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Urinary fluoride excretion by preschool children in six European countries

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Abstract – *Objective:* To measure and compare 24-h urinary fluoride excretion in children aged 1.5–3.5 years from European study sites and to use these data to estimate the 24-h fluoride intake. *Method:* Twenty-four-hour urine samples were collected from 3-year-old children ($n = 86$) who were already participating in a European multicentre study. Samples were collected from Cork, Ireland ($n = 19$) where the water is fluoridated to a concentration between 0.8 and 1.0 ppm and from five sites with a water fluoride concentration <0.15 ppm: Knowsley, England ($n = 18$); Oulu, Finland ($n = 18$); Reykjavik, Iceland ($n = 4$); Haarlem, the Netherlands ($n = 6$); Almada/Setubal, Portugal ($n = 21$). The volume of the samples was measured; they were analysed for fluoride concentration and the 24-h urinary fluoride excretion was calculated. From this an estimate of the daily fluoride intake was made. *Results:* It was found that the mean fluoride excretion in response to the usual conditions of fluoride intake in the children in the nonfluoridated areas ranged from 0.16 mg (±0.08) in Oulu to 0.33 mg (±0.27) in Almada/Setubal with an overall mean of 0.23 mg (±0.19). The mean 24-h fluoride excretion in fluoridated Cork was 0.37 mg (±0.11). There was a significant difference between the fluoride excretion in the nonfluoridated areas and that in the fluoridated areas, and the data were broadly in agreement with WHO standards. *Conclusions:* The daily urinary fluoride excretion and estimated fluoride intake in these children appeared to be within acceptable limits.

Key words: children; fluoride excretion; urinary fluoride

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There is concern that toothpaste swallowed by young children is an important source of systemic fluoride, which may result in dental fluorosis. Preschool children, in whom the ability to spit out thoroughly during toothbrushing may not be fully developed, may be at an even greater risk because the aesthetically important central incisors are developing at this time (1). In an attempt to reduce this risk lower fluoride toothpastes have been developed and marketed at this age group (2). However, there are some groups of young children for whom caries remains a problem, and there is concern that such lower fluoride 'children's' toothpastes do not offer the caries protection of their higher fluoride counterparts (3, 4). Current recommendations are that young children at high caries risk should use regular fluoride toothpaste, but should use only a 'pea-sized' amount and should be encouraged to spit out rather than swallow to avoid ingestion of excess fluoride (5). In communities where both fluorosis and caries are potential problems, fluoride exposure should be monitored at regular intervals (6). One of the recommended methods for this is by the measurement of urinary fluoride excretion (7).

This study formed part of a larger multicentre European Project, 'Project FLINT', that aimed to investigate the link between the ingestion of fluoride from toothpaste in young children and the prevalence of enamel fluorosis (8). The collection of the data was in two stages. In the first stage data relating

to the use and ingestion of toothpaste were collected from a sample of approximately 200 children, aged between 1.5 and 3.5 years (9, 10). In this second stage of the study, a smaller subsample of these children who were toilet trained and dry at night was studied to determine their daily fluoride excretion.

The aim of this part of the study was therefore to measure and compare the 24-h urinary fluoride excretion in children aged 1.5–3.5 years from seven European study sites. A secondary aim was to estimate the daily fluoride intake in these children from the excretion data.

Materials and methods

Approval to conduct the study was obtained from the Local Research Ethics Committee in each of the participating countries. The sampling procedure has been described previously (9).

At the end of a home visit during which toothpaste use and ingestion were measured (10), parents of all children who were toilet trained from both age groups were invited to participate in an investigation of fluoride excretion. Written consent was then obtained from those agreeing to participate in this stage of the study.

The urine collection was conducted over a 24-h period during the week over which a week-long fluoride toothpaste-use measurement was being made. For 3 days before the collection of urine the parents were asked to avoid routine visits to the dentist for the child as this may have resulted in the application of topical fluoride. This was subsequently checked with the parent and indicated on the label of the sample bottle. There were otherwise no instructions to alter the diet of the participating children or their toothbrushing habits or use of fluoride toothpaste during this study period. On the study day the time that the first urine was passed after the child rose in the morning was recorded by the parent on the label of the urine sample bottle. This urine was discarded but the recorded time marked the beginning of the timed 24-h period. During the following 24 h all urine passed by the child was pooled and stored in one 2000 ml polyethylene leak-proof screw-topped sample bottle. The time of each urination was recorded on the bottle label. The first urine passed the following morning was also collected and pooled and this marked the end of the timed 24-h period. This time was also recorded on the label. The parents were requested to keep the urine sample in a refrigerator or other cool place during the 24-h collection period.

Parents were also given a smaller (500 ml) polyethylene bottle to use for urine collection should they leave the home during the 24-h collection period. Any urine collected in this sample bottle was then added to the larger sample via a funnel on arriving back at the house. Parents were also asked to record any lost or spilt urine or discarded samples and estimate quantities lost on the bottle label.

The pooled 24-h urine was collected by the research worker on the same morning that the last timed urine sample was collected. The research worker then checked with the parent that all the urine passed by the child during the 24-h collection period had been saved and that any losses were documented. The 24-h urine sample was returned to the research laboratory where the volume (ml) was measured and recorded. Following thorough mixing, two samples, one of 5 ml and one of 10 ml, were then pipetted off into separate labelled polyethylene containers and then stored frozen at $-18^{\circ}C$. The frozen 5-ml samples were then despatched to Cork on dry ice. The frozen 10-ml samples were retained by each research centre as a backup.

The body weight (kg) and height (cm) of each child were recorded and a complete record of dietary intake, including times and amounts of food eaten, was kept for each child during the 24-h urine collection period. A written record was kept of toothpaste use, and the use of other fluoride-containing products, such as fluoride tablets, was recorded during the interview/questionnaire with the parents.

Urine samples were analysed in one central laboratory in Cork using the standard technique with a fluoride ion-specific electrode and meter 720 A series (Orion Research) (11). Samples indicating a urinary flow rate of less than 9 ml/h or over 420 ml/h were discarded as recommended as they were assumed to be incomplete or supplemented with water, respectively (12). The 24-h fluoride excretion (mg) was calculated as the total volume of the 24-h sample (l) multiplied by its fluoride concentration (mg/l). Data were analysed for each study site and intersite differences were compared using analysis of variance. Study sites were also grouped according to whether they were fluoridated or nonfluoridated, and differences were analysed using independent *t*-tests.

Results

Six of the seven 'Project FLINT' partners participated in this study although recruitment of subjects varied widely between participating countries.

Table 1. Mean age, weight and height for the children from each of the six participating countries

	Age (years)		Weight (kg)		Height (cm)	
	mean (SD)	95% CI	mean (SD)	95% CI	mean (SD)	95% CI
Cork	3.4 (0.2)	3.3, 3.5	16.7 (2.4)	15.6, 17.8	102.2 (4.9)	100.0, 104.4
($n = 19$)	2.7–3.7					
Knowsley	3.1 (0.6)	2.8, 3.4	16.0 (1.4)	14.0, 17.9	95.3 (6.0)	92.5, 98.1
($n = 18$)	1.8–4.2					
Oulu	3.1 (0.4)	2.9, 3.3	15.0 (2.4)	13.9, 16.1	94.7 (5.8)	92.0, 97.4
($n = 18$)	2.3–3.6					
Reykjavik	3.6 (0.3)	3.3, 3.9	16.3 (1.2)	8.9, 18.6	100.0 (2.2)	97.9, 102.1
($n = 4$)	3.2–3.9					
Haarlem	3.2 (0.5)	2.8, 3.7	15.8 (1.8)	14.3, 17.3	99.8 (5.8)	95.2, 104.5
($n = 6$)	2.6–4.0					
Almada/Setubal	3.1 (0.4)	2.9, 3.2	14.5 (1.9)	13.7, 15.3	94.5 (5.9)	92.0, 97.0
($n = 21$)	2.5–3.6					
Overall	3.2 (0.4)	3.1, 3.3	15.5 (2.7)	14.8, 16.0	97.0 (3.6)	95.7, 98.4
($n = 86$)						

From Table 1 the mean age (±SD) of the children recruited ($n = 86$) was 3.2 years (±0.4). The mean body weight of these children was 15.5 kg (±2.7) and their mean height was 97.0 cm (±6.3). Analysis of variance demonstrated some significant differences between the weight and height of the children; *t*-tests subsequently identified that the children from Cork were significantly taller than the other children ($t = -4.45$, $P < 0.001$) and that the children from Almada/Setubal were significantly both lighter ($t = 2.1$, $P = 0.039$) and shorter ($t = 2.18$, $P = 0.032$).

From Table 2 the mean urine collection period was 24.0 h (±1.2) and the mean volume of urine collected in this period was 571 ml (±249). Thirty-three subjects (38%) reported some losses or missed collections of urine. When these were taken into consideration and the collection time was corrected to 24 h the mean 24-h urine volume was 584 ml (±242) and the mean urinary flow rate was 24.3 ml/h (±10.1).

The mean urinary fluoride concentration of the samples collected was 0.51 ppm (±0.39). The 24-h urinary fluoride excretion, calculated from the urinary fluoride concentration (mg/l) multiplied by the corrected 24-h urine volume (l), ranged from 0.16 mg in Oulu to 0.37 mg in Cork (Fig. 1). Ten of the subjects (12%) (four from Oulu, four from Almada/Setubal and two from Haarlem) took fluoride supplements on a regular basis. In six of these subjects the 24-h fluoride excretion was below 0.25 mg, in three it was between 0.30 and 0.50 mg and in the other one it was 1.10 mg. All of the children were brushing with fluoride toothpaste regularly, which ranged in concentration from <400 to 1500 ppm F (9). In Cork,

Table 2. Mean urine collection period, mean volume of urine collected, mean corrected 24-h urine volume, mean urinary fluoride concentration and mean 24-h fluoride excretion

Collection period	Urine volume collected		Corrected 24-h urine volume		Corrected 24 h F excretion		Corrected 24-h F excretion (mg/kg body weight)
	(hours)	(ml)	(ml)	(ml/h)		(mg)	
Cork	23.5 (1.2)	474 (163)	499 (167)	20.8 (7.0)	0.78 (0.27)	0.37 (0.11)	0.022 (0.008)
($n = 19$)	23.0, 24.0	401, 547	423, 574	17.6, 23.9	0.66, 0.90	0.32, 0.42	0.019, 0.026
Knowsley	23.9 (1.1)	493 (379)	498 (377)	20.8 (7.15)	0.56 (0.48)	0.20 (0.14)	0.014 (0.010)
($n = 18$)	23.5, 24.4	318, 668	324, 672	13.5, 28.0	0.33, 0.78	0.13, 0.26	0.009, 0.016
Oulu	24.8 (1.30)	632 (257)	646 (235)	26.9 (8.9)	0.30 (0.24)	0.16 (0.08)	0.011 (0.007)
($n = 18$)	24.2, 25.4	513, 750	537, 754	22.4, 31.4	0.19, 0.41	0.12, 0.20	0.008, 0.014
Reykjavik	24.0 (0.0)	440 (152)	440 (152)	18.3 (4.6)	0.42 (0.20)	0.17 (0.01)	0.011 (0.001)
($n = 4$)	24.0, 24.0	291, 590	291, 590	12.1, 24.6	0.23, 0.62	0.15, 0.18	0.009, 0.011
Haarlem	23.0 (2.5)	514 (149)	540 (114)	22.5 (4.8)	0.41 (0.35)	0.21 (0.15)	0.014 (0.010)
($n = 6$)	21.0, 25.0	395, 633	448, 631	18.7, 26.3	0.13, 0.69	0.08, 0.33	0.005, 0.021
Almada/Setubal	24.0 (0.0)	717 (94)	721 (89)	30.0 (3, 7)	0.46 (0.41)	0.33 (0.27)	0.022 (0.019)
($n = 21$)	24.0, 24.0	676, 757	683, 759	28.5, 31.6	0.29, 0.64	0.21, 0.44	0.015, 0.031
Overall	24.0 (1.2)	571 (249)	584 (242)	24.3 (1.10)	0.51 (0.39)	0.26 (0.18)	0.017 (0.013)
($n = 86$)	23.7, 24.2	519, 624	533, 635	22.2, 26.5	0.43, 0.59	0.22, 0.30	0.014, 0.020

All values given are mean with SD in parentheses.

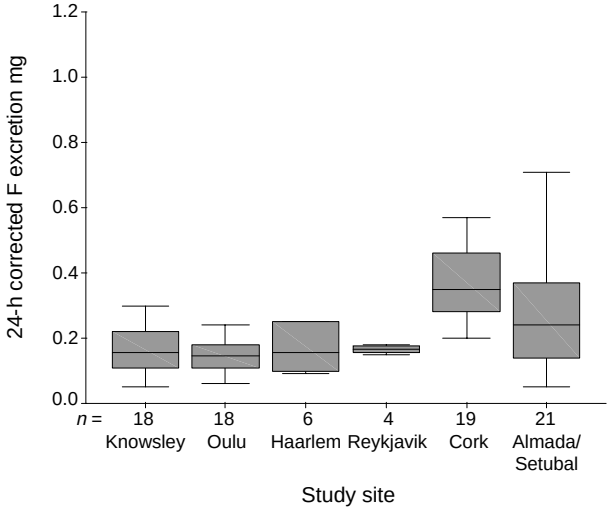

Fig. 1. 24-h corrected F excretion in each of six European study sites.

Knowsley and Haarlem approximately two-thirds of the children were using fluoride toothpaste with a concentration of 400–800 ppm, and most of the remainder used toothpaste containing 800–1200 ppm F. In Oulu, Reykjavik and Almada/Setubal approximately two-thirds of the children used toothpaste with a fluoride concentration of 800–1200 ppm and the remainder used toothpaste containing 400–800 ppm F. Detailed data on fluoride ingestion from toothpaste in these children are given elsewhere (10). Analysis of the dietary records showed that all the children ate similar diets with no abnormally high intakes of fluoride-rich foods such as tea or fish, with the exception of the children from Almada/Setubal who all appeared to have a diet rich in bony fish.

Table 3 shows that the overall mean 24-h urinary fluoride excretion for the five sites with a water supply of low fluoride concentration (<0.15 ppm) was 0.23 mg (±0.19) or 0.015 mg/kg body weight (±0.013). In contrast to this the mean 24-h fluoride excretion in the children from fluoridated Cork was 0.37 mg (±0.11) or 0.022 mg/kg body weight (±0.008). This difference between the fluoridated and nonfluoridated sites was found to be significant (*t*-test, $t = -3.1$, $P = 0.003$).

Discussion

This study was the second part of a larger study the overall aim of which was to investigate toothpaste use and ingestion in 1.5–3.5 years old children (9, 10). The main study group was chosen at random from birth or doctors' registers in the countries involved, with the exception of Athens where it was not possible to achieve this sampling method. The Athens group therefore declined to participate in this second part of the study. The sample for this second part of the study was taken from the main study group and comprised children who were toilet trained and dry at night and whose parents agreed to co-operate with urine collection. There appear to be different attitudes to investigations of this nature among parents of subjects from the different countries involved. This is reflected in the low numbers of children enlisted to participate. In addition, the attendance of many children, for example in Reykjavik, at some form of day-care away from the home make urine collection impractical for this type of study design. However, compliance with the protocol was good among those parents who agreed to participate. The highest number of subjects was 21 in Almada/Setubal; in Cork, there were 19 subjects and in both Oulu and Knowsley 18 subjects were recruited. However, in Haarlem and in Reykjavik it was only possible to recruit six and four children, respectively. In common with other recent similar studies (13, 14) the study samples were not chosen at random but as maximum co-operation was essential, this was not considered a disadvantage. It was considered that those children participating in each of the study sites were not sufficiently different from the rest of the population for the sampling procedure to have any influence on the results obtained. Any differences in fluoride

Table 3. Mean urinary fluoride concentration and mean 24-h fluoride excretion in the nonfluoridated and fluoridated areas.

	Urinary F concentration (ppm)	Corrected 24-h F excretion (mg)	Corrected 24-h F excretion (mg/kg body weight)
Non-fluoridated areas	0.44 (0.38)	0.23 (0.19)	0.015 (0.013)
($n = 67$)	0.35, 0.53	0.18, 0.27	0.012, 0.019
Fluoridated area	0.78 (0.27)*	0.37 (0.11)*	0.022 (0.008)*
(Cork, $n = 19$)	0.66, 0.90	0.32, 0.42	0.019, 0.026
	*t-test, $t = 3.7$, $P < 0.001$	*t-test, $t = 3.1$, $P = 0.003$	*t-test, $t = 2.2$, $P = 0.034$

Values are given as mean (SD) with 95% confidence intervals below this.

excretion between the groups were therefore unlikely to be caused by biased selection of the subjects.

In this study, the 24-h fluoride excretion was investigated in young children aged between 1.8 and 4.2-years in six different European study sites under usual conditions of fluoride intake, i.e. customary diet and usual oral-hygiene procedures with fluoride toothpaste. Analysis of dietary records indicated an abnormally high dietary intake of a potentially fluoride-rich food in one study site only: this was Almada/Setubal where 10 (48%) of the children were reported to consume a diet rich in bony fish. In Cork, the water is artificially fluoridated to a concentration between 0.8 and 1.0 ppm. In the other five study sites the water fluoride concentration was in the range 0.01–0.13 ppm. The 24-h urinary fluoride excretion in Cork was found to be in the range 0.20–0.57 mg, mean 0.37 mg (±0.11). In the remaining five nonfluoridated sites it was found to be in the range 0.05–1.10 mg, mean 0.23 mg (±0.19). As would be expected, this difference between the fluoridated and nonfluoridated sites was significant ($P = 0.003$). The widest range in fluoride excretion occurred in the Portuguese samples – despite the water fluoride concentration being relatively low (<0.08 ppm), the 24-h excretion ranged from 0.05 to 1.10 mg. The reason for this is unclear. Despite the apparent high dietary fluoride intake and the use of fluoride supplements in some of the Portuguese children this did not appear to be reflected consistently in the urinary fluoride excretion of these children. Of the 10 children who were reported to have high intake of fish, six of these had a 24-h fluoride excretion below the Portuguese average. Of the four children who were reported to be taking fluoride tablets regularly two had a fluoride excretion below the average for Portugal.

A secondary aim of this study was to estimate the daily fluoride intake from urinary fluoride excretion data in these children. Monitoring fluoride exposure is an important part of community-based fluoride supplementation programmes (6) and various methods have been used to estimate fluoride ingestion from excretion data. Some authors have collected 24-h excretion data and simply multiplied these by two to estimate fluoride ingestion (11, 15). This fractional excretion is based on the earlier classical studies of Machle and Largent (16) who measured total fluoride intake (by direct measurements of all ingested food and fluoride supplements) and total fluoride excretion (i.e. in urine, faeces and sweat) over a 2-year period. Their results showed that approximately 50% of the ingested dose was excreted. Although this 50% fractional excretion is possibly valid at high levels of fluoride intake in adults, it may be inaccurate at more 'normal' fluoride intake levels and in actively growing young children whose bone turnover is higher. Various studies have attempted to quantify this fractional fluoride excretion in young children, with a range of, seemingly conflicting, results. While some workers have reported fractional excretion rates in the region of 20% (17–20), others have reported it to be around 30% (6, 21, 22), 50% (23) and as high as 80% (24). Various explanations for this apparent range in fractional excretion have been proposed, largely relating to the variables influential in fluoride excretion (22, 24–26). It has also been suggested that the proportion of absorbed fluoride which is excreted in the urine is proportional to the amount of the ingested dose (22).

It is apparent therefore that it is difficult to estimate fluoride intake from fluoride excretion data. Based on a fractional excretion of 30% it could be estimated that the daily fluoride intake in the children participating in the current study was approximately 0.052 (±0.044) mg/kg body weight in the nonfluoridated areas and 0.075 (±0.026) mg/kg body weight in the fluoridated area. Based on a fractional excretion of 50% the estimated daily fluoride intake in the children in the nonfluoridated areas was approximately 0.031 (±0.027) mg/kg body weight and 0.045 (±0.016) mg/kg body weight in the fluoridated area.

The concept of optimal fluoride intake has been discussed at some length in two reviews (27, 28). It is based on the early studies of Dean (29) and refers to a level of fluoride intake which causes significant caries reduction with only a minor increase in the prevalence of dental fluorosis. McClure (30) estimated the fluoride intake of children aged 1–12 years to be within the range 0.4–1.7 mg/day, and to average about 0.05 mg/kg body weight. The 'optimal' range of fluoride intake in children of this age has since been quoted as 0.05–0.07 mg/kg body weight (31, 32) and, although not based on definitive evidence, Burt concluded that this was a 'useful guideline for fluoride intake in children' (28). The United States Public Health Service (33), estimated that total daily fluoride intake in children receiving fluoride supplementation was within the range 0.95–2.3 mg or 0.05–0.12 mg/kg body weight. However, it is important to note that these ranges are only estimates and that the 'optimal' level of fluoride intake is very much dependent on what is deemed to be an acceptable level for dental fluorosis

within a particular community. It has been suggested that the threshold level of fluoride intake for the development of fluorosis is 0.03–0.04 mg/kg body weight (34, 35) although this refers to the mildest forms of the condition, i.e. those which Dean would have classified as 'questionable'. This concept of a threshold level for acceptable dental fluorosis is important in terms of planning dental-health policies and is one which must be considered by dental-health decision-makers when planning fluoridation or fluoride supplementation programmes. The ultimate decision therefore regarding what constitutes optimal fluoride intake in the children within their population rests with these dental-health policy makers. The decision must follow careful consideration of the existing caries prevalence and what would be regarded as an acceptable level of enamel fluorosis within that particular community. Clearly these values will change with changes in the prevalence, and perhaps distribution, of dental caries within the community.

In the light of these difficulties in estimating fluoride intake from urinary fluoride excretion data it has been suggested that use of excretion data *per se* and comparatively is a preferable means of monitoring fluoride exposure (7). Examples from the published literature show that the mean 24-h urinary fluoride excretion, under conditions of low fluoride intake, is usually below 0.2 mg (36, 37) while that under conditions of optimal fluoride intake is somewhat in excess of 0.4 mg/day (21, 38, 39). These other studies, however, were all carried out on slightly older children than those in the current study, with the mean age being between 4 and 5 years. More recently the World Health Organization has proposed that the standard for 24-h fluoride excretion in 3–5-year-old children with low fluoride intake is 0.17–0.29 mg and for those with an optimal fluoride intake it is 0.36–0.48 mg (7). The average fluoride excretions in the children in this study were therefore in accordance with these standards.

In conclusion, the methods adopted in this study were largely suitable for collecting urinary fluoride excretion data from children in this age group from seven European countries. Recruitment was difficult, particularly from the age group originally specified and especially in two of the countries. In one of the countries, compliance with the protocol was not possible. The urinary fluoride excretion in the children from the nonfluoridated areas was found to be significantly lower than that from the children living in a fluoridated area and the values were broadly in agreement with those of other workers. Finally, the estimated daily fluoride intake in the children studied appeared to be within acceptable limits, although, as discussed, the appropriateness of this method for calculating fluoride intake must be questioned.

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References

1. Evans RW, Stamm JW. An epidemiologic estimate of the critical period during which human maxillary central incisors are most susceptible to fluorosis. J Public Health Dent 1991;51:251–9.
2. Winter GB, Holt RD, Williams BF. Clinical trial of a low-fluoride toothpaste for young children. Int Dent J 1989;39:227–35.
3. O'Mullane D. Introduction and rationale for the use of fluoride in caries prevention. Int Dent J 1994; 44:257–61.
4. Clarkson JJ. Role of fluoride in oral health promotion. Int Dent J 2000;50:119–28.
5. Holt RD, Nunn JH, Rock WP, Page J. British Society of Paediatric Dentistry: a policy document on fluoride dietary supplements and fluoride toothpastes for children. Int J Paediatr Dent 1996;6:139–42.
6. World Health Organisation. Fluorides and Oral Health. Report of a WHO expert committee on oral health status and fluoride use. (WHO Technical Report Series 846). Geneva: WHO; 1994.
7. Marthaler TM. Monitoring of Renal Fluoride Excretion in Community Preventive Programmes on Oral Health. Geneva: WHO; 1999.
8. O'Mullane DM, Cochran JA, Whelton HP. Fluoride ingestion from toothpaste: background to European Union-funded multicentre project. Community Dent Oral Epidemiol 2004;32(Suppl. 1):5–8.
9. Cochran JA, Ketley CE, Duckworth RM, van Loveren C, Holbrook WP, Seppä L, et al. Development of a standardized method for comparing fluoride ingested from toothpaste by 1.5–3.5-year-old children in seven European countries. Part 1: Field work. Community Dent Oral Epidemiol 2004;32(Suppl. 1): 39–46.
10. Cochran JA, Ketley CE, Duckworth RM, van Loveren C, Holbrook WP, Seppä L, et al. Development of a standardized method for comparing fluoride ingested from toothpaste by 1.5–3.5-year-old children in seven European countries. Part 2: Ingestion results. Community Dent Oral Epidemiol 2004;32 (Suppl. 1):47–53.
11. Marthaler TM, Menghini G, Steiner M, et al. Excrecion urinaria de fluoruro en ninos suizos que consumen suplementos de fluoruro en la sal o el agua. Arch

Odontoestomatologia Preventiva y Comunitaria 1992; 4:27–35.
12. Marthaler TM, Steiner M, Menghini G, De Crousaz P. Urinary fluoride excretion in children with low fluoride intake or consuming fluoridated salt. Caries Res 1995;29:26–34.
13. Ketley CE, Lennon MA. Urinary fluoride excretion in children drinking fluoridated school milk. Int J Paediatric Dent 2000;10:260–70.
14. Ketley CE, Lennon MA. Determination of fluoride intake from urinary fluoride excretion data in children drinking fluoridated school milk. Caries Res 2001;35:252–7.
15. Kolesnik AG, Pakhomov GN. Annual and biannual monitoring of fluoride intake with 2.5 ppm milk by its excretion in urine in Russian children. Caries Res 1997;31:303 (abstract 67).
16. Machle W, Largent EJ. The absorption and excretion of fluoride II The metabolism at high levels of intake. J Ind Hygiene Toxicol 1959;25:112–23.
17. Ekstrand J, Fomon SJ, Ziegler EE, Nelson SE. Fluoride pharmacokinetics in infancy. Pediatr Res 1994;35: 157–63.
18. Whitford GM. The physiological and toxicological characteristics of fluoride. J Dent Res 1990;69(Special issue):539–49.
19. Ekstrand J, Ziegler EE, Nelson SE, Fomon SJ. Absorption and retention of dietary and supplemental fluoride by infants. Adv Dent Res 1994;8:175–80.
20. Hargreaves JA, Ingram GS, Wagg BJ. Excretion studies on the ingestion of a monofluorophosphate toothpaste by children. Caries Res 1970;4: 256–68.
21. Villa A, Salazar G, Anabalon M, Cabezas L. Estimation of the fraction of an ingested dose of fluoride excreted through urine in pre-school children. Community Dent Oral Epidemiol 1999;27:305–12.
22. Villa A, Anabalon M, Cabezas L. The fractional urinary fluoride excretion in young children under stable fluoride intake conditions. Community Dent Oral Epidemiol 2000;28:344–55.
23. Haftenburger M, Viergutz G, Neumeister V, Hetzer G. Total fluoride intake and urinary excretion in German children aged 3–6 years. Caries Res 2001;35:451–7.
24. Zohouri FV, Rugg-Gunn AJ. Total fluoride intake and urinary excretion in 4-year old Iranian children residing in low-fluoride areas. Br J Nutrition 2000;83:15–25.
25. Whitford GM 1996 The Metabolism and Toxicity of Fluoride. Augusta GA: Karger; 1996. p. 1–4, p. 59–106.
26. Ekstrand J, Ehrnebo M, Whitford GM, Jarnberg PO. Fluoride pharmacokinetics during acid–base changes in man. European J Clin Pharmacol 1980;18:189–94.
27. Levy SM. Review of fluoride exposures and ingestion. Community Dent Oral Epidemiol 1994;22:173–80.
28. Burt BA. The changing patterns of systemic fluoride intake. J Dent Res 1992;71:1228–37.
29. Dean HT. The investigation of physiological effects by the epidemiologic model. In: Moulton FR, editor. Fluorine and Dental Health, Washington: American Association for the Advancement of Science 1942. p. 23–31.
30. McClure FJ. Ingestion of fluoride and dental caries. Quantitative relations based on food and water requirements of children from 1 to 12 years old. Am J Dis Children 1943;66:362–9.
31. Farkas CS, Farkas EJ. Potential effect of food processing on the fluoride content of infant foods. Sci Total Environ 1974;2:399–405.
32. Ophaug RH, Singer L, Harland BF. Estimated fluoride intake of average two-year old children in four dietary regions of the United States. J Dent Res 1980;59:777–81.
33. United States Public Health Service. Ad hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Review of Fluoride Benefits and Risks Washington DC: Public Health Service. Department of Health and Human Services; 1991. p 16.
34. Fejerskov O, Stephen KW, Richards A, Speirs R. Combined effect of systemic and topical fluoride treatments on human deciduous teeth – case studies. Caries Res 1987;21:452–9.
35. Baelum V, Fejerskov O, Manji F, Larsen MJ. Daily dose of fluoride and dental fluorosis. Tandlaegebladet 1987;91:452–6.
36. Ministry of Health Scottish Office Ministry of Housing and Local Government. Reports on Public Health and Medical Subjects, no. 105. The Conduct of the Fluoridation Studies in the United Kingdom and the Results Achieved After Five Years. London: Her Majesty's Stationery Office 1962.
37. Warpeha RA, Marthaler TM. Urinary fluoride excretion in Jamaica in relation to fluoridated salt. Caries Res 1995;29:35–41.
38. Rugg-Gunn AJ, Nunn JH, Ekanayake L, Saparamadu KDG, Wright WG. Urinary fluoride excretion in 4 year old children in Sri Lanka and England. Caries Res 1993;27:478–83.
39. Baez RJ, Baez MX, Marthaler TM. Urinary fluoride excretion by children 4–6 years old in a south Texas community. Pan Am J Public Health 2000;7:242–7.