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ORIGINAL RESEARCH

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Potential risk of dental fluorosis associated with different baby formulas and water brands marketed in Spain

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Abstract

Despite efforts to promote breastfeeding, many babies aged <6 months receive only baby formula reconstituted with bottled water. The intake of high levels of fluoride during amelogenesis has been associated with hypomineralization of the tooth enamel, with aesthetic and mechanical repercussions. The objective of this study was to determine the potential risk of dental fluorosis associated with baby formulas marketed in Spain. We measured 26 baby formulas frequently consumed in Spain; 17 brands for babies aged <6 months, 5 for those aged >6 months, and 4 ready-to-use brands. They were prepared with 4 types of water: distilled water and three brands of bottled water with different levels of fluoride. The fluoride concentration (mg/L or ppm F) was measured with an ion-specific electrode coupled to an ion analyzer. Each sample was prepared according to the manufacturer's instructions and analyzed in triplicate. A descriptive analysis was carried out. The minimum fluoride level found was 0.04 mg/L and the maximum was 1.02 mg/L. Considering the daily intake of these formulas, none exceeded the clinically-acceptable daily dose limit risk for fluorosis (0.07 mg F/day/kg body weight) when mixed with bottled water with a low level of fluoride (0.1 mg/L). However, when the same brands of formula were reconstituted with bottled water with a higher fluoride content (0.99 mg/L), they all exceeded the daily dose limit for the risk of fluorosis. As the potential risk of dental fluorosis associated with the formulas tested depends exclusively on the fluoride concentration of the waters used for reconstitution, formula packaging should contain a warning.

Keywords

Dental fluorosis; Bottle feeding; Fluoride intake; Bottled water; Baby formula

1. Introduction

Fluorides have played a crucial role in reducing the prevalence of caries worldwide, with its preventive effect achieved mainly through the topical route, interfering in the process of demineralization/remineralization of tooth enamel [1, 2].

The main sources of systemic fluoride intake are fluoridated water, baby formula, fluoridated salt and oral fluoride supplements and to lesser extent beverages such as black tea and wine, and foods such as seafood. Of the fluoride absorbed, adults retain about 50% while babies retain between 80 and 90%, and the rest is excreted in the urine [3]: 99% is distributed in mineralized tissue (teeth and bones) and 1% in the soft tissue [4]. During pregnancy, a small amount of fluoride reaches the fetal circulation [5]. Fluoride can pass through plasma into breast milk, but at low levels [6].

Excess systemic fluoride during tooth development may lead to dental fluorosis. The degree of involvement depends on the dose of fluoride consumed and the frequency of exposure (mg F/day/kg body weight) [7, 8]. The dose/effect ratio remains unknown, although a dose of 0.07 mg F/day/kg body weight is accepted as the upper limit in terms of the risk of clinically-acceptable dental fluorosis [9]. Thus, the daily intake of 0.1 mg F/kg body weight during the period of enamel calcification is sufficient to produce mild fluorosis [10, 11] and Iheozor-Ejiofor *et al*. [12] (2015) estimated that with a level of 0.7 ppm in drinking water the probability of the population presenting dental fluorosis with aesthetic implications is 12%, which increases to 40% when dental fluorosis of any level is considered.

During the enamel maturation period, the increase in mineralization is accompanied by the loss of the protein matrix produced during the secretion phase of amelogenesis. High levels of fluoride alter this process, producing hypomineralized enamel, which shows symmetrical opaque areas and increased porosity [13].

The effects of exposure to fluoride can vary depending on the different stages of growth and tooth development. Babies and children under the age of 4 years are considered to be at risk of dental fluorosis of permanent incisors and first molars, because the calcification and maturation of these teeth occur during this period of life. The longitudinal Iowa study found that exposure to fluoride during the first 3 years of life was most important for fluorosis development on the permanent maxillary incisors, but other individual periods were also important [14, 15].

In the age group from 4 to 6 years the posterior teeth (premolars and second molars) are calcifying and maturing, and at risk of dental fluorosis. Nevertheless, when this occurs, it is a minor cosmetic problem, which needs to be weighed against the marked benefit of caries prevention brought about by the use of fluoride. The risk for enamel fluorosis in children older than 6 years old is negligible, except for third molars [16, 17].

It is important to note that the timing of tooth eruption and development can vary among individuals, so these age ranges are approximate. Additionally, to timing, the impact of fluoride on tooth development depends on the concentration and duration of exposure [14].

Breast milk has been shown to have low levels of fluoride (0.005–0.01 ppm) and, although the American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months, and continued breastfeeding for up to at least 12 months, almost 20% of mothers, both in the United Kingdom and the United States, feed their babies only with formula from birth [11, 13]. In Spain, the latest data published by the National Institute of Statistics and the Ministry of Health and Consumer Affairs indicate that 29.3% of Spanish children are fully fed with artificial lactation at 6 weeks, 36.7% at 3 months and 61.3% at 6 months after birth [18].

In the National Health Survey, data on the prevalence of dental fluorosis reveal that in the 12-year-old group the prevalence of this pathology is low (8.1%). Regarding the severity of this pathology, it is shown that most are cases of fluorosis classified as questionable (3.5%) or very light (3.5%). The percentage of individuals with moderate fluorosis is 0.7%. There is no statistically significant association of fluorosis with sex, social level or birth [19].

In mild and moderate cases of dental fluorosis, affected dentition is resistant to caries, while severe lesions with increased enamel porosity show increased fragility on the external surface, which can easily fracture with mechanical chewing forces. Moderate and severe forms can sometimes compromise aesthetics and generate treatment needs and concerns about their impact on quality of life [20].

Primary-tooth fluorosis is mostly regarded as less prevalent and generally less severe than the fluorosis seen in the permanent dentition [21]. Occurrence of primary-tooth fluorosis has been found to be closely associated with fluorosis in the permanent dentition [22].

Systemic fluoride intake through fluoridated water is the main risk factor for the development of dental fluorosis, but other factors may influence the development of this enamel defect. There is strong evidence that the use of toothpaste containing fluoride can prevent tooth decay (caries) in both children and adults. However, a possible adverse effect associated with the use of fluoride toothpaste is the mottling of permanent teeth due to the swallowing of excessive fluoride by young children with developing teeth [23].

The use of fluoride rinses in children under 6 years of age as well as the inappropriate use of fluoride gels at this age pose a risk of fluorosis. Therefore, the use of fluoride varnishes is recommended at preschool age. Individuals have differing risk and resistance to developing dental fluorosis based on their genetic makeup and health. Studies suggest that a number of genes are important in defining the population's variance for dental fluorosis risk [24].

A systematic review commissioned by the American Dental Association [13] concluded that the consumption of formula reconstituted with water was associated with a high prevalence of fluorosis in the permanent dentition, and that the degree of fluorosis depended on the concentration of fluoride present in the water used to reconstitute formula, as the concentration of fluoride present in formula milk is very low and insufficient to produce fluorosis by itself [13, 14].

The hypothesis of the present study is that using bottled water to reconstitute formulas may result in mild dental fluorosis.

The aim of this study is to determine the potential risk of dental fluorosis associated with formulas marketed in Spain.

2. Material and methods

2.1 Sample

Twenty-two brands of formula milk for reconstitution (17 of consumption "from the first day" and 5 "from the 6th month") were reconstituted with 4 types of water: distilled water (control group), Solán de Cabras (Solán de Cabras spring; Beteta, Cuenca), Nestlé Aquarel (Avets spring; Arbúcies, Girona) and Cabreiroá (Cabreiroá spring; Ourense, Galicia).

The formulas were provided by pediatricians from different health centres. Water-brands were the most commonly sold in supermarkets.

Before preparation and analysis, containers were kept closed, stored at room temperature, and protected from sunlight and moisture. Each brand of formula was mixed according to the manufacturer's instructions with each type of water. The reconstitution was the same for all brands, 1 scoop for 30 mL of water. To avoid errors in the mixture, the amount of powder contained in a scoop was weighed on a precision scale (Entris, Sartorius Lab Instruments GmbH & Co. KG, Göttinge, Germany) and the 30 mL of water was measured with a test tube. The water was heated with a microwave (Samsung GE 87M-X, Seoul, South Korea).

Each brand of formula was analyzed in triplicate. Samples were shaken before each reading (Classic Vortex Mixer, Velp Scientifica, Italy).

In addition to the 22 reconstituted formulas, the fluoride content of four ready-to-use formulas was analyzed.

2.2 Fluoride measurement

Measurements were made using a fluorine-specific ion-electrode (Orion 9609 BNWP, Thermo Fisher Scientific Inc. Waltham, MA, USA) coupled to an ion analyzer (Orion

EA-940 Thermo Fisher Scientific Inc. Waltham, MA, USA). Before each measurement session, the electrode was calibrated with standard solutions of 0.125 to 2.0 ppm F, mixing 1 mL of each standard solution with 1 mL of TISAB II (1.0 M acetate buffer pH 5.0; 1.0 M sodium chloride (NaCl) and 4% cyclohexanediaminetetraacetic acid (CDTA); Hanna Instruments, Woonsocket, RI, 02895 USA). To read the samples, 1 mL of formula milk was mixed with 1 mL of TISAB II. The electrode reading was collected in mV and through the calibration curve the results were transferred to mg F/L (ppm F).

2.3 Calculation of daily fluoride intake

We calculated the daily intake of fluoride by newborns and 6-month-old infants (Table 1) according to the average daily consumption of formula milk recommended by the American Association of Pediatrics (75 mL/453 g of child weight) [25] and the 50th percentile of the weight of Spanish children published by the Faustino Orbegozo Foundation [26].

2.4 Statistical analysis

Descriptive statistics were calculated. Fluoride values are expressed as the mean ± SD.

3. Results

The fluoride concentration in distilled water was 0.04 ± 0.02 ppm F, 0.1 ± 0.02 ppm F for Solán de Cabras, 0.58 ± 0.05 ppm F for Nestlé aquarel and 1.01 ± 0.07 ppm F for Cabreiroá. The fluoride concentration found in formulas for babies aged <6 months ranged from 0.04–0.11 ppm when reconstituted with distilled water, 0.04–0.16 ppm when reconstituted with Solán de Cabras, 0.22–0.64 ppm when reconstituted with Nestlé Aquarel, and 0.49–1.02 ppm when reconstituted with Cabreiroá (Table 2).

Formulas for infants aged ≥6 months had a fluoride concentration of 0.03–0.07 ppm when reconstituted with distilled water, 0.05–0.12 ppm with Solán de Cabras, 0.44–0.60 with Nestlé Aquarel, and 0.80–0.98 with Cabreiroá (Table 3).

In the four brands of milk sold ready-made, fluoride levels were between 0.03 and 0.09 ppm (Table 4).

All formulas reconstituted with Nestlé Aquarell, except for Blemil Plus 1 Hydrolyzed Rice, Nutramigen 1 pro and Novalac Hydrolyzed, and all those reconstituted with Cabreiroá, led to excessive fluoride consumption (Tables 5 and 6) calculated according to milk consumption per average weight (75 mL/453 g child weight/day; Table 1).

All ready-to-use brands provided a fluoride level lower than the maximum recommended doses (Table 7).

4. Discussion

The first years of a child's life are a critical period in enamel formation. Excessive fluoride consumption during this period could lead to defective enamel. For this reason, the objective of this study was to determine the potential risk of dental fluorosis associated with marketed formulas. We reconstituted 22 formulas with three brands of water commonly marketed in supermarkets in Spain. In addition, we measured the concentration of fluoride contained in 4 ready-to-use formulas.

The information that appears on the labels of all the formulas analysed indicates that the amount of fluoride after reconstruction is less than 100 μg F/100 mL (1 mg F/L or 1 ppm F), the maximum amount allowed by the European Commission Directive 2006/141/EC [27].

When the milk samples were reconstituted, the maximum allowed was reached only in some brands mixed with Cabreiroá, the highest being Nutriben Soja with 1.02 ± 0.06 mg F/L. This indicates that the total dose consumed by the child does not depend solely on the fluoride content of the formula powder, but mainly on the concentration of fluoride in the water used for reconstitution [11, 28] which was 0.04 ± 0.02 ppm F for distilled water, 0.1 ± 0.01 ppm F for Solán de Cabras, 0.66 ± 0.05 ppm F for Nestlé Aquarel and 0.95 ± 0.21 ppm F for Cabreiroá [29].

In 2011, the ADA [13] recommended that formula should be mixed with fluoride-free or low-concentration water (<0.6 mg F/L) or that formulas that were already reconstituted should be used to provide better control of the amount of fluoride ingested [11, 30]. In fact, the four milk samples already prepared for use in our study showed levels below 0.1 mg F/L.

TABLE 1. Daily consumption of formula (L/day) and daily limit of fluoride according to weight of baby.

Age	Weight (kg)[a]	Formula Consumed (mL/day)[b]	Maximum Daily Limit[c]
Newborn, male	3.24 ± 0.36 kg	0.54 L/day	0.23 mg F/day
Newborn, female	3.13 ± 0.40 kg	0.52 L/day	0.22 mg F/day
6 months, male	7.94 ± 0.92 kg	1.30 L/day	0.56 mg F/day
6 months, female	7.42 ± 0.82 kg	1.20 L/day	0.52 mg F/day

[a] *Mean weight according to Fundación Orbegozo (2011) [18];*
[b] *Mean daily consumption of formula: 75 mL/453 g/weight/day, according to the AAP [17];*
[c] *Upper limit in terms of clinically-acceptable risk of dental fluorosis: 0.07 mg F/day/kg [9].*

TABLE 2. Brands of formula for babies aged less than 6 months. Fluoride levels for various brands of formula reconstituted with different brands of water.

Brands of formula for use from day 1 to 6 months	Company, city, country	Proportion powder/water (1 scoop/30 mL)	µg F/100 g of powder*	µg F/100 mL*	Distilled water (mg F/L)$^{+}$	Solán de Cabras (mg F/L)	Nestlé Aquarell (mg F/L)	Cabreiroá (mg F/L)
Almirón Advance Digest	Numil Nutrición, Madrid (Spain)	4.6 g/30 mL	275 µg	35.8 µg/100 mL	0.04 ± 0.01	0.10 ± 0.01	0.57 ± 0.02	0.95 ± 0.08
Blemil Optimum 1	Ordesa, Huesca (Spain)	4.3 g/30 mL	<40 µg	<6.0 µg/100 mL	0.08 ± 0.02	0.16 ± 0.06	0.54 ± 0.05	0.90 ± 0.07
Blemil Plus 1 Arroz Hidrolizado	Ordesa, Huesca (Spain)	4.5 g/30 mL	275 µg	37.1 µg/100 mL	0.08 ± 0.01	0.16 ± 0.08	0.42 ± 0.04	0.72 ± 0.08
Blemil Plus 1 FH (hydrolyzed formula)	Ordesa, Huesca (Spain)	4.7 g/30 mL	275 µg	38.5 µg/100 mL	0.11 ± 0.01	0.14 ± 0.02	0.52 ± 0.05	0.86 ± 0.06
Hero Pedialac 1 without lactose	Hero Laboratorios, Murcia (Spain)	4.7 g/30 mL	–	<69.0 µg/100 mL	0.06 ± 0.02	0.11 ± 0.03	0.53 ± 0.12	0.92 ± 0.06
Hero Pedialac FEH (extensively hydrolyzed formula)	Hero Laboratorios, Murcia (Spain)	4.6 g/30 mL	<495 µg	<69.0 µg/100 mL	0.06 ± 0.01	0.14 ± 0.02	0.58 ± 0.06	0.98 ± 0.09
Miltina AC	Humana GmbH 26911, Brake (Germany)	4.5 g/30 mL	50 µg	10.0 µg/100 mL	0.06 ± 0.02	0.13 ± 0.01	0.64 ± 0.02	0.99 ± 0.06
Miltina AR	Humana GmbH 26911, Brake (Germany)	4.3 g/30 mL	20 µg	3.0 µg/100 mL	0.05 ± 0.01	0.12 ± 0.02	0.63 ± 0.05	0.99 ± 0.12
NAN A.R. (anti-regurgitation)	Nestlé Switzerland, Vevey (Switzerland)	4.4 g/30 mL	–	<70.0 µg/100 mL	0.05 ± 0.01	0.11 ± 0.02	0.56 ± 0.08	0.94 ± 0.12
NAN Confort Total (anti-colic and anti-constipation)	Nestlé Switzerland, Vevey (Switzerland)	4.3 g/30 mL	–	66.0 µg/100 mL	0.05 ± 0.01	0.11 ± 0.01	0.58 ± 0.09	1.00 ± 0.09
Nutramigen 1 Pro	Mead-Johnson Nutrition, USA	4.5 g/30 mL	–	–	0.04 ± 0.01	0.04 ± 0.01	0.22 ± 0.07	0.49 ± 0.11
Novalac hidrolizada	Medi-Europa, Geneva (Switzerland)	4.5 g/30 mL	<490 µg	<60.0 µg/100 mL	0.04 ± 0.01	0.05 ± 0.01	0.37 ± 0.07	0.68 ± 0.07
Novalac A.C. (anti-colic)	Medi-Europa, Geneva (Switzerland)	4.3 g/30 mL	<500 µg	<65.0 µg/100 mL	0.05 ± 0.01	0.12 ± 0.02	0.56 ± 0.05	0.95 ± 0.09
Nutribén Hidrolizada	Alter farmacia, Madrid (Spain)	4.3 g/30 mL	20 µg	2.6 µg/100 mL	0.06 ± 0.01	0.15 ± 0.02	0.60 ± 0.06	0.99 ± 0.07
Nutribén Confort	Alter farmacia, Madrid (Spain)	4.5 g/30 mL	<100 µg	<10.0 µg/100 mL	0.07 ± 0.01	0.14 ± 0.02	0.61 ± 0.06	0.99 ± 0.08
Nutribén Soja	Alter farmacia, Madrid (Spain)	4.4 g/30 mL	<100 µg	<10.0 µg/100 mL	0.09 ± 0.02	0.16 ± 0.00	0.64 ± 0.06	1.02 ± 0.06
Nutribén Low Weight	Alter farmacia, Madrid (Spain)	5.7 g/30 mL	20 µg	3.4 µg/100 mL	0.05 ± 0.01	0.12 ± 0.02	0.56 ± 0.07	0.92 ± 0.10

**Fluoride levels indicated on product packaging.*

$^{+}$Fluoride levels measured after reconstitution of formulas (1 mg F/L = 1 ppm F).

TABLE 3. Brands for infants aged more than 6 months. Fluoride levels of different formulas reconstituted with different brands of water.

Brands of formula for infants aged more than 6 months	Company, city, country	Proportion powder/water (1 scoop/30 mL)	µg F/100 g of powder*	µg F-100 mL*	Distilled water (mg F/L)+	Solán de Cabras (mg F/L)	Nestlé Aquarell (mg F/L)	Cabreiroá (mg F/L)
Almirón Pro-futura 2	Numil Nutrición, Madrid (Spain)	4.5 g/30 mL	40 µg	<6.0 µg/100 mL	0.03 ± 0.01	0.07 ± 0.01	0.45 ± 0.03	0.86 ± 0.04
NAN Supreme Pro 2	Nestlé Switzerland, Vevey (Switzerland)	4.6 g/30 mL	<60 µg	<8.3 µg/100 mL	0.04 ± 0.01	0.09 ± 0.02	0.55 ± 0.07	0.95 ± 0.07
Hero Pedialac 2	Hero Laboratorios, Murcia (Spain)	4.9 g/30 mL	<470 µg	<70.0 µg/100 mL	0.07 ± 0.03	0.12 ± 0.02	0.57 ± 0.06	0.96 ± 0.07
Novalac Pre-minum 2	Medi-Europa, Geneva (Switzerland)	4.4 g/30 mL	<450 µg	<60.0 µg/100 mL	0.03 ± 0.01	0.05 ± 0.00	0.44 ± 0.05	0.80 ± 0.08
Miltina Probalance 2	Humana GmbH 26911, Brake (Germany)	4.5 g/30 mL	30 µg	0.0 µg/100 mL	0.04 ± 0.01	0.11 ± 0.02	0.60 ± 0.05	0.98 ± 0.10

**Fluoride levels indicated in brand packaging.*
+Fluoride levels after reconstitution of formulas (1 mg F/L = 1 ppm F).

TABLE 4. Fluoride levels in formulas ready to use in newborns.

Formulas ready to use from the first day onwards	Company, city, country	µg F/100 mL*	(F) analyzed (mg/L)
Blemil Optimum 1	Ordesa, Huesca (Spain)	5.5 µg	0.05 ± 0.01
Pre NAN (low birth weight and premature)	Nestlé Switzerland, Vevey (Switzerland)	-	0.03 ± 0.01
Nutribén Innova 1	Alter farmacia, Madrid (Spain)	-	0.06 ± 0.01
Damira Natur 1	Lactalis Nutrición Iberia, Barcelona (Spain)	-	0.09 ± 0.01

**Fluoride levels indicated on brand packaging.*

TABLE 5. Fluoride consumed calculated for babies aged less than 6 months according to brand of formula and brand of water.

Formulas for use from day 1 until 6 months	Newborn, male (mg F/day)			Newborn, female (mg/F/day)			6 months, male (mg F/day)			6 months, female (mg F/day)		
	Solán de Cabras	Nestlé Aquarel	Cabreiroá	Solán de Cabras	Nestlé Aquarel	Cabreiroá	Solán de Cabras	Nestlé Aquarel	Cabreiroá	Solán de Cabras	Nestlé Aquarel	Cabreiroá
Almirón Advance Digest	0.05	0.31*	0.51*	0.05	0.30*	0.50*	0.13	0.74*	1.20*	0.12	0.68*	1.14*
Blemil Optimum 1	0.09	0.29*	0.50*	0.08	0.28*	0.47*	0.21	0.70*	1.17*	0.21	0.70*	1.17*
Blemil Plus 1 Arroz Hidrolizado	0.09	0.23	0.39*	0.08	0.22	0.37*	0.21	0.55	0.94*	0.19	0.50	0.86*
Blemil Plus 1 FH (hydrolyzed formula)	0.08	0.28*	0.46*	0.07	0.27*	0.45*	0.18	0.68*	1.12*	0.17	0.62*	1.03*
Hero Pedialac 1 without lactose	0.06	0.29*	0.50*	0.06	0.28*	0.48*	0.14	0.69*	1.20*	0.13	0.64*	1.10*
Hero Pedialac FEH (extensively hydrolyzed formula)	0.08	0.31*	0.53*	0.07	0.30*	0.51*	0.18	0.75*	1.30*	0.17	0.70*	1.18*
Miltina AC	0.07	0.35*	0.53*	0.07	0.33*	0.51*	0.17	0.83*	1.29*	0.16	0.77*	1.19*
Miltina AR	0.06	0.34*	0.53*	0.06	0.33*	0.51*	0.16	0.82*	1.29*	0.14	0.76*	1.19*
NAN A.R. (anti-regurgitation)	0.06	0.30*	0.51*	0.06	0.29*	0.49*	0.14	0.73*	1.22*	0.13	0.67*	1.13*
NAN Confort Total (anti-colic and anti-constipation)	0.06	0.31*	0.54*	0.06	0.30*	0.52*	0.14	0.75*	1.30*	0.13	0.70*	1.20*
Nutramigen 1 Pro	0.02	0.12	0.27*	0.02	0.11	0.25*	0.05	0.29	0.64*	0.05	0.26	0.59*
Novalac hidrolizada	0.03	0.20	0.37*	0.03	0.19	0.35*	0.07	0.48	0.88*	0.06	0.44	0.82*
Novalac A.C. (anti-co lic)	0.06	0.30*	0.51*	0.06	0.29*	0.49*	0.16	0.73*	1.23*	0.14	0.67*	1.14*
Nutribén Hidrolizada	0.08	0.32*	0.53*	0.08	0.31*	0.51*	0.20	0.78*	1.29*	0.18	0.72*	1.19*
Nutribén Confort	0.08	0.33*	0.53*	0.07	0.32*	0.51*	0.18	0.79*	1.30*	0.17	0.73*	1.19*
Nutribén Soja	0.09	0.35*	0.55*	0.08	0.33*	0.53*	0.21	0.83*	1.33*	0.19	0.77*	1.22*
Nutribén Low Weight	0.06	0.30*	0.50*	0.06	0.29*	0.48*	0.16	0.73*	1.20*	0.14	0.67*	1.10*

**Greater than recommended daily dose of fluoride.*

TABLE 6. Fluoride consumption calculated for infants aged more than 6 months according to brand of formula and brand of water.

Brands for use in babies aged >6 months	Solán de Cabras (mg F/day)		Nestlé Aquarel (mg F/day)		Cabreiroá (mg F/day)	
	Males	Females	Males	Females	Males	Females
Almirón Profutura 2	0.09	0.08	0.59*	0.54*	1.11*	1.03*
NAN Supreme Pro 2	0.12	0.11	0.72*	0.66*	1.23*	1.14*
Hero Pedialac 2	0.16	0.14	0.74*	0.68*	1.25*	1.15*
Novalac Premium 2	0.07	0.06	0.57*	0.53*	1.04*	0.96*
Miltina Probalance 2	0.14	0.13	0.78*	0.72*	1.30*	1.18*

**Greater than recommended daily dose of fluoride.*

TABLE 7. Fluoride consumed calculated for newborns receiving ready-to-use formulas.

Ready To Use Formulas	Newborn, male (mg F/day)	Newborn, female (mg F/day)
Blemil Optimum 1	0.027	0.026
PreNAN Nestlé	0.016	0.015
Nutribén Innova 1	0.030	0.030
Damira Natur 1	0.050	0.050

The difficulty for parents is to determine fluoride levels in the water they use to reconstitute the prepared milk. Very few bottled waters indicate fluoride concentrations on their labels [29, 31]. Of those used in this study, only Cabreiroá indicated this (0.96 mg F/L). Solán de Cabras specified "indicated for the preparation of baby food". Other authors [11, 31] detected small discrepancies between the fluoride concentration found and the levels on the labels. In order for parents, pediatricians and dentists to make informed decisions about the amount of fluoride that infants are consuming, it should be mandatory to regularly report the concentration of fluoride present in formula and in bottled and tap water. Many parents use tap water to reconstruct prepared formula and, although public water is not usually fluoridated (<0.7 ppm F), there are some regions where the concentration is high [32, 33].

The amount of fluoride consumed by the child depends directly on the amount of milk ingested. We estimated the daily intake of fluoride using the average daily consumption of formula recommended by the American Association of Pediatrics (75 mL/453 g of the child's weight) [25] and the 50th percentile of the weight of Spanish children published by the Faustino Orbegozo Foundation [26] and calculated the maximum amount of daily intake in terms of risk of dental fluorosis [9] (Table 1). According to our calculations, with formula reconstituted with distilled water or with Solán de Cabras, both for children under 6 months of age and for adults, the maximum daily limit in terms of clinically acceptable dental fluorosis risk of 0.07 mg F/day/kg body weight was not exceeded [9, 34]. Formulas for children aged <6 months reconstituted with Nestlé Aquarell, except for Blemil Plus 1 Hydrolyzed rice, Nutramigen 1 pro and Novalac Hidrolizada, and all those reconstituted with Cabreiroá, exceeded the risk limits, as did all formulas for children aged >6 months reconstituted with both Nestlé Aquarell and Cabreiroá.

However, it is not the amount of fluoride consumed but its bioavailability that determines systemic toxicity. The net absorption surface and the ease of the liquid in reaching the intestinal mucosa determine the bioavailability. Coagulation of milk in the stomach due to acidity and calcium fluoride formation reduces fluoride absorption in the stomach and intestine [35], explaining the decreased absorption of fluoride from cow's milk. However, the opposite is true for soy-based formulas. Some authors suggest that the phosphorus contained in these formulas increases the bioavailability of fluoride, since this is bound to phosphorus, and would have a lower rate of calcium fluoride formation, with fluoride being largely absorbed by the intestinal wall [10].

The soy protein-based formula analyzed in our study showed similar levels of fluoride to the other formulas. Other studies found higher fluoride values than in conventional formulas. Therefore, some authors advise that soy formula should be consumed with caution and only by infants with lactose intolerance or allergy [10, 33, 36].

5. Conclusions

As the potential risk of dental fluorosis of the formulas tested depends exclusively on the fluoride concentration of the water used for reconstitution, formula packaging should contain a warning.

AVAILABILITY OF DATA AND MATERIALS

The datasets used for the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

AJOR and JAC—conceptualization; supervision. AJOR, SMGR and IFP—methodology. AJOR—formal analysis. SMGR, JAC and APS—investigation. CSM and AJOR—data curation. SMGR and AJOR—writing-original draft preparation. JAC, YMB, AJOR, CSM and APS—writing-review and editing. CSM, APS and AJOR—visualization. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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