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1 **Arsenic: Geochemical distribution and age-related health risk in Italy**

2

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24

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26 Arsenic, Water, Soil, Stochastic, Human health risk, Italy

27

28 **Abstract**

29 This study is the first attempt to evaluate occurrence, distribution and potential health
30 impacts of As at a national scale in Italy. In various environmental matrices, As
31 geochemical distribution was investigated and carcinogenic and non-carcinogenic risks
32 were assessed with respect to different exposure routes and age groups. Both
33 deterministic and probabilistic methods were used to determine the health risks.
34 Geochemical mapping at a sub-continental scale provided a useful tool to spatially
35 represent As concentration and the critical areas posing a health threat to inhabitants.
36 The results show that significant As concentrations in tap water and soil (up to 27.20
37 µg/l and 62.20 mg/kg, respectively) are mainly governed by geological features. In the
38 central parts of Italy, where alkaline volcanic materials and consequently high levels
39 of As occur, the residents are prone to health issues. Daily exposure to As in tap water
40 is unparalleled playing an important role in the potential cancer and non-cancer risks.
41 The Incremental Lifetime Cancer Risk for skin cancer and also lung and bladder cancer
42 associated with tap water ingestion interestingly shows that (i) almost 80% of the
43 computed values fall above the internationally accepted benchmark value of 1×10^{-5} ;
44 (ii) majority of the data exceed the acceptable risk proposed by most jurisdictions, such
45 as that of Italian law (1×10^{-6}). Further, geographical variation of health risk highlights
46 high carcinogenic and non-carcinogenic risk associated with water ingestion for those
47 living in the northern Alps (including the city of Trento) and the central and southern
48 Italy (including the capital Rome and the cities of Napoli and Catanzaro). According
49 to the results, application of the probabilistic method which considers variability and
50 uncertainty is preferred to the deterministic approach for risk assessment. The
51 sensitivity analysis showed that As concentration in drinking water and exposure
52 duration are the factors with the greatest impact on the outcome of risk assessment (for
53 all age groups). The results of the current study may be a good starting point for
54 authorities to urgently decide about the needed policy actions in order to prevent the
55 adverse health effects and to reduce the human health risk due to As exposure.

57 **1. Introduction**

58 Arsenic (As) toxicity is a global health hazard affecting hundreds of millions of people
59 worldwide (Carlin et al., 2016). The International Agency for Research on Cancer
60 (IARC) classifies As in the Group I elements, which are known as human carcinogens
61 that induce other non-cancer effects (ATSDR (Agency for Toxic Substances and
62 Disease Registry), 2007; IARC International Agency for Research on Cancer, 2012).

63 Arsenic is one of the most toxic metalloids in the natural environment (Chappell et al.,
64 1999; Appelo and Heederik, 2008; Panagiotaras and Nikolopoulos, 2015) and toxicity
65 of the organic species is lower than that of the inorganic ones (WHO, 2001). Human
66 exposure to ar-senic in contaminated drinking water, food, soil and dust occurs through
67 inhalation, dermal absorption and ingestion. Although dietary As exposure assessment
68 continues to be investigated (EFSA (European Food Safety Authority), 2004), drinking
69 water remained as a major concern (Naujokas et al., 2013; Roh et al., 2017; Saint-
70 Jacques et al., 2018; Zhang et al., 2017). Contamination of drinking water is mainly
71 due to natural geological sources and processes, and sometimes because of
72 anthropogenic sources like mining, smelting, and agricultural activities (application of
73 pesticides or fertilisers). Worldwide chronic As toxicity has been recognised as a
74 human health threat (Matisoff et al., 1982; Chen et al., 1994; Morton and Dunnette,
75 1994) since the World Health Organisation (WHO) took a public position on As in
76 drinking water in 1958 (WHO, 1958).

77 There are several well-documented cases of large-scale drinking-water As
78 contamination in many countries, e.g., Bangladesh (Argos et al., 2010), Chile (Smith
79 et al., 1998), Europe (Selinus et al., 2010; Tarvainen et al., 2013, 2014), Ghana
80 (Smedley et al., 1996), India (Dissanayake et al., 2010); United States of America
81 (Matisoff et al., 1982; James et al., 2014), Taiwan (Chen et al., 2010), and Pakistan
82 (Rasool et al., 2016). Arsenic contamination is also a long-standing health-related
83 hazard in Italy because previous studies revealed that As levels in drinking water

84 (Cicchella et al., 2010; Dinelli et al., 2012; Pompili et al., 2017) and soil (Cicchella et
85 al., 2015) of the volcanic areas exceed the corresponding European and Italian
86 regulatory limits.

87 In 2014, the European Commission opened infringement proceedings against Italy for
88 its failure to ensure that water intended for human consumption meets the European
89 standards. D'Ippoliti et al. (2015) assessed chronic exposure to low-medium As levels
90 via drinking water using a large sample of 165,609 residents in 17 municipalities of
91 central Italy from 1990 to 2010. In this study, a correlation between As exposure and
92 several diseases was found, suggesting that even concentrations below the European
93 regulatory limit of 10 µg/l for drinking water (EC, 1998) carry a mortality risk.

94 On the basis of the above-mentioned discussion, the available sub-continental scale
95 dataset on As occurrence and distribution in different environmental matrices in Italy
96 was used to explore the potential human health impacts. The main objectives of this
97 study were: (1) to investigate the As levels and its spatial distribution in different
98 sample types in Italy; (2) to assess human exposure to As by estimating daily intake
99 via different exposure routes; (3) to define the potential health risk to the Italian
100 population, and (4) to delineate critical areas where interventions and follow-up studies
101 are necessary because of low-dose chronic As exposure.

102

103 **2. Arsenic: an overview**

104 ***2.1. Source and occurrence of As in the environment***

105 Arsenic is a metalloid trace element widely distributed throughout the natural
106 environment (i.e. air, water and soil). It is the 40th most abundant element in the Earth's
107 upper continental crust (Hu and Gao,
108 2008) being one of the most hazardous toxic elements for the ecological

109 and human health (Chappell et al., 1999; Reimann et al., 2009). The mobilisation of As
110 in the environment is due to a sequence of natural processes such as geo-biochemical
111 weathering reactions, volcanic emissions, as well as anthropogenic activities. The
112 principal factors influencing As concentration in soil are the geochemistry of parent
113 rocks and human activities. In addition, climate, organic and inorganic components and
114 redox potential status in soil play a role in the As re-distribution in the environment
115 (Kabata-Pendias and Pendias, 2001; Kabata-Pendias and Mukherjee, 2007;
116 Panagiotaras and Nikolopoulos, 2015). Natural low-temperature processes such
117 biomethylation and microbial reductions also mobilize As in aerobic and anaerobic
118 conditions. Arsenic has a strong chalcophile character resulting in its association with
119 sulphides and sulphosalts, such as arsenopyrite, pyrite, orpiment, realgar, enargite and
120 tennantite, which are typically related to sulphide deposits. Despite the large number
121 of As minerals (more than 200 minerals; Table 1), the most common arseniferous
122 mineral in crustal rocks is pyrite. It can be formed under reducing conditions in low-
123 temperature sedimentary environments and it is often present, in its authigenic form,
124 in sediment of rivers, lakes, oceans and aquifer.

125 Arsenic, in As^{3+} and As^{5+} oxidation states, can substitute for P^{5+} , Si^{4+} , Al^{3+} , Fe^{3+} , and
126 Ti^{4+} in various mineral structures and consequently many rock-forming minerals
127 contain different As concentrations. Strong sorption of As to secondary Fe, clay and
128 organic matter leads to limited mobility of the element in soil and sediments.

129 Arsenic concentration in sandstones (about 0.5–1.2 mg/kg) is regularly lower than
130 granitoid rocks (1–2.5 mg/kg), coal (up to 24 mg/kg) and shale (13 mg/kg), as reported
131 by Kabata-Pendias and Mukherjee (2007). The element is associated with magmatic
132 and hydrothermal processes and it is a ‘pathfinder’ for metallic ore deposits, e.g., Au,
133 Sn, Cu and W (Boyle, 1974; Howell et al., 2014).

134 Arsenic dispersion and mobilisation is possible at the typical pH values of groundwater
135 (from 6.5 to 8.5) under oxidising and reducing conditions. Biological activities can
136 produce organic As compounds in surface water that are predominant in biological

137 tissues although their quantity is usually negligible (Smedley and Kinniburgh, 2002;
138 Wang et al., 2019). Arsenic content of water can also be associated with volcanic,
139 geothermal and anthropogenic (especially mining activity) inputs (Smedley and
140 Kinniburgh, 2002; Webster and Nordstrom, 2003).

141 Natural concentrations of As in groundwater reveal a very large range from less than
142 0.5 to 5000 µg/l covering natural As contaminations found in more than 70 countries
143 including Bangladesh, West Bengal, Chile, Argentina, China, Mexico, Vietnam, and
144 some parts of Canada and the U.S.A.; (Bowell et al., 2014; Shankar et al., 2014).
145 Anomalous As levels are related to bedrock types, hydrogeological features and
146 geochemical environments which may influence dissolution/desorption processes. The
147 mechanisms of As release to ground-water include reduction of Fe hydroxides and
148 arseniferous minerals, sulphide oxidation, competitive sorption with other oxyanions
149 and interaction of groundwater with deep-rising geothermal fluids (Smedley and
150 Kinniburgh, 2002).

151 Anthropogenic activities such as mining, mineral processing, and combustion of fossil
152 fuels contribute to the redistribution and enrichment of As in the environment (Bowell
153 et al., 2014). In addition, As has historically been used in a variety of commercial
154 applications. It is mainly utilized as a component of wood preservatives and
155 agricultural chemicals, such as insecticides, herbicides, algacides, and growth
156 stimulants. Smaller amounts of the element are applied in the production of glass and
157 nonferrous alloys along with other applications in the electronics and pharmaceutical
158 industries.

159

160 ***2.2. Arsenic and health implications***

161 Arsenic is ubiquitous in the environment and the primary source of human exposure to
162 As is dietary intake from food, beverages and drinking water (Rose et al., 2007; Jorhem
163 et al., 2008; Heitkemper et al., 2009; Liang et al., 2010; Chung et al., 2014).

164 Notwithstanding, As toxicity is greatly dependent on speciation. Carcinogenicity of
165 inorganic arsenic, negatively affecting the quality of drinking-water worldwide
166 (Chowdhury, 2004; IARC International Agency for Research on Cancer, 2004), is
167 strongly confirmed (IARC International Agency for Research on Cancer, 2004; 2012).
168 However, organic arsenic compounds (such as arsenobetaine and arsenocholine in
169 seafood) are less harmful to human health (Francesconi, 2010) because As atoms are
170 firmly incorporated in the organic compounds and less available for bonding with
171 important biomolecules such as proteins. Consequently, the body absorbs in-organic
172 forms more than organic species.

173 Nevertheless, human and several other mammals can partially metabolize inorganic
174 arsenic to methylarsonic acid (MMA) and dimethylarsinic acid (DMA) by alternating
175 reduction of AsV to AsIII and addition of a methyl group. Such a process has long been
176 considered as a de-toxification mechanism that helps to produce end metabolites less
177 re-active with tissue constituents (Vahter and Concha, 2001). However, several studies
178 also demonstrated that biomethylation of inorganic arsenic, particularly the production
179 of the intermediary trivalent metabolites (MMAIII and DMAIII), is a process that
180 activates arsenic as a toxin and enhances its affinity for sulfhydryl (–SH) groups (Hall
181 and Gamble, 2012; Petrick et al., 2001; Styblo et al., 2000). Thus, As methylation has
182 recently attracted attention of researchers as a mechanism for bioactivation and
183 detoxification (Khairul et al., 2017) because the toxicity is closely linked to the
184 methylation and valence of the metabolites.

185 The toxic effects of As might also depend on exposure frequency and As concentration.
186 According to Khairul et al. (2017), bioactivation process is feasibly more important for
187 chronic exposure; however, de-toxification probably plays a significant role in the
188 other cases (including exposure to a single low dose and acute exposure).

189 The effects of acute and chronic As exposure are well documented in the scientific
190 literature (Table 2). Acute As poisoning mostly occurs after accidental ingestion of
191 insecticides or pesticides that causes problems in the gastrointestinal system such as

192 nausea, vomiting, colicky abdominal pain and diarrhoea. Other clinical symptoms are
193 acute psychosis, a diffuse skin rash, toxic cardiomyopathy and seizures. The fatal dose
194 of ingested As in humans is difficult to determine from case reports due to its
195 dependence upon many factors (e.g., solubility, valence state, etc.). Long-term As
196 toxicity leads to multisystem diseases and the most serious consequence is cancer.
197 These effects may take many years to become clinically apparent. Chronic As toxicity
198 in hu-mans has been documented in many countries worldwide, particularly in south
199 and south-east Asia (Xu et al., 2019) and also some areas in Europe (e.g., the Pannonian
200 Basin) (Senila et al., 2017). Significant inorganic As chronic exposure mostly occurs
201 via drinking As-contaminated water (Rahman et al., 2009). A larger number of
202 scientific articles have been published about the association between chronic As
203 exposure and adverse health effects (e.g., Kapaj et al., 2006; Brinkel et al., 2009; Saha
204 et al., 2010) together with the clinical evidence of As toxicity (Ratnaike, 2003;
205 Dangleben et al., 2013; Jain and Chandramani, 2018).

206 The main dermatological symptoms observed in As-affected people are melanosis
207 (change of pigmentation) and keratosis (dry, rough, papular skin lesions) (Guo et al.,
208 2001; Ramasamy and Lee, 2015). Chronic As exposure may also cause reproductive,
209 neurological, cardiovascular (Ramasamy and Lee, 2015; Mendez et al., 2016),
210 respiratory and pulmonary (Mazumder et al., 2000; Islam et al., 2007; Ramasamy and
211 Lee, 2015), gastrointestinal, hepatic, haematological, and diabetic effects in humans
212 (Chiu et al., 2004; Ramasamy and Lee, 2015). A relationship between chronic As
213 exposure and impairment of the development and reproductive systems were reported
214 as well (Hopenhayn et al., 2003; Milton et al., 2005). Moreover, inorganic As is a potent
215 human carcinogen which was recognised as a cause of skin, bladder, kidney, and lung
216 cancer (IARC International Agency for Research on Cancer, 2004).

217

218 ***2.3. Guidelines for As***

219 WHO expressed its public position on As in drinking water since 1958 with publication
220 of the first International Standards for Drinking-Water (WHO, 1958) that
221 recommended a maximum allowable concentration of 0.2 mg/l for As based on health
222 concerns. This value was lowered to 0.05 mg/l five years later (WHO, 1963) and
223 retained in 1971 and 1984 (WHO, 1971, 1984). However, the fourth edition of WHO
224 Guidelines for Drinking-Water Quality established 10 µg/l as a provisional guideline
225 value for As in drinking water (WHO, 2011). In this study, inorganic As compounds
226 are considered carcinogenic to humans regarding IARC classification (Group 1; IARC
227 International Agency for Research on Cancer, 2004).

228 Currently, the permissible limit for As in drinking water is 50 µg/l in most of the As-
229 affected Asian countries and Russia (Table 3). Nonetheless, European as well as Italian
230 threshold values for As in drinking water are set at 10 µg/l in accordance with the WHO
231 (2011) guidelines. Italy (and the other EU Member States) have the obligation to ensure
232 that regular monitoring (established by the competent authorities) of the water quality
233 is carried out in order to check that the water available to consumers meets the
234 requirements of the Drinking Water Directive (EC, 1998). If high levels of arsenic or
235 other pollutants are found, EU Member States may derogate from the thresholds
236 established by the directive for a limited period of time to search for durable solutions.

237 On the other hand, widely divergent guidelines and clean-up targets for As in soil have
238 been established by regulatory organisations over the past decades in the world. The
239 Japanese soil quality guidelines for As state a limit of 0.01 mg/l in a sample solution
240 and a threshold of 15 mg/kg in soil for agricultural lands (i.e. paddy fields only) (MEJ
241 , 2019). In Italy, 20 mg/kg is set as the limit of As value in soil of recreational/
242 residential areas (D.L. 152/2006). U.S.A and Australian environmental legislation also
243 consider the same target value (Henke, 2009). Although significantly higher As limits
244 are set for soil in residential and recreational areas (50 mg/kg and 125 mg/kg,
245 respectively) in the German Federal Soil Protection Act (BBodSchG, 1998), the lowest

246 limit (2 mg/ kg) is used in Russia (Vodyanitskii, 2009). A summary of the guideline
247 limits for As in drinking water and soil in various countries is shown in Table 3.

248 The guidelines are regularly monitored, improved and enforced Meanwhile this article
249 was under preparation, the Italian Ministry of the Environment was adopting a
250 Statutory Instrument (effective from June 22, 2019) for the areas destined for
251 agricultural production and breeding concerning their remediation, environmental
252 restoration and safety (D.M. 46/2019). In particular, it has been established that the
253 geochemical background value should be used as the contamination threshold limit. It
254 also defined the criteria for exposure-based risk analysis based on the consumption of
255 agrifood products.

256

257 **3. Material and methods**

258 **3.1. Data sets**

259 The As concentration data used for this investigation are retrieved from previous
260 European projects in various environmental media with active participation of the
261 authors of this article. Specifically, tap and bottled mineral water was studied within
262 the ‘European Groundwater Geochemistry Project’ (EGG; Reimann and Birke, 2010)
263 in which 157 tap and 186 bottled mineral water samples were collected throughout
264 Italy from 2007 to 2008. Sample preparation and analytical methods can be found in
265 Birke et al. (2010), Dinelli et al. (2012), Banks et al. (2015) and Flem et al. (2015). Soil
266 data are from the Geochemical mapping of agricultural and grazing land soil of Europe
267 (GEMAS) project (Reimann et al., 2014). In total, 118 agricultural (0–20 cm) and 118
268 grazing land (0–10 cm) topsoil samples were collected between 2008 and early 2009
269 according to the Field Manual of the GEMAS project (EGS, 2008). Sampling methods,
270 sample preparation, analytical methods and other technical and operative information
271 are available in Birke et al. (2014), Reimann et al. (2014) and Cicchella et al. (2015).
272 Stream sediment (n = 51 samples), stream water (n = 48) and floodplain sediment (n =

273 50) data are from the FOREGS (Forum of European Geological Surveys) Geochemical
274 Atlas of Europe project (Salminen et al., 2005), where all the relevant information for
275 sampling, sample preparation and analytical methods can be found.

276

277 ***3.2. Data treatment and mapping***

278 Univariate statistical analysis was conducted to show the single-element statistical
279 distribution. Geochemical maps displaying the spatial As distribution in the different
280 types of samples were generated using the Multifractal Inverse Distance Weighted
281 (MIDW) interpolation method with the GeoDAS™ software; for more details on this
282 methodology refer to Cheng (1999). In previous studies, it was demonstrated that this
283 algorithm preserves high frequency information (anomalies) by considering both
284 spatial associations and local singularities in the geochemical data at continental (Lima
285 et al., 2008; Jordan et al., 2018), sub-continental (Cicchella et al., 2015), regional and
286 local scales (Lima et al., 2003; Albanese et al., 2007, 2015; Thiombane et al., 2017).
287 The concentration intervals of the interpolated surfaces were set by the concentration–
288 area (C–A) fractal method (Cicchella et al., 2005) in order to better visualise the
289 different geochemical distribution patterns.

290

291 ***3.3. Exposure and human health risk assessment (HHRA)***

292 A human health risk assessment (HHRA) was performed for exposure to As in soil and
293 water through the procedure described by US EPA (1989) and transposed by the Italian
294 legislation (D.L. 152/2006 and D.L. 4/2008). Arsenic species in drinking water and soil
295 are almost exclusively inorganic (Barret, 2017; Aide et al., 2016); consequently the
296 data in this investigation (total As) adapt well to risk assessment. The deterministic risk
297 assessment was initially used and the study was extended to a stochastic approach
298 based on the obtained results.

299 Once the hazard was identified for As, the exposure (presented as chronic daily intake
300 - CDI) assessment was performed for different age groups (children, teenagers and
301 adults) and multiple exposure path-ways (ingestion and dermal exposure to water and
302 soil) in order to determine the amount of arsenic to which people are exposed. It is
303 important to underline that As intake through dermal contact is usually small in
304 comparison to the oral route (ATSDR (Agency for Toxic Substances and Disease
305 Registry), 2007; US EPA, 2004). Inorganic As in drinking water can be absorbed
306 almost entirely (more than 90%) by the gastrointestinal tract being greater than that of
307 other potentially toxic metals (Zheng et al., 2002; Hong et al., 2014; US EPA, 2004).
308 Consequently, a value equal to 100% of the ingested dose is recommended as the
309 default oral absorption rate for As risk assessment (ECHA -European Chemicals
310 Agency, 2013). Nevertheless, the reported dermal absorption rates for inorganic As
311 compounds range from < 1% to 6% regarding several in vivo and in vitro scientific
312 studies (e.g. Wester et al., 1993; Lowney et al., 2005; ECHA - European Chemicals
313 Agency, 2013). “The findings suggest that dermal exposure leads initially to arsenic
314 binding to skin, and that the bound arsenic may slowly be taken up into the blood, even
315 after exposure ends” (ATSDR (Agency for Toxic Substances and Disease Registry),
316 2007). The US EPA screening procedure (Appendix A of US EPA, 2004) indicates that
317 although the dermal exposure to As is essentially negligible compared to the ingestion
318 exposure, risk assessors may decide to proceed to a quantitative assessment. Since one
319 of the main objectives of this study was to estimate the risks of chronic low-level
320 arsenic, dermal exposure during regular indoor and outdoor activities cannot be
321 ignored. European Chemicals Agency (ECHA - European Chemicals Agency, 2013)
322 indicated that a dermal absorption rate for As is necessary in risk assessment and
323 recommended a value of 1% to account for the pieces of evidence about low absorption
324 through the skin.

325 Exposure to As in water mainly occurs through residential use of tap water for drinking,
326 bathing and showering purposes. Hence, the chronic Exposure to As in water mainly
327 occurs through residential use of tap water for drinking, bathing and showering

328 purposes. Hence, the chronic daily intake via ingestion of water ($CDI_{w(ing)}$) and dermal
329 contact with water ($CDI_{w(derm)}$) were calculated according to Equations (1) and (2) (US
330 EPA, 1989; 2004):

$$331 \quad CDI_{w(ing)} = CW * IR * EF * ED / BW * AT \quad (1)$$

$$332 \quad CDI_{w(derm)} = CW * SA * PC * ET * EF * ED * CF / BW * AT \quad (2)$$

333 where CW is the chemical concentration in water (mg/l); IR is the ingestion rate
334 (litres/day); ET is the exposure time (hours/day); EF is the exposure frequency
335 (days/year); ED is the exposure duration (years); SA is the skin surface area available
336 for contact ($cm^2/event$); PC is the chemical-specific dermal permeability constant
337 (cm/hr); CF is the volumetric conversion factor for water ($1 L/1000 cm^3$); BW is the
338 body weight (kg), and AT is the average time period over which exposure is averaged
339 (days).

340 Exposure to As in soil may simultaneously occur via ingestion and dermal contact
341 when children play outdoors or adults engage in gardening and participate in
342 agricultural activity. Therefore, the chronic daily intake via accidental ingestion of soil
343 ($CDI_{s(ing)}$) and the absorbed dermal dose through soil contact ($CDI_{s(derm)}$) were
344 calculated according to Equation (3) (modified) and 4 (US EPA, 1989; 2004):

$$345 \quad CDI_{s(ing)} = CS * IR * CF * ET * EF * ED / BW * 16 * AT \quad (3)$$

$$346 \quad CDI_{s(derm)} = CS * CF * SA * AF * ABS * EF * ED / BW * AT \quad (4)$$

347

348 where CS is the chemical concentration in soil (mg/kg), IRsoil is the ingestion rate
349 (mg/day); ET is the exposure time (0–16 h/day, where 16 is the maximum waking hours
350 per day); EF is the exposure frequency (days/year); ED is the exposure duration
351 (years); CF is the conversion factor ($10^{-6} kg/mg$); SA is the skin surface area available
352 for contact ($cm^2/event$); AF is the soil to skin adherence factor (mg/cm^2); ABS is the
353 absorption factor for the skin (unitless – 0.03 for arsenic as stated by US EPA (2004));

354 BW is the body weight (kg), and AT is the average time period over which exposure is
355 averaged (days). Equation (3) represents a modified version of the US EPA equation
356 for CDI of soil ingestion in which exposure time – ET (0–16 h/day) – was included to
357 obtain more realistic results.

358 Exposure (presented as CDI) assessment was carried out for children (1–8 years old),
359 teenagers (9–16 years old) and adults (16–70 years old) along with lifetime exposure.
360 The values and description of the para-meters for deterministic and probabilistic
361 approaches (water ingestion scenario) are summarised in Table S1 in the
362 Supplementary Material. Tables S2, S3 and S4 (in the Supplementary Material) show
363 the age related parameters used for water dermal contact, soil ingestion and soil dermal
364 contact scenarios, respectively. The values of the factors for the deterministic
365 assessment were based on a standard approach with the default values from US EPA,
366 Italian National Institute for Environ-mental Protection and Research (IPRA - Italian
367 National Institute for Environmental Protection and Research, 2008) and peer-
368 reviewed articles. Conversely, values of the parameters for stochastic modelling were
369 country specific to get the results as close as possible to the real scenario.

370 After exposure assessment, the results were integrated with the in-formation from
371 toxicity (dose/response) analysis through risk characterization. It is generally
372 accomplished by calculating Hazard Quotient (HQ) for threshold contaminants and
373 Incremental Lifetime Cancer Risk (ILCR) for non-threshold contaminants. Arsenic is
374 regarded as a threshold and a non-threshold contaminant. A threshold response is
375 characterized by a toxic effect occurring above a certain level of exposure
376 concentration (i.e. Tolerable Daily Intake or Reference Dose (RfD, US EPA)). It is
377 unlikely for even sensitive groups to experience adverse health effects at concentrations
378 below this value. Therefore, HQ was calculated as follows:

$$379 \quad HQ = CDI / RfD \quad (5)$$

380 where CDI is the Chronic Daily Intake (mg/kg/day) and RfD is the Oral Reference
381 Dose of arsenic for assessing non-cancer health effects (0.0003 mg/kg/day as stated by

382 US EPA, 1998). The health risk is not generally expected when $HQ < 1$ (Khan et al.,
383 2008); however, potential non-cancer effects might occur at values greater than unity
384 (US EPA, 1998).

385 Conversely, non-threshold acting contaminants exhibit effects at virtually all levels of
386 exposure. Thus, the estimated exposure (CDI) is multiplied by the appropriate Cancer
387 Slope Factor (CSF) to derive an estimate of the potential Incremental Lifetime Cancer
388 Risk (ILCR) as-associated with that particular exposure. ILCR (Equation (6)) is the
389 incremental probability of an individual developing cancer over a lifetime as a result
390 of exposure to a potential carcinogen. US EPA generally adopt a risk range from $1 \times$
391 10^{-6} to 1×10^{-4} (i.e., 1 case of cancer in 1,000,000 exposed people to 1 case of cancer
392 in 10,000 exposed people) to suggest the point at which risk management decisions
393 should be taken. However, in the context of drinking water guidelines, WHO reference
394 lifetime risk level is 1×10^{-5} and the US EPA's Office of Water (US EPA, 2018) advises
395 consideration of conservative cancer risk levels (10^{-5} , 10^{-6}). The Italian legislation
396 (D.L. 4/2008) sets as a maximum acceptable cancer risk level at 1×10^{-6} for a single
397 substance.

$$398 \quad ILCR = CDI * CFS \quad (6)$$

399 where CDI is the previously calculated chronic daily intake (mg/kg/ day) and CSF is
400 the oral cancer slope factor (mg/kg/day). Skin cancer risk was separately calculated for
401 dermal and ingestion exposure routes using the oral slope factor of 1.5 mg/kg/day,
402 derived from the EPA Integrated Risk Information System (IRIS). However, risk of
403 combined lung and bladder cancers was computed by the oral slope factor of 25.7 and
404 16.9 mg/kg/day for females and males, respectively (US EPA, 2010; Nigra et al., 2017).

405 Quantitative toxicity estimates (i.e. RfD and CSF) for dermal exposure have not been
406 developed by US EPA. However, oral reference doses and oral cancer potency factors
407 were used to assess systemic toxicity from dermal exposures as suggested by US EPA
408 (2004). Hence, HQ and ILCR were estimated for (i) ingestion of water and soil and (ii)
409 dermal contact with water and soil. Based on the above considerations about absorption

of As in water through dermal contact, a value of 1% of CDI was selected for the risk calculation. Finally, the calculated ILCR and HQ values associated with each water and soil sampling point were mapped after undergoing MIDW interpolation.

413

4. Results and discussion

4.1. Arsenic concentration levels in different environmental samples

Table 4 summarises the descriptive statistics of As concentration in different environmental samples.

The agricultural soils show the largest variability in As concentration ranging from 0.79 to 62.20 mg/kg, with a median of 7.56 mg/kg. The As content in grazing land soils (median: 8.08 mg/kg) varies between 0.97 and 54.28 mg/kg. According to the Italian legislation (D.L. 152/2006), arsenic in 8.5% of the agricultural and grazing land soils exceed the intervention limit of 20 mg/kg for soil intended for residential/recreational use. Stream and floodplain sediment samples are characterized by maximum As values of 38.00 and 51.00 mg/kg, respectively. Since the Italian environmental legislation has not yet established intervention limits for stream and floodplain sediments, the intervention limit for soils (residential/recreational use) has been chosen as a reference. Hence, in comparison with soils, a lower percentage of stream and floodplain sediments (3.9 and 8%, respectively) exceed the limit. The measured As concentrations range from 0.08 to 13.00 µg/l (median: 0.47 µg/l) in stream waters. Italian bottled mineral waters contain 0.01–8.91 µg/l arsenic, with a median of 0.25 µg/l. The concentration range of As in tap water is 0.02–27.20 µg/l (median: 0.25 µg/l) being higher than that of bottled mineral waters. In general, As levels in water samples are within the normative limits, except for tap water (0.6% of the analysed samples exceed the Italian and European maximum admissible concentrations of 10 µg/l). The large standard deviations (SD) in most of the datasets suggest a significant spatial variability (Table 4).

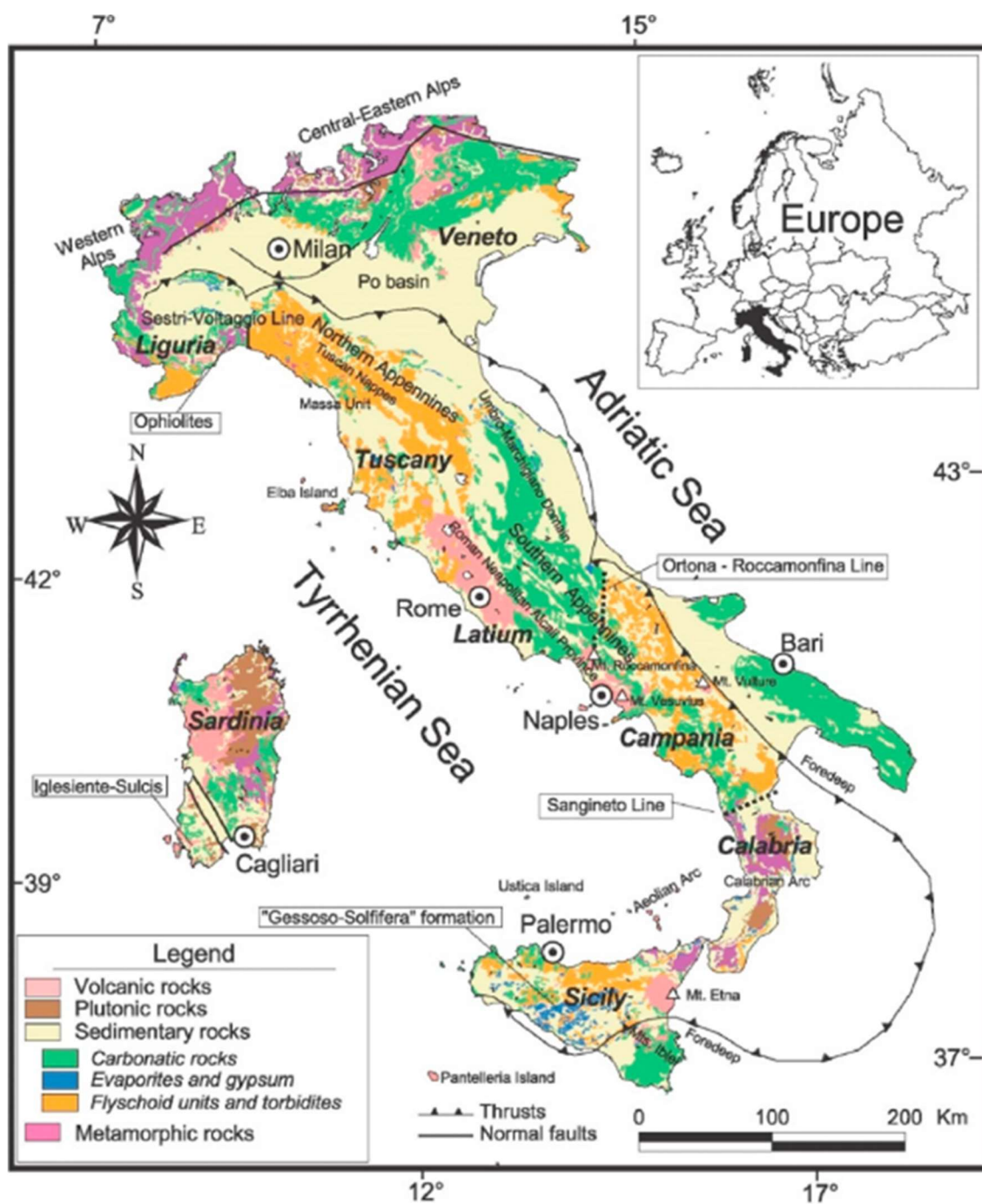
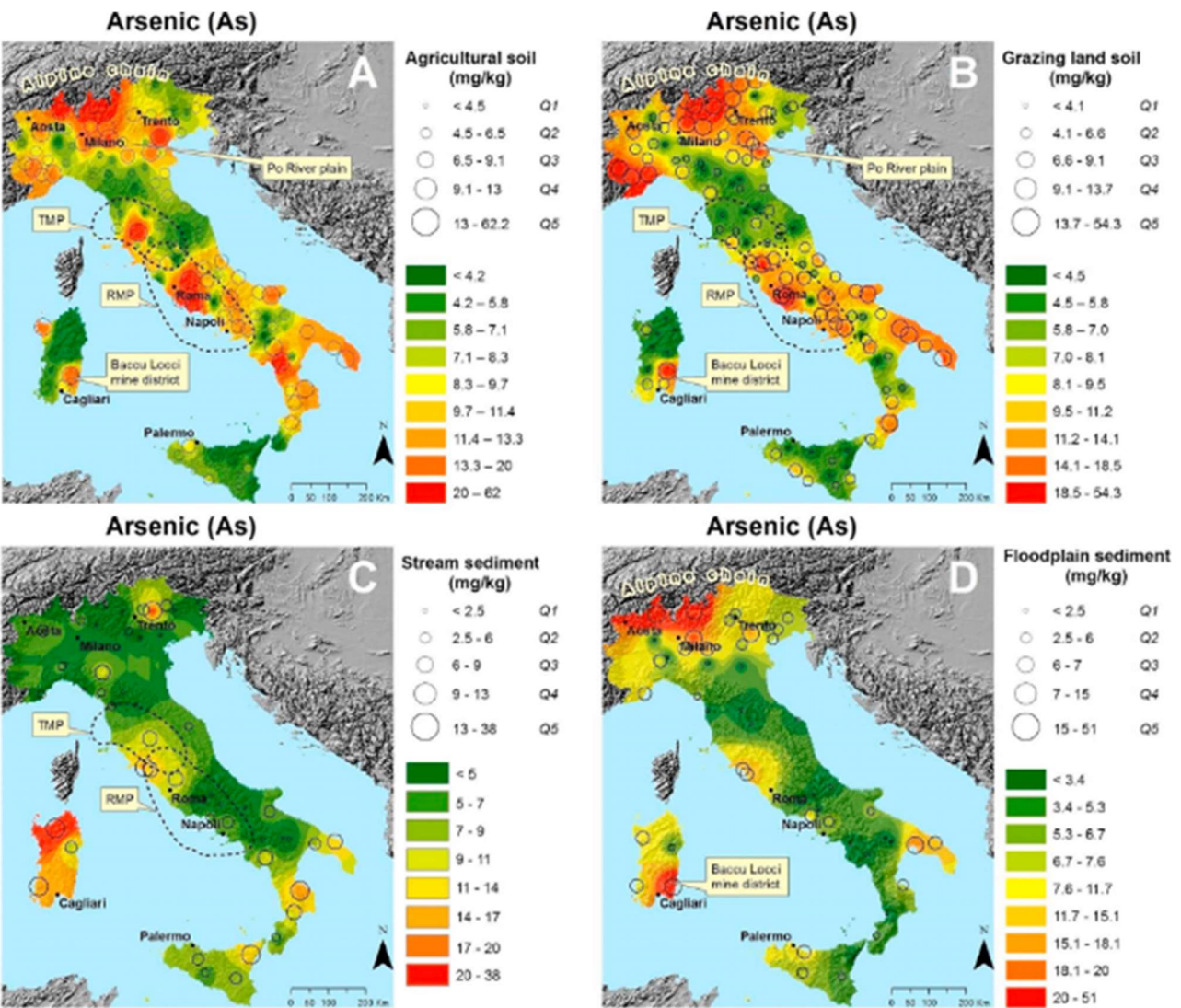


Fig. 1. Geological-sketch-map-of-Italy (De Vivo et al., 2008).

4.2. Environmental occurrence and geochemical distribution of As in Italy

4.2.1. As anomalies in soil

The geological features of Italy (Fig. 1) well explain the As anomalies in soil (> 20 mg/kg) (Fig. 2A and B).



445
446 Fig. 2. Deterministic geochemical maps showing arsenic distribution in (A)
447 agricultural soils, (B) grazing land soils, (C) stream sediments, and (D) floodplain
448 sediments. TMP = Tuscany Magmatic Province (Conticelli et al., 2004); RMP = Roman
449 Magmatic Province (Conticelli et al., 2004). Arsenic intervention limit for soil is 20
450 mg/kg. Circles on the map represent the quintile distribution of As concentrations.
451

452 The major As enrichments, in fact, occur in correspondence with Alpine chain, alluvial
453 sediments of the Po River plain, pyrite-poly-metallic deposits of Tuscany Magmatic
454 Province (TMP), pyroclastics of the Roman Magmatic Province (RMP), Calabrian
455 metamorphic rocks and mineralised areas of Sardinia. In the Alps, disseminated small
456 sulphide mineralisations are likely responsible for As enrichment in soil (Tarvainen et
457 al., 2013) and As-oxide minerals formed by remobilization of the element during

458 Alpine metamorphism (e.g. hydrothermal alterations and skarn formation) can be
459 another source of anomalies (Augustithis, 1995).

460 Subdividing the Alpine arch into three geographical sectors (the West, the Central and
461 the East sectors) helps to explain elevated As concentrations in soil. Arsenic enrichment
462 in the West sector (between Milano and Aosta) can be associated with a former gold
463 mining site along the Toce River and also metamorphic rocks such as biotitic gneiss
464 and amphibolitic norite. However, high As levels in the Central sector of the Alps are
465 probably resulted from the metamorphic rocks such as two-mica gneiss and
466 orthogneiss. In the East sector, the anomalous As can be due to moraine deposits
467 containing transported materials from the upper group of Atesine volcanites (i.e.
468 ignimbrite, lava and tuff).

469 In the Po River plain (between Milan and Venice) high As levels in soil are probably
470 related to the underlying alluvial deposits featured by a fine grain size and rich in
471 organic matter; these latter characteristics lead to reducing conditions favouring the
472 adsorption of the As onto Fe-hydroxides (Tarvainen et al., 2013).

473 In TMP, the occurrence of arsenopyrite and sulphosalts can explain As concentration
474 values (Costagliola et al., 2010).

475 In RMP, elevated amount of As in soil can be explained by their volcanic origin
476 (Quaternary pyroclastic deposits from Plinian type eruptions) and by hydrothermalism.

477 In the Tyrrhenian Calabrian margin, characterized by a complex geodynamic evolution
478 associated with subduction, As anomalies can be related with the upwelling of
479 hydrothermal fluids and the occurrence of some specific sedimentary (shales, marl),
480 metamorphic (phyllite, quartzite) and oceanic magmatic (ophiolite) rocks normally
481 richer in As than other geological materials. In Sardinia, As anomalies can be explained
482 by the occurrence of well-known sulphide mineralisations and the linked weathering
483 processes.

484

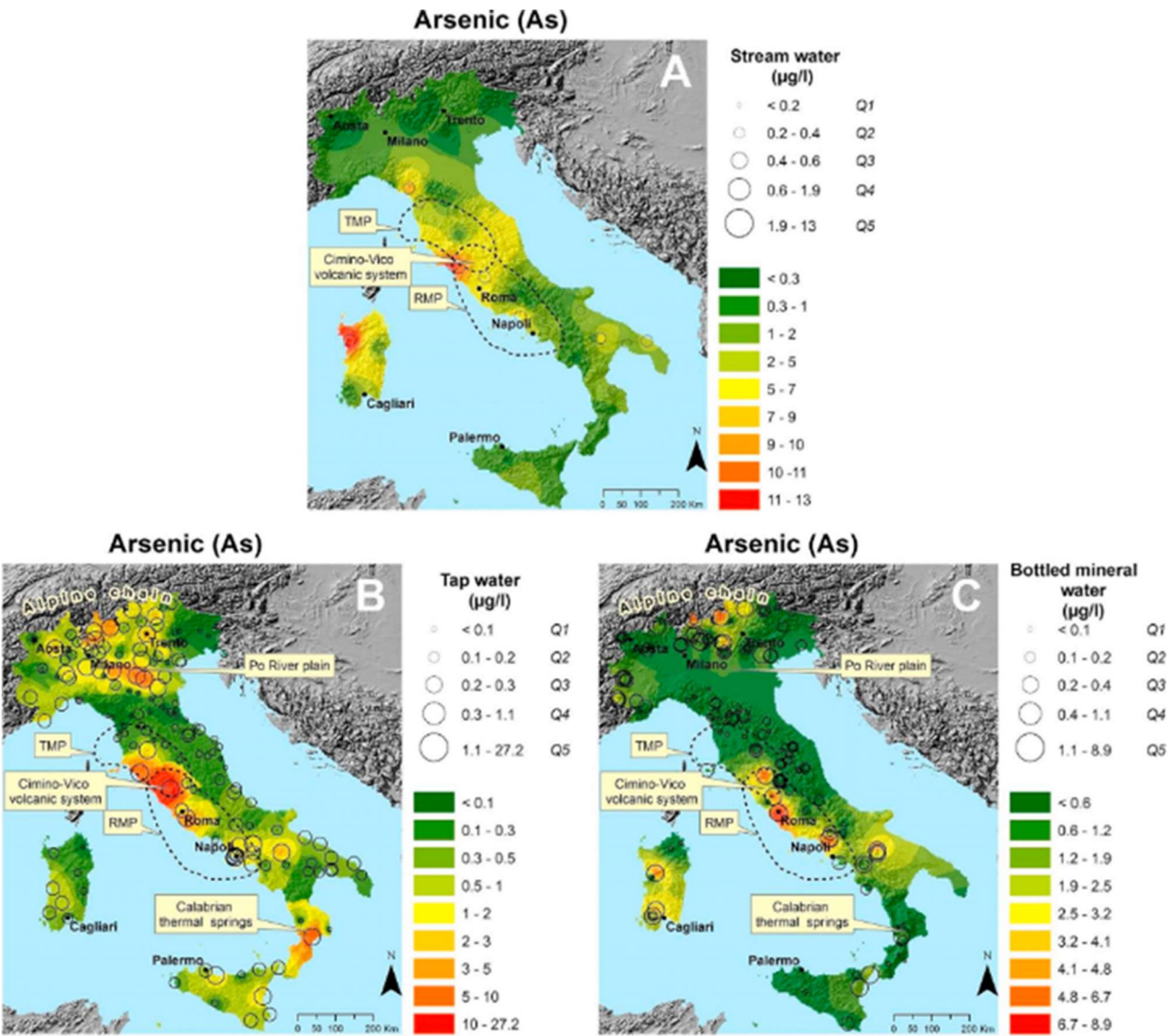
4.2.2. *As anomalies in sediment*

The RMP, Sardinia (due to sulphide mineralisation and mining activities), and Calabrian coastal metamorphic rocks (Fig. 1) account for the main As anomalies in stream sediments (Fig. 2C). In the Brenta River plain, the high As levels can be related to stream sediments de-rived from the Trentino Alps and the Alpine foothills, where two of the most important intrusive Alpine masses are located (the Masino-Bregaglia valley pluton and the Adamello pluton). Overbank sedimentation as a long-term As storage (Matys Grygar et al., 2016) and metal mining feasibly influenced As enrichment (> 20 mg/kg) in floodplain sediments of the Swiss Alpine sector and of southern Sardinia (Fig. 2D). Moderate As levels were also found in Apulia region in south-eastern Italy.

4.2.3. *As anomalies in water*

Arsenic concentration in water has been attracted attention of many researchers worldwide because it can be easily absorbed by the human body and lead to some adverse health effects. Arsenic-rich bottled mineral and stream waters are observed in the central sector of the Alps, RMP and northern Sardinia. Stream waters in the latter two region contain up to $13 \mu\text{g/l}$ of As (Fig. 3A). The reported high As levels in the water from Bacchu Locci stream by Ardau et al. (2013) are not fully captured due to the wide-spaced sampling design (approximately 1 site/4800 km^2) in the dataset of current study. In the Central Alps, elevated As concentrations in water are possibly related to the occurrence of arseniferous mineralisation and moraine deposits containing the mineralised materials. A former As mining area is located around Alpe Stabiello-Sondalo. The geological peculiarity of the RMP, particularly the northern area of Lazio, feasibly contributed to the high As values in water. The hydrothermal activities in the Cimino-Vico volcanic system (near Viterbo city) play an important role in the high As contents in the waters from volcano-sedimentary aquifers (Cinti et al., 2019). Previous studies (e.g., Baiocchi et al., 2007) indicated that this volcanic aquifer discharges

513 mainly into the adjoining springs and streams. Northern Sardinia is characterized by
 514 As anomalies in stream waters and bottled mineral waters (Fig. 3) ascribed to a
 515 hydrogeological complex of volcanites affected by widespread hydrothermal events.
 516 The As content in tap waters (0.02–27.2 $\mu\text{g/l}$) is higher than bottled mineral waters
 517 (0.01–8.91 $\mu\text{g/l}$). Spatial variation of As concentration in bottled and tap waters is
 518 mainly due to changes in the aquifer geology. However, the tap water composition
 519 (especially in metropolitan areas) is often influenced by the mixing of the water
 520 originated from different reservoirs and sources.



521 Fig. 3. Deterministic geochemical maps showing arsenic distribution in (A) stream
 522 waters, (B) tap waters, and (C) bottled mineral waters. TMP = Tuscany Magmatic
 523 Province (Conticelli et al., 2004); RMP = Roman Magmatic Province (Conticelli et al.,
 524

2004). Arsenic intervention limit for water is 10 µg/l. Circles on the map represent the quintile distribution of As concentrations.

4.3. Estimation of health risk for the Italian population

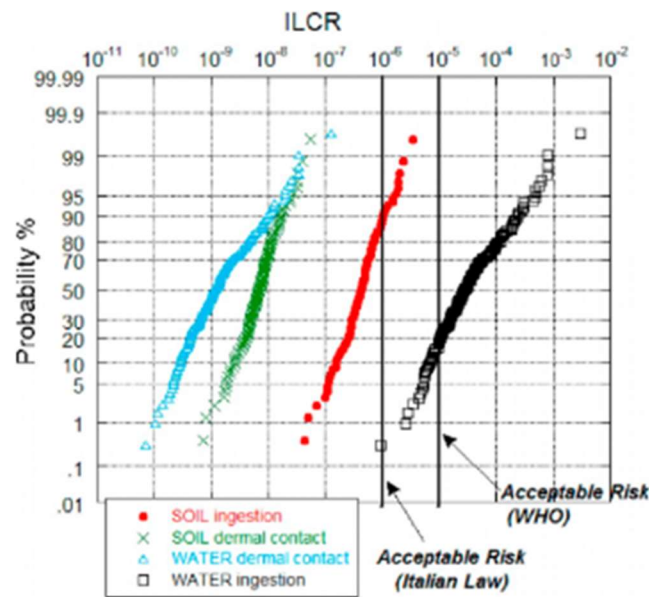
In order to highlight relevance of the analysed sources of exposure (soil and water) to the age-related health risk, the daily As intake via different exposure pathways together with carcinogenic (ILCR) and non-carcinogenic (HQ) risks were estimated for different age groups (children, teenagers and adults). Further, the lifetime risk was modelled by considering the duration of As exposure from birth to an average age of 70 years. The calculated values of Incremental Lifetime Cancer Risk for skin cancer ($ILCR_{skin}$), Incremental Lifetime Cancer Risk for combined lung and bladder cancers ($ILCR_{lb}$) and HQ are summarised in Tables 5–7, respectively.

Considering the age groups, the average pseudo-total $ILCR_{skin}$ values are in the order of adults (3.4×10^{-5}) > children (1.4×10^{-5}) > teenagers (1.2×10^{-5}). It indicates almost 12, 14 and 34 additional cases of cancer in one million exposed teenagers, children and adults, respectively. The average pseudo-total $ILCR_{skin}$ modelled over a lifetime (from birth to 70 years old) is 5.7×10^{-5} (i.e., almost 57 additional cases of cancer in one million). In 2010, US EPA proposed a much larger CSF for combined lung and bladder cancers which also reflects higher sensitivity of women compared to men. Although the proposed slope factor is currently under external review, it has been used in peer reviewed research articles. In this study, it was utilized for assessing the risk of water ingestion representing the most influential route of exposure. Table 6 shows the computed $ILCR_{lb}$ because of drinking water consumption throughout Italy. Females and males are potentially exposed to moderate to very high cancer risk. On average, 97 additional cases of bladder and lung cancer in 100,000 exposed females are potentially expected due to arsenic ingested through tap water.

There are no absolute criteria for the acceptable number of additional cancers over a lifetime. In most jurisdictions (e.g. the Italian one), the value of one additional case of

553 cancer in one-million (1×10^{-6}) is frequently used as a management goal for the risks
 554 posed by environ-mental contaminants. Fig. 4 indicates contribution of different
 555 exposure scenarios (i.e., soil ingestion, soil dermal contact, water dermal contact and
 556 water ingestion) to $ILCR_{skin}$. The cumulative probability plot shows that oral ingestion
 557 pose the highest skin cancer risk because the total As intake is considered to be
 558 absorbed. For soil ingestion, the probability of skin cancer development ($> 1 \times 10^{-6}$
 559 according to the acceptable risk set by Italian law) is 6.8% over a lifetime.

560



561 Fig. 4. Cumulative Probability plot of the Incremental Lifetime Cancer Risk for skin
 562 cancer ($ILCR_{skin}$) posed by different expousure scenarios (i.e., soil ingestion, soil
 563 dermal contact, water dermal contact and water ingestion) for Italian population.

564

565 Nonetheless, water ingestion is evidently the most relevant exposure route because the
 566 probability of a lifetime cancer risk over 1×10^{-6} is about 100%. The acceptable WHO
 567 risk level (1×10^{-5}) is also exceeded by almost 80% of cases (Fig. 4). The incremental
 568 lifetime skin cancer risk induced by drinking water provides interesting information
 569 for the Italians when the variation from children to adults is taken into account. The
 570 $ILCR_{skin}$ ranges from 9.6×10^{-7} to 1.7×10^{-3} over a lifetime with several orders of
 571 magnitude between lower and upper percentiles (Fig. 5). Duration of exposure seems
 572 to play a decisive role in risk estimation.

573 Approximately 20% of the analysed tap water samples exceed the threshold of 1×10^{-4}
574 indicating a potential carcinogenic risk to the local residents. Contribution of dermal
575 As absorption from water and soil to the pseudo-total $ILCR_{skin}$ can be considered
576 negligible for all three age groups.

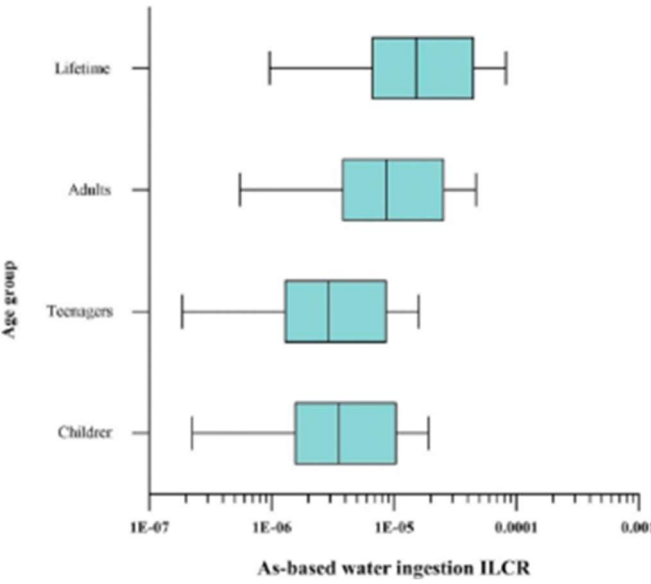
577 Spatial distribution of the potential cancer risk for the most influential exposure routes
578 is presented in Fig. 6. The potential high skin cancer risk ($ILCR > 1 \times 10^{-4}$; Wang et
579 al., 2011) deriving from water ingestion occurs in the densely populated areas of Italy
580 such as northern Alps (including the city of Trento), a great part of central and southern
581 Italy (including the capital Rome and the cities of Napoli and Catanzaro). Based on the
582 geographical distribution of the computed $ILCR_{skin}$ values, the hazardous $ILCR_{skin}$ zone
583 ($> 1 \times 10^{-3}$) is located in the central area of Italy including the township of Viterbo
584 (Fig. 6).

585 The incremental probability of developing skin cancer over a life-time (Fig. 6B) is
586 almost 350 cases of cancer in 322,000 exposed people in Viterbo province. While
587 spatial variation of $ILCR_{skin}$ computed for soil ingestion is mostly characterized by the
588 practical safety ($ILCR_{skin} < 10^{-6}$), few hotspot areas show a moderate potential skin
589 cancer risk (Fig. 6A).

590 Soil ingestion is usually an accidental route of exposure for children playing outdoors
591 and adults working in the agricultural industry. The determined values of Hazard
592 Quotient (HQ) indicate that As concentrations in soil do not result in higher likelihood
593 of non-carcinogenic health effects for the inhabitants (Table 7). However, a significant
594 potential health risk, associated with chronic exposure to As, occurs through water
595 ingestion. Non-carcinogenic adverse effects (e.g., hyperpigmentation, keratosis, and
596 possible vascular complications) are not expected from the other exposure routes.

597 The most susceptible age groups are children and teenagers, with more than 5.7% of
598 the HQ values above 1. Potential non-cancer effects might pose a threat to 12.7% of
599 the population during a lifetime exposure (from birth to an average age of 70 years).

600 Geographical distribution of the HQ values derived from water in-gestion exposure
 601 scenario reveals that a large area of Italy is characterized by medium to high non-
 602 carcinogenic risk (Fig. 7). A potential high carcinogenic risk was surprisingly found in
 603 the same areas as well. Hence, epidemiological and toxicological studies may be able
 604 to evaluate and reduce degree of uncertainty in health risk assessment.



605
 606 Fig. 5. Multiple boxplot graph comparing the Incremental Lifetime Cancer Risk for
 607 skin cancer ($ILCR_{skin}$) estimated for children (1–8 years old), teenagers (9–16 years
 608 old), adults (16–70 years old) and lifetime (from birth to 70 years old) in water
 609 ingestion scenario.

611 4.4. Stochastic simulation of health risk

612 As an extension of the deterministic approach, a probabilistic ana-lysis of health risk
 613 was performed to consider uncertainty and variability in the drinking water scenario
 614 accounting for the highest health risk. Because of using a wide range of population-
 615 related parameters in health risk characterization, integration of uncertainty and
 616 variability into the investigation can lead to a more realistic risk assessment. Thus, the
 617 Monte-Carlo simulation technique was applied using Oracle Crystal Ball software
 618 (version 11.1.1.1.00, Oracle, Inc., USA). Monte-Carlo simulation uses the inherent
 619 variability and uncertainty in risk assessment and provides a more meaningful estimate
 620 of the probable ranges of exposure (Wu et al., 2016) rather than calculating point

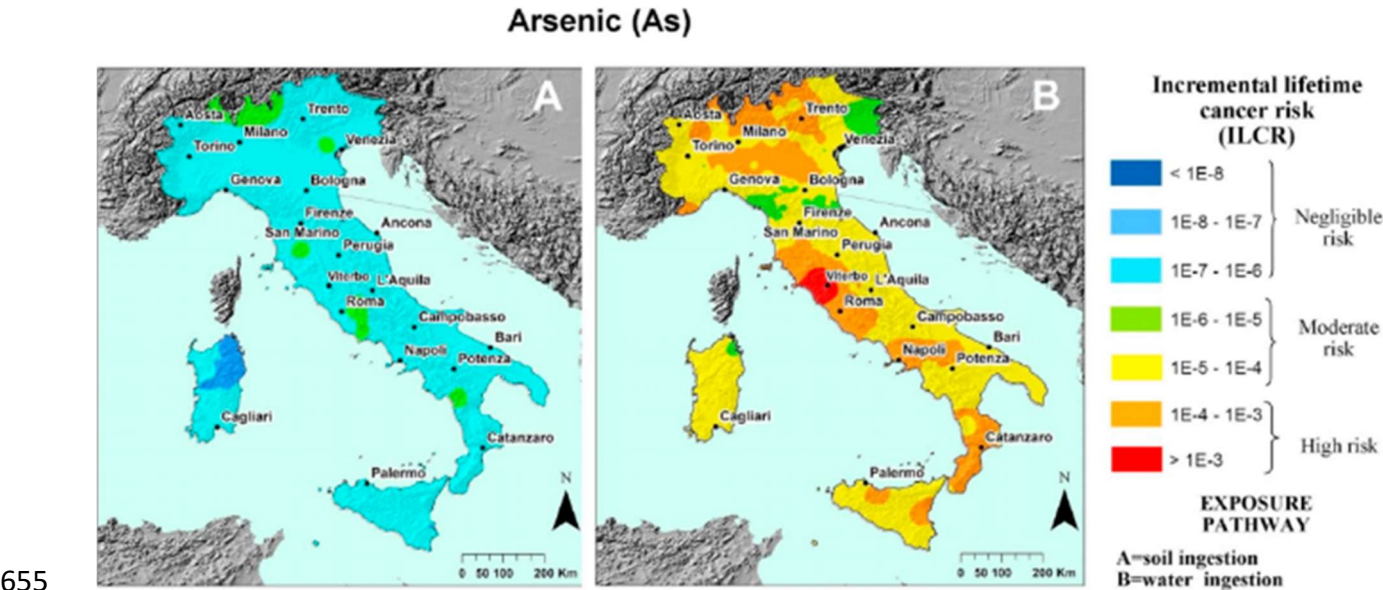
estimates. The statistical distribution of the random variables are presented in Table S1 in the Supplementary Material. The log-normality of As concentration values was verified by the fitdistrplus routine within the R software package (Delignette-Muller et al., 2014).

The anthropometric and water consumption data were extrapolated from the Italian National Food Consumption Survey INRAN-SCAI 2005–06 (Leclercq et al., 2009); the survey was conducted on a re-presentative sample of randomly selected households and then stratified into the four main geographical areas of Italy (North-West, North-East, Centre, South and Islands) between October 2005 and December 2006.

After 500, 1000, 1500, 2000, 3000, 5000 and 10000 iterations, the results showed that 2000 trials ensure stability of the estimations. Fig. 8 demonstrates the results of Monte Carlo simulation for the incremental lifetime cancer risks posed by exposure to As in drinking water. Overall, the $ILCR_{skin}$ values estimated for different age groups follow the order of adults > children > teenagers being in accordance with the deterministic approach. The $ILCR_{skin}$ values for the children exposed to As in drinking water are orders of magnitude above the acceptable cancer risk threshold of 1×10^{-6} accounting for 50% probability. Nonetheless, the chance of potential health risk is greater than 70% and about 33% for adults and teenagers, respectively. The probability that $ILCR_{skin}$ exceeds the abovementioned threshold is 97% over a lifetime (Fig. 9A). Although the results of probabilistic exposure estimates and deterministic point estimates are comparable, a slight overestimation is observed in the deterministic approach.

Sensitivity analysis was also performed to evaluate the impact of single variables on the results of the risk assessment. Fig. 9B reveals that contaminant concentration in drinking water (Cw) has the greatest influence on the outcome of risk assessment for all age groups, followed by exposure duration (ED) and ingestion rate (IR). As expected by observing equations (1)–(4), the slightly negative coefficient of body weight (BW) indicate decreasing health risk with increasing BW. This latter condition seems to be, apparently, in contrast with Steinmaus et al. (2015) stating that

649 “environmentally-related cancer risks may be markedly increased in people with
 650 elevated body mass index (BMI), especially in those with an elevated BMI in early-
 651 life”. In fact, BMI, mostly used as a measure of the degree of overweight, and BW,
 652 which is a measure of the whole mass in living beings, give complementary in-
 653 formation; hence the inclusion of BMI as a corrective factor in the assessment
 654 procedure should lead to a more reliable evaluation of risk.



656 Fig. 6. Spatial distribution of skin cancer risk (calculated as $ILCR_{skin}$) due to As
 657 exposure through (A) soil ingestion and (B) water ingestion over a lifetime.
 658

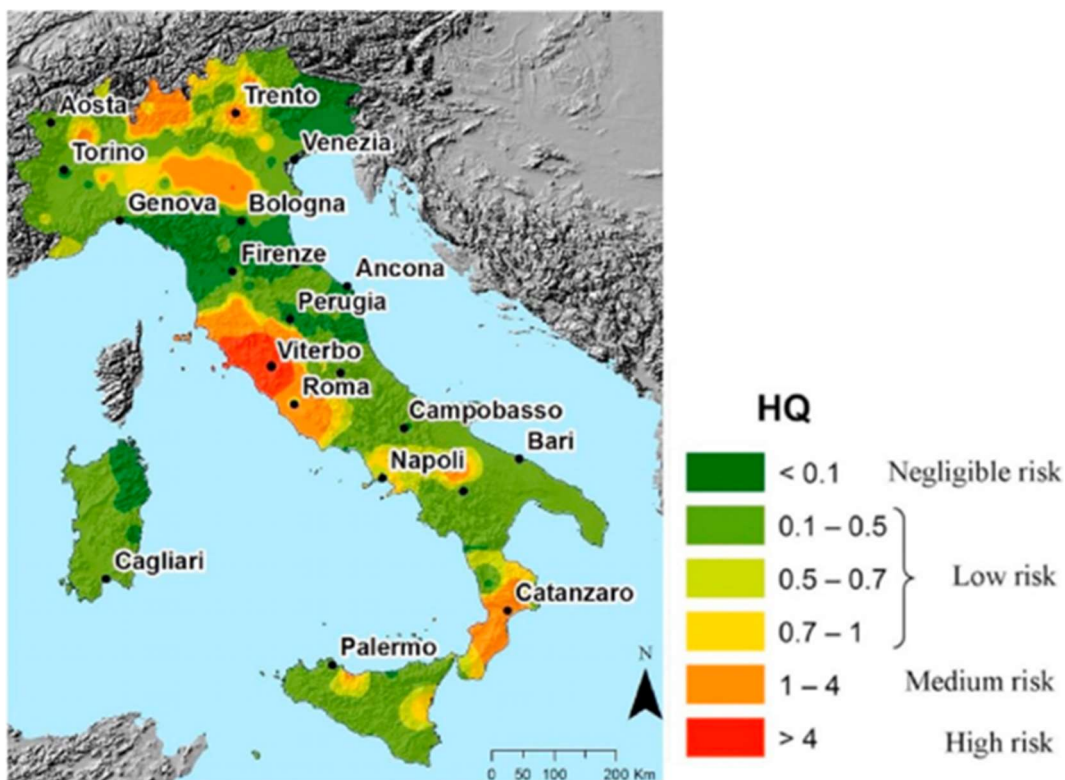


Fig. 7. Spatial distribution of non-carcinogenic risk, calculated as Hazard Quotient for exposure to As due to water ingestion over a lifetime. Risk classes for HQ are based on Chowdhury and Maiti (2016).

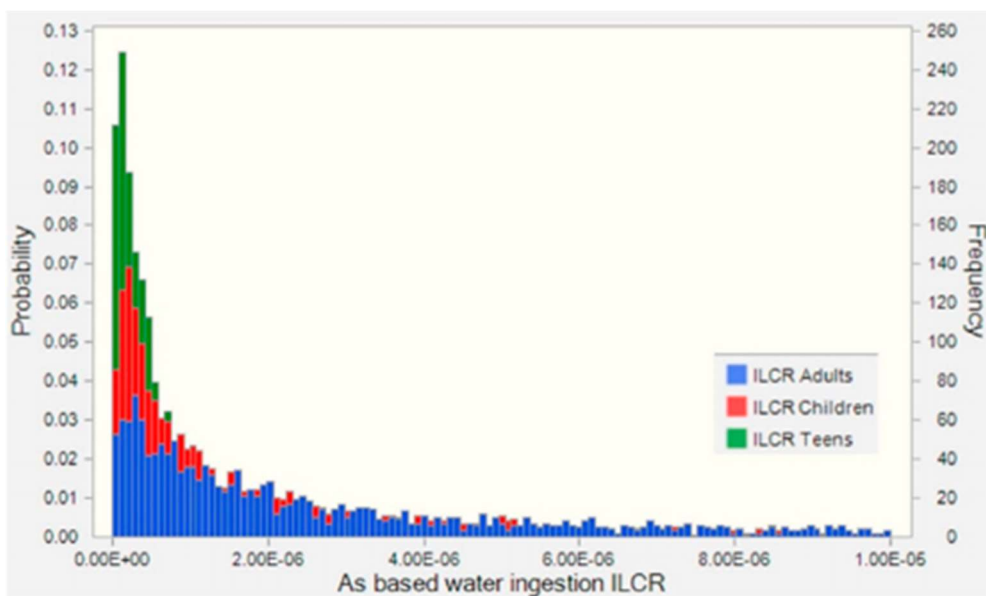


Fig. 8. Predicted probability density functions of ILCRs computed for As exposure through water ingestion for the three age groups (children, teenagers and adults).

5. Conclusions

669 This study is the first research carried on the occurrence and spatial distribution of As
670 in different environmental media at a national scale in Italy. Human health risk due to
671 As exposure through different pathways (dermal contact and ingestion) was also
672 assessed (using deterministic and stochastic approaches) and spatial arsenic exposure
673 was evaluated.

674 Arsenic is widely distributed in water and soil throughout Italy reflecting the natural
675 geochemical patterns at the investigated scale quite well. The dataset and the spatial
676 analysis are suitable for the objectives of the current study. In particular, the sub-
677 continental-scale sampling density appropriately explain As variability in the analysed
678 matrices mainly due to the geochemical background. Arsenic enrichment in soil and
679 water is mostly associated with the geological features such as volcanic rocks in TMP
680 and RMP and the disseminated sulphide mineralisations in the Alps.

681 A reasonable assessment of the health risk associated with natural occurring As shows
682 that water consumption by the residents accounts for majority of the risk. In this
683 investigation, the end-user tap water compositions are representative of the water an
684 Italian drinks at home and in public places (bars, restaurants, offices and public taps)
685 every day. Based on the results of carcinogenic and non-carcinogenic risk assessment,
686 tap water ingestion plays an important role in potential cancer and non-cancer risks due
687 to human exposure to As. Comparison of the deterministic and probabilistic risk values
688 indicates that integration of uncertainty and variability into investigation leads to a
689 more realistic understanding of human health risk in the latter approach. Risk is slightly
690 overestimated in results of the deterministic method. Because randomness is
691 considered in the probabilistic models, they are preferred to the deterministic approach.

692 Interestingly, the computed values of the Incremental Lifetime Cancer Risk for skin
693 cancer ($ILCR_{skin}$) due to ingestion of As-rich water (obtained by probabilistic approach)
694 show that almost 97% of the waters are responsible for an increment of skin cancer risk
695 ($> 1 \times 10^{-6}$, the acceptable limit of most jurisdictions (including Italian legislation) and
696 international agencies). In addition, the $ILCR$ values for combined lung and bladder

697 cancers (ILCR_{lb}) indicates that the both genders are potentially exposed to moderate to
698 very high cancer risk; however, the risk for females is higher.

699 Regarding the results of the present study, adults would be affected by As related cancer
700 risk more severely than the other age groups, due to their greatest cumulative exposure.
701 High As contents in both water and soil analysed samples collected from central Italy
702 is associated with the presence of alkaline volcanic materials leading to high
703 carcinogenic risk for the residents. Geographical distribution of cancer risk also
704 highlights a high risk in northern Alps (including the city of Trento) and central and
705 southern Italy (including the capital Rome and the cities of Napoli and Catanzaro).
706 Moreover, potential non-carcinogenic risk is high in these areas.

707 For completeness of our study, it is necessary to recognize that there are intrinsic
708 limitations concerning our results. For instance, quantitative risk estimates may
709 provide an impression of certainty that they do not have in reality. Moreover sampling
710 size may have affected the range of uncertainty around the estimated exposure level
711 and the projected number of people who may be exposed to As. Also information gaps
712 (e.g., lifestyle and dietary habits) may be considered inherent limitations to the
713 outcomes. Nevertheless, the use of stochastic simulation partially overcame the
714 aforementioned limits, since it rely on the use of probability distribution functions. In
715 addition, our study can be considered a nationally-representative survey, since it
716 evaluated exposure based on specific parameters of the target population. Also
717 sensitivity analysis represented a strength of the adopted procedure as it apprised about
718 the impact of the risk model parameters.

719 Our results ultimately provide useful indications of exposure levels and set priorities
720 at the regional and national levels. This study can be considered as a critical example
721 for challenging the current international and Italian As regulatory levels. Although
722 more than 80% of the analysed water samples are responsible for an excess cancer risk
723 (higher than the WHO benchmark value of 1×10^{-5}), most of the measured As
724 concentrations are lower than the current As statutory level for drinking water (10 µg/l).

725 Further, Tchounwou et al., (2003) estimated cancer risks of 10^{-5} , 10^{-6} and 10^{-7} for
726 drinking waters containing 0.022, 0.0022, and 0.00022 $\mu\text{g/l}$ As, respectively. While the
727 debate about low-dose exposure is ongoing, D'Ippoliti et al. (2015) provided new
728 evidence that even As concentrations below the EU limit of 10 $\mu\text{g/l}$ can raise mortality
729 risks. US EPA, in agreement with EU and WHO limits, sets the highest level of As that
730 is allowed in drinking water (Maximum Contaminant Level - MCL) at 10 $\mu\text{g/l}$, but
731 even sets the Maximum Contaminant Level Goal (MCLG), which is the level of a
732 contaminant below which there is no known or expected risk to health, at 0 $\mu\text{g/l}$.

733 In light of the above discussion, a question obviously arises: “Should the As standard
734 levels for drinking water be reviewed? Can the current HHRA approach lead to a risk
735 overestimation?” Both epidemiological and toxicological studies clearly may be able
736 to evaluate and reduce the inherent degree of uncertainty in health risk assessment.

737 At the same time the guideline values should be upgraded based on the recent scientific
738 findings on the mechanisms of toxicity caused by xenobiotics, e.g. chemical forms.
739 Meanwhile this article was under preparation, the Italian Ministry of the Environment
740 was adopting a Statutory Instrument (effective from June 22, 2019) for remediation,
741 environmental restoration and safety of the areas destined for agricultural production
742 and breeding (D.M. 46/2019). In line with the US EPA approach, it defines the criteria
743 for exposure-based risk analysis for the consumption of agrifood products and
744 introduces the concept of bio-accessibility test.

745 Although specific regulatory levels might be debatable, there is an agreement about
746 minimising As exposure as the best solution, especially in the early life. Strategies to
747 reduce the As intake (public water treatment or residential purification systems) and
748 changes in daily habits of the vulnerable groups can be a great starting point to decrease
749 the potential health risk for the Italian people. In addition, reducing the duration of
750 exposure to As-rich waters feasibly limits risk as shown by the parameter sensitivity
751 analysis in this study. The return on investment can also be substantial because the

752 reduced incidence of chronic diseases and cancers results in lower expenses for medical
753 treatments.

754 It is, therefore, concluded that further research on specific human exposure routes and
755 geomedical investigations can help to understand the link between low-dose As
756 exposure and the induced human diseases in some areas of Italy.

757 **Declaration of competing interest**

758 None.

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770 Appendix A. Supplementary data

771

772

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1314 Table 1

1315 Typical ranges of As concentrations (mg/kg) in common rock-forming minerals (from
1316 Smedley and Kinniburgh, 2002).

1317 **Sulphide mineral**

1318 Pyrite 100–77,000

1319 Pyrrhotite 5–100

1320 Marcasite 20–126,000

1321 Galena 5–10,000

1322 Sphalerite 5–17,000

1323 Chalcopyrite 10–5000

1324 **Oxide minerals**

1325 Haematite up to 160

1326 Fe(III) oxyhydroxide up to 76,000

1327 Magnetite 2.7–41

1328 Ilmenite <1

1329 **Sulphate minerals**

1330 Gypsum/anhydrite < 1–6

1331 Baryte < 1–12

1332 Jarosite 34–1000

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Silicate minerals

Quartz 0.4–1.3

Feldspar < 0.1–2.1

Biotite 1.4

Amphibole 1.1–2.3

Olivine 0.08–0.17

Pyroxene 0.05–0.8

Carbonate minerals

Calcite 1–8

Dolomite < 3

Siderite < 3

— —

Other minerals

Apatite < 1–1000

Halite < 3–30

Fluorspar < 2

1335 Table 2

1336 Effects of As oral exposure adapted from ATSDR (Agency for Toxic Substances and
1337 Disease Registry) (2007).

1338	System	Exposure duration	Exposure level	Effects	Source
1339			(As mg/kg/day)		
1340	HIGH DOSE EXPOSURE				
1341	Death	1 week	2	death	Armstrong et al. (1984)
1342	Death	once	22	death	Levin-Scherz et al. (1987)
1343	Gastrointestinal	1 week	0.2	vomiting, diarrhoea, abdominal pain	Armstrong et
1344	al. (1984)				
1345	Haematological	2 weeks	0.2	pancytopenia, leukopenia	Armstrong et al.
1346	(1984)				
1347	Hepatic	once	2	slight increase in serum bilirubin	Hantson et al. (1996)
1348	Ocular	once	13	constricted vision	Kamijo et al. (1998)
1349	Cardiovascular	once pregnancy – week 30	6	hypotension, rapid pulse	Lugo et al. (1969)
1350	Gastrointestinal	once pregnancy – week 30	6	abdominal pain, vomiting	Lugo et al. (1969)
1351	Haematological	once pregnancy – week 30	6	high leukocyte count, low haematocrit	Lugo et al.
1352	(1969)				
1353	Renal	once pregnancy – week 30	6	acute renal failure	Lugo et al. (1969)
1354	LOW-DOSE EXPOSURE				
1355	Respiratory	2–3 weeks	0.05	sore throat, rhinorrhoea, cough, sputum	Mizuta et al.
1356	(1956)				
1357	Dermal	>8 years	0.0012	increased risk of premalignant skin lesions	Ahsan et al.
1358	(2006)				
1359	Cardiovascular	> 10 years	0.022	increased risk of ischemic heart disease mortality	Chen
1360	et al. (1996)				
1361	Haematological	lifetime	0.002	anemia during pregnancy	Hopenhayn et al. (2006)
1362	Hepatic	55 years	0.03	portal fibrosis and hypertension, bleeding from	
1363	oesophageal varices	Szuler et al. (1979)			
1364	Neurological	lifetime	0.005	reduced performance in neuro behavioural tests	
1365	Wasserman et al. (2004)				
1366	Reproductive	lifetime	0.006	increased incidence of spontaneous abortion	
1367	Milton et al. (2005)				
1368	Developmental	continuous	0.002	reduced birth weigh	Hopenhayn et al. (2003)
1369	Cancer	NS*	0.003	bladder cancer	Chiou et al. (2001)
1370	Cancer	NS*	0.0011	lung cancer	Ferreccio et al. (1998)
1371	Cancer	NS*	0.0049	squamous cell carcinoma of the skin	Guo et al. (2001)
1372	Cancer	>1 year	0.0075	basal or squamous skin carcinoma	Hauptert et al. (1996)
1373	Cancer	5 years	0.033	lung, urinary tract cancer	Tsuda et al. (1995)

1374 Table 3

1375 Currently accepted national maximum permissible guideline limits in different
1376 countries for As in drinking water and soil.

1377	Sample type	Maximum permissible limit	Country	Reference
1378	Drinking water (µg/l)	10	European Union	European Union (1998)
1380			Japan MEJ	Ministry of the Environment (2008)
1381			New Zealand	Ministry of Health (2005)
1382			U.S.A.	CFR (2006)
1383			Canada	CDWG (2007)
1384		50	Bangladesh	BRAC Bangladesh Rural Advancement
1385			Committee (2000)	
1386			China	Guo and Wang (2005)
1387			India	Indian Bureau of Standards (1991)
1388			Chile	Caceres et al. (2005)
1389			Nepal	Shrestha et al. (2003)
1390			Pakistan	NSDWQ (2008)
1391			Vietnam	Berg et al. (2001)
1392	soil (mg/kg)	12 ^a	Vietnam	Trang Hoang and Hahn (2015)
1393		15 ^a	Japan	MEJ Ministry of the Environment (2008)
1394		20	Italy ^b	D.L. 152/2006
1395			Canada ^c	CCME (2001)
1396			Norway	Hansen and Danielsberg (2009)
1397			Australia	Henke (2009)
1398			U.S.A.	(New Jersey) Henke (2009)
1399		50 ^d	Germany	BBodSchG (1998)

1400 ^a Soil for agricultural land (i.e. paddy fields only).

1401 ^b Recreational/residential soil.

1402 ^c Agricultural soil.

1403 ^d Agricultural soil with partially reducing conditions

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1407 Table 4

1408 Main statistical parameters of total As content in different sample types collected
1409 throughout Italy.

1410	Sample type	n	Unit	Min	Q25	Mean	Q50	Q50 Europe	Q75	Q95	Max	SD
1411	Agricultural soil ^a	118	mg/kg	0.79	5.04	10.04	7.56	5.50	11.40	28.18	62.20	9.07
1412	Grazing land soil ^a	118	mg/kg	0.97	4.72	9.76	8.08	5.60	11.90	22.88	54.28	7.53
1413	Stream sediment ^b	51	mg/kg	< 5.00	< 5.00	7.20	6.00	6.00	9.50	15.50	38.00	6.23
1414	Floodplain sediment ^b	50	mg/kg	< 5.00	< 5.00	8.86	7.00	6.00	9.00	26.50	51.00	9.78
1415	Bottled mineral water ^c	186	µg/l	0.01	0.13	0.89	0.25	0.24	0.67	5.08	8.91	1.54
1416	Stream water ^b	48	µg/l	0.08	0.27	1.79	0.47	0.63	1.71	9.94	13.00	3.21
1417	Tap water ^c	157	µg/l	0.02	0.11	0.94	0.25	0.19	0.73	4.39	27.20	2.51

1418 ^a (GEMAS) Geochemical mapping of agricultural and grazing land soil of Europe project (Reimann et al., 2014).

1419 ^b FOREGS (Forum of European Geological Surveys) Geochemical Atlas of Europe project (Salminen et al., 2005).

1420 ^c (EGG) European Groundwater Geochemistry Project’ (Reimann and Birke, 2010).

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Table 5

Range of the calculated Incremental Lifetime Cancer Risk for skin cancer (ILCR_{skin}) values based on the 1.5 mg/kg/day cancer slope factor (US EPA); the values are summarised for different age groups (children, teenagers, adults and lifetime), sample types (tap water and soil) and exposure pathways (ingestion and dermal contact).

Sample type	Exposure pathway	Age group			
		Children	Teenagers	Adults	Lifetime
Tap water $\times 10^{-3}$	ingestion	Range of ILCR _{skin} $2.2 \times 10^{-7} - 3.9 \times 10^{-4}$	$1.9 \times 10^{-7} - 3.2 \times 10^{-4}$	$5.5 \times 10^{-7} - 9.4 \times 10^{-4}$	$9.6 \times 10^{-7} - 1.7$
	dermal contact ^a	$1.2 \times 10^{-11} - 2.1 \times 10^{-8}$	$1.1 \times 10^{-11} - 1.8 \times 10^{-8}$	$4.7 \times 10^{-11} - 8.1 \times 10^{-8}$	$6.9 \times 10^{-11} -$
1.2×10^{-7}					
Soil $\times 10^{-6}$	ingestion	$1.2 \times 10^{-8} - 9.4 \times 10^{-7}$	$5.5 \times 10^{-9} - 4.3 \times 10^{-7}$	$1.7 \times 10^{-8} - 1.3 \times 10^{-6}$	$3.4 \times 10^{-8} - 2.7$
	dermal contact	$1.2 \times 10^{-10} - 9.8 \times 10^{-9}$	$9.6 \times 10^{-11} - 7.5 \times 10^{-9}$	$4.7 \times 10^{-10} - 3.7 \times 10^{-8}$	$6.9 \times 10^{-10} -$
5.4×10^{-8}					
Pseudo-total ILCR _{skin}	Mean	1.4×10^{-5}	1.2×10^{-5}	3.4×10^{-5}	5.7×10^{-5}

b It is represents the multi-pathway skin cancer risk calculated as sum of mean values for the ingestion and the dermal contact routes.

a Based on 1% of the calculated TDI, as suggested by ECHA - European Chemicals Agency (2013).