

## Children's Menu Diversity: Influence on Fluoride Absorption and Excretion

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### ABSTRACT

**Aim:** The aim of this study is to determine the influence of children's menu diversity on the absorption and excretion of fluoride.

**Materials and methods:** The experimental, longitudinal, quantitative study was carried out in a city without fluoridation in water supply. A total of 16 adult volunteers (>63.9 kg) participated in the study who, after a 12-hour fast, ingested two types of children's meals, whose quantity and diversity were determined after weighing the meals best consumed by children at a kindergarten in Campinas, São Paulo: Simple child meal (SCM; n = 8) and hearty child meal (HCM; n = 8). The fluoride gel residual after professional application (12,300 ppm, 30.75 mg F, pH = 4.65) was simulated 15 minutes after feeding. Saliva samples (in time intervals of 0, 15, 30, and 45 minutes and 1, 2, 3, 4, 6, and 12 hours after ingestion of the fluorine solution) and urine of the volunteers were analyzed at 24 hours. Fluoride concentrations were determined using a selective ion electrode. Data were analyzed by analysis of variance for repeated measurements (PROC MIXED)/Tukey–Kramer.

**Results:** The concentrations of fluoride in saliva at 0 and 15 minutes and after 6 hours were the same between groups ( $p > 0.05$ ). From 30 minutes to 4 hours after ingestion, the SCM group showed a higher concentration of fluoride in the saliva, which has a higher absorption ( $p < 0.05$ ). The fluoride concentration in the urine did not differ between groups at both collection times ( $p > 0.05$ ), and for both, the fluoride concentration in the urine increased in the final measurement ( $p < 0.05$ ).

**Conclusion:** The children's menu diversity influenced the absorption of fluoride so that the topical application of fluoride should be performed in infants fed preferably after the fuller diet and following the established guidelines to ensure the safety of the procedure.

**Clinical significance:** Knowledge of the influence of the children's menu diversity on fluoride metabolism after professional

application is important so that the actions of fluoride therapy may be planned in a safer manner and be based on the reality of the universe of children.

**Keywords:** Children's menu, Fluoride, Randomized clinical trial, Time.

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### INTRODUCTION

There have been reports of cases of acute fluoride poisoning by the ingestion of dental products related to the ingestion of doses higher than 5 mg/kg.<sup>1-4</sup> These reports were related to children at a young age.<sup>4-8</sup>

Considering children under the age of 6 years, the potentially toxic dose (PTD) may be attained with the use of dental products, in view of the mean body weight.<sup>9-11</sup> Among the factors that regulate this situation, in addition to the concentration of the product used and quantity ingested, other factors that interfere in absorption must be considered, such as the gastric content.

The influence of meals before the use of fluoridated compounds has been evaluated in previous studies.<sup>12-16</sup> Some studies have considered the use of products with a low concentration of fluoride, such as toothpastes and fluoride tablets, and it has been pointed out that a meal before fluoride ingestion reduced fluoride absorption to the order of 19% when the compound was used after breakfast and by around 33% when it was used after lunch.<sup>2,13-15</sup> Cavalli et al<sup>16</sup> testing the influence of the type of meal on the rate of fluoride absorption resulting from ingesting 1.23% acidulated phosphate fluoride (APF) gel emphasized that a meal before professional application was a factor of extreme importance because it guaranteed the safety of application, even in situations of accidental

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ingestions and that the time after a more robust meal must be the choice when planning clinical attendance, because a reduction of 28.3% in the absorption of fluoride has been verified, considering application after lunch.

Nevertheless, the fact that meals consumed by children differ in quantity, quality, and diversity from those consumed by adults must be taken into consideration because this is related to the socioeconomic conditions of families, seeing that the adoption of healthier items of food was associated with groups of higher socioeconomic levels.<sup>17-19</sup>

Previous studies on the topic have considered the menus of main meals including four slices of bread, ham, roast beef, and mayonnaise; French fries, an apple, and 300 mL of orange juice; rice (170 gm), meat, and potatoes (160 gm); and lettuce, cucumber, and tomato salad (60 gm), which differ in quantity and quality from the meals consumed by children.<sup>14-16</sup>

Fluoride is one of the most widely used dental products for professional application in dental offices, and its clinical efficacy has been demonstrated in controlled studies. In Brazil, its use in children has been endorsed by the national oral health policy, capable of being used in the school environment, under the indirect supervision of dentists.<sup>20-22</sup>

Therefore, knowledge of the influence of the diversity of the children's menu on the ingestion of fluoride gel used in professional application is important so that the actions of fluoride therapy may be planned in a safer manner at both individual and collective levels.

## MATERIALS AND METHODS

The study was approved by the Research Ethics Committee of São Leopoldo Mandic Faculty of Dentistry and Center for Dental Research, Campinas, São Paulo, under Opinion No. 042.426/2016.

### Sample Selection

All the participants, who were resident in the same city (Balsas, State of Maranhão, Brazil; that does not have fluoride in the public water supply) and weighed a minimum of 63.9 kg received information about the nature and details of the study and gave their written and informed consent to participate in the study. The sample size was based on the previous studies that used a similar methodology.<sup>14,15,23</sup>

A total of 16 ( $n = 16$ ) adult volunteers (19–33 years of age, 7 females and 9 males) participated in this study, which was approved by the Research Ethics Committee of São Leopoldo Mandic School of Dentistry.

The volunteers were submitted to a medical consultation and in the anamnesis reported that they had no

cardiac, liver, or kidney problems and were not under any medication.

### Stage of Preparation of Participants

The volunteers were instructed not to use fluoridated products 7 days before the study began, and for all toothbrushing, they were to use toothpaste without fluoride provided by the researcher [Malvatrikids Baby (composition: Cellulose gum, glycerin, *Malva sylvestris* extract, silica, sodium benzoate, sodium lauroyl sarcosinate, sorbitol, sucralose, xylitol, aroma, CI 54530, and water); Laboratório Daudt Oliveira Ltda].

All the stages were performed in a clinical analysis laboratory, thereby guaranteeing that the volunteer would be under the researcher's supervision and would have medical assistance, if it were necessary.

### Elaboration of the Menus and Composition of the Study Groups

The menu diversity and quantities were elaborated according to the meals served to the children at a nursery school in Campinas, São Paulo. In conjunction with the school nutritionist, the most consumed meal on the dinner menu considered a lighter meal—spaghetti bolognese was chosen—and the most consumed heartier meal on the lunch menu: Rice, beans, meat stew in gravy, and tomato, cucumber, and vegetable salad.

The quantities of each component were determined after the school nutritionist had weighed the lunches and dinners of five children in the age range from 5 to 6 years. Each component was weighted, and after the meal, the remainders left on the plates were weighted, seeking to determine the quantity effectively consumed by the children. These quantities were used to define the quantity of the components of meals offered to the volunteers of the study groups:

- *SCM*: spaghetti bolognese (155 gm);
- *HCM*: rice (69 gm), beans (20 gm), meat stew in gravy (30 gm), and tomato, cucumber, and vegetable salad (30 gm).

### Initial Procedures

By means of a random draw with the use of an urn and numbered papers, the 16 volunteers were divided into two study groups ( $n = 8$ ) and after fasting through the night (12 hours); at the same time, the volunteers received the meal according to the study group in which they were included. Fifteen minutes after the meals, a solution containing 2.5 mL APF gel (12,300 ppm; pH = 4.65; 30.75 mgF) diluted in 10 mL distilled water was ingested by all the volunteers, corresponding to the residual fluoride gel applied in trays.<sup>24,25</sup>

As from this moment, a questionnaire was applied, which was self-filled every hour, up to 4 hours of the experiment (period during which the volunteers remained in the laboratory), using a visual analog scale (VAS) for follow-up of the presence of eventually feeling ill.<sup>26,27</sup>

### Collection and Analysis of Fluoride in the Volunteers' Saliva

Saliva was collected from the volunteers in the following time intervals: 0 (before ingesting the fluoride-containing solution), 15, 30, 45 minutes, 1, 2, 3, 4, 6, and 12 hours after ingesting the fluoride-containing solution. For each collection, each volunteer received a wide-necked plastic flask with a capacity of 30 mL, in which each sample was collected in an unstimulated manner.<sup>15,28</sup> At 6 and 12 hours, the samples were collected at the home of each volunteer; they had been informed about the correct storage of the samples, which had to remain frozen until delivered to the researcher.<sup>29</sup> Each volunteer was provided with a thermal box to maintain the sample temperature during transportation. At the end of 12 hours, each volunteer delivered their samples to the laboratory.

For potentiometric determination of the ion concentration, a calibration curve was constructed, using sodium fluoride solutions at concentrations ranging from 0.05 to 0.5 ppmF as standard, with the initial standard used being the NaF solution at 1000 ppmF. About 1 mL of saliva was then added to 1 mL of buffer solution, and the samples were then dosed.<sup>29</sup>

On conclusion of the study, with the purpose of ameliorating possible gastric symptoms, the volunteers were offered flasks of Simeco plus (Laboratórios Supera Farma), containing aluminum hydroxide (120 mg/mL), magnesium hydroxide (60 mg/mL), and simethicone (7 mg/mL). Of the 16 volunteers, 5 related that they had made use of the medication at home, after the 12-hour duration of the experiment.

### Collection and Analysis of Fluoride in the Volunteers' Urine

The volunteers collected urine 24 hours before and after the experiment. For the collection 24 hours before the experiment, each volunteer received two 1,000 mL plastic flasks (basal urine), and on the day of the experiment, they received another two flasks with the same capacity for the urine collection 24 hours after the experiment.<sup>12,15,28</sup> The urine samples received were measure as regards volume, and immediately afterward, aliquots of 10 mL were separated, centrifuged at 2500 rpm for 10 minutes, and then analyzed relative to pH, using a combined glass

potentiometer electrode system. After the pH measurements had been made, the aliquots were frozen for later fluoride analysis.<sup>12,15,30</sup>

The analysis of fluoride in urine was determined in one single time interval, with the use of an ion-selective electrode.<sup>2,5</sup>

### Statistical and Pharmacokinetic Analysis

Computer software (PK Solutions, Summit Research Services, Montrose, Colorado, USA) was used to obtain the following parameters: Cmax, maximum concentration observed during the 12-hour study period; Tmax, the time at which Cmax occurred; and AUC0-12, the area beneath the saliva concentration-time curve from 0 to 12 hours.

Exploratory data analysis indicated two outliers (discrepant values ) for the area under the curve (saliva). After removing the outliers, Student's *t*-test was applied for comparison of the areas under the curve between the types of meals. Methodologies of mixed models for repeated measures (PROC MIXED) with the Tukey-Kramer test were used to analyze the concentration of fluoride in the saliva considering the type of meal and time of fluoride ingestion, quantity of fluoride present in the urine considering the type of meal and time of fluoride ingestion, and pH in urine considering the type of meal and time of fluoride ingestion. All the analyses were performed in the software program SAS (SAS Institute Inc., Cary, North Carolina, USA), Release 9.2, 2010, considering the level of significance of 5%.

## RESULTS

Table 1 summarizes the relationship between the quantity of fluoride ions ingested (30.75 mg) considering the volunteers' weight, for both groups.

**Table 1:** Relationship between volunteers' weight and proportion of fluoride ions ingested

Volunteer	SCM		Volunteer	HCM	
	Body weight (kg)	F/kg		Body weight (kg)	F/kg
1	76.0	0.40	9	74.0	0.41
2	78.8	0.39	10	70.4	0.43
3	72.0	0.42	11	66.2	0.46
4	74.0	0.41	12	68.0	0.45
5	65.0	0.47	13	75.8	0.40
6	75.4	0.40	14	78.6	0.39
7	63.9	0.48	15	76.9	0.39
8	72.0	0.42	16	80.2	0.38
Mean SCM	72.1	0.42	Mean HCM	73.7	0.41



**Table 2:** Mean (standard deviation) of the fluoride concentration in saliva (ng/mL) considering the type of meal and time after ingesting the fluoride-containing solution

Time	Study group	
	SCM	HCM
0	21.50 (2.39) Ahi	21.50 (1.31) Ag
15 minutes	27.62 (1.85) Ag	28.62 (1.41) Af
30 minutes	88.12 (1.73) Ac	79.12 (± 0.99) Bc
45 minutes	167.50 (3.54) Aa	129.38 (0.92) Ba
1 hour	147.62 (3.38) Ab	119.50 (0.76) Bb
2 hours	66.62 (4.24) Ad	59.38 (0.74) Bd
3 hours	45.37 (3.62) Ac	39.38 (0.92) Be
4 hours	36.00 (3.02) Af	29.00 (1.20) Bf
6 hours	24.12 (1.73) Ah	21.38 (1.50) Ag
12 hours	20.00 (1.41) Ai	21.25 (1.16) Ag

Means followed by different letters (capitals in the horizontal and lower case in the vertical) differ among them ( $p \leq 0.05$ ); p-value: meal: <0.0001; time: <0.0001; meal × time: <0.0001

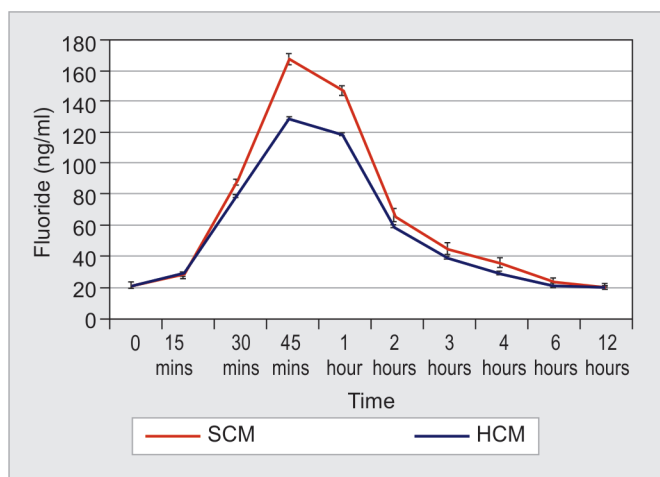
### Fluoride Concentration in Saliva and Maximum Time of Absorption

The fluoride concentrations in saliva were equal between the groups in the time intervals of 0 and 15 minutes, and from 6 hours (Table 2). From 30 minutes up to 4 hours after ingestion, group SCM presented a higher fluoride concentration in saliva that characterizes a higher level of ion absorption ( $p < 0.05$ ).

The fluoride concentration in saliva increased up to 45 minutes after ingesting the solution, and afterward, decreased in the two groups evaluated ( $p < 0.05$ ; Graph 1).

### Area under the Curve of Salivary Concentration

The area under the curve of salivary concentration was calculated for each volunteer, considering the initial instant up to the final time of observation (last quantifiable concentration). The difference noted between the areas under the curve ( $SCM = 28760.26 \pm 1089.87$ ;



**Graph 1:** Mean and standard deviation of the fluoride concentration in saliva considering the type of meal and time after ingesting the fluoride-containing solution

**Table 3:** Relationship between mean value of fluoride excreted by volunteers and percentage of fluoride ions ingested

Volunteer	SCM	Volunteer	HCM
	Fluoride excreted (mg) (%)		Fluoride excreted (mg) (%)
1	1.90 (6.17)	9	1.65 (5.36)
2	2.45 (7.96)	10	1.80 (5.85)
3	1.89 (6.14)	11	1.70 (5.52)
4	1.92 (6.24)	12	2.27 (7.38)
5	2.10 (6.82)	13	2.29 (7.44)
6	2.43 (7.90)	14	2.24 (7.28)
7	1.80 (5.85)	15	1.90 (6.17)
8	1.87 (6.08)	16	2.10 (6.82)
Mean SCM	2.04 (6.63)	Mean HCM	1.99 (6.47)

**Table 4:** Mean (standard deviation) of fluoride concentration in urine, before fluoride ingestion and at the end of the measurement time intervals

Time	Study group	
	SCM	HCM
Before ingestion	0.57 (0.21) Ab	0.89 (0.27) Ab
End of measurements	2.04 (0.26) Aa	1.99 (0.26) Aa

Means followed by different letters (capitals in the horizontal and lower case in the vertical) differ among them ( $p \leq 0.05$ ); p-value: meal: 0.2941; time: <0.0001; meal × time: <0.0001

HCM = 25814.88 ± 692.28 mg-minutes/mL) was significantly higher for SCM (Student's t-test:  $p < 0.001$ ), with test power of >0.80. The reduction in fluoride absorption considering the type of meal was of the order of 10.2%.

### Fluoride Concentration in Urine

Table 3 summarizes the results, for both groups, of the mean quantity of fluoride excreted in urine after the ingestion of the fluoride-containing solution and their percentages in relation to total fluoride ingested (30.75 mg).

In Table 4, it may be verified that the fluoride concentration in urine did not differ between the groups in both time intervals of collection ( $p > 0.05$ ) and that for both groups, the fluoride concentration in urine increased significantly in the final measurement ( $p < 0.05$ ).

In Table 5, please note that the pH in urine did not differ between the groups and times ( $p > 0.05$ ).

As regards the volunteers' perception of feeling ill, light discomfort was verified in five of the volunteers,

**Table 5:** Mean (standard deviation) of pH in volunteers' urine, before fluoride ingestion and at the end of the measurement time intervals

Time	Study group	
	SCM	HCM
Before ingestion	6.11 (0.54) Aa	6.67 (0.28) Aa
End of measurements	6.21 (0.76) Aa	6.76 (0.28) Aa

Means followed by different letters (capitals in the horizontal and lower case in the vertical) differ among them ( $p > 0.05$ ); p-value: meal: <0.0736; time: <0.2849; meal × time: 0.9715

with the mean value for group SCM being  $0.75 \pm 1.14$  points on the VAS scale (three volunteers related discomfort level 2) and group HCM presented a mean of  $0.5 \pm 0.95$  points on the VAS scale (two volunteers related discomfort level 2).

## DISCUSSION

The interference of the meal in the gastrointestinal absorption of fluoride ingested has been evaluated in controlled studies considering the ingestion of fluoride tablets, fluoridated toothpastes, and fluoride gel. As methodologies in these experiments, different situations of stomach contents were adopted and emphasized that the meal before fluoride ingestion reduced its absorption; however, the simulated meal situations were based on the adult meal pattern.<sup>2,12-16,28</sup>

The professional application of APF gel is routinely indicated for individuals at high risk, at both individual and collective levels.<sup>1,31,32</sup> After topical application, a considerable quantity of fluoride gel remains retained in the oral cavity and is later swallowed.<sup>20,21</sup> This quantity ingested may represent a high risk for children, because the total quantity of fluoride to which they are exposed, administered by a unit of body weight, is much higher when compared with the quantity ingested by adults.<sup>10,11</sup> The gastric contents are known to interfere in the absorption of fluoride; and a factor that must be taken into consideration on this subject is that meals consumed by children differ from those consumed by adults, particularly with reference to quantities, and frequently with reference to the diversity of the foods.<sup>1,18,19,33-35</sup> In the present study, the volunteers received two types of meals, taking into consideration the diversity in both foods and quantities that are consumed by children. The definition of quantities and items of menus was made considering the follow-up of diets in a nursery school after each component had been analyzed and weighed.

The present study was conducted in the sense of mimicking the quantity corresponding to the residual fluoride gel applied in trays, thereby guaranteeing that the dose used for ingestion by the volunteers was equal. In this study, we included healthy persons with a minimum weight that guaranteed the volunteers' complete safety, seeing that the dose ingested was ten times smaller than the PTD.<sup>24,25</sup>

The volunteers were under medical supervision during the study, and a questionnaire was applied every hour, using the VAS to follow-up on the presence of the volunteer eventually feeling ill, with slight discomfort being verified in five of the volunteers.<sup>26,27</sup> A similar symptom was related by the participants of the studies in which toothpastes and residual 1.23% acidulated fluoride gel were ingested.<sup>12,36,37</sup> None of the volunteers desisted

from the experiment or required medical assistance during the study.

In this study, fluoride absorption evaluated by saliva analysis allowed a noninvasive method of collection that presented sensitive results, since the pharmacokinetic curve of fluoride in saliva and plasma is very similar, presenting a proportion of 0.63:1.<sup>12,15,29,38</sup>

The type of meal did not influence the time of maximum salivary concentration of fluoride, verified 45 minutes after the meal in the two groups, which could be explained by the pharmacokinetic curve of fluoride, in which the process of absorption has a mean duration of 30 to 60 minutes.<sup>39,40</sup> A similar result was found in relation to the time of maximum plasma concentration, when they evaluated the interference of meals in the gastrointestinal absorption of fluoride ingested considering fluoridated toothpaste, reaffirming that the pharmacokinetic curve of fluoride in saliva and plasma is very similar.<sup>12,15,29,38</sup>

In a previous study, Cavalli et al<sup>16</sup> verified that the peak plasma absorption occurred 2 hours after the meal for both groups, a fact that may be related to the type and quantity of the meals served to the volunteers, which is contrary to the present study, and did not take into consideration the quantities ingested by children.<sup>4,41</sup> In children, acute poisoning may occur long before this, bearing in mind their mean body weight and other factors that interfere in absorption, such as the physical form and solubility of the compound administered.<sup>1,10,11</sup>

Although we evaluated meals that were similar in quantity and quality to those that children eat in real life, the volunteers were adults, for obvious ethical and safety reasons. This may be a limitation of the present study, since the data obtained may be overestimated considering that the ionic fluoride concentration in plasma increases with age, due to the increased resorption by the bone structure and reduction in the ability of the skeleton to remove it from the blood.<sup>42</sup> Nevertheless, the results were important because they allowed us to know the pharmacokinetic parameters in a more critical manner than the real situation.

In the period between 30 minutes and 4 hours, the fluoride concentration in the saliva of volunteers in group SCM was always higher than that verified in the volunteers in group HCM and so was the mean value of the area under the curve, as may also be observed in the literature considering the ingestion of toothpaste.<sup>15</sup> This is probably because fluoride absorption is related to the fullness of the stomach.<sup>7,40</sup> The velocity of fluoride absorption can be influenced by the following factors: the speed of stomach emptying, the fluoride compound, and whether ingestion occurred in a stomach empty.<sup>2</sup>

In 6 hours, the authors noted that, in both groups, the fluoride concentration returned to the basal values.

This demonstrated that fluoride followed its trajectory in the gastrointestinal tract, then crossed the cell membranes, and reached the bloodstream. The quantity of fluoride that was absorbed but not fixed by the mineralized tissues would be excreted almost exclusively in the urine, which is in agreement with the process of fluoride elimination that occurred from 6 to 24 hours after it was ingested.<sup>1,4,39</sup>

The quantity of fluoride excreted in the urine corresponds to that which was absorbed but not fixed by the mineralized tissues.<sup>28</sup> The percentage excreted in relation to that ingested and absorbed is a function of the individual's age, and as the participants were close in age to one another, the excretion verified was in agreement with this condition.<sup>2</sup> The process of elimination is strongly influenced by urine pH since alkaline urine favors excretion, and acid urine facilitates tubular resorption.<sup>4</sup> In the present study, urine pH did not differ significantly between the groups, a fact that was reflected by the fluoride concentrations in urine and was in agreement with the data found by Sakata and Cury<sup>12</sup> and Cury et al.<sup>15</sup> Moreover, the pH values obtained were within the accepted range of normality, which may vary from 4.5 to 8.0.<sup>43</sup>

The reduction in fluoride absorption considering the type of meal was to the order of 10.2% for the hearty meal, and a value almost two times lower than that verified in a previous study.<sup>16</sup> Therefore, children's diet, even a hearty meal, presented less influence on the rate of absorption than the value verified in previous studies, which places even greater value on the care taken to avoid ingestion.<sup>12-16</sup>

For group HCM, in none of the time intervals of analysis was the plasma concentration higher than that verified in group SCM, suggesting that the topical application of fluoride should be performed up to 45 minutes after a heartier meal, considering that the increase in concentration was related to gastric emptying. The present study strengthened the recommendation that when planning collective actions that involve the application of fluoride in children, the children's universe and school routine must always be taken into consideration so that this application may be performed in children who have eaten, preferably after a heartier meal, because this will guarantee the safety of the procedure, without, however, underestimating the need for placing value on expectoration after the application and providing clinical care to avoid ingestion.

## CONCLUSION

The authors concluded that the quality of the children's menu diversity influenced the absorption of fluoride so that the topical application of fluoride should be performed in infants fed, preferably, after the fuller diet and following the established guidelines to ensure the safety of the procedure.

## Clinical Significance

Knowledge of the influence of the composition and quantity of food on the children's menu on fluoride application after professional application is important so that the actions of fluoride therapy may be planned in a safer manner and be based on the reality of the universe of children.

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