Sustainable Water Resources Management (2022) 8:167
https://doi.org/10.1007/s40899-022-00745-7

ORIGINAL ARTICLE

# Hydrochemistry of mountain rivers in the Sierra de Velasco, La Rioja, Argentina: implications on dental fluorosis through statistical modeling

**Gimena Mariel Uran[1] · Andrea Inés Pasquini[2,3] · Viviana Giampaoli[4] · Mariano Alexis Larrovere[1,5] · María Florencia Cortés Montiel[6] · Rita Esther Pautasso[7]**

Received: 16 June 2022 / Accepted: 17 August 2022


**Abstract**

Dental fluorosis is a disease associated with prolonged intake of high concentrations of fluoride, mainly by drinking water consumption. In a rural region in NW Argentina, several localities are supplied for domestic use by surface waters with variable contents of dissolved $F^-$ (from 0.3 to 3.1 mg $L^{-1}$) of geogenic origin. Dental fluorosis, from very mild to severe, has been registered in the population according to the spatial variability of dissolved $F^-$. In this work, statistical models demonstrated that the concentrations of dissolved $F^-$ that determine the occurrence of dental fluorosis (and its severity) depend on the concentrations of dissolved $Ca^{2+}$. In children and adolescents, the probability of presenting this disease, at any degree, increases with age and dissolved $F^-$; whereas moderate-to-severe degree is controlled by an inverse relationship between dissolved $F^-$ and $Ca^{2+}$. This last result was also obtained in the group of adults, for any degree of dental fluorosis. Thus, for a particular concentration of dissolved $F^-$, as dissolved $Ca^{2+}$ increases, the probability of developing dental fluorosis decreases. The findings of this work could be useful to adjust the current regulations, since guidelines of dissolved $F^-$ in drinking water for different degrees of dental fluorosis are not considered, nor the relationship between $F^-$ and $Ca^{2+}$.

**Keywords** Fluorosis · Probit regression model · Drinking water · Dental health · Surface water

## Introduction

Dental fluorosis is a fluoride-induced alteration that occurs mainly during tooth formation, resulting in a hypomineralized enamel with greater porosity. The severity of such a clinical condition may vary from the appearance of very fine white lines to serious structural defects (Fejerskov et al. 1977; Hidalgo Gato Fuentes et al. 2007; Zou and Ashley 2014). It is widely recognized that the most important risk factor for dental fluorosis is the amount

✉ Gimena Mariel Uran
g.uran@conicet.gov.ar; gimeuran@gmail.com

1 Centro Regional de Investigaciones Científicas y Transferencia Tecnológica de La Rioja (CRILAR) (CONICET-SEGEMAR-Provincia de La Rioja-UNCA-UNLAR), Entre Ríos y Mendoza S/N, CP 5301 Anillaco, La Rioja, Argentina

2 Centro de Investigaciones en Ciencias de la Tierra (CICTERRA), CONICET y Universidad Nacional de Córdoba, Córdoba, Argentina

3 Facultad de Ciencias Exactas, Físicas y Naturales, Av. Vélez Sarsfield 1611, X5016CGA Córdoba, Argentina

4 Departamento de Estatística, Instituto de Matemática e Estatística, Universidade de São Paulo, Rua do Matão, 1010, São Paulo CEP 05508-090, Brazil

5 Instituto de Geología y Recursos Naturales, Centro de Investigación e Innovación Tecnológica, Universidad Nacional de La Rioja (INGeReN-CENIIT-UNLaR), La Rioja, Argentina

6 Hospital Seccional Pinchas, Ruta Nacional N° 75, Km 72, Pinchas, La Rioja, Argentina

7 Cátedra de Microbiología y Parasitología, Facultad de Odontología, Universidad Nacional de La Rioja, Av. Luis M. de la Fuente S/N, Ciudad Universitaria de la Ciencia y de la Técnica, F5300 La Rioja, Argentina

Published online: 13 September 2022

of fluoride consumed from all sources during the critical period of tooth development (e.g., Beltrán Valladares et al. 2005; Mehta and Shah 2013; Zou and Ashley 2014). This endemic disease affects particularly children and adolescents in different regions around the world. According to the World Health Organization (WHO 2011), more than 200 million individuals in at least 25 countries are affected by dental and skeletal fluorosis. The latter is a more severe condition of fluorosis caused by chronic ingestion of fluoride, which produces high levels of accumulation in bones and joints (Srivastava and Flora 2020).

Drinking water represents the major source of fluoride intake, causing about 65% of endemic fluorosis (Yuan et al. 2020). Fluoride is usually present in surface water at low concentrations (< 1.5 mg $L^{-1}$), while groundwater normally contains higher concentrations (e.g., Warren et al. 2005; Gómez et al. 2009; Borgnino et al. 2013; Gevera et al. 2019; Zhang et al. 2020; Arya et al. 2; among others). A significant number of studies have analyzed the relationship between high contents of dissolved fluoride and its implications for human health, and most of them focused on groundwater sources (e.g., Yadav et al. 2009; Arveti et al. 2011; Rafique et al. 2015; Irigoyen Camacho et al. 2016; Ramadan and Ghandourb 4; Raju 2017; Rasool et al. 2018; Gevera et al. 2019; Zhang et al. 2020; Arya et al. 2021; among others). Similar studies centered in surface water sources are less known (e.g., Berger et al. 2012; García et al. 2012; Kitalika et al. 2018).

Fluoride is released into natural waters from the dissolution of fluoride-bearing minerals (Pradhan and Biswal 2018). Although anthropogenic emissions from certain industrial processes can also contribute fluoride from the atmosphere to the water (Chapman 1996; García and Borgnino 2015), most of the dissolved fluoride has a geogenic origin. Therefore, the occurrence of fluoride in natural waters mainly depends on its abundance in the local lithology (Edmunds and Smedley 2013). Several authors have explored the mechanism of fluoride release into the solution from solid phases (e.g., Jacks et al. 2005; Chae et al. 2006; Chaïrat et al. 2007; Zhu et al. 2009; Keshavarzi et al. 2010; Borgnino et al. 2013; García et al. 2014). On the other hand, a number of geochemical processes determine the dynamics of fluoride in natural waters, such as adsorption, precipitation, dissolution, and desorption (e.g., García and Borgnino 2015; and references therein). Moreover, it has been pointed out that in natural waters, dissolved $F^-$ largely depends on the solubility equilibrium of Ca-bearing minerals. For instance, calcite precipitation, along with other geochemical processes that scavenge $Ca^{2+}$ from the solutions (e.g., ion exchange), enhances the dissolution of fluorite (e.g., Chae et al. 2006) and fluorapatite (e.g., Borgnino et al. 2013; Kechiched et al. 2020).

In Argentina, high concentrations of fluoride have been reported in groundwater of the Pampean plain, with values that can reach 12.00 mg $L^{-1}$ (e.g., Kruse and Ainchil 2003; Warren et al. 2005; Gómez et al. 2009; Borgnino et al. 2013; Zabala et al. 2016; Rondano Gomez et al. 2020). Nevertheless, there are few references that address the problem of fluoride in surface waters and its relationship with dental fluorosis in Argentina (e.g., García et al. 2012). In the Sierra de Velasco (Sierras Pampeanas, Argentina), several mountain rivers are the main freshwater source for rural communities housed in small towns. To the North of this region, many cases of severe dental fluorosis have been reported, whereas toward the South, this condition tends to decrease significantly (National Observatory of Land Degradation and Desertification 2022: http://www.desertificacion.gob.ar/). This suggests that dissolved $F^-$ concentrations in the northern sector are higher than the maximum allowed for drinking water in the national (1.3 mg $L^{-1}$; CAA 2012) and international (1.5 mg $L^{-1}$; WHO 2011) regulations.

Most of the previous studies in the literature propose that dental fluorosis is caused by an excessive intake of fluoride; however, little is known about the joint effect of calcium and fluoride on the development of fluorosis; only a few studies have observed an inverse relationship between these parameters in sheeps (Simon et al. 2014) and mice (Yu et al. 2019). The aim of this paper is to formulate a statistical model that allows to explain the association between dissolved fluoride and calcium and its implications in the development and severity of dental fluorosis. For this purpose, the hydrochemical composition of surface waters was characterized, and the first systematical registry of dental fluorosis in the region was carried out. The obtained results provide novel information, with statistical support, about the relationship among dental fluorosis and the inverse co-variation between dissolved $Ca^{2+}$ and $F^-$ in drinking water, which has been little explored in the previous literature. In addition, these results may be useful to review national and international legislation, regarding the water quality required to prevent dental fluorosis.

## Study area

The area where the study was carried out is situated in the northwest of the Sierra de Velasco, a mountain range located in La Rioja Province, Argentina (28° 40′–29° 00′ S and 66° 50′–67° 10′ W, Fig. 1). Along the eastern slope of the western ridge of the Sierra de Velasco, eight small towns are located; from North to South, they are: Santa Vera Cruz, Anjullón, Los Molinos, Anillaco, Aminga, Chuquis, Pinchas, and Agua Blanca; all of them are part of the Castro Barros department (Fig. 1).

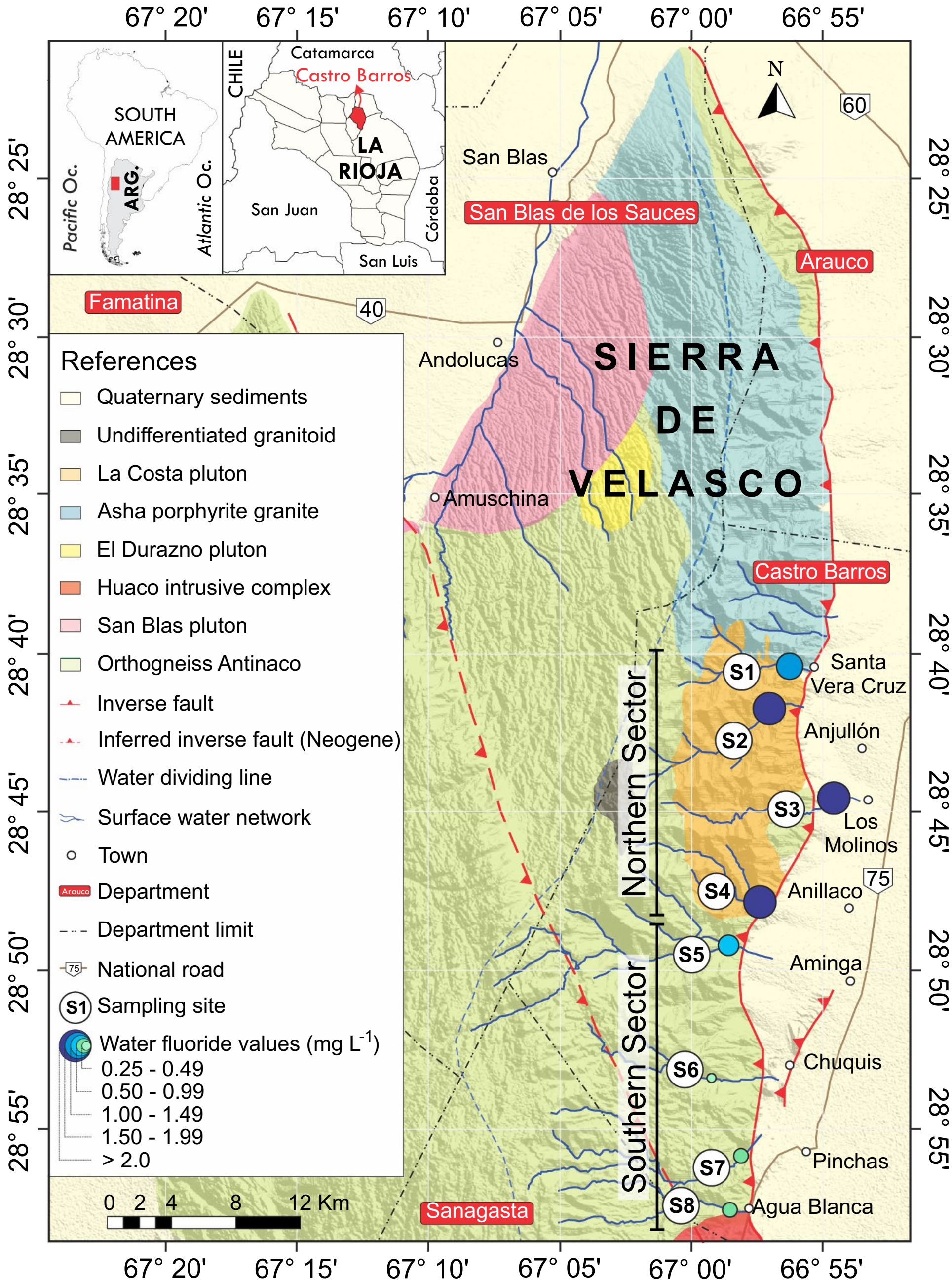


**Fig. 1** Geological map of the study area showing the sampling sites (S). The northern sector includes: S1 (Santa Vera Cruz), S2 (Anjullón), S3 (Los Molinos), and S4 (Anillaco). The southern sector includes: S5 (Aminga), S6 (Chuquis), S7 (Pinchas), and S8 (Agua Blanca). Fluoride concentrations in rivers (in mg $L^{-1}$) at the different sites are represented by circles

Geologically, the region is characterized by regionally widespread granitoids named Orthogneiss Antinaco (OA), assigned to the Ordovician (Grosse et al. 2011) and affected by ductile deformation (Larrovere et al. 1). This unit is the dominant lithology in the southern sector of the study area (Fig. 1). The OA was intruded by an igneous peraluminous geological unit named La Costa Pluton (LCP) of carboniferous age (Alasino et al. 2, 2010), which mainly crops out in the northern sector of the study area (Fig. 1). The LCP is composed of equigranular monzogranites and granodiorites (Alasino et al. 2006, 2010). Although the mineralogical composition of the two main lithological units in the area (i.e., OA and LCP) is quite similar, high-fluoride contents were recognized in biotite, muscovite, tourmaline, and fluorapatite of LCP (Alasino et al. 2006, 2010; Toselli et al. 2011).

Several rivers drain the eastern slope of the Sierra de Velasco. They are typical mountain rivers characterized by high slopes, short trajectories, and torrential hydrological regimes, and they usually infiltrate a few kilometers downstream of the piedmont of the Sierra de Velasco. These rivers usually take the names of the towns they cross (Fig. 1). From Santa Vera Cruz to Anillaco, they flow through the LCP, whereas from Aminga to Agua Blanca, the rivers drain the OA. All of them constitute the main freshwater source for the homonymous towns, which are provided by public supply.

The climate in this region is warm and semi-arid. Irregular rainfall concentrated in one season (i.e., austral summer), and occasional snowfall in austral winter at the highest elevations are typical features. Precipitations rarely exceed 400 mm per year, and the mean annual rainfall is 270 mm. Summers are long, hot, and slightly humid; whereas winters are short, cold and dry. With large thermal amplitudes, both annual and daytime, the temperature generally varies from 5 to 35 °C, and occasionally falls below 0 °C during winter or rises above 39 °C during summer; the mean annual temperature is 16 °C (http://www.desertificacion.gob.ar/).

The population in the region is rural and it is characterized by a low socioeconomic level. According to the last National Population, Household and Housing Census (INDEC Argentina, 2010), only 38.9% of the houses have a satisfactory constructive quality. Moreover, the potential dependence index, defined as the quotient between population potentially inactive (0–14 years old and more than 65 years old) and the population "theoretically" active (15–64 years old), is 58.04% (INDEC Argentina, 2010). Concerning health, there is a District Hospital in Anillaco, a Sectional Hospital in Pinchas and Primary Health Care Center in the other towns. Respiratory and gastrointestinal diseases, and being overweight are the most common health problems registered in children, whereas diabetes and hypertension are the most common diseases in adults. Regional diseases include dental fluorosis and thyroid-related problems due to lack of iodine in the diet (http://www.desertificacion.gob.ar/).

## Materials and methods

### Sampling and analytical determinations

A total of 27 samples were taken from rivers that provide water for public supply to 8 towns in the study area (eight sampling sites, Fig. 1). The sampling campaigns were carried out during 2018 and 2019, at the end of the wet and dry seasons (April and October, respectively). Routine physicochemical parameters were measured in situ. Temperature and pH were measured using a portable Hach digital pH meter, and electrical conductivity (EC) and total dissolved solids (TDS) were registered by means of a portable conductivity meter model 44,600 (Hach Co.). Alkalinity was also determined in the field by titration with $H_2SO_4$ using a Hach Co. kit. All samples were filtered through 0.22 µm cellulose acetate membrane (Millipore Corp.). Aliquots of 15 ml, taken for cations determinations, were acidified to pH < 2 with ultrapure $HNO_3$, whereas 50 ml aliquots without acidifying were drawn for anions determinations. Samples were stored in pre-cleaned polyethylene bottles and preserved at 4 °C.

Major anions ($Cl^-$ and $SO_4^{2-}$) and $F^-$ were determined by chemically suppressed ion chromatography with conductivity detection at CIQA Laboratory, Universidad Tecnológica Nacional, Córdoba, Argentina, following the APHA 4110 Method B (Rice et al. 2012). Cations were measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Perkin Elmer Sciex ELAN 900) at ActLabs Laboratories, Canada (https://actlabs.com), were a blank and IV-STOCK-1643 were run for material control and validation.

PHREEQCI.v.3 (Parkhurst and Appelo 2013) was used to calculate ions balance (the accepted error was ≤ 10%), and mineral saturation indices (SI) using the Phreeqci.dat database.

### Dental data collection

The dental data collection was carried out during the months of April–October 2019, in the Primary Health Care Centers and in primary schools of the Castro Barros department. A total of 338 patients of different ages, from 3 to 84 years, were examined covering the 8 towns (Table 1). The analyzed patients represent almost 10% of the total population of the

**Table 1** Population of Castro Barros department according to the National Population, Household and Housing Census (National Institute of Statistics and Censuses of the Argentine Republic - National Census of Population, Households and Housing 2010)

| Sector | Site | Towns | N° of inhabitants (%) | N° of patients (%) |
|---|---|---|---|---|
| North | S1 | Santa Vera Cruz | 123 (3.22) | 16 (4.73) |
| | S2 | Anjullón | 418 (10.95) | 27 (7.99) |
| | S3 | Los Molinos | 244 (6.39) | 6 (1.78) |
| | S4 | Anillaco | 1573 (41.21) | 164 (48.52) |
| South | S5 | Aminga | 833 (21.82) | 92 (27.22) |
| | S6 | Chuquis | 236 (6.18) | 14 (4.14) |
| | S7 | Pinchas | 390 (10.22) | 14 (4.14) |
| | S8 | Agua Blanca | Dispersed rural population | 5 (1.48) |
| Total | | | 3817 (100) | 338 (100) |

department, according to the National Population, Household and Housing Census (INDEC Argentina, 2010).

Dental exams were made by five dentists, who generated the first local registry of dental fluorosis in the region. The dental check-up consisted mainly of recording the presence or absence of dental fluorosis. The type of dentition (i.e., temporary, mixed, permanent), the age of the patient and its provenance (town), were also registered. When dental fluorosis was detected, its score was evaluated using the Dean's index (Dean 1934; Tamuch and Ruiz 2018), which establishes six degrees:

1. Normal: smooth, bright, pale creamy-white translucent surface. No white discoloration of teeth.
2. Questionable: a few white flecks or white spots mainly on the edge of the incisors and cusps.
3. Very mild: small opaque white areas covering less than 25% of the tooth surface.
4. Mild: opaque white areas covering less than 50% of the tooth surface.
5. Moderate: all tooth surfaces are affected; a marked deterioration of occlusal surfaces; brown stains may be present.
6. Severe: all tooth surfaces are affected; discrete or confluent holes; brown stains present.

### Statistical analysis

Data collection of dental fluorosis, type of dentition, age of the patients, town of residence, along with dissolved $F^-$ and $Ca^{2+}$ concentrations, and water pH were used to generate the database employed for statistical modeling.

Three different statistical analyses were performed. In a first analysis, the association between the degree of dental fluorosis and the provenance (i.e., town of residence) was assessed by means of the Fisher's test. In the second analysis, with the aim to analyze the difference between the median of the ages in each town, the Kruskal–Wallis test was performed. The third analysis consisted of probit regression models, which were achieved to verify the influence of independent variables (i.e., age of the patients, dissolved $F^-$ concentration, dissolved $Ca^{2+}$ concentration, pH, and type of dentition), in the variable responses to the presence and severity of dental fluorosis. For this last analysis, the probit model was selected from those suitable for binary responses (i.e., logit and probit) using the Wald test to analyze the significance of the models coefficients, as well as the corresponding diagnostic analyses.

To adjust the different models, the sample of patients was divided into two groups: the first one is formed by children and adolescents aged less than or equal to 14 years, with 213 (63%) individuals, and the second one is composed of 125 (37%) individuals older than 14 years old. These two groups were defined considering patients with temporary and/or mixed dentition (first group) and individuals with permanent dentition (second group). In both groups, two probit regression models were formulated (e.g., Demidenko 2013), resulting in 4 models. A first approach was performed with the presence or absence of fluorosis as the dependent variable (Models 1 and 3). The second one was modeled with moderate or severe dental fluorosis as the dependent variable (Models 2 and 4). In the 4 models, the independent variables considered were dissolved $F^-$ concentrations, dissolved $Ca^{2+}$ concentrations, water pHs, and the age of the patients. Only for the first group of patients (i.e., individuals of 14 years old or less, Models 1 and 2), the type of dentition was also included as an independent variable. To avoid scale problems, all quantitative independent variables were standardized. As a random effect, the provenance (town) was considered in the models 1 and 2, which allows including the correlation or variability existing by the individuals sharing the same environment. To adjust the models, the software glmer function R 4.0.4 was used (R Core Team 2021).

## Results

### Water chemistry

Table 2 shows the concentration of major dissolved ions and selected physico-chemical parameters measured at the eight sampling sites, listed from North to South (Fig. 1). All rivers exhibit similar major hydrochemical characteristics, and waters are slightly alkaline (pHs range between 7.50 and 8.16) and diluted (TDS values between 45.90 and 100.80 mg $L^{-1}$). Major cations show an order of abundance characterized by $Ca^{2+} > Na^+ > Mg^{2+} > K^+$, whereas the anionic sequence is represented by $HCO_3^- > SO_4^{2-} > Cl^-$ in all analyzed waters (Table 2); consequently, they can be classified as bicarbonate-calcium type according to Piper (1944). No seasonal variations were registered in the major water composition. The incongruent dissolution of the primary silicates contained in the rocks of the LCP and the OA units is responsible for such chemical composition, since there is no evidence of spatial variability in the major hydrochemistry. Table 2 also includes the saturation indices of selected mineral phases. It is clear from SI values that all waters are undersaturated with respect to plagioclases, calcite, and $CO_2$ (g), whereas they are subsaturated with respect to illite and kaolinite. This reinforce the hypothesis mention above.

Figure 2a shows the molar correlation between $HCO_3^-$ and the major cations, where waters from North and South of the study area have been identified separately. The theoretical dissolution lines of several primary minerals are also included in the figure, according to the number of moles that each one releases into solution by incongruent

**Table 2** Physico-chemical parameters and major hydrochemistry of the studied rivers

| Site | River basin | Sample | pH | TDS | $Na^+$ | $K^+$ | $Mg^{2+}$ | $Ca^{2+}$ | $Cl^-$ | $HCO_3^-$ | $SO_4^{2-}$ | $F^-$ | Mineral saturation indices | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | mg $L^{-1}$ | meq $L^{-1}$ | | | | | | | mg $L^{-1}$ | Al | An | C | $CO_2$ (g) | I | K |
| S1 | Santa Vera Cruz | R-SAN-5-1 | 7.90 | 90.80 | 0.761 | 0.089 | 0.154 | 1.068 | 0.127 | 1.719 | 0.137 | **1.75** | − 0.20 | − 1.46 | − 0.33 | − 2.96 | 4.13 | 5.61 |
| | | R-SAN-5-2 | 7.78 | 96.10 | 0.853 | 0.042 | 0.146 | 1.008 | 0.123 | 1.680 | 0.131 | **1.72** | − 0.17 | − 1.72 | − 0.49 | − 2.85 | 3.92 | 5.68 |
| | | R-SAN-5-3 | 7.94 | 84.80 | 0.683 | 0.036 | 0.122 | 0.868 | 0.108 | 1.439 | 0.126 | **1.73** | − 0.29 | − 1.73 | − 0.44 | − 3.07 | 3.61 | 5.30 |
| S2 | Anjullón | R-ANJ-2-3 | 7.59 | 45.90 | 0.410 | 0.031 | 0.104 | 0.639 | 0.052 | 1.060 | 0.091 | **2.27** | − 1.68 | − 2.43 | − 0.84 | − 2.77 | 1.80 | 4.15 |
| | | R-ANJ-2-4 | 7.96 | 58.80 | 0.535 | 0.023 | 0.106 | 0.709 | 0.056 | 1.196 | 0.097 | **2.33** | − 0.39 | − 1.35 | − 0.56 | − 3.17 | 3.77 | 5.61 |
| | | R-ANJ-2-5 | 7.74 | 55.00 | 0.422 | 0.023 | 0.090 | 0.589 | 0.058 | 1.060 | 0.093 | **2.16** | − 0.92 | − 2.52 | − 0.92 | − 3.00 | 2.94 | 5.11 |
| S3 | Los Molinos | R-MOL-8-1 | 7.95 | 68.50 | 0.548 | 0.022 | 0.097 | 0.664 | 0.054 | 1.168 | 0.087 | **3.07** | − 0.92 | − 1.86 | − 0.53 | − 3.14 | 2.63 | 4.63 |
| | | R-MOL-8-2 | 7.72 | 57.60 | 0.522 | 0.022 | 0.090 | 0.624 | 0.061 | 0.980 | 0.092 | **3.10** | − 0.64 | − 1.94 | − 0.94 | − 3.01 | 3.44 | 5.57 |
| S4 | Anillaco | R-ANI-3-1 | 7.50 | 50.60 | 0.355 | 0.028 | 0.097 | 0.684 | 0.037 | 1.023 | 0.076 | **2.65** | − 1.83 | − 2.40 | − 0.92 | − 2.70 | 1.83 | 4.33 |
| | | R-ANI-3-3 | 7.72 | 61.80 | 0.496 | 0.032 | 0.105 | 0.729 | 0.063 | 0.840 | 0.087 | **2.87** | − 1.50 | − 2.09 | − 0.76 | − 3.01 | 1.96 | 4.17 |
| | | R-ANI-3-7 | 7.78 | 64.10 | 0.465 | 0.028 | 0.098 | 0.689 | 0.049 | 1.125 | 0.077 | **2.66** | − 0.65 | − 2.30 | − 0.86 | − 3.03 | 3.54 | 5.61 |
| | | R-ANI-3-9 | 7.87 | 61.20 | 0.613 | 0.030 | 0.111 | 0.783 | 0.061 | 0.980 | 0.082 | **2.87** | − 0.48 | − 1.83 | − 0.81 | − 3.08 | 3.67 | 5.64 |
| | | R-ANI-3-12 | 7.57 | 59.30 | 0.444 | 0.027 | 0.090 | 0.664 | 0.051 | 1.040 | 0.081 | **2.73** | − 0.73 | − 2.37 | − 1.10 | − 2.85 | 3.63 | 5.88 |
| | | R-ANI-3-13 | 7.76 | 36.40 | 0.561 | 0.026 | 0.101 | 0.729 | 0.063 | 1.240 | 0.088 | **2.86** | − 0.62 | − 2.04 | − 0.75 | − 2.95 | 3.40 | 5.46 |
| S5 | Aminga | R-AMI-1-4 | 7.64 | 88.10 | 0.631 | 0.055 | 0.229 | 0.928 | 0.084 | 1.600 | 0.242 | 1.02 | − 1.95 | − 3.04 | − 0.48 | − 2.65 | 1.06 | 3.30 |
| | | R-AMI-1-5 | 8.00 | 96.30 | 0.722 | 0.046 | 0.228 | 0.898 | 0.078 | 1.500 | 0.280 | 1.03 | − 0.44 | − 1.58 | − 0.38 | − 3.12 | 3.82 | 5.50 |
| | | R-AMI-1-6 | 7.95 | 76.20 | 0.692 | 0.047 | 0.203 | 0.818 | 0.082 | 1.280 | 0.259 | 1.05 | − 0.57 | − 2.26 | − 0.55 | − 3.14 | 3.34 | 5.07 |
| S6 | Chuquis | R-CHU-7-1 | 8.00 | 67.90 | 0.394 | 0.041 | 0.176 | 0.674 | 0.052 | 1.260 | 0.159 | 0.33 | − 1.30 | − 2.15 | − 0.51 | − 3.18 | 2.72 | 4.64 |
| | | R-CHU-7-2 | 7.87 | 60.30 | 0.365 | 0.051 | 0.165 | 0.629 | 0.053 | 0.980 | 0.159 | 0.27 | − 1.65 | − 3.36 | − 0.80 | − 3.16 | 1.91 | 3.96 |
| S7 | Pinchas | R-PIN-6-1 | 8.16 | 100.80 | 0.796 | 0.057 | 0.247 | 1.083 | 0.090 | 1.790 | 0.246 | 0.90 | − 0.93 | − 2.07 | 0.01 | − 3.18 | 2.42 | 4.00 |
| | | R-PIN-6-2 | 8.03 | 98.70 | 0.748 | 0.053 | 0.233 | 1.038 | 0.078 | 1.860 | 0.202 | 0.80 | − 0.83 | − 2.23 | − 0.18 | − 3.05 | 2.85 | 4.56 |
| S8 | Agua Blanca | R-BLA-4-1 | 7.70 | 75.10 | 0.487 | 0.074 | 0.197 | 0.923 | 0.064 | 1.560 | 0.169 | 0.57 | − 2.18 | − 3.14 | − 0.43 | − 2.72 | 0.90 | 3.08 |
| | | R-BLA-4-3 | 7.75 | 93.70 | 0.700 | 0.067 | 0.227 | 1.018 | 0.109 | 1.589 | 0.247 | 0.57 | − 1.13 | − 2.17 | − 0.51 | − 2.83 | 3.05 | 5.08 |
| | | R-BLA-4-5 | 7.63 | 60.80 | 0.487 | 0.046 | 0.166 | 0.753 | 0.060 | 1.400 | 0.175 | 0.54 | − 1.46 | − 3.06 | − 0.83 | − 2.77 | 2.45 | 4.73 |

High dissolved fluoride concentrations are indicated in bold. Saturation indices of selected mineral phases are also included

*Al* albite, *An* anorthite, *C* calcite, *I* illite, *K* kaolinite

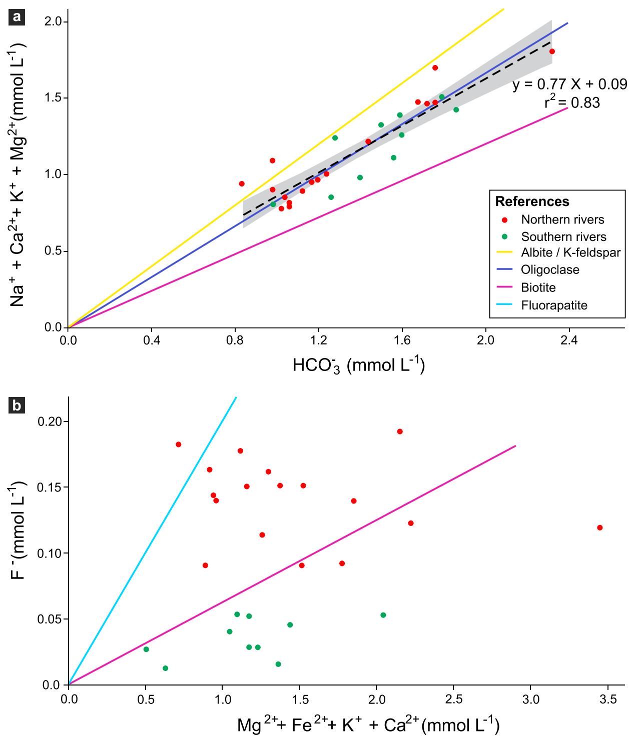


**Fig. 2** **a** Bivariate plot showing the relation between $HCO_3^-$ and major cations measured in the analyzed waters. The lines represent the stoichiometric dissolutions of primary minerals: for albite, $HCO_3^-$: $Na^+ = 1$; for oligoclase $HCO_3^-$: $Na^+ + Ca^{2+} = 0.833$; for K-feldspar $HCO_3^-$: $K^+ = 1$; for biotite $HCO_3^-$: $K^+ + Mg^{2+} = 0.6$. Dashed line is the linear trend for all samples; the gray area represents the confidence band at 95%. **b** Molar relationship between $Mg^{2+} + Fe^{2+} + K^+ + Ca^{2+}$ vs. $F^-$ in the studied waters. The theoretic dissolution lines of fluorapatite and biotite are also plotted. See text for explanation

dissolution, assuming that kaolinite is the new stable phase. For instance, albite releases into solution, 1 mol of $HCO_3^-$ and 1 mol de $Na^+$, whereas biotite releases 5 mol of $HCO_3^-$, 2 mol of $Mg^{2+}$, and 1 mol of $K^+$ (e.g., Faure 1998). Linear trend between $HCO_3^-$ and major cations ($r^2 = 0.883$, $p < 0.05$) is the same for all rivers (i.e., northern and southern rivers), indicating a common control in its dissolved concentrations (Fig. 2a).

Mean dissolved $F^-$ concentration of the rivers from Santa Vera Cruz to Agua Blanca are also compiled in Table 2. Accordingly, Fig. 1 also shows this information, represented by circles proportional to the mean fluoride concentration measured at each site. Fluoride contents range from 0.27 to 3.10 mg $L^{-1}$. As in the case of the major ions, dissolved $F^-$ do not register seasonal variations in its concentrations; however, it shows a clear spatial variability. Rivers draining the northern sector of the study area exhibit the highest values (i.e., sites S1–S4), whereas toward the South, dissolved $F^-$ clearly decrease (i.e., sites S5–S8). In the northern sector, dissolved fluoride ranges between 1.72 and 3.10 mg $L^{-1}$, always exceeding the guideline established by the World Health Organization (WHO 2011) and by the Argentinian national regulation (i.e., Código Alimentario Argentino, CAA, 2012) for $F^-$ in water for human consumption. Conversely, in the southern sector (sites S5–S8), $F^-$ concentrations range between 0.27 and 1.05 mg $L^{-1}$ (Table 2).

As mentioned above, the presence of biotite and muscovite with high-fluoride contents in the monzogranite of LCP has been reported (Alasino et al. 2, 2010; Toselli et al. 2). These authors have also found high-fluoride content in accessory minerals such as fluorapatite and tourmaline. Considering that biotite and fluorapatite could be the main sources of dissolved fluoride, as occurs in other granitic regions (e.g., Reddy et al. 2010; García et al. 2012), the relationship between dissolved cations coming from these minerals and dissolved fluoride has been tested in the study area. Figure 2b shows the obtained results, where the lines of the theoretical dissolution of biotite and fluorapatite are also included. To define these lines, the molar proportions of these weathering reactions were considered. For this purpose, it was assumed that $Ca^{2+}$ comes from the dissolution of fluorapatite, whereas the biotite releases $Fe^{2+}$, $Mg^{2+}$ and $K^+$. It is clear in Fig. 2b that the waters draining the southern portion of the study area are represented below the biotite dissolution line, while the waters flowing from the North show the contribution of both fluorapatite and biotite. Although a part of the dissolved cations comes from the weathering of other silicates (i.e., plagioclase, $K^+$ feldspar), the dispersion diagram of Fig. 2b reinforces the assumption that biotite and fluorapatite are the main sources of dissolved fluoride from Anillaco to the North.

## Statistical analysis and modeling

Dental data collected in the different towns are summarized in Table 3, which includes the number of patients with dental fluorosis in each town, the median of the ages of the patients, and the degree of dental fluorosis (if present). It is possible to observe that the median of the ages in each town is different (Kruskal–Wallis chi-squared = 15.95, $df = 7$, $p$ value = 0.0256) with high IQR (i.e., interquartile range), indicating a dispersion of age values. The highest median of the age values was recorded in the localities of Santa Vera Cruz and Agua Blanca. A statistically significant difference between the severity of fluorosis and the town of residence was determined using the Fisher's exact test for count data, with simulated $p$ value = 0.0005. Table 3 clearly shows that in the southern sector of the study area, there are no cases of severe fluorosis, whereas to the North, most sites present more than 45% of moderate-to-severe dental fluorosis. For instance, In Anillaco (S4), about 32.3% of the cases correspond to mild dental fluorosis, 31.1% are cases of moderate dental fluorosis, and 15.2% of the patients present severe

**Table 3** Summary of dental data collection. Degree of dental fluorosis according to Dean's index (Dean 1934)

| Site | Number of patients | Median age (IQR) | Degree of dental fluorosis $N$ (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Questionable | Very Mild | Mild | Moderate | Severe |
| S1 | 16 | 8 (2) | 4 (25%) | 0 | 3 (18.8%) | 3 (18.8%) | 5 (31.2%) | 1 (6.2%) |
| S2 | 27 | 9 (8) | 0 | 0 | 2 (7.4%) | 1 (3.7%) | 10 (37.0%) | 14 (51.9%) |
| S3 | 6 | 14 (12.75) | 0 | 0 | 0 | 1 (16.7%) | 1 (16.7%) | 4 (66.7%) |
| S4 | 164 | 11 (14) | 27 (16.5%) | 0 | 8 (4.9%) | 53 (32.3%) | 51 (31.1%) | 25 (15.2%) |
| S5 | 92 | 12 (23.5) | 74 (80.4%) | 0 | 1 (1.1%) | 14 (15.2%) | 3 (3.3%) | 0 |
| S6 | 14 | 11 (23.75) | 9 (64.3%) | 0 | 1 (7.1%) | 3 (21.4%) | 1 (7.1%) | 0 |
| S7 | 14 | 10.5 (3) | 5 (35.7%) | 0 | 3 (21.4%) | 6 (42.9%) | 0 | 0 |
| S8 | 5 | 8 (1) | 1 (20%) | 0 | 0 | 3 (60%) | 1 (20%) | 0 |


**Fig. 3** Pictures showing different degrees of dental fluorosis in children residing in Anillaco (S4). **a** Severe dental fluorosis. **b** Moderate dental fluorosis. **c** Mild dental fluorosis. Classification according to Dean's index (Dean 1934). Photographs by Elita Chumbita de Meyer

degrees. Figure 3 illustrates some examples of the different degrees of dental fluorosis in children residing in this site (S4).

The results of the probit regression models are presented in Table 4. These models predict the probability that an individual presents dental fluorosis according to the considered independent variables. Model 1 was run with data of the group of children and adolescents with ages less than or equal to 14 years. Within this group, 136 patients (63.8%) evidence dental fluorosis, with moderate or severe degree in 65 cases (30.5%). In Model 1 (Table 4), where the dependent variable was the presence or absence of fluorosis, the independent variables dissolved $Ca^{2+}$ ($p$ value = 0.4755), pH ($p$ value = 0.9203), and type of dentition ($p$ value = 0.9611) were not statistically significant. This model shows an excellent fit with an AUC = 0.89. Moreover, it is possible to observe that as the dissolved $F^-$ concentration (0.70 [0.012, 1.40]) and age (0.41 [0.19, 0.64]) increase, the probability of developing dental fluorosis also increases. Since the $p$ value for dissolved $F^-$ concentration is 0.046 (Table 4), the confidence level is 95%.

Model 2 (Table 4) was performed for the same group of patients as Model 1 (i.e., children and adolescents), but in this case, the dependent variable was the presence (or not) of moderate or severe degree of dental fluorosis. In this case, the independent variables pH ($p$ value = 0.2373), age ($p$ value = 0.56779), and type of dentition ($p$ value = 0.9224) were not statistically significant. Model 2 has a good adjustment with an AUC = 0.77, and dissolved $F^-$ (0.65 [0.26, 1.03]) and $Ca^{2+}$ (− 0.33 [− 0.63, − 0.03]) were statistically significant. According to this model, when dissolved $F^-$ increases, the probability of presenting moderate or severe fluorosis also increases. Dissolved $Ca^{2+}$ concentration exhibits an opposite behavior, since at higher values, the probability of developing dental fluorosis decreases (Fig. 4a).

Models 3 and 4 were run considering the second group, i.e., the group of patients over 14 years old ($N$ = 125), 82 of which (65.6%) have dental fluorosis, and 51 of them (40.8%) evidence a moderate or severe degree of fluorosis (Table 3). In this group, the random effect of the provenance (town of residence) cannot be included due to numerical problems of singularities. The output of Model 3, in which the dependent variable was the presence or absence of fluorosis, is also shown in Table 4. In this case, the results show that the independent variables pH ($p$ value = 0.7437) and age ($p$ values = 0.2467) were not statistically significant, whereas dissolved $F^-$ concentration

**Table 4** Results of the probit regression models

| Model | Parameter estimates [CI 95%] | OR [CI 95%] | *p*-value |
|---|---|---|---|
| Model 1[a] | | | |
| Intercept | 1.04 [0.17, 1.91] | 5.7 [1.30, 34.8] | 0.020 |
| Dissolved $F^-$ concentration | 0.70 [0.012, 1.40] | 3.2 [1.00, 11.40] | 0.046 |
| Age | 0.41 [ 0.19, 0.64] | 1.9 [1.40, 2.80] | < 0.001 |
| Model 2[b] | | | |
| Intercept | – 0.50 [– 0.93, – 0.08] | 0.44 [0.21, 0.89] | 0.003 |
| Dissolved $F^-$ concentration | 0.65 [0.26, 1.03] | 2.86 [1.52, 5.59] | < 0.001 |
| Dissolved $Ca^{2+}$ concentration | – 0.33 [– 0.63, – 0.03] | 0.59 [0.36, 0.85] | 0.010 |
| Model 3[c] | | | |
| Intercept | 0.56 [0.28, 0.839] | 2.5 [1.58, 3.98] | < 0.001 |
| Dissolved $F^-$ concentration | 0.92 [0.63, 1.208] | 4.6 [2.78, 7.81] | < 0.001 |
| Dissolved $Ca^{2+}$ concentration | – 0.43 [– 0.79, – 0.074] | 0.5 [0.27, 0.89] | 0.0127 |
| Model 4[d] | | | |
| Intercept | – 0.45 [– 0.77, – 0.13] | 0.48 [0.28, 0.82] | |
| Dissolved $F^-$ concentration | 1.27 [0.86, 1.68] | 8.77 [4.10, 20.55] | < 0.001 |
| Dissolved $Ca^{2+}$ concentration | – 0.68 [– 1.07, – 0.28] | 0.33 [0.17, 0.64] | < 0.001 |

*PCC* percentage of correctly classified

[a]Variance = 0.7469; AUC = 0.89; PCC = 0.84 (0.03); sensitivity = 0.82 (0.03); specificity = 0.86 (0.04)

[b]Variance = 0.1375; AUC = 0.77; PCC = 0.65 (0.03); sensitivity = 0.86 (0.04); specificity = 0.55 (0.04)

[c]AUC = 0.82; PCC = 0.80 (0.04); sensitivity = 0.80 (0.04); specifity = 0.79 (0.06)

[d]AUC = 0.85; PCC = 0.78 (0.03); sensitivity = 0.96 (0.03); specificity = 0.65 (0.06)

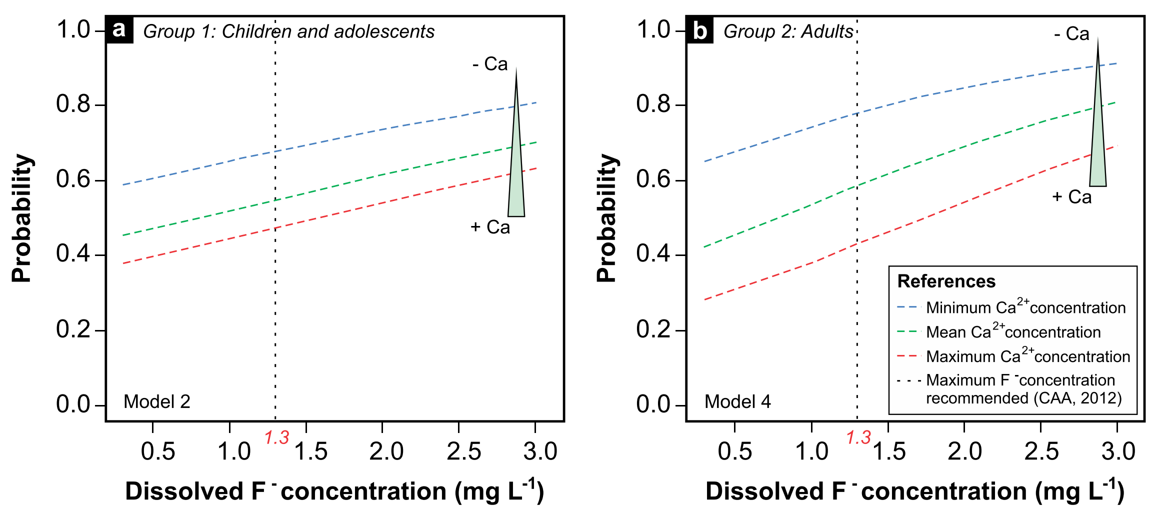


**Fig. 4** Predicted probabilities of dental fluorosis development by probit regression models. **a** Model 2 for severe dental fluorosis in Group 1. **b** Model 4 for severe dental fluorosis in Group 2

(*p*-value < 0.001) and dissolved $Ca^{2+}$ concentration (*p* value = 0.0181) showed statistical significance. In Model 4 (Fig. 4b), in which the dependent variable was moderate or severe fluorosis (Table 4); the independent variables pH (*p* value = 0.89152) and age (*p* value = 0.69752), as in Model 3, were not statistically significant; dissolved $F^-$ concentration (*p* value < 0.001) and dissolved $Ca^{2+}$ concentration (*p* value < 0.001) were statistically significant. Both models (3 and 4) show excellent performances with an AUC = 0.88 and 0.89, respectively. The results are similar to those obtained in Model 2.

It is important to note that the main objective of these analysis (i.e., logit and probit regression models) is to determine the probability of developing dental fluorosis considering the co-variation between dissolved $F^-$ and $Ca^{2+}$, not performing predictions. However, the predictive power of this analysis resulted very good, as it is indicated by the value of AUC, the specificity and the sensitivity. Furthermore, in all performed models the rule of the minimum number of 10 events per predictor variable (EPV) was satisfied, since the lowest one resulted in greater than 20 (Peduzzi et al. 1996; Vittinghoff and McCulloch 2007). Therefore, the sample size was enough to consider that these statistical models are suitable.

## Discussion

There is an agreement among specialists that the main cause for dental fluorosis is the amount of fluoride consumed from all sources during the critical period of tooth development (e.g., WHO 2011; DenBesten and Li 2011; Mehta and Shah 1; Zou and Ashley 2014; Buzalaf 2). National and international institutions regulate the guideline values for dissolved $F^-$ in drinking water. Particularly, in the Argentinian national regulation (CAA 2012), the maximum amount of fluoride is given as a function of the average temperature of the area, taking into account the daily consumption of drinking water. In the study area, the average annual temperature is 16 °C. For this temperature, the upper limit allowed for dissolved $F^-$ is 1.3 mg $L^{-1}$. Alternatively, the WHO (2011) sets a general value of 1.5 mg $L^{-1}$ of dissolved $F^-$. According to these regulations, $F^-$ concentrations above these values carry an elevated risk of dental fluorosis, and higher concentrations would lead to developing skeletal fluorosis.

In this work, the probability of developing different degrees of dental fluorosis has been statistically explored as a result not only of the concentration of dissolved $F^-$ in drinking water but also for the co-variation between this ion and dissolved $Ca^{2+}$. The area selected for the analysis is located in the NW of Argentina, where high dissolved $F^-$ concentrations have been measured in surface waters used as domestic supply, along with a high number of cases of dental fluorosis registered in the population. In the northern sector of the study area, dissolved $F^-$ varies between 1.72 mg $L^{-1}$ and 3.10 mg $L^{-1}$, exceeding the guide values above mentioned. In contrast, to the South, the maximum registered value of dissolved $F^-$ is 1.05 mg $L^{-1}$. It has been established that the highest concentrations of dissolved $F^-$ in the region are a result of a geogenic control. According to these values of dissolved $F^-$ in drinking waters, 85.4% of the population in the northern region present dental fluorosis. Moreover, more than 50% exhibit moderate-to-severe dental fluorosis levels. In contrast, to the South, only 28.8% of the patients present the disease, mostly at very mild-to-mild levels (24.8%).

Although some authors have evaluated the importance of $Ca^{2+}$ in dental health, they have focused mainly on the influence of fluoride and calcium in protecting against dental caries (e.g., Arvin et al. 2018). In the present research, statistical modeling revealed an inverse relationship between dissolved $Ca^{2+}$ and $F^-$ controlling the presence and the degree of dental fluorosis. Thus, for a particular concentration of dissolved $F^-$, as dissolved $Ca^{2+}$ increases the probability of developing dental fluorosis decreases. The statistical models showed that for $Ca^{2+}$ concentrations less than 0.7 meq $L^{-1}$, moderate-to-severe dental fluorosis would develop at any age from $F^-$ concentrations below 1.0 mg $L^{-1}$. Particularly, in the group of adults, these concentrations of dissolved $Ca^{2+}$and $F^-$ also predict the development of dental fluorosis at any degree. On the other hand, for $Ca^{2+}$ concentrations higher than 1.0 meq $L^{-1}$, moderate-to-severe dental fluorosis would develop from dissolved $F^-$ above 2.2 mg $L^{-1}$ for children and adolescents. In the case of adults, for the same concentration of dissolved $Ca^{2+}$ (i.e., > 1.0 meq $L^{-1}$), a dissolved $F^-$ concentration of 2.5 mg $L^{-1}$ is required to develop moderate-to-severe dental fluorosis. Hence, for a particular concentration of dissolved $Ca^{2+}$, children and adolescents are more likely to develop moderate-to-severe dental fluorosis from lower values of dissolved fluoride than those required for adults. Furthermore, considering the guide value of dissolved $F^-$ established in the national regulation (1.3 mg $L^{-1}$, CAA 2012), a concentration equal or higher than 1.1 meq $L^{-1}$ of dissolved $Ca^{2+}$ is required to avoid the dental fluorosis development at any age.

Several authors have explored the relationship between dissolved $F^-$ concentrations in drinking water and the presence and severity of dental fluorosis. For instance, Raju (2017) reported cases of mild, moderate, and severe dental fluorosis from values of 2, 4, and 5 mg $L^{-1}$ of dissolved $F^-$, respectively. Although in this work (Raju 2017), the influence of dissolved $Ca^{2+}$ in the development of dental fluorosis was not analyzed, a negative linear correlation between dissolved calcium and fluoride in drinking water was reported. Here, statistical modeling demonstrated that severe dental fluorosis could appear with lower values of dissolved $F^-$ than those reported by Raju (2017). Therefore, dissolved $Ca^{2+}$ concentration coupled with $F^-$ could be an important factor in controlling the occurrence and severity of dental fluorosis.

Another important result to consider is that cases of dental fluorosis were also detected where dissolved $F^-$ concentrations are according to those established by national and international regulations as safety values. Nonetheless, it is not the first time that dental fluorosis is reported from water consumption with dissolved $F^-$ values according to the limits allowed by different normative. For instance, Raju (2017) has pointed out that dental fluorosis is common even in areas with lower levels of fluoride in water, questioning the values recommended by the WHO (2011). Similar considerations were made by other authors (e.g., Ramadan and Ghandourb 2016; Akuno et al. 6). The fact that dental fluorosis has been detected in different regions worldwide, even in communities consuming water with low levels of fluoride, may be due to other variables that could have a significant relevance in the development of dental fluorosis, besides dissolved $F^-$ concentrations. In this work, it has been shown that the variability of dissolved $Ca^{2+}$ exerts a control over minimum fluoride concentrations necessary to develop this disease. Since both national and international regulations do not establish precise limits for different degrees of dental fluorosis (from very mild to severe), it would be important that future works focus on the relationship between dental fluorosis and other chemical variables, in addition to the total intake of fluoride in the diet. Those investigations could also better adjust the guidelines established in the current regulations.

## Concluding remarks

In this work, the relationship between dental fluorosis and drinking water in a rural region of NW of Argentina was statistically modeled. In the northern sector of the study area, dissolved $F^-$ exceeds 1.72 mg $L^{-1}$; in contrast, to the South, the maximum registered value is 1.05 mg $L^{-1}$. The presence and severity of dental fluorosis in the population has been detected in agreement with the spatial variability of $F^-$. However, different statistical models have shown that dissolved $F^-$ distribution is not the unique variable controlling dental fluorosis development. For a particular concentration of dissolved $F^-$, as dissolved $Ca^{2+}$ increases, the probability of developing dental fluorosis decreases. Moreover, for a particular concentration of dissolved $Ca^{2+}$, children and adolescents are more likely to develop moderate-to-severe dental fluorosis from lower values of dissolved $F^-$ than those required for adults. Hence, the dissolved $Ca^{2+}$ exerts a control over minimum fluoride concentrations necessary to develop dental fluorosis. Therefore, the results presented in this work suggest considering other variables, besides the total intake of fluoride, to better adjust the guidelines for drinking water established in current regulations.

**Acknowledgements** We thank the dentists who collaborated selflessly with the dental data collection, in the different health centers of Castro Barros department: E. Chumbita de Meyer, A. Villafañe, P. Villafañe, and D. Álvarez. We also thank the Directors of the School Institutions: P. Quinteros (School N° 103 "Coronel Nicolás Barros J. C.", Anillaco), J. J. Reinoso (School N° 270 "Belindo de la Fuente", Anjullón), and A. Martinez (School N° 137 "Virgen del Rosario de San Nicolás", Santa Vera Cruz). We want to thank the people who collaborated in the field work: T. Fariñas, V. Reinoso, F. Morinigo, H. Aciar, and C. Bustamante. We also thank M. Macchioli Grande for his valuable comments. G. M. Uran acknowledges a doctoral fellowship from CONICET.

**Author contributions** GMU: conceptualization, methodology, formal analysis, investigation, writing—original draft, writing—review and editing, and visualization. AIP: conceptualization, investigation, resources, writing—original draft, visualization, and funding acquisition. VG: methodology, software, formal analysis, writing—original draft, and visualization. MAL: conceptualization, investigation, resources, writing—review, and funding acquisition. MFCM: methodology, investigation, and resources. REP: methodology and investigation.

**Funding** This work was funded by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, Argentina, PUE-0125 and PIP 112-201701-00088), the Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, PICT-2017-2026), the Universidad Nacional de La Rioja (CICYT-042), and the Universidad Nacional de Córdoba (SECyT-UNC 33620180100385CB).

**Data availability** All the data included in this work were collected by the authors.

## Declarations

**Conflict of interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Animal research** This study does not involve animals; only previous bibliographic works are cited.

**Consent to participate** This is an observational study that does not put people's health and integrity at risk. Verbal informed consent was obtained from all individual participants prior to the study.

**Consent to publish** The authors affirm that participants provided informed consent for publication of the images in Fig. 3.

## References

Alasino PH, Dahlquist JA, Galindo C, Casquet C (2006) Plutón La Costa, una expresión de magmatismo tipo-S en el sector noreste de la sierra de Velasco, Sierras Pampeanas, Argentina. Rev Asoc Geol Argent 61(2):161–170
Alasino PH, Dahlquist JA, Galindo C, Casquet C, Saavedra J (2010) Andalusite and Na- and Li-rich cordierite in the La Costa pluton, Sierras Pampeanas, Argentina: textural and chemical evidence for a magmatic origin. Int J Earth Sci 99:1051–1065. https://doi.org/10.1007/s00531-009-0445-1
Akuno MH, Nocella G, Milia EP, Gutierrez L (2019) Factors influencing the relationship between fluoride in drinking water and dental fluorosis: a ten-year systematic review and meta-analysis. J Water Health 17(6):845–862. https://doi.org/10.2166/wh.2019.300
Argentinian National Regulation (CAA) (2012) Capítulo XII, Artículos: 982 al 1079 - Bebidas Hídricas, Agua y Agua Gasificadas. https://www.argentina.gob.ar/anmat/codigoalimentario
Arveti N, Sarma MRS, Aitkenhead-Peterson JA, Sunil K (2011) Fluoride incidence in groundwater: a case study from Talupula, Andhra Pradesh, India. Environ Monit Assess 172(1):427–443. https://doi.org/10.1007/s10661-010-1345-3
Arvin E, Bardow A, Spliid H (2018) Caries affected by calcium and fluoride in drinking water and family income. J Water Health 16(1):49–56. https://doi.org/10.1007/s10661-010-1345-3
Arya S, Subramani T, Vennila G, Karunanidhi D (2021) Health risks associated with fluoride intake from rural drinking water supply and inverse mass balance modeling to decipher hydrogeochemical processes in Vattamalaikarai River basin, South India.

Environ Geochem Health 43(2):705–716. https://doi.org/10.1007/s10653-019-00489-y

Beltrán Valladares PR, Cocom Tun H, Casanova Rosado JF, Vallejos Sánchez AA, Medina Solís CE, Maupomé G (2005) Prevalencia de fluorosis dental y fuentes adicionales de exposición a fluoruro como factores de riesgo a fluorosis dental en escolares de Campeche, México. Rev Investig Clin 57(4):532–539

Berger T, Peltola P, Drake H, Åström M (2012) Impact of a fluorine-rich granite intrusion on levels and distribution of fluoride in a small boreal catchment. Aquat Geochem 18:77–94. https://doi.org/10.1007/s10498-011-9151-2

Borgnino L, Garcia MG, Bia G, Stupar YV, Le Coustumer P, Depetris PJ (2013) Mechanisms of fluoride release in sediments of Argentina's central region. Sci Total Environ 443:245–255. https://doi.org/10.1016/j.scitotenv.2012.10.093

Buzalaf MAR (2018) Review of fluoride intake and appropriateness of current guidelines. Adv Dent Res 29(2):157–166. https://doi.org/10.1177/0022034517750850

Chae GT, Yun ST, Kwon MJ, Kim YS, Mayer B (2006) Batch dissolution of granite and biotite in water: implication for fluorine geochemistry in groundwater. Geochem J 40:95–102. https://doi.org/10.2343/geochemj.40.95

Chaïrat C, Oelkers EH, Schott J, Lartigue JE (2007) Fluorapatite surface composition in aqueous solution deduced from potentiometric, electrokinetic, and solubility measurements, and spectroscopic observations. Geochim Cosmochim 71:5888–5900. https://doi.org/10.1016/j.gca.2007.09.026

Chapman D (1996) Water quality assessments: a guide to the use of biota, sediments and water in environmental monitoring, 2nd edn. CRC Press, London. https://doi.org/10.1201/9781003062103

Dean HT (1934) Classification of mottled enamel diagnosis. J Am Dent Assoc 21:1421–1426. https://doi.org/10.14219/jada.archive.1934.0220

Demidenko E (2013) Mixed models: theory and applications with R, 2nd edn. Wiley, New York

DenBesten P, Li W (2011) Chronic fluoride toxicity: dental fluorosis. Monogr Oral Sci 22:81–96. https://doi.org/10.1159/000327028

Edmunds WM, Smedley PL (2013) Fluoride in natural waters. In: Selinus O, Alloway B, Centeno JA (eds) Essentials of medical geology. Springer, Dordrecht, pp 311–336. https://doi.org/10.1007/978-94-007-4375-5_13

Faure G (1998) Principles and applications of geochemistry: a comprehensive textbook for geology students, 2nd edn. New Jersey, p 600 **(ISBN: 0023364505 9780023364501)**

Fejerskov O, Thylstrup A, Larsen MJ (1977) Clinical and structural features and possible pathogenic mechanisms of dental fluorosis. Eur J Oral Sci 85:510–534. https://doi.org/10.1111/j.1600-0722.1977.tb02110.x

García MG, Borgnino L (2015) Fluoride in the context of the environment. In: Preddy V (ed) Fluorine: chemistry, analysis, function and effects, pp 3–21. https://doi.org/10.1039/9781782628507-00003

García MG, Lecomte KL, Stupar Y, Formica SM, Barrionuevo M, Vesco M, Gallará R, Ponce R (2012) Geochemistry and health aspects of F-rich mountainous streams and groundwaters from Sierras Pampeanas de Córdoba, Argentina. Environ Earth Sci 65:535–545. https://doi.org/10.1007/s12665-011-1006-z

García MG, Borgnino L, Bia G, Depetris PJ (2014) Mechanisms of arsenic and fluoride release from Chacopampean sediments (Argentina). Int J Environ Health 7(1):41–57. https://doi.org/10.1504/IJENVH.2014.060122

Gevera P, Mouri H, Maronga G (2019) Occurrence of fluorosis in a population living in a high-fluoride groundwater area: Nakuru area in the Central Kenyan Rift Valley. Environ Geochem Health 41:829–840. https://doi.org/10.1007/s10653-018-0180-2

Gómez ML, Blarasin MT, Martínez DE (2009) Arsenic and fluoride in a loess aquifer in the central area of Argentina. Environ Geol 57:143–155. https://doi.org/10.1007/s00254-008-1290-4

Grosse P, Bellos LI, de los Hoyos CR, Larrovere MA, Rossi J, Toselli AJ (2011) Across-arc variation of the Famatinian magmatic arc (NW Argentina) exemplified by I-, S- and transitional I/S-type Early Ordovician granitoids of the Sierra de Velasco. J South Am Earth Sci 32:110–126. https://doi.org/10.1016/j.jsames.2011.03.014

Hidalgo Gato Fuentes I, de Estrada D, Riverón J, Mayor Hernández F, Zamora Díaz JD (2007) Fluorosis dental: no sólo un problema estético. Rev Cubana Estomatol 44:1–12

Irigoyen Camacho ME, García Pérez A, Mejía González A, Huizar AR (2016) Nutritional status and dental fluorosis among schoolchildren in communities with different drinking water fluoride concentrations in a central region in Mexico. Sci Total Environ 541:512–519. https://doi.org/10.1016/j.scitotenv.2015.09.085

Jacks G, Bhattacharya P, Chaudhary V, Singh KP (2005) Controls on the genesis of some high-fluoride groundwaters in India. Appl Geochem 20:221–228. https://doi.org/10.1016/j.apgeochem.2004.07.002

Kechiched R, Nezli IE, Foufou A et al (2020) Fluoride-bearing groundwater in the complex terminal aquifer (a case study in Hassi Messaoud area, southern Algeria): hydrochemical characterization and spatial distribution assessed by indicator kriging. Sustain Water Resour Manag 6:54. https://doi.org/10.1007/s40899-020-00415-6

Keshavarzi B, Moore F, Esmaeili A, Rastmanesh F (2010) The source of fluoride toxicity in Muteh area, Isfahan. Iran Environ Earth Sci 61:777–786. https://doi.org/10.1007/s12665-009-0390-0

Kitalika AJ, Machunda RL, Komakech HC, Njau KN (2018) Fluoride variations in rivers on the slopes of Mount Meru in Tanzania. J Chem. https://doi.org/10.1155/2018/7140902

Kruse E, Ainchil J (2003) Fluoride variations in groundwater of an area in Buenos Aires Province, Argentina. Environ Geol 44:86–89. https://doi.org/10.1007/s00254-002-0702-0

Larrovere MA, Alasino PH, Baldo EG (2016) La faja de cizalla dúctil doble-vergente del noroeste de la Sierra de Velasco, Argentina: Deformación de la corteza media durante la Orogenia Famatiniana. Rev De La Asoc Geol Argen 73(1):117–133

Mehta DN, Shah J (2013) Reversal of dental fluorosis: a clinical study. J Nat Sci Biol Med 4(1):138–144. https://doi.org/10.4103/0976-9668.107278

National Institute of Statistics and Censuses of the Argentine Republic - National Census of Population, Households and Housing (2010). https://sitioanterior.indec.gob.ar/

National Observatory of Land Degradation and Desertification (2022). http://www.desertificacion.gob.ar/sitiospiloto/introduccion/?sp=106&tipo=info

Parkhurst DL, Appelo CAJ (2013) Description of input and examples for PHREEQC version 3: a computer program for speciation, batch-reaction, one-dimensional transport, and inverse geochemical calculations. U.S. Geological Survey Techniques and Methods, book 6, chapter A43. http://pubs.usgs.gov/tm/06/a43/

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49(12):1373–1379. https://doi.org/10.1016/s0895-4356(96)00236-3

Piper AM (1944) A graphic procedure in the geochemical interpretation of water-analyses. EOS Trans Am Geophys Union 25:914–928. https://doi.org/10.1029/TR025i006p00914

Pradhan RM, Biswal TK (2018) Fluoride in groundwater: a case study in Precambrian terranes of Ambaji region, North Gujarat, India. Proc IAHS 379:351–356. https://doi.org/10.5194/piahs-379-351-2018

R Core Team (2021) A language and environment for statistical computing. R Foundation for Statistical Computing

Rafique T, Naseem S, Ozsvath D, Hussain R, Bhanger MI, Usmani TH (2015) Geochemical controls of high-fluoride groundwater in Umarkot Sub-District, Thar Desert, Pakistan. Sci Total Environ 530–531:271–278. https://doi.org/10.1016/j.scitotenv.2015.05.038

Raju NJ (2017) Prevalence of fluorosis in the fluoride enriched groundwater in semi-arid parts of eastern India: geochemistry and health implications. Quat Int 443(Part B):265–278. https://doi.org/10.1016/j.quaint.2016.05.028

Ramadan A, Ghandourb I (2016) Dental fluorosis in two communities in Khartoum state, Sudan, with potable water fluoride levels of 1.36 and 0.45 mg/L. Fluoride 49(4):509–520

Rasool A, Farooqi A, Xiao T, Ali W, Noor S, Abiola O, Ali S, Nasim W (2018) A review of global outlook on fluoride contamination in groundwater with prominence on the Pakistan current situation. Environ Geochem Health 40:1265–1281. https://doi.org/10.1007/s10653-017-0054-z

Reddy DV, Nagabhushanam P, Sukhija BS, Reddy AGS, Smedley PL (2010) Fluoride dynamics in the granitic aquifer of the Wailapally watershed, Nalgonda District, India. Chem Geol 269:278–289. https://doi.org/10.1016/j.chemgeo.2009.10.003

Rice EW, Baird RB, Eaton AD, Clesceri L (2012) Standard methods for the examination of water and wastewater, 2nd ed. American Water Works Association. Water Environment Federation, Washington DC

Rondano Gomez K, Lopez Pasquali CE, Paniagua Gonzalez G, Fernandez Hernando P, Garcinuño Martínez RM (2020) Statistical evaluation of fluoride contamination in groundwater resources of Santiago del Estero Province, Argentina. Geosci Front 11:2197–2205. https://doi.org/10.1016/j.gsf.2020.02.018

Simon MJK, Beil FT, Rüther W, Busse B, Koehne T, Steiner M, Pogoda P, Ignatius A, Amling M, Oheim R (2014) High fluoride and low calcium levels in drinking water is associated with low bone mass, reduced bone quality and fragility fractures in sheep. Osteoporos Int 25:1891–1903. https://doi.org/10.1007/s00198-014-2707-4

Srivastava S, Flora S (2020) Fluoride in drinking water and skeletal fluorosis: a review of the global impact. Curr Environ Health Rep 7:140–146. https://doi.org/10.1007/s40572-020-00270-9

Tamuch Y, Ruiz GDC (2018) Fluorosis en dientes permanentes. Concordancia entre tres índices diagnósticos. Rev Académica Electrónica de la UNR, 21(11), vol 1. http://hdl.handle.net/2133/17628

Toselli AJ, Rossi JN, Basei MAS, Larrovere M (2011) Controles geoquímicos e isotópicos en la petrogénesis de los granitos Devónico-Carboníferos Santa Cruz y Asha: Sierra de Velasco, Argentina. Ser Correl Geol 27(2):77–98

Vittinghoff E, McCulloch C (2007) Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 165(6):710–718. https://doi.org/10.1093/aje/kwk052

Warren CJ, Burgess W, García MG (2005) Hydrochemical associations and depth profiles of arsenic and fluoride in quaternary loess aquifers of northern Argentina. Mineral Mag 69:877–886. https://doi.org/10.1180/0026461056950295

World Health Organization (2011) Guidelines for drinking-water quality, 4th ed. https://www.who.int/publications/i/item/9789241549950

Yadav JP, Lata S, Kataria SK et al (2009) Fluoride distribution in groundwater and survey of dental fluorosis among school children in the villages of the Jhajjar District of Haryana, India. Environ Geochem Health 31:431–438. https://doi.org/10.1007/s10653-008-9196-3

Yu Q, Shao D, Zhang R, Ouyang W, Zhang Z (2019) Effects of drinking water fluorosis on L-type calcium channel of hippocampal neurons in mice. Chemosphere 220:169–175. https://doi.org/10.1016/j.chemosphere.2018.12.078

Yuan L, Fei W, Jia F, Jun-ping L, Qi L, Fang-ru N, Xu-dong L, Shu-lian X (2020) Health risk in children to fluoride exposure in a typical endemic fluorosis area on Loess Plateau, north China, in the last decade. Chemosphere. https://doi.org/10.1016/j.chemosphere.2019.125451

Zabala ME, Manzano M, Vives L (2016) Assessment of processes controlling the regional distribution of fluoride and arsenic in groundwater of the Pampeano Aquifer in the Del Azul Creek basin (Argentina). J Hydrol 541(10):1067–1087. https://doi.org/10.1016/j.jhydrol.2016.08.023

Zhang L, Zhao L, Zeng Q, Fu G, Feng B, Lin X, Liu Z, Wang Y, Hou C (2020) Spatial distribution of fluoride in drinking water and health risk assessment of children in typical fluorosis areas in north China. Chemosphere. https://doi.org/10.1016/j.chemosphere.2019.124811

Zhu Y, Zhang X, Chen Y, Xie Q, Lan J, Qian M, He N (2009) A comparative study on the dissolution and solubility of hydroxyapatite and fluorapatite at 25 °C and 45 °C. Chem Geol 268:89–96. https://doi.org/10.1016/j.chemgeo.2009.07.014

Zou J, Ashley JW (2014) Fluoride. In: McManus LM, Mitchell RN (eds) Pathobiology human disease. Elsevier, Amsterdam, pp 893–898. https://doi.org/10.1016/B978-0-12-386456-7.03113-0