, and genitourinary system) were detected [7]. It is assumed that everyone in the study population is a resident of the study area, that they all drink tap water, and that they all have the same socioeconomic status. The research includes both urban-industrial and rural areas. None of the study groups used had a complete medical history of underlying causes, which may increase the risk of carcinogenesis (excluding metastatic liver cancer in those who died). As a result, the cause of death may be misclassified, attributing the death to a type of cancer (e.g., liver or kidney) when another disease was the primary cause of death. The duration of monitoring in a small population sample is indicated (1999–2009). It is given that the results of a study with a longer exposure time are more objective [66].

In a child population, cancer and non-cancer lifetime risk were assessed, emphasizing the contribution of each route of exposure (ADDinhale, ADDingest, and ADDdermal) and significantly reducing the bias error for the overall result. Similarly, another study investigated the health index (HQ, HI) of total chromium exposure, with the study population divided into three groups: children, adolescents, and adults. In both studies, children are considered high risk, with low body weight being the primary measure of the study [46,47]. The daily chromium intake index, the chromium content of the location, and the low body weight all contribute to the increased HQ index.

A significant relationship was found between summer and winter climate change and total chromium levels in groundwater suitable for drinking and irrigation [48]. Similarly, in another study [47], the HQ and HI indices were evaluated, which increased during the winter season. As a result, because the concentration of chromium depends on the accumulation of a larger volume of water and its path, climatic conditions have a significant impact on it. In addition, a sampling area from large water storage basins is critical (e.g., dams). Both studies [47,48] concluded that impoundment of runoff water was required for sampling. Dietary habits in the general population, especially in children, may represent an additional source of chromium in the human body.

Case studies [49–55] evaluated the potential risk of carcinogenesis through the examination of health indicators and the quality of surface and drinking water. The collection of data for surface water and drinking water, as well as the evaluation of health indicators separately for age groups, significantly reduces the possible errors for the correlation of chromium and carcinogenesis. However, data on exposure parameters (such as concentrations of total or hexavalent chromium in drinking water and surface and groundwater, the different body weights of each age group, the consumption of drinking water, the distance from the source of exposure, etc.), and also the outcome parameters (such as the dose–response relationship, the functions, and the data applied for the underestimation of each indicator of risk as well as death), are based on statistical analyses with incomplete data.

Particular focus must be directed toward the correlation between dose and response. The human body's ability to convert hexavalent chromium (Cr (VI)) to trivalent chromium (Cr (III)) can lead to false positives in certain biomedical and chemical tests. This conversion can occur when Cr (VI) is ingested through drinking water or food and can result in an overestimation of Cr (III) or Cr (VI) levels in the body.

The conversion of Cr (VI) to Cr (III) is a redox reaction that can occur under certain conditions in the human body. Cr (VI) can be reduced to Cr (III) under physiological conditions, such as in the presence of reducing agents such as ascorbic acid (vitamin C) and other organic matter, and also through several biochemical mechanisms, including enzymatic reduction and non-enzymatic reduction via reduced glutathione or ascorbic acid. It is also important to note and pay particular attention to pH conditions, as well as time and temperature. In particular, the rate of the reduction reaction increases with time and temperature.

The assay may not be able to differentiate between the two forms of the element. This reduction can lead to false positive results and can affect the toxicity and bioavailability of hexavalent chromium in the body. It is important to note that the specific conditions under which the reduction reaction occurs in the human body may vary based on factors such as the individual's metabolic rate, exposure to reducing agents, and Cr (VI) exposure. Therefore, it is required to carefully control the conditions in these assays to prevent such interference and to ensure the accuracy and reliability of the results.

Below is an overview of the study's key results and gaps:

1. There is a significant association between exposure to total or hexavalent chromium through the oral route, specifically through the consumption of water, and human carcinogenic risk.
2. Six (6) epidemiological studies indicated a positive association between total or hexavalent chromium exposure in humans through the use or consumption of wa-

ter and carcinogenic impact. Chromium levels in the water exceeded the maximum acceptable limits, with the result that there is a high risk of carcinogenesis. The three ecological studies based on statistical data show higher mortality rates from cancer, including stomach cancer, in areas exposed to hexavalent chromium-polluted water. Seven (7) studies found a negative correlation between the two factors. The study areas were characterized by low concentrations of total or hexavalent chromium, while the carcinogenic and non-carcinogenic risk indicators did not show a significant result.

3. A total of 10 of the 13 epidemiological studies of the systematic review are characterized by high methodological quality, 2 studies by moderate methodological quality, and only 1 by low methodological quality.
4. An objective study requires more detailed information, such as the classification of socioeconomic level, the complete health history of each person, their eating habits, the rate of consumption, and the duration of exposure to the potentially toxic element. The sampling at regular intervals and at various times, the assessment of climate change, the frequent monitoring of groundwater and surface water quality, particularly near potentially affected areas, the determination of the source of drinking water intake, and the use of chemical elements are necessary for the improvement of the study.
5. The influence of groundwater on the quality of water consumed by humans has not been adequately studied. There is a lack of data regarding the hydrogeology of the affected areas.
6. There are notable differences in concentration of chromium between the populations examined in different studies, but also within the same study. Cr (VI) has the property of being reduced to Cr (III) under specific conditions, during its processing in the gastrointestinal system. Analysis of the response dosage is required.

The results of human health indices for carcinogenic risk (LCR, ILCR, CR, HQ, HRA, DALY, CDI, SMR, and Relative Risk and Rate Ratio—RR), for each study population, will be more representative if a more extensive study is conducted by collecting all the above data.

5. Conclusions

The current systematic review considers the possibility of a correlation between two variables, chromium in drinking water and carcinogenic risk. The findings of this study show that:

1. The exposure to harmful chromium and contamination of the general population significantly increases the hazard of carcinogenic and non-carcinogenic markers, and the incidence of cancer in each age group, especially in sensitive groups such as children and older people.
2. Methodological quality of epidemiological ecological studies shows a high level of reliability, while the methodological quality of epidemiological case studies shows a low to high level of reliability.
3. The degree of absorption through the gastrointestinal tract and the degree of reduction of Cr (VI)′ to Cr (III) are key factors in highlighting the risk of carcinogenesis.
4. Experts of the environment and public health should regularly monitor the presence of hexavalent chromium in surface and groundwater, as well as in drinking water supplies. In the natural environment, it is necessary to monitor it separately, effectively, and reliably from total chromium in water by reliable methods.
5. It is essential to conduct a thorough methodical examination of the geological, petrological, mineralogical, geochemical, hydrogeological, and hydrochemical properties, as well as to keep anthropogenic activities under control.

The findings of this study have many important implications for future public health practice. The proper implementation of programs for systematic monitoring and management of the quality of drinking and domestic water would ensure that all citizens have safe drinking water. The investigation of carcinogenic risk assessment and the possibility of cancer, due to other exposure sources such as airborne and dietary factors, is critical for future extensive studies.

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