Toxic chromium in water and the effects on the human body: a systematic review

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ABSTRACT

Both in developed and developing countries, there is a growing concern about the dangerous hexavalent chromium, in the consumption of drinking water. Hexavalent chromium is recognized to have a negative impact on the human body, both in the short and long term. The purpose of this study is to evaluate the relationship between hexavalent chromium in water and its impact on human health. A systematic review of the international literature is applied, according to the instructions of PRISMA protocol, in the databases PubMed and Scopus, for the years 2005–2022. The systematic literature review was conducted using inclusion and exclusion criteria, and appropriate keywords for exposure and outcome. A total of 18 studies met all inclusion criteria. Most research concludes that hexavalent chromium is a risk factor for humans, as opposed to trivalent chromium who is a protective factor. A study indicates the consumption of drinking water with high concentrations of hexavalent chromium, as a protective factor for human life, while eight of the total studies suggest hexavalent chromium as a potential risk factor. It is necessary to clarify the origin, the mode of action, and the negative impact has on human health, to create appropriate preventive and intervention measures.

Key words: drinking water, exposure, hexavalent chromium, systematic review, water pollution

HIGHLIGHTS

- Assessment of the relationship between harmful hexavalent chromium in water and human health effects (systematic review – PRISMA protocol).
- Data on hexavalent chromium from an epidemiological point of view.
- A study indicates the consumption of drinking water with high concentrations of hexavalent chromium is a protective factor for human life.
- Eight of the studies suggest hexavalent chromium as a possible risk factor.
INTRODUCTION

Water pollution is a major public health problem (WHO 2000). In both developing and developed countries, the degradation of the quality of surface and underground water, and so drinking water, raises serious concerns about human health (UNESCO 2003). Ensuring everyone’s access to safe drinking water is a necessity to protect human health. According to the World Health Organization, a large percentage of people, at least 785 million, do not have access to safe drinking water, while everyone having access to basic sanitation facilities and maintaining good hygiene could have avoided at least 2 million deaths in due time (Galal-Gorchev & Ozolins 1993; WHO 2000, 2006).

The degradation of the quality of surface and underground water is due to natural sources but also anthropogenic activities. The presence of chemical major and trace elements in higher quantities than the permitted limit in the natural environment is the outcome of anthropogenic processes (Marconi et al. 2011; Canepari et al. 2018). In other words, their primary sources of contamination are indicated by the creation of urban, domestic, and industrial waste, the use of pesticides and fertilizers on crops, and the disposal and depositing of trash in water receivers (Hammer 1986).

Any animal or human body exposed to potentially harmful materials abundant in water poses a considerable risk to his health, both in the short and long term (Ullah et al. 2009). It is argued that exposure to chromium can cause serious illness in the exposed population. Exposure factors such as the form, dose, duration, and source of chromium exposure led to a wide range of mild or acute outcomes (ATSDR 2012). According to the literature, depending on the duration and time of exposure to hexavalent chromium, exposure is classified into acute (14 days of exposure), intermediate (from 75 to 364 days of exposure), and chronic (365 days of exposure) (Shekhawat et al. 2015; Yang et al. 2020) report. Chromium can be ingested,
inhaled, or absorbed via the skin by any organism. A substantial number of studies, including experimental and non-experimental studies, methodologically design, investigate, and demonstrate the health risk of the exposed population due to environmental exposure to hexavalent chromium (ATSDR 2012).

Chromium is known to occur in nature in three main stable forms (Jiang et al. 2015), namely, metallic chromium, trivalent chromium, and hexavalent chromium. Depending on the potency and route of exposure, its degree of toxicity is determined. Trivalent chromium, found in a wide range in nature, is an essential dietary trace element for human health (NIH 2007; EFSA et al. 2010), enhances the activity of insulin, and contributes significantly to the treatment of all types of diabetes (Shanker 2019). Conversely, hexavalent chromium intake has a negative impact on human health (Pellerin & Booker 2000; Liang et al. 2021). International literature states that hexavalent chromium can be responsible for significant dysfunctions of the digestive, gastrointestinal, urinary, reproductive, respiratory, and immune systems of the human body (Pellerin & Booker 2000; ATSDR 2008, 2012).

Trivalent chromium is an essential trace element required for normal carbohydrate metabolism, is the most stable oxidation state (Greenwood & Earnshaw 1997), and presumably is the form in the food supply due to the presence of reducing substances in foods. However, in contrast to trivalent chromium, as already mentioned, hexavalent chromium is toxic and not necessary for human health. Trivalent chromium was shown to be an essential trace element by Mertz and Schwarz (1959) who observed that rats fed certain stock laboratory diets had impaired tolerance to a glucose load. This intolerance was reversed by an insulin potentiating factor that was present in brewer’s yeast, meat, and other foods. This compound was later shown to be an organic chromium complex (Scawarz & Mertz 1959). The essentiality of Cr for humans was subsequently demonstrated in 1975 (Jeejeebhoy et al. 1977). Some of the physiological functions that are known to require Cr are glucose tolerance, glucose oxidation, glucose uptake, nerve disorders, protein synthesis, and mental outlook.

Dietary trends such as consuming even larger percentages of highly processed foods that are low in Cr and the sustained intake of high levels of sucrose and other simple carbohydrates that stimulate Cr excretion may be leading to serious dietary insufficiencies of chromium in humans. Suboptimal dietary Cr may explain the decrease in tissue chromium with age and may be related to the high incidence of diabetes and cardiovascular problems in the U.S. and other developed countries whose people tend to consume large amounts of processed foods (Mathur et al. 1977). The quantity and frequency of intake should reflect on the level of functional improvement to determine the size of the chromium effect. There has not yet been any comprehensive investigation into dose-response relationships, though (Jeejeebhoy et al. 1977).

According to Venitt & Levy (1974), Nishioka (1975), and Pellerin & Booker (2000), hexavalent chromium is a poisonous, carcinogenic, and mutagenic substance. A significant number of studies demonstrate the toxicity of the hexavalent form of chromium, which is characterized by high solubility in surface and groundwater (Health Canada 2016). Human exposure to toxic chromium occurs through the oral, respiratory, or dermal route. Oral exposure, which occurs through the consumption of contaminated drinking water, is a significant risk factor for human health (ATSDR 2000, 2012). According to the research (Costa & Klein 2006), after oral exposure to hexavalent chromium, the body absorbs significantly more than trivalent chromium. However, the reducing activities of human body fluids, such as blood, saliva, gastric fluid, and liver, contribute significantly to reducing the toxicity of hexavalent chromium (DeFlora et al. 2016).

Although the number of epidemiologic studies on respiratory exposure to hexavalent chromium and the risk of lung cancer and other diseases is significantly large, the information and epidemiologic studies on the impact of hexavalent chromium through drinking water are limited. Studies that have been published in scientific journals and have examined human population samples’ exposure to hexavalent chromium through the aquifer and drinking water have frequently produced contradictory findings.

It is crucial to point out what standards and regulations have been defined for human exposure to toxic chromium. The EPA, FAO, and WHO, among other organizations, have standards that outline the permissible limit of chromium in soil and water (Table 1). However, no chromium (Cr) acceptable limits exist in wastewater (industrial applications). For public water systems, the EPA has established a 100 g/L (100 ppb) maximum contamination level for total chromium in drinking water (EPA 1999). Chromium levels in industrial wastewater must be reduced to 0.5 mg/l before being released into the environment (EPA) for public water systems (EPA 1998, 1999). Similarly, less than 0.05 mg/l of chromium should be contained in drinking water. Even at low concentrations, chromium (Cr), which has agricultural applications, is harmful and non-essential to plants (Asati et al. 2016; Minari et al. 2020). There is a reference that indicates that the recommended maximum concentration of Cr is 0.10 mg/l, according to the FAO agriculture section. The permitted limit for chromium concentrations in agricultural soils is 20 mg/kg of soil, according to additional studies (FAO/WHO 2001).
In 1993, near Hinkley, CA, Erin Brockovich first highlighted the public risk of hexavalent chromium contamination of groundwater. A non-scientific study by the Environmental Working Group (2010) found significant levels of hexavalent chromium in U.S. drinking water, highlighting the interest for further research. Reliable data for the correlation under consideration are given in the studies by Zhang & Li (1987), Beaumont et al. (2008), and Kerger et al. (2009), conducted in areas of China, reaching contradictory conclusions between them. Zhang & Li’s (1987) ecological study found increased mortality from all types of cancer, including stomach cancer, in residents of rural Liaoning, China, who consumed drinking water enriched with hexavalent chromium daily, coming from the neighboring areas where, for a long time, metallurgical activities were carried out. However, in two recent studies of the same area under consideration, it is observed that the statistical study of Beaumont et al. (2008) confirms the initial association between the two exposure and outcome factors, in contrast to the study of Kerger et al. (2009), which reaches contradictory conclusions. According to a related study conducted in the Greek region of Oinophyta by Linos et al. (2011), one in four fatalities in a community exposed to hexavalent chromium in drinking water was caused by the emergence of liver, lung, and genitourinary cancer.

Important limitations of the studies evaluating the present association include the significantly small number of observed cancer and disease events, the short duration of follow-up, the absence of control of intermediate confounding variables, and other risk factors, such as dose, source, duration of drinking, and demographic characteristics of residents (Proctor et al. 2002; Kerger et al. 2009). It is worth emphasizing that although epidemiological studies were conducted in the past, focusing on the possibility of developing cancer in humans, their results were not based on reliable data and statistics on the potential exposure, resulting in weak statistical conclusions (IARC 2012). Bearing in mind that the results, interpretations, and conclusions of previous studies are called into question, it is especially useful to reexamine the association in a timely and systematic way.

**METHODS**

For this systematic review, the PRISMA Statement for Diagnostic Test Accuracy Protocol was used as the reference guideline (Page et al. 2021). The PRISMA diagnostic method checklist includes research question hypothesis, search strategy, study types, study population definition, exposure and outcome, bias assessment, and literature review. It is worth emphasizing that a search of the ‘grey’ literature was not performed for any conference abstracts, government reports, and unpublished articles in scientific databases that investigate the topic under consideration.
The systematic review focuses on English-language contemporary scientific articles, with dates of publication of these, from 01 January 2005 to 01 April 2022 (31 December 2022). The period of publishing restriction was put in place to restrict the use of current scientific data. The systematic review excludes unpublished papers, essays, letters, book chapters, systematic reviews, and meta-analyses from earlier years. The electronic databases used to search the international scientific literature on the subject under study are PubMed and Scopus. Tables 2–4 give the characteristics of the search strategy, using MESH terms for PubMed and Scopus and the final logarithm in each search.

Conducting the systematic review is based on specific inclusion and exclusion criteria. Specifically, the studies were published in the English language, with publication dates years 2005–2022 [01 January 2005 to 01 April 2022]. Experimental and non-experimental studies are searched. Excluded are older chronological systematic reviews, studies that conduct their research in experimental animals and not with a human sample, case series, and case reports, and epidemiological studies that do not study the relationship between exposure to contaminated drinking water and human health effects.

The content of the study focuses on randomized and non-randomized controlled studies, which analyze the association of toxic chromium in drinking water and the effect on human health, emphasizing the development of cancer, disease, or death. Although the potential health effects of many chemicals in the environment are investigated and assessed using the health risk assessment (HRA) index and water quality degradation, the studies were not included in the final set of studies in the systematic review, as epidemiological studies are not included. The study sample is the general population, regardless of gender, age, and occupation. Exposure was defined as toxic chromium through drinking water, and as a result, the effects of exposure (various types of cancer, physical illness, or death) were analyzed. Air and food exposure studies are not included.

The concept of PICOS (P = Population, E = Exposure, C = Control, O = Outcome, S = Study type) was defined as follows: 
P = General population, E = Hexavalent chromium via aquifer and drinking water, C = No exposure to hexavalent chromium via aquifer and drinking water, O = Body diseases, development of various types of cancer and death, S = Patient control studies, cohort studies, cross-sectional and ecological studies (Mette 2018).

**Table 2** | Keywords for the systematic search of studies investigating the relationship between exposure to hexavalent dyes through the aquifer and drinking water and adverse effects on human health in the PubMed and Scopus databases

<table>
<thead>
<tr>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium OR hexavalent chromium OR Cr (VI) OR chrome OR chromate OR chromic</td>
</tr>
<tr>
<td>Water OR polluted water OR contaminated water OR drinking water OR potable water</td>
</tr>
<tr>
<td>Cancer OR carcinogenicity OR carcinogenic OR tumor OR neoplasm OR malignancy OR noncancer OR disease OR damage OR infection OR mutagenic OR DNA OR genetic OR toxic* OR death</td>
</tr>
<tr>
<td>Incidence OR risk OR rate OR exposure OR hazard</td>
</tr>
</tbody>
</table>

**Table 3** | Final PubMed database search algorithm

```
((chromium OR "hexavalent chromium" OR "Cr (VI)" OR chrome OR chromate OR chromic) AND (water OR "polluted water" OR "contaminated water" OR "drinking water" OR "potable water")) AND (cancer OR carcinogenicity OR carcinoma OR tumor OR neoplasm OR malignancy OR noncancer OR disease OR damage OR infection OR DNA OR genetic OR toxic* OR death)) [MeSH Terms].
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**Table 4** | Final Scopus database search algorithm

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(TITLE-ABS-KEY (chromium OR "hexavalent chromium" OR 'Cr(VI)') AND TITLE-ABS-KEY ("polluted water" OR "contaminated water" OR "drinking water" OR "potable water") AND TITLE-ABS KEY (cancer OR carcinogenicity OR carcinoma OR tumor OR neoplasm OR malignancy OR noncancer OR disease OR damage OR infection OR DNA OR genetic OR toxic* OR death)) AND KEY (incidence OR risk OR rate OR exposure OR hazard) AND PUBYEAR >2004 AND PUBYEAR <2003 AND (LIMIT-TO(SRCTYPE, 'j')) AND (LIMIT-TO (PUBSTAGE, 'final')) AND (LIMIT-TO (DOCTYPE, 'ar') OR LIMIT-TO (DOCTYPE, 're')) AN (LIMIT-TO (LANGUAGE, 'English')) AND (LIMIT-TO (EXACTKEYWORD, 'Human') OR LIMIT-TO (EXACTWORD, 'Humans') OR LIMIT-TO (EXACTKEYWORD, 'Human Health Risk Assessment')).
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RESULTS AND DISCUSSION

The search code found a total of 762 studies in the two databases. Specifically, PubMed identified 507 articles and Scopus identified 255 articles. After removing duplicate studies from the two databases, 717 studies were evaluated according to their title and abstract. Reading the titles of the original 717 studies showed that 316 did not fit the requirements for inclusion and were eliminated, while 401, 254 from PubMed and 147 from Scopus were evaluated further for their summaries. From a total of 401 studies, reading the abstract revealed that 174 studies did not concentrate on the connection between total or hexavalent chromium in water and its effects on human health. They concentrated particularly on a subject irrelevant to the research objective, the risk of cancer or sickness from exposure to other heavy metals, primarily lead and arsenic, in an animal sample.

A significant number of studies focus on environmental factors and their impact on human health, without specific reference to hexavalent chromium, on the determination of chromium concentrations in water samples and cell lines, and not on the correlation of the chromium with the development of cancer or any disease. Consequently, 227 studies were chosen for full-text analysis. After reading the whole text, 209 papers were discarded, while 18 satisfied the inclusion criteria and were included in the final evaluation. More specifically, out of 209, 27 studies are reviews or meta-analyses, 64 studies do not focus their study on total or toxic chromium or even other heavy metals, human health, and water pollution, while the rest 118 are not epidemiological studies. The HRA index is the subject of numerous studies, many of which are neither randomized nor non-randomized.

The studies are summarized and shown in the flowchart after applying the inclusion criteria and the search algorithm against each database (Table 5; Figure 1).

Characteristics of main findings

After reading the full text of each study, a total of 18 studies were included in the review (Beaumont et al. 2008; Tubek et al. 2008; Kerger et al. 2009; Linos et al. 2011; Unisa et al. 2011; Sharma et al. 2012; Coelho et al. 2013; Szakli et al. 2014; Karagiannis et al. 2015; Cárdenas-González et al. 2016; Arcega-Cabrera et al. 2017, 2018; Filler et al. 2017; Marouf et al. 2017; Herath et al. 2018; Sánchez-Díaz et al. 2018; Whitaker et al. 2020; Vogel et al. 2021). Tables 6–11 give the main characteristics of the studies included in the final review.

Country and date

All the articles studied concern the period 2008 to 2021. The studies studied took place in regions of Greece (n = 3) (Linos et al. 2011; Szakli et al. 2014; Karagiannis et al. 2015), Mexico (n = 3) (Cárdenas-González et al. 2016; Arcega-Cabrera et al. 2017, 2018), China (n = 2) (Beaumont et al. 2008; Kerger et al. 2014), India (n = 3) (Unisa et al. 2011; Sharma et al. 2012; Herath et al. 2018), the USA (n = 1) (Whitaker et al. 2020), Germany (n = 1) (Vogel et al. 2021), Finland (n = 1) (Filler et al. 2017), Poland (n = 1) (Tubek et al. 2008), Spain (n = 1) (Sánchez-Díaz et al. 2018), Portugal (n = 1) (Coelho et al. 2013), and Iraq (n = 1) (Marouf et al. 2017).

Table 5 | Positive association between exposure–outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Health impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaumont et al. (2008)</td>
<td>Increased mortality from lung and stomach cancer</td>
</tr>
<tr>
<td>Tubek et al. (2008)</td>
<td>Increased hospitalization due to arterial hypertension, psoriasis, chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Unisa et al. (2011)</td>
<td>Gallbladder diseases</td>
</tr>
<tr>
<td>Linos et al. (2011)</td>
<td>Increased mortality from cancer of the stomach, lung, kidney, and other organs of the genitourinary system</td>
</tr>
<tr>
<td>Sharma et al. (2012)</td>
<td>Problems related to the gastrointestinal and dermatological systems, high values of hematological variables</td>
</tr>
<tr>
<td>Karagiannis et al. (2015)</td>
<td>Urogenital diseases (malignant and non-malignant)</td>
</tr>
<tr>
<td>Arcega-Cabrera et al. (2017)</td>
<td>High blood concentrations</td>
</tr>
<tr>
<td>Arcega-Cabrera et al. (2018)</td>
<td>High blood concentrations</td>
</tr>
<tr>
<td>Whitaker et al. (2020)</td>
<td>Low suicide mortality</td>
</tr>
</tbody>
</table>
**Design and type study**

The majority of articles included and evaluated in this systematic review are cross-sectional studies (Unisa et al. 2011; Sharma et al. 2012; Sazakli et al. 2014; Cárdenas-González et al. 2016; Arcega-Cabrera et al. 2017, 2018; Filler et al. 2017; Herath et al. 2018; Vogel et al. 2021), ecological studies (Beaumont et al. 2008; Tubek et al. 2008; Kerger et al. 2009; Linos et al. 2011; Sánchez-Díaz et al. 2018; Whitaker et al. 2020), while the remaining two are studies of control patients (Coelho et al. 2013; Marouf et al. 2017) and one cohort study (Karagiannis et al. 2015).

**Participant characteristics**

The systematic review focused on the general population, regardless of gender, age, and occupation. All studies consisted of both women and men, aged 18–69, as well as children and adolescents, girls and boys, aged 4–17. In five studies, the study sample consisted of an adult population (Unisa et al. 2011; Sharma et al. 2012; Coelho et al. 2013; Sazakli et al. 2014; Karagiannis et al. 2015), in five studies, the study sample consisted of a child and adolescent population (Cárdenas-González et al. 2016; Arcega-Cabrera et al. 2017, 2018; Filler et al. 2017; Vogel et al. 2021), while in one study, the sample population consisted of adolescents and adults (Marouf et al. 2017). In six studies, the study population sample did not meet specific eligibility criteria (Beaumont et al. 2008; Tubek et al. 2008; Kerger et al. 2009; Linos et al. 2011; Herath et al. 2018; Sánchez-Díaz et al. 2018; Whitaker et al. 2020), while in one study, population size and characteristics were not reported (Sánchez-Díaz et al. 2018).

**Water samples – exposure**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Methodological quality</th>
<th>Country</th>
<th>Participants</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Beaumont et al. (2008)</td>
<td>Ecological study</td>
<td>Medium</td>
<td>China</td>
<td>9 study areas (5 exposed and 4 unexposed areas). No individual exposure data.</td>
<td>Sampling from the 5 exposed areas. Concentrations of hexavalent chromium in drinking water &gt;20 mg/l.</td>
<td>1. Mortality for estimated person-years at risk, according to population census data. 2. SMR, RR for all cancer types. 3. Calculation of confidence intervals (CIs).</td>
</tr>
<tr>
<td>2. Tubek et al. (2008)</td>
<td>Ecological study</td>
<td>Low</td>
<td>Poland</td>
<td>12 regions, with the study population from 44,000 to 151,000. No individual exposure data.</td>
<td>Annual content of elements in rainwater. Data from the Provincial Environmental Protection Inspection Office. Chromium concentrations range between 0.0026 and 0.0035 kg/ha yr.</td>
<td>Data from the Hospital Statistical Register of Poland. Average annual number of hospitalizations, for each disease (arterial hypertension, CPDU, psoriasis) was calculated for each region and sex separately and expressed as the number of hospitalizations per 10,000 inhabitants.</td>
</tr>
<tr>
<td>3. Kerger et al. (2009)</td>
<td>Ecological study</td>
<td>Medium</td>
<td>China</td>
<td>4 areas without contamination in hexavalent chromium. No individual exposure data.</td>
<td>Data for the 5 hexavalent chromium exposed areas from an earlier study.</td>
<td>Cancer deaths, according to person-years at risk, based on data from an earlier study (Zhang and Li 1980), relative risks (RR), and dose-response trends in villages exposed to hexavalent chromium through water.</td>
</tr>
<tr>
<td>4. Unisa et al. (2011)</td>
<td>Cross-sectional study</td>
<td>Medium</td>
<td>India</td>
<td>8,421 (3,821 men and 4,600 women)</td>
<td>Collection of water samples from tap or wells or pipes or boreholes.</td>
<td>Adjusted odds ratio (ORs) as an estimate of relative risk of GBD (GST, cholecystitis, polyps, and GBC) and confidence intervals (CIs). Ultrasound examination for GBD and GST (prevalence of gallbladder diseases and cholelithiasis).</td>
</tr>
<tr>
<td>Study</td>
<td>Type of study</td>
<td>Methodological quality</td>
<td>Country</td>
<td>Participants</td>
<td>Eligibility criteria</td>
<td>Exposure</td>
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<tr>
<td>7. Coelho et al. (2013)</td>
<td>Case-control study</td>
<td>Medium</td>
<td>Portugal</td>
<td>102: 34 persons exposed to environmental factors, 33 persons exposed due to mine work, 35 non-exposed persons</td>
<td>For non-exposed individuals: 1. People living in the villages for at least 5 years. 2. Age 18 or over. 3. Work in administrative offices.</td>
<td>No water sample data.</td>
</tr>
<tr>
<td>Study</td>
<td>Type of study</td>
<td>Methodological quality</td>
<td>Country</td>
<td>Participants</td>
<td>Eligibility criteria</td>
<td>Exposure</td>
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</tbody>
</table>
                          |               |         |         | 2. Residents of the study area for the last seven consecutive years. | 1. Drinking water samples (N = 50) and crop samples (N = 48). Examination of bottled water (N = 16).  
                          |               |         |         | 2. Database (10 years), determination of total chromium (676) and hexavalent chromium (572) of municipal drinking water. | 2. Database (10 years), determination of total chromium (676) and hexavalent chromium (572) of municipal drinking water.  
                          |               |         |         | 2. Permanent residents of the Municipality of Oinofyta, Greece. | 1. Morbidity rate for diseases related to the urinary system.  
                          |               |         |         | | 2. Unadjusted OR ratios, when focusing on the length of stay in Oinofyta and ORs when adjusting for confounders and CIs. | 2. Unadjusted OR ratios, when focusing on the length of stay in Oinofyta and ORs when adjusting for confounders and CIs. |

(Continued.)
A significant number of studies focused on collecting data on total and hexavalent chromium concentrations in water from available databases (Tubek et al. 2008; Filler et al. 2017; Sánchez-Díaz et al. 2018; Whitaker et al. 2020) or in evidence from earlier studies (Kerger et al. 2009; Sazakli et al. 2014; Karagiannis et al. 2015). At least four studies collected groundwater and surface water samples (Unisa et al. 2011; Sharma et al. 2012; Cárdenas-González et al. 2016; Herath et al. 2018), around the study areas. One (1) study was related to a bottled water sample (Sazakli et al. 2014), while in three studies, no water samples or water data were collected from other databases (Coelho et al. 2013; Marouf et al. 2017).

Outcome
In Table 5, the parameters calculated and evaluated in each study are given to estimate the degree of human health impact from the concentrations of total and hexavalent chromium in surface and groundwater, as well as in drinking water. Specifically, the parameters used are: standardized mortality ratios (SMRs) and proportional mortality ratios (PMRs), according to sex, age, calendar year, and cause-specific death, together with confidence intervals (CI – confidence interval), incidence rate (RR – rate ratio), and relative risk (RR – relative ratio), quality control (QC) and quality control quantification (LOQ), adjusted (OR – odds ratio)/non-adjusted ratios for age, occupation, place of residence, daily habits (e.g. smoking, diet), adjusted (COR) and unadjusted odds ratios (AORs) for systemic health problems in areas with hexavalent chromium (gastrointestinal, dermatological, ocular, urinary problems), the incidence reference rate (IRR) for exposed and unexposed areas.

More specifically, the measures of association contrast the frequency of a disease in one group with that of a disease in a different group (such as relative risk or relative ratio, rate ratio, odds ratio, and mortality ratio). The rate ratio (RR) indicates how frequent (or uncommon) a particular incident was among those exposed. The risk of the incident in an experimental group in comparison to that in a control group is known as the relative risk (RR). The odds ratio (OR) represents the probability of an accident in an experimental group compared with a control group. Both the rate ratio and linear relative ratio models provide an acceptable fit to the data that is simple to understand. In the majority of studies, a linear comparable rate model with highly statistically significant exposure effects was selected to describe the various types of cancer-chromium exposure-response and to determine lifetime risk after consideration of a variety of log-linear and additive relative rate forms for modeling chromium effects (Breslow 1996).

A significant number of studies assessing the association between chromium concentrations and human health determine suicide mortality rates, motor neuron disease (MND) mortality, dose-response trends for various types of cancer, the average annual number of hospitalizations for arterial hypertension, psoriasis, chronic obstructive pulmonary disease (COPD), the prevalence of gallbladder diseases and gallstones (GBD – gallbladder diseases, GBC – gallbladder cancer, and GST – gallstone), the kidney damage biomarkers in the blood (KIM-1 – kidney injury molecule and NGAL – neutrophil gelatinase-associated lipocalin) and the morbidity of the urogenital system (LUTS – lower urinary tract symptoms, BPH – Benign prostatic hyperplasia).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Methodological quality</th>
<th>Country</th>
<th>Participants</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
</table>
Blood analysis was performed [(e.g., total leukocyte count (TLC), differential leukocyte count (DLC), red blood cell count (RBC), mean body volume (MCV), and platelet count (PLT)], analysis of urine, hair and nails (hand and foot), spirometry (FEV1 – forced expiratory volume after 1 second, PEFR – peak expiratory flow rate), motor control for fitness assessment, RNA isolation and microRNAs measurement, routine clinical tests (e.g., SCr – serum creatinine, GFR – glomerular filtration rate, eGFR – estimated glomerular filtration rate, ACR – albumin creatinine ratio), and calculation of genotoxicity (TCR – T-cell receptor) and immunotoxicity.

Table 9 | Main characteristics of the selected studies of the systematic review (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Methodological quality</th>
<th>Country</th>
<th>Participants</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Marouf et al. (2017)</td>
<td>Case-control study</td>
<td>Medium</td>
<td>Iraq</td>
<td>54 = 29 patients (cancer patients) and 25 healthy.</td>
<td>The waters of the lake are an important source of electricity, they are used for irrigation purposes (fishing), for drinking water and for recreational purposes.</td>
<td>Venous blood sampling of 5 ml of patients and controls.</td>
</tr>
<tr>
<td>12. Arcega-Cabrera et al. (2017)</td>
<td>Cross-sectional study</td>
<td>Medium</td>
<td>Mexico</td>
<td>4,390 (2,190 girls and 2,200 boys)</td>
<td>Sampling and analyzes of drinking and domestic water (washing dishes and cooking).</td>
<td>Sampling of 150 ml of urine and 4 ml of blood from each participating child.</td>
</tr>
</tbody>
</table>
Specifically, 10 of the 18 studies conclude with a positive correlation between human exposure to chromium (Table 5), through the use or consumption of water and the positive or negative effect on his health, while the remaining 8 conclude with a negative correlation. Nine of the 10 studies (Beaumont et al. 2008; Tubek et al. 2008; Linos et al. 2011; Unisa et al. 2011; Sharma et al. 2012; Karagiannis et al. 2015; Arcega-Cabrera et al. 2017, 2018; Sánchez-Díaz et al. 2018) conclude a positive association, with a negative health outcome, 1 (Whitaker et al. 2020) out of 10 studies report a positive association, with a positive health outcome of the population study, while in 1 of 8 studies, chromium was described as a non-detectable element in water (Marouf et al. 2017).

Increased mortality from lung and stomach cancer was observed in areas exposed to hexavalent chromium-contaminated water (Beaumont et al. 2008). However, in the statistical analysis of the data, death rates from other types of cancer, except for

### Table 10 | Main characteristics of the selected studies of the systematic review (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Methodological quality</th>
<th>Country</th>
<th>Participants</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Herath et al. (2018)</td>
<td>Cross-sectional</td>
<td>Low</td>
<td>India</td>
<td>84 (60 endemic CDu and 24 non-endemic CDu)</td>
<td>Water sampling from wells and pipes in the study area (1,435 samples).</td>
<td>Urine sampling (84 samples), for the analysis of chromium and liver-type fatty acid-binding proteins (L-FABPs).</td>
</tr>
</tbody>
</table>
lung and stomach cancer, were not increased in the exposed areas. In a similar case, the drinking water of Oinophyta of Greece, rich in hexavalent chromium, is characterized as a possible carcinogen for humans, through the oral route (Linon et al. 2011). It should be noted that the latent period, specifically for cancer, is greater than 15 years (Howard 2014). The researchers reported that the residents of the industrial area of Oinophyta, compared with the total population of the prefecture of Viotia, show statistically increased mortality from lung cancer (SMR: 145.1, 95% CI 100.5–202.8), liver (SMR: 1,104.2, 95% CI 405.2–2,403.3) and in women, from cancer of the kidney and other organs of the genitourinary system (SMR: 367.8, 95% CI 119.4–858.3). The findings are consistent with the study by Zhang & Li (1987), where mortality rates from all types of cancer including lung and stomach cancer were higher for the hexavalent chromium-exposed population compared with the general population. Previous epidemiological and animal studies have shown that hexavalent chromium in water is a carcinogen (Sedman et al. 2006; Stout et al. 2009). However, Beaumont et al. (2008) did not take into account in the conclusion, the absence of a relationship between the dose-response data and the mortality rates, while in most studies, the collection of

### Table 11 | Main characteristics of the selected studies of the systematic review (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Methodological quality</th>
<th>Country</th>
<th>Participants</th>
<th>Eligibility criteria</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Whitaker et al. (2020)</td>
<td>Ecological study</td>
<td>Low</td>
<td>USA</td>
<td>67 counties</td>
<td>No individual exposure data.</td>
<td>Determination of chromium concentrations in drinking water at the county level and information from available databases: Safe Drinking Water Information System (SDWIS) and Consumer Confidence Reports (CCR). Total chromium levels per prefecture, calculated for the years 2005–2015. County average chromium concentration 0.0828 ± 0.1885 ppb.</td>
<td>Mortality rates due to suicide for the years 2005–2015. Data from the Alabama Department of Public Health (average suicide rate per 100,000), in each Alabama county, separately for each sex and race. Gender and race were considered as associative variables.</td>
</tr>
</tbody>
</table>

IGME, Institute of Geological and Mining Research; NOS, Newcastle Ottawa Scale Assessment; BPH, Benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; CKD, chronic kidney disease; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; PPIs, proton-pump inhibitors; SNC, standardized coefficients; TLC, total leucocyte count; DLC, differential leucocyte count; RBC, red blood cell; MCV, mean corpuscular volume; PLT, platelet; FEV1, forced expiratory volume after 1 second; MND, motor neuron disease; SDWIS, Safe Drinking Water Information System; CCRs, Consumer Confidence Reports; CAS, Chemical Abstract Service; GerES, German Environmental Survey; HBM, human biomonitoring; LOQ, limit of qualification; QC, quality control; L-FABP, liver fatty acid-binding protein; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine; ACR, albumin-creatinine ratio; GBD, gallbladder disease; GST, gallstones; GBC, gallbladder cancer; USG, ultrasound sonography test; COPD, chronic obstructive pulmonary disease; TCR, T-cell receptor; ICD-9, International Classification of Diseases, Ninth Revision, Clinical Modification; SMR, standardized mortality ratio; PMR, proportional mortality ratio; RR, rate ratio; OR, odds ratio.

It should be noted that the latent period, specifically for cancer, is greater than 15 years (Howard 2014). The researchers reported that the residents of the industrial area of Oinophyta, compared with the total population of the prefecture of Viotia, show statistically increased mortality from lung cancer (SMR: 145.1, 95% CI 100.5–202.8), liver (SMR: 1,104.2, 95% CI 405.2–2,403.3) and in women, from cancer of the kidney and other organs of the genitourinary system (SMR: 367.8, 95% CI 119.4–858.3). The findings are consistent with the study by Zhang & Li (1987), where mortality rates from all types of cancer including lung and stomach cancer were higher for the hexavalent chromium-exposed population compared with the general population. Previous epidemiological and animal studies have shown that hexavalent chromium in water is a carcinogen (Sedman et al. 2006; Stout et al. 2009). However, Beaumont et al. (2008) did not take into account in the conclusion, the absence of a relationship between the dose-response data and the mortality rates, while in most studies, the collection of
data on the duration and dose of chromium exposure is absent. The effects of toxic chromium on human health are related to the dose, duration, and type of exposure (Tchounwou et al. 2012; Shanker et al. 2019).

The study by Kerger et al. (2009) concludes with contradictory results. In five exposed villages in China, with demographically similar populations, cancer mortality rates were not associated with the degree of exposure to hexavalent chromium through drinking water. The two exposed villages, which were furthest away from the alloy plant and had the lowest water hexavalent chromium contents, had the highest cancer mortality rates. Population groups B (unexposed area) and C (exposed area) had higher stomach cancer mortality rates and relatively lower lung cancer mortality rates compared with group A (industrial area). There was no dose-response relationship seen in any of the five exposed villages. The main risk factors for developing stomach cancer are bacterial infections, radiation, alcohol, poor diet, and smoking (IARC 1994; Shibata & Parsonnet 2006).

Tubek et al. (2008) observed significant associations between chromium levels in rainwater and the frequency of hospitalization for arterial hypertension, psoriasis, and COPD, in both women and men. The concentrations of elements, including chromium, in rainwater, are a risk factor for human health and contribute to the course of the diseases studied. Concerning dermal exposure to hexavalent chromium, skin necrosis, allergic reaction, dermatitis, eczema, sensitivity, and skin ulceration have been observed (Lee et al. 1989; Pellerin & Booker 2000). However, in the international literature, no significant reports of sex-specific associations between environmental exposure to toxic metals such as chromium and COPD have been identified. Unisa et al. (2011) report a significant association between exposure to environmental factors, including chromium in surface and groundwater, used for drinking water, and the occurrence of various gallbladder diseases. In a similar study by Sánchez-Díaz et al. (2018), it was reported that environmental exposure, including chromium in water, may contribute to the etiology of the development of MND, according to the conditions, duration, and dose of exposure, which is one of the main health risk factors. Heavy metals, such as chromium, are toxic to health and health effects vary according to duration and conditions of exposure, dose, and bioavailability (Tchounwou et al. 2012).

It is not clear what causes motor neurons to stop working properly. In about 5% of cases, there is a family history of either MND or a related condition called frontotemporal dementia. In recent years, the association between the development of MND and environmental factors has been monitored significantly. MND has been associated with heavy metal exposure for more than 150 years, ever since heavy metals were found in the tissues and bodily components of MND patients (Rosen et al. 1993; Kiernan et al. 2011; Roos 2013). The heavy metals participate in a wide range of processes in various receiving environments, such as air, soil, or water. Hexavalent chromium (Cr (VI)) is a carcinogen that is found in the environment, mainly in water throughout the world and is increasingly understood to be associated with effects on the nervous system. Although heavy metals such as selenium and mercury have been widely discussed in the context of motor system degeneration, research on essential and non-essential trace elements, such as chromium, is significantly limited (Huisman et al. 2011; Kiernan et al. 2011).

The hexavalent chromium-contaminated water population of the city of Kanpur, India, showed significantly increased spirometric abnormalities, and a higher prevalence of health problems, with an emphasis on the gastrointestinal and dermatological systems, and hematological parameters outside normal limits (Sharma et al. 2012). The population exposed for a long time to hexavalent chromium through drinking water had a high tendency for urogenital diseases (malignant and non-malignant) (Karagiannis et al. 2015). In contrast, the consumption of drinking water with high concentrations of chromium is inversely related to the suicide rates of the people who lived in the study area. Long-term exposure may have a protective effect on human life, reducing the likelihood of suicide, at least in the population studied (Whitaker et al. 2020). In the literature, the association between elevated chromium concentrations in water and the protection of human life has not been demonstrated again.

The identification of potential sources of exposure to hexavalent chromium was investigated with factor analyses, based on specific groups of variables (Arcega-Cabrera et al. 2017, 2018). The first variable (chromium in household water and chromium in blood), highlights household water as a possible source of exposure (Arcega-Cabrera et al. 2017, 2018) and finds a significant positive correlation between chromium levels in household water and blood chromium (p: 0.584, p: 0.023). The second variable (contribution to drinking water) is referred to as a source of exposure, always in combination with other environmental and individual sources of exposure. Hexavalent chromium in drinking and domestic water is a potential risk factor, usually in conjunction with other causal variables (Arcega-Cabrera et al. 2017, 2018).

Three (3) studies (Cárdenas-González et al. 2016; Filler et al. 2017; Herath et al. 2018) concluded a negative correlation between chromium concentrations in water and the occurrence of kidney function disorders. High levels of hexavalent
chromium in drinking water were not the main risk factor, but the KIM-1 index may be used as an early biomarker to detect kidney toxicity and possible exposure in children (Cárdenas-González et al. 2016). In the study by Herath et al. (2018), the levels of chemical substances like chromium in urine samples from patients with CKDu were comparable to those in urine samples from patients without CKDu. As a result, there was no link between chromium levels and the prevalence of CKDu. It is known worldwide that hypertension, obesity, and diabetes are the main causes of CKDu (Jha et al. 2013). Despite the elevated chromium levels seen in the study population, according to Filler et al. (2017), it does not seem to be the main cause of pediatric CKDu patients. When comparing the map to patient residences and high chromium concentrations, no exact match was found. Of the 36 patients, 28 did not reside in a region where the drinking water was contaminated with dangerous substances. As a result, both the environmental influences (water intake) and the patient’s decreased renal function (low eGFR) are emphasized.

Increased concentrations of heavy metals in water, and by extension in the blood of exposed people, may contribute to the occurrence and development of carcinogenesis (Marouf et al. 2017). Regarding the blood metal concentrations, there were noticeable differences between cancer patients and non-cancer individuals. However, there were no chromium concentration differences between the two groups’ blood. Finally, in the studies of Sazakli et al. (2014) and Vogel et al. (2021), no positive correlation was observed between the two exposure–outcome factors and human health burden. Therefore, hexavalent chromium is not a risk factor for the study population.

**Study limitations**

It is important to emphasize that in the present systematic review, key limitations are involved that must be addressed to assess potential bias. However, when the epidemiological study is completed, it is difficult to identify all the parameters that jeopardize the validity of its results. The degree of bias for the completeness and accuracy of observational data, such as personal information (health status and history), obtained from the population under study is related to the type and design of the research, databases, and methodological evaluation of quality (Greenland & Morgenstern 1989). The validity of the results presupposes neutralization of possible systematic errors and control of risk factors.

Most of the epidemiological studies evaluated have insufficient data on hexavalent chromium exposure. Most of the reported research employs data as surrogates for quantifiable exposure, such as occupation, industrial activities, home, and school addresses, or distance from the probable source of exposure. Uncertainties arise in the exposure measurements of hexavalent chromium in water, and valid information on the intensity, frequency, duration, and route of exposure is lacking.

Individual outcome data, including information about the study disease or cause of death (such as type of primary or metastatic cancer), latency period, risk-disease time, and many samples, tend to be constrained or incomplete, making it more difficult to identify potential effects and producing an inadequate outcome (Checkoway et al. 1989). The quality and validity of the results, through the correct distribution and assessment of confounding factors, among the comparable groups, are related to the limitation of the effect of confounding, which can overestimate or underestimate the exposure–outcome relationship. A few studies have shown the value of using reliable statistical models to account for confounders.

The ecological studies of mortality and morbidity included in the systematic review do not collect information on exposure on an individual basis, presenting results on the exposure–outcome relationship exclusively at the population level. In this case, the risk of the ‘ecological fallacy’ may arise. Results at the aggregate level may not represent an analogous relationship at the individual level (Comstock 1980). An important limitation is the possibility of misclassification of the cause of death, because the outcome in both comparison groups might be due to a different cause that’s not controlled through death certificates.

In general, in the conduct of case-control studies, the collection of exposure data is done using questionnaires or personal interviews, or a review of previous health history records, increasing the problem of information recall. Participants, patients, and controls may misremember or not remember important personal information, or even conceal information, related to the confounding factors, exposure, and outcome under study, thereby strengthening or weakening the association of the two factors.

The review focused on nine cross-sectional studies, of which five (Cárdenas-González et al. 2016; Arcega-Cabrera et al. 2017, 2018; Filler et al. 2017; Vogel et al. 2021) focused on childhood-adolescence and the remaining four (Unisa et al. 2011; Sharma et al. 2012; Sazakli et al. 2014; Herath et al. 2018) focused on the general population, regardless of gender. Childhood and adolescence are considered a high-risk group, since the possibility of malignancy and chronic diseases is
related to specific factors (e.g. genetic factors), making it difficult to determine the time of exposure to the risk factor (hexavalent chromium).

CONCLUSION
From this review, the relationship between toxic chromium and its effect on the human body highlights the following health problems: stomach, lung, kidney, and general urinary cancer, dermatological disorders, hematological disorders, immune, genitourinary, and gastrointestinal system. Especially gallbladder diseases, chronic renal failure, COPD, arterial hypertension, and MND. Therefore, the knowledge about the existence of these diseases contributes to the systematic control of their possible association with chromium toxicity.

The optimal installation of programs for systematic monitoring and control of the quality of drinking and domestic water will ensure safe water for every citizen. The occurrence of hexavalent chromium in surface and groundwater, as well as in drinking water supplies, should be regularly monitored by environmental and public health professionals. Different approaches, such as the application of laboratory studies (e.g. major and trace element leachability testing), are used to identify, assess, and analyze hazardous toxic substances such as chromium in water and the human body. It is necessary to carry out extensive and frequent samplings in industrial and urban areas, which may burden the natural environment and health, and to draw up programs for the timely restoration of polluted waters based on them. Consequently, for the effective strategy of monitoring and removing the risk factor, the knowledge, understanding, and use of thorough methods of the disciplines, especially hydrogeology, chemistry-geochemistry, biology, and environmental health, are required.

The limitations mentioned in each type of study investigated indicate the importance of knowing and processing qualitative and quantitative data, not only for the environment but also for the citizen. Conducting studies at regular intervals, collecting sufficient water samples, and collecting data with targeted biological indicators of human health of the population, even with a thorough examination of confounding factors, which may affect the association being studied, will provide important information on the effect of chromium toxicity. The results of the current systematic review raise new issues that need for a more thorough information extraction process and the planning of future, more in-depth studies that will focus on enhancing drinking water quality, ensuring a healthy environment, and enhancing human quality.

DATA AVAILABILITY STATEMENT
All relevant data are available from an online repository or repositories.

CONFLICT OF INTEREST
The authors declare there is no conflict.

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