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Tooth Whiteners & Oral Hygiene Products containing hydrogen peroxide

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5. Can tooth whitening products containing hydrogen peroxide harm teeth?

5.1 What have clinical safety trials revealed about potential effects on teeth?

The SCCP opinion states:

3.3.11.8 Clinical safety data

In a survey by Clinical Research Associates, 91% of 8,143 dentists stated that they had used vital tooth bleaching, 79% reported success, while 12% were not satisfied with the concept. Side effects reported by the respondents included the following: 62.2% noted tooth hypersensitivity 10.7 % of the time; 45.9% reported soft-tissue irritation 5.6% of the time; 2.1% noted systemic effects 0.2% of the time; and 18.8% reported no side effects (Christensen, 1997).

The most commonly observed clinical effects of treatments with tooth whiteners include mild tooth hypersensitivity to temperature changes and irritation of oral mucosa in some patients (Li et al. [Abstract], 1996, Haywood, 1993, 1997). Some patients have also reported burning palate, throat and gingiva (Howard, 1992). Tooth hypersensitivity often occurs during the early stage of bleaching treatment, and it is usually transient. The tray rather than the tooth whitening materials may cause the mucosal irritation.

Industry has reported several studies concerning the use of peroxide (2.7-7% hydrogen peroxide) containing tooth whitening products for less than 6 months, resulting in the same adverse events (oral soft tissue irritation and tooth sensitivity) observed in two week studies. The majority of the adverse events were mild and all had resolved within 3 days after the products use was discontinued. No adverse events resolution related to treatment was required. There was a trend toward a slight increase in adverse event incidence with increasing hydrogen peroxide concentration. Oral soft tissue irritation or oral hard tissue adverse incidence in groups using hydrogen peroxide products was not significantly different compared to the concurrent placebo in any study. In only 2 of 14

studies, the total adverse events incidence was statistically significantly greater in subjects using hydrogen peroxide compared to the concurrent placebo groups. Even 6 months continuous use of either a strip or a custom tray peroxide product caused the same mild, transient adverse events (tooth sensitivity and oral soft tissue irritation) as those observed after 14 or 28 days of product use.

A company producing teeth bleaching strips has reported that some of the users of the gel strips have swallowed a strip. In several of these cases, consumers reported minor gastrointestinal symptoms.

The majority of the published peroxide based teeth whitening studies with carbamide peroxide are done with a type of product only available via the dental office. With this system, a carbamide peroxide gel is delivered in a custom-fitted mouthguard, designed to cover either the upper or lower dentition. The filled bleaching tray is worn at home from 2-3 hours for daytime exposure to 8-10 hours for overnight exposure. Treatment is generally daily, and ranges in duration from one week to six months, or until the patient is satisfied with the results achieved. Ten percent carbamide peroxide is a commonly used gel concentration and is equivalent to 3.6% hydrogen peroxide.

Up to two weeks: Matis et al. (1998) reported 79% incidence of gingival “sensitivity” and 55% incidence of tooth sensitivity during a 2-weeks exposure to 10% carbamide peroxide. Kowitz et al. (1994) reported 1% of patients discontinuing use of 10% carbamide peroxide due to tooth sensitivity. No other adverse events were reported during this 2-weeks exposure. In both studies, adverse effects returned to normal following the bleaching period. Nathoo et al. (1994) reported no adverse effects of 2-weeks bleaching with 10% carbamide peroxide.

Forty-four subjects were divided into two groups and used either 6% strips or a 3.3% hydrogen peroxide gel in a custom tray. Only the maxillary arch was treated twice daily for 30 minutes over a 14-day treatment period. Thirty-three percent of subjects using the 6% strips had oral soft tissue adverse events and 19% had tooth sensitivity. The numbers in the groups using 3.3% hydrogen peroxide tray system were 23% and 5%, respectively. All of the adverse effect in this study resolved during the study or within several days after product use has been discontinued (Report 2001 111, not received).

The safety and efficacy of Colgate Simply White, Rembrandt Night Time Whitening, and WHIT-005-C13 whitening gel (Study no 05L10104 HTR 03-122638 Hilltop Research, inc, 2004) were studied. The primary endpoint was the change in tooth shade. Test groups (N=30 per group to complete) applied the whitening gels as directed once daily in the evening. The vita shade scores were measured at baseline and at days 8 and 15. All the gels changed the tooth from darker to lighter shade. No significant differences were found between the three whitening products. Likewise the self reported tooth sensitivity and oral irritation were similar.

Up to one month: In a 3-weeks exposure to 10% carbamide peroxide, 95 of the subjects reported tooth sensitivity and 32% reported minor oral discomfort (Reinhardt et al., 1993). Treatment with 10% carbamide peroxide for 4 weeks resulted in no changes in pulp sensitivity or pulpal response, as measured by electric pulp testing, although 14% of the subjects dropped from the study because of tooth sensitivity (Schulte et al., 1994). No changes in pulp sensitivity during 4 weeks exposure to 10% carbamide peroxide film-forming gel were noted. None of the subjects reported oral soft tissue irritation (Kozlovsky et al., 1996).

Nachnani ([Report] 1997) reported that there were no statistically significant difference between the placebo group and the group using bleaching gel at baseline and day 14 and between baseline and 6 months for measurements of pulpal vitality, gingival index, soft tissue evaluation and attached gingiva. Similar results were also reported in a second report (Leonard [Report], 1997). No differences in gingival index scores were detected before, during, or after the use of a whitener containing 10% carbamide peroxide for up to 7 hours daily for 28 days (Schulte et al, 1993).

Beyond one month: A whitening product with 10% carbamide peroxide was used for 5 weeks on 5 women smokers and 6 women who were not smokers. The authors found with the use of biopsies an increase in the thickness of the epithelium producing an increase in cellular proliferation in the basement and parabasal membranes of the gingival epithelium. The authors pointed out that it is not possible to conclude that 10% carbamide peroxide is carcinogenic in clinical situations, but in the present study, it was possible to observe that it alters cellular proliferation and consequently, it could act as a tumour promoter (da Costa Filho et al., 2002).

A 38% incidence of adverse events (tooth sensitivity) in a 2 months study with 10% carbamide peroxide gel; symptoms resolved during treatment or immediately following treatment (Migliore et al., 1991). In a review article by Haywood et al. (1997) several longer-term studies with patients using 10% carbamide peroxide for 6 weeks up to 6 months were reported. Adverse events (tooth sensitivity and gingival irritation) were experienced by 67% of the clinical subjects; symptoms were gone 24 hours post-treatment. Leonard et al (1999) reported an 80% incidence of adverse events in a 6 month study with a 10% carbamide peroxide gel; resolution of symptoms was not reported.

The safety of three months use of strips was evaluated. This product is designed as a one-week use and the present conditions represent a twelve times overuse. Forty subjects were divided into two groups and were assigned to either 6% hydrogen peroxide strips or 9.5% hydrogen peroxide strips. Subjects used their product on the maxillary teeth for 30 minutes twice a day for 3 months. For the 6% hydrogen peroxide strips, 6% of subjects had oral soft tissue adverse effects and 44% reported tooth sensitivity. For the 9.5% hydrogen peroxide strips, 6% of subjects had oral soft tissue adverse effects and 59% reported tooth sensitivity. One severe tooth sensitivity adverse effect was reported with the 9.5% hydrogen peroxide strips. All of the adverse effects resolved quickly when product use was discontinued (Report 2002 063).

An in vivo study on the effect of carbamide peroxide on enamel was carried out. The action on the morphology of the enamel surface of two whitening products with 10% carbamide peroxide that are on the market was studied (Colgate Platinium and Starbrite). 24 subjects divided into two groups used the products for two weeks. Immediately after the treatment, porosity was increased in the Colgate group whilst erosive alterations were observed in the Starbrite group. After three months, the situation was as it was before treatment (Turkum et al., 2002).

A study involving 13 adults with teeth stained by tetracycline ingestion and treated with tooth bleaching agent nightly for six months is reported (Haywood and Leonard [Abstract], 1996). Average treatment time was 958 hours (ranging from 568 to 1,322 hours). Tooth hypersensitivity or gingival irritation occurred, but was managed by reduction in treatment time per application, less frequent application, or interruption of treatment. None of the

teeth had required endodontic therapy or crowns, nor had any patient experienced gingival sensitivity or tooth hypersensitivity since completion of the treatment.

In a study, 70 subjects (35 controls and 35 using a 10% carbamide peroxide in anhydrous glycerol as an oral hygiene substance) were followed for up to 3 years. No evidence of adverse effect on oral tissues was observed (Fogel and MaGill, 1971). In another study where two tooth bleaching agents containing 10% carbamide peroxide were used (the mean treatment time was 302.5 hours), the main adverse effects were tooth hypersensitivity (52%) and gingival irritation (31%). Either or both occurred in 66% of the patients. The adverse effects were transient, with an average duration of 4-7 days. At 18 months (range 14-25 months) after the treatment, no side effects had re-occurred or continued (Haywood et al., 1994). However, in a study involving 40 patients which is probably an update, four of the patients reported tooth hypersensitivity at 7 years while none had reported tooth hypersensitivity at 1.5 and 3 years. Three of these had also reported tooth hypersensitivity prior to the initial treatments. No patient reported having a crown or restoration on any tooth whitened because of fracture, nor did anyone report having a root canal on any treated tooth. It is concluded that side effects occur during treatment, but not afterwards and that there are no significant long-term side effects up to 3 years associated with the use of two tooth bleaching agents containing 10% carbamide peroxide (Leonard, 1998).

It is stated in the dossier that a number of investigators reported that the use of 10% carbamide peroxide in anhydrous glycerol was effective in reducing risk of gingivitis (Zinner et al, 1978) and dental caries (Fogel and MaGill, 1971) and improving oral hygiene (Tartakow et al, 1978). Its use for four times daily up to 3 years did not have any adverse effects on gingival tissues or any evidence of other side effects.

Juvenile study: In twenty-eight day study, 9.5% hydrogen peroxide strips were used by adolescence (12-18 years). The product is designed as one-week kit, but the study represents a two-times overuse. Subjects either used 9.5% hydrogen peroxide strips (30 min, twice a day) or a 3.3% hydrogen peroxide gel in a custom tray (8 hours at night). Subject used their assigned product on the maxillary arch only for two weeks followed by their mandibular arch only for two weeks. In the 9.5% hydrogen peroxide strip group, 13% had oral soft tissue adverse effects and 18% reported tooth sensitivity. There were no oral soft tissue adverse effects in the 3.3% hydrogen peroxide tray group and 42% of the subjects reported tooth sensitivity. All of the adverse effects resolved quickly when product use was discontinued (Report 2003 016).

3.3.11.9 Summary / Comment on clinical safety data

The cosmetic industry and their organisations have pointed out that over 100 published and unpublished clinical studies, comprising approximately 4000 subjects in total are available. In addition, there exists a 7.5-year follow-up study on a small group of tooth whitening products users. It should be noted that only 9 of the 15 persons in the long-term study agreed to clinical examination. Six studies, all with less than 100 people, had up to 6 months follow-up. The majority of the studies seemed to be less than 1.5 month and involve less than 150 persons. Only one 28-day study has been reported with adolescence (12 – 18 years old). For a case-reference study to detect a doubling of the risk for an adverse effect that occurs at a level of 1:1000 in the reference group, the study group must have at least 1000 people. The majority of the studies were judged to be at high risk of bias and were either sponsored or conducted by the manufacturers. Thus,

there is a need of good clinical studies during the use of tooth whitening products as well as long-term clinical data and epidemiological studies that assess the possible adverse effects of tooth whitening products within the oral cavity.

In a large survey of dentists, 91% of 8,143 dentists stated that they had used vital tooth bleaching, 79% reported success, while 12% were not satisfied with the concept. Side effects reported by the respondents included the following: 62.2% noted tooth hypersensitivity, 45.9% reported soft-tissue irritation, 2.1% noted systemic effects, and 18.8% reported no side effects.

The most commonly observed clinical effects of treatments with tooth whiteners include mild tooth hypersensitivity to temperature changes and irritation of oral mucosa. Some patients have also reported burning palate, throat and gingiva. Tooth hypersensitivity often occurs during the early stage of bleaching treatment, and it is usually transient.

The safety of three months use of strips was evaluated. The product was designed as a one-week use and the present conditions represent a twelve times overuse. Forty subjects were divided into two groups and were assigned to either 6% hydrogen peroxide strips or 9.5% hydrogen peroxide strips. Subjects used their product on the maxillary teeth for 30 minutes twice a day for 3 months. For the 6% hydrogen peroxide strips, 6% of subjects had oral soft tissue adverse effects and 44% reported tooth sensitivity. For the 9.5% hydrogen peroxide strips, 6% of subjects had oral soft tissue adverse effects and 59% reported tooth sensitivity. One severe tooth sensitivity adverse effect was reported with the 9.5% hydrogen peroxide strips. All of the adverse effects resolved when product use was discontinued.

According to industry, market experience indicates that hydrogen peroxide tooth whitening products are well tolerated by consumers, with an adverse event incidence rate of 0.1%. The top five complaints received by consumers have been mouth irritation, oral miscellaneous, tooth hypersensitivity, gastrointestinal, and stained teeth. Oral cavity related effects represent the majority of health effects reported, with 58% of symptoms reported being tooth sensitivity and 56% of symptoms reported being oral soft tissue irritation. Whitening products that contain peroxide are known to have the potential to produce oral irritation and tooth hypersensitivity. These effects have usually been transient in nature and resolved shortly after cessation of product use.

3.3.12 Special investigations

Industry (Submission III) states that the reactivity of peroxides is limited to endogenous and exogenous sources of colour – including dietary stains and possibly non-functional matrix components of the teeth. It is claimed that bleaching per se, even with concentration of up 16% hydrogen peroxide under exaggerated use conditions (up to 6 weeks in vitro), does not damage either enamel, coronal dentin (subsurface to bleaching) or root dentin and that bleaching did not disperse or dissolve smear layers of exposed root dentin. It is claimed that current bleaching systems do not adversely affect tooth vitality, since pulp concentrations of peroxide do not reach levels needed to produce damage. Bleaches do not significantly damage restorations, although restoring teeth should be avoided immediately after bleaching due to a transient reduction in bond strength, which quickly returns to normal. In vitro studies, under exaggerated conditions of use, have demonstrated release of small amounts of mercury from amalgams at levels, which are well within the limits for mercury exposure in the guidelines set out by the WHO.

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5.2 Can tooth whitening affect enamel and dentin?

The SCCP opinion states:

> Enamel and Dentine Surface Morphology and chemistry
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> Scanning electron microscopy (SEM) has been used for qualitatively analysing the surface morphology of enamel and dentine specimens following bleaching. In addition profilometry has been used to measure the surface roughness.
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> Some authors have reported alterations of enamel surfaces, including shallow depression, increased porosity and slight erosion, associated with whitening treatments (Bitter, 1992; Bitter and Sander, 1993; Josey et al., 1996). In one study with two bleaching gels containing 16% and 35% carbamide peroxide, the authors concluded that the results indicated a need to warn patients of the potential for enamel alteration and its detrimental effect on tooth structure even if the long-term consequences have yet to be conclusively determined (Bitter 1998). It should be noted that studies have demonstrated that also soft drinks (e.g., Coca-Cola, Pepsi Cola) and fruit juices cause demineralisation and alteration of enamel (Grobler et al., 1990; Grando et al., 1996) which are comparable to those reported for whitening agents (McCracken and Haywood, 1996).
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> Shannon et al. (1993) subjected enamel slabs to different bleaching agents containing 10% carbamide peroxide for 15 hours a day for 2- and 4-week periods and evaluated by scanning electron microscopy. During the remaining 9 hours, the slabs were exposed to human saliva in vivo. Significant surface alterations in enamel topography were observed for slabs treated with the bleaching solutions for 4 weeks. Cubbon and Ore (1991) and Hammel (1998) have reported two clinical cases of serious adverse effects on enamel associated with whitening agents, both of which involved the use of “over-the-counter” products.
>
> Attin et al. (1997) assessed effects of bleaching on enamel concurrent with fluoride remineralization. While bleaching produced a slight surface softening in their protocol, the group found that topical fluoride reversed this effect, promoting surface hardening through remineralization. Rothuijzen et al. [abstract](to be published) found that in vitro bleaching without intermittent remineralisation periods VivaStyle (10% carbamide peroxide; pH 5.2) rendered enamel vulnerable for subsequent demineralization, while bleaching with Opalescence (10% carbamide peroxide + 0.11% fluoride; pH 6.7) had a protective effect.
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> Numerous studies have indicated neglible changes in enamel surface texture associated with peroxide bleaching (McGuckin et al., 1992). When changes are observed, they are for the most part minor, involving the formation of shallow depressions or increased porosities. These are likely to be a side effect of the bleaching matrices. These changes are expected to be normalized through later prophylaxis or through salivary remineralization.

The majority of studies confirming the safety of bleaching systems are contrasted with a few investigations that have shown surface degradative changes associated with bleaching processes. Rotstein et al. (1996) reported that application of 35% carbamide peroxide produced etching and demineralisation on dental enamel surfaces and in subsurface areas.

From submission IV

The majority of the more recent studies that have used scanning electron microscopy or profilometry during the last years showed no significant changes in enamel surface morphology following bleaching even with one of the highest concentrations of hydrogen peroxide (35%) (Sulieman et al., 2004). Similarly, the lower levels of 6.5% hydrogen peroxide (Duschner et al., 2006) and 6.0% hydrogen peroxide (Duschner et al., 2006; Joiner et al., 2004; Nucci et al., 2004), and 10% carbamide peroxide (Nucci et al., 2004; Justino et al.,[abstract] 2004) were also shown to have no significant effects on enamel surface morphology following simulated 2 weeks product usages. This is contrasted with studies by Pinto et al. (2004), Cavalli et al. (2004a) and Yeh et al. (2005) who observed some changes in enamel morphology following bleaching with hydrogen peroxide or carbamide peroxide.

The differences between the positive and null effects on enamel may be due to differences in the in vitro protocols used and this is reflected in their differences with respect to replicating the in vivo environment. For example, Yeh et al. (2005) stored their samples between bleaching sessions in distilled water. Pinto et al. (2004) and Cavalli et al. (2004a) used artificial saliva consisting only of inorganic calcium and phosphate components, and were devoid of any organic components which could have the potential of forming a protective salivary pellicle. In the case of three studies which showed no effect of bleaching products on enamel surface morphology, (Duschner et al. 2006; Joiner et al. 2004; Justino et al. [abstract] 2004) human whole saliva was used as a key part of replicating the in vivo situation. Indeed, Justino et al. [abstract] (2004) demonstrated that any adverse effects evident for in vitro bleached and stored in water enamel specimens were not seen for similarly treated specimens placed on an intra-oral device and worn in the mouth.

In terms of changes in human enamel surface chemical composition, no differences were found between enamel treated with 30% hydrogen peroxide (120 hr treatment), 10% carbamide peroxide (6 h/day for 14 days) or water controls as measured by Raman spectroscopy (Park et al. 2004; Goo et al 2004). Similar results were obtained for electron spectroscopy for chemical analysis (ESCA) techniques used on human enamel treated with either 10% carbamide peroxide, 7% hydrogen peroxide or 12% hydrogen peroxide (7 h/d for 14 days) (Pugh et al. 2005).

COLIPA concluded that the majority of studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant deleterious effects on enamel and dentine surface morphology and that the contrasting studies that do show an effect, in general, have some limitations in the in vitro methodologies used which do not reflect the in vivo situation accurately.

Enamel and Dentine Surface Microhardness

Surface microhardness (SMH) measurement has been a frequently used technique for evaluating the effects of peroxide and bleaching products on enamel and dentine.

There are numerous published in vitro reports in the literature detailing the detrimental effects or lack of effects of peroxide-containing tooth whitening products on enamel microhardness (Seghi and Denry, 1992; Murchison et al., 1992), enamel resistance to abrasion (Seghi and Denry, 1992), dentin microhardness (Nathoo et al., 1994; Pecora et al., 1994), dentin roughening (Zalkind et al., 1996; Atrushkevich and Vasiukova, 1996), and restoration microhardness (Bailey and Swift, 1992; Nathoo et al., 1994). Results are dependent on the methodology used and the materials or products tested.

Several studies also reported minimal or no effects of whitening agents containing 10% carbamide peroxide on microhardness and mineral content of human enamel surfaces (Shannon et al., 1993; McCracken and Haywood, 1995, 1996; Nathoo et al., 1994; Murchison et al., 1992).

Crest Whitestrips gel containing up to 6.5% hydrogen peroxide was applied for up to 70 hours bleaching (five kits). Human tooth enamel specimens were cycled through a daily regime including salivary immersions and treatment with commercial tooth whitening gels containing hydrogen peroxide or carbamide peroxide. Following in vitro laboratory cycling, the teeth were cross-sectioned and remounted for observation of microhardness and ultrastructural characteristics in subsurface regions. It was concluded that the peroxide bleaching gels produced no changes in subsurface enamel and dentin ultrastructure or architecture. Tooth preparation - Human teeth were collected by dentists and periodontists in the course of their typical practice in the Cincinnati region. These teeth were collected as part of a longstanding Procter and Gamble program of tooth collection and preservation for their laboratory requirements. The results provided support for the clinical experience that vital tooth bleaching produces no effects on the structure or function of teeth (White et al., 2004a).

A 10% carbamide peroxide bleaching agent was evaluated against a placebo agent. Two hundred and forty dental fragments were randomly fixed on the vestibular surface of the first superior molars and second superior premolars of 30 volunteers. The results suggest that treatment with 10% carbamide peroxide bleaching materials for three weeks alters the enamel microhardness, although it does not seem to alter the dentin microhardness (Basting et al. 2001).

An in vitro study aimed to evaluate the effect of bleaching agents on dentin microhardness during and after bleaching was performed. Specimens were randomly assigned to seven groups using different bleaching agents as well as a placebo agent. The 42-day whitening treatment consisted of daily application of the agents to the dentin surface for 8 hours, followed by immersion in artificial saliva for 16 hours. After the bleaching treatment, specimens were kept immersed in artificial saliva for 14 days. Microhardness was measured at baseline as well as different times during bleaching and during the post-treatment period. It is concluded that throughout the bleaching treatment, depending on the agent applied, dentin showed a transitory decrease in microhardness values. In the post-treatment period, artificial saliva presented a remineralizing effect on the bleached surfaces (de Freitas et al. 2004).

Research has been carried out supporting the hard tissue safety of bleaching processes associated with strip bleaching gels (White et al., 2000). Studies included the assessment of strip gels containing different peroxide concentrations ranging from 5.3 to 16% hydrogen peroxide. Studies also included the application of gels for time periods up to 5x recommended consumer use. In a novel in vitro cycling protocol, bleach activity was first

confirmed with image analysis colorimetry of enamel and dentin surfaces. Surface microhardness and texture assessments were complemented with analyses on cross sections samples. Hardness evaluations were then further complemented with ultrastructural observations realized through application of 3D confocal laser scanning microscopy image reconstructions, carried out on naturally wet specimens. Results illustrate the safety of the 6% hydrogen peroxide bleaching gels to both topically treated enamel and dentin and to surface regions of these specimens for all concentrations of hydrogen peroxide and all exposure regimens.

Sulieman et al. (2004) showed that 35% hydrogen peroxide treatment for 30 mins and Park et al. (2004) showed that 30% hydrogen peroxide treatment for 120 hours, both on human enamel, showed no significant reduction of SMH. Cycling experiments on enamel with 6-9.5% hydrogen peroxide where treatments were 30 mins, twice per day for 14 days simulated use (Teixeira et al. 2004), 6% and 6.5% hydrogen peroxide for 30 mins twice/day for 28 days (Duschner, 2006), 12% hydrogen peroxide for 7 h/day for 14 days (Pugh et al., 2005), 6% hydrogen peroxide for 20 mins, twice/day for 14 days (Joiner et al., 2004) all showed no reduction in SMH. A similar conclusion was obtained for similar simulated use cycling experiments when 10% carbamide peroxide (Justino et al., 2004; Unlu et al., 2004; Pugh et al., 2005; Leonard et al., 2005), 11% carbamide peroxide (Wong et al.,[abstract] 2006) and 15% carbamide peroxide (Unlu et al., 2004) were tested. Leonard et al.(2005), however, point out that when evaluating enamel microhardness, consumer available paint-on bleaching solutions may adversely affect enamel microhardness compared to a control and 10% carbamide peroxide dentist-prescribed, home-applied bleaching product.

Lewinstein et al. (2004) observed a reduction in SMH following 35% hydrogen peroxide or 35% carbamide peroxide treatments on human enamel which was reversed when treated with a 0.05% fluoride solution. Similarly, Basting et al.[abstract] (2005) also observed a slight reduction in SMH of human enamel following 8 h/day for 42 days of 10% carbamide peroxide treatments. In an in situ type study, Rodrigues et al. (2005) noted a slight reduction in SMH following in office 37% carbamide peroxide treatment (30 minutes x 2 on 3 days) plus at home use of 10% carbamide peroxide (6 h for 21 days). However, this was not significantly different from an equivalent series of placebo treatments and the authors considered the observed SMH reductions as clinically insignificant.

A reduction in enamel SMH was observed by Hairul Nizam et al (2005) following 24 h treatment with 30% hydrogen peroxide solution. Also two other studies observed a reduction in enamel SMH following bleaching with up to 35% hydrogen peroxide or 35% carbamide peroxide (Pinto et al., 2004; Attin et al., 2004). COLIPA points out that the conflicting data may be due to differences of the in vitro methods used. In particular, the two last studies used artificial saliva containing no organic components which could have formed a protective layer, there were no fluoride treatments to aid remineralisation and the study by Attin et al (2004) used bovine enamel which is known to have a three-fold faster rate of lesion progression compared to human enamel (see also Attin, 2006).

For dentine, no significant changes in SMH were reported in experiments involving 35% hydrogen peroxide for 30 minutes (Sulieman et al 2004) and 10% or 15% carbamide peroxide treatments for up to 28 hours (Unlu et al., 2004), or in cycling experiments using, 6% or 6.5% hydrogen peroxide treatments for 30 minutes twice/day for 28 days (Duschner et al., 2006) or 6% hydrogen peroxide for 20 minutes twice/day for 14 days (Joiner et al., 2004).

A transitory decrease in dentine SMH has been observed in some studies but recovered following a remineralisation period (Freitas et al., 2004a, 2004b) or 0.05% fluoride solution treatment (Lewinstein et al., 2004). Arcari et al. (2005) reported small reductions in dentine SMH (5.4%). A significant reduction in dentine SMH was observed for one 10% carbamide peroxide product (Basting et al., [abstract] 2005). In addition, the study by Hairul Nizam et al. (2005) showed a reduction in dentine SMH.

COLIPA concluded that overall, the majority of studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant deleterious effects on enamel and dentine SMH, even if one of the highest levels of hydrogen peroxide is used. The few contrasting studies that do show an effect, in general, again have some limitations in the in vitro methodologies used which do not reflect the in vivo situation accurately. Indeed, some studies demonstrated a transitory reduction in SMH which were recovered following a remineralisation period.

Subsurface Enamel and Dentine

Since hydrogen peroxide will diffuse through enamel towards the enamel-dentine junction, some studies have investigated the effects of bleach agents on subsurface enamel and dentine. This is typically accomplished by bleaching whole teeth or fragments and then cutting and polishing the specimens to reveal the internal subsurface enamel and dentine areas, followed by micro-hardness measurements.

Using the above approach, Teixeira et al. (2004) found no reductions in enamel subsurface microhardness following treatments with 6%-9.5% hydrogen peroxide (30 minutes x 2/day) or 10% carbamide peroxide (6 h/day) for 14 days in total. Similar results were found for both subsurface enamel and dentine following 6% hydrogen peroxide for 20 minutes x 2/day, for 14 days (Joiner and Thakker 2004) or for 14 hours and 70 hours total bleaching time with 5.3% hydrogen peroxide (White et al., 2004). In contrast, the study by Attin et al. (2005) showed some reduction in subsurface enamel but not subsurface dentine following bleaching protocols with up to 35% hydrogen peroxide or 35% carbamide peroxide. Again this contrast may be due to differences in the methodology.

An alternative approach to investigating the effects of bleaching on subsurface enamel, dentine and the enamel-dentine junction is to use confocal laser scanning microscopy which enables their ultrastructure to be investigated. Studies on bleached tooth specimens have demonstrated no changes in enamel and dentine ultrastructure (White et al., 2004; Duschner et al., 2006). On the other hand, Markovic et al. (2007) exposed teeth in vitro to either 10% or 16% carbamide peroxide for 4 hours per 7 days. The statistical analysis showed significantly higher microroughness for both groups of carbamide peroxide exposed enamel surfaces.

The ultimate tensile strength of subsurface enamel following treatment with up to 35% hydrogen peroxide and 37% carbamide peroxide (Silva et al.,[abstract] 2005) and 10 – 20% carbamide peroxide (Cavalli et al., 2004b) has been shown to be reduced compared to non bleached controls. Cavalli et al. (2004b) point out that the effects of bleaching agents on the mechanical properties of enamel have not been extensively studied. Although it is quite difficult to clinically associate enamel cracking or fractures with previous bleaching treatments, there is increasing evidence that enamel structural changes may occur due to exposure to such substances that may ultimately compromise

its strength. There study showed that the ultimate tensile strength of enamel was significantly reduced when a routinely used bleaching regimen was followed and that the clinical implications must be further investigated.

Tam et al. (2007) have studied the effects of in vitro prolonged tooth bleaching on the fracture toughness of human dentin. Dentin from recently extracted molar teeth was directly or indirectly treated to simulate a prolonged at-home (10% carbamide peroxide or 3% hydrogen peroxide, 6 hours/day, 5 days/week for 8 weeks) or in-office (30% hydrogen peroxide, 1 hour/week for 8 weeks) bleaching regimen (N = 8/group). For direct bleach application, the treatment materials were applied onto dentin that was already prepared as compact tension specimens. For indirect bleach application, bleach was applied to the enamel of intact teeth prior to specimen preparation. There was a significant decrease in dentin fracture toughness after 8 weeks of direct bleach treatment. There were no significant differences between the bleach and control groups after 8 weeks of indirect bleach treatment ($p = 0.19$). The authors conclude that caution should be considered when using bleach for prolonged treatment times in clinical cases where there is dentin exposure such as occlusal attrition or gingival recession.

COLIPA concluded that the majority of relevant in vitro studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant deleterious effects on subsurface enamel and dentine microhardness or ultrastructure. Only one in vitro study showed a decrease in the subsurface microhardness of enamel.

Effects of Acid Challenges and Abrasion on Bleached Enamel/Dentine

Sulieman et al. (2004) found that pre-bleaching human enamel and dentine with 35% hydrogen peroxide for 30 minutes had no subsequent deleterious effect on enamel and dentine loss caused by citric acid erosive challenges or brushing with toothpaste, as measured by profilometry. Similarly, bleaching human enamel and dentine with 10%-22% carbamide peroxide for 2 h x 20 treatments did not increase their susceptibility to acid erosion or caries lesion formation as measured by quantitative light-induced fluorescence and transverse microradiography (Pretty et al., 2005).

Cia Worschech et al. (2006) studied how tooth bleaching abrasive dentifrices might change the outer superficial enamel. Human enamel slabs were exposed in vitro to a 10% carbamide peroxide bleaching agent at different times and submitted to different superficial cleaning treatments. Bleaching was performed on the enamel surface for six hours daily. After that, each slab received a cleaning surface treatment and was stored in artificial saliva. The study showed that the sole use of 10% carbamide peroxide did not alter the enamel surface roughness, but the cleaning treatments that employed the use of brushing with abrasive dentifrices resulted in a significant increase of enamel surface roughness.

The study by Wiegand et al. (2004) showed that bleaching with 35% or 38% hydrogen peroxide (15 min x 2/d, for 4 d) or 35% carbamide peroxide (1 h on 4 d) gave no significant increase in enamel wear caused by brushing with toothpaste. In the same study, they did show a significant increase in enamel wear following treatment protocols with 5.3% hydrogen peroxide, 10% carbamide peroxide and 15% carbamide peroxide. The authors conclude that bleaching treatment may result in increased tooth brushing abrasion. Acidic agents or long duration of bleaching seem to lead to an increased susceptibility to enamel loss by tooth brushing abrasion.

COLIPA concluded that in vitro studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant clinically relevant effects on subsequent enamel and dentine loss caused by acidic erosive challenges, toothpaste abrasion or caries lesion formation.

Source & ©: SCCP, Opinion on Hydrogen peroxide, in its free form or when released, in oral hygiene products (2007), 3.3 Toxicological evaluation, 3.3.12. Special investigations, p.53-58

5.3 Can tooth whitening affect dental pulp?

The SCCP opinion states:

Uptake of bleach and transport to dental pulp

It is well established that a common adverse effect of vital tooth bleaching is dentinal hypersensitivity. As discussed previously, uptake studies have confirmed that peroxide is taken up into dental pulp from 30 – 35% peroxide in-office treatments and 6% peroxide consumer bleaching systems. Several studies have examined the effects of vital bleaching on pulp histology. These studies involve the use of vital teeth scheduled for orthodontic extraction that are then exposed to bleach or control treatments prior extraction, fixation and assessments. Researchers have observed that vital tooth bleaching produces histological evidence of minor inflammation of superficial layers of pulp adjacent to the pulp-dentin junction (Robertson and Melfi, 1980). It is noteworthy that the minor inflammatory response of the pulp to the introduction of bleaching seems to be concurrent with the pain response expressed by consumers having increased hypersensitivity.

In two studies, extracted human teeth were sectioned above the cemento-enamel junction and oriented so that an enamel surface was immersed in a solution of hydrogen peroxide (Bowles and Ugwuneri, 1987) or a gel of hydrogen peroxide or carbamide peroxide (Cooper et al., 1992). After exposure, acetate buffer that had been placed in the pulp cavity was subjected to a peroxidase-based assay to measure the extent of peroxide penetration through enamel and dentin. Peroxide was detected in the pulp cavity as early as 15 minutes following exposure of enamel to 1, 10 or 30% hydrogen peroxide, and the amounts detected showed a significant dose relationship (Bowles and Ugwuneri, 1987). Carbamide peroxide appears to result in less penetration than the equivalent amount of hydrogen peroxide. Exposure to a 15% carbamide peroxide gel (equivalent to 5.3% hydrogen peroxide) resulted in a mean pulp cavity concentration of peroxide that was less than half that caused by exposure to gelled 5% hydrogen peroxide (Cooper et al., 1992).

Laboratory research has demonstrated that hydrogen peroxide is readily transported through tooth enamel into dentin and pulp and it is reported that significant amounts of hydrogen peroxide diffuse through dentin after application of carbamide peroxide and hydrogen peroxide-based bleaching agents (Hanks et al. 1993). Despite this uptake, the development of pulpal damage associated with vital tooth bleaching is remarkably low. It is pointed out that peroxide concentration from 14% hydrogen gel was far below levels required for the initiation of significant enzyme inhibition (White et al., 2004b).

In a study of Slezak et al. (2002) the pulp penetration was studied with 6.5% hydrogen peroxide and 9% hydrogen peroxide paint-on gel. It was claimed that pulpal penetration over two 30 minutes applications of peroxide under in vitro conditions produced a level of approximately 1000 times lower than the amount of peroxide required to inhibit pulpal enzymes. The levels were also well below concentrations shown to result in no damage to the pulp tissue.

Source & ©: SCCP, Opinion on Hydrogen peroxide, in its free form or when released, in oral hygiene products (2007), 3.3 Toxicological evaluation, 3.3.12. Special investigations, p.59

5.4 Can tooth whitening affect fillings and other dental restorative materials?

The SCCP opinion states:

Effects on restorative materials

While dental enamel is the focus of peroxide whitening reactions, dental restorative materials can be visualized as a collateral substrate for bleaching effects. With respect to bleach effects on restoration colour, research supports the conclusion that restorative materials are generally unaffected by peroxide bleaching procedures (Swift, 1997, 1998). However, composite restorations may lighten a very small amount during bleaching, but this is detectable by colorimeter measurements only.

The effects of peroxide bleaching on restoration surface texture and chemistry are strongly dependent upon restoration type (Swift, 1998). Thus, porcelain or other ceramic restoratives as well as dental gold appear generally unaffected by bleaching procedures. Composite restorations, on the whole would seem to be more reactive to bleach effects, but these still may include only minor etching or softening depending upon treatment conditions. In studies of strip bleaching gels, glass ionomers were largely unaffected (Schenk-Meuster et al., 2002, Nathoo et al., 1994).

The most noteworthy chemical interactions that have been reported with bleaching procedures include cements and amalgam restorations. Zinc phosphate cement has been previously observed to be completely solubilized by a carbamide peroxide bleaching gel (Christensen et al., 1991). Dental amalgams show signs of oxidative reactivity with bleaching gels with minor localized spotting and colour changes observed on amalgam surfaces (Schenk-Meuster et al., 2002). In vitro studies, under exaggerated conditions of use, have demonstrated release of very small amounts of mercury from amalgams, which are at levels well within the limits for mercury exposure in the guidelines of WHO (Hummert et al., 1993, Rotstein et al., 1997).

3.3.12.1 Summary / Comments on special investigations

Enamel and Dentine Surface Morphology and Chemistry. The majority of studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant deleterious effects on enamel and dentine surface morphology. However, there are some

limitations in the in vitro methodologies used which do not reflect the in vivo situation accurately.

Enamel and Dentine Surface Microhardness. The majority of studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant deleterious effects on enamel and dentine surface microhardness. Some studies demonstrated a transitory reduction in dentin surface microhardness which were recovered following a remineralisation period.

Effects of Acid Challenges and Abrasion on Bleached Enamel/Dentine. In vitro studies indicate that hydrogen peroxide and carbamide peroxide containing products have no significant clinically relevant effects on subsequent enamel and dentine loss caused by acidic erosive challenges, toothpaste abrasion or caries lesion formation.

Effects on Restorative Materials. Research supports the conclusion that restorative materials are generally unaffected by peroxide bleaching procedures. However, composite restorations may lighten a very small amount during bleaching, but this is detectable by colorimeter measurements only.

The effects of peroxide bleaching on restoration surface texture and chemistry are strongly dependent on restoration type. Porcelain or other ceramic restoratives as well as dental gold appear generally unaffected by bleaching procedures. Composite restorations seem to be more reactive to bleach effects, mainly minor etching or softening depending in relation to treatment.

The most noteworthy chemical interactions that have been reported with bleaching procedures on cements and amalgam restorations. Zinc phosphate cement has been previously observed to be completely solubilized by a carbamide peroxide bleaching gel. In vitro studies have demonstrated release of very small amounts of mercury from amalgams.

Uptake of Bleaches and Transport to Dental Pulp. Uptake studies have confirmed that peroxide is taken up into dental pulp from 30 – 35% peroxide in-office treatments and 6% peroxide consumer bleaching systems. It has been found that vital tooth bleaching produces histological evidence of minor inflammation of superficial layers of pulp adjacent to the pulp-dentin junction. The minor inflammatory response of the pulp to the introduction of bleaching seems to be concurrent with the pain response expressed by consumers having increased hypersensitivity.

It is claimed that pulpal penetration under in vitro conditions produced a level much lower than the amount of peroxide required to inhibit pulpal enzymes. Carbamide peroxide appears to result in less penetration to the pulp than the equivalent amount of hydrogen peroxide.

Source & ©: SCCP, Opinion on Hydrogen peroxide, in its free form or when released, in oral hygiene products (2007), 3.3 Toxicological evaluation, 3.3.12. Special investigations, p.58-60

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