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Review

Tooth whitening products and the risk of oral cancer

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Abstract

Tooth whitening products (TWP) containing hydrogen peroxide (HPO) or carbamide peroxide (CPO) were evaluated in relation to potential oral cancer risk from their use. HPO is genotoxic in vitro, but such activity is not expressed in vivo. The genotoxic risk of HPO exposure of the oral mucosa encountered from TWP use is likely therefore to be vanishingly small. Available animal data on the carcinogenicity of HPO are of limited relevance to risk assessment of oral hazard of HPO exposure from TWP, and where relevant, do not indicate that there is an increased oral cancer risk for people using TWP. Clinical data on HPO-containing TWP only show evidence of mild, transient gingival irritation and tooth sensitivity, with no evidence for the development of pre-neoplastic or neoplastic oral lesions. Exposures to HPO received by the oral cavity, including areas commonly associated with oral cancer, are exceedingly low and do not plausibly pose a risk for the promotion of initiated cells or for induction of co-carcinogenic effects in conjunction with cigarette smoke or alcohol. The use of TWP was concluded not to pose an increased risk for oral cancer in alcohol abusers and/or heavy cigarette smokers. Furthermore, TWP were concluded to be safe for use by all members of the population, including potential accidental use by children.

Keywords: Tooth whitening; Hydrogen peroxide; Oral cancer

Contents

Abbreviations: bw, body weight; CHO, Chinese hamster ovary; CPO, carbamide peroxide; DMBA, 7,12-dimethylbenza[*a*]anthracene; DNA, deoxyribonucleic acid; GI, gastrointestinal; GLP, Good Laboratory Practice; HPO, hydrogen peroxide; MNNG, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; i.p., intraperitoneal; i.v., intravenous; MAM, methylazoxymethanol acetate; MTD, maximum tolerated dose; SCCP, European Union's Scientific Committee on Consumer Products; SCE, sister-chromatid exchanges; TWP, tooth whitening products; UDS, unscheduled DNA synthesis.

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1. Introduction

Tooth whitening products (TWP) (e.g., strips, gels, varnishes) that contain hydrogen peroxide (HPO), or carbamide peroxide (CPO), a product that degrades to form urea and HPO, have been in common use throughout North America, particularly over the past 15 years. Even though tooth whitening products have been in use for over 100 years, heightened interest in tooth whitening arose following the introduction in 1989 of a particularly popular form of dentist-supervised bleaching, called nightguard vital bleaching (Haywood and Heymann, 1989). Moreover, in North America, TWP have been available directly to the consumer since early 2001. During this time no significant health effects from use of TWP have been noted. In Europe, by contrast, TWP containing HPO or CPO, are available to consumers only from a dental practitioner. The legal status of TWP, with respect to availability directly to the consumer as cosmetic products was recently assessed by the European Union's Scientific Committee on Consumer Products (SCCP, 2005). The Committee was of the opinion that TWP containing from >0.1% to 6.0% were safe for use upon consultation and approval of the consumer's dentist. The SCCP raised concerns with respect to the potential for HPO, including HPO generated from CPO, to be associated with an increased risk of oral cancer, especially in smokers and alcohol abusers (SCCP, 2004, 2005). Smokers and alcohol abusers have a significantly elevated risk for the development of oral cancer, with a reported synergistic effect of these 2 factors (Blot et al., 1988; Maier et al., 1992; Baron et al., 1993).

Given the SCCP (2004, 2005) opinion, we undertook a review of the available safety data on various TWP, and HPO in particular, to assess the genotoxic and/or carcinogenic risks posed by HPO exposures from the use, both intended and exaggerated, of TWP. As part of this evaluation, in vitro and in vivo genotoxicity studies, experimental animal studies, clinical tolerance studies involving TWP and human pharmacokinetic studies were reviewed and assessed. In addition to these data, the results of a large number of unpublished, and several published, short- and longer-term clinical trials were critically analyzed. The following presents a review of the above safety data and conclusions with respect to the potential for HPO to influence the development of oral cancer in humans.

2. Genotoxicity

2.1. In vitro data

HPO generates reactive hydroxyl radicals that can oxidize lipid (Kanner et al., 1987; O'Brien, 1988) and produce oxidative deoxyribonucleic acid (DNA) damage (Williams and Jeffrey, 2000; Cadet et al., 2003). In particular, the hydroxyl radical formed from HPO reacts with deoxyguanosine to form 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-oxo-dG) DNA adducts (Rosen et al., 1996). The 8-oxo-dG adducts are potentially promutagenic adducts and mispair during DNA replication to yield point mutations (Wood et al., 1992; Kamiya, 2003). However, for mutagenicity to occur, the DNA adducts must escape the effective DNA repair process (Asagoshi et al., 2000; Slupphaug et al., 2003), which is continuously dealing with the substantial levels of endogenous DNA oxidation that arise from cellular metabolic activity (Williams and Jeffrey, 2000; Cooke et al., 2003). In mammalian cells, the degradation of HPO is carried out by catalase and hydroxyl radicals formed from HPO are scavenged by peroxidase and the cellular stores of nucleophiles such as glutathione and protein (Griffith and Mulcahy, 1999). As noted, any 8-oxo-dG adducts that may be formed as a result of exceeding the free radical scavenging capacity of the cells, including cells of the oral mucosa, are known to be excised by DNA repair enzymes. In particular, in humans 8 oxo-dG adducts are readily repaired by such enzymes to the point that these adducts are not easily converted into a mutagenic lesion (Asagoshi et al., 2000; Lunec et al., 2002).

As expected, the in vitro genetic toxicity data clearly show genotoxic effects of HPO. In the bacterial mutagenicity assays, positive results have been reported in *Salmonella typhimurium* strains TA102 and TA104, strains that are known to be sensitive to oxidative DNA damage (Levin et al., 1982; De Flora et al., 1984; Carlsson et al., 1988; Glatt, 1989; Kensese and Smith, 1989; Abu-Shakra and Zeiger, 1990; Wilcox et al., 1990; Li et al., 1992; Nakayama et al., 1993).

The results of in vitro mammalian gene mutation assays, including the Chinese hamster ovary (CHO) V-79 *hprt* and the mouse lymphoma L5178Y *hprt* locus assays, are mixed. One (Ziegler-Skylakakis and Andrae, 1987) of 6 studies (Bradley et al., 1979; Tsuda, 1981; Bradley and Erickson, 1981; Nishi et al., 1984; Speit,