Overall Safety of Peroxides

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Abstract

Current tooth whiteners contain peroxides as active ingredients, which release hydrogen peroxide (H_2O_2) in the process of application. The primary source of safety concerns with the peroxide-based tooth whiteners is the capability of H_2O_2 to produce oxidative free radicals or reactive oxygen species (ROS), which have been associated with various pathological consequences including carcinogenesis and degenerative diseases. This chapter will review and discuss the toxicology of H_2O_2, its presence in the human body, and its potential systemic effects, genotoxicity, and carcinogenicity on the basis of evidence available in the literature.

3.1 Background

Safety concerns with peroxide-based tooth whiteners primarily originated from its content of peroxide compounds (Li 1996, 1997, 2011; Li and Greewall 2013). Carbamide peroxide ($CH_6N_2O_3$) and hydrogen peroxide (H_2O_2) are the most commonly used peroxide compounds as the active ingredient in current extracoronal tooth whitening products, while sodium perborate ($NaBO_3$) is primary for intracoronal bleaching procedures (Rotstein and Li 2008). Carbamide peroxide, or urea hydrogen peroxide, is a white crystal or a crystallized powder. Chemically carbamide peroxide is composed of approximately 3.5 parts of H_2O_2 and 6.5 parts of urea; a tooth whitener of 10% carbamide peroxide thus contains approximately 3.5% H_2O_2. Sodium perborate is also a white powder available either as monohydrate, trihydrate, or tetrahydrate. The monohydrate and tetrahydrate forms are

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commonly used for intracoronal bleaching, with H_2O_2 content theoretically around 34% and 22%, respectively. In an aqueous medium, both carbamide peroxide and sodium perborate decompose to release H_2O_2, which, therefore, is the true active ingredient of the peroxide-based tooth whitening products.

3.2 Toxicology of Hydrogen Peroxide

H_2O_2 as a chemical was first identified in 1818, and the well-known Fenton reaction was proposed in 1894. Two enzymes, peroxidase and catalase, found in 1898 and 1901, respectively, were quickly recognized to play important roles in H_2O_2 metabolism in humans. Shortly after the discovery of another important enzyme, superoxide dismutase (SOD), in 1969, research efforts on biological properties of H_2O_2 have significantly increased (Li 1996).

The toxicology of H_2O_2 has been investigated extensively, and there are a number of comprehensive reviews on the topic available in the literature (IARC 1985; ECETOX 1993; Li 1996; SCCP 2005; CEU 2011). A key characteristic of H_2O_2 is its capability of producing reactive oxygen species (ROS), which are known to induce various toxicities, including hydroxyl free radicals that have been implicated in various stages of carcinogenesis (Floyd 1990; Li 1996). Oxidative reactions of ROS with proteins, lipids, and nucleic acids are believed to be involved in a number of potential pathological consequences; the damage by oxidative free radicals may be associated with aging, stroke, and other degenerative diseases (Harman 1981; Floyd et al. 1988; Lutz 1990; Li 1996).

The major mechanism responsible for the observed toxicity of H_2O_2 is believed to be the oxidative reactions and subsequent damage in cells by ROS. In cell culture studies, H_2O_2 is highly cytotoxic at concentrations ranging from 1.7 to 19.7 μg/mL or 0.05 to 0.58 mmol/L (Rubin and Farber 1984; Bates et al. 1985; Ramp et al. 1987; Tse et al. 1991; Woolverton et al. 1993; Hanks et al. 1993; Li 1996, 2003). Hepatocytes were less sensitive to the cytotoxicity of H_2O_2 than fibroblasts and endothelial cells (Sacks et al. 1978; Simon et al. 1981; Rubin and Farber 1984), while human gingival fibroblasts derived from primary cultures and L929 mouse fibroblasts (ATCC CCL 1; Manassas, VA) were found to respond similarly to the cytotoxicity of H_2O_2 (Li 1996).

On the other hand, the human body is equipped with various defensive mechanisms available at cellular and tissue levels to prevent potential damage of H_2O_2 to cells during oxidative reactions and to repair any damages sustained. A number of enzymes, such as catalase, SOD, peroxidase, and selenium-dependent glutathione peroxidase, exist widely in body fluids, tissues, and organs, to effectively metabolize H_2O_2 (Floyd 1990; Li 1996). Simply adding iron chelators and antioxidants or increasing serum concentration in culture media effectively reduces or eliminates the cytotoxicity of H_2O_2 (Sacks et al. 1978; Rubin and Farber 1984). In a cell culture study, 20 mM H_2O_2 was undetectable after 30 min in the culture media alone and after 15 min in the media with bone tissues, indicating decomposition and inactivation of hydrogen peroxide in cell culture systems (Ramp et al. 1987). These enzymes also exist in human saliva; in fact, salivary peroxidase has been suggested to be the

body's most important and effective defense against the potential adverse effects of H_2O_2 (Carlsson 1987). Marshall et al. (2001) found that the human oral cavity, including that of adults, juveniles, infants, and adults with impaired salivary flow, was capable of eliminating 30 mg H_2O_2 in less than 1.5 minutes.

3.3 Peroxides in the Human Body

H_2O_2 was first detected in human respiration in 1880; however, it was not until 1969 when the SOD was discovered. H_2O_2 was recognized as an important by-product in oxygen metabolism of humans (Li 1996, 2011). H_2O_2 is now known as a normal intermediate metabolite in humans. It exists in human serum, and it is present in human breath at levels ranging from 0.34 to 1.0 μg per liter (Sies 1981; Williams et al. 1982). The daily production of H_2O_2 in the human liver is approximately 6.48 grams in a period of 24 h (FDA 1983). An important source of endogenous H_2O_2 is from phagocytic cells, such as neutrophils and macrophages, which play an essential role in defense against various pathological microorganisms.

3.4 Systemic Effects

Systemic effects of H_2O_2 have been investigated for both the acute and chronic exposures. A unique characteristic of H_2O_2 in inducing systemic toxicity is its concentration in addition to the dosage.

The reported acute systemic toxic effects of H_2O_2 in animals vary widely according to the H_2O_2 concentration as well as the application mode. In rats, the intravenous 50% lethal dose (LD_{50}) of H_2O_2 was found to be 21 mg/kg (Spector 1956). Using the up-and-down method, in which the dosing is adjusted up or down according to the outcome (death or survival) of the animal that received the previous dosage, the oral LD_{50} of 4% H_2O_2 solution in male and female rats was estimated at 780 and 600 mg/kg, respectively (Li 1996). The LD_{50} for percutaneous application of H_2O_2 is much higher, which was >7500 mg/kg (FDA 1983). The values of LD_{50} are inversely related to the concentrations of H_2O_2, and they vary markedly between different animal species and strains (IARC 1985; FDA 1983; ECETOX 1993; Li 1996). Tissue responses to topical application of H_2O_2 are also related to the H_2O_2 concentration, but they are usually minimal at low concentrations of ≤3%.

Acute toxicity, including fatalities, has been reported in humans who accidentally ingested large amounts of concentrated H_2O_2 solutions (Spector 1956; Giusti 1973; Giberson et al. 1989; Humberston et al. 1990; Rackoff and Merton 1990; Christensen et al. 1992; Cina et al. 1994; Sherman et al. 1994; Asanza et al. 1995; Ijichi et al. 1997; Rider et al. 2008; Byrne et al. 2014). A retrospective survey of a regional poison control center found that over a 36-month period, 325 cases were caused by H_2O_2 poisoning, which accounted for 0.34% of all the reported causes (Dickson and Caravati 1994); however, the majority of the 325 cases (71%) was pediatric population (age < 18 years), with ingestion of H_2O_2 solution being the most common route of exposure (83% of cases). One major factor associated with

the toxicity of H_2O_2 is its concentration. Ingestion of H_2O_2 solutions of less than 10% usually produces no significant adverse effects, although it may cause mild irritation to mucous membranes that results in spontaneous emesis or mild abdominal bloating (Humberston et al. 1990; Dickson and Caravati 1994). Exposure to H_2O_2 concentrations higher than 10%, however, can result in severe tissue burns and significant systemic toxicity. In addition to the tissue damage caused by oxidative reactions, gas embolism is responsible for various pathological consequences of H_2O_2 ingestion (Rackoff and Merton 1990). Each milliliter of 1% H_2O_2 releases 3.3 mL oxygen; therefore, 10 mL of 30% H_2O_2 can produce 1 L oxygen (Giberson et al. 1989; Humberston et al. 1990). Common symptoms observed in acute toxicity of H_2O_2 include stomach and chest pain, retention of breath, foaming at the mouth, loss of consciousness, motor and sensory disorders, fever, gastric hemorrhage, and liver damage. Although rare, death can occur.

Several animal studies have been conducted on acute systemic toxicity of tooth whiteners containing carbamide peroxide. Oral gavage of 5 g/kg tooth whiteners containing 10% and 22% carbamide peroxide produced no evidence of acute systemic toxicity in rats (Cherry et al. 1993; Adam-Rodwell et al. 1994). One study reported unusually low LD_{50} (87.18 to 143.83 mg/kg) of two products containing 10% carbamide peroxide in female Swiss mice (Woolverton et al. 1993). The reasons for the low LD_{50} values are unclear but may be attributed to differences in animal species, materials, and method. Using the up-and-down method, the LD_{50} of a tooth whitening gel with 10% carbamide peroxide was estimated at 23.02 g/kg in female rats (Li et al. 1996).

Chronic systemic toxicity of H_2O_2 has been investigated using animal models. No visible abnormalities were detected in mice drinking 0.15% H_2O_2 (about 150 mg/kg/day) ad libitum for 35 weeks, and their growth was also normal (FDA 1983). Necropsy results, however, showed changes in the liver, kidney, stomach, and small intestine. Solutions of >1% H_2O_2 (>1 g/kg/day) caused pronounced weight loss and death of mice within 2 weeks. A rat study by Ito et al. (1976) found that, when administered by an oral gastric catheter 6 days weekly for 90 days, the dose of 506 mg/kg suppressed body weight gain, decreased food consumption, and caused changes in hematology, blood chemistry, and organ weights. The principal tissue affected was gastric mucosa, and the effects were local. The no-observed-effect level (NOEL) of H_2O_2 was 56.2 mg/kg/day. Another rat study found that the NOEL of H_2O_2 was 30 mg/kg/day when animals were treated by oral gastric catheter daily for 100 days (Kawasaki et al. 1969). The same study showed no adverse effects in rats receiving the diet containing 6 mg H_2O_2 in 20 g of food.

3.5 Genotoxicity

The genotoxic potential of H_2O_2 has been investigated extensively using microbes, plants, insects, cultured mammalian cells, and animals (IARC 1985; ECETOX 1993; Li 1996; SCCP 2005). In a number of bacterial systems, H_2O_2 induced point mutations or single-strand breaks in DNA. Positive mutagenicity of H_2O_2 has also

been detected in some newer tester strains of the Ames *Salmonella* mutagenicity test; however, effects are eliminated when tested with S9 activation. S9 is a rat liver microsomal preparation that contains various enzymes. It has been found to increase the sensitivity and overall performance of the Ames *Salmonella* mutagenicity test, and therefore, experiments both with and without S9 are required for the Ames *Salmonella* mutagenicity test (Maron and Ames 1983). The results obtained from mammalian cells are similar to those from the Ames *Salmonella* mutagenicity test; i.e., the genotoxic effects of H_2O_2 are detected only in test systems without S9 activation. The effect of S9 on H_2O_2-induced DNA or chromosomal changes in mammalian cells in vitro is believed to originate from the H_2O_2-degrading enzymes in the S9, which is the same as that observed in the Ames *Salmonella* mutagenicity test.

The genotoxicity of H_2O_2 has also been examined using in vivo systems, and results indicate that H_2O_2 is not genotoxic in various animal models (IARC 1985; ECETOX 1993; Li 1996; SCCP 2005). The overall data available so far show that H_2O_2 is genotoxic only in in vitro systems without enzymatic activation. When enzymatic activation is incorporated in in vitro systems or when tested in animals, H_2O_2 is non-genotoxic.

3.6 Carcinogenicity

The carcinogenicity of H_2O_2 was the subject of a number of critical reviews (IARC 1985; ECETOX 1993; Li 1996, 1998, 2000, 2011). Several investigators found no evidence of carcinogenicity of H_2O_2 or carbamide peroxide. Repeated subcutaneous injections of 0.5% H_2O_2 for up to 332 days did not induce tumors in a mouse study (Nakahara and Fukuoka 1959). Another 56-week study showed that 5% carbamide peroxide and 3% H_2O_2 were inactive as tumor promoters (Bock et al. 1975). Klein-Szanto and Slaga in 1982 reported that twice-weekly application of 15% and 30% H_2O_2 on mouse dorsal skin for 50 weeks did not induce any squamous cell carcinomas, and they thus concluded that H_2O_2 at 15% and 30% was not a complete carcinogen. The same study also found that at 15% and 30% concentrations, H_2O_2 was not a tumor initiator but exhibited extremely weak tumor-promoting activity after 25 weeks of twice-weekly application following previous application of the carcinogen DMBA as the initiator. At concentrations <15%, H_2O_2 did not cause tumor promotion. In contrast, Nagata et al. (1973) reported that a single subcutaneous injection of 0.6% H_2O_2 was not carcinogenic, and in fact, repeated applications of 0.6% H_2O_2 on mouse skin significantly inhibited tumor development induced by the potent carcinogen benzo(α)pyrene.

The studies that reported carcinogenicity of H_2O_2 and subsequently generated safety concerns about the use of H_2O_2 or peroxide-containing tooth whiteners were conducted by Ito's group (1981; 1982; 1984) and Weitzman et al. (1986). In the 1981 study by Ito and coworkers, male and female C57Bl/6 J mice received 0.1% or 0.4% H_2O_2 in drinking water for up to 100 weeks, with distilled water as the negative control. An increased incidence of duodenal carcinoma was observed in females

only in the 0.4% H_2O_2 group (4 of 50 mice), and 1 carcinoma was observed in 1 male mouse in each of the 0.1% and 0.4% groups. However, results showed no dose-related incidence of duodenal adenomas. Using standard methods for data analysis in which sexes are analyzed separately, no significant increase in carcinoma incidence was noted in males or females. Statistical significance was achieved only when the data from males and females were combined.

In the second study by Ito's group (1982), three strains of mice, including the C57Bl/6 N strain that was used in the initial study, received 0.1% or 0.4% H_2O_2 solution in drinking water for up to 740 days. Duodenal cancer (pathologically not defined as benign, malignant, carcinoma, or adenoma) was observed only in C57Bl/6 J mice between 420 and 740 days, with an incidence of 1% and 5% for the 0.1% and 0.4% H_2O_2 groups, respectively. However, temporary cessation of H_2O_2 and replacement with distilled water for 10, 20, or 30 days decreased the incidence of lesions in both the stomach and duodenum.

The third study by Ito's group (1984) investigated four strains of mice that received 0.4% H_2O_2 solution in drinking water for 7 months (C57Bl/6 N mice) and 6 months (other three strains). The incidence of duodenal lesions was highly strain-dependent and inversely related to duodenal, liver, and blood catalase activity. C57Bl/6 N mice had low catalase activity, and the number of tumors was 41 times that observed in mice with high catalase activity and about 10 times higher than that for the strain with normal catalase activity. Of particular interest is the observation that another strain of catalase-deficient mice had a lower duodenal tumor incidence, both in total number of tumors and number of tumors per mouse, than that of the C57Bl/6 N mice.

Because of the potential significance of the results reported by Ito's team, these studies were reviewed and carefully evaluated for study design, experimental conduct, and data presentation (FDA 1983; IARC 1985; FDA 1988; ECETOX 1993). Major limitations of the research include unverified H_2O_2 concentration and stability in drinking water, inadequate control and documentation of tumor pathology, and lack of information on food consumption and survival. In addition, these studies did not measure individual animal water intake, which is relevant because reduced water intake may contribute to the development of lesions. When water consumption is decreased, the texture of the stomach contents changes, which may increase the likelihood of tissue injury when coarse materials transverse the duodenum, resulting in an increased rate of cell proliferation or regenerative hyperplasia (Bertram 1991). From a 14-day study in C57Bl/6 N mice, water consumption was found to decrease with increasing H_2O_2 content (Weiner et al. 2000). Therefore, in the same strain of mice, it is appropriate to assume that the decrease in water intake also occurred during H_2O_2 exposure in Ito's studies. As a consequence, gastrointestinal irritation occurred. As observed in Ito studies, changes to the epithelia were primarily localized to the duodenum, indicating that the lesions are not chemically induced but indicative of mechanical irritation. On the other hand, as demonstrated by Ito and coworkers, the C57Bl/6 N mouse strain used in their studies has a low level of duodenal catalase activity and a high spontaneous incidence of premalignant duodenal lesions. The difference in catalase activity among animal strains

likely is one of the reasons that other studies, including one (Ishikawa and Takayama 1984) that used a similar experimental design to the study of Ito's group, have not found carcinogenicity of H_2O_2. As such, after evaluating the Ito studies, the Cancer Assessment Committee (CAC) of the US Food and Drug Administration (FDA) concluded that Ito's studies did not provide sufficient evidence that H_2O_2 was a duodenal carcinogen.

The study by Weitzman et al. (1986) examined the effects of topical application of H_2O_2 on the cheek porch mucosa of male Syrian golden hamsters. Animals were treated twice weekly with DMBA, a carcinogen, in combination with 3% or 30% H_2O_2 for 19 or 22 weeks. Groups receiving DMBA or 30% H_2O_2 alone were also included. Results showed that 30% H_2O_2 alone did not induce any tumors at either of the two time periods. At 19 weeks, no tumors were observed in animals receiving the DMBA and 3% H_2O_2, and 30% H_2O_2 had no tumor-enhancing effect. After 22 weeks, there was no tumor-enhancing effect with 3% H_2O_2. The incidence of carcinomas was higher in animals receiving a combination of 30% H_2O_2 and DMBA (five of five animals) compared to those treated with DMBA alone (three of seven animals), but the significance level was marginal ($p = 0.054$). The significance of the observed increase in incidence of carcinoma associated with 30% H_2O_2 at 22 weeks has been questioned because of the small number of animals used and the marginal statistical significance observed (Li 1996; Marshall et al. 1996). It is also difficult to explain the marked differences in results between the two time periods, an interval of only 3 weeks. In addition, repetitive treatment with H_2O_2 solutions greater than 15% was considered too irritating to tissues to enable detection of tumor-promoting activity, because cells would not survive the toxic effects of high concentrations of H_2O_2 (Klein-Szanto and Slaga 1982). Marshall et al. (1996), using the similar experiment design to the Weitzman study, found that H_2O_2 up to 3% was not carcinogenic or cocarcinogenic. The studies by Weitzman et al. (1986) and Marshall et al. (1996) are particularly significant in that they do not demonstrate a synergistic effect between H_2O_2 and the polycyclic aromatic hydrocarbon DMBA during coadministration. Tumor promotion studies (Bock et al. 1975; Klein-Szanto and Slaga 1982) provide additional evidence for a lack of interaction between chemical carcinogens and H_2O_2. The study by Marshall et al. (1996) found a reduction in tumor incidence following H_2O_2 administration, and such an effect was observed with 3% H_2O_2 and baking soda in the hamster cheek pouch model.

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