Science of the Total Environment 538 (2015) 802–816

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Epidemiology of chronic disease related to arsenic in Argentina: A systematic review

Ariel Esteban Bardach [a,*], Agustin Ciapponi [a], Natalie Soto [a], Martin R. Chaparro [a], Maria Calderon [a], Agustina Briatore [b], Norma Cadoppi [c], Roberto Tassara [c], Marta I. Litter [d]

[a] Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina
[b] Hospital Italiano, Buenos Aires, Argentina
[c] Foro Estratégico para el Desarrollo Nacional, Argentina
[d] National Atomic Energy Commission, National Scientific and Technical Research Council, Argentina

HIGHLIGHTS

- Arsenic content in Argentina was associated with increased risk of chronic diseases.
- The median arsenicosis prevalence was 2.6% in exposed areas.
- The relative risk of mortality by skin cancer was 2.5 to 5.2 in affected areas.
- The median percentage of water samples above the cut-off point value was 87% in BA.
- We found important gaps in literature regarding the impact of arsenic on health.

ARTICLE INFO

Article history:
Received 2 June 2015
Received in revised form 12 August 2015
Accepted 13 August 2015
Available online xxxx

Editor: D. Barcelo

Keywords:
Arsenic
Epidemiology
Argentina
Cancer
Health

ABSTRACT

Four million people in Argentina are exposed to arsenic contamination from drinking waters of several center-northern provinces. A systematic review to examine the geographical distribution of arsenic-related diseases in Argentina was conducted, searching electronic databases and gray literature up to November 2013. Key informants were also contacted. Of the 430 references identified, 47 (mostly cross-sectional and ecological designs) referred to arsenic concentration in water and its relationship with the incidence and mortality of cancer, dermatological diseases and genetic disorders. A high percentage of the water samples had arsenic concentrations above the WHO threshold value of 10 μg/L, especially in the province of Buenos Aires. The median prevalence of arsenicosis was 2.6% in exposed areas. The proportion of skin cancer in patients with arsenicosis reached 88% in case-series from the Buenos Aires province. We found higher incidence rate ratios per 100 μg/L increment in inorganic arsenic concentration for colorectal, lung, breast, prostate and skin cancer, for both genders. Liver and skin cancer mortality risk ratios were higher in regions with medium/high concentrations than in those with low concentrations. The relative risk of mortality by skin cancer associated to arsenic exposure in the province of Buenos Aires ranged from 2.5 to 5.2. In the north of this province, high levels of arsenic in drinking water were reported; however, removal interventions were scarcely documented. Arsenic contamination in Argentina is associated with an increased risk of serious chronic diseases, including cancer, showing the need for adequate and timely actions.

Contents

* Corresponding author at: Health Technology Assessment and Health Economic Department, Institute for Clinical Effectiveness and Health Policy (IECS), Dr Emilio Ravignani 2024, C1414CPV Buenos Aires, Argentina.
E-mail address: abardach@iecs.org.ar (A.E. Bardach).

http://dx.doi.org/10.1016/j.scitotenv.2015.08.070
0048-9697/

1. Introduction

Arsenic (As) is the 20th most common element in the Earth's crust (IARC, 2012). It is a metalloid and can be easily solubilized in groundwaters depending on pH, redox conditions, temperature, and solution composition (Nordstrom, 2002). Human exposure occurs from ingestion of water and food contaminated with As coming from natural and anthropogenic sources (IARC, 2012). Water pollution by As is a worldwide problem with high impact in the poorest regions of the world (Litter, 2010), with over 226 million persons exposed (Murcott, 2012; McCarty et al., 2011; Smedley and Kinnirugh, 2013). The highest concentrations and, consequently, the most important health problems are localized in Argentina, Bangladesh, Nepal, Chile, China, Hungary, India, Mexico, Rumania, Taiwan, Vietnam and the USA (Bundschuh et al., 2008). In Latin America, the problem affects at least 14 countries (Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Peru and Uruguay), and the number of exposed people is about 14 million. The most critical areas are in Argentina, Chile and Mexico (Figueiredo et al., 2010). It is currently estimated that the population living in areas with As contaminated water in Argentina rises to about 4,000,000 people (International Society of Groundwater for Sustainable Development, 2014). The anthropogenic activities in mining areas that enhance the mobilization of As and other copollutants makes the environmental problem more dramatic (Bundschuh et al., 2012). Additionally, the use of arsenic-contaminated groundwater for irrigation purposes in crop fields elevates the arsenic contamination (Rosas-Castor et al., 2014). Both pathways were observed in a recent review from Colombia that revealed that As is present in soil sediments, water and in the food chain, exceeding the national and international limits, particularly in mining and agricultural areas (Alonso et al., 2014).

The US Environmental Protection Agency (USEPA) classifies As as carcinogenic in group “A” (US Environmental Protection Agency) and the International Agency on Research on Cancer (IARC) includes it in group “I” (IARC, 2004). In 1993, the World Health Organization (WHO) updated the recommendations on the limits in drinking water, decreasing the guideline value from 50 to 10 μg/L (WHO, 2011). At present, in Argentina, the threshold is still under discussion. In 2007, a joint resolution (No. 68 and 196/2007) modified the 982 and 983 articles of the Argentine Food Code (CAA, Código Alimentario Argentino), decreasing the normative in drinking water from 50 to 10 μg/L, and a 5-year period to reach it. In 2012, this normative was modified again, indicating that the adopted value would be determined after the end of an epidemiological study undertaken by governmental institutions (ANMAT, 2012).

Chronic exposure to As has been associated with a variety of health problems including several types of cancer (skin, lung, bladder, kidney), neurological disease, cardiovascular disease, perinatal conditions and other benign diseases (Smith et al., 1998; Chen et al., 1992; Hopenhayn-Rich et al., 1996; Brouwer et al., 1992; Rahman et al., 1999; Bates et al., 2004). Palmoplantar thickening and hyperkeratosis, increase of skin pigmentation and development of skin, lung and larynx cancers are the health problems most frequently reported in the literature (Hopenhayn-Rich et al., 1996; Besuschio et al., 1980). In Argentina, since the beginning of the 20th century, the set of symptoms and signs associated with the consumption of water or food contaminated with As has been denominated chronic endemic regional hydroarsenicism (HACRE from its Spanish acronym) (Litter, 2010; Ayerza, 1917a, 1917b, 1918; Gerstenfeld et al., 2012). A clinical definition of the condition can be found in Supplementary material 1. It has been documented that up to 30% of patients with HACRE in Argentina will die of skin, liver, lung, bladder, stomach and pancreas cancer (Padial, 2004). Lower-limb vascular pathologies, diabetes mellitus, hypertension and reproductive conditions are also common conditions among exposed subjects (United Nations Synthesis Report on Arsenic in Drinking Water, 2009; Mazumder et al., 2000; Biagini, 1996).

In 2006, a comprehensive study was conducted in Argentina where levels of As in water were reported for each Argentine province with the available information up to 2005 (National Commission of Health Research Programs, 2006). In many provinces such as Santiago del Estero and Santa Fe, elevated levels of As in water and food as well as elevated excretion of As in urine of the population have been reported (Carballo et al., 2006; Swiecky et al., 2006). Furthermore, several neoplasms were reported to be at increased frequency in relation to the high concentrations detected in the province of Chaco (Hopenhayn-Rich et al., 1996; Besuschio et al., 1980).

Therefore, it is important to have updated information on As levels in Argentine waters nationwide and, in particular, in the Buenos Aires province, where more than one third of the country population lives. It is also crucial to identify the arsenic abatement techniques available for future implementation of cost-effective programs for safe water supply in the exposed areas.

The overall objective of this systematic review (SR) was to examine the evidence of As concentrations in surface and drinking water aquifers, and its relation to the geographical distribution of disease caused by arsenic in terms of morbidity, mortality and population risk in Argentina, especially for the province of Buenos Aires.

2. Methods

A systematic review of the published and gray literature has been performed. A meta-analysis was not possible due to significant heterogeneity of populations, study designs and methods. However, by protocol, we followed the Meta-Analysis of Observational Studies in Epidemiology guidelines (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and meta-analyses statement (PRISMA statement) (Liberati et al., 2009; Moher et al., 2009) for reporting SRs and meta-analyses.

2.1. Search strategy

A systematic search was conducted on the main international and regional literature databases such as Cochrane CENTRAL, MEDLINE, EMBASE, LILACS, GeoRef, Library HQ OPS, CAS (Chemical Abstracts Services), CAB-Abstracts from inception date up to November 2013 using the following search strategy: (Arsenic Poisoning[Mesh] OR Arsenicals[Mesh] OR Arsenic[Mesh] OR arsenic*[tiab]) AND (Arsenic Poisoning[Mesh] OR Arsenicals[Mesh] OR Arsenic[Mesh] OR arsenic*[tiab]) AND (Argentina[Mesh] OR Argentin*[tiab] OR Argentin*[ad]).

In order to identify gray literature, we performed a generic and academic search on the Internet. Institutional and special reports of the Ministry and Department of Health of Argentina, databases containing regional proceedings, annals of related specialties, books and theses were searched. We also contacted key informants in the province of Buenos Aires to improve the information. Authors of included studies were contacted for missing or additional information when necessary. Additionally, we updated the information from those sources searched in 2006 by the National Commission of Sanitary Research Programs, such as the annals of chemistry and hydrogeology congresses, information available from the School of Pharmacy and Biochemistry and from the Chair of Toxicology of the School of Medicine, both of the University of Buenos Aires, different university laboratories, information from official institutions controlling the water quality, population census, and doctoral theses.

2.2. Inclusion criteria

Studies included were those reporting primary or secondary epidemiologic data or evaluation of interventions, systematic reviews, randomized or not randomized controlled trials and observational studies. No restrictions on age or ethnicity were imposed. Health-related studies were excluded if they did not refer simultaneously to arsenic levels in water and associated diseases. Data was extracted only if the population under study lived for at least 6 months in the study area assessed. Articles reporting primary data only on arsenic levels in groundwater were excluded if the date of the samples was before 2000, if they did not refer to the Province of Buenos Aires, or they duplicated information from another identified study.

2.3. Outcome measures

The outcome measures considered were morbidity and mortality from cancer and other conditions associated to As. Also, As-related genotoxicity and As concentration levels in drinking water in the province of Buenos Aires from 2000 onwards were reported, in order to update the official report from 2006 (National Commission of Health Research Programs, 2006).

2.4. Article selection and data abstraction

Pairs of reviewers independently evaluated articles by title and abstract according to pre-specified criteria, assessed the methodological quality, and abstracted data from full texts. Discrepancies were solved by consensus of the whole team. Authors of the articles were contacted when necessary to obtain missing or supplementary information. We utilized Early Reviewer Organizer Software, a Web-based software to facilitate the initial phases (Ciapponi et al., 2011).

2.5. Risk of bias assessment

We used the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) and additional criteria developed by the Cochrane Effective Practice Group and Organization of Care (EPOC CEPOoCG, 2009) for risk of bias assessment. We evaluated the following domains: comparability of groups, selection of participants, conflicts of interest, confounding control, and statistical methods other than confounding. We valued each domain as "low risk", "high risk", "moderate risk" or "unclear risk." When the criteria was rated as "unclear", the reviewer assigned attempted to obtain more details by contacting the study authors.

2.6. Statistical analysis

For dichotomous variables, we planned to estimate relative risks (RR) with confidence intervals (95% CI) whenever possible. For continuous variables, it was proposed to calculate the mean difference (MD), also with its variability. Some of the percentages reported were calculated from published data.

3. Results

Of the 430 references identified by the search strategy after removing duplicates, 259 were excluded by screening title and abstract. Of the remaining 171, 124 were excluded by full-text assessment and 47 were finally included (Fig. 1). The characteristics of the included studies are described in Table 1 (Gerstenfeld et al., 2012; Carballo et al., 2006; Aballay et al., 2012; Ameer et al., 2014; Auge, 2014; Bartolotta et al., 2011; Blanco et al., 2012; Bobillo et al., 2014; Bonafina and Ratto, 2009; Cabrera and Gomez, 2003a; Campaña et al., 2014; Concha et al., 2006; Corey et al., 2005; Engstrom et al., 2009, 2011; Escalante et al., 2009; Esposito et al., 2011; Ferral et al., 2014; Gonzalez Uriarte et al., 2002; Guber et al., 2009; Heredia and Fernandez, 2009; Hick and Carballo, 2005; Matos et al., 2000; Medina et al., 2004; Molina et al., 2014; Moschione et al., 2014; Navoni et al., 2006, 2012; Olivera et al., 2006; Olmos et al., 2014; Paoloni et al., 2005, 2009; Peluso et al., 2011, 2012; Pou et al., 2011; Rigacci et al., 2013; Roman et al., 2014; Rosso et al., 2011, 2013; Schenone et al., 2007; Schlebusch et al., 2013; Soria et al., 2014; Soria de et al., 2009; Soria de Gonzalez et al., 2011; Steinmaus et al., 2010; Vazquez et al., 2014; Villagra Cocco et al., 2014; Ward et al., 2014). Represented Argentine provinces were Buenos Aires (including the Autonomous City of Buenos Aires, i.e. the Federal District), Chaco, Córdoba, La Pampa, Salta, Santa Fe, Santiago del Estero and Tucumán. Regarding the type of identified biological samples, six studies used blood samples, six oral mucosa swabs, eight urine samples and one evaluated skin tissue. A total of 37 of these studies analyzed water samples. Regarding the impact of chronic arsenic exposure on health, nine studies evaluated dermatologic manifestations, while 13 analyzed the association of exposure levels and the prevalence of different As-related cancers. Regarding epidemiological designs, they were all observational; 32 were cross-sectional surveys, one was a retrospective cohort, ten were ecological studies, three were case–control studies and one study was a case series. Because of the high degree of heterogeneity observed in populations, outcomes, study designs and sampling methods, meta-analyses could not be performed.

3.1. Methodological quality

We analyzed the different risks of bias by the study design. Of the ten ecological studies included in the SR, the majority was of low risk of reverse causality, ecologic fallacy and information bias. However, only half studies carried low risk of confounding, three studies were high risk and two, moderate. The rest of the observational studies were heterogeneous regarding the domains analyzed, most carrying low risk for

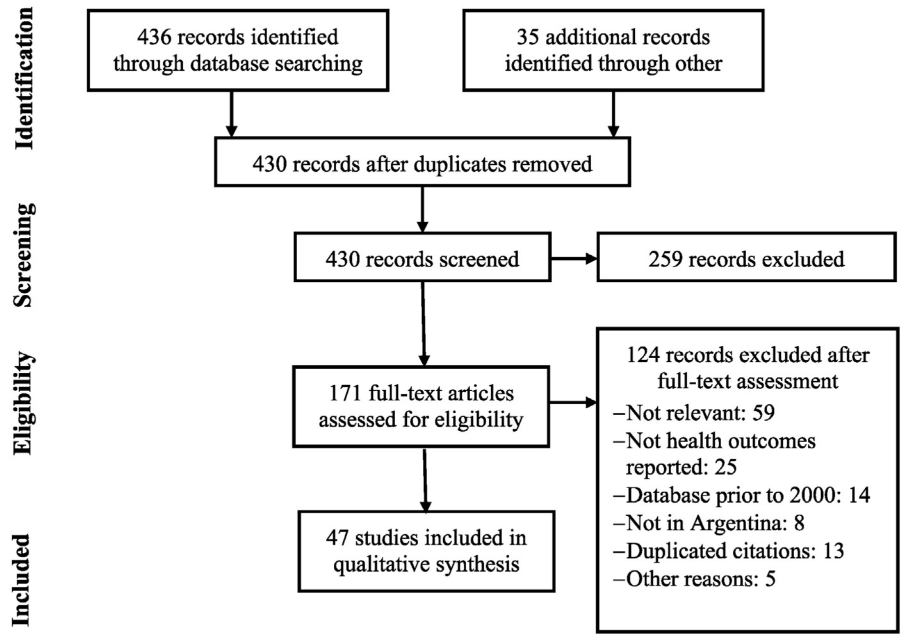

Fig. 1. Systematic review flowchart.

conflict of interest and moderate to high risk of selection bias. Detailed results can be found in Supplementary material 2.

3.2. Arsenic associated to cancer

Studies on the effect of As on the incidence of cancer were conducted in Buenos Aires City and in the provinces of Buenos Aires, Córdoba, and La Pampa, using a variety of epidemiological methods. They were mostly of ecological design. The type of cancer studied were stomach, liver, breast, skin, prostate, lungs, colon, cervix uteri and endometrium. The most commonly assessed outcomes were incidence and mortality related to As exposure. Some of the articles stratified the results by gender (Table 2).

3.3. Arsenic associated to genetic changes

Table 3 shows the results of four studies relating arsenic exposure to genetic changes. The studies were conducted in Buenos Aires City and in the provinces of Buenos Aires, Santiago del Estero, Salta and Chaco. The samples were collected from oral mucosa swabs and blood, and the reported genetic outcomes were the percentage of micronuclei found in oral mucosa samples, the relationship between the presence of polymorphisms As3MT and urinary arsenic metabolite (III), the mitotic rate, the presence of micronuclei and other markers of genetic damage in oral mucosa by level of exposure to arsenic. Studies also showed the frequency of protective haplotype CTA AS3MT and T860C polymorphism (Table 3). The association of As to urinary metabolite levels and the development of polymorphisms were reported in many studies (See Supplementary material 3).

3.4. Arsenic associated to skin pathologies

Regarding studies about arsenic-related skin pathologies, several studies were found and the associations found are shown in Table 4. One study described the high prevalence of skin cancer in 23 patients with chronic arsenic poisoning who attended a hospital in the province of Buenos Aires (Cabrera and Gomez, 2003b). Another study in Tucuman showed the prevalence of HACRE in subjects consuming drinking water with As levels that exceeded the threshold of 10 and 50 μg/L (Gerstenfeld et al., 2012). Four studies also published research in Tucumán on the prevalence of dermatological signs of As poisoning in subjects exposed and unexposed to arsenical waters (Escalante et al., 2009; Guber et al., 2009; Soria et al., 2014; Soria de et al., 2009).

Other studies identified several health outcomes that were more difficult to group, such as: differences in homocysteine levels, plasma hemoglobin and blood pressure in patients exposed and unexposed to As, the difference in specific types of disease in patients with gingival HACRE versus control patients, the correlation between values of As in saliva and hair, relative risk of hypertension in exposed and not exposed subjects and neurological manifestations and changes in the EEG patterns. All these results are shown in Supplementary material 4.

3.5. Arsenic levels in water

Although it was not the primary focus of this review, Table 5 compiles data of As concentrations both in well water and network sources, from those articles fulfilling the inclusion criteria. Most of the samples were taken from surface waters. The content of As in the samples was determined mostly by atomic absorption spectroscopy (AAS) or inductively coupled plasma (ICP), alone or combined with other methods. The included studies showed that a high percentage of the samples presented As concentrations above the WHO threshold value of 10 μg/L, especially in the province of Buenos Aires. The median percentage of samples above the cut-off point value was 87%, ranging from 21% to 100% of the total sample reported in the studies (Table 5). Additionally, Fig. 2 shows the As content in water samples from public network and wells in Buenos Aires, as assessed by the School of Pharmacy and Biochemistry of the University of Buenos Aires.

4. Discussion

There are several good quality primary studies and reviews related to As distribution in water in Argentina (Farias et al., 2003; Nicolli et al., 2010, 2012; Smedley et al., 2002, 2005; Bundschuh et al., 2004). The present work, based on an exhaustive bibliographic search, focused on those studies related to health-related outcomes. It identified 47 relevant studies, predominantly cross-sectional ones, of moderate to good methodological quality.

While it is true that reducing arsenic exposure may decrease health risks, elevated rates of cancer may persist for many years after high-

Table 1
General characteristics of the main studies identified in the review.

Study reference	Province	As in water	As and health outcomes	Year of sample collection	Population (N)	Type of data	Samples water (n)	Biological samples (n)	Age	Gender	Type of study
Aballay et al. (2012)	Cordoba	Yes	Yes	2004	0	Secondary data	0	0	General population	Both	Ecological study
Ameer et al. (2014)	Salta	No	Yes	2008/2011	244	Primary data	0	488	15–64	Female	Cross-sectional
Auge (2014)	Buenos Aires	Yes	No	N/A	N/A	Primary data	640	0	N/A	N/A	Ecological study
Bartolotta et al. (2010)	Buenos Aires/CABA/Santiago del Estero	Yes	Yes	2007	59	Primary data	59	59	General population	Both	Cross-sectional
Blanco et al. (2012)	Buenos Aires	Yes	No	N/A	N/A	Primary data	111	0	N/A	N/A	Cross-sectional
Bobillo et al. (2014)	Santiago del Estero/Chaco	Yes	Yes	N/A	70	Primary data	70	140	0–14	Both	Cross-sectional
Bonafina and Ratto, (2009)	Buenos Aires	Yes	No	1970/2006	N/A	Secondary data	0	0	N/A	N/A	Cross-sectional
Cabrera and Gomez, (2003)	Buenos Aires	No	Yes	1988–1998	23	Primary data	0	0	15–64	Both	Clinical series
Campaña et al. (2014)	Buenos Aires	Yes	No	2012–2013	N/A	Primary data	56	0	N/A	N/A	Ecological study
Carballo et al. (2006)	Córdoba	Yes	Yes	2005	84	Both	20	84	N/A		Cross-sectional
Concha et al. (2006)	Salta	Yes	Yes	1994–2004	153	Primary data	31	137	N/A	Female	Cross-sectional
Corey et al. (2005)	Santa Fe	Yes	Yes	1999	Variable	Both	196	0	15–64		Cross-sectional and ecological
Engstrom et al. (2009)	Salta	No	Yes	2004–2005	104	Primary data	0	208	15–64	Female	Cross-sectional
Engstrom et al. (2011)	Salta	No	Yes	2008	172	Primary data	0	344	15–64	Female	Cross-sectional
Escalante et al. (2009)	Tucumán	Yes	Yes	2008–2009	71	Primary data	71	0	N/A		Cross-sectional
Esposito et al. (2011)	Buenos Aires	Yes	No	2008	N/A	Primary data	37	0	N/A	N/A	Cross-sectional
Ferral et al. (2014)	Buenos Aires	Yes	No	N/A	N/A	Primary data	18	18	N/A	N/A	Ecological study
Gerstenfeld et al. (2012)	Tucumán	Yes	Yes	2008	119	Primary data	20	119	15–64		Cross-sectional
Gonzalez Uriarte et al. (2002)	Buenos Aires	Yes	No	N/A	N/A	Primary data	20	0	N/A	N/A	Cross-sectional
Guber et al. (2009)	Tucumán	Yes	Yes	N/A	122	Primary data	235	0	15–64		Cross-sectional
Heredia and Fernandez, (2009)	Buenos Aires	Yes	No	2004	N/A	Primary data	43	0	N/A	N/A	Cross-sectional
Hick and Carballo, (2005)	Santiago del Estero/Santa Fe	No	Yes	2005	50	Primary data	0	100	15–64		Cross-sectional
Matos et al. (2000)	Buenos Aires/CABA	No	Yes	1994–1996	199	Primary data	0	0	15–64	Male	Case control
Medina et al. (2004)	Chaco	Yes	Yes	2001–2002	40	Both	0	80	15–64	Both	Case control
Molina et al. (2014)	La Pampa	Yes	Yes	2003–2007	0	Both	N/A	0	General population	Both	Ecological study
Moschione et al. (2014)	Buenos Aires	Yes	No	2013	N/A	Primary data	33	0	N/A	N/A	Cross-sectional
Navoni et al. (2006)	Santiago del Estero	No	Yes	N/A	14	Both	0	79	0–14	Both	Cross-sectional
Navoni et al. (2012)	Buenos Aires	Yes	Yes	2003–2008	0	Both	152	0	15–64	Both	Ecological study
Olivera et al. (2006)	Santiago del Estero	Yes	Yes	2005	66	Primary data	64	66	General population	Both	Cross-sectional
Olmos et al. (2014)	Santiago del Estero/Chaco	Yes	Yes	N/A	120	Primary data	120	240	General population	Both	Cross-sectional
Paoloni et al. (2005)	Buenos Aires	Yes	No	N/A	N/A	Primary data	104	0	N/A	N/A	Cross-sectional
Paoloni et al. (2009)	Buenos Aires	Yes	No	2007	N/A	Primary data	81	0	N/A	N/A	Cross-sectional
Peluso et al. (2012)	Buenos Aires	Yes	Yes	2005–2007	0	Primary data/Modelo	12	0	All ages		Ecological study
Peluso et al. (2014)	Buenos Aires	Yes	Yes	2008–2010	0	Primary data/Modelo	90	0	All ages		Ecological study
Pou et al. (2011)	Córdoba	No	Yes	1986–2006	0	Secondary	0	0	15–64	Both	Ecological study

						data					
Rigacci et al. (2013)	Buenos Aires	Yes	No	2009–2010	N/A	Primary data	36	0	N/A	N/A	Ecological study
Roman	Córdoba	No	Yes	2008–2013	426	Primary data	0	426	61–79	Both	Case–control
Rosso et al. (2011)	Buenos Aires	Yes	No	2009	N/A	Primary data	39	0	N/A	N/A	Cross-sectional
Rosso et al. (2013)	Buenos Aires	Yes	No	2008–2009	N/A	Primary data	20	0	N/A	N/A	Cross-sectional
Schenone et al. (2007)	Buenos Aires	Yes	No	2004/2005	N/A	Primary data	19	0	N/A	N/A	Cross-sectional
Schlebusch et al. (2013)	Salta	No	Yes	1994/1996–1997/2004–2005/2008	346	Primary data	0	346	15–64	96% Female	Cross-sectional
Soria et al. (2014)	Tucuman	Yes	Yes	N/A	395	Primary data	395	0	15–64		Cross-sectional
Soria de Gonzalez et al. (2009)	Tucuman	Yes	Yes	N/A	115	Primary data	115	115	15–64		Cross-sectional
Soria de Gonzalez et al. (2011)	Tucuman	Yes	Yes	2005–2009	161	Primary data	161	161	15–64		Cross-sectional
Steinmaus et al. (2010)	Cordoba	No	Yes	2000–2006	250	Primary data	0	250	15–64		Case control study
Vazquez et al. (2014)	Buenos Aires	Yes	No	N/A	18	Primary data	12	18	N/A		Cross-sectional
Villagra Cocco et al. (2014)	Cordoba	Yes	Yes	N/A	154	Primary data	32	0	15–64	Both	Cross-sectional
Ward et al. (2014)	Buenos Aires	Yes	No	2005–2013	N/A	Primary data	62	0	N/A	N/A	Cross-sectional

Table 2
Effect of Arsenic in drinking water and cancer frequency, by type of cancer and gender.

Cancer (organ affected)	Gender	Outcome measure	Estimates (p value)	Study (reference)
Colon	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.07 ($p > 0.77$)	Molina et al. (2014)
Colon	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.29 ($p > 0.26$)	Molina et al. (2014)
Colon	Female	IRR with 1 mg/L increased in iAs concentration	12.21 (5.72–26.07)	Aballay et al. (2012)
Colon	Male	IRR with 1 mg/L increased in iAs concentration	0.03 (0.02–0.06)	Aballay et al. (2012)
Cervix uteri	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.30 ($p > 0.25$)	Molina et al. (2014)
Endometrium	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.17 ($p > 0.52$)	Molina et al. (2014)
Stomach	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.13 (0.9–1.43)	Corey et al. (2005)
Stomach	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.08 (0.92–1.28)	Corey et al. (2005)
Stomach	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.05 ($p > 0.84$)	Molina et al. (2014)
Stomach	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1 (0.96–1.26)	Corey et al. (2005)
Liver	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.38 (1.17–1.63)	Corey et al. (2005)
Liver	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.33 (1.04–1.71)	Corey et al. (2005)
Liver	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.42 (1.14–1.6)	Corey et al. (2005)
Breast	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.32 ($p > 0.22$)	Molina et al. (2014)
Breast	Female	IRR with 1 mg/L increased in iAs concentration	1.09 (0.74–1.6)	Aballay et al. (2012)
Skin	Both	Skin Cancer Prevalence (%) in patients with chronic Arsenic exposure attended in a general hospital	88%	Cabrera
Skin	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.89 (1.15–3.09)	Corey et al. (2005)
Skin	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	2.46 (1.06–5.72)	Corey et al. (2005)
Skin	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.64 (0.89–1.64)	Corey et al. (2005)
Skin	Female	Mortality rates ratio from skin cancer in medium/high Arsenic concentration regions with worse SE conditions compared to low Arsenic concentration regions	3.9 (2.9–5.2)	Navoni et al. (2012)
Skin	Male	Mortality Rate Ratio of skin cancer in medium/high Arsenic concentration regions with worse SE conditions compared to low Arsenic concentration regions	3.1 (2.5–3.9)	Navoni et al. (2012)
Prostate	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.19 ($p > 0.46$)	Molina et al. (2014)
Prostate	Male	IRR with 1 mg/L increased in iAs concentration	0.05 (0.03–0.08)	Aballay et al. (2012)
Prostate	Male	OR adjusted prostate cancer in individuals exposed to arsenic drinking water (iAs upper than 10 mcg/L)	3.55 (1.59–7.94)	Roman et al. (2014)
Lungs	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.01 ($p > 0.96$)	Molina et al. (2014)
Lungs	Female	IRR with 1 mg/L increased in iAs concentration	56.03 (24.08–130.4)	Aballay et al. (2012)
Lungs	Male	IRR with 1 mg/L increased in iAs concentration	9.61 (6.59–14)	Aballay et al. (2012)
Lungs	Male	Mean OR lung cancer in individuals exposed to iAs	1.5 (0.6–3.5)	Matos et al. (2000)
Lungs	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	0.99 (0.92–1.06)	Corey et al. (2005)
Lungs	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1 (0.82–1.21)	Corey et al. (2005)
Lungs	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	0.98 (0.91–1.07)	Corey et al. (2005)
Lungs	Female	Mortality Rate Ratio of skin cancer in medium/high Arsenic concentration regions with worse SE conditions compared to low Arsenic concentration regions	3.2 (2.9–3.5)	Navoni et al. (2012)
Lungs	Male	Mortality Rate Ratio of skin cancer in medium/high Arsenic concentration regions with worse SE conditions compared to low Arsenic concentration regions	3 (2.8–3.1)	Navoni et al. (2012)
Colon	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.07 ($p > 0.77$)	Molina et al. (2014)
Colon	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.29 ($p > 0.26$)	Molina et al. (2014)
Colon	Female	IRR with 1 mg/L increased in iAs concentration	12.21 (5.72–26.07)	Aballay et al. (2012)
Colon	Male	IRR with 1 mg/L increased in iAs concentration	0.03 (0.02–0.06)	Aballay et al. (2012)
Cervix	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.30 ($p > 0.25$)	Molina et al. (2014)
Endometrium	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.17 ($p > 0.52$)	Molina et al. (2014)
Stomach	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.13 (0.9–1.43)	Corey et al. (2005)
Stomach	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.08 (0.92–1.28)	Corey et al. (2005)
Stomach	Male	Spearman correlation between Ca Incidence and iAs concentration in drinking water	0.05 ($p > 0.84$)	Molina et al. (2014)
Stomach	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1 (0.96–1.26)	Corey et al. (2005)
Liver	Both	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.38 (1.17–1.63)	Corey et al. (2005)
Liver	Female	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.33 (1.04–1.71)	Corey et al. (2005)
Liver	Male	Mortality Rate Ratio (individuals exposed at iAs concentration upper than 50 mcg compared to lower than 50 mcg)	1.42 (1.14–1.6)	Corey et al. (2005)
Breast	Female	Spearman correlation between Ca Incidence and iAs concentration in drinking water	−0.32 ($p > 0.22$)	Molina et al. (2014)
Breast	Female	IRR with 1 mg/L increased in iAs concentration	1.09 (0.74–1.60)	Aballay et al. (2012)

IRR: Incidence Rate Ratio; OR: Odds Ratio, RR: Risk Ratio; Ca: Cancer, M: Male; F: Female SEC: Socio Economic Conditions.

Table 3
Genetic outcomes assessed in studies in Argentina (2000–2012).

Outcome	Location	Exposure to As (cut off > 50 ppb)	Point estimates (% or index)	p Value	Study reference
Micronuclei in buccal cells	Navarro, Buenos Aires	Yes	0.27%	$p = 0.0002$	Bartolotta et al. (2010)
Micronuclei in buccal cells	Buenos Aires (capital)	No	0.15%		Bartolotta et al. (2010)
Micronuclei in buccal cells	La Firmeza, Santos Lugares, Santiago del Estero	Yes	2.15%	$p = 0.0005$	Bartolotta et al. (2010)
Micronuclei in buccal cells	Monte Quemado, Urutaú, Santiago del Estero	No	0.94%		Bartolotta et al. (2010)
DNA damage	County of Copo/Urutaú, Monte Quemado, Santos, Lugares, Venado Solo y La Firmeza (Santiago del Estero)	Yes	32.79%	$p < 0.001$	Navoni et al. (2006)
DNA damage	County of Copo/Urutaú, Monte Quemado, Santos, Lugares, Venado Solo y La Firmeza	No	9.77%		Navoni et al. (2006)
Haplotype protective CTA AS3MT	San Antonio de los Cobres (Salta)	***	68.7%	$p = 0.00002$	Schlebusch et al. (2013)
Haplotype protective CTA AS3MT	Rosario de Lerma/J.V. González/Taco Pozo	***	36.7%		Schlebusch et al. (2013)
Mitotic index[a]	Firmeza y Santos Lugares (Santiago del Estero)	Yes	4.18*	$p = 0.01$	Hick and Carballo (2005)
Sister chromatid exchange[b]			8.33%	$p < 0.001$	
Replication index[c]			2.15		
Micronuclei in buccal cells			15.46%*		
Damage index			148.5		
Mitotic index	Urutaú (Santiago del Estero)	No	5.01		Hick and Carballo, (2005)
Sister chromatid exchange			8.04%		
Replication index			2.13		
Micronuclei in buccal cells			12.75%		
Damage index			144.11		
Mitotic index	Providencia (Santiago del Estero)	Yes	4.92		Hick and Carballo, (2005)
Sister chromatid exchange			6.23%		
Replication index			2.15		
Mitotic index	Providencia (Santiago del Estero)	No	4.84		Hick and Carballo, (2005)
Sister chromatid exchange			6.37%		
Replication index			1.98		

[a] Mitotic index: Number of cells division (metaphase) in relation to the number of cells stimulated.
[b] Number of genetic material exchanges during metaphase process in fifty metaphases of second division in each individual.
[c] Cell count in each mitotic division after analyzing 100 consecutive metaphases.
* Statistically significant.
*** N/A (information not available)

dose exposure (Steinmaus et al., 2013). The severity and degree of disease is very dependent on several factors such as the levels of As in drinking water, the local climate, the duration of exposure, the age and the body weight. Few papers have attempted to define dose–response relationships between As exposure through drinking water and chronic toxicity because of the difficulty to determine a precise estimation of individual exposure. The most desirable indexes for evaluating As exposure for a long period may be obtained considering biomarkers and exposure durations in each period (Yoshida et al., 2004). A recent review suggests the existence of a dose–response relationship for cancer in subjects exposed to sufficient dose and duration (Cohen et al., 2013). Ecological studies of cancer mortality in a large population in Taiwan exposed to high arsenic levels in well waters have been the focus of dose–response assessments of arsenic cancer risk by the USA (Chen et al., 1992; Wu et al., 1989; Tseng et al., 1968; Tseng, 1977).

Regarding the As levels in water and their relationship with health outcomes, our findings are consistent with the evidence existing in the Latin American region; epidemiological studies found that arsenic exposure in the early life is strongly associated with an increased

Table 4
Frequency of skin conditions by gender in subjects chronically exposed to arsenic in water (>50 ppb).

Outcome	Estimates	Province	City	N subjects	Water samples (n)	Study reference
Proportion of Skin lesions (%)	58.00	Tucumán	Santa Rosa de Leales	36	36	Escalante et al. (2009)
	12.4	Tucumán	Leales	89	140	Guber et al. (2009)
	39.4	Tucumán	Graneros	33	95	Guber et al. (2009)
	38.4	Tucumán	County Graneros	188	188	Soria et al. (2014)
	9.00	Tucumán	County Graneros	207	207	Soria et al. (2014)
	26.45	Tucumán	Leales y Graneros	115	115	Soria de Gonzalez et al. (2009)
Prevalence (%) of skin cancer in patients with chronic arsenicism	88.00	Patients came from endemic areas attending in hospital	Endemic areas	23	0	Cabrera and Gomez, (2003)
Prevalence of HACRE (%)	2.86	Santa Fe	Carcarañá	35	0	Corey et al. (2005)
	0.00	Santa Fe	Angélica	32	0	Corey et al. (2005)
	2.58	Santa Fe	Elortondo	155	0	Corey et al. (2005)
	2.15	Santa Fe	Progreso	93	0	Corey et al. (2005)
	2.78	Santa Fe	San Jenaro Norte	144	0	Corey et al. (2005)
	2.46	Santa Fe	Villa Cañás	285	0	Corey et al. (2005)
	4.17	Santa Fe	Centeno	48	0	Corey et al. (2005)
	2.5	Santa Fe	Chañar Ladeado	120	0	Corey et al. (2005)
	5.66	Santa Fe	Murphy	53	0	Corey et al. (2005)
	1.47	Santa Fe	Cañada Rosquín	136	0	Corey et al. (2005)
	0.00	Santa Fe	Logroño	22	0	Corey et al. (2005)
	2.6	Tucumán	Villa Belgrano	119	20	Gerstenfeld et al. (2012)

Table 5
Studies identified that reported on As concentration in water samples of different locations of Argentina.

Study reference	Water samples														
	Year of publication	Province	County/city/region	Area	Total number	Well water	Public water	Others	No data	Depths (mts)	Method of as analysis	As (mcg/L)	Estimate	% > 10 mcg/L	% > 50 mcg/L
Aballay et al. (2012)	2004	Córdoba	70% of the population lived in Córdoba city	Rural	N/A	N/A	N/A	N/A	N/A	N/A	N/A			90	N/A
Auge (2014)	N/A	Buenos Aires		Rural and urban	640	?	?	?	640	N/A				N/A	87
Bartolotta et al. (2010)	2007	Buenos Aires/CABA/ Santiago del Estero	Monte Quemado, Urutaú, La Firmeza, Santos Lugares, Navarro, CABA	Rural and urban	59	18	41	0	0	N/A	N/A	4.4–401	Mean		
Blanco et al. (2012)	N/A	Buenos Aires	Cnel. Dorrego	Rural and urban	111	111	0	0	0	N/A	HG–ICP–OES	0–500	Range	95	68
Bobillo et al. (2014)	N/A	Santiago del Estero/Chaco	Paraje El Puesto, Sta. Teresa de Carballo/San Telmo	Rural	70	70	0	0	0	N/A	FI–HG–AAS	N/A	N/A	100	N/A
Bonafina and Ratto, (2009)	1970–2006	Buenos Aires	Bolívar, Cnel. Dorrego, Gral. Lamadrid, Gral. Villegas, 9 de Julio, C. Casares, Junín, Pehuajo, Guamini, Puan, Suipacha	Rural and urban	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2–800	Range	N/A	N/A
Campaña et al. (2014)	2012–2013	Buenos Aires	Bahía blanca y Cnel. Rosales	Rural and urban	56	?	?	?	56	5–40	ICP	15–267	Range	100	84
Carballo et al. (2006)	2005	Córdoba		N/A	20	20	0	0	0	N/A	ICP/atomic absorption	58.17	Mean	97.5	42
Concha et al. (2006)	1994–2004	Salta	San Antonio de los Cobres	Rural and urban	31	?	?	?	31	N/A	HG–AAS	189	Mean	N/A	N/A
Corey et al. (2005)	1999	Santa Fe		Rural and urban	196	0	196	0	0	N/A		>50	Median		
Escalante et al. (2009)	2008–2009	Tucumán	Leales	Rural and urban	71	71	0	0	0	125–150	Spectrophotometric method	7–15		51	N/A
Esposito et al. (2011)	2008	Buenos Aires	Bahía Blanca y Punta Alta	Rural	37	?	?	?	37	N/A	ICP–AES	0–114	Range	97.3	N/A
Ferral et al. (2014)	N/A	CABA	Mataderos Neighborhood	Urban	18	18	0	0	0	120	Atomic absorption	180–250	Range	40	0
Gerstenfeld et al. (2012)	2008	Tucumán	Villa Belgrano	Urban	20	20	0	0	0	0.011–0.089	Atomic absorption	N/A		100	30
Gonzalez Uriarte et al. (2002)	N/A	Buenos Aires	Puan	Rural and urban	20	?	?	?	20	0–50	N/A	N/A		40	40
Guber et al. (2009)	N/A	Tucumán	Leales y Graneros	Rural	235	235	0	0	0	N/A	Gutzei method	N/A		78	N/A
Heredia and Fernandez, (2009)	2004	Buenos Aires	Escobar — Acuífero Pampeano	Rural and urban	43	43	0	0	0	Surface water	ICP–OES	24.79	Mean	N/A	N/A
Medina et al. (2004)	2001–2002	Chaco	Presidencia Roque Sáenz Peña, Santa Sylvina, Villa Berthet, Charata, Gancedo y Chorotis,	Rural and urban	N/A	N/A	N/A	N/A	N/A	Ground water	N/A	1000	Mean	N/A	N/A
Molina et al. (2014)	2003–2007	La Pampa	Atreucó/Maracó/ Rancul/Chapaleufú/La Pampa Capital/Conhelo/Realicó/ Utracán/Caleu Caleu/Catriló /Guatraché/Hucal/Toay/Trenel/ Loventué/Quemú	Rural and urban	N/A	N/A	N/A	N/A	N/A	N/A		35–390		N/A	N/A

Moschione et al. (2014)	2013	Buenos Aires	Trenque Lauquen	Rural and urban	33	33	0	0	0	N/A	Atomic absorption	7	Mean	34	0
Navoni et al. (2012)	2003–2008	Buenos Aires	52 cities	Rural and urban	152	53	75	8	16	N/A	Atomic absorption	40.1	Mean	82	40
Olivera et al. (2006)	2005	Santiago del Estero	Copo	Rural and urban	64	?	?	?	64	300–350 m	ICP/Atomic absorption	10–926	Range	46.88	31.25
Olmos et al. (2014)	N/A	Santiago del Estero/Chaco		Urban	120	?	?	?	120	N/A	HG–AAS	13–1147	Range		
Paoloni et al. (2005)	N/A	Buenos Aires	Coronel Dorrego	Rural	104	104	0	0	0	N/A	CVAAS	0–500	Range	83.5	56.3
Paoloni et al. (2009)	2007	Buenos Aires	Bahía Blanca	Rural and urban	81	?	?	?	81	1.2–55.8 m	HG–ICP–OES	0–300	Range	97	N/A
Peluso et al. (2012)	2005–2007	Buenos Aires	Azul	Urban	12	0	0	12	0	30 cm	Atomic absorption	28	Mean	N/A	N/A
Peluso et al. (2014)	2008–2010	Buenos Aires	Tres Arroyos	Rural and urban	90	0	0	90	0	Surface water	Atomic absorption	72.8	Mean	N/A	N/A
Rigacci et al. (2013)	2009–2010	Buenos Aires	Rio Reconquista	Rural and urban	36	0	0	36	0	N/A	Atomic absoption	N/A		N/A	N/A
Rosso et al. (2011)	2009	Buenos Aires		Rural and urban	39	?	?	?	39	0.5 m	ICP	113.69	Mean	59	59
Rosso et al. (2013)	2008–2009	Buenos Aires	Rio Salado, Rio Quequen Salado, Rio Sauce Grande	Rural and urban	20	?	?	?	20	N/A	ICP	125.95	Mean	100	100
Schenone et al. (2007)	2004–2005	Buenos Aires	Bahía de Samborombón	Rural and urban	19	?	?	?	19	N/A	ICP–OES			N/A	5
Soria et al. (2014)	N/A	Tucumán	Graneros	Rural	395	395	0	0	0	N/A	Gutzei method	Variable			
Soria de Gonzalez et al. (2009)	N/A	Tucumán	Leales y Graneros	Rural	115	115	0	0	0	N/A	Spectrophotometric method (Vasak-Sedivek)	120–160	Range	100	N/A
Soria de Gonzalez et al. (2011)	2005–2009	Tucumán	Graneros	Rural	161	161	0	0	0	N/A	Gutzei method	0–820	Range	21.1	N/A
Vazquez et al. (2014)	N/A	Buenos Aires	La Matanza (barrio Los Alamos)	Urban	12	12	0	0	0	N/A	others			100	N/A
Villagra Cocco et al. (2014)	N/A	Córdoba	Río Cuarto (Chajan)	Rural	32	32	0	0	0	N/A		500	Mean	N/A	N/A
Ward et al. (2014)	2005–2013	13 Provinces (reported only BA data)		Rural and urban	62	62	0	0	0	Ground water	ICP	6.5–191	Range	N/A	N/A

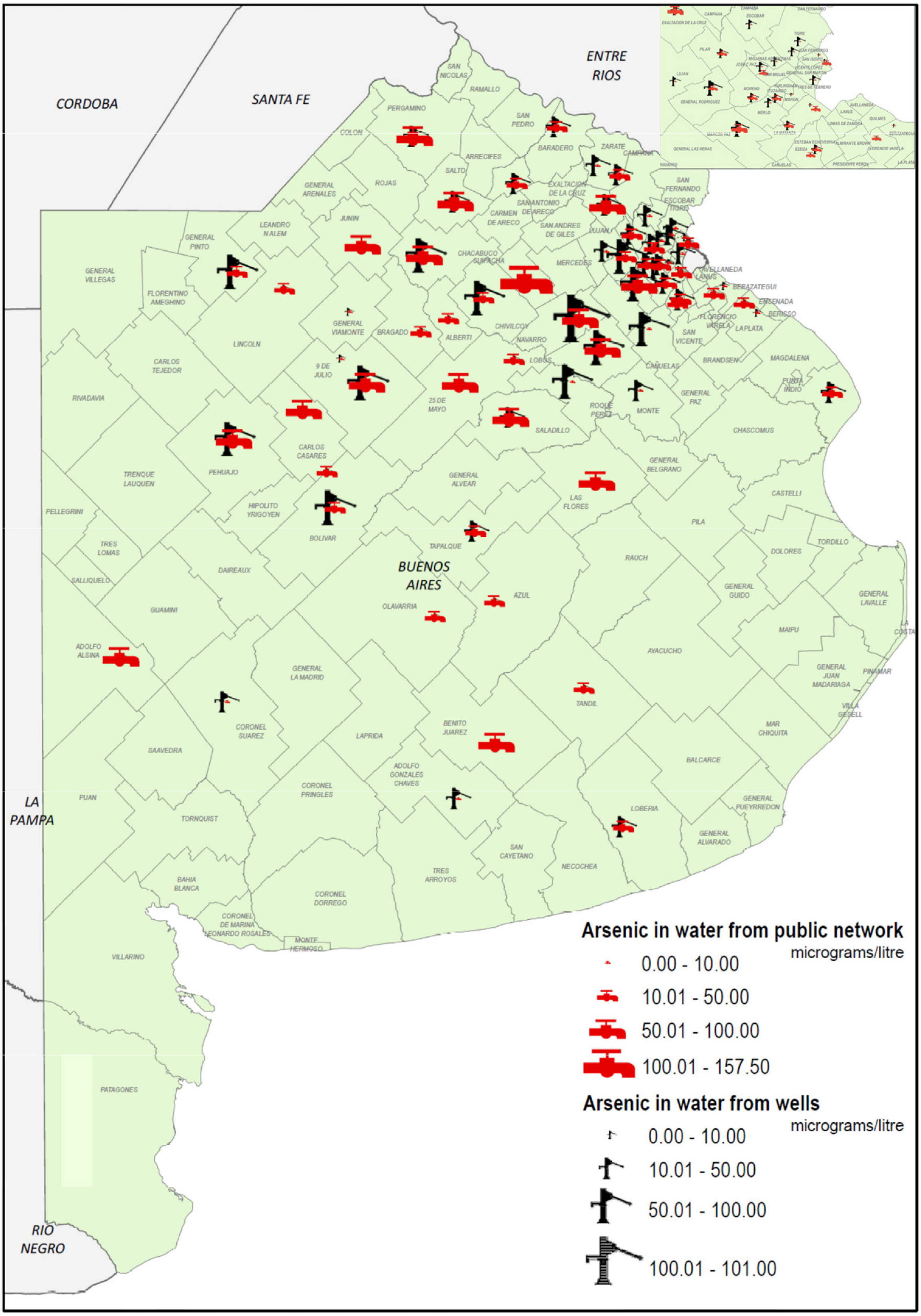

Fig. 2. Arsenic content in water samples from public network and wells in Buenos Aires.

mortality from bladder cancer, laryngeal cancer, liver cancer, and chronic renal disease in adults (Hopenhayn-Rich et al., 2000), and perinatal arsenic exposures were associated with increases in late fetal, neonatal, and postneonatal mortality (Smith et al., 2012).

The health risk assessments of As in Argentina, like in many other countries, focus on cancer (Tsuji et al., 2014). In our study, the incidence rate ratio (IRR) of colorectal cancer with every 100 μg/L increment in inorganic As (iAs) concentration was 0.03 (95% CI 0.02–

0.06) in men and 12.21 (5.72–26.07) in women, who also showed a higher IRR for lung cancer, being the estimates 9.61 (6.59–14) and 56.03 (24.08–130.4) for males and females, respectively. The estimate for breast cancer was 1.09 (0.74–1.6) and for prostate cancer 0.05 (0.03–0.08). The mortality rate ratio (MRR) due to skin cancer was 1.64 (0.89–1.64) and 2.46 (1.06–5.72) for males and females, respectively. This effect on MRR was consistent when the comparison was made between regions with medium/high As concentration and those with low As concentration for both genders, at least for liver and skin cancer. Central estimations are potentially important for mortality outcomes and should be confirmed by studies with the proper statistical power.

Arsenic poisoning from drinking As-contaminated underground water was often triggered by the introduction of deep tube-pump wells to replace surface water usage in many areas in Bangladesh or China at late 1970s. Only after three decades, As contamination of groundwater in Bangladesh has been reported as the biggest arsenic catastrophe in the world since more than 50% of the total population is estimated to be at risk of contamination (Khan et al., 2003). The time of exposure is relatively short in terms of cancer; only recently small numbers of skin cancer cases started to appear in Bangladesh (Smith et al., 2000). It appears that skin is very sensitive to As, and As-induced skin lesions, as dyspigmentation and hyperkeratosis, are the earliest nonmalignant health effects related to chronic As exposure. Yoshida et al. found an increase in the prevalence of skin lesions even at 5–10 μg/L in the drinking water, a lower level than the drinking water quality standard of WHO (Yoshida et al., 2004).

Cancers of the lung and urinary bladder appear to be the most common ones in chronic As exposed populations, and showed relatively high mortality rates even at relatively low As exposure levels. Wu et al. evaluated the mortality rates among malignancies of skin, lung, bladder, and kidney in Taiwan. The highest OR of skin cancer was 5.31 for male or 12.01 for female in the group exposed over 600 μg/L of drinking water against 290 μg/L group (Wu et al., 1989). Tseng et al. also observed a dose-dependent correlation between skin cancer and As level in Taiwan (Tseng et al., 1968). A meta-analysis of cohort and case–control epidemiologic studies that examined low-level arsenic exposure and bladder cancer risk showed a summary relative risk of 1.11 (95%CI 0.95–1.30) (Mink et al., 2008). However, another review predicted that lifetime exposure to arsenic in drinking water at 10 μg/L would result in a bladder cancer risk of about 2 in 1000 (NRC, 2001). Therefore, the effect of low-level arsenic exposure remains uncertain for bladder cancer.

Regarding the evidence of genetic changes associated to As exposure, the association of urinary metabolite levels and the development of nuclear polymorphisms was explored in four studies. The median percentage of micronuclei found in oral mucosa of samples pertaining to exposed subjects was 0.61%, the median mitotic Index was 4.88, the DNA damage ranged from 10 to 33% and the frequency of protective haplotype CTA AS3MT polymorphism ranged from 37 to 69%. A growing body of evidence indicates that As carcinogenicity results from epigenetic changes, particularly in DNA methylation (Reichard and Puga, 2010). Two single nucleotide polymorphisms (SNPs), AS3MT 12390 (rs3740393) and 14458 (rs11191439) were consistently related to arsenic methylation in different populations. Thus, these SNPs may be useful indicators to predict the arsenic metabolism via methylation pathways (Agusa et al., 2011). In Antofagasta, Chile, the cancer mortality rate for As-associated cancers might be at least partly related to differences in As biotransformation. Genetic biomarkers such as 2A and GSTM1 polymorphisms in addition to DR70 as screening biomarkers might provide relevant information to identify individuals with a high risk for lung cancer (Adonis et al., 2005).

A study in Latin America showed that chromosomal aberrations were more frequent in an As highly exposed Mexican population (Ostrosky-Wegman et al., 1991). Genotoxic effects were also observed through evaluation of micronucleus induction in cases of both environmental and occupational exposure in studies from Chile (Paiva et al., 2008; Martinez et al., 2004) and from Mexico (Andrew et al., 2006). Several authors showed the As-related DNA damage specifically in the bladder, observed in micronuclei of exfoliated cells (McClintock et al., 2012).

Arsenical skin lesions serve as an indicator of persistent As exposure. They were reported to occur from exposure to concentrations as low as 10 μg/L in prospective cohort studies (Argos et al., 2011). The median frequency of skin lesions in subjects chronically exposed to As was shown to be 32.43% in the province of Tucumán in 2009–2014. In another study done in 2005, the median prevalence of HACRE syndrome in the Santa Fe province was 2.52%. The proportion of skin cancer in patients with arsenicosis reached levels as high as 88% in a case series from the province of Buenos Aires (Cabrera and Gomez, 2003c). A clear dose–response relationship with skin cancer was found when exposure was measured by way of urinary concentration of monomethyl arsenic (MMA), a metabolic intermediate of arsenic (Council NCoIABoESaTDoEaLSNR, 2014). The mutagenicity was observed not only with MMA but also with dimethylarsinous acid (DMA) (Klein et al., 2007).

In Argentina the highest As contents in groundwater were found in the Chaco–Pampean Plain (provinces of Buenos Aires and La Pampa), in the Northwest and Cuyo region (provinces of Mendoza, San Juan and San Luis), although the Patagonia region needs to be studied with higher detail. The Chaco–Pampean Plain is the most populated geographical region of Argentina, covering more than one million km^2. Risk areas have been identified in the north of the province of La Pampa, south and southeast of the provinces of Córdoba, in specific localities of the provinces of Buenos Aires, Santa Fe, Santiago del Estero, Chaco and Salta, and in the east of Tucumán (Figueiredo et al., 2010). In particular, in Buenos Aires, the Pampean aquifer — the largest source of groundwater of the whole region — presents As levels between 100 and 300 μg/L in the Atlantic coast. Fortunately, the northern, the most populated part of the Province, is supplied by the Puelche aquifer, with As levels less than 10 μg/L. Data from the CETOX laboratory (Faculty of Pharmacy and Biochemistry UoBA, 2012), which updated the national CONAPRIS study (Swiecky et al., 2006), showed that around 87% of the total area of the Buenos Aires province (307,000 km^2) has groundwater with As concentrations above 50 μg/L, and more than 90% above 10 μg/L. Fortunately, only 9% of the total population of the province lives in these areas, but still affecting a huge number of persons (1.37 million). These results are in agreement with those obtained in another study (González et al., 2005) indicating that the inhabitants of 31 cities of the province of Buenos Aires consume water with high As levels (around 200 μg/L). The cities with the highest identified As levels in water were Junín, Baradero and Tornquist. With the 10 μg/L limit, most of the territory with groundwater supply would be unfit for domestic use in the Buenos Aires province. A recent report (Auge, 2014) showed results of 640 groundwater samples from 74 departments and 159 cities of the Buenos Aires province supplied by the Pampeano aquifer, and the dunes of the Atlantic coast. A remarkable predominance of concentrations exceeding 50 μg/L was observed particularly in the north of the province, e.g., in the localities of Suipacha, 9 de Julio and Chacabuco.

In the province of Buenos Aires the studies documenting As removal are scarce. The implementation of removal facilities using coagulation–adsorption as a centralized system, the use of the same system in households, the use of commercial adsorbents in the points of use (POU) and reverse osmosis plants at different locations in the province such as Suipacha, were the only identified methods. The University of Rosario has patented a process based on coagulation–coprecipitation–adsorption. Removal plants based on this technique have been implemented particularly in Lezama, province of Buenos Aires (Ingallinella and Fernández, 2010).

In 2009, the National Institute of Industrial Technology of Argentina (INTI) developed an intervention model for the abatement of As in drinking water to provide solutions for communities supplied by public water networks and private wells. The equipment is based on an optimized coagulation/filtration technology with a previous oxidation step, which does not need electric supply. This system was applied in the province of Chaco and in the groundwater of the town of Lobos, province of Buenos Aires (INTI-Química, 2009; Frangie et al., 2014). Another experience is the implementation of POU based on adsorption on synthetic granular ferric hydroxide fixed beds (Bahr and Ewy, 2014) in four localities of Argentina including Junín, Suipacha and Chivilcoy in the province of Buenos Aires. To our knowledge, the only documented results are those from the Argentine company AySA (Agua y Saneamientos Argentinos, Water and Sanitation from Argentina), which has installed the largest reverse osmosis water treatment plant in South America, treating water from boreholes in González Catán and Virrey del Pino, and benefiting 400,000 inhabitants (Agua y Saneamientos Argentinos SA, 2014). Low-cost technologies at small scale are still under constant investigation. Examples are solar oxidation processes, adsorption on biomass, clay, phytoremediation, and others (Litter et al., 2008).

In Argentina, the creation of a multidisciplinary governmental body facing the problem from different points of view including epidemiological surveillance, and for undertaking specific technological research should be proposed. A law project for the creation of a National Program against HACRE has been recently presented at the Argentine National Senate.

Regarding the strengths of the present study, it is important to highlight the completeness of the search on the main electronic databases and the effort for the identification of unpublished studies, including proceedings of important congresses and direct contact with experts. However, we were not allowed to access official data about As concentration levels from several consulted authorities. Moreover, making inferences from ecological studies is challenging because of numerous methodological concerns considering the absence of individual level data, confounding, and misclassification. Populations differ in terms of levels of exposure, nutritional status, prevalence of comorbidities, socioeconomic factors, access to medical care, lifestyle factors, and genetic characters limiting the generalizability and the identification of clear effect patterns. Considering the evidence gaps identified by this systematic review, further studies should be performed with a higher periodicity and covering still non relieved regions.

Some limitations of this review are related to the fact that some factors such as multiple exposure pathways and synergistic effects were not adequately described in the primary studies. The present study focused on the effect of exposure only from water sources. Although speciation is relevant for the severity of damage — As(III) being more toxic than As(V) — several unpublished results indicate that the main species present in waters of Argentina for human consumption is As(V). Recent published studies indicate that only in some surface waters of the San Juan, La Pampa and Neuquén provinces, the predominant species is As(III), while in groundwaters of Buenos Aires and Santa Fe, the main As species is the pentavalent one (O'Reilly et al., 2010). Similarly, in Copahue (province of Neuquén), arsenite predominated only along the upper río Agrio, but the species distribution changed at lago Caviahue and arsenate became the main species up until Salto del Agrio (Farnfield et al., 2012).

Although several removal technologies are available in Latin America, it is still urgent to develop technologies and methods with a particular focus towards small-scale rural operations (Alarcon-Herrera et al., 2013).

5. Conclusions

To our knowledge, this study represents the first systematic review of the epidemiology of arsenic in Argentina. Although we found important gaps about the impact of arsenic on health outcomes, studies converge to show a clear association between high levels of arsenic in water and the frequency of related diseases in Argentina.

Prevention, health promotion, epidemiological and environmental surveillance, efficient methods to abate As drinking water and strict national and subnational policies are some of the key actions to control this major public health problem.

Financial support

This research project was endorsed by the National Council of Scientific and Technical Research CONICET, Argentina, and sponsored by the National University of Central Buenos Aires - UNICEN, under an Agreement for Cooperation and Technical Assistance signed between these institutions and the Strategic Forum for National Development. These institutions were not involved in the study design, data collection, analysis and interpretation of data; in the writing of the report; or the decision to submit the article for publication.

Acknowledgments

We are particularly grateful to Dr. Edda Villaamil Lepori, from the School of Pharmacy and Biochemistry, University of Buenos Aires for the technical support and provision of primary data, to Dr. Julio Navoni for his support during the production of this work and also for providing primary data, to Dr. Susana García, Chair of Toxicology, University of Buenos Aires for technical advice in the early stages of this work and for providing relevant information, and finally to librarian Daniel Comandé of the IECS for his important contribution in the search strategies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2015.08.070.

References

Aballay, L.R., Diaz Mdel, P., Francisca, F.M., Munoz, S.E., 2012. Cancer incidence and pattern of arsenic concentration in drinking water wells in Cordoba, Argentina. Int. J. Environ. Health Res. 220–231.

Adonis, M., Martinez, V., Marin, P., Gil, L., 2005. CYP1A1 and GSTM1 genetic polymorphisms in lung cancer populations exposed to arsenic in drinking water. Xenobiotica 35 (5), 519–530 (May).

Agua y Saneamientos Argentinos SA, 2014. Planta potabilizadora por el sistema de ósmosis inversa. http://www.aysa.com.ar/index.php?id_seccion=562 (Accessed 06 14).

Agusa, T., Fujihara, J., Takeshita, H., Iwata, H., 2011. Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms. Int. J. Mol. Sci. 12 (4), 2351–2382.

Alarcon-Herrera, M.T., Bundschuh, J., Nath, B., et al., 2013. Co-occurrence of arsenic and fluoride in groundwater of semi-arid regions in Latin America: genesis, mobility and remediation. J. Hazard. Mater. 262, 960–969 (Nov).

Alonso, D.L., Latorre, S., Castillo, E., Brandao, P.F., 2014. Environmental occurrence of arsenic in Colombia: a review. Environ. Pollut. 186, 272–281 (Mar).

Ameer, S.S., Engström, K., Harari, F., Concha, G., Vahter, M., Broberg, K., 2014. Arsenic Exposure and Blood Pressure, Homocysteine and Haemoglobin Concentrations: a Study From Northern Argentina. 5th International Congress on Arsenic in the Environment.

Andrew, A.S., Burgess, J.L., Meza, M.M., et al., 2006. Arsenic exposure is associated with decreased DNA repair in vitro and in individuals exposed to drinking water arsenic. Environ. Health Perspect. 114 (8), 1193–1198 (Aug).

ANMAT, 2012. Capitulo XII: Bebidas Hídricas, Agua y Agua Gasificada. Sección: Agua Potable. Administración Nacional de Medicamentos, Alimentos y Tecnologías, Argentina.

Argos, M., Kalra, T., Pierce, B.L., et al., 2011. A prospective study of arsenic exposure from drinking water and incidence of skin lesions in Bangladesh. Am. J. Epidemiol. 174 (2), 185–194 (Jul 15).

Auge M. Arsenic in the groundwater of the Buenos Aires province, Argentina. In: M.I. Litter HBN, J.M. Meichtry, N. Quici, J. Bundschuh, P. Bhattacharya, R. Naidu, 2014., ed. Argentina: Interdisciplinary Book Series: "Arsenic in the Environment", Series Editors: Jochen Bundschuh and Prosun Bhattacharya, CRC A.A. Balkema Publishers, Taylor and Francis Publishers; 2014.

Ayerza, A., 1917a. Arsenicismo regional endémico (keratodermia y melanodermia combinadas). Bol. Acad. Med. 2–3, 11–24.

Ayerza, A., 1917b. Arsenicismo regional endémico (keratodermia y melanodermia combinadas) (continuación). Bol. Acad. Med. 2–3, 41–55.

Ayerza, A., 1918. Arsenicismo regional endémico (keratodermia y melanodermia combinadas) (continuación). Bol. Acad. Med. 1–24.
Bahr, C., Ewy, W., 2014. Drinking Water Dearsenification with Granular Ferric Hydroxide: Comparison of Field Experience with Waterworks Units in Germany and POU Units Argentina.
Bartolotta, S.A., Pacskowski, M.G., Hick, A., Carballo, M.A., 2011. Micronuclei assay in exfoliated buccal cells from individuals exposed to arsenic in Argentina. Arch. Environ. Contam. Toxicol. 61, 337–343 (10/20 ed2011).
Bates, M.N., Rey, O.A., Biggs, M.L., et al., 2004. Case–control study of bladder cancer and exposure to arsenic in Argentina. Am. J. Epidemiol. 159 (4), 381–389 (Feb 15).
Besuschio, S., Desanzo, A., Perez, A., Croci, M., 1980. Epidemiological associations between arsenic and cancer in Argentina. Biol. Trace Elem. Res. 2, 41–55.
Biagini, R., 1996. Hidroarsenicismo crónico y cáncer de pulmón. Arch. Argent. Dermatol. 16, 172–184.
Blanco, MdC, Paoloni, J.D., Morras, H., et al., 2012. Partition of arsenic in soils sediments and the origin of naturally elevated concentrations in groundwater of the southern pampa region (Argentina). Environ. Earth Sci. 2075–2084.
Bobillo, C., Navoni, J.A., Olmos, V., Merini, L.J., Villaamil Lepori, E., Corach, D., 2014. Ethnic characterization of a population of children exposed to high doses of arsenic via drinking water and a possible correlation with metabolic processes. Int. J. Morphol. Epidemiol. Genet. 5 (1), 1–10.
Bonafina, C., Ratto, S.E., 2009. Arsenic in groundwater in the north and center of Argentina. Agron. Sch. Buenos Aires Univ. J. 29 (2), 153–162.
Brouwer, O.F., Onkenhout, W., Edelbroek, P.M., de Kom, J.F., de Wolff, F.A., Peters, A.C., 1992. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. Clin. Neurol. Neurosurg. 94 (4), 307–310.
Bundschuh A, Pérez Carrera M, Litter MI. Distribución del arsénico en la región Ibérica e Iberoamericana. In: Desarrollo EPIdCyTpe, ed. Vol ISBN 978-84-96023-61-1. Argentina: Litter; 2008: http://www.cnea.gov.ar/pdfs/actividades_ambientales/LIBROdistribucionarsenico.pdf.
Bundschuh, J., Farias, B., Martin, R., Storniolo, A., Bhattacharya, P., Cortes, J., 2004. Groundwater arsenic in the Chaco–Pampean plain, Argentina: case study from Robles county, Santiago del Estero province. Appl. Geochem. 19, 231–243.
Bundschuh, J., Litter, M.I., Parvez, F., et al., 2012. One century of arsenic exposure in Latin America: a review of history and occurrence from 14 countries. Sci. Total Environ. 429, 2–35 (Jul 1).
Cabrera, H.N., Gomez, M.L., 2003a. Skin cancer induced by arsenic in the water. J. Cutan. Med. Surg. 7 (2), 106–111 (Mar-Apr).
Cabrera, H.N., Gomez, M.L., 2003b. Skin cancer induced by arsenic in the water. J. Cutan. Med. Surg. 106–111.
Cabrera, H.N., Gomez, M.L., 2003c. Skin cancer induced by arsenic in the water. J. Cutan. Med. Surg. 7 (2), 106–111.
Campaña, D.H., Airasca, A., Angeles, G., 2014. Paper Presented at: “Proceedings of the 5th International Congress On Arsenic in the Environment, Buenos Aires, Argentina, 11–16 May 2014, One Century of the Discovery of Arsenicosis in Latin America (1914–2014) As 2014” (Buenos Aires, Argentina).
Carballo, M.A., Badini, R.G., Gonzalez, G.M., 2006. Epidemiología del HACRE en la República Argentina. Unidad Ceprocor (33 pp.).
Chen, C.J., Chen, C.W., Wu, M.M., Kuo, T.L., 1992. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. Br. J. Cancer 66 (5), 888–892 (Nov).
Ciapponi, A., Glujovsky, D., Bardach, A., García Martí, S., Comande, D., 2011. EROS: a new software for early stage of systematic reviews. Paper Presented at: ISPOR 3rd Latin America Conference; 8–10 September 2011 (Mexico DF).
Cohen, S.M., Arnold, L.L., Beck, B.D., Lewis, A.S., Eldan, M., 2013. Evaluation of the carcinogenicity of inorganic arsenic. Crit. Rev. Toxicol. 43 (9), 711–752.
Concha, G., Nermell, B., Vahter, M., 2006. Spatial and temporal variations in arsenic exposure via drinking-water in Northern Argentina. J. Health Popul. Nutr. 317–326.
Corey, G., Tomasini, R., Pagura, J., 2005. Epidemiological Study of Arsenic Exposition Through Drinking Water. Ente REgulador de Servicios Sanitarios (ENRESS), Argentina.
Committee on Inorganic Arsenic, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council, 2014. Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report. Washington, DC.: National Academy of Sciences.
Engstrom, K., Nermell, B., Concha, G., Stromberg, U., Vahter, M., Broberg, K., 2009. Arsenic metabolism is influenced by polymorphisms in genes involved in one-carbon metabolism and reduction reactions. Mutat. Res. Fundam. Mol. Mech. Mutagen. 4–14.
Engstrom, K., Vahter, M., Mlakar, S.J., et al., 2011. Polymorphisms in arsenic(+III oxidation state) methyltransferase (AS3MT) predict gene expression of AS3MT as well as arsenic metabolism. Environ. Health Perspect. 182–188.
Cochrane Effective Practice Organisation of Care Group (EPOC), 2009. Draft EPOC ‘Risk of Bias’ guideline. January 2009. http://epoc.cochrane.org/en/handsearchers.html Accessed 06 2014.
Escalante, R., Soria, N., Feldman, G., Martínez, Riera N., 2009. Estudio del hidroarsenicismo crónico regional endémico en la población de Santa Rosa de Leales, Tucumán: Study of endemic regional chronic hidroarsenicism in the population of Santa Rosa of Leales, Tucumán. Acta Toxicol. Argent. 17, 2–56.
Esposito, M.E., Paoloni, J.D., Sequeira, M.E., Amiotti, N.M., Blanco, MdC, 2011. Natural contaminants in drinking waters (arsenic, boron, fluorine and vanadium) in the Southern Pampean Plain, Argentina. J. Environ. Prot. 2 (1), 97–108.
Faculty of Pharmacy and Biochemistry UoBA, 2012. CETOX Laboratory Database.
Farias, S.S., Casa, V.A., Vazquez, C., Ferpozzi, L., Pucci, G.N., Cohen, I.M., 2003. Natural contamination with arsenic and other trace elements in ground waters of Argentine Pampean Plain. Sci. Total Environ. 309 (1–3), 187–199 (Jun 20).
Farnfield, H.R., Marcilla, A.L., Ward, N.I., 2012. Arsenic speciation and trace element analysis of the volcanic rio Agrio and the geothermal waters of Copahue, Argentina. Sci. Total Environ. 433, 371–378 (Sep 1).
Ferral, A.E., Alaniz, E., Sarmiento Tagle, M., Ferral, A., Petrusevski, B., 2014. Hydrogeochemical characterization of the presence of arsenic in the Puelche aquifer in the area of Mataderos, Buenos Aires province, Argentina. 5th International Congress on Arsenic in the Environment.
Figueiredo, B.R., Silva, C.R., Mañay, N., et al., 2010. Medical geology: a regional synthesis. In: Selinus, O., RBF, Centeno, J.A. (Eds.), Medical Geology Studies in South AmericaBook Series International Year of Planet Earth. Springer, Netherlands.
Frangie, M.S., Hernandez, A., Orsini, M.P., 2014. Intervention Model on Removal of Arsenic from Drinking Water. Instituto Nacional de Tecnología Industrial, San Martin, Argentina.
Gerstenfeld, S., Jordán, A., Calli, R., et al., 2012. Determinación de zonas de riesgo al agua arsenical y prevalencia de hacer en Villa Belgrano, Tucumán, Argentina (Determination of zones exposed to arsenical water and CERHA prevalence in Villa Belgrano, Tucumán, Argentina). Rev. Argent. Salud Publica 24–29.
Gonzalez Uriarte, M., Paoloni, J.D., Navarro, E., Fiorentino, C.E., Sequeira, M., 2002. Landscape, surface runoff, and groundwater quality in the district of Puan, province of Buenos Aires, Argentina. J. Soil Water Conserv. (Ankeny) 192–195.
González, M.J., Barone, V.L., Schalamuk, I.B., Botto, I.L., 2005. Arcillas ferruginosas de la provincia de Buenos Aires como adsorbente para la eliminación de contaminantes en aguas. Paper presented at: XVI Congreso Geológico Argentino; 20 al 23 de Septiembre de 2005 Universidad de La Plata (UNLP), National University of La Plata (NULP); Argentina.
Guber, R.S., Tefaha, L., Arias, N., et al., 2009. Contenido de arsénico en el agua de consumo en Leales y Graneros (Provincia de Tucumán — Argentina) Levels of arsenic in the drinking water in Leales and Graneros (Tucumán — Argentina). Acta Bioquím. Clín. Latinoam. 43 (2), 201–207.
Heredia, O.S., Fernandez, Cirelli A., 2009. Trace elements distribution in soil, pore water and groundwater in Buenos Aires, Argentina. Geoderma 409–414.
Hick, A., Carballo, M., 2005. Evaluacion de la genotoxicidad en las provincias de Santiago del Estero y Santa Fe. Final Report. Ministry of Health Argentina: Carrillo-On~ativia Scholarship 2005.
Higgins, J., Green, S. (Eds.), 2011. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration (Available from http://www.cochrane-handbook.org).
Hopenhayn-Rich, C., Biggs, M.L., Fuchs, A., et al., 1996. Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiology 7 (2), 117–124 (Mar).
Hopenhayn-Rich, C., Browning, S.R., Hertz-Picciotto, I., Ferreccio, C., Peralta, C., Gibb, H., 2000. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. Environ. Health Perspect. 108 (7), 667–673 (Jul).
IARC, 2004. Monographs on the evaluation of carcinogenic risks to humans: some drinking-water disinfectants and contaminants, including arsenic. Summary of Data Reported and Evaluation vol. 84. World Health Organization, International Agency for research on cancer.
IARC, 2012. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Arsenic and Health Outcomes. p. 100c.
Ingallinella, A.M., Fernández, R., 2010. Experiencia argentina en la remoción de arsénico por diversas tecnologías. Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo, Argentina.
International Society of Groundwater for Sustainable Development, 2014. V International Congress of Arsenic in the environment. International Society of Groundwater for Sustainable Development, Argentina (http://www.as2014.com.ar/es/home.html).
INTI-Química, 2009. Informe de arsénico en agua. INTI-Química, Argentina (http://www.inti.gob.ar/quimica/pdf/asenagua.pdf. Accessed 06 14).
Khan, M.M., Sakauchi, F., Sonoda, T., Washio, M., Mori, M., 2003. Magnitude of arsenic toxicity in tube-well drinking water in Bangladesh and its adverse effects on human health including cancer: evidence from a review of the literature. Asian Pac. J. Cancer Prev. 4 (1), 7–14 (Jan-Mar).
Klein, C.B., Leszczynska, J., Hickey, C., Rossman, T.G., 2007. Further evidence against a direct genotoxic mode of action for arsenic-induced cancer. Toxicol. Appl. Pharmacol. 222 (3), 289–297 (Aug 1).
Liberati, A., Altman, D.G., Tetzlaff, J., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6 (7), e1000100 (Jul 21).
Litter, M.I., 2010. La problemática del arsénico en la Argentina: el HACRE. Rev. Soc. Argent. Endocrinol. Ginecol. Reprod. (SAEGRE) 17, 5–10.
Litter, M.I., Fernandez, R.G., Cáceres, R.E., Grande Cobián, D., Cicerone, D., Fernández Cirelli, A., 2008. Tecnologías de bajo costo para el tratamiento de arsénico a pequeña y mediana escala. Rev. Ing. Sanit. Ambient. Nº100, 41–50 (septiembre/diciembre 2008;Edición).
Martinez, V., Creus, A., Venegas, W., et al., 2004. Evaluation of micronucleus induction in a Chilean population environmentally exposed to arsenic. Mutat. Res. 564 (1), 65–74 (Nov).
Matos, E.L., Vilensky, M., Mirabelli, D., Boffetta, P., 2000. Occupational exposures and lung cancer in Buenos Aires, Argentina. J. Occup. Environ. Med. 653–659.
Mazumder, D., Haque, R., Ghosh, N., et al., 2000. Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. Int. J. Epidemiol. 29, 1047–1052.
McCarty, K.M., Hanh, H.T., Kim, K.W., 2011. Arsenic geochemistry and human health in South East Asia. Rev. Environ. Health 26 (1), 71–78.
McClintock, T.R., Chen, Y., Bundschuh, J., et al., 2012. Arsenic exposure in Latin America: biomarkers, risk assessments and related health effects. Sci. Total Environ. 429, 76–91 (Jul 1).
Medina, M.L., Merino, L.A., Miranda, O., Gorodner, J.O., 2004. Hidroarsenicismo crónico regional endémico (HACRE) y patologías gingivoperiodontales en pobladores del Chaco (Argentina). Bol. Inst. Med. Reg. 94–99 (n.esp).

Mink, P.J., Alexander, D.D., Barraj, L.M., Kelsh, M.A., Tsuji, J.S., 2008. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. Regul. Toxicol. Pharmacol. 52 (3), 299–310 (12).

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097 (Jul 21).

Molina, R., Schulz, C., Bernardos, J., Dalmaso, M., 2014. Association between arsenic in groundwater and malignant tumors in La Pampa, Argentina. 5th International Congress on Arsenic in the Environment.

Moschione, E., Cuzzio, G., Campins, M., Zamora, A., 2014. Water quality data and presence of arsenic in groundwater in Trenque Lauquen County, province of Buenos Aires (Argentina). 5th International Congress on Arsenic in the Environment.

Murcott, S., 2012. Arsenic Contamination in the World — an International Sourceboo. IWA Publishing, London, UK.

National Commission of Health Research Programs, 2006. Epidemiology of the Chronic Endemic Regional Hydroarsenicism in the Republic of Argentina. National Commission of Health Research Programs, Argentina (http://www.msal.gov.ar/images/stories/ministerio/intoxicaciones/hacre/libro-hidroarsenicismo.pdf).

Navoni, J.A., González Cid, M., Olivera, M., et al., 2006. Daño al ADN asociado al contenido de arsénico urinario en una población de jóvenes expuesta al arsénico por el agua de bebida. Acta Toxicol. Argent. 14 (Suppl.), 48–51.

Navoni, J.A., De Pietri, D., Garcia, S., Lepori, E.C.V., 2012. Health risk for the vulnerable population exposed to arsenic in the province of Buenos Aires, Argentina. Rev. Panam. Salud Publica 1–8.

Nicolli, H.B., Bundschuh, J., Garcia, J.W., Falcon, C.M., Jean, J.S., 2010. Sources and controls for the mobility of arsenic in oxidizing groundwaters from loess-type sediments in arid/semi-arid dry climates — evidence from the Chaco–Pampean plain (Argentina). Water Res. 44 (19), 5589–5604 (Nov).

Nicolli, H.B., Bundschuh, J., Blanco Mdel, C., et al., 2012. Arsenic and associated trace-elements in groundwater from the Chaco–Pampean plain, Argentina: results from 100 years of research. Sci. Total Environ. 429, 36–56 (Jul 1).

Nordstrom, K., 2002. Worldwide occurrences of arsenic in ground water. Science 296, 2.

NRC, 2001. Arsenic in Drinking Water: 2001 Update. National Research Council (NRC), Washington, DC.

Olivera, N.M., Villaamil Lepori, E., Atilde, sup, nica, 2006. Epidemiologia del hidroarsenismo cronico regional endemico (HACRE) en la Republica Argentina. Facultad de Farmacia y Bioquimica. Centro de Asesoramiento Toxicologico Analitico, p. 27.

Olmos, V., Navoni, J.A., Villamil Lepori, E.C., 2014. High level of exposure to arsenic and its influence on arsenic urinary methylated metabolites: a study from Argentina. 5th International Congress on Arsenic in the Environment.

O'Reilly, J., Watts, M.J., Shaw, R.A., Marcilla, A.L., Ward, N.I., 2010. Arsenic contamination of natural waters in San Juan and La Pampa, Argentina. Environ. Geochem. Health 32 (6), 491–515 (Dec).

Ostrosky-Wegman, P., Gonsebatt, M.E., Montero, R., et al., 1991. Lymphocyte proliferation kinetics and genotoxic findings in a pilot study on individuals chronically exposed to arsenic in Mexico. Mutat. Res. 250 (1–2), 477–482 (Sep-Oct).

Padial, C., 2004. Estado actual del Hidroarsenicismo Crónico Regional Endémico en el departamento Banda, Provincia de Santiago del Estero, Argentina. Presented at: Encuentro sobre usos y resultados de tecnologías económicas para la purificación de aguas en América Latina, Proyecto OEA/AE 141; 8 y 9 de noviembre de 2004 (Buenos Aires, Argentina).

Paiva, L., Marcos, R., Creus, A., Coggan, M., Oakley, A.J., Board, P.G., 2008. Polymorphism of glutathione transferase Omega 1 in a population exposed to a high environmental arsenic burden. Pharmacogenet. Genomics 18 (1), 1–10 (Jan).

Paoloni, J.D., Sequeira, M.E., Fiorentino, C.E., 2005. Mapping of arsenic content and distribution in groundwater in the southeast Pampa, Argentina. J. Environ. Health 50–53.

Paoloni, J.D., Sequeira, M.E., Esposito, M.E., Fiorentino, C.E., del, C.B.M., 2009. Arsenic in water resources of the southern Pampa Plains, Argentina. J. Environ. Public Health 2009, 216470.

Peluso, F., González Castelain, J., Othax, N., Rodríguez, L., 2011. Riesgo sanitario por sustancias tóxicas en aguas superficiales de Tres Arroyos. Argentina. Acta Bioquím. Clín. Latinoam. 45, 311–321.

Peluso, F., Othax, N., Gonzalez Castelain, J., Dubny, S., 2014. Applying health risk analysis to assess the chemical quality of water for recreational bathing: the case of Tres Arroyos Creek, Buenos Aires. Argentina. Hum. Ecol. Risk Assess. 45–68.

Peluso, F., Gonzalez Castelain, J., Rodriguez, L., Othax, N., 2012. Assessment of the chemical quality of recreational bathing water in Argentina by health risk analysis. Hum. Ecol. Risk. Assess. 1186–1215.

Pou, S.A., Osella, A.R., Diaz Mdel, P., 2011. Bladder cancer mortality trends and patterns in Cordoba, Argentina (1986–2006). Cancer Causes Control 22 (3), 407–415 (Mar).

Rahman, M., Tondel, M., Ahmad, S.A., Chowdhury, I.A., Faruquee, M.H., Axelson, O., 1999. Hypertension and arsenic exposure in Bangladesh. Hypertension 33 (1), 74–78 (Jan).

Reichard, J.F., Puga, A., 2010. Effects of arsenic exposure on DNA methylation and epigenetic gene regulation. Epigenomics 2 (1), 87–104 (Feb).

Rigacci, L.N., Giorgi, A.D.N., Vilches, C.S., Ossana, N.A., Salibian, A., 2013. Effect of a reservoir in the water quality of the Reconquista River, Buenos Aires, Argentina. Environ. Monit. Assess. 9161–9168.

Román, M.D., Muñoz, S.E., Niclis, C., Díaz, M.P., 2014. Arsenic, diet and occupational exposure on prostate cancer risk in Córdoba, Argentina. In: Litter, Marta I ., Nicolli, Hugo B, Meichtry, Martin, Quici, Natalia, Bundschuh, Jochen, Bhattacharya, Prosun, Naidu, Ravi (Eds.), Proceedings of the 5th International Congress on Arsenic in the Environment, May 11-16, 2014, Buenos Aires, Argentina. CRC Press, pp. 640–641 ISBN: 978-1-138-00141-1 eBook ISBN: 978-1-315-77888-4.

Rosas-Castor, J.M., Guzman-Mar, J.L., Hernandez-Ramirez, A., Garza-Gonzalez, M.T., Hinojosa-Reyes, L., 2014. Arsenic accumulation in maize crop (Zea mays): a review. Sci. Total Environ. 488–489, 176–187 (Aug 1).

Rosso, J.J., Troncoso, J.J., Fernandez Cirelli, A., 2011. Geographic distribution of arsenic and trace metals in lotic ecosystems of the Pampa Plain, Argentina. Bull. Environ. Contam. Toxicol. 129–132.

Rosso, J.J., Schenone, N.F., Perez Carrera, A., Fernandez Cirelli, A., 2013. Concentration of arsenic in water, sediments and fish species from naturally contaminated rivers. Environ. Geochem. Health 201–214.

Schenone, N., Volpedo, A.V., Cirelli, A.F., 2007. Trace metal contents in water and sediments in Samborombon Bay wetland, Argentina. Wetl. Ecol. Manag. 303–310.

Schlebusch, C.M., Lewis Jr., C.M., Vahter, M., et al., 2013. Possible positive selection for an arsenic-protective haplotype in humans. Environ. Health Perspect. 121, 53–58.

Smedley, P.L., Kinnirugh, D.G., 2013. Chapter 12: Arsenic in goundwater and the environment. In: Selinus, O., Alloway, B., Centeno, J.A., et al. (Eds.), Essentials of Medical Geology. Springer, United Kingdom, pp. 279–310.

Smedley, P.M., Nicolli, H.B., Macdonald, D.M.J., Barros, A.J., Tullio, J.O., 2002. Hydrogeochemistry of arsenic and other inorganic constituents in groundwaters from La Pampa, Argentina. Appl. Geochem. 17, 259–284.

Smedley, P.M., Kinniburg, D.G., Macdonald, D.M.J., et al., 2005. Arsenic associations in sediments from the loesss aquifer of La Pampa, Argentina. Appl. Geochem. 20, 989–1016.

Smith, A.H., Goycolea, M., Haque, R., Biggs, M.L., 1998. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. Am. J. Epidemiol. 147 (7), 660–669 (Apr 1).

Smith, A.H., Lingas, E.O., Rahman, M., 2000. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bull. World Health Organ. 78 (9), 1093–1103.

Smith, A.H., Marshall, G., Liaw, J., Yuan, Y., Ferreccio, C., Steinmaus, C., 2012. Mortality in young adults following in utero and childhood exposure to arsenic in drinking water. Environ. Health Perspect. 120 (11), 1527–1531 (Nov).

Soria de Gonzalez, A., Tefaha, L., Guber, R., et al., 2011. Total prostatic specific antigen levels among subjects exposed and not exposed to arsenic in drinking water. Rev. Med. Chil. 1581–1587.

Soria de González, A., Guber, R.S., Martínez, M., et al., 2009. Alteraciones bioquímicas en individuos expuestos al arsénico en el agua de bebida en Tucumán, Argentina. Acta Bioquim. Clin. Latinoam 611–618.

Soria, A.G., Guber, R.S., Sandoval, N.G., et al., 2014. Clinical and biochemical features among subjects exposed to arsenic through drinking water. 5th International Congress on Arsenic in the Environment.

Steinmaus, C., Yuan, Y., Kalman, D., et al., 2010. Individual differences in arsenic metabolism and lung cancer in a case–control study in Cordoba, Argentina. Toxicol. Appl. Pharmacol. 247 (2), 138–145 (Sep 1).

Steinmaus, C.M., Ferreccio, C., Romo, J.A., et al., 2013. Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. Cancer Epidemiol. Biomark. Prev. 22 (4), 623–630 (Apr).

Stroup, D.F., Berlin, J.A., Morton, S.C., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283 (15), 2008–2012 (Apr 19).

Swiecky, C., Garcia, S., Villaamil Lepori, E., et al., 2006. Epidemiología del hidroarsenicismo crónico regional endémico en la república Argentina. Estudio colaborativo multicéntrico. Ministerio de Salud, Buenos Aires, Argentina (accessed 03/22/2015 at http://www.msal.gov.ar/images/stories/ministerio/intoxicaciones/hacre/libro-hidroarsenicismo.pdf).

Tseng, W.P., 1977. Effects and dose—response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19, 109–119 (Aug).

Tseng, W.P., Chu, H.M., How, S.W., Fong, J.M., Lin, C.S., Yeh, S., 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40 (3), 453–463 (Mar).

Tsuji, J.S., Perez, V., Garry, M.R., Alexander, D.D., 2014. Association of low-level arsenic exposure in drinking water with cardiovascular disease: a systematic review and risk assessment. Toxicology 323, 78–94 (9/2).

United Nations Synthesis Report on Arsenic in Drinking Water. http://www.who.int/water_sanitation_health/dwq/arsenic3/en/.

Environmental Protection Agency, U.S., 2012. Arsenic in Drinking Water. United States: US Environmental Protection Agency.

Vazquez, C., Marco, L., Rodr, 2014. Integrated study of arsenic contamination in different matrices and targets in La Matanza, Buenos Aires province, Argentina. 5th International Congress on Arsenic in the Environment.

Villagra Cocco, A., Goldaracena, V., NdV, Gait, Quinteros, L., Mondino, C., 2014. Chronic ingestion of arsenic? fluorine and its repercussion in the peripheral nervous system of inhabitants of the Córdoba province (Argentina). One Century of the Discovery of Arsenicosis in Latin America (1914-2014) As2014. CRC Press, pp. 605–606.

Ward, N.I., Lord, G., Farnfield, H., acirc, €™Reilly, J., Al Rawahi, W., 2014. Arsenic speciation analysis of water in Argentina. 5th International Congress on Arsenic in the Environment.

WHO, 2011. Guidelines for Drinking-water Quality. 4th ed. World Health Organization, Switzerland (http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf?ua=1. Accessed 06 14).

Wu, M.M., Kuo, T.L., Hwang, Y.H., Chen, C.J., 1989. Dose–response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am. J. Epidemiol. 130 (6), 1123–1132 (Dec).

Yoshida, T., Yamauchi, H., Fan, Sun G., 2004. Chronic health effects in people exposed to arsenic via the drinking water: dose–response relationships in review. Toxicol. Appl. Pharmacol. 198 (3), 243–252 (Aug 1).