Use of Hydrogen Peroxide-Based Tooth Whitening Products and its Relationship to Oral Cancer

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ABSTRACT

Tooth whitening products containing hydrogen peroxide or carbamide peroxide were evaluated in this review for potential oral cancer risk from their use. Hydrogen peroxide is genotoxic in vitro, but not in vivo. Hydrogen peroxide was not considered to pose a genotoxic risk to humans. The animal toxicology data relevant to the assessment of the carcinogenicity of hydrogen peroxide do not indicate that it has significant carcinogenic activity at any site, including the oral cavity. Hydrogen peroxide was found to enhance the carcinogenic effects of potent DNA reactive carcinogens in experimental animals. However, these experimental conditions are artificial as they are related to high exposures and are of no relevance to potential human exposures to low quantities of hydrogen peroxide from the use of tooth whitening products. Clinical data on hydrogen peroxide-containing tooth whitening products show no evidence for the development of preneoplastic or neoplastic oral lesions. Exposures to hydrogen peroxide received by the oral cavity are exceedingly low, of short duration (30–60 minutes), and could not plausibly enhance any carcinogenic risk associated with exposure of the oral cavity to chemicals in cigarette smoke or to alcohol, both known risk factors for the development of oral cancer.

CLINICAL SIGNIFICANCE

Based on a comprehensive review of the available literature and research, the use of tooth whitening products containing hydrogen peroxide or carbamide peroxide does not appear to pose an increased risk of oral cancer in the general population, including those persons who are alcohol abusers and/or heavy cigarette smokers.

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INTRODUCTION

Tooth whitening products (eg, strips, gels, varnishes) that contain hydrogen peroxide, or carbamide peroxide, a product that degrades to form urea and hydrogen peroxide, have been in common use throughout North America, particularly over the past 15 years. During this time no significant health effects from the use of tooth whitening products have been noted. In Europe, by contrast, tooth whitening products containing hydrogen peroxide or carbamide peroxide are available to consumers only from a dental practitioner. Recently, the European Union's Scientific Committee on Consumer Products[1,2] raised concerns with respect to the potential of hydrogen

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peroxide, including hydrogen peroxide generated from carbamide peroxide, to convey an increased risk of oral cancer, especially in smokers and alcohol abusers. Given this opinion, a comprehensive review was undertaken of the available safety data on various tooth whitening products, and hydrogen peroxide in particular, to assess the carcinogenic risks posed to humans by hydrogen peroxide exposures from the use, both intended and exaggerated, of tooth whitening products.[3] This article presents a summary of this review regarding the safety of tooth whitening products with respect to their potential carcinogenicity in humans.

GENOTOXICITY

Under certain conditions hydrogen peroxide generates reactive hydroxyl radicals that can oxidize lipid[4,5] and produce oxidative DNA damage.[6,7] However, for mutagenicity to occur in vivo, the DNA adducts must escape the effective DNA repair process. Also, in mammalian cells, the degradation of hydrogen peroxide is carried out by catalase, and hydroxyl radicals formed from hydrogen peroxide are scavenged by peroxidase and the cellular stores of nucleophiles such as glutathione and protein.

The in vitro genetic toxicity data clearly show genotoxic effects of hydrogen peroxide. In the bacterial mutagenicity assays, positive results have been reported in *Salmonella typhimurium*.[8–13] In mammalian cells, mixed results have been reported for hydrogen peroxide in in vitro tests designed to detect mutation[14] and/or chromosome breakage/damage.[15–24]

In contrast to the in vitro assays, in whole animal (rats, mice, and hamsters) in vivo studies,[25,26] including a mouse micronucleus assay[25] in which hydrogen peroxide was administered by intraperitoneal injection at doses of up to 1,000 mg/kg body weight, hydrogen peroxide has exhibited no evidence of DNA-damaging potential. The lack of effect of hydrogen peroxide in whole animals is a result of the fact that the in vitro experiments[17,19,27] do not contain the in vivo levels of the enzymes responsible for the detoxification of hydrogen peroxide. Taking into consideration the foregoing, the genotoxic risk of exposures of the oral mucosa (having considerable catalase activity in saliva as well as the oral mucosa) to hydrogen peroxide encountered from tooth whitening products under recommended conditions of use is considered to be negligible.

CARCINOGENICITY

The International Agency for Research on Cancer[28] has evaluated the carcinogenic potential of hydrogen peroxide and concluded that hydrogen peroxide is "not classifiable as to its carcinogenicity to humans." This essentially means that the data were considered insufficient for making a decision on the potential carcinogenicity of hydrogen peroxide to humans.

Studies to assess the carcinogenicity of hydrogen peroxide in rodents include an unpublished drinking water study of the carcinogenicity of hydrogen peroxide in F344 rats,[29] oral administration to several strains of mice,[29–32] several dermal skin painting assays,[33,34] and an oral initiation-promotion study in rats.[35]

The 2-year carcinogenicity study conducted in F344 rats showed no evidence of a carcinogenic effect—at any site, including the oral cavity—of hydrogen peroxide when administered in the drinking water at a concentration of up to 0.6%.

Hydrogen peroxide at high concentrations (0.4% in the drinking water) was weakly carcinogenic to the duodenum of mice deficient in catalase enzymes which are responsible for the metabolism/detoxification of hydrogen peroxide.[29–33] This animal model is of limited relevance to humans because humans have high levels of catalase activity, especially in the oral cavity where exposure to hydrogen peroxide would occur with the use of tooth whitening products. These results however support the view that catalase enzymes are responsible for the

detoxification of hydrogen peroxide. Similarly, the relevance of forestomach tumors reportedly induced in rats by a high drinking water concentration of 1% hydrogen peroxide,[35] and to a greater degree in rats pretreated with the potent stomach carcinogen N-methyl-N-nitro-N-nitrosoguanidine, is highly questionable given the lack of a human correlate for this organ and the fact that chronic tissue irritation over a sustained period often underlies forestomach tumor development in rodents.

Other studies of the carcinogenic activity of hydrogen peroxide have evaluated the effects of combinations with other known potent DNA-reactive carcinogens, including concomitant exposure to methylazoxymethanol acetate in the drinking water of rats,[36] skin painting of mice in concert with 7,12-dimethylbenza[a]anthracene,[33,34,37,38] and painting of hamster buccal cheek pouches in combination with 7,12-dimethylbenza[a]anthracene.[39,40]

The available skin painting initiation-promotion studies in mice pretreated with 7,12-dimethylbenz[a]anthracene, followed by treatment with hydrogen peroxide, failed to elicit any clear evidence of a tumor promoting effect of hydrogen peroxide.[33,34,37,38]

The combined exposure studies of Hirota and Yokoyama[36] (rats exposed to hydrogen peroxide along with methylazoxymethanol acetate) and Weitzman et al.[39] (painting of hamster cheek pouches with hydrogen peroxide and 7,12-dimethylbenza[a]anthracene) document the interactive effects of hydrogen peroxide with DNA-reactive carcinogens. Duodenal tumors induced by methylazoxymethanol acetate were enhanced by hydrogen peroxide treatment in the Hirota and Yokoyama[36] study. This finding, however, is not relevant to human risk assessment because the experimental conditions used, namely concomitant exposure to potent DNA-reactive carcinogens, were highly artificial. In the hamster cheek pouch experiments,[39,40] conceptually more relevant to assessment of oral cancer risk, no clear effect of hydrogen peroxide was observed.

In addition to the limitations of the combined exposure studies with respect to human relevance, their results must be interpreted in light of the exposure conditions experienced by humans with tooth whitening products use. Salivary concentrations of hydrogen peroxide following application of a tooth whitening product rapidly decline to near undetectable levels within 15 to 60 minutes.[41,42] An analysis of potential human exposure to hydrogen peroxide from the use of tooth whitening products indicates that exposures in the carcinogenicity/tumor promotion/interaction studies were orders of magnitude higher than could be experienced by humans using tooth whitening products. Also, human exposures to hydrogen peroxide from the use of tooth whitening products are generally short-term (minutes post-application) and intermittent in nature (eg, exposure periods of up to 14 days, two or three times per year). As a result, the weak carcinogenic, promoting, and/or enhancing effects of repeated or sustained exposures to much higher concentrations of hydrogen peroxide reported in some rodent assays, cannot be compared to the very low, short-term, and intermittent exposures to hydrogen peroxide from tooth whitening products use in humans.

CLINICAL STUDIES

There are over 100 sponsored clinical studies, most as yet unpublished, comprising approximately 4,000 subjects in total, that have been conducted on hydrogen peroxide-containing (5.33–16%) tooth whitening products. The results of these studies were made available for review and inclusion in this report by the manufacturers in the consortium supporting this investigation. In addition, Leonard et al.[43] reported a 7.5-year follow-up study on a small group of tooth whitening product users. In this follow-up

study of 15 subjects who received 6 months of continuous hydrogen peroxide treatment for tetracycline stains, no evidence of adverse effects in the oral cavity were noted in the 9 subjects who agreed to a clinical examination. While the study is small in terms of number of subjects, thus limiting the value of statistical analyses, none of the 15 participants reported any side effects that they believed to have been related to treatment.

Studies have evaluated the effects of tooth whitening products under recommended use conditions (1–2 weeks) and under conditions of extended (up to 6 months) and exaggerated use (four times application per day). In these studies, the incidence of adverse effects, while quite variable, was in all cases mild and transient and limited to gingival irritation and tooth sensitization. These effects resolved within a few days of ending product use.

Mild gingival irritation has not been reported to be a risk factor for the development of oral cancer. Moreover, the gingiva is a very rare site for the development of oral cancers. The most common sites, the floor of the mouth and the lateral edge of the tongue, were not adversely affected in any of the clinical studies on tooth whitening products. Also, at these sites, hydrogen peroxide concentrations in saliva (maximum concentration of 0.03% 1-minute post application[41]) are very low in comparison to hydrogen peroxide concentrations achieved on the gingiva.

In addition to the published and unpublished clinical data accumulated to support the safety of tooth whitening products over the last 4 to 5 years, millions of tooth whitening kits have been sold directly to consumers, and bleaching procedures have been extensively conducted under the supervision of dental professionals for the last 15 years. Yet, no published reports of preneoplastic or neoplastic lesions associated with their use have appeared in the scientific literature to date.

An unpublished meeting abstract[44] suggested a possible association between the development of oral cancer and use of tooth whitening products in younger adults (<45 years of age). The authors stated that among three cases of primary oral cancer in young adults who had used tooth whitening products, two were cases of tongue cancer in patients who reported using tooth whitening products 2 to 3 years prior to diagnosis; however, that is not a sufficient interval for the induction of malignant, metastatic tumors. As a result, there is no biologically plausible basis for any potential association between the use of tooth whitening products and the reported two cases of tongue cancer. Moreover, in no clinical studies to date have adverse effects on the tongue been reported to occur in response to the use of tooth whitening products.

EFFECTS OF TOOTH WHITENING PRODUCTS ON SMOKERS/ALCOHOL ABUSERS

More than 90% of persons who develop oral cancer are smokers. Similarly, excessive consumption of alcohol is a pronounced risk factor for oral cancer development of nearly the same order of magnitude as smoking status. Given the potential, if not likely, use of tooth whitening products by smokers and/or alcohol consumers, it is of interest to evaluate the potential exacerbation of oral cancer risks by tooth whitening products use, and hydrogen peroxide exposure, in these subjects. As with smoking and alcohol consumption, an increased cancer risk from combined exposures can arise when both exposures each convey a cancer risk. For example, combined smoking and asbestos exposures, which individually present cancer risks, convey greatly increased risks for lung cancer. However, as there is no established human cancer risk from tooth whitening products or hydrogen peroxide, there is no basis to postulate that there would be an increased risk from the use of tooth whitening products by individuals with exposure to products associ-

ated with risk of oral cancer, such as in smokers and/or heavy drinkers.

The clinical studies on tooth whitening products, many of which would have included smokers and/or alcohol consumers, provide no evidence to indicate that the rate or severity of the adverse effects of tooth whitening products, namely mild, transient gingival irritation and tooth sensitivity are significantly different from nonsmokers/nonalcohol consumers. Although there are no long-term follow-up data (eg, greater than 7.5 years) in smokers and nonsmokers, no visible pathological changes that could plausibly be related to future preneoplastic or neoplastic lesion development were seen in any of the subjects in the over 100 clinical trials.

CONCLUSIONS

In conclusion, the available genetic toxicity and animal toxicity data do not indicate that hydrogen peroxide poses a carcinogenic risk to the human oral mucosa at exposures levels associated with the use of tooth whitening agents. This conclusion is further bolstered by the results of the dosimetric exposure analyses from tooth whitening product users showing margins of safety on the order of 100- to 1,000-fold or more between no-effect levels in animal studies and transient peak hydrogen peroxide concentrations in saliva at the floor of the mouth. Moreover, hydrogen peroxide concentrations are highest in the gingiva, a site where oral cancer is rarely found, and humans have sufficient catalase activity in saliva and in the oral mucosa to effectively detoxicate hydrogen peroxide at such low exposure levels. The clinical trial data indicates that the only effect of hydrogen peroxide from the use of tooth whitening products is mild, transient gingival irritation and tooth sensitivity. There is no evidence of preneoplastic or neoplastic lesion development in humans. Because hydrogen peroxide from tooth whitening products use itself carries negligible carcinogenic risk, there is likely to be no enhancement of carcinogenic risks to the oral cavity caused by smoking and/or alcohol abuse.

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