

Strontium and Caries: A Long and Complicated Relationship

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ABSTRACT

Investigations into the role of strontium (Sr) in caries prevention have attracted great interest in the research community in the past, with its peak in the 1970-~~and~~-80ies. To this date, no clear indication of the relative importance of Sr in caries prevention has been provided. A vast number of animal caries, epidemiological and mechanistic studies have been conducted. ~~Albeit~~ Although ~~a great level of~~ there is much discrepancy ~~exists in the literature~~, the majority of studies suggest that Sr exhibits some cariostatic properties ~~and~~, predominantly in the presence of fluoride (F). An optimum Sr concentration of 5 to 10 ppm in drinking water has been proposed as a direct result of several epidemiological caries studies. Despite these results, no direct link can be established between Sr and caries prevention as, to date, no relevant, randomized control trials have been reported. The extrapolation of potential cariostatic properties of Sr from epidemiological studies is difficult due to the co-presence of several other trace elements in the water of the study areas, with many of these elements being attributed cariostatic properties in their own right. Furthermore, the role of caries risk factors was not taken into consideration. There is a clear need for further research, especially on the mineral phases in the dental hard tissues, plaque and plaque fluid associated with Sr as these may give rise to a better understanding of this subject matter. Based on the current data, the ~~, at least by some authors, proposed~~ cariostatic properties of Sr, or at least those proposed by some authors, cannot be supported.

INTRODUCTION

The caries-preventative effects of fluoride (F), and especially its sodium salt, have long been established and are beyond any reasonable doubt. However, despite F's proven track record, caries is still endemic in ~~parts of the world~~ populations globally and its elimination will remain the main challenge for dental researchers for decades to come. Its main negative side effect, fluorosis, has led investigators to conduct research on other, preferably non-toxic, (trace) elements, ideally exhibiting synergy with F, and their relative anti-caries effects – one being strontium (Sr).

Due to its similarity ~~with~~ to calcium (Ca), Sr has attracted considerable amounts of interest in the caries and caries-related research community, with its peak in the 1970~~ies~~ and 1980~~ies~~. Despite a vast number of animal caries, epidemiological and mechanistic studies conducted by various investigators, to this date, no clear indication of the role of Sr in caries prevention has been provided. Previous reviews on the relationship ~~of~~ between trace elements in general and caries [e.g. Büttner, 1969; Losee and Ludwig, 1970; Navia, 1972; Curzon and Crocker, 1978; (anonymous), 1978; Beaton, 1983; Olson, 1987] highlighted the complexity of the matter, but were also somewhat limited in scope. Therefore, the aim of the present paper was to critically and comprehensively review the literature concerned with the role of Sr in the caries process.

CRITICAL REVIEW

Search Strategy and Structure

A search strategy was developed for articles indexed in MEDLINE, Web of Science® and PubMed databases written in English up to August 30, 2011. Several hand searches were required to obtain articles which could not be retrieved via the aforementioned databases. The following key words were used in the searches in combination with 'strontium' or 'sr': 'caries', 'tooth', 'teeth', 'enamel', 'dentin*', 'demin*', 'remin*', 'apatite', 'hydroxyapatite', 'calcium phosphate', 'fluoride'.

Articles were then divided into the following groups based on the topics investigated ~~topics~~, which will also form the order of the present review:

1. Animal studies – Sr effects on enamel and dentin, caries studies
2. Caries ~~e~~Epidemiological ~~caries~~-studies
3. Sr in oral care products
4. Sr in the oral cavity – presence in teeth, plaque and saliva
5. Sr and calcium phosphates (CaPi)
6. Discussion
7. Conclusions

Articles concerned with multiple topics were considered in all relevant groups.

1. Sr Studies in Animals

Sr Effects on Dentin and Enamel

There is a discrimination against Sr in CaPi mineralization when Ca is present (see also chapter 5.), which was shown by Likins et al. [1959] in weanling rats. Later studies [Likins et al., 1961; Menczel et al., 1962] were able to support these findings, and a higher Sr discrimination was found in dentin in relation to enamel [Likins et al., 1961].

Studies in weanling rats [Likins et al., 1959] have shown that when both Ca and Sr were present during tooth formation, Ca was incorporated into the apatitic lattice preferentially, resulting in a higher Ca:Sr ratio in the subsequent mineral than might be expected. Later studies [Likins et al., 1961; Menczel et al., 1962] were able to support these findings, with the effect more pronounced in dentin than in enamel [Likins et al., 1961].

Sr injections were shown to cause dentin hypomineralisation in rats, resulting in the formation of a hypomineralized layer of dentin, comparable to that seen after F injection [Weinmann, 1942; Irving and Weinmann, 1948; Yaeger, 1963]. These effects were almost entirely confined to dentin as enamel was not affected [Weinmann, 1942]. Yaeger and Eisenmann [1963] showed that the degree of dentin hypomineralisation was positively correlated to [Sr] (i.e. Sr concentrations). Although a similar correlation was found for [F], the wider zones of hypomineralized dentin observed for Sr and the lack of a thinner hypermineralized layer of

dentin as observed for F suggested differences in their etiology. A later study [Yaeger et al., 1964] suggested that Sr (or F) inhibit or reverse the matrix aggregation normally occurring at the dentin-predentin junction, thus inhibiting mineralization. Grady and Yaeger [1965] reported that, while in normal dentin collagen fibrils are orientated perpendicular to the dentinal tubules, in hypomineralized layers caused by Sr (or F), fibrils are arranged at 45° to the fibrils of the normal dentin. The possibility ~~for that~~ hypomineralized dentin ~~can't~~ recover after Sr injection ~~seizes~~ ceases was shown by Yager [1966]. Regions of hypomineralized rat dentine induced by Sr (or F) were reported to show greater ability to mineralize than adjacent ~~normal-untreated~~ dentine in vitro [Eisenmann and Yaeger, 1972]. Johnson et al. [1970] demonstrated that Sr was not lost preferentially ~~lost~~ from high-Sr dentin and suggested that Sr was not predominantly surface located at the surface. In addition, many studies reported that Sr injection causes the formation of more than one hypomineralized layer in dentin [Yaeger and Eisenmann, 1963; Yaeger et al., 1964; Eisenmann and Yaeger, 1969; Ogawa et al., 1981]; however, while two hypomineralized layers were reported in labial dentin, only a single layer was found in lateral, medial and lingual walls [Ogawa et al., 1981; Appleton, 1993]. Ogawa et al. [1981] postulated that Sr may exert its effect on dentin hypomineralisation not only because of its ability to retard crystal growth, but also because of a direct effect on odontoblasts and collagen synthesis.

Castillo Mercado and Bibby [1973] studied the effects of Sr injections on molar morphology and found wider fissures and thicker dentin. A subsequent study [Curzon et al., 1982] investigating Sr effects when given in drinking water found an increase in horizontal and vertical dentin thickness at a [Sr] of 50 ppm, but not at 150 ppm which was indistinguishable in its effect to the water control.

While Sr effects on dentin were studied almost solely as a result of Sr injections ~~with~~ Sr.i.e. systemically, its effects on enamel were predominantly studied as a result of dietary Sr administration. Johnson et al. [1966] and Johnson [1967] demonstrated that isomorphous substitution of Sr for Ca occurs in the enamel-HAp and postulated that Sr may form $\text{Sr}_6\text{H}_3(\text{PO}_4) \cdot 2 \text{H}_2\text{O}$, which was shown to be a precursor of SrHAp [Collin, 1966]. Furthermore, Johnson and Singer [1967] found a gradient of increasing [Sr] from the incisal to apical areas in enamel of rats raised on a Sr-rich diet.

Similar to its effects on dentin, Sr has been shown to cause disturbances in ameloblast morphology and amelogenesis [Weinmann, 1943; Neiman and Eisenmann, 1975] in rats when

injected. White et al. [1980] demonstrated that the enamel organ limits Sr uptake in both the secretory and maturation phases of enamel formation. A further study by Suga et al. [1987] supported these findings and reported that Sr, unlike F, inhibits the early stage of enamel maturation and that mineralization ceases earlier in the inner layers of Sr-treated rats than in control groups.

Sr uptake ~~by~~ surface enamel of rats given water with different [Sr] (0 – 100ppm) was studied by Spector et al. [1978]. The authors found a dose-response relationship between [Sr] administered and [Sr] in surface enamel, but only when Sr was given pre- and post-eruptively. When given pre-eruptively only, a [Sr] of 50 ppm yielded the highest Sr uptake. Comparing the relative pre- and post-eruptive contributions to [Sr] in surface enamel, the present authors calculated that at $[Sr] \leq 50$ ppm, 70 to 74% of [Sr] in surface enamel of rats was due to Sr given pre-eruptively, while at $[Sr] = 100$ ppm, only 29% could be attributed to Sr given pre-eruptively. A subsequent study [Curzon and Spector, 1980] showed some variations between different Sr salts in Sr uptake by enamel, especially when administered pre-eruptively. A dose-response relationship between [Sr] administered through the diet and [Sr] in surface and near-surface enamel was also observed by Ashrafi et al. [1980].

Animal Caries Studies

Before relevant Sr animal caries ~~will be~~ are discussed, some light must be shed on differences in the etiology of caries in animals and humans ~~must be shed~~. Ericsson [1962] and Tatevossian and Wright [1974] have shown that rat in comparison to human saliva exhibits ~~larger~~ higher pH values, lower [P] but higher [Ca] and a considerably higher buffering capacity, presumably due to higher $[CO_3]$. In addition, Haldi et al. [1960] have demonstrated that the pH at the tooth surface of rats 'rarely fell as low as 7.0' after the administration of a cariogenic diet or sugar alone. In a review, White [1992] concluded that while animal models have tremendous value in studying the caries process they are by no means perfect profile tools and that results of animal caries studies on new anti-caries agents and formulations do not necessarily mirror clinical results (differences in anti-caries effectiveness and efficacy observed in animal caries studies and RCTs between amine fluoride, MFP and NaF are worth noting in this context). Furthermore, the duration and frequency of administration, salivary clearance of actives and the effect of diet on

retention of actives are not well understood in animals, making comparisons to caries in humans difficult and highlighting that further research is warranted in this area.

Animal studies on the effects Sr in preventing caries have been equivocal as no effects [Johnson and Hein, 1953; Olson et al., 1978], an increase [Hunt and Navia, 1972, 1975; Joseph et al., 1977] or a decrease [Losee and Adkins, 1968; Gedalia et al., 1975; Meyerowitz et al., 1979; Ashrafi et al., 1980; Curzon and Spector, 1981; Curzon, 1988] in caries incidence ~~were~~ have been reported. Generalization of ~~overall~~-Sr effects, however, is unjustified as differences depending on the dose and time of administration (pre- and/or post-eruptively) or the combined administration of Sr and F need to be analyzed for separately. In addition, scoring of animal caries was not uniform between these studies, thus further complicating the matter. Accordingly, ~~t~~The present authors decided to conduct further analyzes only on studies using the caries scoring method according to Keyes [1958]. Individual 'E' scores (enamel units) for bucco-lingual, sulcal and proximal lesions were combined to yield a total caries score in line with the 'Indiana rat caries model', and subsequently, percentage values of caries reduction were calculated in relation to appropriate controls [Stokey et al., 1995]. The results of the rat caries studies conducted by Meyerowitz et al. [1979], Ashrafi et al. [1980] and Curzon [1988] are presented in table 5. Studies are ~~somewhat~~-comparable to some extent due the same diet (MIT 200) being fed, although rats were inoculated with *S. mutans* only in the study by Curzon [1988]. Comparing these data it can be noted that there is a curvilinear relationship between [Sr] administered and caries reduction, regardless of whether Sr was administered pre- and/or post-eruptively. However, caution must be issued as no statistical analysis is possible to the unavailability of the raw data. The reason for this curvilinear behavior is not clear and cannot be sufficiently explained based on what is currently known. However, Driessens [1982, 1986] provided proposed some hypotheses which ~~,-however,~~ will be discussed at a later stage. In this context, it is wWorth mentioning ~~in this context is~~ that data can be over- or even mis-interpreted if only caries scores ~~on~~ from only one particular site, or ~~if~~ the wrong comparisons, are considered. Meyerowitz et al. [1979] concluded that a combination of 50 ppm Sr and 10 ppm F resulted in the greatest reduction in bucco-lingual rat caries scores. The authors, however, ignored sulcal and proximal caries scores where Sr + F was less effective in reducing caries than F alone. The present authors combined all three scores and found a 7.6 % increase in rat caries in comparison to F alone (table 5), thus the opposite result (this may or may not be of statistical significance).

Other animal caries studies will now be considered. Johnson and Hein [1953] found no cariostatic effect for Sr when administered to hamsters at 50 ppm (as SrCl₂) in the drinking water. Shaw and Griffiths [1961] studied the effects of dietary Sr supplementation on rat caries (using the sparingly soluble SrCO₃). A positive effect, i.e. a ~~on~~ caries reduction, was noted when administered post-eruptively; however, this was paired with a decrease in weight gain by the animals (at 2 % SrCO₃). When given pre-eruptively, an increase in caries occurrence was noted, and this could not be offset by giving Sr post-eruptively to the same rats. Losee and Adkins [1968] studied the effects of a dietary supplementation with the ash of green beans cooked in water containing different amounts of trace elements. The lowest overall caries scores could be related to the water sourced from Ohio, rich in Li, Mo, Sr, B and F. As multiple trace elements were present, no direct relationship for Sr in reducing caries could be established. A later study [Losee et al., 1976], investigating the effect of the 'Ohio water' when given to rats in comparison to deionized water, concluded that these trace minerals may act synergistically with fluoride in reducing caries prevalence in rats.

When Sr (as SrCl₂) was administered pre-eruptively at concentrations of 1000 or 2000 µg per 10 g body weight (~~100x or 200x the maximum [Sr] as compared to the study by Meyerowitz et al. [1979] and therefore of questionable physiological relevance~~), an increase in rat caries was noted [Hunt and Navia, 1972]. However, at 100x or 200x the maximum [Sr] as compared to the study by Meyerowitz et al. [1979] the physiological relevance is questionable. A later study by the same authors [Hunt and Navia, 1975] found similar effects at [Sr] = 500 µg in the presence or absence of [F] = 100 µg per 10 g body weight, thus indicating no additive or synergistic Sr + F effects. However, both studies reported incomplete rat caries scores which does not allow for decisive conclusions to be drawn. Gedalia et al. [1975] found a somewhat similar curvilinear relationship as noted above when studying the effects of Sr in water on caries in hamsters when given post-eruptively. [Sr] = 25 ppm resulted in overall increase, whereas [Sr] = 75 ppm resulted in a decrease of caries occurrence. Considerably stronger Sr effects were noted when Sr was administered pre-eruptively, and both [Sr] resulted in a marked decrease in caries in a dose-response manner. These results mirror later observations by Meyerowitz et al. [1979] and it was concluded that Sr exhibits its cariostatic effect mainly because it is laid down in enamel and dentin before eruption, therefore ~~somewhat~~ excluding topical effects to some extent.

Joseph et al. [1977] found a marginal increase in caries in hamsters when Sr was given pre- and post-eruptively as part of the drinking water at 10 and 25 ppm. F was found to offset the negative Sr effects. Similar ~~results-effects~~ were ~~obtained-reported~~ on rats exposed to Sr post-eruptively by Olson et al. [1978]. Curzon and Spector [1981] studied the effects of different Sr salts at [Sr] = 50 ppm on rat caries reduction and concluded that SrF₂ was most effective, mainly because of its [F] = 22 ppm. Other salts varied in their effectiveness based on their bioavailability. In addition, Sr effects were somewhat greater when given post- than pre-eruptively.

Seppä et al. [1988] reported that a total of two treatments with 500 ppm Sr with or without NaF varnish application had no effect ~~in-reducing-on~~ rat caries in comparison to the appropriate controls. Luoma et al. [1984] studied the effects of chlorhexidine (CHX)-F-Sr ([Sr] = 1000 ppm) and found a reduction in fissure caries and approximal lesions, but an increase in plaque scores in relation to CHX-F. In a subsequent study, Spets-Happonen et al. [1996] found a similar curvilinear Sr caries relationship as reported before, as a CHX-F gel supplemented with 50 ppm Sr did show some marginal benefits in reducing rat caries, whereas 250 ppm Sr appeared to markedly weaken the CHX-F effect.

2. Epidemiological Caries Studies

Several major questions are pertinent when analyzing data from epidemiological studies: a) ~~i~~s the relationship between Sr and caries reduction causative or simply incidental?, and b) ~~i~~s the reduction in caries related to the sole contribution of Sr, or is it due to the additive or synergistic action of two or more trace elements present at the same time? Furthermore, as both topical and systemic effects are thought to play roles in the caries-preventative action of Sr (see ‘Animal Caries Studies’), it ~~must-also-be~~ necessary to ~~considered~~ whether subjects were lifelong residents of ₁ or if they immigrated to ₂ the study area (i.e. the area from which water or soil samples were taken and analyzed for [Sr]). In case they immigrated, when (i.e. pre- or post-eruptively in relation to their permanent dentition), and what were environmental [Sr] in their previous area. ~~And-f~~Finally, what were the oral care habits of the study subjects, their age, socioeconomic status and sugar intake/dietary habits; i.e. have caries risk factors been

considered? To the author's knowledge, not a single study was concerned with all these aspects, thus making it almost impossible to perform an unbiased review of the available studies, which, sadly, are therefore only of very limited value. Nonetheless, epidemiological studies will be discussed in chronological order and ~~based on the extent in the context~~ of the information provided.

Anderson [1966] studied a relatively small group of 12-year old children (n = 51) from an area in Gloucestershire (UK) ~~which~~-whose soil is rich in SrSO₄. [Sr] in water in this area was estimated at 0.33 ppm and therefore extremely low in comparison to later studies (see below), whereas [F] was 0.15 ppm. No differences in ~~children's~~-DMF scores (6.03 vs. 5.63) between the study area and a control area (n = 537; [Sr] = nil; [F] = 0.13 – 0.15 ppm) were observed, but considerably lower DMF scores (4.36 and 4.38) were noted in 'F' (n = 74; [F] = 0.9 ppm) and 'Mo areas' (n = 270; [Mo] = 0.0036 ppm; [F] = 0.09 ppm).

During a sA study on caries-resistant navy recruits [Losee and Adkins, 1969], which was perhaps ~~was~~ the key study that sparked ~~the~~ interest in Sr in the caries research community in the 1970ies, it was ~~able~~-possible to correlate the high number of caries-resistant recruits from NW Ohio (USA) with the simultaneous occurrence of elevated [B], [Li], [Mo], [Sr] in NW Ohio water in combination with F. A median [Sr] of 6100 ppm was found in the water of the study area and the transfer of F, Li, Mo and Sr from water to green beans during cooking was shown. A subsequent rat caries study [see above; Losee et al., 1976] was able to support the findings of this epidemiological study. Losee and Bibby [1970] were able to negatively correlate [Sr], [B] and [F] in water with DMFT scores ($r < -0.8$ for Sr, B and F) based on the data from six cities in Illinois (USA). A more comprehensive study by Adkins and Losee [1970] compared trace elements in water between low and high caries statues (in the USA) and found significant differences between the two for Ba, B, Li, Mo and Sr with higher concentrations observed in states with lower caries incidence. Strong, positive co-variations were found between these trace elements, and Sr was found to exhibit the lowest correlation coefficient with caries prevalence ($r = -0.59$), thus indicating the strongest effect. F, however, was not considered.

A study [Curzon et al., 1970] on 251 children aged 12 to 14 from two towns in Ohio (USA) with different [Sr] (5.37 vs. 0.2 ppm) and [B] (0.35 vs. 0.04 ppm) and similar [F] (1.2 vs. 1 ppm) showed mean DMFS scores of 3.56 vs. 5.54 and mean DMFT scores of 2.25 vs. 3.04, and it was concluded that differences in [B] and [Sr] in water were attributable to the reduction

in caries rather than the 0.2 ppm difference in [F]. It must be noted that only subjects with fully erupted canines, premolars and second molars were included in the study. A ten-year follow-up study [Curzon, 1983] found essentially the same caries distribution pattern between these communities and the changes in DMFS scores were attributed to changes in [Sr] in water. Ludwig et al. [1970] also studied children aged 12 to 14 (who were lifelong residents) from 19 towns in various states (in the USA) with very low [F] in water (0 – 0.30 ppm) but different DMFT scores (3.8 – 9). [Sr] in water ranged from 12 to 2200 ppm, but only a weak negative correlation between [Sr] and DMFT was established ($r = -0.29$). Again, Sr and B ($r = -0.3$) showed similar effects. However, the present authors calculated that the exclusion of the two towns with the highest [Sr] of 1300 and 2200 ppm (leaving [Sr] = 280 ppm the next highest) would have yielded $r = 0.03$ and therefore no correlation at all. An investigation into differences in caries activity between two semi-isolated communities in Colombia with [F] < 0.2 ppm in water by Bowen et al. [1977] did not find a relationship between [Sr] in water (8 – 120 ppm in low- and 14 ppm in high-caries activity communities) and caries activity. However, water [B] were substantially different (21 – 85 ppm vs. 1.5 ppm).

Perhaps the most compelling set of data was reported by Curzon et al. [1978] who conducted caries examinations on 1313 children aged 12 to 14 years, lifelong residents and immigrants, living in seven communities in Wisconsin (USA). [F] in drinking water was comparable between communities with 1 to 1.29 ppm; however, [Sr] varied between 0.022 and 33.94 ppm. Figure 1 shows the results of this study in combination with the results of two comparable studies by Curzon et al. [1970] and Curzon [1985]. As water [F] were almost identical and as the caries evaluation was performed similarly, all three studies were combined. Considering lifelong residents only, ~~some sort of~~ an optimum [Sr] in water in relation to caries prevention ~~can be seen~~ is suggested. It is worth mentioning that as concentrations of other trace elements in water were also provided, the present authors found a very similar relationship for [Fe] and a linear relationship for [B]. In relation to these findings ~~about~~ with regard to Fe and B it must be mentioned that a follow-up study by Curzon [1983] found essentially the same [B] but considerably lower [Fe] in water in the areas studied. Somewhat surprising were the results of the immigrants, showing an almost inverse relationship compared to lifelong residents. No information regarding their previous Sr exposure was presented and, regrettably, the authors did not discuss these data, making it difficult to provide any comments now. The final study by

Curzon [1985] ~~was also able to also reported an~~ inversely correlation between caries prevalence ~~with and~~ [Sr] in water in communities with water [F] of 0.9 to 1.2 ppm. It ~~must-should~~ also be mentioned that the method for determining carious surfaces was somewhat inappropriate as ‘any fissure or enamel surface in which the explorer stuck and penetrated into dentine was regarded as carious’ [Curzon et al. 1978].

In contradiction to earlier studies [Ludwig et al., 1970; Bowen et al., 1977], showing no or only marginal anti-caries benefits for Sr in the presence of low [F], Athanassouli et al. [1983] was able to correlate lower DMFT scores (5.26 vs. 6.95) in 582 children aged 11 to 14 years with an area of higher [Sr] in water (2.9 – 7 ppm vs. 0.2 – 1.3 ppm). [F] in water was very low (< 0.06 ppm) in both districts. Furthermore, Vrbic and Stupar [1980] ~~were also able to found a~~ negatively correlation between [Sr] in water with DMFT scores in areas with low [F] (< 0.15 ppm).

In addition to the studies ~~trying to establish~~ investigating a possible link between caries reduction and [Sr] in drinking water, several studies ~~were also concerned with attempted to~~ establish ~~ing-athis~~ similar link for Sr in surface enamel and/or in plaque. Little and Barrett conducted two studies [1976a,b] investigating possible relationships between [Sr] and [F] in surface and near-surface enamel and caries prevalence. Studies were conducted on teeth obtained from lifelong residents of either east or west coast in the USA. Contradicting results were found when teeth were grouped according to DMFT scores of < 3 or > 7. In ~~east coast~~ samples from the east coast, both [Sr] and [F] were higher in surface and near-surface enamel in low caries teeth, whereas in ~~west coast~~ samples from the west coast, this was only true for [F], with [Sr] being higher in high caries samples. It must be noted that, in general, [Sr] and [F] were somewhat higher in west compared to east coast samples, although [Sr] were virtually identical in low caries teeth on east and west coast. The authors explained the east coast-west coast discrepancy with the above-proposed optimum [Sr] as an excess in Sr or lack thereof may increase the tooth’s susceptibility to caries. Two comparable studies by Curzon and Losee [1977b, 1978] were able to provide similar results, showing a stronger relationship between [Sr] in whole enamel and lower caries incidence in east than in west coast enamel samples.

Furthermore, Curzon and Losee [1977a] were able to demonstrate that high [Sr] in enamel were associated with low caries prevalence by studying 147 samples obtained from 59 communities in 19 states in the USA. Other elements, such as F, were not studied. A subsequent

study by Spector and Curzon [1979] did involve [Sr] and [F] analyses. However, the authors were not able to demonstrate a relationship between [Sr] in surface enamel and DMFT scores. A weak correlation between [F] and DMFT was found ($r = -0.16$) and also between [Sr] and [F] ($r = 0.48$). In contradiction, Vrbic and Stupar [1980] were able to demonstrate a negative correlation between [Sr] in enamel and caries incidence, which was supported by ~~the~~ later studies ~~of~~ Athanassouli et al. [1983] and Curzon [1985].

Only very few studies ~~were concerned with~~ investigated the possible correlation between Sr in plaque and caries prevalence. Schamschula et al. [1977b] reported a negative correlation between [Sr] and DMFT ($r = -0.15$) in a primitive population in Papua New Guinea ($n = 301$; 12 – 24 years of age), which, however, was weaker than ~~those correlations~~ for [Ca] and [F]. Similar results ($r = -0.23$) were obtained by the same group [Schamschula et al., 1978a] when studying 72 children aged 9.7 to 13 years. Curzon [1985] was also able to demonstrate this relationship ($r = -0.83$) in addition to the ~~earlier reported~~ negative correlations between [Sr] in water, and in enamel and DMFS scores, reported earlier.

Only two studies on salivary Sr and caries prevalence could be ~~retrieved~~ found. Curzon [1984] was able to demonstrate a weak, negative relationship between [Sr] in saliva ~~and~~ caries prevalence ($r = -0.13$) in 105 children aged 14 years. In contradiction, during one very recent study [Shigemi et al., 2008] on 521 children aged 6 to 12 years ~~was able to demonstrate a~~ positive correlation between [Sr] in saliva and using the author's terminology 'caries experience' (no DMFT/S scores were recorded) was reported. In addition, the authors showed that in groups with high 'fluoride experience rates' (due to F mouth rinsing at school), [Sr] in saliva tended to be lower.

In the context of epidemiological studies, it ~~must also~~ should be mentioned that Curzon and Spector [1977] reported ~~en~~ enamel mottling when examining 1313 12 to 14-year old children in seven towns in Wisconsin (USA). As water [F] were very similar in the study area (1 – 1.29 ppm), only a correlation between [Sr] in water (0.02 – 33.9 ppm) and mottling scores ($r = 0.85$) could be established, and, interestingly, only in lifelong residents.

Finally, Riyat and Sharma [2010] reported ~~, although only in a relatively small group of subjects,~~ that [Sr] in blood was higher in a group ($n = 15$) who had no history of caries in comparison to a group ($n = 15$) with previous caries experience, although only in a relatively small group of subjects. A similar relationship was found for [F] and [Se].

3. Sr in Oral Care Products

Considering the interest in Sr within the caries research community, it was not surprising that awareness of Sr was also raised ~~awareness~~ in the oral care industry.

Zero et al. [1982] conducted a series of investigations, ~~which are~~ perhaps better ~~termed~~ described as 'product safety studies' as a dentifrice containing not only Sr but also EDTA was evaluated ~~for~~ changes in surface enamel morphology, [Sr] in enamel and enamel solubility. The test dentifrice was compared to a commercially available control dentifrice. No significant changes in surface morphology were noted; however, both products rendered the enamel surface less soluble and [Sr] in enamel increased in the test but not in the control dentifrice.

It appears that several manufacturers of oral care products were pursuing Sr as a novel anti-caries agent in the late 1980ies. A total of three in situ studies, two enamel fluoride uptake (EFU) studies [Bowman et al., 1988a,b] and one de-/remineralization caries study [Wefel et al., 1995] were reported. All studies evaluated NaF formulations containing a so-called 'polyampholyte delivery system' (PAA-Sr), which was essentially a combination of a soluble Sr salt (not specified) and a polyacrylic acid (MW = 4500 Da). Substantially enhanced EFU values were reported for PAA-Sr, ~~for~~ both ~~the~~ mouth rinse [Bowman et al., 1988a] and dentifrice [Bowman et al., 1988b] delivery formats, ~~in~~ comparison to controls with the same [F]. The study by Wefel et al. [1995] was able to demonstrate anti-caries effectiveness of PAA-Sr which was comparable to a 2800 ppm F (as NaF) control dentifrice. Two studies [Mellberg and Fletcher, 1990; Afflitto et al., 1992] conducted by a direct competitor and comparing PAA-Sr with a different control dentifrice were also reported. The study by Mellberg and Fletcher [1990] found comparatively lower EFU in vitro for PAA-Sr. The more comprehensive study by Afflitto et al. [1992] reported comparatively lower salivary fluoride bioavailability and less cariostatic activity in the rat caries model for PAA-Sr.

A Polish group conducted two in situ studies on experimental dentifrices containing Sr + F [Kaczmarek et al., 2005] and Sr-HAP [Surdacka et al., 2007]. Both studies were primarily concerned with investigating the deposition of Sr into artificial white spot lesions, and both

studies were able to demonstrate an increase in [Sr] in enamel after 3 and 6 months of study duration.

Two further studies are worth mentioning here. Nishino [1981] investigated the effect of a Zn-acetate/Sr-acetate/tannic acid mouth rinse on caries reduction in 24 children aged 3 to 10.3 years and using the Cariostat test. A reduction in 'caries activity' was achieved by this rinse, but due to the study design no Sr effect can be extrapolated. Klinger and Wiedemann [1986] studied the effect of a mineralizing solution containing Ca, Sr, Pi and tartrate in comparison to an amine F solution on the remineralization of approximal lesions in vivo. The mineral rinse did not induce measureable remineralization, whereas the F solution did.

No reports on potential cariostatic properties of products containing $\text{SrCl}_2 \times 6 \text{H}_2\text{O}$ (SCH), designed for the relief of dentin hypersensitivity, could be retrieved.

4. Sr in the Oral Cavity

Sr in Teeth

A summary of results from various investigators can be found in supplementary data tables 1 (enamel) and 2 (dentin), with similar Sr concentrations reported for both tissues. Regardless of the investigator, study site or analytical technique employed, considerable variations in Sr concentration were found, and especially in enamel.

~~Not taking into account~~ With the exception of the osteoporosis drug Sr ranelate [for review see Marie et al., 2001], the dentine hypersensitivity treatment agent SCH [for review see Addy and Dowell, 1983] or Sr-containing glass ionomers cements (Sr-GIC) [Kim et al., 2010]; the diet is the only Sr source for the human body (approx. 2.1-2.4 mg/day) [Schroeder et al., 1972].

Comparatively higher [Sr] were found in enamel of permanent than in deciduous teeth [Cutress, 1972a; Nixon and Helsby, 1976; Shashikiran et al., 2007], whereas Zaichick and Ovchjarenko [1996] found no differences. To the author's knowledge, only two studies [Steadman et al., 1958; Lundberg et al., 1965] ~~were concerned with the~~ conducted Sr analysis ~~of~~ enamel from unerupted, permanent teeth, thus ~~limiting~~ assuring that any ~~Sr present incorporation into the dental hard tissues via systemic means would have been incorporated~~

systemically. Both studies reported similar [Sr] in relation to the enamel of erupted teeth, suggesting that most of the Sr is incorporated before eruption and that little change in [Sr] in enamel occurs with age. Later studies either proved-supported [Little and Steadman, 1966] or disproved-contradicted [Derise and Ritchey, 1974] these findings.

Several studies ~~were concerned with~~investigated the ~~depth~~-distribution of Sr- in enamel with respect to depth, in enamel, and, again, considerable variation was noted. Steadman et al. [1958] found an almost uniform Sr distribution in enamel which was supported by other studies [Vrbic and Stupar, 1980; Noren et al., 1983; Frank et al., 1989], whereas Cutress [1972a] reported either higher surface or higher bulk [Sr] depending on the sample's origin. The concept of a Sr gradient in teeth was also supported by Little and Barrett [1976a,b], who reported higher [Sr] in surface than in bulk enamel.

Strong, positive linear relationships were found ~~a)~~ a) between a) [Sr] in water and deciduous as well as permanent (bulk) enamel and b) between [Sr] and [F] in water; but only a weak, positive relationship ~~were was~~ found between [Sr] and [Ca] in water [Nixon and Helsby, 1976]. However, later studies [Spector and Curzon, 1978; Curzon, 1985] conducted in the USA, ~~however~~, found only weak, positive correlations between [Sr] in water and [Sr] in surface enamel. Cutress [1972a] reported positive correlations between Sr and Ca and Sr and F in surface and near-surface enamel, which was supported for Sr-Ca in general [Noren et al., 1983; Brown et al., 2004] and for Sr-F in surface enamel [Spector and Curzon, 1979].

Sr in the Oral Fluids –Plaque and Saliva

[Sr] in plaque (supplementary data table 3) and saliva (supplementary data table 4) exhibited similar variability compared to values reported in teeth, presumably due to environmental and dietary influences. Schamschula et al. [1977b] found strong, positive correlations in plaque for Sr-Ca and Sr-P, which was confirmed by further studies [Schamschula et al., 1978a,b]. However, weaker Sr-F and Sr-Mg correlations and no correlation between [Sr] and the dry weight of plaque were found. Curzon [1984, 1985] reported considerable differences depending on the geographical origin of the donor with plaque and saliva [Sr] being positively correlated with the water [Sr]. Comparatively high Sr plaque values were reported by a more recent study [Spets-Happonen et al., 1998], presumably due to dietary Sr [Rytömaa et al., 1975]. In saliva, positive correlations were found for Sr-Ca and Sr-Mg, but not for Sr-F [Schamschula et

al., 1978b]. By far the highest plaque and the only plaque-fluid [Sr] were reported by Shields et al. [1984] who found plaque fluid [Sr] of up to 1570 ppm. Study subjects were from an area known for its high drinking water [Sr] of up to 12.3 ppm, clearly demonstrating environmental effects of Sr accumulation in the oral cavity.

5. Sr and CaPi

Sr has been shown to be adsorbed by enamel and to a greater extent by dentin and HAp [Hodge et al., 1946]. It is generally assumed that Sr is incorporated into the crystal lattice of HAp due to the similarity in ionic radii between Sr (1.12 Å) and Ca (0.99 Å) [Elliott, 1973]. Studies on HAp [Collin, 1959; Likins et al., 1960; Schoenberg, 1963; Koutsoukos and Nancollas, 1981; Markovic and Brecevic, 1992], and monetite [Likins et al., 1959] have shown that precipitates formed in the presence of Ca and Sr had Ca:Sr ratios which were higher than the Ca:Sr ratio in solution, suggesting a marked discrimination against preferential incorporation in favor of calcium –strontium. Collin [1959] also demonstrated that a_0 and c_0 lattice constants increase linearly with Sr substitution, which was supported by other studies [Lagergren and Carlström, 1957; Schoenberg, 1963; LeGeros et al., 1977; Okayama et al., 1991; Markovic and Brecevic, 1992]. Pan et al. [2009b] studied HAp nucleation from simulated body fluid in the presence of various [Sr] and found that only $[Sr]_s \geq 0.3$ mM (at $[Ca] = 2.5$ mM) induce the formation of Sr-HAp, whereas no Sr was detected in the formed-HAp formed at $[Sr] \leq 0.1$ mM, highlighting some sort of a threshold [Sr], or perhaps more importantly a threshold Sr:Ca ratio. While Sr incorporation into HAp is limited to a few mol %, Sr is more favorably substituted in OCP than in HAp, thus stabilizing this HAp precursor phase [Matsunaga and Murata, 2009].

In addition to the incorporation of Sr into the crystal lattice, several studies [Dedhiya et al., 1973; Dedhiya et al., 1974] reported the formation of surface Sr complexes, approximately one unit-cell thick, with the formulae of $Ca_6Sr_4(PO_4)_6(OH)_2$ in the absence of F, and $Ca_6Sr_4(PO_4)_6F_2$ in the presence of F. These complexes were shown to form in the presence of Sr (and F) and under conditions resembling cariogenic attacks. A later study by Stranick and Root [1991] suggested the formation of a surface apatitic phase with a Sr:Ca ratio of 3.4:6.6 and an increase in surface SrFAP formation with increasing [Sr]. Investigations into the metastable equilibrium solubility (MES) behavior of carbonated HAp by Heslop et al. [2004, 2005]

supported earlier investigations by Dedhiya et al. [1973], but only for solution Sr:Ca ratios > 1.5 . At Sr:Ca ratios $< 2/3$, however, the stoichiometry yielding MES data superpositioning was found to be that of HAp.

Bachra and Fischer [1969] reported that Sr can slow down HAp crystal growth, which was supported by other studies for HAp [Koutsoukos and Nancollas, 1981; Christoffersen et al. 1997; Verberckmoes et al., 2004], for ACP [Root, 1990; Hidaka et al., 1991], for ACP to OCP to HAp conversions [Markovic and Brecevic, 1992], and for the α -tricalcium phosphate to HAp conversion [Boanini et al., 2010]. Bigi et al. [1988] suggested that Sr does not ‘greatly affect’ the conversion of OCP and BR into HAp, ~~but still~~ and to a lesser extent than Mg. Sr can, however, also be seen to stabilize HAp precursor phases [Matsunaga and Murata, 2009] and therefore to increase the number of biological nucleation sites [Drouet et al., 2008]. Pan et al. [2009b] also postulated that nucleation of SrHAp is easier than HAp, and that this may act as a template for HAp growth. This would explain the results of Thuy et al. [2009], who demonstrated enhanced in vitro remineralization of caries lesions in the presence of Sr and F compared to F alone.

Since the incorporation of Sr into the lattice somewhat distorts the crystallinity and leads to an expansion of the crystallite, the incorporation of elements with smaller ionic radii is therefore possible [Lappalainen and Knuuttila, 1982]. Li et al. [2007] studied Sr-HAp prepared with different [Sr] and found considerably higher [CO₃] with increasing [Sr] in Sr-HAp. Vice versa, a greater ability of carbonated in comparison to non-carbonated HAp to ‘fix’ Sr was found by Drouet et al. [2008]. In addition, Featherstone and Nelson [1980] as well as Nelson et al. [1982] reported that Sr can at least partially offset the paracrystalline disorder in HAp induced by carbonate, and Sr and F in combination were shown to improve the crystallinity of carbonated HAp to a greater extent than by Sr or F alone, suggesting synergistic effects between Sr and F in low-carbonated HAp, which is very similar to enamel [Featherstone et al., 1983]. Earlier investigations by Featherstone et al. [1981] postulated that Sr (or Zn) is incorporated into Ca-deficient areas of enamel, which were related to carbonate inclusion. LeGeros et al. [1988] showed that the simultaneous presence of F and Sr will negate the otherwise negative impact of Sr on the formation and stability of HAp, presumably due to simultaneous substitution of Sr for Ca and of F for OH [LeGeros et al., 1977; Stranick and Root, 1991]. It has also been reported that greater Sr HAp incorporation is possible in the presence of F [LeGeros et al., 1988] or monofluorophosphate [Stranick and Root, 1991].

Considering the aforementioned effects of Sr incorporation into the crystal lattice, it is not surprising that SrHAp [Saleeb and DeBruyn, 1972] or partially-substituted Sr-HAp [LeGeros et al., 1988; LeGeros, 1990; Okayama et al., 1991; Christoffersen et al., 1997; Verberckmoes et al., 2004; Pan et al., 2009a] have been shown to be more soluble than HAp, and that even a Sr for Ca substitution at 1 mol% drastically increased HAp dissolution rates [Pan et al., 2009a]. Similar results were obtained for Sr-substituted carbonated HAp and fluoridated HAp by LeGeros [1990]; however, Featherstone et al. [1983] reported synergistic effects between Sr and F in reducing the dissolution of low and high carbonated HAp when incorporated into the HAp crystals.

6. Discussion

When studying the (primarily dental) literature concerned with Sr and caries or caries-related areas, two facts are apparent – the lack of RCTs and the level of discrepancy in the literature in general. To understand potential Sr effects on decreasing caries prevalence, several questions must and will be answered:

How and where does Sr accumulate in the oral cavity?

What are the effects of Sr incorporation into the dental hard tissues?

How does solution Sr affect CaPi dissolution, formation or transformation?

Does Sr exhibit antimicrobial activity?

It has been established by many investigators that Sr is present in enamel, dentin, saliva and plaque. [Sr] have been found to vary considerably (supplementary data tables 1 to 4), and it is safe to assume that both the geographical origin of the sample (i.e. the direct result of the [Sr] in soil and water) and ~~the donor's~~ diet are accountable for these differences. Sampling techniques, sample preparation and analyses can add further error [e.g. Curzon, 1984]. In enamel, not only overall [Sr] but also its distribution was found to vary considerably [Rytömaa et al., 1975] and ~~several reports exist on~~ Sr gradients in enamel have been reported by several researchers, with higher [Sr] found in surface than in bulk enamel [Little and Barrett, 1976a,b]. Again, it is safe to assume that both topical and systemic effects are involved in Sr accumulation in the dental hard tissues, and especially in enamel. Animal studies have shown that Sr causes ~~at~~

~~least~~ disturbances in ameloblast morphology and amelogenesis [Weinmann, 1943; Neiman and Eisenmann, 1975], whereas several reports exist on Sr-mediated dentin hypomineralisation [e.g. Yaeger and Eisenmann, 1963]. In humans, information is limited to one epidemiological study [Curzon and Spector, 1977] which established a link between [Sr] in water and enamel mottling, but only for lifelong residents, thus indicating that Sr can ~~cause disturbances during~~ affect amelogenesis and is actually incorporated into the dental hard tissues during their formation. Several laboratory studies [e.g. Neumann et al., 1963] have shown that Sr can be incorporated into the (carbonated) HAp crystal lattice, substituting for Ca. In addition, Sr surface complexes were proposed to form during HAp dissolution in the presence of Sr, suggesting a different form of Sr accumulation [Dedhiya et al., 1973, 1974]. At present, however, only one report exists on the mineral phase associated with Sr in enamel in vivo. Although LeGeros et al. [1977] ~~only~~ found apatitic phases only in enamel with varying [Sr], the relationship between lattice parameters ~~did not vary clearly with and~~ [Sr] was not strong, suggesting that Sr was associated with enamel in another form. Furthermore, as Sr was shown to stabilize HAp precursor phases [Matsunaga and Murata, 2009] and to slow down HAp conversion [e.g. Markovic and Brecevic, 1992], it cannot be excluded that Sr is present in enamel or dentin, and possibly exclusively, ~~(also or solely)~~ in a non-apatitic CaPi phase. This is further supported by the Sr discrimination during HAp formation [e.g. Collin, 1959], which ~~, however,~~ is not, however, -the case for other CaPi phases, such as OCP [Matsunaga and Murata, 2009]. Driessens [1982, 1986] suggested that Sr is associated with whitlockite (WH) $[Ca_{10}(HPO_4)(PO_4)_6]$ a CaPi phase not normally found in enamel. As no direct proof can be provided for apatitic or non-apatitic Sr phases in enamel and dentin, further research is clearly needed in this area.

~~While~~ If the accumulation of Sr in enamel during amelogenesis leaves several questions unanswered, post-eruptive Sr- accumulation in (surface) enamel ~~post-eruptively~~ is equally poorly understood, especially when the mineral phase with which Sr is associated ~~with Sr~~ is considered. Several epidemiological studies [e.g. Spector and Curzon, 1978] have ~~undoubtedly proven the~~ clearly shown a positive correlation between [Sr] in water and surface enamel. Based on the aforementioned laboratory experiments, ~~It~~ whether or not Sr replaces Ca in the HAp lattice can only be speculated ~~now upon, based on the aforementioned laboratory experiments,~~ that Sr substitutes for Ca in the enamel HAp lattice, as other forms of accumulation or adsorption, as shown for F [White et al., 1994], have not (yet) been reported ~~(yet)~~. The fact that

Sr can easily substitute for Ca in enamel can be explained as carbonate (one of the major impurities in enamel) expands the HAP crystal lattice and therefore allows ions with bigger ionic radii than Ca (such as Sr) to enter and substitute for Ca [Nelson et al., 1982]. At the same time, Sr incorporation into the lattice allows for better F-OH substitution [Featherstone et al., 1983]. Does this mean there is a synergistic accumulation of Sr and F? Although plausible, ~~t~~This theory cannot currently ~~not~~ be supported, primarily ~~based on~~because previous studies [e.g. Steadman et al., 1958] ~~which have~~ failed to show associations between Sr and F. The potential consequences of these lattice substitutions have been studied by many investigators. Although there is some discrepancy, the majority of the literature supports the proposition that Sr incorporation into (carbonated) HAP increases its solubility, and that F greatly minimizes but not fully mitigates the negative effect of Sr [e.g. LeGeros, 1990].

Few reports exist on potential antimicrobial effects of Sr, and based on the current literature, it can be concluded that Sr does not exhibit antimicrobial properties at the [Sr]_s found in saliva and, more importantly, plaque (hence, the relevant literature was not discussed).

Considering what has been discussed so far, it appears that Sr is more likely to show caries-potentiating rather than –preventing effects. How can the results of the numerous animal caries and epidemiological studies, which, according to the authors, show caries-preventative effects, (even although strongly [Sr] dependent), be explained? As pointed out earlier (~~see ‘Animal Caries Studies’~~), animal caries studies are a close good, but by no means ~~a~~ complete, surrogate for caries studies in humans. Therefore, ~~these studies~~their findings should be seen regarded with some caution. Nonetheless, the results of several studies do ~~somewhat~~ mirror the findings of epidemiological studies, at least to some extent. Sr effects were observed in the presence or absence of F, and ‘optimum’ [Sr] were seen in most studies. In this context, it must be mentioned that animal caries studies often give rise to mis- or at least over-interpretation as caries scores are rarely combined (no DMFS/DMFT etc. equivalent exists), leaving the authors ~~the no other~~ option than to concentrate ~~only~~ on one particular site of occurrence where observed caries reductions were as observed in line with what the authors may have hoped for. The present authors found at least one study where this biased practice of ‘cherry picking’ led to misinterpretation of data. Nonetheless, the observed reduction in caries is compelling, and even more so as an ‘optimum’ [Sr] was proposed.

The results of several epidemiological studies are presented in Figure 1. In agreement with the rat caries studies, a [Sr]-dependent reduction in caries was observed with an optimum [Sr] of approximately 5 to 10 ppm in water. However, ~~three-four~~ facts must be mentioned in this context: a) [F] in water in all study areas was approximately 1 ppm; b) no correlations with other trace elements were conducted by the authors; c) the results of immigrants do show a completely different [Sr] caries prevalence pattern compared to lifelong residents, and d) sadly, none of the studies were concerned with caries risk factors, such as socioeconomic status and dietary habits. With regards to c) it is difficult to judge whether these effects were causative or co-incidental as the study population was relatively small (as low as 22 subjects in one of the towns); not to mention that no information ~~wasere~~ provided about the caries historiesy of the subjects, their oral care or dietary habits. This, however, can also be ~~seen-made~~ as a general comment about the presented epidemiological studies, making it difficult and perhaps impossible to extract any meaningful conclusions from them. Considering b), this is perhaps the greatest weakness of most epidemiological studies concerned with Sr. Early studies [e.g. Losee and Adkins, 1968, 1969] suggested that perhaps not Sr alone is associated with the observed caries reduction, whereas later studies were solely concerned with Sr. In one more than one study, the present authors would have been able to ‘make a case’ for B or Fe as similar relationships compared to Sr were found for these trace elements and caries reduction. In relation to this ~~thought-suggestion~~ it is perhaps time to review the role of trace elements in general (and not just Sr) in relation to caries ~~prevention~~— again, as the latest review (published in English) that could be retrieved dates back to 1987. In more than one previous review [e.g. Curzon and Crocker, 1978], it was concluded that apart from F and Sr, other trace elements, such as Al, Fe and Se, also exhibit negative correlations with caries prevalence. In relation to a) it must be noted that two epidemiological studies [Athanasouli et al., 1983; Vrbic and Stupar, 1980] were reported, correlating [Sr] with a decrease in caries in areas with negligible [F] in water. The ~~voiced~~ criticism by LeGeros [1990], that the ‘possible ‘cariostatic’ effect of Sr...may be due principally to the effect of F which was simultaneously present’₂ is therefore not entirely justified.

Overall, it must be noted that the available literature on Sr and its role in caries prevention, despite its many flaws, discrepancies and the lack of RCT’s, is compelling to say the least. One particular aspect, the ~~more than once noted~~ ‘optimum’ [Sr], noted more than once, is particularly especially interesting. So far, only Driessens [1982, 1986] has provided a hypothesis

for this phenomenon, which will now be discussed. It is worth mentioning that his hypothesis is, strangely, ignored by the research community, as the present authors were not able to retrieve a single article even presenting his reasoning. Driessens [1982, 1986] proposed that Sr is incorporated into whitlockite (WH) rather than an apatitic phase during tooth formation. As Sr stabilizes WH it renders it ~~therefore~~ less susceptible to acid attack. Mg, one of the major impurities in enamel-HAp and present at [Mg] between 0.21 and 0.44 %, is also strongly associated with WH. The introduction of Sr decreases the solubility of Mg-WH, without increasing the amount of that phase in relation to enamel-HAp. This would only explain the generally noted reduction in susceptibility to caries in rat caries studies. Considering the ‘optimum’ [Sr], Driessens [1982] hypothesized that ~~in when SR is in~~ excess-Sr, the WH phase would ~~then~~ be extended at the expense of the less soluble enamel-HAp phase, therefore rendering the enamel more susceptible to caries at elevated [Sr]. Although only a hypothesis, it is the ~~sole only~~ explanation proposed for the ‘optimum’ [Sr] observed in many studies so far. Whereas Driessens suggested that Sr exhibits its cariostatic properties only pre-eruptively, the ~~here data~~ presented ~~heredata~~ do not support this, although stronger pre- than post-eruptive effects were noted in rat caries studies (table 5).

For the moment, the thought that a [Sr] in water of 5 to 10 ppm in the presence of 1 ppm F would present an optimum concentration of both trace elements in caries prevention is entertained. How could this be implemented and what are the practicalities? Water fluoridation is considered ‘a relevant and valid choice as a population measure for the prevention of dental caries’ [Parnell et al., 2009], although this is only practiced in some countries, and then only after lengthy debates, mainly due to concerns about fluorosis. The opposition to Sr-~~enrichment~~ of drinking water is therefore unthinkable as, unlike for F, no clear ~~indication about it~~ evidence exists for its possible caries preventative efficacy ~~have been provided;~~ and the present data on Sr simply do not allow for any ‘final’ conclusions to be drawn.

Sr can also be found in dentifrices designed for the relief of dentin hypersensitivity. However, no information about the relative anti-caries benefits of these products, which often contain F at approximately 1000 ppm, could be retrieved. These products typically contain 10 % (w/w) SCH, which, at a twice daily application of 1.5 g, would result in a total Sr dose of 100 mg per day. Although ~~this a somewhat flawed~~ comparison ~~is somewhat flawed~~, this is similar to the proposed ‘optimum’ [Sr] as a consumption of 2 l of water at a [Sr] of 10 ppm would result in a

daily Sr dose of 20 mg alone, not taking into account other Sr sources. Information on these products would therefore be beneficial, as some anti-caries benefits of Sr-containing dentifrices and mouthwashes, although not commercially available anymore, ~~were~~ have been reported [Bowman et al., 1988a,b; Wefel et al., 1995]. Furthermore, the addition of Sr to oral care products would perhaps provide an opportunity to increase oral F retention. Unlike Ca, Sr can be formulated in the presence of F without greatly reducing F bioavailability, as SrF₂ is 77 times more soluble than CaF₂ ($KSP_{SrF_2} = 3 \times 10^{-9}$; $KSP_{CaF_2} = 3 \times 10^{-11}$) [Cameron et al., 1961]. The overall benefits of Ca pre-rinses on increasing oral F retention have been shown in many studies [e.g. Vogel et al., 2006], and Sr + F rinses would be expected to show a similar potential due to the similarity between Ca and Sr and the earlier reported possibility to accumulate Sr in plaque through environmental means, thus reducing the number of rinses to one and therefore increasing compliance (providing commercialization of these products). However, further research is necessary to prove these hypotheses and the suggestion that an increase in [Sr] in plaque (fluid) is directly correlated with the ability of plaque to acquire more F.

Finally, the present authors were somewhat surprised by the current lack of interest in Sr and caries in the dental research community as the related caries research has come to an almost standstill over the last ten years. Considering the many unanswered questions and the phenomenon that an ‘optimum’ [Sr] for caries prevention may exist, the lack of interest is ~~somewhat~~ rather puzzling. In view of the long and complicated relationship between Sr and caries, is it now time to ‘file for divorce’? To put it simply, ye, no, not yet.

7. Conclusions

Sr has ~~been shown to~~ exhibited some cariostatic properties in the majority of animal caries and epidemiological studies reported to date. The results of several epidemiological studies (Figure 1) led investigators to suggest (and almost believe in) an ‘optimum’ [Sr] in water. However, no definite proof of the role of Sr in caries prevention or ~~about~~ the existence of an ‘optimum’ [Sr] can be provided based on the current data, mainly due to the lack of RCTs and ~~the~~ insufficient information provided in the epidemiological studies. A thorough understanding of the role of Sr in caries prevention is therefore required, especially regarding its association with the dental hard

tissues, plaque and plaque fluid and the mineral phases involved. Furthermore, associations between F, Ca and Sr in the oral cavity need to be investigated.

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Table 1. Concentrations of Sr found in EEenamel (in chronological, then alphabetical order; permanent teeth unless noted otherwise)

| Reference | Tooth type | Age of teeth | Analysis depth | n | ppm (SD) | Range (ppm) | Method of Analysis |
|--------------------------------|------------------------|--------------|------------------------------------|-----|--------------------------|---------------------|-----------------------|
| Steadman et al. [1958] | | | whole enamel in layers | >12 | | 24-583 ^a | AES |
| Söremark and Samsahl [1961] | Premolars | 14-16 yrs. | whole enamel | 15 | 91 (22) ^a | | GRS |
| Calonius and Visapää [1965] | | | whole enamel | 16 | | 10-100 | WDXRF |
| Lundberg et al. [1965] | unerupted premolars | 14-25 yrs. | | 10 | 81 (32) ^{ab} | | GRS |
| Little and Steadman [1966] | | <30 yrs. | near-surface and bulk enamel | 328 | | 60-110 | AES |
| | | >30 yrs. | near-surface and bulk enamel | 332 | | 60-110 | AES |
| Hardwick and Martin [1967] | | | | 2 | | 100- 1000 | MS |
| Retief et al. [1971] | | | whole enamel | 7 | 111 (10) | | INAA |
| Cutress [1972a] | Premolars | | surface and near-surface enamel | | | 97-633 | ES |

| | | | | | | | |
|------------------------------|-------------------|------------|----------------------------------|------|----------------------|----------------------|------|
| | deciduous canines | | surface and near-surface enamel | | | 18-165 | ES |
| Derise and Ritchey [1974] | | 10-12 yrs. | whole enamel | 39 | 33 (27) | | AAS |
| | | 13-16 yrs. | whole enamel | 47 | 308 (24) | | AAS |
| | | 17-24 yrs. | whole enamel | 43 | 231 (25) | | AAS |
| | | ≥25 yrs. | whole enamel | 44 | 283 (25) | | AAS |
| Helsby [1974] | | | whole enamel | 1 | 116 ^a | | AAS |
| Losee et al. [1974a] | first premolar | <20 yrs. | coronal 2/3 of buccal cusp | 93 | 76 (8) | 14-450 | AAS |
| Losee et al. [1974b] | first premolar | <20 yrs. | coronal 2/3 of buccal cusp | 28 | 79 (11) ^a | 25-272 ^a | MS |
| Brudevold et al. [1975] | Incisors | 9-15 yrs. | surface enamel | 35 | 67 (20) | 26-132 | AAS |
| Curzon et al. [1975] | Premolars | 11 yrs. | whole enamel | 36 | 93 (5) | 39-170 | MS |
| Rytömaa et al. [1975] | (deciduous) | | whole enamel | 2327 | | 28-157 | AAS |
| Ahlberg and Akselsson [1976] | | | 'external' and 'internal' enamel | 1 | | 120-170 | PIXE |
| Little and Barrett | premolars | 12-14 yrs. | surface, near-surface and | 87 | | 30-1200 ^b | MS |

| | | | | | | | |
|-------------------------------|-----------|------------|--|-----|------------------|----------------------|------|
| [1976a] | | | bulk enamel | | | | |
| Little and Barrett [1976b] | Premolars | <20 yrs. | surface, near-surface and bulk enamel | 84 | | 115-600 ^b | MS |
| Nixon and Helsby [1976] | | deciduous | whole enamel | 114 | | 56-203 ^a | AAS |
| | | | whole enamel | 181 | | 70-232 ^a | AAS |
| Curzon and Losee [1977a] | Premolars | 11-19 yrs. | coronal 2/3 of buccal cusp | 147 | 183 (15) | 21-1200 | MS |
| Curzon and Losee [1977b] | Premolars | <20 yrs. | whole enamel | 208 | | 60-210 ^b | AAS |
| Frostell et al. [1977] | Premolar | | whole enamel as depth profile | 1 | | 150-250 ^c | SIMS |
| Helsby [1977] | | | whole enamel | 1 | 100 ^a | | AAS |
| Curzon and Losee [1978] | Premolars | <20 yrs. | whole enamel | 83 | | 50-170 ^b | AAS |
| Schamschula et al. [1978a] | | 12-14 yrs. | surface enamel | 299 | 101 (29) | 83-116 | ES |
| Spector and Curzon [1978] | Premolars | 10-20 yrs. | surface enamel | 223 | | 50-540 ^b | AAS |
| Spector and Curzon [1979] | premolars | 10-70 yrs. | surface enamel | 439 | 366 (435) | | AAS |
| Vrbic and Stupar | premolars | 8-15 yrs. | surface and near-surface | 100 | | 68-122 | AAS |

| | | | | | | | |
|------------------------------------|---------------------------------|--------------------------|---------------------------------|----|--------------|--|-------|
| [1980] | | | enamel | | | | |
| Athanassouli et al. [1983] | premolars | | surface enamel | 27 | | 39-152 | AAS |
| | | deciduous | surface enamel | 13 | | 38-150 | AAS |
| Curzon [1985] | premolars | 14 yrs. | surface enamel | 80 | 421 (31) | nd ^d - 1270 ^c | AAS |
| Antilla [1986] | incisors, canines | deciduous, 6- 9 yrs. | | 77 | | 40-110 ^{ab} | PIXE |
| Frank et al. [1989] | premolars, molars | 9-64 yrs. | near-surface and bulk enamel | 22 | | 40-270 ^b | EDXRF |
| Zaichick and Ovchjarenko [1996] | incisors, canines, premolars | | whole enamel | 10 | 352 (101) | | EDXRF |
| | incisors, canines | deciduous | whole enamel | 10 | 354 (95) | | EDXRF |
| Zaichick et al. [1999] | incisors, canines, premolars | 12-60 yrs. | surface enamel | 35 | | 50-800 ^b | EDXRF |
| Shashikiran et al. [2007] | incisors | deciduous, 7- 12 yrs. | whole enamel | 10 | 131 (1) | 129-133 | AAS |
| | premolars | 14-20 yrs. | whole enamel | 10 | 209 (1) | 209-210 | AAS |

^a corrected for enamel water content of 2.8%

- b estimated values based on reported mean and standard error/deviation for multiple sampling depths and/or populations
- c estimated value based on profile data
- d not detectable
- * acronyms used: AES – arc emission spectrometry; GRS – gamma-ray spectroscopy; WDXRF – wavelength dispersive X-ray fluorescence; MS – mass spectrometry; INAA – instrumental neutron activation analysis; ES – emission spectography; AAS – atomic absorption spectrometry; PIXE – proton-induced X-ray emission; SIMS – secondary ion mass spectrometry; EDXRF – energy dispersive X-ray fluorescence (EDXRF)

Table 2. Concentrations of Sr found in Dentin of Permanent Teeth (in chronological, then alphabetical order)

| Reference | Tooth type | Age of teeth | Analysis depth | n | ppm (SD) | Range (ppm) | Method of Analysis |
|----------------------------------|------------|--------------|---------------------------------|-----|----------------------|----------------------|--------------------|
| Steadman et al. [1958] | | | whole root dentin in layers | >12 | | 90-558 ^a | AES |
| Söremark and Samsahl [1962] | premolars | 14-16 yrs. | whole dentin | 15 | 63 (18) ^a | | GRS |
| Calonius and Visapää [1965] | | | whole dentin | 16 | | 10-100 | WDXRF |
| Hardwick and Martin [1967] | | | | 2 | | 100-1000 | MS |
| Retief et al. [1971] | | | whole dentin including cementum | 6 | 94 (12) | | INAA |
| Derise and Ritchey [1974] | | 10-12 yrs. | whole dentin | 39 | 179 (17) | | AAS |
| | | 13-16 yrs. | whole dentin | 47 | 219 (16) | | AAS |
| | | 17-24 yrs. | whole dentin | 43 | 183 (16) | | AAS |
| | | ≥25 yrs. | whole dentin | 44 | 139 (16) | | AAS |
| Ahlberg and Akselsson [1976] | | | whole dentin | 1 | 200 | | PIXE |
| Frostell et al. [1977] | premolar | | whole dentin as depth profile | 1 | | 220-250 ^b | SIMS |
| Lappalainen and Knuutyila [1982] | | 10-76 yrs. | whole dentin | 123 | 73 (24) ^a | | AAS |
| Möller and Carlsson [1984] | premolars | | coronal circumpulpal | 11 | | 24-251 | PIXE |

| | | | | | | | |
|--|--|--|--------|--|--|--|--|
| | | | dentin | | | | |
|--|--|--|--------|--|--|--|--|

a corrected for dentin water content of 10%

b estimated value based on profile data

Table 3. Concentrations of Sr found in Plaque (in chronological order)

| Reference | n | Age | Geographical area | ppm (SD) | Comments |
|------------------------------|-----|---------------|---|--------------------------|---------------|
| Schamschula et al. [1977a] | 72 | 9.7-13.0 yrs. | New South Wales, Australia | 2.6 (2.2) | in dry weight |
| Schamschula et al. [1978a,b] | 293 | 12-24 yrs. | several small, neighboring villages in Papua New Guinea | 20.4 (17.4) | in dry weight |
| Shields et al. [1984] | 32 | 14 yrs. | Ohio, USA | 140 (106) | in solids |
| Shields et al. [1984] | 19 | 14 yrs. | Ohio, USA | 338 (449) | in fluid |
| Curzon [1985] | 80 | 14 yrs. | Ohio, USA | 12.3 (14.6) | in dry weight |
| Curzon [1985] | 80 | 14 yrs. | Ohio, USA | 1.4 (1.6) | in wet weight |
| Pearce and Sissons [1987] | 4 | | Wellington, New Zealand | 58.7 (14.9) ^a | in dry weight |
| Spets-Happonen et al. [1998] | 19 | 30-55 yrs. | Kuopio, Finland | 17.8 | in dry weight |

^a measured after the use of a Sr-free mouthrinse

Table 4. Concentrations of Sr found in Saliva (in chronological order)

| Reference | n | Age | Geographical area | ppb (SD) | Range (ppb) | Comments |
|----------------------------|-----|------------|---|-------------|-------------|----------------------------|
| Arwill et al. [1967] | 6 | 22-24 yrs. | Umea, Sweden | 11.3 (3.5) | 7.7-16 | resting |
| | 6 | 22-24 yrs. | Umea, Sweden | 21.7 (20.8) | 8-63 | stimulated (paraffin) |
| Dreizen et al. [1970] | 15 | adults | Texas, USA | 5 (6) | <5-24 | stimulated (pilocarpine) |
| | 11 | adults | Texas, USA | 13 (23) | <5-89 | stimulated (paraffin) |
| Cutress [1972b] | 31 | 6-23 yrs. | Wellington, New Zealand | 20 (20) | 0-? | stimulated, mixed saliva |
| | 31 | 6-23 yrs. | Wellington, New Zealand | 20 (20) | 0-? | stimulated, parotid saliva |
| Schamschula et al. [1978b] | 283 | 12-24 yrs. | several small, neighboring villages in Papua New Guinea | 89 (122) | | stimulated |
| Curzon [1984] | 91 | 14 yrs. | Wisconsin, USA | 35 (30) | 20-2930 | resting |
| Shigemi et al. [2008] | 521 | 6-12 yrs. | Kitakyushu, Japan | 7.7 (3.6) | 1.7-20.6 | resting |

Table 5. Rat Caries Reduction as a Function of Sr Dose Pre- and Post-eruptively in the Presence or Absence of F

| Reference | Pre-/Post- ^a | n | Sr ^b | F ^b | E (total) ^c | % change vs. water ^d | % change vs. fluoride ^d |
|--------------------------|-------------------------|----|-----------------|----------------|------------------------|---------------------------------|------------------------------------|
| Meyerowitz et al. [1979] | Pre- | 10 | 0 | 0 | 29.6 | - | - |
| | | 10 | 2.5 | 0 | 23.2 | -21.6 | - |
| | | 9 | 5 | 0 | 21.5 | -27.4 | - |
| | | 10 | 10 | 0 | 25.4 | -14.2 | - |
| | | 10 | 0 | 1 | 28.5 | -3.7 | - |
| | | 9 | 2.5 | 1 | 26.5 | -10.5 | -7.0 |
| | | 10 | 5 | 1 | 24.4 | -17.6 | -14.4 |
| | Post- | 10 | 10 | 1 | 26.7 | -9.8 | -6.3 |
| | | 10 | 0 | 0 | 21.4 | - | - |
| | | 9 | 50 | 0 | 18.2 | -15.0 | - |
| | | 10 | 100 | 0 | 23.4 | +9.3 | - |
| | | 10 | 150 | 0 | 21.3 | -0.5 | - |
| | | 10 | 0 | 10 | 13.2 | -38.3 | - |
| | | 8 | 50 | 10 | 14.2 | -33.6 | +7.6 |
| Ashrafi et al. [1980] | Pre- + Post- | 10 | 100 | 10 | 15.4 | -28.0 | +16.7 |
| | | 5 | 0 | 0 | 35.4 | - | - |

| | | | | | | | |
|---------------|--|----|----------|---------|------|-------|-------|
| | | 5 | 0.5 + 5 | 0 | 29.3 | -17.2 | - |
| | | 5 | 1.0 + 10 | 0 | 24.8 | -29.9 | - |
| | | 4 | 2.5 + 25 | 0 | 28.3 | -20.2 | - |
| | | 8 | 5.0 + 50 | 0 | 29.9 | -15.6 | - |
| | | 6 | 7.5 + 75 | 0 | 21.5 | -39.3 | - |
| Curzon [1988] | | 10 | 0 | 0 | 34.9 | - | - |
| | | 10 | 0 | 10 + 10 | 21.7 | -37.8 | - |
| | | 10 | 0.5 + 5 | 10 + 10 | 24.1 | -30.9 | 11.1 |
| | | 10 | 5 + 50 | 10 + 10 | 17.0 | -51.3 | -21.7 |
| | | 10 | 10 + 100 | 10 + 10 | 19.2 | -45.0 | -11.5 |
| | | 10 | 15 + 150 | 10 + 10 | 17.8 | -49.0 | -18.0 |
| | | 8 | 20 + 200 | 10 + 10 | 19.1 | -45.3 | -12.0 |
| | | 10 | 30 + 300 | 10 + 10 | 20.0 | -42.7 | -7.8 |

^a Sr and/or F given pre- or post-eruptively

^b concentration in µg/10 g body weight if given pre-eruptively, or in mg/l if given post-eruptively (water)

^c sum of buccolingual, sulcal and proximal enamel caries scores

^d negative values are indicative of a caries reduction, positive values indicate increase

Figure 1. Summary of three epidemiological studies on effects of Sr in water on caries occurrence (measured as DMFS scores): ■□ data from Curzon et al. [1978]; ● data from Curzon et al. [1970]; ◆ data from Curzon [1985].

