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From

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Peroxides have been used for tooth bleaching/whitening for more than 30 years and the use of hydrogen peroxide or hydrogen peroxide releasers as tooth bleaching/whitening actives in a custom-fitted tray has been available since the 1980's. The safety and efficacy of hydrogen peroxide and carbamide peroxide bleaching/whitening agents is well documented and there are over 20 different products (10 - 30% carbamide peroxide releasing 3.6 - 10% hydrogen peroxide) are currently on the market via dental offices for home use. At least 10 different tooth bleaching/whitening products with varying levels of hydrogen peroxide or hydrogen peroxide releasers (3.6 - 6% hydrogen peroxide) are also currently available as direct to consumer products in Canada and the United States.

#### **Oral Soft Tissue:**

There are a large number of clinical studies published or reported at international dental meetings which have been conducted on a variety of tooth bleaching products delivering 3.6 - 16% hydrogen peroxide using a variety of delivery systems. Studies have evaluated effects of intended use (typically 2 weeks), extended use (approx. 3 months), exaggerated use and use by juveniles. The adverse event profile for each product type, and from each study design and duration, are comparable. If adverse events occurred they were typically gingival irritation and/or tooth sensitivity, regardless of mode of delivery. The majority of adverse events were mild and all resolved either spontaneously or within 2 days after product use was discontinued. All resolved fully without dentist intervention and were without long term effect. Even 6 months continuous use caused the same mild, transient adverse events as those observed after 14 or 28 days of product use.

Studies have generally been conducted with hydrogen peroxide containing products in one leg and non-peroxide-containing product as placebo or marketed carbamide peroxide product to act as a benchmark. Assessment of the results following usage of the placebo legs showed that the adverse events experienced were similar in type and severity to those experienced by the subject following use of the hydrogen peroxide-containing tooth whitening products. These data support the conclusion that the adverse events seen were attributable to the matrix also.

The adverse event profiles (incidence and severity) from clinical studies conducted were similar to those following use of currently marketed tooth whitening products (data available from industry consumer relations telephone lines). Market experience continues to indicate that  $\leq 6\%$  hydrogen peroxide tooth whitening products are well tolerated by consumers.

Few studies have been conducted specifically to assess the effect of tooth whiteners on subjects suffering with gingivitis and periodontitis. Data available from studies shows no initiation or exacerbation of inflammation, other than the well-documented transient gingival irritation experienced by some users. Hydrogen peroxide has been used specifically in the treatment of periodontitis and has been successful in long-term therapy when used daily in subgingival irrigation of affected sites for up to two week periods intermittently over 17.5 years (Kawamura et al. 2004).

#### **Oral Hard tissue:**

Hard tissue safety of hydrogen peroxide has been extensively evaluated and is well published.

Testing has confirmed the safety of hydrogen peroxide up to 6% in modern day bleaching gels with respect to the dentition (enamel, dentine and pulp) and restorative materials even under highly exaggerated exposure conditions *in vitro*. Such data provide positive reassurance that no adverse effects will result if such products are potentially overused *in vivo*.

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 very small amounts of mercury from amalgams at levels which are well within the limits for mercury exposure in the guidelines set out by the World Health Organisation (WHO, 1976). Thus, there is no *in vivo* risk from additional vapour exposure following tooth bleaching (Hummert et al. 1993; Rotstein et al. 1997).

A number of 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 to 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; Cohen and Chase, 1979 and Anderson et al., 1999). 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. The histological and immunostaining studies also confirm *in vivo* observations that the response of pulp to bleaching appeared self-limiting. Evidence of pulp inflammation did not worsen with increased time of bleaching, and in all cases, responses appeared self-resolving.

Additional supporting data for the minor, self-limiting and rapidly resolving (even during treatment) effects of peroxides on pulp tissues may be provided from studies. Varvara et al. (Varvara et al., 2003) found significant quantities of active catalase in vital pulp – supporting that rapid degradation of peroxide would likely take place during the limited penetration of peroxide associated with tooth bleaching. In addition, they found that the catalase activity was 3-fold increased in inflamed pulps as opposed to normal pulp tissue the concentrations of hydrogen peroxide required to produce enzyme inhibition were some 1000-10,000 fold higher than concentration observed to penetrate pulp under even idealized *in vitro* treatment conditions.

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