

# Promoting the Oral Health of Children

2<sup>a</sup> edition

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## Use of Fluorides in the Control of Dental Caries

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### Introduction

Epidemiological data have clearly shown that caries levels have decreased substantially in the last 50 years. The decline has been mainly associated with the worldwide use of fluoridated toothpastes.<sup>1</sup> The discovery that fluoride in drinking water lowered rates of caries<sup>2</sup> was the basis for the first theories about the mechanisms of how fluoride acts. That in turn influenced the use of fluoride regimens implemented during the second half of the last century.

However, the belief that fluoride would act pre-eruptively increasing the mineral resistance of the teeth against acid attacks<sup>3</sup> was gradually replaced by evidence of its local post-eruptive action.<sup>4-6</sup> Nevertheless, although it is scientifically recognized that the post-eruptive effect of fluoride (local and nonsystemic effect) is the main factor responsible for the reduced rates of caries observed in modern societies,<sup>7,8</sup> the pre-eruptive paradigm is still present.<sup>9,10</sup> More than a simple matter of knowing the mechanism of action of fluoride, how it works orients how it is used to control caries. The dichotomization of the mode of fluoride use into "systemic" and "topical" shows that an understanding of how caries occurs as a disease (through the accumulation of dental plaque (or biofilm) and frequent exposure to sugars) and of how fluoride is able to reduce the speed of appearan-

ce of the clinical signs of this disease, the progression of carious lesions (by interfering with the de-/remineralization of the enamel, when available in the oral fluids),<sup>11</sup> has not yet been incorporated into clinical practice. Hence, for example, when children live in areas where the water is not fluoridated, medications containing fluoride ("nutritional supplements") are still recommended instead of other more rational forms of fluoride use, since the concept that caries can be prevented by fluoride intake (ingestion) is still prevalent, although it is widely acknowledged that the effect of fluoride on the factors responsible for the disease is marginal.<sup>12</sup>

Given that the main mechanism of action of all the methods or forms of fluoride is the same, namely, making fluoride available in the oral fluids, the classification in systemic and topical methods would be better replaced with one that takes into account the scope of fluoride use, such as: community means, for example fluoridated water; individual means, for example, fluoride toothpaste; professional means, for example, application of fluoride in gel, varnishes, or a combination of these.<sup>13,14</sup> Moreover, considering that dental caries results from frequent episodes of demineralization during each exposure of the dental biofilm to sugars,<sup>15</sup> the constant availability of increased fluoride concentrations in the oral fluids is desirable to control caries.<sup>11</sup>



On the other hand, the greater benefits of the availability of fluoride in the mouth has to be weighed up against the risk of developing fluorosis. That may occur by the greater possibility of systemic exposure to fluoride, whether involuntary such as with fluoridated water, or through the inadvertent ingestion of fluoride toothpaste by very young children. In this regard, only the level of fluoride that is ingested and absorbed in the gastrointestinal tract can potentially cause fluorosis when that occurs during the formation and calcification of the teeth. However, when considering the risk of fluorosis, the importance of the bioavailability of fluoride (the fraction of intake that is absorbed and circulates through the bloodstream), has been disguised by numerous studies, showing that children risk developing fluorosis if they ingest fluoride, in their diet and from toothpastes, at levels which are generally higher than the ingested fluoride dose that would provoke fluorosis of lower severity than those causing aesthetic concerns.<sup>16</sup> However, fluoride absorbed and circulating in the bloodstream<sup>17,18</sup> has not been taken into consideration,<sup>19,20</sup> increasing the concern over the use of fluoride by children, causing uncertainty and lack of confidence in the recommendations of use. Therefore, based on overestimated intake doses, recommendations regarding the use of fluoride toothpaste have been made in the absence of good scientific evidence.<sup>21,22</sup> In addition, longitudinal studies have not found any correlation between the dose of fluoride ingested by children during the formation of dental enamel and the degree of resulting fluorosis.<sup>23,24</sup> Accordingly, there is a need to balance the benefits and risks of fluoride use.<sup>7,8</sup> Therefore, considering that all the fluoride maintained constantly in the oral cavity is able to control caries by its local effect,<sup>11</sup> but if ingested

and absorbed daily, the systemic effect can provoke a certain degree of fluorosis in the enamel during the mineralization phase,<sup>25</sup> the choice of the best method(s) of fluoride use to control caries must be based on the best scientific evidence available regarding the balance between benefits and risks of the intervention.

The main focus of this chapter is therefore to present the most recent scientific evidence available on the effectiveness and safety of fluoride use to control dental caries. That is based on the research methods used in pursuit of the best evidence.

## Scientific basis for assessing the effects of fluoride

Many studies have attempted to address the uncertainties regarding the effects of the various forms of fluoride-based interventions. This may not come as a surprise, since fluorides has been the subject of basic and clinical research for much more than half a century. A simple and rapid search in PubMed (the free US National Library of Medicine (NLM) electronic database accessing primarily the MEDLINE database of citations on life sciences and biomedical topics), employing the search terms "fluoride" or "fluoride and caries" can be used to indicate the considerable quantity of any kind of research published on the topic in the last six decades. Such a search resulted in 43171 hits for "fluoride" and 8372 hits for "fluoride and caries". These separate search results for the terms "fluoride" and "fluoride and caries" draw attention to the fact that not all studies on the subject are related exclusively to caries, although there have probably been more reports published about the caries-inhibitory properties of fluoride than on any other subject in dentistry. Furthermore,



The proviso is that all research must be of high quality. The quality of a study is defined as the confidence that its design, conduct and analysis have minimized or avoided bias. The quality or internal validity does not depend on the study design alone, which mostly depends on the question that the study aims to answer; its clinical and epidemiological focus, but also on the way the study was carried out and reported. With this regard, it is important to note that Cochrane reviews, systematic reviews of health care interventions that employ rigorous research methods, have been shown to be of

higher methodological quality than other systematic reviews.<sup>30-33</sup> These reviews concentrate mainly, but not exclusively, on synthesizing the evidence from randomized studies, and are published in full in the Cochrane Library (<http://www.thecochranelibrary.com>) following an editorial process that is common to all the reviews of the Cochrane Collaboration (<http://www.cochrane.org/>), an international nonprofit organization created in the early 1990s to guarantee that up-to-date information about the effects of health care interventions is readily available all over the world.

**Table 10.1** – Levels of evidence of scientific research on the effectiveness of health interventions.<sup>42</sup>

Type	Strength of evidence
I	Strong evidence generated by at least one systematic review of multiple well-designed RCTs
II	Strong evidence generated by at least one well-designed RCT of appropriate size
III	Evidence generated by nonrandomized experimental studies, or observational studies (cohort, multiple time series or case-control studies)
IV	Evidence generated by well-designed non-experimental studies from more than one centre or research group
V	Evidence generated by reports of expert committees based on the sources of evidence cited, descriptive studies (cross-sectional, ecological and case series studies) or opinions of respected authorities based on clinical evidence

### Main characteristics of the available evidence on the effects of fluorides on caries control

A variety of study designs have been used to assess the effectiveness of fluorides in controlling caries. While several interventions using fluoride applied topically have been submitted to intensive clinical tests in randomized controlled trials, less conclusive study designs have been used to assess the effectiveness of water fluoridation. Although the aspects that characterize the design and the conduct of studies that

assess the effects of therapy with fluoride applied topically are very different from those that assess the effects of water fluoridation, both study types have been traditionally summarized in a similar manner: namely, in narrative literature reviews.

However, traditional narrative methods to compile the evidence available on a topic tend to ignore the levels of evidence and the variable quality of studies, and are therefore unlikely to present an objective view of the evidence. Moreover, such reviews frequently produce very different estimates of effectiveness due



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to differences in the way the literature to be included was selected, often ignore the uncertainty involved in the estimates of effect, and rarely formally explore the causes of variability in the reported effectiveness. Nevertheless, a large number of these reviews have highlighted important aspects relevant to the evaluation of the effectiveness of fluoride in caries prevention, which were formally taken into account in the systematic reviews/meta-analyses carried out on the topic throughout recent decades<sup>34-58</sup>. Furthermore, the recommendations systematically developed for the appropriate use of fluorides in caries prevention in different contexts and countries are increasingly being made in clinical practice guidelines. Such guidelines are largely based on results of systematic reviews published in the last decade. This is especially noted in relation to the series of Cochrane reviews on the effects of topically-applied fluorides in dentifrices, mouth rinses, gels and varnishes<sup>42-48,57,58</sup> and the systematic review on water fluoridation commissioned by the Centre for Reviews and Dissemination of the National Health Service (NHS CRD) in the United Kingdom, at the University of York.<sup>38</sup>

Considered the most comprehensive and detailed evidence to date, these systematic reviews consistently gather and summarize the large body of knowledge available about the effects of the main modalities of fluorides used nowadays for the prevention of dental caries, and systematically examine the main factors that can influence their effectiveness. In addition, since the York review on the effects of water fluoridation was published,<sup>38</sup> there has been no other high quality systematic review that could change the conclusions of that review, which has been chosen to form the basis of scientific evidence on the

effects of water fluoridation in subsequent overviews on the topic, like in the review produced by the National Health and Medical Research Council in Australia.<sup>59</sup>

Therefore, the evidence originating from the abovementioned York review on the effects of water fluoridation and Cochrane reviews on the effects of fluorides applied topically – in fluoride dentifrices, mouthwashes, gels and varnishes – will be highlighted in the following section. The evidence of the effects of fluoridated milk and of slow-release fluoride devices will be only briefly discussed based on the results of the Cochrane reviews identified on these topics. However, the evidence originating from Cochrane reviews in progress on other fluoride-based interventions, such as on salt fluoridation and on tablets/supplements, is not addressed here, since these are Cochrane reviews under development, and not yet complete when the search was conducted in July 2011.

### **Evidence from systematic reviews on the effectiveness of fluoride-based interventions in the control of dental caries**

The best scientific evidence available on the effects of fluoride in the control of caries was located and selected as reported below:

Relevant Cochrane reviews were sought in the Cochrane Database of Systematic Reviews (CDSR), Edition 7, 2011, of the Cochrane Library, using the terms "Fluoride" and "Caries". All the electronically identified records were scrutinized by title, and all the complete reviews evaluating mainly the effectiveness of a fluoride-based intervention

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in the prevention of caries in children were selected. Reports of Cochrane reviews in progress in protocol form were not considered. A specific supplementary search to identify the York review on the effects of water fluoridation, using the terms "Fluoridation" and "Caries", was conducted in the Health Technology Assessment (HTA) database, Edition 7, 2011, of the Cochrane Library.

The search in the CDSR yielded 19 reports on Cochrane systematic reviews of controlled trials, produced under the auspices of the Cochrane Oral Health Group (COHG). Four of these reports are outside the scope of this chapter (ozone therapy for caries

treatment, chlorhexidine for caries prevention, sealants of pits and fissures vs. fluoride varnish for caries, fluorides for the prevention of white stains in orthodontic patients), and 4 others are reports of relevant reviews still under development in the form of protocols (salt fluoridation to prevent caries, fluoride supplements for caries prevention, fluoride solutions for caries control, and topical fluoride for caries treatments), and for this reason are not covered here. Eleven complete Cochrane systematic reviews on the effects of fluorides in caries prevention were identified and are evaluated below (Table 10.2).

**Table 10.2** – Completed Cochrane reviews on fluorides in the CDSR in July 2011 (Cochrane Library, Edition 7, 2011).

<b>Reviews on fluoride dentifrices, mouthwashes, gels and varnishes</b>	
Citation	Title
Marinho et al. <sup>42</sup>	(1 <sup>st</sup> ) Fluoride gels for preventing dental caries in children and adolescents
Marinho et al. <sup>43</sup>	(2 <sup>nd</sup> ) Fluoride varnishes for preventing dental caries in children and adolescents
Marinho et al. <sup>44</sup>	(3 <sup>rd</sup> ) Fluoride dentifrices for preventing dental caries in children and adolescents
Marinho et al. <sup>45</sup>	(4 <sup>th</sup> ) Fluoride mouthwashes for preventing dental caries in children and adolescents
Marinho et al. <sup>46</sup>	(5 <sup>th</sup> ) Fluorides applied topically (dentifrices, mouthwashes, gels and varnishes) for preventing dental caries in children and adolescents
Marinho et al. <sup>47</sup>	(6 <sup>th</sup> ) One topical fluoride (dentifrices, mouthwashes, gels or varnishes) compared to another to prevent dental caries in children and adolescents
Marinho et al. <sup>48</sup>	(7 <sup>th</sup> ) Combinations of fluorides (dentifrices + mouthwashes, gels, or varnishes) compared to a single fluoride (dentifrice) to prevent dental caries in children and adolescents
Walsh et al. <sup>57</sup>	(8 <sup>th</sup> ) Dentifrices with different concentrations of fluoride to prevent dental caries in children and adolescents
Wong et al. <sup>58</sup>	(9 <sup>th</sup> ) Topically applied fluoride as a cause of dental fluorosis in children

**1. Other fluoride reviews**

2. Yeung et al. 2005      Fluoridated milk for preventing dental caries
3. Bonner et al. 2006      Slow-release fluoride devices for the control of dental caries



The search in the HTA produced two reports, of which only the York review on the fluoridation of public water supplies<sup>38</sup> is considered relevant. As mentioned previously, since this was published in October 2000 there has been no other scientifically defensible systematic review capable of changing the results of the York review, hence the continuous recognition of its importance as the main source of evidence for the effects of water fluoridation on caries prevention.<sup>59,60</sup>

A description of the main aspects of the evidence originating from these systematic reviews is presented below in a structured format, to facilitate the understanding and application of the results of the research in practice. The main characteristics of the York review, its results and conclusions are presented first of all. This is followed by a general description of the main methodological features of the Cochrane reviews and a qualitative compilation (summary) of the results of the reviews. This is done mainly in terms of the preventive effectiveness of the various topically-applied fluoride modalities evaluated, and where reported, according to the factors that influence the effectiveness of these interventions, their comparative effectiveness, and that of the combined use of the interventions, as well as in terms of the safety (and acceptability) of these interventions, in an attempt to take into account any assessment of their benefits and undesirable (adverse) effects.

## **Water Fluoridation**

### ***The compiled/reviewed evidence***

The NHS CRD review covering all the available evidence on the effectiveness and safety of water fluoridation

was published in 2000.<sup>38</sup> The complete report is available on the CRD website (<http://www.york.ac.uk/inst/crd/fluorid.htm>).

### ***The objectives of the York review***

- Which are the effects of fluoridation of drinking water on the incidence of caries?
- If water fluoridation is shown to have positive effects, what is the effect over and above that offered by the use of alternative interventions and strategies?
- Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?
- Does water fluoridation have negative effects?
- Are there any differences in the effects of natural and artificial water fluoridation?

### ***Inclusion criteria, search strategy, data collection and analysis***

The review specifically analysed the effects of fluoridation of drinking water on dental caries, social inequalities and any harmful effects in the populations that receive fluoridated water. Studies included were classified at levels/hierarchy of evidence (A-C) based on the study design and on adjustment for confounding factors and measurement bias factors. Evidence classified below a moderate level of quality/moderate risk of bias (level B, equivalent to type III in table 10.1) was not considered in the effectiveness assessment. In the safety assessment, all the levels of evidence were considered.

Searches were undertaken in 25 electronic databases, in bibliographies of the studies included, and in other



online resources. Published and unpublished studies in any language were sought. Inclusion decisions, quality assessment and data extraction were duplicated by two reviewers and consensus was obtained by discussion or by a third reviewer.

Where the data were in an adequate format, measures of effect and 95% confidence intervals (CI) were plotted. Random effects meta-analysis were carried out where the data could be pooled. Potential sources of heterogeneity were examined in random effects meta-regression analyses (effects of baseline levels of caries, of age, study duration, validity scores and others). Multilevel regression analysis was used to combine studies and to investigate the association of fluoride concentration in water with the prevalence of fluorosis.

### **Main results of the review**

A total of 214 studies were included, with none at level of evidence A (high

quality, bias unlikely); In other words, there were no randomized trials of water fluoridation.

The study designs included 102 cross-sectional studies, 47 ecological studies, 45 controlled before-and-after studies, 13 cohort studies, and seven case-control studies. Table 10.3 shows the main characteristics and results of the York review.

**Effectiveness of water fluoridation in caries prevention:** The best evidence available (level B, moderate quality - 23 controlled before-and-after studies and three cohort studies) from studies on the initiation and discontinuation of water fluoridation suggests that fluoridation effectively reduces the prevalence of caries, both when measured by the proportion of caries-free children and by the mean dmft/DMFT score. The degree of caries reduction, however, is not clear from the available data: The range (median) of the mean difference in the proportion of children without caries

**Table 10.3** – Summary of the characteristics of the York Review on the Fluoridation of Public Water Supplies.

Study	Focus	Inclusion criteria	Data gathering/Analysis	Main results/Conclusions
Mc-Donagh et al. <sup>38</sup>	Evaluation of the positive and negative effects of fluoridation of public water supplies to prevent caries	Assessment of efficacy (positive effects - dental caries - studies with level of evidence A and B): Prospective studies comparing at least 2 populations, (F/NF), with at least 2 points in time evaluated. Assessment of safety (adverse effects, including fluorosis) and of social inequalities (SES) - studies with level of evidence A, B or C): Any study design comparing 2 populations (F/NF)	25 electronic databases, other online resources and references (2000) were used to locate published and unpublished studies. Inclusion decisions, quality assessment and extraction of data was duplicated by two reviewers, and consensus obtained by discussion/a third party. Meta-analyses of random effects were carried out in order to group the data, and potential sources of heterogeneity were examined in a meta-regression analysis.	The best evidence available suggests that: Water fluoridation reduces the prevalence of caries. Water fluoridation increases the prevalence of dental fluorosis. There is no conclusive evidence in relation to other adverse effects (the quality of this evidence was methodologically weak). The evidence on the reduction of inequalities in dental health is not clear (also of poor quality). The prevalence of caries increases with the suspension of water fluoridation.



was from -5.0% to 64% (14.6%), the range (median) of mean change in decayed, missing and filled primary/permanent teeth (dft/DMFT) was from 0.5 to 4.4 (2.25) teeth. There was significant heterogeneity among the studies included. Meta-regression showed that the proportion of children without caries at the beginning of the study, the setting (place), and the validity score show a significant association with the difference in risk in the proportion of children without caries. Baseline Decayed, missing and filled primary/permanent teeth (dmi/DMFT), age, setting (place) and study duration show a significant association with the mean difference in DMFT/ dmt.

**Effect of the suspension (termination) of water fluoridation on caries levels:** Based on 22 analyses (level B, moderate quality), the authors concluded that the prevalence of caries increases after the withdrawal of water fluoridation.

**Effect on caries beyond that offered by the use of alternative fluoride-based interventions:** An effect of water fluoridation was still evident in studies concluded after 1974 in spite of the assumed exposure to fluoride originating from other sources by the populations studied. However, the small number of studies in this analysis and the poor quality of the studies limited the confidence with which this question could be answered. Moreover, using the study publication date may not have been a sufficiently sensitive factor to identify any change/effect.

**Social class effects:** The available evidence on social class effects of water fluoridation in reducing caries appears to suggest a benefit in the reduction of the differences in severity of dental caries (measured by dmt/DMFT) between social classes among

five and 12 year-old children, but no effect on the overall measurement of the proportion of caries-free children was detected. The quality of the evidence is low (level C), and is based on a relatively small number of studies.<sup>15</sup> Therefore the association between water fluoridation, caries and social class still needs clarifying.

**Negative effects of water fluoridation:** These were examined in as comprehensive a manner as possible and the effects on dental fluorosis are the clearest.

There is a dose-response relationship between the level of fluoride in the water and the prevalence of fluorosis (shown in the meta-regression analysis). Fluorosis appears to occur frequently at levels of fluoride typically used in artificial fluoridation schemes (1 ppm F), but the proportion of fluorosis that is aesthetically concerning is lower at these levels: the pooled estimate of the prevalence of fluorosis at a fluoride concentration in water of 1.0 ppm was 48% (95% CI: 40% to 57%) and for fluorosis of aesthetic concern (defined as TF  $\geq$  3, or mild or higher Dean index, or TSIF  $\geq$  2) it was 12.5% (95% CI: 7% to 21.5%). The estimated proportion of the population with any fluorosis at different levels of fluoride in the water ranged from 15% (95% CI: 10% to 22%) at a level of 0.1 ppm F to 72% (95% CI: 62% to 80%) at a level of 4 ppm F. There was, however, considerable heterogeneity between the results of the individual studies. Although 88 fluorosis studies were included, these were of low quality (level C – the majority of the studies were cross-sectional, while only four were controlled before-and-after studies). Additionally, the efforts to reduce observer bias or to control potential confounding factors were not common in the studies included.

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The best scientific evidence available on the association of water fluoridation and bone fractures or cancer does not show defined patterns of association.

The various other adverse effects studied did not present enough good quality evidence on any outcome in particular to reach clear conclusions. The outcomes related to infant mortality, congenital defects and IQ indicate the need for further higher quality investigations, using adequate analytical methods to control for confounding factors. While fluorosis can occur within a few years of fluoride exposure during tooth development, other potential adverse effects may require long-term exposure to occur, and this long-term exposure may not have been captured by these studies.

**Differences between the effects of natural and artificial water fluoridation:** No considerable differences were apparent in this review, where direct comparisons were not possible for most of the outcomes. The available evidence is extremely limited, and was not sufficient to reach a conclusion about this aspect.

### ***Reviewer's (Author's) Conclusions***

The review presents a summary of the best and most reliable evidence available on the safety and effectiveness of water fluoridation. The quality of the data on benefits and harms ranges, however, from moderate to low. The evidence of benefit in the reduction of caries should be considered together with the increase in the prevalence of dental fluorosis. The research evidence is of insufficient quality to allow reliable statements about other potential harms, or regarding a possible impact on social inequalities. Any future research on the

safety and effectiveness of water fluoridation should be conducted with appropriate methodology.

### **Fluoride toothpastes, mouthwashes (rinses), gels, varnishes**

#### ***The compiled/reviewed evidence***

The relevant Cochrane reviews on the effects of the main modalities of self-applied and professionally-applied fluorides, used separately or in conjunction (with one another), were published from 2003 to 2010<sup>42-48,57,58</sup> and are available in the Cochrane Database of Systematic Reviews CDSR in the Cochrane Library (<http://www.thecochranelibrary.com>). Cochrane reviews are updated when new evidence appears and in response to comments, and the Cochrane Library should always be consulted for the latest version of these reviews.

#### ***Objectives of the Cochrane Reviews***

The main issues that were considered in the Cochrane reviews on the effects of the main types/therapies of topical application of fluoride include:

- the potential benefits that can be expected of fluoride therapies in the form of toothpastes, mouthwashes, gels and varnishes, especially in terms of the overall reduction of caries increment;
- how the benefits of these fluoride treatments may vary according to the influence of potentially important effect-modifiers, including the initial level of caries severity, background exposure to other fluoride sources, frequency of application, and more specifically, the fluoride concentration (which has been the focus of a more recent review from the Co-



tiveness of dentifrices with different fluoride concentrations);

- whether the benefits differ among these fluoride treatments when these are used alone or when used in conjunction;
- the potential adverse effects, especially dental fluorosis, which are, however, rarely investigated or reported in conjunction with the estimates of effectiveness in experimental studies (hence the production of another recent review on the relationship between the use of fluoride applied topically, particularly in toothpaste, and the risk of developing dental fluorosis, which considers the evidence of experimental and observational studies in young children).

4 treatments; the seventh review also involved direct comparisons between these 4 treatments, but when these were used in combination compared with the use of just one of them (mainly use of fluoride applied topically in combination with fluoride dentifrice versus fluoride dentifrice only). The most recent reviews, eighth and ninth, evaluated the relative effectiveness of fluoride dentifrices of different concentrations (in which a network meta-analysis was employed, using both the direct and indirect comparisons from the RCTs included), and the association between the use of fluoride applied topically in young children and the risk of developing fluorosis (in which the evidence from nonrandomized studies was considered as well).

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### **Overview of the methodology (inclusion criteria, search strategy, data collection and analysis)**

The Cochrane topical fluoride reviews are based on thorough and unprecedented searches of published or unpublished evidence, in the form of randomized clinical trials (RCTs) mainly. These reviews identified and assessed the studies included, using similar methodology and measures of effect for caries. The first four reviews individually investigated the effectiveness of fluoride gel, varnish, mouthwashes and dentifrices in studies using placebo or no treatment control groups, and examined the factors that potentially influence effectiveness (caries reductions). The fifth review was a summary of the first 4, with additional investigations of differences of effectiveness between interventions, based on meta-regression analyses, using the treatments as covariables. The sixth review

### ***Overview of the main results and conclusions .***

The main results and conclusions from the Cochrane topical fluoride reviews are summarized below.

#### ***Effect on caries increment in the surfaces of permanent and primary teeth – comparisons with placebo/untreated groups***

The evidence on the beneficial effects of fluoride toothpaste, mouthwash, gel and fluoride varnish is consistent and strong. Research involving more than 65,000 children and adolescents in more than 130 RCTs shows a clear reduction in the increase of caries in both the permanent dentition (for all the forms of topical application of fluoride examined) and the primary dentition (for fluoride gels and varnishes) (Table 10.4).



**Table 10.4** – Pooled D(M)FS/d(ef)s estimates of the effects of topical treatment with fluorides, measured as preventive fractions (PF).

Type of Fluoride (**)	Preventive fraction	CI 95%	Type of Fluoride (***)	Preventive fraction	CI 95%
<b>Permanent dentition</b>					
Varnish (7)	46%	30–63%	Varnish (3)	40%	09–72%
Gel (23)	28%	19–37%	Gel (13)	21%	14–28%
Mouthwash (34)	26%	23–30%	Mouthwash (30)	26%	22–29%
Dentifrice (70)*	24%	21–28%	Dentifrice (70)	24%	21–28%
All 4 interventions (133)	26%	24–29%	All 4 interventions (116)	24%	22–27%
<b>Primary dentition</b>					
Varnish (3)	33% PF	19–48%	Varnish (1)	20% PF	2–38%
Gel (2)*	26% PF	–11–63%	Gel (2)	26% PF	–11–63%
Varnish and gel (5)	33% PF	22–44%	Varnish and gel (3)	27% PF	8–48%

CI = Confidence interval; \* Comparisons w/Placebo only; \*\* number of placebo/no treatment comparisons; \*\*\* number of placebo comparisons.

### *Effect of factors that influence the effectiveness of topical application of fluoride in preventing caries*

The Cochrane reviews show that topical application of fluoride (compared to placebo/no treatment) can reduce dental caries, regardless of the exposure to water fluoridation. It is also shown that supervising a child in the use of self-applied fluoride (in toothpaste or mouthwash) leads to greater benefits. A significant influence of the initial level of caries, and of the frequency and intensity of fluoride application, was also indicated in the reviews. In particular, the caries-preventive effect fluoride toothpaste can increase with higher initial levels of caries in the population and when a higher concentration of fluoride is used in the dentifrice formulation, even though the benefit is only significant for fluoride concentrations above 1000 ppm F. The effect of fluoride concentration is shown in the results of the Cochrane review on the relative effectiveness of fluoride dentifrices of different concentrations (Table 10.5).

### *Comparative effect on caries increment among the various topically-applied fluoride modalities*

The Cochrane reviews indicate that fluoride toothpaste can protect the teeth against dental caries as much as fluoride mouthwashes or fluoride gels (important comparisons of dentifrices with fluoride varnishes were lacking); the pooled preventive fraction for decayed, missing and filled permanent surfaces, for nine RCTs combined was 1% (95 % CI -13% to 14%). Taking into account these results together with those of a detailed investigation conducted subsequently based on the same data from the Cochrane reviews, on the relative effectiveness of the four main topical fluoride modalities (varnish, gel, mouthwash solution, and dentifrice), in which a simultaneous analysis of direct and indirect comparisons was employed (multiple-treatments or network meta-analysis), no clear evidence was found that any one of the topically-applied fluoride intervention is more effective than another (Salanti et al., 2009).



**Table 10.5** – Pooled D(M)FS/d(ef)s estimates of the effects fluoride dentifrices used in different concentrations, measured as preventive fractions (PF) – comparisons with placebo only.

Fluoride concentrations, in ppm F	Direct comparison meta-analysis (Confidence interval of 95%)	Network meta-analysis (Credibility interval of 95%)
Placebo vs. fluoride dentifrices	Preventive fraction	Preventive fraction
250	8,90 [-1,62, 19,42]	9,14 [-3,62, 21,96]
440/500/550	7,91 [-6,11, 21,94]	15,35 [-1,89, 32,53]
1000/1055/1100/1250	22,20 [18,68, 25,72]	22,99 [19,34, 26,58]
1450/1500	22,07 [15,26, 28,88]	29,29 [21,24, 37,46]
1700/2000/2200		33,7 [16,52, 50,77]
2400/2500/2800	36,55 [17,46, 55,64]	35,52 [27,23, 43,62]

### ***Comparative effect on other outcomes***

Other outcomes such as acceptability were assessed indirectly in the Cochrane topical fluoride reviews. The acceptability of the various interventions differed. The Cochrane reviews showed that children are more likely to persist with the use of toothpaste than with the use of any other topical fluoride application.

### ***Comparative effect on caries increment between the combined and single fluoride intervention use - direct comparisons***

Combining two methods of fluoride treatment, such as fluoride toothpaste with another topically-applied fluoride intervention, produced an additional caries reduction of 10% (95% CI: 2% to 17%) compared to the use of fluoride dentifrice alone. That cannot be considered substantial.

### ***Adverse effects of topically-applied fluoride treatments***

The evidence from the relevant Cochrane review on the risk of fluorosis in small children from topical application of fluoride focused mainly on fluoride toothpaste and on the outcome of mild fluorosis. Based mainly on the results of observational studies, there is weak evidence that the use of fluoride toothpaste commenced in children aged under 12 months may be associated with an increased risk of fluorosis. The evidence of an increase in the risk of fluorosis associated with fluoride toothpaste use in the age range between 12 and 24 months is equivocal. Moreover, the use of higher fluoride concentrations in toothpastes of >1000 ppm of F, when evaluated in randomized clinical trials (2 RCTs), was associated with an increase in fluorosis in young children.



## Final observations

It can be concluded that the benefit of regular brushing with fluoride dentifrice is firmly established, but there may be continuous scientific controversy concerning the effects of water fluoridation, especially potential adverse effects until better studies are conducted and produce more definitive evidence.

The Cochrane reviews of therapies with fluoride of topical use are being updated, and as the evidence arising from new RCTs is gradually incorporated into existing reviews, the precision of the estimated effects should increase, although no further change is expected in the conclusions. This is the case for fluoride varnishes, with at least seven new additional controlled trials on the effect of fluoride varnishes on the primary teeth being included in the updated review,<sup>61-67</sup> as well as three RCTs assessing the effect of varnishes on permanent teeth.<sup>68-70</sup>

The appropriate use of fluoride has always required an evaluation of its relative risks and benefits. A informed knowledge of the mechanism of action of fluoride and of the rationale and methods used in the evaluation of health care interventions was provided as a basis to understand and to present the scientific evidence available on the effects of the various types of fluoride use in the control of caries. A range of study designs have been used in recent decades to evaluate the various interventions. While the main topically-applied fluoride treatments have been tested intensively in randomized controlled trials, research conducted on the effects of water fluoridation was of inferior methodological quality.

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