

# High Fluoride Concentration Toothpastes for Children and Adolescents

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## Key Words

Adolescents · Caries · Children · Effectiveness · High fluoride dentifrices

## Abstract

The purpose of this review is to present the available evidence to support the use of dentifrices with high (>1,500 ppm) concentrations of fluoride to help in the prevention and treatment of caries in high-risk children and adolescents. Recent evidence from high-quality systematic reviews supports the dose-response relationship between caries prevention and fluoride levels, and there is good evidence from randomised clinical trials to support the use of high fluoride dentifrices. Such products are typically prescribed oral pharmaceuticals that require thorough risk assessment by the clinician and restricting use in those less than 6 years old to cases where the risk of severe morbidity caused by caries is greater than that of aesthetically objectionable fluorosis and which should mitigate the risk of fluorosis. Further research is required on the use of population- or community-based interventions using such products and currently, the evidence for dentifrices containing more than 2,900 ppm is weaker than for those containing 2,800 ppm or less.

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It is now accepted that caries is a dynamic process of de- and re-mineralisation and, when the balance of factors favours de-mineralisation, then caries will progress [Pretty and Ellwood, 2013]. There are opportunities during the progression of the carious lesion to arrest and reverse the process, although these are largely limited to the non-cavitated stages [Featherstone, 2004]. The use of systems to detect early carious lesions, and hence those suitable for preventive rather than surgical intervention, have been adopted in light of this [Gomez et al., 2013].

Since the late 1960s, following the introduction of widespread use of fluoridated dentifrices, there has been a substantial decrease in caries within Western populations [Kassebaum et al., 2015]. The biological presentation of caries has changed during this time, with the majority of new lesions occurring on occlusal rather than smooth surfaces [Biesbrock et al., 2001]. This biological change has been accompanied by an epidemiological shift from a ubiquitous disease to one that is increasingly restricted to sub-population groups, especially those in lower social economic groups and those with special needs [McGrady et al., 2012]. This ‘ghettoisation’ of caries is of concern to those with public health responsibilities as such groups are often hard to reach, have a low utilisation of dental services and face a range of other

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**Table 1.** Determinants of high caries risk in children and adolescents [Davies and Davies, 2008]

Factor	Feature
Diet	Characterized by high sugar intake
Current disease	Previous caries or high DT/DS
Saliva	Low flow
Appliances	Orthodontic fixed appliances
Dental attendance patterns	Infrequent, symptomatic attendance
Restorations	Evidence of previous disease
Socio-economic Family	Deprived communities Family and sibling history of caries and poor attendance
Medications	Sugared medications

DT/DS = Decayed teeth/decayed surfaces.

health care issues of concern [Schwendicke et al., 2015]. Table 1 provides some of the characteristics of these groups.

Children with caries also face considerable morbidity as a result of the disease, with many having extractions under general anaesthetic [Goodwin et al., 2015a]. Recent research has revealed that these children suffer from continued pain, sleepless nights and missed school. Such comorbidities further exacerbate the consequences of what is a preventable disease [Goodwin et al., 2015b]. In the UK, the most common reason for children to be admitted to hospital continues to be multiple tooth extraction under general anaesthetic [Goodwin et al., 2015a].

There is, therefore, a need to consider means by which caries in these groups can be addressed. While community-based water fluoridation is often advocated for such groups in many jurisdictions, this is not possible for logistical or political reasons. Therefore, in the absence of water fluoridation, do toothpastes with higher concentrations of fluoride than those traditionally accessed by consumers (1,000 through 1,450 ppm fluoride) offer additional therapeutic benefits for those children and adolescents at high risk of caries?

### The Fluoride Dose Response

There is a well-established dose-response relationship between the concentration of fluoride present in dentifrices and caries prevention [Moller et al., 1968; Reed, 1973; Tavss et al., 2003] and the evidence to support the use of fluoridated toothpastes is described by Cochrane

as unequivocal [Wong et al., 2011]. A recent Cochrane review examined the use of fluoride toothpastes containing up to 2,800 ppm and described a dose-response effect to this level but stated that this was not always statistically significant between individual concentrations. The review found that the highest probability of caries preventive benefits was found in those toothpastes containing greater fluoride concentrations [Walsh et al., 2010]. In previous comparisons with placebos, low concentrations (400–550 ppm) demonstrated no significant benefit (and hence should not be recommended for use), with those with ‘standard’ levels of fluoride having a median preventive fraction of 25% and those with the highest levels of fluoride (2,800 ppm) a preventive fraction of 45%. These findings were mirrored in an earlier review by Amari et al. [2003] that considered differences between pastes with as low as 250 up to 1,055 ppm.

The Cochrane systematic review provides high-quality evidence based on 79 trials and 73,000 children that higher concentrations of fluoride confer additional benefit in the form of caries prevention [Walsh et al., 2010]. Given the extent of this review, and its recent publication, it is not appropriate to re-review the topic here. It is worth noting, however, that the majority of the contributing studies were examining the comparison of lower fluoride concentration pastes with standard products.

Consequently, it is worthwhile to consider some of the detail of the contributing studies (those with interventions over 1,500 ppm), as well as to consider the evidence for dentifrices with fluoride concentrations in excess of 2,800 ppm (typically 5,000 ppm) that were not considered within the review.

A search was therefore conducted in the PubMed, Web of Science and Ovid MEDLINE databases using a modified version of the search criteria employed within the Cochrane systematic review [Walsh et al., 2010]. Modifications to fluoride level and study design were employed in order to obtain the widest possible literature base. The following studies, divided into fluoride levels, are described below.

### From 1,600 to 2,800 ppm

Marks et al. [1992] reported a study examining the use of products containing 2,000 and 2,500 ppm fluoride compared with levels of 1,000 and 1,500 ppm. The study demonstrated that the DMFS increment in those subjects receiving the standard products was 4.23. This dropped to 4.08 and 3.77 with increasing concentrations. This

**Table 2.** Summary of traditional caries studies examining dentifrices containing >2,400 ppm [Davies and Davies, 2008]

Study	Duration, years	Age at baseline, years	Fluoride species (concentration, ppm)	Increment	Difference, %	Significance
Lu et al. [1985]	3	7–15	NaF (1,100) NaF (2,800)	4.40 3.88	12	significant
Alexander and Ripa [2000]	3	10–13	NaF/MFP (1,000) NaF/MFP (2,500)	3.63 3.67		n.s.
Stephen et al. [1994]	3	11–14	MFP (1,000) MFP (1,500) MFP (2,500)	6.83 6.27 5.56	8 18	significant
Marks et al. [1992]	3	6–14	MFP (1,000) MFP (2,500)	4.23 3.77	11	significant
Chesters et al. [2002]	2	11–14	MFP (1,000) MFP (2,500)	5.47 4.96	9	significant
Stookey et al. [2004] (examiner A)	2	9–12	NaF (1,100) NaF (2,800)	6.27 5.45	13	significant
Stookey et al. [2004] (examiner B)	2	9–12	NaF (1,100) NaF (2,800)	4.95 3.80	23	significant

n.s. = Non-significant; NaF = sodium fluoride; MFP = sodium monofluorophosphate.

study reports the clear directionality of the fluoride preventive effect – although, like the Cochrane review, statistical significance is not always observed between successive fluoride levels within clinical studies.

Biesbrock et al. [2001] presented data from a trial conducted in the 1980s. Children aged 6–15 years ( $n = 5,439$ ) were randomised into groups receiving dentifrices containing 1,100, 1,700, 2,200 and 2,800 ppm F. While the study ran for 3 years, data from the second and third year were confounded by a concurrent fluoride rinse programme. Results indicated that, after year 1, the 2,200 ppm (18.6%) and 2,800 ppm (20.4%) were statistically superior to 1,100 ppm (control) when reductions in DMFS were considered. These results were similar to those found in studies by Lu et al. [1985] (2,800 ppm delivering statistically superior results to 1,100 ppm over 3 years) and Stephen et al. [1994] (2,500 ppm delivering a statistically significant reduction in DMFS of 16–20% when compared with 1,000 ppm control).

A meta-analysis of 6 randomised clinical trials, examining fluoride concentrations of 1,700, 2,200 and 2,800 ppm, found that the use of a paste containing 2,800 ppm resulted in ‘statistically significant lower caries increment than the use of a dentifrice with 1,100 ppm. This result

was noted after one, two, and three years of dentifrice use’ [Bartizek et al., 2001]. The other concentrations demonstrated directional advantages over the 1,100 ppm control but these were not statistically significant.

Chesters et al. [2002] presented data examining the use of 1,000 versus 2,500 ppm dentifrice in a 24-month abbreviated study design. After 12 months, there was no difference in the groups, but by the second-year examination point, the 2,500 ppm group had 1.5 less decayed surfaces than the control group. A total of 2,011 children aged 13 years completed the study with a low level of drop out.

Stookey et al. [2004] describes a supervised brushing study comparing 2,800 ppm with 1,100 ppm as part of a larger study investigating an experimental stannous fluoride product. As with previous works, statistically significant differences were found between the low, standard and 2,800 ppm groups. Children using the product containing 2,800 ppm experienced a 23.2% reduction (when attending more than 60% of supervised brushing sessions) compared with 1,100 ppm when scored by one examiner, but a much smaller reduction by another – 13%; both, however, were significantly superior to control. Table 2 presents a summary of the relevant studies.

## From 2,800 to 5,000 ppm

These concentrations are less well studied in the contemporary literature and did not form part of the Cochrane review or their meta-analysis. This is likely to be due to the heterogeneity of the studies, not least in their reported outcomes. Many of the studies were undertaken prior to the wide acceptance of good clinical practice and reporting standards such as CONSORT. In many cases, key components are missing from the published reports including, for example, loss to follow-up, randomisation methodology and the blinding of the study.

However, the totality of the evidence should be considered alongside the dose-response data previously described. The use of these products for the prevention and treatment of root caries is described by Ekstrand [2015] and not covered here again. It should also be noted that there are various methods of fluoride delivery and while the focus of this review is delivery via dentifrice, the tray-based and gel studies have been included for completeness.

### *Tray-Based Studies*

Englander et al. [1967] were the first to report a study examining the use of 5,000 ppm fluoride on coronal caries. This was a school-based clinical trial where custom-fitted trays were filled with either a gel containing 5,000 ppm fluoride or inactive (placebo) ingredients daily for 21 months. The children were aged 11 through 14 years. The results were striking, with an overall reduction of 75% in DMFT in the intervention group compared with the control group. A further study replicated the main methodology of the earlier work but examined the impact of the presence of optimally fluoridated water supplies on the efficacy of high fluoride applications [Englander et al., 1971]. This is an important consideration in the USA where a large proportion of the population is served by fluoridated water supplies. The study reported that there was a significant improvement in the fluoridated group, proving additional benefit from the topical application of 5,000 ppm fluoride.

### *Dentifrice Studies*

The following studies delivered 5,000 ppm fluoride via the traditional tooth-brushing method, using either dentifrice or gels.

A school-based program, utilising supervised brushing with a range of fluoride products (from 1,250 through to 5,000 ppm), was undertaken by Cutress et al. [1992].

Over a period of 26 months, 300 children in each intervention group received the brushing treatment and the final results support the previously described fluoride dose response. There was a clear relationship between the levels of fluoride in the products and caries preventive fraction, with the group taking products with 5,000 ppm fluoride reporting a 40–45% lower DMFT than those treated with the formulation containing 1,250 ppm fluoride. A total of 520 children fully participated in the study and were available for the final examination.

A further clinical study considering the efficacy of 5,000 ppm fluoride on coronal caries is that by Nordstrom and Birkhed [2010]. This 2-year, randomised clinical trial compared the use of twice daily 1,450 versus 5,000 ppm on adolescents aged 14–16 years. The outcomes of the study reported that those using the product containing 5,000 ppm had significantly lower caries progression and lower incidence than those using the control paste. The study also examined the impact of compliance on the efficacy of high fluoride products in this particular age group. An independent review of this study stated that:

The 5,000 ppm toothpaste therefore appears to be an important vehicle for the treatment and prevention of caries in patients with a high caries risk. The data may indicate that 5,000 ppm toothpaste has a greater impact on individuals who do not use toothpaste regularly or do not brush twice a day [Duane, 2012].

While the majority of caries studies reporting the use of high concentration fluorides are ‘conventional’ in design and population, typically school based and in areas of high caries prevalence with outcomes reported as DMFT/DMFS, it should be noted that such products may be of use to other high-risk groups, including those who may be deemed ‘high risk’ as a result of the presence of fixed orthodontic appliances.

Research suggests that 72.9% of patients undergoing fixed orthodontic appliance treatment will develop at least 1 white spot lesion and many will develop cavitations. Given the largely aesthetic drivers for such elective treatment, the prevention of caries is essential [Richter et al., 2011].

Examining this group of patients, Alexander and Ripa [2000] reported that while the overall caries incidence in their orthodontic patients increased, those subjects that were allocated to the product containing 5,000 ppm fluoride had statistically significantly less caries than those in the control group (dentifrice with 1,000 ppm fluoride combined with an acidulated rinse).

Orthodontic populations were also the group of interest in a further study that assessed the twice-daily use



of a dentifrice containing 1,450 ppm fluoride versus 5,000 ppm [Sonesson et al., 2014]. A well-described study, with an average treatment duration of nearly 2 years and with over 200 subjects per group, the findings indicate that those subjects in the 5,000 ppm group had a statistically significant reduction in caries (32% preventive fraction) compared to the 1,450 ppm group. The study concluded that the use of high fluoride dentifrice products in those individuals undergoing fixed orthodontic treatment should be recommended [Sonesson et al., 2014].

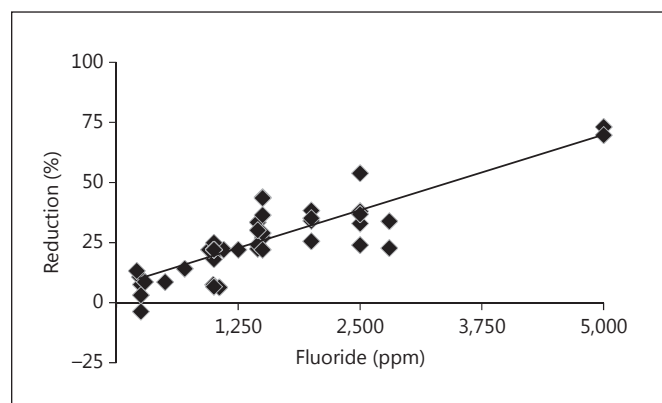
In summary, the data surrounding the use of 5,000 ppm on younger patients is limited and is highly heterogeneous, being comprised of school-based studies, orthodontic studies and mixed delivery methodologies. There is, however, a consistency to the outcomes of the trials and this, combined with the biological plausibility and dose-response data, suggests that, for high-risk children and adolescents, such products have significant potential benefit. Figure 1 demonstrates a collective dose response from the described studies. This shows that, collectively, there is a 12.7% caries (DMFS) reduction per 1,000 ppm F in toothpaste. Hence, 2,500–2,800 ppm is 15–20% more effective than 1,000 ppm, and 5,000 ppm is 30–40% more effective than 1,000 ppm.

## Fluorosis

The use of higher fluoride products in children who are at risk of fluorosis (especially to their anterior teeth) must be carefully considered. This consideration should include the following:

- 1 the age and risk for fluorosis;
- 2 the status of water fluoridation in the community;
- 3 the use of any other fluoride-containing products;
- 4 the sources of any other non-therapeutic fluorides;
- 5 the risk of caries and its morbidities.

A Cochrane review stated that there was evidence to support that toothpastes with 1,000 ppm were associated with a higher risk of fluorosis when used in children aged 5–6 years [Wong et al., 2010]. They did, however, caveat this statement by indicating that the benefit of caries prevention may well outweigh the risk of aesthetically objectionable fluorosis [Wong et al., 2010]. It should also be noted that fluoride toothpastes above 1,450 ppm are usually restricted to individuals aged over 6 years and, in most jurisdictions, are prescribed by health professionals following an appropriate risk assessment.



**Fig. 1.** Collective dose-response model from reported, published studies, showing the percentage of caries reduction compared with placebo.

## Research Challenges

While the systematic reviews demonstrate good levels of support for dentifrices up to 2,800 ppm, there is a lack of contemporary clinical trial data (suitable for meta-analyses) regarding the use of 5,000 ppm in younger patients. This is important as 2,800 ppm is available in only a small number of markets, leaving 5,000 ppm as the only alternative to consumer brands.

Developing clinical trials of these therapeutics is difficult for a number of reasons. Notably, the target populations of high caries risk children are often reluctant to join clinical trials and regularly demonstrate poor compliance when they do. Additionally, due to the prescription requirements of these products, trials involving these drugs are subject to high levels of event reporting and regulatory surveillance. These factors result in complex and expensive trials. The current indications for high fluorides are the *treatment* of existing lesions and the *prevention* of new lesions developing – each requires a different clinical study with a different design.

## Conclusion

There is a strong evidence base for the use of high fluoride toothpastes in groups at a greater risk of caries. The decision on the concentration of fluoride will be based on a number of factors, not least product availability in the prescriber's market. A thorough risk assessment of the patient is required prior to the prescription of such therapeutics and it is important to re-assess risk on a regular

basis to determine whether the intervention is still required. The use of higher concentration fluoride products as community- or population-based interventions requires further research, but early studies on 5,000 ppm suggest that they may have a role to play in addressing the burden of disease in hard-to-reach groups.

## Author Contributions

Prof. Iain Pretty undertook the literature review and wrote the manuscript.

## Disclosure Statement

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