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Tooth Bleaching—a Critical Review of the Biological Aspects

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ABSTRACT: Present tooth-bleaching techniques are based upon hydrogen peroxide as the active agent. It is applied directly, or produced in a chemical reaction from sodium perborate or carbamide peroxide. More than 90% immediate success has been reported for intracoronoral bleaching of non-vital teeth, and in the period of 1-8 years’ observation time, from 10 to 40% of the initially successfully treated teeth needed re-treatment. Cervical root resorption is a possible consequence of internal bleaching and is more frequently observed in teeth treated with the thermo-catalytic procedure. When the external tooth-bleaching technique is used, the first subjective change in tooth color may be observed after 2-4 nights of tooth bleaching, and more than 90% satisfactory results have been reported. Tooth sensitivity is a common side-effect of external tooth bleaching observed in 15%-78% of the patients, but clinical studies addressing the risk of other adverse effects are lacking. Direct contact with hydrogen peroxide induced genotoxic effects in bacteria and cultured cells, whereas the effect was reduced or abolished in the presence of metabolizing enzymes. Several tumor-promoting studies, including the hamster cheek pouch model, indicated that hydrogen peroxide might act as a promoter. Multiple exposures of hydrogen peroxide have resulted in localized effects on the gastric mucosa, decreased food consumption, reduced weight gain, and blood chemistry changes in mice and rats. Our risk assessment revealed that a sufficient safety level was not reached in certain clinical situations of external tooth bleaching, such as bleaching one tooth arch with 35% carbamide peroxide, using several applications per day of 22% carbamide peroxide, and bleaching both arches simultaneously with 22% carbamide peroxide. The recommendation is to avoid using concentrations higher than 10% carbamide peroxide when one performs external bleaching. We advocate a selective use of external tooth bleaching based on high ethical standards and professional judgment.

Key words. Enamel, esthetics, ethics, toxicology.

(I) Introduction

Tooth discoloration varies in etiology, appearance, localization, severity, and adherence to tooth structure. It may be classified as intrinsic, extrinsic, and a combination of both (Hattab et al., 1999). Intrinsic discoloration is caused by incorporation of chromogenetic material into dentin and enamel during odontogenesis or after eruption. Exposure to high levels of fluoride, tetracycline administration, inherited developmental disorders, and trauma to the developing tooth may result in pre-eruptive discoloration. After eruption of the tooth, aging, pulpal necrosis, and iatrogenesis are the main causes of intrinsic discoloration. Coffee, tea, red wine, carrots, oranges, and tobacco give rise to extrinsic stain (Hattab et al., 1999; Watts and Addy, 2001). Wear of the tooth structure, deposition of secondary dentin due to aging (Watts and Addy, 2001) or as a consequence of pulp inflammation, and dentin sclerosis affect the light-transmitting properties of teeth, resulting in a gradual darkening of the teeth.

Scaling and polishing of the teeth remove many extrinsic stains. For more stubborn extrinsic discoloration and intrinsic stain, various bleaching techniques may be attempted. Tooth bleaching can be performed externally, termed night guard vital bleaching or vital tooth bleaching, or intracoronal in root-filled teeth, called non-vital tooth bleaching. The aims of the present paper are to review critically the literature on the biological aspects of tooth bleaching, including efficacy and side-effects of such treatments. In addition, the safety of vital tooth bleaching is especially addressed.

(II) History of Bleaching

Bleaching of discolored, pulpless teeth was first described in 1864 (Truman, 1864), and a variety of medicaments such as chloride, sodium hypochlorite, sodium perborate, and hydrogen peroxide has been used, alone, in combination, and with and without heat activation (Howell, 1980). The “walking bleach” technique that was introduced in 1961 involved placement of a mixture of sodium perborate and water into the pulp chamber that was sealed off between the patient’s visits to the clinician (Spasser, 1961). The method was later modified and water replaced by 30-35% hydrogen peroxide, to improve the whitening effect (Nutting and Poe, 1963). The observation that carbamide peroxide caused lightening of the teeth was made in the late 1960s by an orthodontist who had prescribed an antiseptic containing 10% carbamide peroxide to be used in a tray for the treatment of gingivitis (Haywood, 1991). The observation was communicated to other colleagues and must be regarded as the beginning of the night guard bleaching era. More than 20 years later, the method describing the use of 10% carbamide peroxide in a mouth guard to be worn overnight for lightening tooth color was published (Haywood and Heymann, 1989).

(III) Medicaments

Tooth bleaching today is based upon hydrogen peroxide (CAS No 7722-84-1) as the active agent. Hydrogen peroxide may be applied directly, or produced in a chemical reaction from sodium perborate (CAS No. 7632-04-4) (Hägg, 1969) or carbamide
peroxide (CAS No. 124-43-6) (Budavari et al., 1989) (Fig. 1). Hydrogen peroxide acts as a strong oxidizing agent through the formation of free radicals (Gregus and Klaassen, 1995), reactive oxygen molecules, and hydrogen peroxide anions (Cotton and Wilkinson, 1972) (Fig. 1). These reactive molecules attack the long-chained, dark-colored chromophore molecules and split them into smaller, less colored, and more diffusible molecules. Carbamide peroxide also yields urea (Budavari et al., 1989) that theoretically can be further decomposed to carbon dioxide and ammonia. It is unclear, however, how much ammonia is formed during tooth bleaching with carbamide peroxide. The high pH of ammonia facilitates the bleaching procedure (Sun, 2000). This can be explained by the fact that, in a basic solution, lower activation energy is required for the formation of free radicals from hydrogen peroxide, and the reaction rate is higher, resulting in an improved yield compared with an acidic environment (Cotton and Wilkinson, 1972). The outcome of the bleaching procedure depends mainly on the concentration of the bleaching agent, the ability of the agent to reach the chromophore molecules, and the duration and number of times the agent is in contact with chromophore molecules.

(IV) Non-vital Tooth Bleaching

(IV-1) Methods

Intracoronal bleaching is a conservative alternative to the more invasive esthetic treatment of non-vital discolored teeth. Careful examination is necessary, since the method requires healthy periodontal tissues and a root canal that is properly obturated to prevent the bleaching agent from reaching the periapical tissues (Baratieri et al., 1995). Both hydrogen peroxide and sodium perborate have been used, and various heat sources have been applied to speed up the reaction and improve the bleaching effect (Howell, 1980). A combination of sodium perborate and water (Spesser, 1961; Holmstrup et al., 1988) or hydrogen peroxide (Nutting and Poe, 1963) has been used in the “walking bleach” technique. The medicament is placed in the pulp chamber, sealed, left for 3-7 days, and is thereafter replaced regularly until acceptable lightening is achieved. If the tooth has not responded satisfactorily after 2-3 treatments, the “walking bleach” technique can be supplemented with an in-office bleaching procedure (Baratieri et al., 1995). The treatment may continue until an acceptable result is obtained (Fig. 2). A modification of the method that reduces the number of in-office appointments has been suggested (Liebenberg, 1997; Caughman et al., 1999). Access to the pulp chamber is gained by removal of the coronal restoration and the coronal part of the root filling. The remaining root filling is sealed off with glass-ionomer cement. The patient places the bleaching agent, usually 10% carbamide peroxide, intracoronarily at regular intervals and covers the lingual aspect of the tooth with a plastic splint. In this method, the pulp chamber is left unsealed during the weeks of treatment.

Figure 1. The formation of hydrogen peroxide from sodium perborate (Eq. 1) (Hägg, 1969) and from carbamide peroxide (Eq. 2) (Budavari et al., 1989). Hydrogen peroxide forms free radicals like hydroxyl and perhydroxyl radicals, and superoxide anions (Eq. 3a) (Gregus and Klaassen, 1995), reactive oxygen molecules that are unstable and transformed to oxygen (Eq. 3b) (Cotton and Wilkinson, 1972), and hydrogen peroxide anions (Eq. 3c) (Cotton and Wilkinson, 1972).

\[
\begin{align*}
(1) \quad & Na_2[B_3(O_2)_{3}(OH)_4] + 2H_2O \rightarrow 2NaBO_3 + 2H_2O_2 \\
(2) \quad & H_2NCONH_2 + H_2O \rightarrow H_2NCONH_2 + H_2O_2 \\
(3a) \quad & H_2O_2 \rightarrow 2HO^* \\
& HO^* + H_2O_2 \rightarrow H_2O + HO_2^* \\
& HO_2^* \leftrightarrow H^+ + O_2^* \\
(3b) \quad & 2H_2O_2 \leftrightarrow 2H_2O + 2(O) \leftrightarrow 2H_2O + O_2 \\
(3c) \quad & H_2O_2 \leftrightarrow H^+ + HOO^- 
\end{align*}
\]

Figure 2. Non-vital tooth bleaching of a discolored tooth in a 21-year-old woman. The tooth had been endodontically treated 6 yrs earlier due to trauma. A slight discoloration, which subsequently became more intense, was visible immediately after the endodontic treatment. (A) Tooth #11 with a dark blue discoloration. (B) The result after 3 wks of internal bleaching with sodium perborate suspended in water and a weekly change of bleaching agent. (C) 5 yrs after internal bleaching. Only slight discoloration is visible, and no retreatment was necessary. (D) 10 yrs after internal bleaching. Recurrence of the discoloration is visible, and the patient needed re-treatment. The relapse after 10 yrs, however, was not as severe as the discoloration before bleaching, and the tooth could be re-bleached to a satisfying result. Although intercoronal bleaching does not have—as do most other treatments—indefinite durability, the long-term aesthetic and biological results of this treatment are considered to be of high quality.
If the seal of the root-filling leaks, contamination of the periapical tissue may lead to endodontic treatment failure, the residual bleaching agent will be ingested due to insufficient rinse of the sticky gel, and intracoronal dentin will be subject to discoloration from pigments in foods or beverages. The chair time saved with this bleaching method does not compensate for the adverse biological consequences.

(IV-2) Efficacy

The efficacy of the different medicaments used for internal tooth bleaching has been evaluated in vitro on artificially stained teeth. After 14 days (Rotstein et al., 1991c) and one year (Rotstein et al., 1993), there was no difference in the shade of the teeth bleached with sodium perborate in 30% hydrogen peroxide, sodium perborate in 3% hydrogen peroxide, or sodium perborate in water. Concurring results were found in a study with sodium perborate mixed with 30% hydrogen peroxide or water and evaluated after 7, 14, and 21 days of treatment (Ari and Üngör, 2002). Increased lightening of the teeth was observed with longer bleaching time, but otherwise no difference was reported. The results with sodium perborate in 30% hydrogen peroxide (93% of the artificially stained and bleached teeth recovered their initial shade) were better than those obtained with sodium perborate in water (53% recovered) (Ho and Goerig, 1989). Artificially stained extracted teeth were used for comparison of the outcome of the "walking bleach" method (sodium perborate in 35% hydrogen peroxide), the thermo-catalytic method (heating a pellet soaked with 35% hydrogen peroxide), and a combination of the two methods (Freccia et al., 1982). No difference was observed between the bleaching methods used. The immediate results after intracoronal bleaching with 10% carbamide peroxide were better than those with sodium perborate in 30% hydrogen peroxide (Vachon et al., 1998). The final outcome after 3 treatments over 14 days was beneficial with sodium perborate in 30% hydrogen peroxide, but none of the teeth attained their initial shade (Vachon et al., 1998). The conclusion of the above in vitro studies was that sodium perborate in water, sodium perborate in 3 and 30% hydrogen peroxide, and 10% carbamide peroxide were efficient for internal bleaching of non-vital teeth. It must be taken into consideration, however, that the conclusion is based on artificially stained teeth and that the clinical situation may give different results.

(IV-3) Esthetic results

The evaluation of the esthetic outcome of a bleaching treatment is subjective, and the patient's opinion may differ from that of the dental surgeon (Glockner et al., 1999). In addition, different terms and definitions of the outcomes have been applied which make comparisons between studies difficult (Friedman et al., 1988; Holmstrup et al., 1988; Glockner et al., 1999). Immediate treatment success has usually been defined as no or slight deviation in color between the treated and non-treated teeth. More than 90% immediate success has been reported with the thermo-catalytic method (Howell, 1980) or the conventional "walking bleach" procedure (Holmstrup et al., 1988). The failure rate may be useful in determining the long-term esthetic results of internal bleaching. Failure, however, has not been defined in the different long-term studies (Brown, 1965; Friedman et al., 1988; Holmstrup et al., 1988; Glockner et al., 1999), but the intuitive definition is "teeth that need to be re-treated". The need for re-treatment increased with the observation time, i.e., 10% after 1 to 2 years (Friedman et al., 1988), 20-25% after 3 to 5 years (Brown, 1965; Holmstrup et al., 1988), and 40% failure in teeth observed up to 8 years (Friedman et al., 1988). In a more recent study, a 7% failure rate was reported after 5 years, but the majority of cases in this study were defined as ideal for bleaching (no other filling than the palatinal endodontic opening) (Glockner et al., 1999). A study of endodontically treated, internally bleached tetracycline-stained teeth that were followed for 3-15 years showed that four out of 20 patients needed re-treatment (Abou-Rass, 1998). At present, no study has provided a good predictor for the long-term outcome of internal bleaching. It appears that teeth with multiple fillings are not ideal candidates for the procedure (Howell, 1980; Glockner et al., 1999).

(IV-4) Adverse effects

Cervical root resorption (Fig. 3) is an inflammatory-mediated external resorption of the root, which can be seen after trauma and following intracoronal bleaching (Friedman et al., 1988). A review of published case reports on cervical root resorption revealed 22 such cases following intracoronal bleaching (Table 1). Table 1 summarizes the results of 4 follow-up studies. Fifty-eight bleached (30% H$_2$O$_2$ and heated) pulpless teeth were followed for 1-8 years, and 4 cases (7%) of external root resorption.
were observed (Friedman et al., 1988). Another 95 teeth examined three years after treatment by the "walking bleach" technique (sodium perborate in water) revealed no cervical resorption (Holmstrup et al., 1988). In a four-year follow-up of 250 teeth with severe tetracycline discoloration, with no evidence of cervical resorption was found (Anitua et al., 1990). An analogous study comprised of 112 teeth bleached with a paste of sodium perborate in 30% hydrogen peroxide and observed for 3-15 years reported no external root resorption (Abou-Rass, 1998).

A high concentration of hydrogen peroxide in combination with heating seemed to promote cervical root resorption (Friedman et al., 1988; Baratieri et al., 1995), in line with observations made in animal experiments (Madison and Walton, 1990; Rotstein et al., 1991b; Heller et al., 1992). The underlying mechanism for this effect is unclear, but it has been suggested that the bleaching agent reaches the periodontal tissue through the dentinal tubules and initiates an inflammatory reaction (Cvek and Lindvall, 1985). It has also been speculated that the peroxide, by diffusing through the dentinal tubules, denatures the dentin, which then becomes an immunologically different tissue and is attacked as a foreign body (Lado et al., 1983). Frequently, the resorption was diagnosed several years after the bleaching (Lado et al., 1983; Friedmann et al., 1988). In vitro studies using extracted teeth showed that hydrogen peroxide placed in the pulp chamber penetrated the dentin (Rotstein, 1991) and that heat increased the penetration (Rotstein et al., 1991d). The penetration has been found, in vitro, to be higher in teeth with cervical defects of the cementum (Rotstein et al., 1991a).

Hydrogen peroxide also increased dentin permeability (Heling et al., 1995), and that may enhance the effects of hydrogen peroxide following repeated exposures. Based on the cited literature, the use of a thermo-catalytic bleaching procedure in teeth with cervical defects of the cementum constitutes a risk factor for the development of cervical resorption. In addition, efficacy studies have shown that 30% hydrogen peroxide was not essential to the attainment of an acceptable treatment outcome.

Tooth crown fracture has also been observed after intracoronal bleaching (Grevstad, 1981), most probably due to extensive removal of the intracoronal dentin. In addition, intracoronal bleaching with 30% hydrogen peroxide has been found to reduce the micro-hardness of dentin and enamel (Lewinstein et al., 1994) and weaken the mechanical properties of the dentin (Chng et al., 2002).

(V) External Tooth Bleaching

(V-1) METHODS

Vital tooth bleaching can be performed at home and in-office. Four different approaches for tooth whitening have been recognized and reviewed by Barghi (1998): (1) dentist-administered bleaching—the use of a high concentration of hydrogen peroxide (from 35 to 50%) or carbamide peroxide (from 35 to 40%), often supplemented with a heat source; (2) dentist-supervised bleaching—by means of a bleaching tray loaded with high concentrations of carbamide peroxide (from 35 to 40%) that is placed in the patient's mouth for 30 min to 2 hrs while the patient is in the dental office; (3) dentist-provided bleaching—known as "at-home" or "night-guard" bleaching and administered by the patient applying from 5 to 22% solution of carbamide peroxide in a custom-made tray; and (4) over-the-counter products, often based on carbamide peroxide or hydrogen peroxide of various concentrations and placed in a pre-fabricated tray, or by the recently introduced strips (Gerlach, 2000), both to be adjusted by the user.
**Efficacy and esthetic results**

Data on the efficacy and duration of external tooth bleaching are mostly related to case presentations, and only a few clinical studies are available for review. It is generally advocated that most teeth are susceptible to bleaching (Figs. 4, 5), provided that the treatment is carried out for a sufficiently long time (Haywood, 1996; Goldstein, 1997; Heymann, 1997; Dunn, 1998; Leonard, 1998). The first subjective change in tooth color was observed after 2-4 nights of tooth bleaching with 10% carbamide peroxide (Tam, 1999a). In a clinical study of night-guard vital bleaching for 6 wks (10% carbamide peroxide), 92% of the 38 patients experienced some lightening of the treated teeth (Haywood et al., 1994). The patients were followed up by mailed questionnaires, and 74% of the 26 respondents and 62% of the 23 respondents experienced no or slight reversal in color after 1.5 and 3 years, respectively. A follow-up of 30 patients whose teeth were bleached with 10% carbamide peroxide revealed that 43% perceived their tooth color as stable 10 yrs after bleaching (Ritter et al., 2002). Another clinical trial examined the effects of the use of 10% carbamide peroxide nightly for 2 wks, and found, on an average, that the teeth were eight shade units lighter on the Vita shade guide, calibrated according to lightness value (Swift et al., 1999). Two years' follow-up revealed that the teeth, on average, darkened two units on this shade guide, and that the regression occurred during the first 6 months after bleaching. No patients found it necessary to re-bleach their teeth. Use of 20% carbamide peroxide resulted in lighter teeth than with 7.5% hydrogen peroxide when evaluated immediately after termination of a 14-day at-home bleaching procedure (Mokhlis et al., 2000). However, no difference between the two treatments with regard to tooth lightness was observed 10 wks later. In a small study which compared bleaching strips and 10% carbamide peroxide in trays, it was claimed that the bleaching strips were more efficient (Sagel et al., 2002), but others have not confirmed this finding, and there are no long-term follow-up data on this issue.

(V-3) Local side-effects

Tooth sensitivity

Tooth sensitivity is a common side-effect of external tooth bleaching (Tam, 1999b) (Table 2). Data from various studies of 10% carbamide peroxide indicate that from 15 to 65% of the patients reported increased tooth sensitivity (Haywood et al., 1994; Schulte et al., 1994; Leonard et al., 1997; Tam, 1999a). Higher incidence of tooth sensitivity (from 67 to 78%) was reported after in-office bleaching with hydrogen peroxide in combination with heat (Cohen and Chase, 1979; Nathanson and Parra, 1987). Tooth sensitivity normally persists for up to 4 days after the cessation of bleaching treatment (Cohen and Chase, 1979; Schulte et al., 1994), but a longer duration of up to 39 days has been reported (Leonard et al., 1997; Tam, 1999a). In a clinical study that compared two different brands of 10% carbamide peroxide bleaching agent, 55% of the 64 patients reported tooth sensitivity and/or gingival irritation, and 20% of those who experienced side-effects terminated the treatment due to discomfort (Leonard et al., 1997).

The mechanisms that would account for the tooth sensitivity after external tooth bleaching have not yet been fully established. In vitro experiments have shown that peroxide penetrated enamel and dentin and entered the pulp chamber (Thitinanthapan et al., 1999), and that the penetration of
restored teeth was higher than that of intact teeth (Gökay et al., 2000). The amount of peroxide detected in the pulp chamber was related to the concentration of hydrogen peroxide in the preparations applied (Gökay et al., 2000), and also varied among different brands of bleaching agents with the same declared concentration of carbamide peroxide (Thitinanthapan et al., 1999). The concentration of peroxide in the pulp chamber was not determined in the above studies, and the clinical significance of the findings is therefore unclear. Structural pulp damage was not observed in human premolars exposed to 35% hydrogen peroxide in vivo and observed up to 30 days before the teeth were extracted and submitted for histological evaluation (Cohen and Chase, 1979; Robertson and Melfi, 1980; Baumgartner et al., 1983). The longest exposure was three times for 30 min each (Cohen and Chase, 1979), and in two of the studies, heat was used to accelerate the bleaching process (Cohen and Chase, 1979; Robertson and Melfi, 1980). Only one study included patient reaction to the treatment, and it reported that 78% of patients suffered from sensitivity to cold and intermittent spontaneous pain lasting up to one day after treatment (Cohen and Chase, 1979). Histological evaluation of the human pulp after vital bleaching overnight with 10% carbamide peroxide revealed mild inflammatory changes in 4 out of 12 teeth after both 4 and 14 days' treatment, and no inflammation in teeth that were bleached with carbamide peroxide for 14 days followed by a "recovery" phase of 14 days (González-Ochoa, 2002).

An in vivo study in dogs indicated that hydrogen peroxide alone or in combination with heat caused alterations in odontoblasts and deposition of dentin (Seale et al., 1981). Hemorrhage and inflammation were observed in teeth 3 and 15 days after bleaching, and the pulpal changes were reversed 60 days after the treatment (Seale et al., 1981). In another study, 15-, 30-, and 45-minute treatments with hydrogen peroxide and heat were applied 4 times at two-week intervals, and the dogs were killed at 13, 62, and 92 days following the last treatment (Seale and Wilson, 1985). Histological examination of the pulp of the bleached teeth revealed pathological changes in odontoblast morphology and dentinogenesis at both the 13- and 62-day time points, and the severity of the changes was related to the length of each treatment. Repair of the lesions was observed 92 days after the last treatment (Seale and Wilson, 1985). Tooth sensitivity was also a common symptom in patients who had not bleached their teeth, and their symptom was correlated with gingival recession (Jorgensen and Carroll, 2002). Patients with a previous history of tooth sensitivity may thus have a higher risk for such an adverse effect from external tooth bleaching, and this should be taken into account before treatment begins.

### Mucosal irritation

A high concentration of hydrogen peroxide (from 30 to 35%) is caustic to mucous membranes and may cause burns and bleeding of the gingiva. In animal experiments, exposure of the gingiva to 1% H₂O₂ for 6 to 48 hrs resulted in epithelial damage and acute inflammation in the subepithelial connective tissue (Martin et al., 1968). Long-term application of 3% or 30% hydrogen peroxide in the hamster cheek pouch twice weekly resulted in inflammatory changes (Weitzman et al., 1986). In clinical trials that used 10% carbamide peroxide in custom-made trays, from 25 to 40% of the patients reported gingival irritation during treatment (Leonard et al., 1997; Tam, 1999a). It is therefore advisable that the tray be designed to prevent gingival exposure by the use of a firm tray that has contact with

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Bleaching Procedure</th>
<th>Duration of Study</th>
<th>No. of Treated Patients</th>
<th>No. of Untreated Controls</th>
<th>Incidence of Hypersensitivity Reactions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office</td>
<td>30% H₂O₂ + heat, 3 visits of 30 min during 3 wks</td>
<td>30 days</td>
<td>19</td>
<td>0</td>
<td>78%</td>
<td>Cohen and Chase, 1979</td>
</tr>
<tr>
<td>In-office</td>
<td>35% H₂O₂ + heat, 2-6 visits of 30 min</td>
<td>ni</td>
<td>15</td>
<td>0</td>
<td>67%</td>
<td>Nathanson and Parra, 1987</td>
</tr>
<tr>
<td>At-home</td>
<td>10% carbamide peroxide, 2 hrs or overnight</td>
<td>28 days</td>
<td>28</td>
<td>0</td>
<td>15%</td>
<td>Schulte et al., 1994</td>
</tr>
<tr>
<td>At-home</td>
<td>10% carbamide peroxide, overnight</td>
<td>14 days</td>
<td>24</td>
<td>0</td>
<td>64%</td>
<td>Tam, 1999a</td>
</tr>
<tr>
<td>At-home</td>
<td>10% carbamide peroxide, day or night</td>
<td>6 wks</td>
<td>37</td>
<td>0</td>
<td>38%</td>
<td>Leonard et al., 1997</td>
</tr>
<tr>
<td>At-home</td>
<td>10% carbamide peroxide, 6-8 hrs/day with solution changes</td>
<td>6 wks</td>
<td>38</td>
<td>0</td>
<td>52%</td>
<td>Leonard et al., 1997</td>
</tr>
<tr>
<td>At-home</td>
<td>10% carbamide peroxide, day + night or day with solution changes</td>
<td>6 wks</td>
<td>27</td>
<td>0</td>
<td>78%</td>
<td>Leonard et al., 1997</td>
</tr>
</tbody>
</table>

a ni = no information given.
b These patients terminated the study due to hypersensitivity, and there is no information about hypersensitivity reactions in the patients who completed the treatment.
c The duration of symptoms was also longer in this group where the solution was changed compared with the group treated daytime or night time without the solution being changed.

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**TABLE 2**

External Tooth Bleaching and Hypersensitivity Reactions
Morphological alteration of the enamel following tooth bleaching is another concern. Solely the teeth are affected. In this respect, the newly introduced bleaching strips may be unfavorable, since the bleaching gel will come into contact with the gingiva.

**Alteration of enamel surface**

Morphological alteration of the enamel following tooth bleaching (Fig. 6) has been addressed in several studies. Enamel slabs were subjected to different bleaching agents containing 10% carbamide peroxide for 15 hrs a day, for two- and four-week periods, and evaluated by scanning electron microscopy (Shannon et al., 1993). During the remaining 9 hrs every day, the slabs were exposed to human saliva in vivo. Significant surface alterations in enamel topography were observed in slabs treated with the bleaching solutions for 4 wks (Shannon et al., 1993). This finding was confirmed in a study with 30% hydrogen peroxide and 30% hydrogen peroxide mixed with sodium perborate (Ernst et al., 1996). Compared with the untreated control surfaces, the enamel surface exposed to the bleaching agents underwent slight morphologic alterations. Teeth that were bleached *in vivo* with 35% carbamide peroxide (30 min/day for 14 days) lost the apismatic enamel layer, and the damage was not repaired after 90 days (Bitter, 1998). By infrared spectroscopic analysis, it was found that *in vitro* treatment of extracted teeth with 35% carbamide peroxide for 30 min/day for 4 days changed the inorganic composition of the enamel, whereas 10% and 16% concentrations did not (Oltu and Gürgan, 2000). Evaluation of casts made from impressions of teeth bleached with 10% carbamide peroxide for 8-10 hrs/day for 14 days revealed no or minimal changes in the enamel surface (Leonard et al., 2001), which may be due to inadequate reproduction of the minor enamel alterations in the impression. A high concentration of carbamide peroxide was detrimental to enamel surface integrity, but the damage was less than that seen after phosphoric acid etch (Ernst et al., 1996). A clinical implication of these findings may be that the teeth are more susceptible to extrinsic discoloration after bleaching due to increased surface roughness.

**Effects on restorations**

Data from laboratory studies documented increased mercury release from dental amalgams exposed to carbamide peroxide solutions for periods ranging from 8 hrs to 14-28 days (Hummert et al., 1993; Rotstein et al., 1997). The amount of mercury released varied with type of amalgam and type of bleaching agent and ranged from 4 times to 30 times higher than in saline controls. It has been suggested that bleaching may increase the solubility of glass-ionomer and other cements (Swift and Perdigão, 1998). Furthermore, the bond strength between enamel and resin-based fillings was reduced in the first 24 hrs after bleaching (Dishmann et al., 1994). After 24 hrs, there was no difference in the strengths of dental composite resin cement bonds to bleached and non-bleached enamel (Homewood et al., 2001). Following bleaching, hydrogen peroxide residuals in the enamel inhibit the polymerization of resin-based materials and thus reduce bond strength (Lai et al., 2002). Therefore, tooth-bleaching agents should not be used prior to restorative treatment with resin-based materials.

**(V-4) General side-effects**

The risk of adverse effects has not been the main focus in the design of clinical studies of external tooth bleaching. For example, for a case-reference study that detects 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, and for detection of a 10% increase in the risk, more than 10,000 people must be enrolled in the study (Bjerre and LeLorier, 2000). In the clinical studies published on tooth bleaching that address adverse effects (Cohen and Chase, 1979; Nathanson and Parra, 1987; Haywood et al., 1994; Schulte et al., 1994; Leonard et al., 1997; Tam, 1999a,b), the number of participants has been small compared with the above numbers, and many studies did not have control groups. Therefore, the potential general adverse effects of external tooth bleaching cannot be assessed at this time.

**(V-5) Genotoxicity and carcinogenicity of bleaching agents**

The genotoxicity of hydrogen peroxide and of tooth whiteners containing carbamide peroxide has been evaluated (IARC, 1985; ECETOX, 1996; Li, 1996). The consensus arising from these evaluations was that direct contact with hydrogen peroxide induced genotoxic effects in bacteria and cultured cells. When hydrogen peroxide was administered to bacteria or cultured cells in the presence of catalase or other metabolizing enzymes, the effect was reduced or abolished. Testing of hydrogen peroxide for systemic genotoxic effects in animals revealed no evidence of *in vivo* mutagenicity. Since hydroxy radicals,
perhydroxyl ions, and superoxide anions formed from hydrogen peroxide are capable of attacking DNA, the genotoxic potential of hydrogen peroxide is dependent on the accessibility of free radicals to target DNA. This may explain why hydrogen peroxide induces genotoxicity in the presence of metabolizing enzymes neither in vitro nor in vivo. Tooth whiteners containing carbamide peroxide were mutagenic in certain bacterial strains and non-mutagenic in the presence of additional activating enzymes. Several in vivo studies addressing the formation of micronuclei in bone marrow cells and sister chromatid exchange after exposure to carbamide-peroxide-containing products revealed no genotoxic effects.

Data on animal experiments evaluating long-term effects of the oral administration of hydrogen peroxide are given in Table 3. A dose-dependent increased incidence of duodenal hyperplasia was observed in a study where 0.1% and 0.4% hydrogen peroxide was administered to mice via drinking water for 100 days (Ito et al., 1981). In addition, the number of adenomas and carcinomas increased in the duodenum of the exposed groups, but not in a dose-related manner (Ito et al., 1981). In another study, mice were given 0.4% hydrogen peroxide in the drinking water for up to 700 days. Benign and malignant lesions were found in the stomach and duodenum after 90 days’ exposure (Ito et al., 1982). The incidence did not increase with exposure time, but more severe lesions were observed later in the experiment. The stomach lesions regressed completely after an exposure-free period of 10-30 days, but some of the duodenal lesions persisted. Strains with different catalase activity and provided to mice with 0.4% hydrogen peroxide in the drinking water resulted in tumor incidence inversely related to the catalase activity (Ito et al., 1984). In mice, topical application of 15% hydrogen peroxide in acetone on the skin for 25 wks resulted in an increased number of papillomas in the treated group, but no malignant changes were observed in mice fol-

<table>
<thead>
<tr>
<th>Type of Study and Animals</th>
<th>Exposure</th>
<th>Duration of Exposure</th>
<th>Observation Time</th>
<th>Dose and Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAa, 100 mice</td>
<td>H2O2 in drinking water</td>
<td>100 wks</td>
<td>100 wks</td>
<td>Control 0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>CAa, 138 mice</td>
<td>H2O2 in drinking water</td>
<td>700 days</td>
<td>700 days</td>
<td>duodenal hyperplasia 9%</td>
<td>40%</td>
</tr>
<tr>
<td>CTb, 85 mice</td>
<td>H2O2 in drinking water</td>
<td>7 months</td>
<td>7 months</td>
<td>duodenal adenoma 1%</td>
<td>6%</td>
</tr>
<tr>
<td>PRc, 61 rats</td>
<td>(A) MNNGf in food</td>
<td>7 months</td>
<td>7 months</td>
<td>duodenal carcinoma 0%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>(B) MNNG in food + 1% H2O2 in drinking water</td>
<td></td>
<td></td>
<td>duodenal tumors 5.3d</td>
<td>1.7d</td>
</tr>
<tr>
<td></td>
<td>(C) 1% H2O2 in drinking water</td>
<td></td>
<td></td>
<td>11%</td>
<td>31%</td>
</tr>
</tbody>
</table>

a = carcinogenicity study.
b = CT = chronic toxicity study.
c = PR = promoter studies.
d = Catalase activity (10^-4 k/mg protein).
e = Duodenal tumors consisting of hyperplasia, adenomas, and carcinomas.
f = MNNG = 1-methyl-3-nitro-1-nitrosoguanidine (CAS no. 70-25-7).

Thus, based on the aforementioned studies, hydrogen peroxide was shown to have a weak local carcinogenic-inducing potential. The mechanism is unclear, but a genotoxic action cannot be excluded, since free radicals formed from hydrogen peroxide are capable of attacking DNA. Several studies of DMBa carcinogenesis in mice skin and hamster cheek pouch indicate that...
hydrogen peroxide may act as a tumor-promoter (Klein-Szanto and Slaga, 1982; Weitzman et al., 1986).

The International Agency for Research on Cancer (IARC) concluded that there is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of hydrogen peroxide and classified the chemical into Group 3: Unclassifiable as to carcinogenicity to humans (IARC, 1999). Recently, the genotoxic potential of hydrogen peroxide in oral health products has been evaluated (SCCNFP, 1999). It appears unlikely that oral health products containing or releasing hydrogen peroxide up to 3.6% $\text{H}_2\text{O}_2$, will enhance cancer risk in individuals except in those who have an increased risk of oral cancer due to tobacco use, alcohol abuse, or genetic predisposition (SCCNFP, 1999). To evaluate higher concentrations of hydrogen peroxide was not the task of the committee.

(V-6) TOXICITY OF HYDROGEN PEROXIDE AND CARBAMIDE PEROXIDE

Case reports of human exposure

The acute effects of hydrogen peroxide ingestion are dependent on the amount ingested and the concentration of the hydrogen peroxide solution. The outcomes of accidental ingestion, or intentional ingestion for suicide, of solutions of 10% hydrogen peroxide and higher were more severe than those seen at lower concentrations (Dickson and Caravati, 1994). Accidental ingestion of 35% hydrogen peroxide has resulted in several fatal or near-fatal poisonings (Giusti, 1973; Giberson et al., 1989; Humberston et al., 1990; Christensen et al., 1992; Sherman et al., 1994; Litovitz et al., 1995; Ijichi et al., 1997). These individuals vomited, were cyanotic, and experienced convulsions and respiratory failure (Giberson et al., 1989)

Cerebral infarction and ischemic changes of the heart due to gas embolism have also been observed (Rackoff and Merton, 1990; Christensen et al., 1992; Luu et al., 1992; Cina et al., 1994; Sherman et al., 1997; Ijichi et al., 1997). Young children are at high risk for accidental ingestion. A two-year-old child died after drinking 100 mL of a 35% hydrogen peroxide solution, which corresponds to a dose of 290 mg hydrogen peroxide/kg BW (Christensen et al., 1992). Also, ingestion of a lower concentration of hydrogen peroxide has resulted in serious injury. Lung edema and diffuse intestinal emphysema were found on autopsy of a 16-month-old child who had swallowed approximately 600 mg hydrogen peroxide/kg BW of a 3% hydrogen peroxide solution. When the child was first seen, white foam emerged from the child’s mouth and nose, and the child died 10 hrs later (Cina et al., 1994). Portal venous gas embolism was observed in a two-year-old child after unintentional ingestion of 3% hydrogen peroxide solution (Rackoff and Merton, 1990).

One syringe (3.5 g) of 18% carbamide peroxide yields 210 mg of hydrogen peroxide. Fatal poisoning is therefore not likely even if a two-year-old child (body weight approximately 12 kg) ingests one syringe of bleaching agent. Ulceration of the oral mucosa, esophagus, and stomach is more likely to occur in such a case, accompanied by symptoms such as nausea, vomiting, abdominal distention, and sore throat, as have been reported for other hydrogen peroxide-containing preparations (Dickson and Caravati, 1994). It is therefore important to keep syringes with bleaching agents out of the reach of children, to prevent any possible accident.

Animal studies

Oral LD$_{50}$ determination is a crude estimate of the toxicity of a compound (van den Heuvel et al., 1990), but such data are often provided and used for toxicological assessment. The single-dose LD$_{50}$ values for non-carbopol-containing 10% carbamide peroxide solutions and a carbopol-containing 10% carbamide peroxide solution in mice were found to be 143 mg/kg and 87 mg/kg, respectively (Woolverton et al., 1993). This corresponds to 15 and 9 mg carbamide peroxide per kg BW. For hydrogen peroxide, the oral LD$_{50}$ value was found to be approximately 1600 mg/kg (Ito et al., 1976), but no other studies have confirmed the above findings. In rats, a single oral dose of 5 g/kg BW of proprietary solutions of 10%, 15%, and 35% carbamide peroxide induced a concentration-dependent acute toxicity, and the rats showed respiratory depression, reduced weight gain and water consumption, changes in estrous cycle, and, at necropsy, histological abnormalities of the stomach, including necrotic mucosa and disrupted gastric glands (Cherry et al., 1993). In the highest-concentration group, 3 animals died of gastric hemorrhage and bloating. Six of 36 rats died within 2 hrs after receiving, orally, 5 g/kg BW of a tooth whitener containing 6% hydrogen peroxide (Redmond et al., 1997). After 15 min, the stomach was grossly bloated with gas, and after 2 hrs the blood hematocrit was elevated, and histology revealed injury to the gastric mucosa. The gastric mucosa appeared normal one week later, and the blood chemistry normalized 2 wks after the exposure. In rats, stomach gavage of 15 and 50 mg carbamide peroxide per kg BW or 150 and 500 mg of tooth whitener containing 10% carbamide peroxide per kg BW resulted in ulceration of the gastric mucosa after 1 hr; the lesions started to heal after 24 hrs (Dahl and Becher, 1995). The ulcerations from the exposure to the tooth-bleaching agent were more pronounced than those observed after a comparable dose of carbamide peroxide. This may be attributed to the hydrophobic nature of the gel and the content of carbopol in the bleaching agent, which likely increases tissue adherence and retards the decomposition of hydrogen peroxide (Dahl and Becher, 1995).

In catalase-deficient mice that were given 100 ppm, 300 ppm, 1000 ppm, or 3000 ppm hydrogen peroxide in distilled water for 13 wks, the "no observed adverse effect level" (NOAEL) was 100 ppm, corresponding to 26 and 37 mg/kg BW/day for males and females, respectively (Weiner et al., 2000). In the 1000- and 3000-ppm groups, small duodenal mucosal hyperplasias were observed; the lesions appeared reversible during a six-week recovery period. In a study of rats given 50 mg/mL hydrogen peroxide by oral gavage 6 times a wk for three months, the NOAEL was found to be 56 mg/kg BW/day (Ito et al., 1976). Deleterious localized effects on the gastric mucosa, decreased food consumption, reduced weight-gain, and blood chemistry changes were observed in the affected animals. Rats exposed daily, by oral gastric tube, to 0.06%-0.6% hydrogen peroxide solutions for 40–100 days, and to doses above the NOAEL (30 mg/kg BW/day), exhibited significant reduction in plasma catalase levels, and, in the highest-dose group, reduced weight-gain and blood chemistry changes were found (Kawasaki et al., 1969).

(V-7) RISK ASSESSMENT OF EXTERNAL TOOTH BLEACHING

Risk assessment is traditionally considered to consist of four steps: the hazard identification, the dose-response relationship, the exposure assessment, and the risk characterization (IPCS, 1999). The risk characterization is founded on a critical comparison of the data on exposure and the dose-response relationship.
The important ingredient in tooth whitening today is hydrogen peroxide. The NOAEL values based on repeated-dose studies with hydrogen peroxide per os have been estimated to be from 26 to 56 mg/kg BW/day (Kawasaki et al., 1976; Ito et al., 1989). These three studies are consistent in their findings of the "no adverse effect" level, and we have selected 26 mg/kg BW/day for the following risk assessment.

The amount of bleaching agent used for bleaching one arch of teeth has been calculated to be 900 mg per application when administered according to the manufacturer’s instruction (Dahl and Becher, 1995), and an average of 500 mg per application based on clinical experiments (Li, 1996). At least 25% of the bleaching agent administered in bleaching trays is ingested during 2 hrs of bleaching (Matis et al., 2002). We have calculated the exposure to hydrogen peroxide from tooth bleaching and the safety factor using different concentrations of the bleaching agent (Fig. 7). The results are given in Table 4. The safety factor (NOAEL/exposure) varies between 350 and 55. In risk assessment based on toxicity data derived from animal studies, the minimum accepted safety factor is 100 (Woodward, 1996). This safety factor is not reached in preparations that deliver or contain more than 12.6% H₂O₂ when 500 mg of bleaching agent is used for bleaching one arch. Longer bleaching periods per day, multiple applications, bleaching maxillary and mandibular teeth at the same time, and overfilling the tray increase the exposure and reduce the safety factor. For example, if both maxillary and mandibular teeth are bleached at the same time, the minimum required safety factor will not be reached for preparations that contain or deliver more than 7.9% H₂O₂, which corresponds to 22% carbamide peroxide (Budavari et al., 1989). According to the exposure data from a previous evaluation (900 mg/application) (Dahl and Becher, 1995), the concentration of H₂O₂ should not exceed 3.5%, which corresponds to 10% carbamide peroxide (Table 4). Based on the risk assessment, it must be concluded that selection of preparations with a low concentration of carbamide peroxide is recommended for the optimum safety of the patient. In addition, overfilling the tray without removing excess material, biting on the tray, and bleaching both maxillary and mandibular teeth at the same time are not advisable.

(V-8) LEGAL AND ETHICAL ASPECTS OF EXTERNAL TOOTH BLEACHING

In the US, tooth-bleaching agents are included in the acceptance program of the American Dental Association (Burrell, 1997). The evaluation is based on laboratory studies, toxicological studies, and clinical data, and the type of study required for each product is dependent on the composition of the product (American Dental Association, 1998). For products with an ingredient for which safety and efficacy have already been evaluated, laboratory studies are sufficient for the evaluation.

Tooth whiteners are generally regarded in Europe as cosmetic products (EU Commission, 1996). According to the cosmetic regulation, the maximum authorized content or release of hydrogen peroxide in such oral hygiene products is 0.1% (EU Commission, 1992). Tooth-whitening products can also be claimed to be medical devices, and evaluated according to the medical device regulation (EU Commission, 1993). Products granted the EU certification, i.e., the CE marking (CE = Communauté Européen), could be used for tooth bleaching provided that the claims of the manufacturer and the definition of a medical device according to the European regulation are followed. The definition of a medical device includes "material or other article intended by the manufacturer to be used for the purpose of treatment or alleviation of disease, or for the purpose of treatment, alleviation of or compensation for a handicap". At least in Europe, the use of bleaching agents containing

### TABLE 4
Calculated Exposures to Hydrogen Peroxide during Two-hour Bleaching of One Arch with Custom-made Tray and the Safety Factors Derived

<table>
<thead>
<tr>
<th>Preparation</th>
<th>H₂O₂ Concentration</th>
<th>Exposure to H₂O₂ (mg/kg BW/application)</th>
<th>Safety Factor</th>
<th>Exposure to H₂O₂ (mg/kg BW/application)</th>
<th>Safety Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamide peroxide 10%</td>
<td>3.6%</td>
<td>0.075</td>
<td>350</td>
<td>0.14</td>
<td>185</td>
</tr>
<tr>
<td>Carbamide peroxide 15%</td>
<td>5.4%</td>
<td>0.11</td>
<td>240</td>
<td>0.20</td>
<td>130</td>
</tr>
<tr>
<td>Carbamide peroxide 22%</td>
<td>7.9%</td>
<td>0.16</td>
<td>160</td>
<td>0.29</td>
<td>89</td>
</tr>
<tr>
<td>Carbamide peroxide 35%</td>
<td>12.6%</td>
<td>0.26</td>
<td>100</td>
<td>0.47</td>
<td>55</td>
</tr>
</tbody>
</table>

a. H₂O₂ concentration determined based on the composition of carbamide peroxide that consists of 36% H₂O₂ (mol w) and 64% urea (Budavari et al., 1989).
b. Exposure based on bleaching 10 teeth with 500 mg bleaching agent (Li, 1996), 25% of the bleaching agent ingested during 2 hrs (Matis et al., 2002), and the WHO body weight estimate (60 kg) (Woodward, 1996).
c. Safety factor = NOAEL/exposure (rounded to nearest 10) (Fig. 7). The NOAEL value is 26 mg/kg BW/day. The minimum acceptable safety factor, based on data derived from animal studies, is 100 (Woodward, 1996).
d. Exposure based on bleaching 10 teeth with 900 mg bleaching agent (Dahl and Becher, 1995), 25% of the bleaching agent ingested during 2 hrs (Matis et al., 2002), and the WHO body weight estimate (60 kg) (Woodward, 1996).
e. This concentration is intended for professional use only. The calculation is included in case the patient uses the preparation at home.
more than 0.1% hydrogen peroxide requires a proper professional diagnosis of a disease or a handicap. Bleaching must therefore be regarded as an alternative to other dental procedures such as laminates and full crown therapy.

**VI) Concluding Remarks**

We advocate a more selective use of tooth bleaching and a limitation on its use to patients for whom such treatment could be professionally justified. The need for bleaching solely to achieve a “perfect” smile and a youthful look (Burrell, 1997) is thus questioned. We urge the dental profession to maintain high ethical standards and not to recommend performing cosmetic adjustment of tooth color just to comply with the demand of the patient. Our concerns are based on the lack of large-scale clinical investigations on adverse effects and the limited toxicological data on carbamide peroxide available in peer-reviewed journals. Furthermore, the risk assessment has shown that the minimum accepted safety factors might not be attained in certain clinical situations.

**Acknowledgments**

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**References**


