Journal of Water & Health

IWA PUBLISHING

Journal of Water and Health Vol 21 No 2, 205 doi: 10.2166/wh.2022.214

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

Maria-Nefeli Georgaki * and Marianna Charalambous

Department of Health Sciences, School of Sciences, European University Cyprus, Nicosia, Cyprus
*Corresponding author. E-mail: nefgeor@gmail.com

M-NG, 0000-0002-1829-4735

ABSTRACT

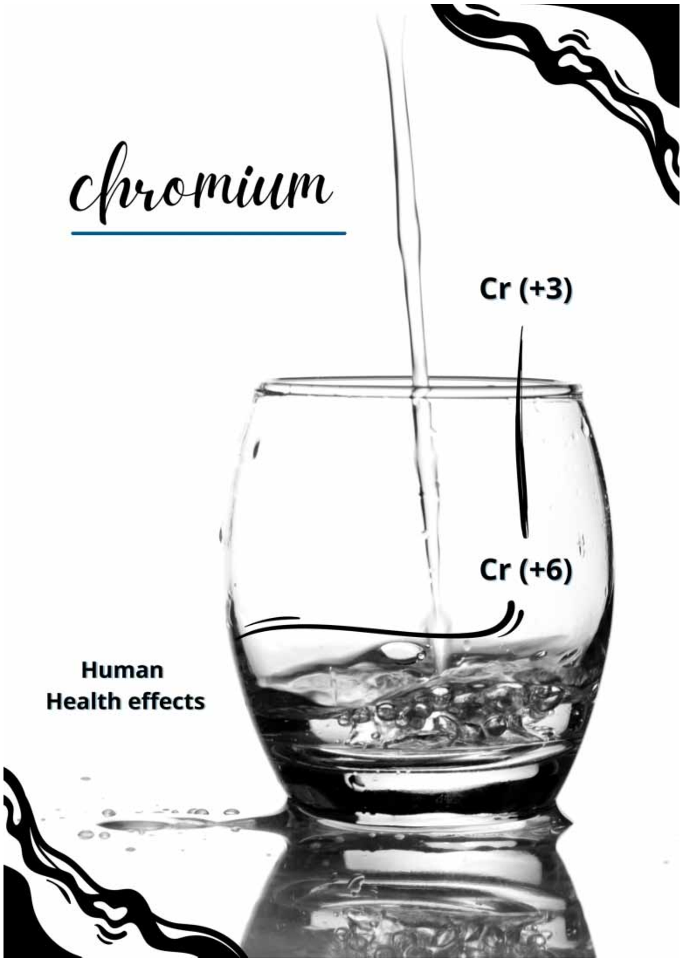
Both in developed and developing countries, there is a growing concern about the dangerous hexavalent chromium, in the consumption of drinking water. Hexavalent chromium is recognized to have a negative impact on the human body, both in the short and long term. The purpose of this study is to evaluate 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.

GRAPHICAL ABSTRACT



INTRODUCTION

Water pollution is a major public health problem (World Health Organization (WHO) & UNICEF 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; World Health Organization (WHO) & UNICEF 2000; WHO 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 & Venkateswarlu 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 Scawarz & Mertz (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 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

Table 1 | Regulations and guidelines for chromium (WHO 1990)

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	10 μg/m^3 as Cr	Advisory; TWA to avoid carcinogenic risk from insoluble Cr (VI) compounds
		50 μg/m^3 as Cr	TWA for water-soluble Cr (VI) compounds
		500 μg/m^3 as Cr	TWA for chromium metal and Cr (III) compounds
National Institute for Occupational Safety and Health	Air: workplace	1 μg/m^3 as Cr	Advisory; TWA (10-hour) for chromic acid and all Cr (VI) compounds
		500 μg/m^3 as Cr	Advisory; TWA (10-hour) for chromium metal and Cr (II) and Cr (III) compounds
Occupational Safety and Health Administration	Air: workplace	5 μg/m^3 as Cr	Regulation; PEL for chromic acid and chromates (8-h TWA)
		500 μg/m^3 as Cr	PEL for Cr (II) and Cr (III) compounds (8-h TWA)
		1,000 μg/m^3 as Cr	PEL for chromium metal and insoluble compounds (8-h TWA)
Environmental Protection Agency	Air: environment	Not available	Chromium is listed as a hazardous pollutant
	Drinking water	100 μg/L	Regulation; current MCL for total chromium

TWA (time-weighted average): TWA concentration for a normal workday and a 40-h workweek to which nearly all workers may be repeatedly exposed.

PEL (permissible exposure limit): highest level of chromium in air, to which a worker may be exposed, averaged over an 8-h workday.

MCL (maximum contaminant level) enforceable level for drinking water.

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

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

Chromium OR hexavalent chromium OR Cr (VI) OR chrome OR chromate OR chromic
Water OR polluted water OR contaminated water OR drinking water OR potable water
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
Incidence OR risk OR rate OR exposure OR hazard

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 carcinogenic OR tumor OR neoplasm OR malignancy OR noncancer OR disease OR damage OR infection OR DNA OR genetic OR toxic* OR death)) [MeSH Terms].

Table 4 | Final Scopus database search algorithm

(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 carcinogenic 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 (LIMI-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’)).

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 (Eriksen & Frandsen 2018).

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 (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; Sazakli *et al.* 2014; Karagiannis *et al.* 2015; Cárdenas-González *et al.* 2016; Arcega-Cabrera *et al.* 2017, 2018; Filler *et al.* 2017; Marouf 2018; Herath *et al.* 2018; Sánchez-Díaz *et al.* 2018; Whitaker *et al.* 2020; Vogel *et al.* 2021). Table 5 gives 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; Sazakli *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.* 2009), 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 2018).

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 2018) 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

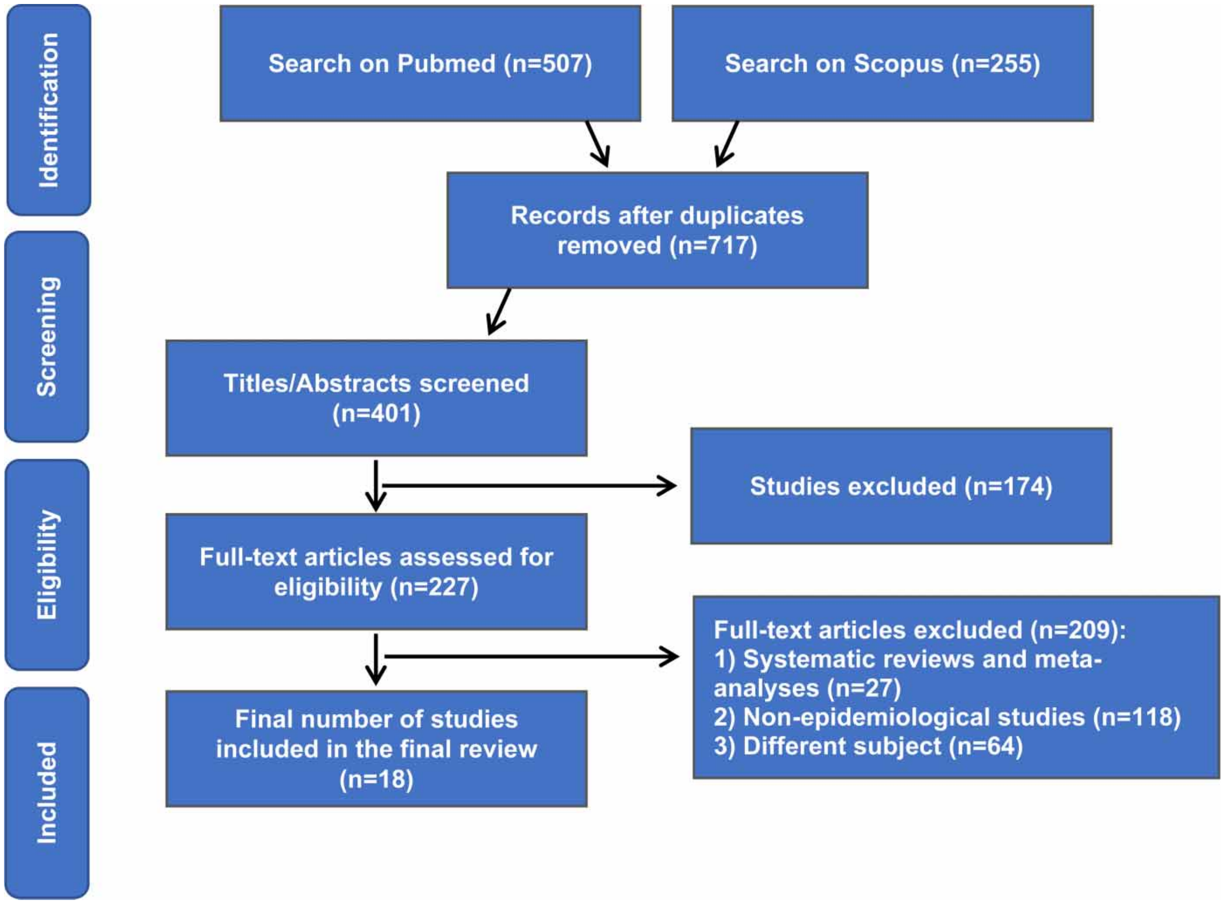


Figure 1 | Flowchart illustrating the results of the systematic review search of strategy (Moher *et al.* 2009).

consisted of adolescents and adults (Marouf 2018). 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

Most studies collected drinking water samples (Beaumont *et al.* 2008; Linos *et al.* 2011; Sazakli *et al.* 2014; Cárdenas-González *et al.* 2016; Arcega-Cabrera *et al.* 2017, 2018; Vogel *et al.* 2021) and domestic water (Cárdenas-González *et al.* 2016; Arcega-Cabrera *et al.* 2017, 2018). 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 2018).

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

Table 5 | Main characteristics of the selected studies of the systematic review

Study	Type of study	Methodological quality	Country	Participants		Exposure	Outcome
				Number	Eligibility criteria		
1. Beaumont *et al.* (2008)	Ecological study	Medium	China	9 study areas (5 exposed and 4 unexposed areas).	No individual exposure data.	Sampling from the 5 exposed areas. Concentrations of hexavalent chromium in drinking water >20 mg/l.	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).
2. Tubek *et al.* (2008)	Ecological study	Low	Poland	12 regions, with the study population from 44,000 to 151,000.	No individual exposure data.	Annual content of elements in rainwater. Data from the Provincial Environmental Protection Inspection Office. Chromium concentrations range between 0.0026 and 0035 kg/ha yr.	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.
3. Kerger *et al.* (2009)	Ecological study	Medium	China	4 areas without contamination in hexavalent chromium.	No individual exposure data.	Data for the 5 hexavalent chromium exposed areas from an earlier study.	Cancer deaths, according to person-years at risk, based on data from an earlier study (Zhang & Li 1980), relative risks (RR), and dose-response trends in villages exposed to hexavalent chromium through water.
4. Unisa *et al.* (2011)	Cross-sectional study	Medium	India	8,421 (3,821 men and 4,600 women)	1. Age >30 years. 2. The villages of an area are divided into 3 layers. 60 villages in each layer. In each village, the population was measured and each person over the age of 30 was selected or	Collection of water samples from tap or wells or pipes or boreholes.	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

(*Continued.*)

Table 5 | Continued

Study	Type of study	Methodological quality	Country	Participants: Number	Participants: Eligibility criteria	Exposure	Outcome
					not for ultrasound examination. 3. Only confirmed GBD diseases.		gallbladder diseases and cholelithiasis).
5. Linos *et al.* (2011)	Ecological study	Medium	Greece	5842	Permanent residents of the Municipality of Oinofyta, Greece, and legal residents registered in the Municipality's records, during the period 1999–2009.	3 sets of measurements of hexavalent chromium in water: 1. (2007 November–2008 February) 35 samples >10 μg/L (max 156 μg/L. 2. (2008 September–2008 December) 3 samples 41–53 μg/L. 3. (2007 July–2010 July) 13 samples >10 μg/L (max 51 μg/L). 4. Recent measurement (2009 July–2010 July), lower levels observed (<0.01–1.53 μg/L).	Standardized mortality ratios by sex, age, and calendar year (SMR), cause-specific mortality ratios (PMR), adjusted for age and sex. Calculation of confidence intervals (CIs).
6. Sharma *et al.* (2012)	Cross-sectional study	High	India	416 (186 exposed and 230 not exposed)	1. General population, residents of Kanpur, India for at least 1 year. 2. Persons aged 18 years. 3. Of Asian Indian origin. 4. They do not drink bottled water. 5. No assessment of their health status.	Groundwater collection and estimation of hexavalent chromium. Extremely high concentrations of hexavalent chromium, 390 times higher than the permissible limit.	1. Spirometric analysis, blood analysis, health questionnaires. Blood sampling 2 ml. 2. Adjusted (COR) and unadjusted odds ratios (AOR) (prevalence for systemic health problems in hexavalent chromium-contaminated areas). Calculation of CIs.
7. Coelho *et al.* (2013)	Case-control study	Medium	Portugal	102: 34 persons exposed to environmental factors, 33 persons exposed due to mine work, 35 non-exposed persons	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	No water sample data.	Sampling of blood, urine, hair, fingernails, and toenails as biomarkers of internal concentration of elements. Genotoxicity and immunotoxicity were evaluated.
		High	Greece	304	1. 25–69 years old. 2. Residents of the study	1. Drinking water samples (N=50) and crop samples	Physical examination and neurological examinations.

(*Continued.*)

Table 5 | Continued

Study	Type of study	Methodological quality	Country	Participants: Number	Participants: Eligibility criteria	Exposure	Outcome
8. Sazakli *et al.* (2014)	Cross-sectional study				area for the last seven consecutive years.	(*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. 3. Personal dose of chromium exposure through drinking water (water analyzes and questionnaire data). 4. Annual exposure dose.	Sampling of total chromium concentrations in blood and hair of study participants (hematological, biochemical, inflammatory, and neurological parameters).
9. Karagiannis *et al.* (2015)	Cohort study	High	Greece	1,811 (962 men and 849 women)	1. Average age 48.6 years. 2. Permanent residents of the Municipality of Oinofyta, Greece.	The measurements of chemical elements in drinking water: Municipality of Oinophyta, IGME and Department of Geology and Geoenvironment – EKPA. High concentrations of chromium, in 2007 to 2008 (>156 μg/L), while in the years 2009–2010 lower concentrations of the element are observed (<0.01–1.53 μg/L). No measurements of hexavalent chromium in drinking water were performed in parallel with our study.	All participants were asked through a questionnaire about personal information. 1. Morbidity rate for diseases related to the urinary system. 2. Unadjusted OR ratios, when focusing on the length of stay of the population in Inofyta and ORs when adjusting for confounders and CIs.
10. Cárdenas-González *et al.* (2016)	Cross-sectional study	Medium	Mexico	83 (36 girls and 47 boys)	1. Children aged 5–12 years. 2. Non-stop accommodation in the Villa de Reyes area.	Sampling and analysis of chromium in drinking and household water from 63 individuals and water sampling from three different depths of the local system.	Blood and urine sampling (KIM-1, NGAL, SCr). RNA isolation and measurement of microRNAs. Routine clinical trials eGFR, ACR. Calculation of confidence intervals (GM).
11. Marouf (2018)		Medium	Iraq		1. Residents of Darbandikhan and Kalar	The waters of the lake are an important source of	

(*Continued.*)

Table 5 | Continued

Study	Type of study	Methodological quality	Country	Participants: Number	Participants: Eligibility criteria	Exposure	Outcome
	Case-control study			54=29 patients (cancer patients) and 25 healthy.	district. Admission to Hiwa Oncology Center in Sulaimani City 2. Controls are healthy individuals from the same area, matched for age and caste. 3. Mean age of patients (54.3 ± 14.8 years) and for controls (51.1 ± 22.8 years).	electricity, they are used for irrigation purposes (fishing), for drinking water and for recreational purposes.	Venous blood sampling of 5 ml of patients and controls.
12. Arcega-Cabrera *et al.* (2017)	Cross-sectional study	Medium	Mexico	4,390 (2,190 girls and 2,200 boys)	1. Between 6 and 9 years of age. 2. Lives in Ticul for at least 3 years. 3. They come from low- and middle-class households. 4. Maya or Mestizo origin. 5. Clinically healthy at the time of the study. 6. Parents/guardians have signed a consent form.	Sampling and analyzes of drinking and domestic water (washing dishes and cooking).	Sampling of 150 ml of urine and 4 ml of blood from each participating child.
13. Filler *et al.* (2017)	Cross-sectional study	Medium	Finland	36 patients (22 boys and 16 girls)	1. Children and adolescents aged 4–18 years. 2. Sufferers of CKD (Stages 1–5). 3. Kidney transplant and eGFR $< 90 ml/min/1.73\ m^2$	Chromium levels in drinking water, from the Government of Ontario Provincial Water Quality Monitoring Network for the year 2014. Chromium levels in the water ranged between 0.0099 and 4.32 μg/L.	Calculation of eGFR, blood plasma chromium (creatinine and cystatin C).
14. Herath *et al.* (2018)	Cross-sectional study	Low	India	84 (60 endemic CDu and 24 non-endemic CDu)	No individual exposure data.	Water sampling from wells and pipes in the study area (1,435 samples).	Urine sampling (84 samples), for the analysis of chromium and liver-type fatty acid-binding proteins (L-FABPs).
15. Arcega-Cabrera *et al.* (2018)	Cross-sectional study	Low	Mexico	32 (17 girls and 15 boys).	1. Children aged 6–9 years. 2. They have lived in Merida for at least 3 years. 3. They come from low-	Sampling and analyzes of drinking and domestic water (washing dishes and cooking).	Sampling of 150 ml of urine and 4 ml of blood for each participating child.

(*Continued.*)

Table 5 | Continued

Study	Type of study	Methodological quality	Country	Participants: Number	Participants: Eligibility criteria	Exposure	Outcome
					and middle-class households. 4. Clinically healthy at the time the study was conducted.		
16. Sánchez-Díaz *et al.* (2018)	Ecological study	Low	Spain	No data.	No data.	Sites with high levels of chromium from the European Pollutant Leaching and Transfer Register (2007–2015). Exposed and non-exposed municipalities were defined. The exposure is defined as the distance of 20 km.	MND death data from the Spanish National Mortality Registry-Annual Death Registry (2007–2016). SMRs and CIs, the mortality ratios for the exposed and unexposed areas (IRRs) (incidence reference rates).
17. Whitaker *et al.* (2020)	Ecological study	Low	USA	67 counties	No individual exposure data.	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.	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.
18. Vogel *et al.* (2021)	Cross-sectional study	Medium	Germany	2,294	1. Children–teenagers aged 3–17 years. 2. Of German origin.	Sampling and analysis of chromium in drinking water.	Blood and urine sampling. Quantitative Quality Control (LQC) (Internal/External Quality Control-QC). Confidence intervals are calculated. (GM).

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; SRC, 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; RR, relative risk; CI, confidence interval; OR, odds ratio.

(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).

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.

Exposure–outcome association

Specifically, 10 of the 18 studies conclude with a positive correlation between human exposure to chromium (Table 6), 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,

Table 6 | Exposure-outcome association

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

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 2018).

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 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 (Linos *et al.* 2011). It should be noted that the latent period, specifically for cancer, is greater than 15 years (Allott *et al.* 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 & Venkateswarlu 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: 0.384, 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' 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 2018). 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 is 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 included in the paper or its Supplementary Information.

CONFLICT OF INTEREST

The authors declare there is no conflict.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) 2008 *What Are the Physiologic Effects of Chromium Exposure?* Chromium Toxicity. Available from: https://www.atsdr.cdc.gov/csem/chromium/docs/chromium.pdf (accessed 9 November 2022).

Agency for Toxic Substances and Disease Registry (ATSDR) 2012 *Toxicological Profile for Chromium*. U.S. Department of Health, and Human Services, Public Health Service. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp7.pdf (accessed 10 July 2022).

Allott, E. H., Howard, L. E., Cooperberg, M. R., Kane, C. J., Aronson, W. J., Terris, M. K., Amling, C. L. & Freedland, S. J. 2014 Serum lipid profile and risk of prostate cancer recurrence: results from the SEARCH database. *Cancer Epidemiology, Biomarkers & Prevention* **23** (11), 2349–2356.

Arcega-Cabrera, F., Fargher, L., Quesadas-Rojas, M., Moo-Puc, R., Oceguera-Vargas, I., Noreña-Barroso, E., Yáñez-Estrada, L., Alvarado, J., González, L., Pérez-Herrera, N. & Pérez-Medina, S. 2017 Water consumption as source of arsenic, chromium, and mercury in children living in Rural Yucatan, Mexico: blood and urine levels. *Bulletin of Environmental Contamination and Toxicology* **99** (4), 452–459.

Arcega-Cabrera, F., Fargher, L., Quesadas-Rojas, M., Moo-Puc, R., Oceguera-Vargas, I., Noreña-Barroso, E., Yáñez-Estrada, L., Alvarado, J., González, L., Pérez-Herrera, N. & Pérez-Medina, S. 2018 Environmental exposure of children to toxic trace elements (Hg, Cr, As) in an urban area of Yucatan, Mexico: water, blood, and urine levels. *Bulletin of Environmental Contamination and Toxicology* **100** (5), 620–626.

Asati, A., Pichhode, M. & Nikhil, K. 2016 Effect of heavy metals on plants: an overview. *International Journal of Application or Innovation in Engineering & Management* **5** (3), 56–66.

Beaumont, J. J., Sedman, R. M., Reynolds, S. D., Sherman, C. D., Li, L. H., Howd, R. A., Sandy, M. S., Zeise, L. & Alexeeff, G. V. 2008 Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. *Epidemiology* **19** (1), 12–23.

Breslow, N. E. 1996 Statistics in epidemiology: the case-control study. *Journal of the American Statistical Association* **91** (433), 14–28.

Canepari, S., Castellano, P., Astolfi, M. L., Materazzi, S., Ferrante, R., Fiorini, D. & Curini, R. 2018 Release of particles, organic compounds, and metals from crumb rubber used in synthetic turf under chemical and physical stress. *Environmental Science and Pollution Research* **25** (6), 1448–1459.

Cárdenas-González, M., Osorio-Yáñez, C., Gaspar-Ramírez, O., Pavković, M., Ochoa-Martinez, A., López-Ventura, D. & Vaidya, V. S. 2016 Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1. *Environmental Research* **150**, 653–662.

Checkoway, H., Pearce, N. E. & Crawford-Brown, D. J. 1989 *Research Methods in Occupational Epidemiology*. Oxford University Press, New York. Available from: https://www.atsdr.cdc.gov/csem/chromium/docs/chromium.pdf (accessed 10 July 2022).

Coelho, P., Costa, S., Silva, S., Walter, A., Ranville, J., Sousa, A. C. & Teixeira, J. P. 2013 Metal(loid) levels in biological matrices from human populations exposed to mining contamination – Panasqueira Mine (Portugal). *Journal of Toxicology and Environmental Health, Part A* **75** (13–15), 893–908.

Comstock, G. W. 1980 The epidemiologic perspective: water hardness and cardiovascular disease. *Journal of Environmental Pathology and Toxicology* **4** (2–3), 9–25.

Costa, M. & Klein, C. B. 2006 Toxicity and carcinogenicity of chromium compounds in humans. *Critical Reviews in Toxicology* **36** (2), 155–163.

DeFlora, S., Camoirano, A., Micale, R. T., LaMaestra, S., Savarino, V., Zentilin, P. & Proctor, D. M. 2016 Reduction of hexavalent chromium by fasted and fed human gastric fluid. I. Chemical reduction and mitigation of mutagenicity. *Toxicology and Applied Pharmacology* **306**, 113–119.

Environmental Protection Agency. US EPA 1998 *Toxicological Review of Trivalent Chromium (CAS No. 16065-83-1)*. National Center for Environmental Assessment, Office of Research and Development, Washington, DC.

Environmental Protection Agency. US EPA 1999 *Environmental Protection Agency*. Code of Federal Regulations. 40 CFR 141.32.

Environmental Working Group 2010 *Chromium-6 Is Widespread in US Tap Water*. Available from: https://www.ewg.org/research/chromium-6-us-tap-water (accessed 10 July 2022).

Eriksen, M. B. & Frandsen, T. F. 2018 The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *Journal of the Medical Library Association: JMLA* **106** (4), *420*.

European Food Safety Authority (EFSA) 2010 Scientific opinion on the safety of trivalent chromium as a nutrient added for nutritional purposes to foodstuffs for particular nutritional uses and foods intended for the general population (including food supplements). *EFSA Journal* **8** (12), 1882.

FAO/WHO, Codex Alimentarius Commission 2001 *Food and Contaminants. Commission Standard Program, ALINORM 01/12A, 1-289*.

Filler, G., Kobrzynski, M., Sidhu, H. K., Belostotsky, V., Huang, S. H. S., McIntyre, C. & Yang, L. 2017 A cross-sectional study measuring vanadium and chromium levels in paediatric patients with CKD. *BMJ Open* **7** (5), e014821.

Galal-Gorchev, H. & Ozolins, G. 1993 WHO guidelines for drinking-water quality. *Water Supply* **11** (3), 1–16.

Greenland, S. & Morgenstern, H. 1989 Ecological bias, confounding, and effect modification. *International Journal of Epidemiology* **18** (1), 269–274.

Greenwood, N. N. & Earnshaw, A. 1997 *Chemistry of the Elements*, 2nd edn. Butterworth-Heinemann, Oxford.

Hammer, M. J. 1986 *Water and Wastewater Technology*. John Wiley Inc, New York, USA.

Health Canada 2016 *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chromium*. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. Available from: https://www.canada.ca/content/dam/hcsc/documents/services/publications/healthyliving/chrom (accessed 10 July 2022).

Herath, H. M. A., Kawakami, T., Nagasawa, S., Serikawa, Y., Motoyama, A., Chaminda, G. G. T., Weragoda, S. K., Yatigammana, S. K. & Amarasooriya, A. A. G. D. 2018 Arsenic, cadmium, lead, and chromium in well water, rice, and human urine in Sri Lanka in relation to chronic kidney disease of unknown etiology. *Journal of Water Health* **16** (2), 212–222.

Huisman, M. H., de Jong, S. W., van Doormaal, P. T., Weinreich, S. S., Schelhass, H. J., van der Kooi, A. J., de Visser, M., Veldink, J. H. & van den Berg, L. H. 2011 Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. *Journal of Neurology, Neurosurgery, and Psychiatry* **82**, 1165–1170.

International Agency for Research on Cancer (IARC) 1994 Schistosomes, liver flukes and Helicobacter pylori. *IARC Monographs on the Carcinogenic Risks to Humans, Lyon, France* **61** 177–241.

International Agency for Research on Cancer (IARC) 2012 *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans: A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts, 100C*. World Health Organization, International Agency for Research on Cancer, Lyon, France, pp. 147–168.

Jeejeebhoy, K. N., Chu, R. C., Marliss, E. B., Greenberg, G. R. & Bruce-Robertson, A. 1977 Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. *The American Journal of Clinical Nutrition* **30** (4), 531–538.

Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B. & Yang, C. W. 2013 Chronic kidney disease: global dimension and perspectives. *The Lancet* **382** (9888), 260–272.

Jiang, B., Liu, Y., Zheng, J., Tan, M., Wang, Z. & Wu, M. 2015 Synergetic transformations of multiple pollutants driven by Cr (VI)-sulfite reactions. *Environmental Science & Technology* **49** (20), 12363–12371.

Karagiannis, D., Deliveliotis, C., Papadimitriou, E., Riza, E., Lykou, A., Petralias, A. & Linos, A. 2015 Oral exposure to hexavalent chromium through drinking water and urologic morbidity in an industrial area of Greece. *Journal of Public Health* **23** (5), 249–255.

Kerger, B. D., Butler, W. J., Paustenbach, D. J., Zhang, J. & Li, S. 2009 Cancer mortality in Chinese populations surrounding an alloy plant with chromium smelting operations. *Journal of Toxicology and Environmental Health, Part A* **72** (5), 329–344.

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., Burrell, J. R. & Zoing, M. C. 2011 Amyotrophic lateral sclerosis. *Lancet* **377**, 942–955.

Lee, K. P., Ulrich, C. E., Geil, R. G. & Trochimowicz, H. J. 1989 Inhalation toxicity of chromium dioxide dust to rats after two years exposure. *Science of the Total Environment* **86** (1–2), 83–108.

Liang, J., Huang, X., Yan, J., Li, Y., Zhao, Z., Liu, Y. & Wei, Y. 2021 A review of the formation of Cr (VI) via Cr (III) oxidation in soils and groundwater. *Science of The Total Environment* **774**, 145762.

Linos, A., Petralias, A., Christophi, C. A., Christoforidou, E., Kouroutou, P., Stoltidis, M. & Karagas, M. R. 2011 Oral ingestion of hexavalent chromium through drinking water and cancer mortality in an industrial area of Greece – an ecological study. *Environmental Health* **10** (1), 1–8.

Marconi, E., Canepari, S., Astolfi, M. L. & Perrino, C. 2011 Determination of Sb (III), Sb (V) and identification of Sb-containing nanoparticles in airborne particulate matter. *Procedia Environmental Sciences* **4**, 209–217.

Marouf, B. H. 2018 Association between serum heavy metals level and cancer incidence in Darbandikhan and Kalar Area, Kurdistan Region, Iraq. *Nigerian Journal of Clinical Practice* **21** (6), 766–771.

Mathur, A. K., Chandra, S. V. & Tandon, S. K. 1977 Comparative toxicity of trivalent and hexavalent chromium to rabbits II. Morphological changes in some organs. *Toxicology* **8** (1), 53–61.

Minari, G. D., Saran, L. M., Constancio, M. T. L., da Silva, R. C., Rosalen, D. L., de Melo, W. J. & Alves, L. M. C. 2020 Bioremediation potential of new cadmium, chromium, and nickel-resistant bacteria isolated from tropical agricultural soil. *Ecotoxicology and Environmental Safety* **204**, 111038.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & PRISMA, Group 2009 Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* **151** (4), 264–269.

National Institutes of Health (NIH) 2007 *Dietary Supplement Fact Sheet: Chromium. Office of Dietary Supplements*. NIH Clinical Center, National Institutes of Health, Bethesda, MD.

Nishioka, H. 1975 Mutagenic activities of metal compounds in bacteria. *Mutation Research* **31** (3), 185–189.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D. & Moher, D. 2021 The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **10** (1), 1–11.

Pellerin, C. & Booker, S. M. 2000 Reflections on hexavalent chromium: health hazards of an industrial heavyweight. *Environmental Health Perspectives* **108** (9), A402–A407.

Proctor, D. M., Otani, J. M., Finley, B. L., Paustenbach, D. J., Bland, J. A., Speizer, N. & Sargent, E. V. 2002 In hexavalent chromium carcinogenic via ingestion? A weight-of evidence review. *Journal of Toxicology and Environmental Health, Part A* **65** (10), 701–746.

Roos, P. M. 2013 *Studies on Metals in Motor Neuron Disease*. Available from: https://openarchive.ki.se/xmlui/bitstream/handle/10616/41419/Thesis_Per_Roos.pdf?sequence=1&isAllowed=y (accessed 9 November 2022).

Rosen, D. R., Siddique, T., Patterson, D., Figlewicz, D. A., Sapp, P., Hentati, A., Donaldson, D., Goto, J., O'Regan, J. P. & Deng, H. X. 1993 Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* **362**, 59–62.

Sánchez-Díaz, G., Escobar, F., Badland, H., Arias-Merino, G., Posada de la Paz, M. & Alonso-Ferreira, V. 2018 Geographic analysis of motor neuron disease mortality and heavy metals released to rivers in Spain. *International Journal of Environmental Research and Public Health* **15** (11), 2522.

Sazakli, E., Villanueva, C. M., Kogevinas, M., Maltezis, K., Mouzaki, A. & Leotsinidis, M. 2014 Chromium in drinking water: association with biomarkers of exposure and effect. *International Journal of Environmental Research and Public Health* **11** (10), 10125–10145.

Scawarz, K. & Mertz, W. 1959 Chromium (III) and the glucose tolerance factor. *Archives of Biochemistry* **85**, 292–295.

Sedman, R. M., Beaumont, J. A. Y., McDonald, T. A., Reynolds, S., Krowech, G. & Howd, R. 2006 Review of the evidence regarding the carcinogenicity of hexavalent chromium in drinking water. *Journal of Environmental Science and Health, Part C* **24** (1), 155–182.

Shanker, A. K. & Venkateswarlu, B. 2019 *Chromium: environmental pollution, health effects and mode of action*. In: Encyclopedia of Environmental Health. Elsevier, Amsterdam, pp. 624–633.

Sharma, P., Bihari, V., Agarwal, S. K., Verma, V., Kesavachandran, C. N., Pangtey, B. S. & Goel, S. K. 2012 Groundwater contaminated with hexavalent chromium [Cr (VI)]: a health survey and clinical examination of community inhabitants (Kanpur, India). *PLoS ONE* **7** (10), e47877.

Shekhawat, K., Chatterjee, S. & Joshi, B. 2015 Chromium toxicity and its health hazards. *International Journal of Advanced Research* **3** (7), 167–172.

Shibata, A., Parsonnet, J., 2006 Stomach cancer. In: *Cancer Epidemiology and Prevention*, 3rd edn (Schottenfeld, D. & Fraumeni, J. F., eds.). Oxford University Press, New York, pp. 707–720.

Stout, M. D., Herbert, R. A., Kissling, G. E., Collins, B. J., Travlos, G. S., Witt, K. L. & Hooth, M. J. 2009 Hexavalent chromium is carcinogenic to F344/N rats and B6C3F1 mice after chronic oral exposure. *Environmental Health Perspectives* **117** (5), 716–722.

Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K. & Sutton, D. J. 2012 Heavy metal toxicity and the environment. *Molecular, Clinical, and Environmental Toxicology* **3**, 133–164.

Tubek, S., Tubek, S. & Szyguła, R. 2008 Gender differences in correlations between the content of elements in rainwater and the frequency of hospitalization for arterial hypertension, chronic obstructive pulmonary disease, and psoriasis in Opole Voivodship, Poland, during 2000–2002. *Biological Trace Element Research* **126** (1), 98–105.

Ullah, R., Malik, R. N. & Qadir, A. 2009 Assessment of groundwater contamination in an industrial city, Sialkot, Pakistan. *African Journal of Environmental Science and Technology* **3** (12), 429–446.

Unisa, S., Jagannath, P., Dhir, V., Khandelwal, C., Sarangi, L. & Roy, T. K. 2011 Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. *HPB* **13** (2), 117–125.

United Nations Educational, Scientific and Cultural Organization (UNESCO) 2003 *Water for People Water for Life*. The United Nations World Water Development Report (UNESCO) and Berghahn Books. Available from: https://unesdoc.unesco.org/ark:/48223/pf0000129726 (accessed 10 July 2022).

Venitt, S. & Levy, L. S. 1974 Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. *Nature* **250** (5466), 493–495.

Vogel, N., Murawski, A., Schmied-Tobies, M. I., Rucic, E., Doyle, U., Kämpfe, A. & Kolossa-Gehring, M. 2021 Lead, cadmium, mercury, and chromium in urine and blood of children and adolescents in Germany – human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V). *International Journal of Hygiene and Environmental Health* **237**, 113822.

Whitaker, C. C., Cates, M. E., Cruthirds, D. L. & Gorman, G. S. 2020 Association between concentrations of chromium in drinking water and mortality due to suicide in Alabama. *Journal of Water and Health* **18** (5), 835–842.

World Health Organization (WHO) 1990 Chromium. In: H. Ara Begum, A. K. M. Monjurul Haque, Md. Didarul Islam, M. Mehedi Hasan, S. Ahmed, Md. Razzak, R. A. Khan, eds. Environmental Health Criteria 61. International Programme on Chemical Safety, Geneva.

World Health Organization (WHO) 2006 Guidelines for drinking-water quality: incorporating first addendum. Vol. 1, Recommendations. Available from: https://apps.who.int/iris/bitstream/handle/10665/43428/9241546964_eng.pdf?sequence=1&isAllowed=y (accessed 27 December 2022).

World Health Organization (WHO) and UNISEF 2000 Global Water Supply and Sanitation Assessment 2000 Report. World Health Organization and United Nations Children's Fund, USA. Available from: https://www.who.int/water_sanitation_health/monitoring/jmp2000.pdf (accessed 16 July 2022).

Yang, W., Song, W., Li, J. & Zhang, X. 2020 Bioleaching of heavy metals from wastewater sludge with the aim of land application. *Chemosphere* **249**, 126134.

Zhang, J. & Li, X. 1980 Study on the effect of environmental pollution on human health in the suburbs of Jin Zhou, I. Analysis of the cause of human death, internal report of the. JinZhou Disease Control and Prevention Station. Original Chinese document and English translation available at http://www.chemrisk.com/public/Zhang.

Zhang, J. D. & Li, X. L. 1987 Chromium pollution of soil and water in Jinzhou. *Zhonghua yu fang yi xue za zhi [Chinese Journal of Preventive Medicine]* **21** (5), 262–264.

First received 3 August 2022; accepted in revised form 14 December 2022. Available online 26 December 2022