
Safety Assessment of Hydrogen Peroxide as Used in Cosmetics

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Hydrogen Peroxide for use in cosmetics. This ingredient is reported to function in cosmetics as an antimicrobial agent, cosmetic biocide, oral health care agent, and oxidizing agent. The Panel reviewed the data relevant to the safety of this ingredient and concluded that Hydrogen Peroxide is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a review of the safety of Hydrogen Peroxide as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as an antimicrobial agent, cosmetic biocide, oral health care agent, and oxidizing agent.¹ The *Dictionary* also lists oral health care drug as a function of Hydrogen Peroxide. However, in the United States (US), this is not considered a cosmetic function, and therefore the Panel will not evaluate safety in relation to this function.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

There are several studies in this report that evaluate the safety of Hydrogen Peroxide mixed with an oxidative hair dye or hair dye ingredient in a 1:1 mixture. The resulting product is not a mixture containing the ingredients in proportional amounts, but instead is a reaction product of the two substances with little to no residual Hydrogen Peroxide. These studies are included in this safety assessment to acknowledge that Hydrogen Peroxide is an ingredient in hair dyes, particularly as an oxidizer.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.² In this safety assessment, ECHA is cited as the references for summaries of information obtained from this website. Also referenced in this safety assessment are summary data found in reports made publically available by the European Commission's (EC) Scientific Committee on Consumer Products (SCCP),³ EC Scientific Committee on Cosmetic Products Non-Food Products Intended for Consumers (SCCNFP),⁴ Australia's National Industrial Chemicals Notification and Assessment Scheme,⁵ and numerous other organizations. Reports by these organizations are cited in this assessment to identify the source of the summary data.

CHEMISTRY

Definition and Structure

Hydrogen Peroxide is the inorganic oxide that conforms to the structure in Figure 1.¹

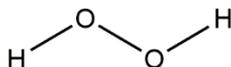


Figure 1. Hydrogen Peroxide

Physical and Chemical Properties

Physical and chemical properties of Hydrogen Peroxide are presented in Table 1.

Pure Hydrogen Peroxide (100%) does not exist commercially, and is only of academic interest.^{6,7} Hydrogen Peroxide is always manufactured as an aqueous (aq.) solution and is supplied commercially at concentrations of 3% to 98% Hydrogen Peroxide.⁸ Pure Hydrogen Peroxide is a crystalline solid below 12 °F (-11.11 °C) and a colorless liquid with a bitter taste above 12 °F.⁹ Hydrogen Peroxide can behave both as an oxidizing agent and as a reducing agent.

Aqueous solutions containing 35%, 50%, 70%, or 90% Hydrogen Peroxide are the most commonly used solutions for industrial applications and in laboratory settings, and require a stabilizer (commonly acetanilide) to prevent rapid decomposition to water and molecular oxygen. Aqueous solutions of 3% to 6% are used for cosmetic and medical applications.

Hydrogen Peroxide and water do not form an azeotropic mixture (two or more liquids whose proportions cannot be altered or changed by simple distillation), and are completely separable.⁶ The dissociation of Hydrogen Peroxide can be a violent and exothermic reaction.^{9,10} Hydrogen Peroxide is nonflammable, but it is a powerful oxidizing agent that can accelerate combustion when it comes in contact with organic material. Aqueous solutions of Hydrogen Peroxide, at low concentrations in clean inert containers, are relatively stable.⁸ Stability is at a maximum in mildly acidic solutions between pH 3.5 to 4.5.

Natural Occurrence

The concentration of Hydrogen Peroxide in the environment results from a dynamic equilibrium between its production and degradation.¹¹ Hydrogen Peroxide may be formed in photochemical, chemical, or biochemical processes.

Hydrogen Peroxide is produced metabolically in intact cells and tissues.⁸ It is formed by reduction of oxygen either directly in a two-electron transfer reaction, often catalyzed by flavoproteins, or via an initial one-electron step to a superoxide anion, followed by dismutation to Hydrogen Peroxide.

Method of Manufacture

Hydrogen Peroxide can be manufactured by anthraquinone autoxidation.¹¹ The anthraquinone derivative is hydrogenated to corresponding anthrahydroquinone using a palladium or nickel catalyst. Hydrogen Peroxide is formed when anthrahydroquinone solution is oxidized back to anthraquinone by bubbling air or oxygen through the solution. Crude Hydrogen Peroxide is extracted with water from the organic solution and the redox cycle is repeated with the generation of additional Hydrogen Peroxide. The extracted crude aqueous solution contains approximately 20% to 40% Hydrogen Peroxide and is normally purified in two or three stages by extraction with organic solvent. Finally, the aqueous solution is concentrated to give 50% to 70% Hydrogen Peroxide solutions.

Several other methods of manufacture have been reported. Hydrogen Peroxide can be manufactured by the electrolytic oxidation of sulfuric acid or a sulfate to persulfuric acid or a persulfuric acid salt with subsequent hydrolysis and distillation of the Hydrogen Peroxide that is formed; by decomposition of barium peroxide with sulfuric or phosphoric acid; by hydrogen reduction of 2-ethylanthraquinone, followed by oxidation with air, to regenerate the quinone and produce Hydrogen Peroxide; or by electrical discharge through a mixture of hydrogen, oxygen, and water vapor. [21CFR184.1366]

High concentration commercial Hydrogen Peroxide grades are stabilized to prevent or slow down decomposition and prevent possibly violent decomposition due to catalytic impurities or elevated temperatures and pressure.^{6,11} The stabilizers are of several types: mineral acids to keep the solution acidic (stability is at a maximum at pH 3.5 to 4.5); complexing/chelating agents to inhibit metal-catalyzed decomposition; or colloidal agents to neutralize small amounts of catalysts or adsorb/absorb impurities. The types of stabilizers used in Hydrogen Peroxide vary between producers and product grades and may have additional purposes.¹² For example, nitrate (sodium and ammonium) is used for pH adjustment and corrosion inhibition, and phosphoric acid is also used for pH adjustment. Colloidal silicate is used to sequester metals and thereby minimize Hydrogen Peroxide decomposition in certain applications that depend on the bleaching ability of Hydrogen Peroxide in alkali. In some applications, a high degree of stabilization is needed; whereas, in others (e.g., drinking water treatment or semiconductor manufacture) product purity is more important.

When added to final cosmetic formulations, ingredients, including stabilizers, are listed on the labels of Hydrogen Peroxide-containing hair dyes and cosmetics. However, stabilizers may be utilized in the production of concentrated raw materials (e.g., to stabilize a 30% industrial solution prior to dilution for cosmetic use). Although such a raw material stabilizer would be significantly diluted for use as a cosmetic ingredient, and even further diluted when formulated into a final cosmetic product or hair dye, some residual/incidental concentration may remain and not appear on the label. A list of stabilizers that have been reported for use in the commercial production of aqueous Hydrogen Peroxide is presented in Table 2. In the European Union (EU), concentrated Hydrogen Peroxide that comes in contact with food is stabilized with a tin-based stabilizer.¹³

Impurities

In the US, to meet the requirements of the Food Chemicals Codex, 30% to 50% aqueous solutions of Hydrogen Peroxide must pass an identification test and meet the following specifications: acidity (as sulfuric acid), 0.03% max; phosphate, 0.005% max; lead, 0.0004% max; tin, 0.001% max; and iron, 0.00005% max.¹⁴

In commercial Hydrogen Peroxide manufactured for the purposes of medical and food biocides in Finland, none of the reported impurities were at concentrations greater than 0.1%.⁶ The sum of organic and inorganic impurities in aqueous solution is reported to be below 0.2 w/w %. Calculated from a 35% aqueous solution of Hydrogen Peroxide, the theoretical total impurity contents is below 0.5 w/w %. In biocidal products, heavy metals in aqueous Hydrogen Peroxide are limited to a maximum of 1 mg/kg each of lead, mercury, cadmium, and arsenic.

USE

Cosmetic

The safety of the cosmetic ingredient included in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetic industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentration by product category.

According to VCRP survey data received in 2018, Hydrogen Peroxide is reported to be used in 390 formulations (18 leave-on products and 372 rinse-off products; Table 3).¹⁵ The majority of these uses are in hair coloring formulations (250

uses) and in products that may be incidentally ingested (93 oral hygiene products).

The results of the concentration of use survey conducted by the Council in 2017 indicate that Hydrogen Peroxide is used at a maximum concentration of 15%; this use is in the category of “other” hair coloring preparations.¹⁶ The product that contains 15% Hydrogen Peroxide is a professional 50 volume developer, and standard dilutions include 10, 20, 30, and 40 volume (i.e., 3%, 6%, 9%, and 12% Hydrogen Peroxide, respectively).

The highest maximum concentration of use reported in hair dyes and colors is 12.4%.¹⁶ Permanent hair dyes, also called oxidative dyes, are the most common type of hair dye.¹⁷ The hair is dyed by oxidation of precursors which penetrate the hair fiber, where they react with Hydrogen Peroxide to produce dyes. Since Hydrogen Peroxide is an excellent decolorizing agent for melanin, the hair's natural coloring matter, manufacturers can balance the amounts of Hydrogen Peroxide and of dye precursors in such a way as to produce lightening, darkening, or matching of the natural color of the hair.

According to the Council survey, Hydrogen Peroxide is being used at up to 12% in hair bleaches.¹⁶ Hair bleaching methods are oxidative processes,¹⁷ and Hydrogen Peroxide is the most common oxidant used in hair bleaching. Hydrogen Peroxide can be used alone to bleach hair, but in hairdressing salons, it is mixed with an alkaline solution, typically comprising aqueous ammonia (in part), before use in order to accelerate the process.

When using hair dyes or relaxers, the FDA recommends that consumers follow all directions in the package, perform a 48-h patch test on the skin before using the dye on hair, wear gloves, and rinse the scalp well with water after use.¹⁸ Consumers should not dye eyebrows or eyelashes, or leave the product on longer than the directions say. For more information, the FDA’s informational website is <https://www.fda.gov/forconsumers/byaudience/forwomen/ucm118527.htm>.

Hydrogen Peroxide is also used in products that can result in incidental oral ingestion; the highest reported maximum concentration of use in oral hygiene formulations is in dentifrices at up to 4.6%. Formulations containing Hydrogen Peroxide can come in contact with the skin, and the maximum concentration of use for leave-on dermal exposure is 2.5% in “other skin care preparations.” Hydrogen Peroxide is also reported to be used in the category of baby lotions, oils and creams at up to 0.0019% and in formulations that are used near the eyes at up to 0.000002% (eye lotions).

Additionally, Hydrogen Peroxide is used in cosmetic sprays and could possibly be inhaled; for example, it is reported to be used at up to 4% in aerosol hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.^{19,20} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{21,22}

The European Commission (EC) restricts the amount of Hydrogen Peroxide that may be present in cosmetic products (Table 4).²³ These restrictions included a maximum concentration of 4% in products applied to skin and 12% in products applied to the hair; dyes that are intended to be used on eyelashes (professional use only) are safe when they contain up to 2% Hydrogen Peroxide.²⁴

Limits for Hydrogen Peroxide in oral care products are included in European Union (EU) cosmetic regulations;²⁵ an SCCP opinion formed the basis of these limits.³ According to Part 1 of Annex III to Directive 76/768/EEC, the maximum authorized concentration of Hydrogen Peroxide in finished oral products in the EU, including mouth rinse, tooth paste and tooth whitening or bleaching products, is ≤ 0.1% (present or released).²⁵ In addition, tooth whitening or bleaching products containing more than 0.1%, but less than 6%, Hydrogen Peroxide should only be sold to dental practitioners and used by those over the age of 18. Based on a no-observable-adverse-effects level (NOAEL) of 20 mg/kg/day Hydrogen Peroxide (concentration not specified) in a 100-day rat gavage study and an estimated daily exposure to toothpaste of 480 mg/day Hydrogen Peroxide (0.1% aq.), the estimated margin of safety (MOS) was calculated to be 2500.³ Based on an estimated daily exposure to mouth-rinse of 3000 mg/day Hydrogen Peroxide, the MOS was calculated to be 400.

NICNAS conducted a Tier II assessment (evaluation of risk on a substance-by-substance or chemical category-by-category basis) on Hydrogen Peroxide under the Multi-tiered Assessment and Prioritisation Framework (IMAP).⁵ In that assessment, it was noted that Hydrogen Peroxide, in hair dyes containing 3%, 6%, or 12% Hydrogen Peroxide, is both a Schedule 5 (caution - substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label) and a Schedule 6 (poison - substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label) substance, according to the Australian Government Poisons Standards.²⁶ It is advised that consumers using products containing Hydrogen Peroxide follow the directions on the label to avoid harm.

Non-Cosmetic

FOOD

Regulations for uses of Hydrogen Peroxide are presented in Table 5.

In the US, the FDA recognizes Hydrogen Peroxide as generally recognized as safe (GRAS) to treat food under specific conditions outlined in the Code of Federal Regulations (CFR); maximum treatment levels range from 0.04% to 1.25%, or as an amount sufficient for the purpose. [21CFR184.1366] Hydrogen Peroxide may be used in several capacities in food preparation (bleaching agent, emulsifier, epoxidizing agent). [21CFR172.182, 21CFR172.814, 21CFR172.892, 21CFR172.723] It may be used in adhesives that come in contact with food. [21CFR175.105] Hydrogen Peroxide is also

permitted to be used as an antimicrobial agent in bottled water (in a silver nitrate solution), to sterilize food-contact surfaces, and in solutions to clean food-processing equipment and utensils. [21CFR172.723, 21CFR178.1005]

The US Environmental Protection Agency (EPA) stipulates that Hydrogen Peroxide, when used as an ingredient in an antimicrobial pesticide formulation, may be applied to food-contact surfaces in public eating places, and food-processing equipment and utensils; when it is ready for use, the end-use concentration is not to exceed 91 ppm (0.0091%) Hydrogen Peroxide. [40CFR180.940]

Hydrogen Peroxide (not to exceed 200 ppm; 0.02%) is used to reduce the bisulfite aldehyde complex in distilling materials for processing spirits. [27CFR24.247]

OVER THE COUNTER (OTC)

Aqueous Hydrogen Peroxide has been historically present in oral mucosal injury drug products for use as an oral wound healing agent. Oral wound healing agents have been marketed as aids in the healing of minor oral wounds by means other than cleansing and irrigating, or by serving as a protectant. Hydrogen Peroxide in aqueous solution is safe up to 3% for use as oral wound healing agents,²⁷ but there are inadequate data to establish general recognition of its effectiveness for this purpose [21CFR310.534]

Hydrogen Peroxide has a history of use as a first aid antiseptic.²⁸ Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of Hydrogen Peroxide for the specified uses of external analgesic drug products to treat dermal poison ivy, poison oak, and poison sumac reactions. [21CFR310.545]

MEDICAL

Hydrogen Peroxide (20% aq.) has been used to treat corneal ulcerations, particularly in herpetic dendritic keratitis.²⁹ A product containing Hydrogen Peroxide (40%) has been approved for the treatment of seborrheic keratoses that are raised.³⁰

In an assessment to establish a permissible daily exposure (PDE) of Hydrogen Peroxide, the FDA Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), in its guidance for the use of reactive chemicals in drugs, stated that even though Hydrogen Peroxide is genotoxic, Hydrogen Peroxide is endogenously produced in the body at such high levels as to exceed the levels encountered in oral care and other personal care products.³¹ Therefore it was not considered appropriate to derive a PDE based on carcinogenicity data. Even an intake 1% of the estimated endogenous production of 6.8 g/day, that is, 68 mg/day (or 68,000 µg/day) would not significantly add to the background exposure of Hydrogen Peroxide in the body.

In veterinary medicine, Hydrogen Peroxide is commonly used as an emetic at a concentration of 3%.³²

AGRICULTURAL

Hydrogen Peroxide is GRAS as a general purpose food additive for animal feed, when used as a bleaching agent in accordance with good manufacturing practices (GMP) or feeding practices. [21CFR582.1366; 40CFR180.940] An exemption from the requirement of a tolerance is established for residues of Hydrogen Peroxide in or on all food commodities at the rate of $\leq 1\%$ Hydrogen Peroxide per application on growing and postharvest crops. [40CFR180.1197]

OTHER

In a safety assessment of Hydrogen Peroxide in household products, the Human and Environmental Risk Assessment (HERA) program concluded that the use of Hydrogen Peroxide in household cleaning products raises no safety concern for consumers.⁷ In the US, Hydrogen Peroxide is used as a 90% solution in rocket propulsion.¹¹

TOXICOKINETIC STUDIES

Dermal Penetration

Hydrogen Peroxide is reactive, and degrades rapidly, due to reactions with all classes of organic biomolecules.⁶ The rapid degradation upon contact with skin explains the absence of systemic effects from dermal exposure to Hydrogen Peroxide. However, it is possible that application of Hydrogen Peroxide solutions to damaged skin, or exceptional cases with excessive amounts of exogenous Hydrogen Peroxide on skin, may result in some systemic exposure. If Hydrogen Peroxide does penetrate the skin, it is presumed to degrade rapidly into molecular oxygen and water when in contact with blood or other body fluids; therefore, measurement of dermal penetration would not be possible. Despite the fact that Hydrogen Peroxide is a normal metabolite in cell metabolism and that Hydrogen Peroxide metabolism is understood (e.g., through catalase and glutathione peroxidase enzymes), data on the effects of exogenous Hydrogen Peroxide exposure in humans or animals are limited and mainly consist of case reports of oxygen embolization following the degradation of Hydrogen Peroxide after exposure to large amounts. No standard dermal penetration studies with Hydrogen Peroxide have been successfully conducted. Based on the physico-chemical properties of Hydrogen Peroxide, 100% dermal penetration should be used in the absence of more accurate information.⁶

After application of 5% to 30% solutions of Hydrogen Peroxide on rat skin in vivo, some Hydrogen Peroxide could be localized in the excised epidermis within a few minutes.¹¹ By contrast, with human cadaver skin in vitro, only after the

application of high Hydrogen Peroxide concentrations for several hours, or after pretreatment with hydroxylamine (inhibitor of catalase), was Hydrogen Peroxide detectable in the dermis. Based on histochemical analysis, Hydrogen Peroxide was not metabolized in the epidermis, and the passage was transepidermal, avoiding the “preformed pathways” of skin appendages. The localization of dermal emphysema, caused by liberation of oxygen, correlated for the most part with the distribution of catalase activity within the tissue.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Hydrogen Peroxide is a normal metabolite in aerobic cells.¹¹ Hydrogen Peroxide passes readily across biological membranes. Under normal, physiological conditions, the concentration of Hydrogen Peroxide in tissues is 1 to 100 nM (0.034 to 3.4 µg/L) depending upon the organ, cell type, oxygen pressure, and cell metabolic activity.³³

In biological systems, Hydrogen Peroxide is metabolized by catalase and glutathione peroxidases.³³ The highest activities are found in highly vascularized tissues such as the duodenum, liver, kidney, and mucous membrane.³⁴ In the metabolism of Hydrogen Peroxide to water and oxygen, the decomposition rate in human plasma is approximately 0.01 to 0.05 M/min. Catalase is more efficient at the decomposition of higher concentrations of Hydrogen Peroxide; glutathione peroxidase is more efficient at decomposing lower Hydrogen Peroxide concentrations.³⁵ Glutathione peroxidase is present in cytosol and mitochondria but not in peroxisomes. A high glutathione peroxidase reduction activity of Hydrogen Peroxide is found in liver and erythrocytes; moderate levels are found in the heart and lungs, and a low activity is present in muscle.

In the presence of transition metals in cells, Hydrogen Peroxide can be reduced via the Haber-Weiss reaction.³⁶ This reaction produces hydroxyl radicals (free radicals) which are highly reactive and can result in lipid peroxidation.

At high uptake rates, Hydrogen Peroxide can pass the absorption surface and enter the adjacent tissues and blood vessels, where it is rapidly degraded by catalases and molecular oxygen is liberated.^{11,33} Consequently, mechanical pressure injury and oxygen embolism may be produced. In the view of the high degradation capacity for Hydrogen Peroxide in blood, it is unlikely that it is systemically distributed; therefore, the endogenous steady state levels of the substance in tissues are unlikely to be affected.

In rat blood diluted 1000 times, the half-life of Hydrogen Peroxide was less than 5 min at both 5 and 10 mg/L.⁶ For 20 mg/ml, the half-life was more than 4 h. In the study, concentrations of Hydrogen Peroxide were much greater than the range of aqueous solutions in products or in-use concentrations. The study demonstrates the high efficacy of the antioxidative system in blood. Furthermore, it supports the view that if Hydrogen Peroxide is entering blood circulation, it is rapidly decomposed in blood and will not be systemically available. For this reason, the distribution of Hydrogen Peroxide in the body is expected to be very limited after exposure to Hydrogen Peroxide solutions. Due to the rapid endogenous transformation into water and oxygen, there is no specific excretion of Hydrogen Peroxide or a determinable degradation product.³³

Inhalation

Anesthetized rabbits (number and strain not specified) were administered aerosolized 1% to 6% aq. Hydrogen Peroxide by inhalation.¹¹ The left atrial blood was found to be supersaturated with oxygen up to levels that corresponded to oxygen administration at 3 atm. When the amount of Hydrogen Peroxide was increased, small bubbles began to appear in the blood samples. The amount of arterial oxygen was the same with both 1% and 6% Hydrogen Peroxide. No further details were provided.

Mucosal

Administration of Hydrogen Peroxide solutions to body cavities lined by mucous membranes, such as via sublingual, intraperitoneal, and rectal administration, resulted in increased oxygen content of the draining venous blood and, if the amounts of Hydrogen Peroxide were sufficiently high, formation of oxygen bubbles.¹¹ Mongrel dogs were treated with dilute saline solutions of Hydrogen Peroxide by colonic lavage or by lavage of the small and large bowel via an enterotomy. Small amounts of a more concentrated solution (1.5% aq. or higher) produced immediate whitening of the mucosa, with prompt appearance of bubbles in the circulation. More dilute (0.75% to 1.25% aq.) solutions had the same effect when left in contact with the bowel for a longer time (not specified) or when introduced under greater pressure or in greater volume for a given length of bowel. Venous bubbling was never observed at concentrations less than 0.75% aq. Hydrogen Peroxide. In none of the dogs did mesenteric thrombosis or intestinal gangrene develop. Application of 1% aq. Hydrogen Peroxide to the serosal membrane caused whitening due to gas-filled small vessels; higher concentrations (up to 30% aq.) on the skin and mucous membranes (of various species) caused lasting damage when subcutaneous emphysema and disturbances of local blood circulation impaired tissue nutrition.

In two cats, sublingual application of 1.5 ml of 9% aq. ¹⁸O-labeled Hydrogen Peroxide or 0.1 ml 19% aq. ¹⁸O-labeled Hydrogen Peroxide was followed up with mass spectrometric analyses in arterial (femoral artery) blood and exhaled air. Within approximately 1 h in the former case, and within half an hour in the latter case, one-third of the labeled oxygen was exhaled. There was a rapid initial rise of the arterial blood ¹⁸O concentration, but the arterial blood oxygen saturation gradually declined, probably because of impaired gas exchange in the lung due to oxygen embolism.¹¹

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

Acute dose toxicity studies in animals summarized below are presented in Table 6.

ANIMAL

Dermal

In general, the acute dermal toxic effects of Hydrogen Peroxide were dependent on concentration as well as dose. The dermal LD₅₀ was > 8000 mg/kg Hydrogen Peroxide in mice; more mice died when the dose was applied at a higher concentration (28% vs 10% aq.).¹¹

Dermally administered Hydrogen Peroxide (90% aq.) caused 4 of 12 rats to die at 4899 mg/kg and 9 of 12 to die at 5520 mg/kg.³³ In one study, dermally administered Hydrogen Peroxide (concentration not specified) did not cause any (n = 6) rats to die at 6900 mg/kg and 2 of 6 to die at 8280 mg/kg. In another study, 50% of the rats (n not specified) died at 4060 mg/kg (concentration not specified).

Dermal LD₅₀s in rabbits were > 2000 mg/kg, 9200 mg/kg, and 690 mg/kg with 35% aq., 70% aq., and 90% Hydrogen Peroxide, respectively, that was administered under occlusion for 24 h.^{2,33} Clinical signs included lacrimation and nasal discharge.

No cats died when 90% aq. Hydrogen Peroxide was dermally administered at 4361 mg/kg.³³ Two of 5 pigs died when dermally administered 2760 mg/kg Hydrogen Peroxide (concentration not specified).³³

Oral

In general, the acute oral toxic effects of Hydrogen Peroxide were dependent on concentration as well as dose. The oral LD₅₀ of Hydrogen Peroxide (90% aq.) for mice was reported to be 2000 mg/kg.³³

Oral LD₅₀s in rats ranged from 1520 mg/kg to > 5000 mg/kg with approximately 10% aq. Hydrogen Peroxide.^{2,33} The LD₅₀s at 35% aq. Hydrogen Peroxide were 1193 mg/kg in male rats and 1270 mg/kg in females.^{2,33} At 60% aq. Hydrogen Peroxide, the LD₅₀s in rats were 872 mg/kg in males and 801 mg/kg in females.¹¹ At 70% aq. Hydrogen Peroxide, the LD₅₀ in rats ranged from 75 mg/kg to 1026 mg/kg.^{2,5,11} Clinical signs in rats administered 35% aq. Hydrogen Peroxide and greater included tremors, decreased motility, prostration, and oral, ocular, and nasal discharge. Most rats that died had reddened lungs, hemorrhagic and white stomachs, and blood-filled intestines; some had white tongues.^{2,5,33}

Dogs administered one or two oral doses (manner of administration not specified) of Hydrogen Peroxide (2 ml/kg; 3% aq.) vomited within 4.5 min; the most severe lesions identified were gastric ulcers and gastric degeneration and necrosis, evident at 4 and 24 h following treatment.³⁷

Inhalation

In inhalation studies, increasing concentrations of Hydrogen Peroxide and times of exposure had increasingly corrosive effects on the pulmonary tract. Mortality rates increased accordingly.

In mice, the concentration at which a 50% reduction of the respiratory rate was observed (RD₅₀) was 665 mg/m³ Hydrogen Peroxide (70% aq.) and the exposure concentration at which a 50% reduction of the minute volume was observed was 696 mg/m³.² In another experiment, the RD₅₀ in mice (n = 8) was 113 ppm (calculated as 157 mg/m³; concentration of Hydrogen Peroxide not specified) when exposure was 60 min.³⁸ At up to 5000 mg/m³ Hydrogen Peroxide (concentration not specified) there were no deaths but there was necrosis of the bronchial epithelium and pulmonary congestion; half of the 10 mice died after 10 to 15 min of exposure at 11,877 and 13,287 mg/m³.³³ Exposure to 920 to 2000 mg/m³ Hydrogen Peroxide (70% aq.) via inhalation was lethal to at least some mice (n not specified).¹¹ At necropsy, subcutaneous emphysema and hemorrhages, red lymph nodes, and diffuse red lungs were observed. No treatment-related mortalities were observed in mice exposed to up to 3220 mg/m³ Hydrogen Peroxide (70% aq.) for up to 30 min; longer exposure to 3130 mg/m³ (1 h) and 880 mg/m³ (2 h) was lethal to all 4 mice.³³ One study reported the lethal dose for mice to be > 16.1 ppm (calculated as 23 mg/m³; only test dose) Hydrogen Peroxide (90% aq.) when exposed for 4 h.³⁹ In mice, concentrations of 3600 to 5200 mg/m³ Hydrogen Peroxide (90% aq.), there was no mortality, but congestion of lungs and necrosis of bronchial epithelium were observed; at 9400 mg/m³, lethal range (LC_{LO}) was reached with death occurring 6 days following exposure.²

In rats, at 170 mg/m³ Hydrogen Peroxide (50% aq.), clinical signs were minimal during inhalation exposure (decreased activity and eye closure), but a few responses, such as nasal discharge, were observed.^{2,33} There were no deaths in rats exposed to vaporized 90% aq. Hydrogen Peroxide for 8 h; at necropsy, most lungs exhibited many areas of alveolar emphysema and severe congestion.⁴⁰ There were no deaths when rats were exposed to 338 to 427 mg/m³ of 90% aq. Hydrogen Peroxide vapor in a glass chamber.⁴⁰ In another study, the lethal dose in rats exposed to 90% aq. Hydrogen Peroxide by inhalation was > 16.1 ppm (only test dose; calculated as 23 mg/m³).³⁹ In rats exposed to vapor-phase Hydrogen Peroxide in a nose-only apparatus for 2 hours, there were no changes observed in light microscopy at 0.014 and 0.025 mg/m³; however, electron microscopy revealed an increase in the number of neutrophils in capillary spaces adjacent to terminal respiratory bronchioles and in alveolar ducts in lungs from rats after inhalation of 0.025 mg/m³.⁴¹ In one study in which rats were exposed to Hydrogen Peroxide vapors for 4 h, the median lethal concentration (LC₅₀) was 2000 mg/m³, the lowest-observed-effective-concentration (LOEC) for respiratory mucosa effects was 60 mg/m³, and the LOEC for skin effects

(moderate hyperemia and transient thickening because of oxygen bubbles in skin) was 110 mg/m³.² Exposure to Hydrogen Peroxide aerosols (up to 37 mg/m³) for 4 hours did not alter baseline airway resistance, dynamic elastance, slope of inspiratory pressure generation, or arterial blood pressure and blood gas measurements in rabbits.⁴²

HUMAN

Dermal

In humans, Hydrogen Peroxide administered to the skin has been reported to cause transient (lasting 10 to 15 min after 1 min exposure) dermal blanching starting at 3% aq.⁴³

Inhalation

Human exposure by inhalation may result in extreme irritation and inflammation of the nose, throat and respiratory tract, pulmonary edema, headache, dizziness, nausea, vomiting, diarrhea, irritability, insomnia, hyper-reflexia, tremors and numbness of extremities, convulsions, unconsciousness, and shock.²⁹ The latter symptoms are a result of severe systemic poisoning.

Subjects (n = 11) were exposed to Hydrogen Peroxide (30% aq.; 0, 0.5, and 2.2 ppm; calculated as 0, 0.7, and 3.08 mg/m³) vapors for 2 h at rest in an exposure chamber (20 m³).⁴⁴ Symptoms related to irritation and central nervous system (CNS) effects were rated with Visual Analog Scales. The ratings varied considerably but were generally low and with no significant differences between exposure conditions, although the ratings of smell, nasal irritation, and throat irritation showed borderline tendencies to increase at 3.08 mg/m³, but not at 0.7 mg/m³. Nasal airway resistance increased after exposure to 3.08 mg/m³, but not at 0.7 mg/m³. No exposure-related effects on pulmonary function, nasal swelling, breathing frequency, and blinking frequency were detected. No clear effects were seen on markers of inflammation and coagulation (e.g., interleukin-6, C-reactive protein, serum amyloid A, fibrinogen, factor VIII, von Willebrand factor, and Clara cell protein in plasma). The authors concluded that Hydrogen Peroxide was slightly irritating at 3.08 mg/m³, but not at 0.7 mg/m³.

In 32 subjects, the threshold of detection for irritation through inhalation exposure was 10 mg/m³ (independent of the exposure time, which was from 5 minutes to 4 h) when Hydrogen Peroxide (concentration not provided) vapor was inhaled through the nose using a face mask.⁵

Short-Term Toxicity Studies

Dermal

No published short-term dermal toxicity studies were discovered and no unpublished data were submitted.

Oral

Short-term oral toxicity studies summarized below are presented in Table 7.

In general, orally administered Hydrogen Peroxide caused inflammation of and erosion to the upper digestive tract of mice and rats. Mice administered Hydrogen Peroxide (0.3% and 0.6%) in drinking water had decreased body weights over 2 weeks; mice died when administered 1% Hydrogen Peroxide or greater.³³ In another 2-week study in mice exposed to Hydrogen Peroxide in drinking water, the mice had reduced water consumption and weight gains at 1000 mg/l and greater; at necropsy, degenerative (minimal to mild erosions) and regenerative (minimal to mild hyperplasia) changes in the mucosa of the stomach and/or duodenum in the 3000 and 6000 mg/l groups in both sexes were observed.³³ The overall NOAEL for pathology was 1000 mg/l for both sexes.

In a 3-week drinking water study in rats of 0.45% Hydrogen Peroxide, there was a decrease in fluid consumption and body weights; there were no differences in relative weights in testes, kidneys, spleen, or heart.⁴⁵ In a 40-day oral study in rats, no deaths were reported and no toxic effects were observed at doses < 30 mg/kg/day (via gavage), but blood effects (reduction of hematocrit values, blood plasma proteins concentrations, and plasma catalase activity) were observed at 60 mg/kg; the lowest-observed-adverse-effects-level (LOAEL) was 30 mg/kg/day.⁴⁶ In another gavage study in rats, administration of 1/5 and 1/10 of the LD₅₀ (actual dose not specified) for 45 days caused blood effects (increased blood peroxidase activity) and inflammatory responses in the stomach wall.³³ In an 8-week drinking water study, 7 of 24 rats died in the 1.5% Hydrogen Peroxide group; dose-dependent extensive carious lesions and pathological changes in the periodontium were observed.⁴⁷ In a 12-week oral gavage toxicity study in rats, there were no mortalities at up to 506 mg/kg of 5% aq. Hydrogen Peroxide, but there were blood effects (reduced hemoglobin concentration, erythrocyte count, blood corpuscle volume, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) at this dose; there were also changes to the weights of kidneys, livers, and hearts (decreased) and to adrenal glands and testes (increased).^{3,33}

Inhalation

Short-term inhalation toxicity studies summarized below are presented in Table 8.

Mice exposed to Hydrogen Peroxide (90% aq.; 79 or 107 mg/m³) for 6 h per day for 2 to 3 day per week, for up to 4

weeks, had nasal discharge, edematous feet, and irritation of the skin at week 2 and hair loss around the nose (probably due to scratching due to irritation) at week 5; seven of nine mice died after eight exposures in the low-dose group, and in the high dose group, five of 10 mice died after eight exposures and eight of 10 died after 18 exposures.⁴⁰ Rats exposed to aerosolized Hydrogen Peroxide (50% aq.) 5 days per week, 6 h per day, for 28 days showed clinical signs at 14.6 mg/m³ (including reddened nose, salivation, irregular breathing), but not at 2.88 mg/m³; the no-observed-effects-level (NOEL) was 2.9 mg/m³ and the LOAEL was 14.6 mg/m³.² Rats exposed to 93 mg/m³ Hydrogen Peroxide (90% aq.) for 6 h per day for 2 to 5 days per week for 7 weeks (30 exposures) showed signs of nasal irritation and profuse discharge at 2 weeks, lung congestion and hair loss (probably due to scratching due to irritation) at 5 weeks.⁴⁰ In black rabbits exposed to 90% Hydrogen Peroxide (30 mg/m³) vapor for 6 h per day, 5 days per week for 12 weeks, there were no effects observed except for the bleaching of the fur and some irritation around the nose.⁴⁰

Subchronic Toxicity Studies

Dermal

Shaved rats (strain and n not specified) were exposed to Hydrogen Peroxide vapor (0.1 to 10.1 mg/m³) 5 h per day, 5 day per week, for up to 4 months in whole body chambers.^{2,33} After 2 months at 1 mg/m³, examination of the epidermis of the backs of the rats revealed an increase in the activity of monoamine oxidase (MAO) and nicotinamide adenine dinucleotide (NAD)-diaphorase, and after 4 months, an increase in MAO, NAD-diaphorase, succinate dehydrogenase activity (SDH), and lactate dehydrogenase. At 4 months, there was significant dysfunction of the horny layer of the skin. The lowest-observed-effect-level (LOEL) was 1.0 mg/m³ and the NOEL was 0.1 mg/m³ for enzyme activities in the skin.

Nine hair dye formulations (1 ml/kg) each in 1:1 mixtures with Hydrogen Peroxide (6% aq.) were applied to the clipped dorsal lateral skin of the thoracic-lumbar area of New Zealand White rabbits (n = 6/sex) twice daily for 13 weeks.⁴⁸ The applications were alternated between the sides of the rabbits to minimize dermal irritation. The skin of three rabbits/sex in each group was abraded before the first treatment. The rabbits were restrained for 1 h after application, and then the application sites were shampooed, rinsed, and dried. Three separate control groups (n = 12/sex) were treated the same as the treatment groups without the hair dye.

There was no evidence of test substance-induced toxicity observed. Body weight gains of all test groups were similar to controls. Five control and five test rabbits died during the study due to complications during cardiac puncture to collect blood. There were some differences in the clinical chemistry and hematologic values between test and control groups at the various sampling intervals that were not considered to be of toxicological significance because of either the direction or continuity of the differences or the fact that they fell within the range of historical control values. There were a few instances when there were differences in relative organ weights between a test group and the combined controls, however there were no differences when the group was compared with each control group separately. In no instance were any of the relative organ weight differences accompanied by histological evidence of toxicity. The results of the urinalyses were unremarkable. The treated skin showed slight thickening in some groups, which was expected due to the frequency of dye application. No gross abnormalities were seen at necropsy, and no microscopic lesions were seen that were deemed to be due to the administration of the hair dye formulations containing Hydrogen Peroxide. The incidence and severity of disease processes common to laboratory rabbits was not affected by the experimental treatments.⁴⁸

Oral

Subchronic oral toxicity studies summarized below are presented in Table 7.

In an approximately 90-day drinking water study in mice, the overall LOEL was 300 ppm and the overall NOEL was 100 ppm (26 and 37 mg/kg/day for males and females, respectively) based on dose-related reductions in feed and water consumption and duodenal mucosal hyperplasia.² All effects noted during the treatment period were reversible. In a 100-day dietary study in rats, there were no deaths reported when Hydrogen Peroxide was administered in feed at up to 60 mg/kg.⁴⁶

Inhalation

Subchronic inhalation studies summarized below are presented in Table 8.

In rats exposed to Hydrogen Peroxide (concentration not specified) in whole body chambers for 5 h per day, 5 days per week for up to 4 months, the threshold for lung effects was 10 mg/m³; the NOEL was 1 mg/m³ and the LOEL was 10 mg/m³.^{2,33} There were no mortalities when rats were exposed to Hydrogen Peroxide (50% aq.) up to 10.3 mg/m³ for 6 h per day, 5 days per week, for 13 weeks; the NOAEL was 3.6 mg/m³ for male and female rats for decreased liver and thymus weights.² Irritation was noted around the nose of rabbits exposed to 90% aq. Hydrogen Peroxide at 22 ppm (calculated as 30.77 mg/m³) for 3 months.²⁹

Chronic Toxicity Studies

Oral

Chronic oral toxicity studies summarized below are presented in Table 7.

In a 100-week drinking water study of Hydrogen Peroxide (0.1% and 0.4% aq.) in mice, erosion in the stomach

occurred after 40 weeks, duodenal hyperplasia after 55 weeks.^{49,50} In a 6-month gavage study in rabbits, the NOAEL was 0.005 mg/kg/day due to changes in hematology and enzyme activities.²

Inhalation

The chronic inhalation study summarized below is presented in Table 8.

In two dogs exposed to aerosolized 90% Hydrogen Peroxide (10 mg/m³) for 6 h per day, 4 to 5 days per week for 26 weeks, the only observed effects were fur bleaching and loss at 14 weeks, and sporadic sneezing and lacrimation at 23 weeks.⁴⁰ At necropsy at 26 weeks, the lungs had areas of atelectasis and emphysema, and there were some hyperplasia in bronchial musculature.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Dermal

The teratogenicity of nine oxidative hair dye formulations was tested using Charles River CD rats (n = 20).⁴⁸ The oxidative formulations were each mixed 1:1 with Hydrogen Peroxide (6% aq.) immediately prior to application (2 ml/kg/day) to shaved backs. The test materials were applied to the shaved dorsoscapular area of pregnant rats on every third gestation day (GD days 1, 4, 7, 10, 13, 16, and 19). Positive controls were administered oral acetylsalicylic acid (250 mg/kg) on GD 6 to 16. Three separate negative control groups were shaved, but not treated. No maternal toxicity was observed, there were no treatment effects on implantation or intrauterine growth, or survival, and there was no evidence of external, visceral, or skeletal malformation.

Six composite test materials, representative of commercial oxidative hair dye formulations, were evaluated in Sprague-Dawley rats (n = 20/sex) in a two-generation study of reproduction.⁵¹ The dyes were each mixed 1:1 with Hydrogen Peroxide (6% aq.) and then applied (0.5 ml) twice weekly to the clipped backs of the rats. The treatment of the F₀ rats began at 6 to 8 weeks of age, and rats of the second litter (F_{1b}) began treatment at weaning. Breeding for both generations began at 100 days of age, and dermal applications continued throughout mating, gestation, and lactation periods. Occasional mild dermatitis was the only adverse effect noted. Body weight gain, feed consumption, survival, and reproductive indices (fertility, gestation, live birth and survival, and weaning weight) in F_{1a}, F_{1b}, F_{2a}, and F_{2b} litters were similar to controls.

Oral

Hydrogen Peroxide (30% aq.; 0.33% and 1%) was administered to male mice (strain and n not specified) in drinking water for 7, 21, or 28 days pre-mating.^{2,4} After mating, the female mice were also administered Hydrogen Peroxide (0, 0.33% or 1%) in drinking water. All mated female mice became pregnant, the pups were healthy, and the litters were of normal size. Pregnant mice in the high-dose group had some delay in parturition compared to controls; however, the effect was small and inconsistent. The concentration, morphology, and motility of the spermatozoa (tested in three mice) after 3 weeks of treatment appeared normal.

Female and male Osborne-Mendel rats (n not specified) were administered Hydrogen Peroxide (0.45%) in drinking water for 5 months prior to mating.⁴⁵ The females continued to be treated through parturition. Six of the male offspring were also administered Hydrogen Peroxide (0.45%) in drinking water for 9 months. The litters of the treated females were normal. The only observed effect in the male offspring was a statistically significant reduction in weight (411 g vs 521 g in controls).

Aqueous solutions of Hydrogen Peroxide (0.02%, 0.1%, 2%, or 10%) were mixed with powdered feed and administered to pregnant Wistar rats (n = 7 to 11) for 1 week "during the critical period of pregnancy" (no further explanation was provided; no control group was specified).¹¹ Most of the dams (n = 5 to 8) were killed and the pups removed and examined on gestation day 20; some (n = 2 to 3) were allowed to deliver their pup and were followed for 4 weeks. The body weights of the dams in the high-dose group did not increase markedly. Fetal resorptions were increased and the fetal body weights were decreased. Most of the fetuses were close to death. No external malformations were observed in any group. Hemorrhaging (in the eyes, parietal region of the brain, cardiopulmonary region, and torso) increased dose-dependently in the 0.1% to 10% dose range. Skeletal hypoplasia was dose-dependent in the two highest dose groups. In the litters that were allowed to be delivered, all of the neonates in the high-dose group died within 1 week post-partum. Body weights were low and the number of live births decreased in the high-dose group. In the other groups there was no major effect on the development of neonates.

It was reported that the concentration of Hydrogen Peroxide in the feed decreased to 1/10 after 24 h and to almost zero at 72 h. The authors of the study stated that "the amount of residue was determined and consumption was estimated;" however, it is not stated how frequently fresh feed was prepared. Nevertheless, it seems likely that the dams did ingest Hydrogen Peroxide evidenced by that there was not much of an increase in dam body weight at the high-dose level. The authors proposed that the observed effects on fetal development were due to the breakdown of essential nutrients in food by Hydrogen Peroxide.

Male and female rats (strain and n not specified) were administered Hydrogen Peroxide (0.005 to 50 mg/kg; 1/10 to 1/5 LD₅₀; vehicle not specified) by gavage for 6 months.⁵² Females had modified estrus cycles and the males had decreased sperm mobility. The rats were then mated. At the highest dose, 3 out of 9 females produced litters, compared to 7 out of 9 in the control group (not described). Body weights of the offspring in the high-dose group were reduced compared to controls.

GENOTOXICITY STUDIES

In vitro and animal in vivo genotoxicity studies summarized below are presented in Table 9.

In Vitro

There are numerous genotoxicity studies of Hydrogen Peroxide. A representative sample is presented here. When available, the starting concentration of the Hydrogen Peroxide tested is stated in Table 9.

The results in Ames assays conducted on Hydrogen Peroxide were not consistent. In most of the Ames assays presented, Hydrogen Peroxide (concentrations not specified in most assays) increased the number of revertant colonies in *Salmonella typhimurium* strains without metabolic activation (3% or 30% in those assays with concentrations of Hydrogen Peroxide provided);⁵³⁻⁵⁸ however, there were a few assays where the results were negative for genotoxicity (3% in two of these assays).^{33,56,58-60} In one assay with metabolic activation, 3% Hydrogen Peroxide was mutagenic in strain TA100, but not in TA98, TA1535, TA1537, and TA1538,⁵⁸ and in another, Hydrogen Peroxide (concentrations not specified) without metabolic activation was weakly mutagenic in strain TA102, but less genotoxic with metabolic activation.^{33,59} In Ames assays in *Escherichia coli*, Hydrogen Peroxide was positive for genotoxicity in one assay (concentrations not specified),⁶¹ and negative for genotoxicity in another assay (3% Hydrogen Peroxide).⁵⁸ In one other assay, Hydrogen Peroxide was genotoxic to *E. coli* without metabolic activation and not mutagenic with metabolic activation.⁶² In other Ames-type assays, Hydrogen Peroxide (concentrations not specified) was mutagenic in *E. coli*, *Bacillus subtilis*, and *Saccharomyces cerevisiae*.⁶³⁻⁶⁵

In bacterial forward mutation assays, Hydrogen Peroxide (30% aq.) was genotoxic to *E. coli* K12 kat(-) and kat(+) strains at 75 and 600 nmol/ml, respectively,⁶⁶ and to *E. coli* (DB2) starting at 24 µg/ml (concentrations not specified).⁶⁷ Hydrogen Peroxide was genotoxic to *B. subtilis* (168DB) at 0.0005% aq.⁶⁴ Hydrogen Peroxide (concentration not specified) was not genotoxic to Chinese hamster lung fibroblast (V79) cells up to 300 µmol.⁶⁸ Results were ambiguous for *S. typhimurium* TA100 up to 7.5 µmol/plate⁶⁹ and positive for TA102 at 75 µg/plate without metabolic activation.⁶¹ In an L-arabinose bacterial forward mutation assay, Hydrogen Peroxide (concentrations not specified) was genotoxic to *S. typhimurium* (BA9 and BA13) starting at 2941 nmol/ml.⁷⁰

In a chromosomal aberration test, Hydrogen Peroxide (concentration not specified) was genotoxic to Chinese hamster ovary (CHO) cells starting at 10 nl/ml with metabolic activation and 25.31 nl/ml without metabolic activation,² and in a second test, Hydrogen Peroxide (30% in saline) was genotoxic to Chinese hamster fibroblasts at 0.25 mg/plate.⁷¹ Hydrogen Peroxide (concentration not specified) was also mutagenic to murine splenocytes,⁷² V79 cells,^{68,73} and Syrian hamster embryo (SHE) cells^{68,74} in chromosomal aberration tests. Hydrogen Peroxide (concentration not specified) was mutagenic to human leukocytes and embryonic fibroblasts.^{33,75} Hydrogen Peroxide increased the number of abnormal metaphases in CHO-K1 cells without, but not with, metabolic activation.⁶⁸

In mouse lymphoma assays, Hydrogen Peroxide increased the mutation frequency in mouse lymphoma cells without metabolic activation.^{2,76} Hydrogen Peroxide did not increase the mutation frequency in mouse lymphoma cells with metabolic activation.

In various assays, Hydrogen Peroxide had mixed results in V79 cells.^{68,77-80} In sister chromatid exchange (SCE) assays, Hydrogen Peroxide (concentrations not specified) was mutagenic in V79 cells without metabolic activation, but was not mutagenic, or was mutagenic to a lesser extent, with metabolic activation.^{73,78,81,82} Hydrogen Peroxide (concentrations not specified) was mutagenic in CHO cells starting at 10 to 20 µM without metabolic activation, but was not mutagenic, or was mutagenic to a lesser extent, with metabolic activation.^{78,83-87} Hydrogen Peroxide (concentrations not specified) increased the number of SCEs at 300 µM in SHE cells.⁸⁸ Hydrogen Peroxide (concentrations not specified) was mutagenic at 20 µM in human lymphocytes but not in whole blood; metabolic activation reduced Hydrogen Peroxide-induced SCEs.⁸⁴ Hydrogen Peroxide (concentrations not specified), without metabolic activation, was mutagenic to D98/AH2 human cells.⁸⁹

In an endo-reduplicated cells assay, Hydrogen Peroxide (concentrations not specified) was mutagenic to CHO AUXB1 cells starting at 160 µM in a dose-dependent manner.⁸⁵ In an unscheduled DNA synthesis (UDS) in mammalian cells assay using rat hepatocytes, Hydrogen Peroxide (35.7% aq.) caused a dose-dependent increase in net nuclear grain (NNG) values at 6.25 to 25 µg/ml.²

In comet assays, Hydrogen Peroxide was mutagenic in mouse lymphoma cells,⁹⁰ rat hepatocytes,⁹¹ *S. cerevisiae*,⁹² and V79 cells (40 µM; 37% aq.).⁹³ Hydrogen Peroxide was also mutagenic to human breast adenocarcinoma cell lines MCF-7 and MCF-10A,⁹⁴ human lymphocytes,^{93,95} human fibroblasts (30 µM; 37% aq.),^{93,96} immortalized cervical cancer (HeLa) cells (30 µM),^{93,97} and liver hepatocellular carcinoma (HEP G2) cells (40 µM; 0.3 M).^{93,98} In a combined comet assay/micronucleus assay using human lymphoblastoid TK6 cells, Hydrogen Peroxide (concentration not specified) was genotoxic in the comet assay at 50 µM and at 100 µM in the micronucleus assay.⁹⁹ In another combined comet assay/micronucleus assay in V79 cells, Hydrogen Peroxide was genotoxic at 80 µM and at 40 µM, respectively.¹⁰⁰

In a multi-test assay, Hydrogen Peroxide (concentration not specified) was not genotoxic in two DNA adduct assays up to 500 µM (but was genotoxic at 500 µM in a comet assay), at 20 µM in a micronucleus test, and at 100 µM in a tk+/- gene mutation assay, all using L5178Y tk+/- mouse lymphoma cells.⁹⁰ Hydrogen Peroxide (37% aq.) was not mutagenic at 110 µM in V79 cells in a hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay.⁹⁶

In Vivo

ANIMAL

In a mammalian erythrocyte micronucleus test using mice, Hydrogen Peroxide, administered by intraperitoneal injection (i.p.), was not genotoxic at up to 2000 mg/kg.² Hydrogen Peroxide, administered in drinking water, was not genotoxic to mice at up to 536 and 774 mg/kg/day for males and females, respectively, in a second mammalian erythrocyte micronucleus test.² In an UDS test, intravenously (i.v.) administered Hydrogen Peroxide (50 mg/kg) did not induce UDS in rats.² Hydrogen Peroxide (200 mmol) was not genotoxic to mice in a dermal genotoxicity assay.²

HUMAN

The gingival tissue of the teeth (central incisors) of subjects (n = 30) was isolated with a light-polymerized resin dam, and a whitening gel containing Hydrogen Peroxide (35%) was administered three times for 15 min over 45 min.¹⁰¹ This procedure was repeated 1 week later. Exfoliated oral mucosa gingival epithelial cells and upper lip lining were collected at baseline and 1 month after the second treatment. The scraped cells were placed on clean glass slides, smears prepared, and two blinded examiners performed cell and micronuclei counts. The frequency of micronuclei was not increased after administration of Hydrogen Peroxide in both the gingival tissue and upper lip. The authors concluded that the test material did not induce DNA damage to the gingival and lip tissue.

In conjunction with an epidemiological study where the treatment group (n = 6 women, 4 men) had their hair dyed 13 times at intervals of 3 to 6 weeks with commercial preparations, SCEs were examined in peripheral lymphocytes.¹⁰² Blood samples were taken 3 weeks before the hair-dyeing treatment, and 24 h after each of the first three and last three dyeing treatments. There were no increases in SCEs at any point in the experiment. [See Epidemiological Studies for more information.]

CARCINOGENICITY STUDIES

Carcinogenicity studies summarized below are described in Table 10.

ANIMAL

Dermal

Hydrogen Peroxide (at up to 15% aq.) was not carcinogenic when dermally administered to mice and rats.^{17,51,103-105} Three different hair dye formulations, each mixed 1:1 with Hydrogen Peroxide (6% aq.), did not cause skin tumors when applied once weekly or every other week to mice for 18 months.¹⁰³ Mice dermally administered Hydrogen Peroxide (30% aq. in a 1:1 mixture with acetone) twice-weekly for 25 weeks did not develop squamous-cell carcinoma when observed up to 50 weeks.¹⁰⁵

Hydrogen Peroxide (6% aq.) in a 1:1 mixture with oxidized *p*-phenylenediamine (5% *p*-phenylenediamine in 2% ammonium hydroxide) did not cause any skin tumors, but caused an increase in other types of tumors in rats when administered subcutaneously and topically once per week for 18 months.⁶⁰ Multiple hair dye formulations, each mixed 1:1 with Hydrogen Peroxide (6% aq.), applied to the skin of rats twice weekly for at least 2 years did not cause any skin tumors.^{51,104}

Oral

In general, Hydrogen Peroxide in drinking water caused duodenal nodules in mice. Hydrogen Peroxide caused mild to minimal duodenal mucosal hyperplasia (reversible during the recovery period) in mice at 1000 and 3000 ppm in drinking water; the NOAEL was 100 ppm (26 and 37 mg/kg/day for males and females, respectively).⁴ Hydrogen Peroxide (0.1%) administered in drinking water for 100 weeks did not increase the numbers of adenomas and carcinomas of the duodenum in mice.⁴⁹ However, at a higher concentration, Hydrogen Peroxide (0.4%) in drinking water caused gastric erosions and duodenal plaques at 30 days that were present consistently at each subsequent time period up to 700 days.⁵⁰ Nodules were observed in both the duodenum and stomach from 90 days until the end of the experiment; lesions were reversible after stopping treatment with Hydrogen Peroxide. In another experiment, Hydrogen Peroxide (0.4%) in drinking water caused duodenal nodules at 90 days in three strains of mice.⁵⁰ Hydrogen Peroxide (0.4%) in drinking water caused duodenal nodules at 6 or 7 months in four strains of mice.³⁴ Hydrogen Peroxide administered in drinking water at up to 0.6% for 78 weeks did not increase the number of tumors in testes, mammary glands, or skin in rats.⁵²

Mucosal

Hydrogen Peroxide (0.75% in a dentifrice) was administered into the buccal cheek pouches of hamsters for 20 weeks.¹⁰⁶ No neoplasms were observed.

HUMAN

IARC determined that there is inadequate evidence in humans to come to a conclusion on the carcinogenicity of Hydrogen Peroxide and that there is limited evidence in experimental animals on the carcinogenicity of Hydrogen Peroxide.¹⁰⁷ IARC concluded that Hydrogen Peroxide “is not classifiable as to its carcinogenicity to humans (Group 3).”

Co-Carcinogenicity

Dermal

Hydrogen Peroxide (3% aq.) was administered to the skin of mice for up to 56 weeks after a single application of 7,12-dimethylbenz[a]anthracene (DMBA; a tumor initiator).¹⁰⁸ There were no skin tumors observed at necropsy at weeks 10, 26, 52, or 58. In another study, Hydrogen Peroxide (up to 30% aq.) was dermally administered for 25 weeks after a single application of DMBA. Hydrogen Peroxide was found to be an ineffective skin tumor promotor.¹⁰⁵

Hydrogen Peroxide (30% aq.) was administered once, followed by weekly applications of 12-*O*-tetradecanoyl-phorbol 13-acetate (TPA; a tumor promoter) for 25 weeks.¹⁰⁵ The initial administration of Hydrogen Peroxide did not cause or increase dermal tumors in the skin of mice.

Oral

Two groups of rats were administered *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG; a carcinogen) in their drinking water for 8 weeks followed by either Hydrogen Peroxide (1%) in their water or plain water for 32 weeks. Hydrogen Peroxide did not increase the number of gastrointestinal tumors.^{33,109}

Mucosal

Hydrogen Peroxide (3% and 30% aq.) was administered to the buccal cheek pouches of hamsters, concurrently with, or without, DMBA for 19 and 22 weeks.⁵² Hydrogen Peroxide at 3% did not cause or increase the instances of preneoplastic lesions alone or with DMBA. However, at 30% Hydrogen Peroxide with DMBA, epidermoid carcinomas were observed by 22 weeks.

In hamsters administered Hydrogen Peroxide (30% aq.) for 24 weeks to the cheek pouches after a single dose of 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK; a carcinogen), 1 out of 32 hamsters developed a cheek pouch adenoma and there was an increase in the instances of other tumors.¹¹⁰ In hamsters that were administered NNK and Hydrogen Peroxide simultaneously, 23 out of 32 developed tumors. There were no instances of tumors in control groups that were administered NNK alone or Hydrogen Peroxide alone.

OTHER RELEVANT STUDIES

Dermatitis and Alopecia

Hair dye ingredients, including Hydrogen Peroxide (concentration not specified), were applied to the dorsal region of female C57BL/6 mice (n = 5 or 6) daily for 3 consecutive days and evaluated for dermatitis and hair loss.¹¹¹ The test materials were applied to the backs of the mice (2 x 5 cm) for 30 min; the test sites were then washed with tap water. The applied concentrations were selected based on their respective contents in commercial hair dye products. Three days after final hair-dyeing, photographs of mice were taken and the extent of hair loss was determined by measuring the area without hair using image processing and analysis software. Signs of hair loss and dermatitis (epidermal hyperplasia and inflammatory cell infiltration in the deep dermis and subcutaneous fat layer) developed in all groups treated with the component combinations containing Hydrogen Peroxide and the neutralized dye mixture (containing monoethanolamine (MEA) and toluene-2,5-diamine sulfate/*p*-phenylenediamine/resorcinol). The groups without either Hydrogen Peroxide or the neutralized dye mixture did not have hair loss or dermatitis, suggesting that both Hydrogen Peroxide and the neutralized dye mixture were necessary for inducing hair loss and dermatitis.

The experiment was repeated with the following test materials: a) control (treated with a basic formulation of hair dye); b) 6% MEA + 10% neutralized dye mixture; c) 4.5% aq. Hydrogen Peroxide; and d) 6% aq. Hydrogen Peroxide + 4.5% MEA + 10% neutralized dye mixture. The group that contained Hydrogen Peroxide and MEA had increased hair loss compared to controls. Hydrogen Peroxide or MEA alone or in other combinations did not increase hair loss.

In a third experiment, Hydrogen Peroxide (6% aq.) was administered to the mice with MEA (0%, 3%, or 6%) and MEA (6%) was administered to the mice with Hydrogen Peroxide (0%, 3%, or 6% aq.). There was no hair loss or dermal damage when Hydrogen Peroxide or MEA were administered alone. There was a concentration-dependent increase in hair loss and dermal damage for Hydrogen Peroxide with the addition of MEA and for MEA with the addition of Hydrogen Peroxide. The authors concluded that hair dye-induced hair loss and dermatitis were caused by the combination of Hydrogen Peroxide and MEA.¹¹¹

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

ANIMAL

Dermal irritation studies in animals are summarized in Table 11.

In rabbits, generally, Hydrogen Peroxide was not irritating at up to 10% aq. and mildly irritating to irritating at 35% aq.; at approximately 50% aq. and above, Hydrogen Peroxide was severely irritating and corrosive.^{2,33} Hydrogen Peroxide was not irritating to intact and abraded skin at 3% and 6% aq. in rabbits.^{2,33} At 8% and 10% aq., erythema and edema were observed, but Hydrogen Peroxide was still rated as a non-irritant.^{2,33} At 35% aq. Hydrogen Peroxide, erythema, edema, and blanching of the test sites were observed in rabbits, and the test substance was found to be a dermal irritant.^{2,33} At 49.2% aq., Hydrogen Peroxide was corrosive to rabbit skin.² Dermal exposure to 50% aq. Hydrogen Peroxide for 1 or 4 h exposure was corrosive.² Dermal exposure to Hydrogen Peroxide at 70% aq. for 3 min caused moderate erythema and mild edema, and exposure for 30 min was corrosive.³³

A single application of 15% or 30% aq. Hydrogen Peroxide caused extensive epidermolysis, inflammation and vascular injury to mouse skin.¹⁰⁵ In rats, skin exposed to 3% to 10% aq. Hydrogen Peroxide had mild focal epidermal thickening, which had keratinocytes with signs of pyknosis.¹¹² Intracytoplasmic edema was sporadically observed at and around thickened skin, especially in the basal layer. The severity of the effects increased in a dose-dependent manner. Different solutions of 3% or 6% Hydrogen Peroxide were non-irritating or mildly irritating to intact guinea pig skin; in abraded skin, one of these solutions at 3% and one at 6% were strongly irritating, while the other preparations were at most only mildly irritating.²

HUMAN

The hands of subjects (n = 32) were exposed to Hydrogen Peroxide vapor (how the vapor was produced was not specified).¹¹³ The lowest-observed-adverse-effects concentration (LOAEC) for skin irritation was 20 mg/m³ (14.2 ml/m³) after 4 h and 180 mg/m³ (128 ml/m³) after 5 min. This study was not used for evaluation by the MAK-Value Documentaries because of the inadequate documentation, but is included here for informational purposes. (A MAK value is the maximum permissible concentration of a substance as a gas vapor or aerosol in the air at the workplace.)¹¹⁴

Sensitization

ANIMAL

In a Magnusson-Kligman assay of Hydrogen Peroxide (0.1 ml), six induction applications at 0.1% aq. (intradermally) or at 3% aq. (epicutaneously to abraded skin) were administered to guinea pigs (n = 5).² Two weeks after the last induction, the test substances were applied once using the same concentrations and application routes. Dermal reactions were observed during the induction phase and at 1, 24, and 48 h after challenge patch. Two or three of the guinea pigs in each group (in both induction and challenge phases) had mild (faint pink) reactions to the application of Hydrogen Peroxide in the induction phase. One had a hemorrhagic reaction in the intradermal group. There were no signs of sensitization.

In a sensitization assay in guinea pigs, Hydrogen Peroxide (3% or 6% aq.) was administered to intact or abraded skin and by intradermal injection 10 times over a 2-week period.³³ After an unspecified time, the challenge under same conditions was administered. There were no signs of sensitization.

OCULAR IRRITATION STUDIES

IN VITRO

A 21-day porcine corneal opacity reversibility assay (PorCORA) was conducted on a hair colorant mixed 1:1 with Hydrogen Peroxide (12% aq.).¹¹⁵ Ocular irritation effects were observed (microscopic changes only in the superficial squamous cell layer), but were fully reversible.

ANIMAL

Ocular irritation studies in animals are summarized in Table 12.

In general, when rabbit eyes were treated with Hydrogen Peroxide, corneal injury depended not only on the concentration of Hydrogen Peroxide, but also on the integrity of the corneal epithelium, which had a protective influence.¹¹⁶ Hydrogen Peroxide at 0.5% to 5% aq. instilled into the eyes caused superficial corneal haze and much conjunctival reaction in rabbits, but these effects were resolved in 24 hr.^{2,116} Hydrogen Peroxide at 6% aq. had mixed results when instilled into the eyes of rabbits and was found to be both an ocular non-irritant and an irritant,^{2,33} while at 8% aq., Hydrogen Peroxide was an ocular irritant.^{2,33} Instillation of 10% to 30% aq. Hydrogen Peroxide caused superficial corneal haze, and, if there were defects in the epithelium, could cause localized swelling and opacities in the corneal stroma.^{2,33} At 70% aq., Hydrogen Peroxide was corrosive to the rabbit eye.^{2,33} In one study, Hydrogen Peroxide (10% and 15% aq.) was severely irritating; both concentrations affected the epithelium and deep stroma.¹¹⁷

Rabbits exposed to 90% Hydrogen Peroxide vapor (30 mg/m³ for 6 hours day, 5 days/week) showed no ocular

changes due to exposure to test material.⁴⁰ Mice exposed to Hydrogen Peroxide (90% aq.) vapors (19 mg/l) for 5-15 minutes showed gross opacities and microscopic lesions in the eyes.²

HUMAN

Instilling 1% to 3% aq. Hydrogen Peroxide solution on the human eye has been reported to cause severe pain, which soon subsides.¹¹⁶ In contrast, Hydrogen Peroxide has been historically used at these concentrations as an ocular antibacterial agent, as much as three to five times per day, without significant injury. While the threshold for irritation in many subjects is considered to be 100 ppm (0.01% aq.), even at 800 ppm (0.08% aq.), Hydrogen Peroxide has been shown to not cause corneal or conjunctival epithelial staining; higher levels may result in greater discomfort. It is possible that pH may play a role in the variation in irritation levels and why similar concentrations of Hydrogen Peroxide may cause severe pain or be tolerated.

Solutions (isotonic and pH-balanced for the human eye; 300 milliosmoles (mOsm), pH= 7) containing Hydrogen Peroxide (30 ppm to 490 ppm; 0.003% to 0.049% aq.) were dropped into one eye of each subject (n = 10; a single group of subjects) and a control dose containing Hydrogen Peroxide (30 ppm; 0.003%) was dropped into the other eye in a single blinded study.¹¹⁸ The tests started with the lowest concentration (30 ppm). The subjects reported their comfort response at 1 and 10 min after the drops were administered. Subjects were asked to compare the discomfort in their eyes and to report if they felt stinging. If there was no stinging reported, the next concentration was administered at the next session. No more than two test sessions were run per day. The mean detection threshold for drops of dilute Hydrogen Peroxide was 812 ppm (0.0812% aq.). The intersubject variability was quite large. If the lowest reported threshold for any stimulus is considered as an individual's threshold level for sensation, the mean value is 247 ppm (0.0247% aq.).

MUCOUS MEMBRANE IRRITATION STUDIES

ANIMAL

Hydrogen Peroxide (30% aq.; 5 µL) was dropped on the tip of the tongues of anesthetized male albino Osborne-Mendel rats (n = 18) four times at 15 min intervals.¹¹⁹ The tongues were rinsed with water 15 min after the last application. Three to six rats were killed either right after rinsing or 1 or 7 days after the last application, and their tongues examined. Hydrogen Peroxide caused an almost immediate marked edema on the anterior part of the tongue. After 1 day, this edema turned into a large ulceration that healed almost completely after 7 days.

Hydrogen Peroxide (1% or 1.2% aq.) was administered to the gingiva or tongues of anesthetized dogs by continuous drip (time and volume not specified).³³ Edema developed, followed by destruction and sloughing of the cornified epithelial layer of the gingiva.

HUMAN

Repeated use of Hydrogen Peroxide topical solution as a mouthwash or gargle may produce a condition known as "hairy tongue" or may cause irritation of the buccal mucous membrane.²⁹ Concentrated solutions (20% to 30% aq. or more) of Hydrogen Peroxide are strongly irritating to mucous membranes.

A mouth rinse containing Hydrogen Peroxide (concentration not specified) was tested in a double-blind, stratified, two-treatment, parallel trial (n = 48) over a 4-week period in cancer patients undergoing chemotherapy from two cancer treatment centers.¹²⁰ Controls were administered baking soda and water rinses or a lemon glycerin solution. There were no adverse effects reported during this study. The original source document, published in 1999, does not provide the concentration of Hydrogen Peroxide in the mouth rinse.

Mucosal Irradiation

Syrian hamsters (n = 15) were used in an oral mucosal irritation assay to study the effects of Hydrogen Peroxide with irradiation.¹²¹ The cheek pouches of the hamsters were treated as follows: group 1 was administered pure water (control); group 2 was administered laser irradiation at 80 mW; Group 3 was administered 3% aq. Hydrogen Peroxide; and groups 4 to 6 were administered 3% aq. Hydrogen Peroxide and laser irradiation at 80, 40, and 20 mW, respectively. The total treatment time was set at 7 min and treatment was repeated three times at approximately 1-h intervals. Macroscopic and microscopic histologic observations of the treated sites were performed immediately after each treatment and/or 24 h after the last treatment. The mean scores in macroscopic and histologic examinations in all six groups were 0. The authors concluded that treatment with 3% Hydrogen Peroxide and/or irradiation had no mucosal irritation potential in hamster cheek pouches under these test conditions.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Dermal

Results for dermatitis patients (n = 210) who underwent patch testing with a standard allergen series (including 15 hairdressing chemicals) and a supplementary "hairdresser series" (18 additional hairdressing chemicals) were reviewed.¹²²

The most common sites of dermatitis were the scalp, face, and hands. Patients had widely varying occupations. The most common occupations were cosmetologist (10.5%), housewife (9.5%), and beautician (5.2%); 14.3% were retired. Positive allergic reactions to Hydrogen Peroxide (3% aq.) were observed in 1% of the subjects tested; 1.4% of the subjects were positive for irritation.

Subjects (n = 121) who worked as hairdressers, and were suspected to have allergies to chemicals that were used in their profession, were administered a patch tests or prick tests (European Standard Series and Hairdressing Series), depending on the center where they were tested.¹²³ One subject (0.9%) had a positive reaction to Hydrogen Peroxide.

During 1991 to 1997, patients (n = 130), mainly hairdressers, were patch tested, including for Hydrogen Peroxide (concentration not specified), at the Finnish Institute of Occupational Health because of suspected occupational skin disease.¹²⁴ None of the patch tests were positive for an allergic reaction to Hydrogen Peroxide; one patient had an irritant patch test reaction. At the Department of Dermatology, University of Turku, during 1995 to 1996, 59 patients who were suspected of having eczema caused by hairdressing compounds were patch tested. None of the patients had an allergic or irritant patch test reaction to Hydrogen Peroxide. Data from the Finnish Register of Occupational Diseases showed that the total number of occupational allergic dermatoses reported during 1975 to 1997 was 10,806 cases; none of these were shown to be caused by Hydrogen Peroxide with patch testing. In the same period, a total of 29,803 occupational dermatoses were reported to the Finnish Register of Occupational Diseases; four were shown to be caused by Hydrogen Peroxide. The concentrations tested were not specified. In a retrospective study of hairdresser's with contact dermatitis during 1974 to 1993 in Finland, none of the patients (n = 355) tested positive for sensitization for Hydrogen Peroxide.¹²⁵

Clinical Trials

Dermal

A mixture of Hydrogen Peroxide (40% w/w) in an aqueous solution of isopropyl alcohol and water was tested in two double-blind, vehicle-controlled clinical trials, in subjects with four clinically typical seborrheic keratoses that were raised on the face, trunk, or extremities.¹²⁶ The subjects were treated with either the Hydrogen Peroxide mixture (n = 467) or the vehicle (n = 470). Subjects ranged from 42 to 91 years of age (mean 68.7 years), 58% percent were female, and 98% were Caucasian. A total of 925 of 937 subjects completed the trials; no reason was given for withdrawals from the study. Each lesion was treated with four applications on day 1 and then again on day 22, if needed, and were followed through day 106. The local skin reactions observed 10 minutes after treatment with the test substance included erythema (98% of the reactions), stinging (93%), edema (85%), pruritus (32%), and vesiculation (18%). The local skin reactions observed 1 week after treatment were scaling (72%), erythema (66%), crusting (67%), pruritus (18%), erosion (9%), and ulceration (4%). The local skin reactions observed 15 weeks after the initial treatment were erythema (21%), hyperpigmentation (18%), scaling (16%), crusting (12%), and hypopigmentation (7%). Less common adverse effects occurring in $\leq 0.5\%$ of subjects treated with the Hydrogen Peroxide mixture included eyelid edema (0.6%) and herpes zoster (0.6%).

Oral/Mucosal

In a randomized, placebo-controlled, 1-year clinical trial conducted to evaluate safety of 6% Hydrogen Peroxide whitening strips under continuous use conditions, subjects (n = 40) were administered either Hydrogen Peroxide (6%; approximately 9 mg/strip) strips or placebo strips.¹²⁷ Strips were worn 5 min daily for 12 months. The first application was done under supervision and the rest were done at home. Safety and tolerability were assessed via oral status interviews and oral examinations at baseline and after 1, 2, 3, 6, 9, and 12 months of use. Oral irritation and tooth sensitivity were the two most common adverse events reported during the study. Perceived oral irritation was reported by 2.5% of subjects in the placebo group and 0% of subjects in the Hydrogen Peroxide strip group; however, upon examination, irritation was observed in 22.5% and 25.0% of the subjects, respectively. Tooth sensitivity was reported by 5% of subjects in the placebo group and 10% of subjects in the Hydrogen Peroxide strip group. The majority of subjects (86%) reported adverse events during the first 3 months of the clinical trial. There were no serious adverse events in the study. Two subjects (5%) in the treatment group left the study because of treatment-related tooth sensitivity. No subjects in the placebo group dropped from the study due to treatment-related adverse events.

The safety of Hydrogen Peroxide (6%) tooth-whitening strips was examined using a clinical trials database accumulated over a 4-year period conducted at a single site.¹²⁸ Each maxillary strip carried approximately 12 mg total Hydrogen Peroxide. The subjects (total n = 148) used the strips twice daily for 30 min over a 2-week period. Safety was assessed by examination and interview methods in all studies. Pooled subject-level data were analyzed. Overall, oral irritation occurred, on average, in 22% (range, 4% to 31% in the clinical trials) of the subjects and tooth sensitivity occurred, on average, in 20% (range, 10% to 28%) of the subjects. Other side effects were unremarkable, and only 1 subject (0.7%) discontinued treatment early due to an adverse event, which in this case, was moderate soft tissue pain that resolved fully 1 day after discontinuing the study. In virtually all circumstances, adverse events were transient in duration. Onset was typically early and resolved during treatment, without affecting strip use. Clinical examination was unremarkable, and other side effects were infrequent.

Hydrogen Peroxide (0.75% or 1.5%) or saline was used as an oral rinse in healthy subjects (n = 11 to 12) four times daily for 2 weeks.^{4,129} Mucosal status, buccal microbial adherence, salivary flow rate (SFR), and subjective reactions were

assessed weekly. In the normal saline group, no significant changes were noted in any of the observed parameters and subjective reports were unremarkable. In both Hydrogen Peroxide groups, significant mucosal abnormalities were observed and subjective complaints included discoloration of the mucosal surfaces and the tongue. Bacterial adherence was significantly reduced in the 0.75% group, but not in the 1.5% group.

Other Clinical Studies

In patch tests using a standard hairdressers' series in subjects (n = 54) who were hairdressers in Australia with occupational contact dermatitis of the skin and nails, none of the subjects had an allergic reaction to Hydrogen Peroxide (concentration tested not specified).¹³⁰ In patch tests in subjects who were hairdressers (n = 164) in Australia with occupational contact dermatitis, none of the subjects had an allergic reaction to Hydrogen Peroxide (concentration tested not specified).¹³¹ In patch tests in subjects who were hairdressers (n = 44) in Bangkok with contact dermatitis of the hands, three of the subjects had an allergic reaction to Hydrogen Peroxide (3% aq.).¹³²

Case Reports

Case reports on dermal, oral, mucosal, ocular, and inhalation exposures to Hydrogen Peroxide are summarized in Table 13.

OCCUPATIONAL EXPOSURE

The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for inhalation of Hydrogen Peroxide is 0.0001% (1.4 mg/m³) averaged over an 8-h work shift. [29CFR1910.1000] The National Institute for Occupational Safety and Health (NIOSH) immediately dangerous to life or health (IDLH) level for Hydrogen Peroxide is 0.0075% and the recommended exposure limit (REL) is 0.0001% (1.4 mg/m³).^{9,133} According to the American Industrial Hygiene Association (AIHA) emergency response planning guideline (ERPG-2), the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action is 50 ppm (0.0050%).

The Scientific Committee on Occupational Exposure Limits (SCOEL) concluded that an occupational exposure limit (OEL) of 0.0001% (1.4 mg/m³) for Hydrogen Peroxide, as an 8-h time-weight average (TWA), is recommended.¹³⁴

NICNAS conducted a Tier II assessment on Hydrogen Peroxide under IMAP (see Non-Cosmetic Use section for more related information).⁵ It is advised that industries should use measures to minimize the risk of oral, dermal, ocular, and inhalation exposure to Hydrogen Peroxide by workers.

EPIDEMIOLOGICAL STUDIES

Chromosomal aberrations in lymphocytes from subjects (n = 6 women, 4 men) who had their hair dyed were studied.¹³⁵ The treatment group had their hair dyed 13 times at intervals of 3 to 6 weeks with commercial preparations containing mixtures of aminotoluenes, aminophenols, and hydroxybenzenes and, in some cases, naphthol, as active ingredients; the coloring products used was chosen according to each subject's hair color, and the same colorant was used on each subject throughout the study. The coloring preparations were each mixed (1:1) with Hydrogen Peroxide (3% to 6% aq.). The subjects in the control group (n = 10) were matched for sex and age and were subjected to sham hair dyes at the same times as the treatment group. Records were taken of smoking habits, alcohol consumption, and medical drug use and, during the experiment, exposure to X-rays, illness, and vaccinations. There were more smokers in the test group. None of the subjects had used hair dyes or shades for at least 1 year before entering the study, and the control group did not use hair colorants during the study. Nine blood samples were taken: 3 weeks before the first treatment, 24 h after a sham dyeing (no dye or Hydrogen Peroxide), and 24 h after each of the first 3 and last 4 dyeing procedures. There were no differences observed between the control and treated groups in the percentage of cells with one or more structural aberration (excluding gaps) before treatment, after sham dyeing, or after treatment. Subdivision of the groups according to sex revealed no differences. A significant increase in aberration rate with age was observed among the male but not the female subjects. Neither smoking nor X-ray exposure had an effect. No clastogenic effect of repeated hair dyeing was established in this study.

SUMMARY

This is a review of the safety of Hydrogen Peroxide as used in cosmetics. According to the *Dictionary*, this ingredient is reported to function in cosmetics as an antimicrobial agent, cosmetic biocide, oral care agent, and oxidizing agent.

Hydrogen Peroxide is always used in cosmetics as an aqueous solution. It can behave both as an oxidizing and as a reducing agent. Hydrogen Peroxide is produced metabolically in intact cells and tissues.

According to VCRP survey data received in 2018, Hydrogen Peroxide is reported to be used in 390 cosmetic formulations (18 leave-on products and 372 rinse-off products). The results of the concentration of use survey conducted by the Council indicate that Hydrogen Peroxide is used at up to 15% in the category of other hair coloring preparations; this formulation is a professional 50 volume developer, and standard dilutions include 10, 20, 30, and 40 volume (i.e., 3%, 6%, 9%, or 12% Hydrogen Peroxide, respectively). The highest maximum concentration of use in hair dyes and colors is 12.4%.

The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 2.5% in "other" skin care preparations. Hydrogen Peroxide is used in oral hygiene formulations, which may be incidentally ingested and come in contact with mucus membranes, at up to 4.6% (dentifrices).

In the U.S, the FDA recognizes Hydrogen Peroxide as GRAS to treat food. Hydrogen Peroxide may be used as a microbial agent, a bleaching agent, and a component of emulsifiers, and it may have other uses in the preparation and packaging of food for human use.

Hydrogen Peroxide is reactive, and it degrades rapidly when in contact with organic material. The rapid degradation upon contact with skin explains the absence of systemic effects from dermal exposure to Hydrogen Peroxide. However, application of Hydrogen Peroxide solutions to damaged skin, or excessive amounts of Hydrogen Peroxide on skin, may result in some systemic exposure. Administration of Hydrogen Peroxide solutions to body cavities lined by mucous membranes resulted in increased oxygen content of the draining venous blood. If the amounts were sufficiently high, Hydrogen Peroxide caused the formation of oxygen bubbles.

In general, acute dermal and oral toxic effects are dependent on concentration as well as dose. The concentration of Hydrogen Peroxide used is dependent upon its intended use. For example, industrial uses utilize concentrations as high as 90%, while in cosmetic use, Hydrogen Peroxide concentration is not reported to exceed 15%. The dermal LD₅₀ was > 8000 mg/kg Hydrogen Peroxide in mice; in this study, more mice died when 28% aq. Hydrogen Peroxide was administered than when 10% aq. Hydrogen Peroxide was used. Dermally administered Hydrogen Peroxide (90% aq.) caused 4 of 12 rats to die at 4899 mg/kg and 9 of 12 to die at 5520 mg/kg. The dermal LD₅₀ in rabbits was > 2000 mg/kg at 35% aq. Hydrogen Peroxide, 9200 mg/kg using 70% aq., and 690 mg/kg using 90% aq. No cats died when administered 4361 mg/kg of a 90% aq. Hydrogen Peroxide solution, dermally. Two of 5 pigs died when 2760 mg/kg (concentration not specified) Hydrogen Peroxide was applied to the skin.

The oral LD₅₀ for Hydrogen Peroxide (90% aq.) in mice was reported to be 2000 mg/kg. Oral LD₅₀s in rats ranged from 1520 to > 5000 mg/kg at approximately 10% aq. Hydrogen Peroxide while at 70% aq. Hydrogen Peroxide, the LD₅₀ in rats ranged from 75 to 1026 mg/kg. Rats that died had reddened lungs, hemorrhagic and white stomachs, and blood-filled intestines; some had white tongues.

In acute inhalation studies in mice, more mice died the longer they were exposed to Hydrogen Peroxide, while rats had only systemic effects. No treatment-related mortalities were observed in mice exposed to up to 3220 mg/m³ Hydrogen Peroxide (70% aq.) for up to 30 min; exposure to 3130 mg/m³ (1 h) and 880 mg/m³ (2 h) was lethal to all 4 mice tested. Rats exposed to saturated vapors of 90% aq. Hydrogen Peroxide survived exposure for 8 h; necropsy showed severe pulmonary congestion and emphysema, but no necrosis of pulmonary mucosa. In rats exposed to vaporized Hydrogen Peroxide for 4 h, the LC₅₀ was 2000 mg/m³, the LOEC for respiratory effects was 60 mg/m³, and the LOEC for skin effects was 110 mg/m³.

Hydrogen Peroxide causes transient dermal blanching in human subjects starting at 3% aq. Hydrogen Peroxide was slightly irritating to the nose and throat at 3.08 mg/m³, but not at 0.7 mg/m³, in humans exposed to vapors for 2 h. In humans, the threshold of detection for irritation through inhalation exposure was 10 mg/m³ when Hydrogen Peroxide vapor was inhaled through the nose.

In general, orally administered Hydrogen Peroxide in repeated dose studies caused inflammation and erosion to the upper digestive tracts of mice and rats, which increased with time and concentration. In repeated-dose drinking water studies (0.3% to 1.5% aq. Hydrogen Peroxide), rats and mice had decreased body weights at 2 to 3 weeks, decreased organ weights at 3 weeks or longer, and duodenal mucosal hyperplasia, duodenal carcinomas, and/or extensive pathological changes in the periodontium in subchronic and chronic studies. Effects observed during treatment were reversible after stopping treatment. In a feeding study using rats, there were no observed effects at up to 60 mg/kg/day in feed.

In mice and rats, systemic effects become more pronounced with time when exposed by inhalation to Hydrogen Peroxide. For example, mice exposed to Hydrogen Peroxide (79 or 107 mg/m³; 90% aq.) had nasal discharge and irritated skin at week 2; seven of nine mice died after eight exposures at 79 mg/m³; and, in the high-dose group, five of 10 mice died after eight exposures, and eight of 10 after 18 exposures. Rats exposed to 93 mg/m³ Hydrogen Peroxide (90% aq.) for 7 weeks showed signs of nasal irritation and profuse discharge at 2 weeks, and lung congestion at 5 weeks. There were no mortalities when rats were exposed to Hydrogen Peroxide (50% aq.) up to 10.3 mg/m³ for 13 weeks; the NOAEL was 10.3 mg/m³ for male and female rats for decreased liver and thymus weights.

Dermal effects of aerosolized Hydrogen Peroxide included bleaching of the fur of rabbits and dogs that increased over time. Shaved rats exposed to Hydrogen Peroxide vapor (0.1 to 10.1 mg/m³) in whole body chambers for 4 months had significant dysfunction of the horny layer of the skin. The LOEL in rats was 1.0 mg/m³ and the NOEL was 0.1 mg/m³ for changes in enzyme activities in the skin.

Studies were performed to evaluate the safety of Hydrogen Peroxide mixed with an oxidative hair dye or hair dye ingredient in a 1:1 mixture (up to 6% aq.) The resulting mixture was a reaction product of the two substances with little to no expected residual Hydrogen Peroxide. In these studies, no signs of toxicity, teratogenicity, maternal toxicity, or carcinogenicity were present. There was no evidence of test substance-induced toxicity when Hydrogen Peroxide (6% aq.), in nine different hair dyes, were administered to the skin of rabbits for 13 weeks. Nine different hair dyes containing Hydrogen Peroxide (6% aq.) administered to female rats caused no maternal or developmental toxicity; the same results were obtained when six different hair dyes, also containing Hydrogen Peroxide (6% aq.), were administered to both the male and female rats.

In human subjects, hair dyes in 1:1 mixtures with Hydrogen Peroxide (3% to 6% aq.) did not cause chromosomal

aberrations in lymphocytes collected from subjects after dyeing their hair 13 times at 3- to 6-week intervals. There were no increases in SCEs at any point in this experiment. Multiple hair dye formulations in 1:1 mixtures with Hydrogen Peroxide (6% aq.) did not cause skin tumors when applied to mice for 18 months and rats for at least 2 years. Hydrogen Peroxide (6% aq.) in a 1:1 mixture with oxidized *p*-phenylenediamine did not cause any skin tumors, but caused an increase in other types of tumors in rats when dermally administered once per week for 18 months.

Orally administered Hydrogen Peroxide caused maternal and fetal effects at higher doses (2% and 10% aq.). Male and female mice administered Hydrogen Peroxide (up to 1% aq.) in drinking water, prior to mating through parturition, produced normal litters. Hydrogen Peroxide (2% and 10% aq.) mixed with feed caused reduced body weights of the dams, fetal resorptions, decreased fetal body weights, and skeletal hypoplasia in rats. All of the neonates in the 10% aq. Hydrogen Peroxide group died. In rats, Hydrogen Peroxide (0.005 to 50 mg/kg) administered for 6 months caused modified estrus cycles in females and decreased sperm mobility in males.

The results in Ames assays conducted on Hydrogen Peroxide were not consistent. In most of the Ames assays presented, Hydrogen Peroxide (concentrations not specified in most assays) increased the number of revertant colonies in *S. typhimurium* strains without metabolic activation (3% or 30% in those assays with concentrations of Hydrogen Peroxide); however, there were a few assays where the results were negative for genotoxicity. In Ames assays, the results for Hydrogen Peroxide (3% in one of these assays) were also mixed in *E. coli*. In other Ames-type assays, Hydrogen Peroxide (concentrations not specified) was mutagenic in *E. coli*, *B. subtilis*, and *S. cerevisiae*. In bacterial forward mutation assays, Hydrogen Peroxide (30% in the one assay) was genotoxic to various strains of *S. typhimurium* and *E. coli*. In chromosomal aberration tests, Hydrogen Peroxide (30% in the one assay; as low as 0.25 to 10 μ M) was genotoxic to multiple cell types, including CHO cells murine splenocytes, V79 cells, SHE cells, and human leukocytes and embryonic fibroblasts. Hydrogen Peroxide (concentration not specified; 500 μ M) increased the number of abnormal metaphases in CHO-K1 cells without, but not with metabolic activation. In mouse lymphoma assays, Hydrogen Peroxide (30% in the assays with a concentrations; 0.075 μ g/ml) increased the mutation frequency in mouse lymphoma cells without metabolic activation, but not with metabolic activation; Hydrogen Peroxide (concentrations not specified) had mixed results in V79 cells in mammalian cell gene mutation assays. In SCE assays, Hydrogen Peroxide (concentrations not specified) was mutagenic in V79, CHO cells, and human lymphocytes without metabolic activation, but was not mutagenic, or was mutagenic to a lesser extent, with metabolic activation. In an UDS assay in rat hepatocytes, Hydrogen Peroxide (35.7% aq.) caused a dose-dependent increase in NNG values at 6.25 to 25 μ g/ml. In comet assays, Hydrogen Peroxide was mutagenic in mouse lymphoma cells (concentration not specified; 500 μ M), rat hepatocytes (concentration not specified; 1 μ M), *S. cerevisiae* (concentration not specified; 20 μ M), V79 cells (37% aq.; 40 μ M), and HepG2 cells (0.3 M aq.). Hydrogen Peroxide was also mutagenic to breast cancer cells (concentration not specified; 200 μ M), human lymphocytes (concentration not specified; 10 μ M), human fibroblasts (concentration not specified; 30 μ M), HeLa cells (37% aq.; 40 μ M), and HEP G2 cells (0.3M aq.; 40 μ M). In a combined comet assay/micronucleus assay using human lymphoblastoid cells, Hydrogen Peroxide (concentration not specified) was genotoxic in the comet assay (50 μ M) and in the micronucleus assay (100 μ M). In another combined comet assay/micronucleus assay in V79 cells, Hydrogen Peroxide (concentration not specified) was genotoxic at 80 μ M and 40 μ M, respectively. In a multi-test assay using mouse lymphoma cells, Hydrogen Peroxide (concentration not specified) was not genotoxic in two DNA adduct assays up to 500 μ M (but was genotoxic at 500 μ M in a comet assay), at 20 μ M in a micronucleus test, and at 100 μ M in a *tk*[±] gene mutation assay. Hydrogen Peroxide (37% aq.) was not mutagenic at 110 μ M in V79 cells in a HPRT assay.

Hydrogen Peroxide was not genotoxic in multiple in vivo assays. In a mammalian erythrocyte micronucleus test using mice, 35% aq. Hydrogen Peroxide, administered i.p., was not genotoxic at up to 2000 mg/kg. In a mammalian erythrocyte micronucleus test, Hydrogen Peroxide (35% aq.) administered in drinking water was not genotoxic to mice at up to 536 and 774 mg/kg/day for males and females, respectively. Hydrogen Peroxide (70% aq; \leq 200 mmol) was not genotoxic to mice in a dermal genotoxicity assay. In an UDS assay, i.v. administered Hydrogen Peroxide (50 mg/kg) did not induce unscheduled DNA synthesis in rats. In human subjects, a whitening gel containing Hydrogen Peroxide (35% aq.) administered to gingival tissue during a teeth-whitening procedure did not induce DNA damage to the gingival and lip tissue.

Mice dermally administered Hydrogen Peroxide (15% aq.) twice-weekly for 25 weeks did not develop squamous-cell carcinoma. In oral carcinogenicity studies, Hydrogen Peroxide in drinking water was not carcinogenic at 0.1%, but at 0.4%, caused duodenal nodules in mice. Lesions observed in the duodenum and stomachs after 90 days of treatment were fully reversible when treatment was terminated. Hydrogen Peroxide administered in drinking water at up to 0.6% did not increase the number of tumors in testes, mammary glands, or skin in rats. In mucosal studies, no neoplasms developed when Hydrogen Peroxide (0.75% in a dentifrice) was administered into the buccal cheek pouches of hamsters for 20 weeks.

When administered to the buccal cheek pouches of hamsters. Hydrogen Peroxide (30% aq.) dermally administered once, followed by applications of TPA for 25 weeks, did not cause or increase dermal tumors in the skin of mice. In two studies, Hydrogen Peroxide (up to 30% aq.) did not promote tumors or cause squamous-cell carcinoma in mice after the administration of DMBA. In an oral study, after the administration of MNNG, Hydrogen Peroxide (1% aq.) in drinking water did not increase the number of gastrointestinal tumors. Hydrogen Peroxide (30% aq.) administered for 24 weeks to the cheek pouches of hamsters after a single dose of NNK did not increase the instance of cheek pouch adenoma, but did increase the instances of other tumors.

Hydrogen Peroxide (4.5% aq.) alone applied to the dorsal region of mice did not cause hair loss or dermatitis. However, when Hydrogen Peroxide (6% aq.) was administered in combination with MEA, there was a concentration-

dependent increase in hair loss and dermatitis.

In rabbits, Hydrogen Peroxide was not irritating at up to 10% aq. and mildly irritating to irritating at 35% aq.; at approximately 50% aq. and above, Hydrogen Peroxide was severely irritating and corrosive. In rabbits, Hydrogen Peroxide was not irritating to intact and abraded skin at 3% and 6% aq.; rated a non-irritant, but with erythema and edema at 8% and 10% aq.; was a dermal irritant at 35% aq. Hydrogen Peroxide with erythema, edema, and blanching of the test sites; and was corrosive at 49.2% aq. Dermal exposure to Hydrogen Peroxide at 70% aq. for 3 min caused moderate erythema and mild edema in rabbits; exposure to 50% aq. Hydrogen Peroxide for 1 or 4 h exposure was corrosive. Dermal exposure to Hydrogen Peroxide at 70% aq. for 30 min exposure was corrosive in rabbits. A single application of 15% or 30% aq. Hydrogen Peroxide caused extensive epidermolysis, inflammation, and vascular injury to mouse skin. In rats, 3% to 10% aq. Hydrogen Peroxide caused mild focal epidermal thickening. A single application of 3% or 6% aq. Hydrogen Peroxide was non-irritating or mildly irritating to guinea pig skin. Hydrogen Peroxide was not sensitizing in guinea pigs at up to 6% aq.

When the hands of human subjects were exposed to Hydrogen Peroxide vapor for 4 h, the LOAEC was 20 mg/m³ (14.2 ml/m³) for skin irritation. The LOAEC was 180 mg/m³ (128 ml/m³) after 5 min.

In a 21-day PorCORA, Hydrogen Peroxide (12% aq.) in a 1:1 mixture with a hair dye caused microscopic changes only in the superficial squamous cell layer; the effects were fully reversible. In rabbit eyes treated with Hydrogen Peroxide, corneal injury generally depended not only on the concentration of Hydrogen Peroxide, but also on the integrity of the corneal epithelium. Hydrogen Peroxide at 0.5% to 5% aq. instilled into the eyes of rabbits caused superficial corneal haze and conjunctival reaction; these effects were resolved in 24 hr. Hydrogen Peroxide at 6% aq. had mixed results in rabbits, while at 8% aq., Hydrogen Peroxide was an ocular irritant. Instillation of 10% to 30% aq. Hydrogen Peroxide caused superficial corneal haze, and, if there were defects in the epithelium, could cause localized swelling and opacities in the corneal stroma. At 70% aq., Hydrogen Peroxide was corrosive to the rabbit eye. Rabbits exposed to Hydrogen Peroxide vapors (30 mg/m³) showed no changes due to exposure to test material. The eyes of mice exposed to Hydrogen Peroxide vapors (90% aq.) showed gross opacities and microscopic lesions.

The threshold for ocular irritation in many human subjects is 0.01% aq., but at 0.08% aq., Hydrogen Peroxide may not cause corneal or conjunctival epithelial staining. It is possible that pH may play a role in irritation levels. The mean detection threshold for drops of dilute Hydrogen Peroxide was 812 ppm in human subjects.

In mucosal studies, Hydrogen Peroxide dropped on the tongues of rats (30% aq.) and dogs (1 or 1.2% aq.) caused marked edema. In rats, edema evolved into large ulcerations that almost resolved in 7 days. In dogs, there was destruction and sloughing of the cornified epithelial layer of the gingiva. Hydrogen Peroxide (3% aq.) was not a mucosal irritant when administered to hamster cheek pouches and then irradiated.

In humans, repeated use of Hydrogen Peroxide as a mouthwash or gargle may cause irritation of the buccal mucous membrane. Concentrated solutions (20% to 30% aq. or more) of Hydrogen Peroxide are strongly irritating to mucous membranes. In a double-blind, stratified, two-treatment, parallel trial over a 4-week period, a mouth rinse containing Hydrogen Peroxide (concentration not specified) caused no adverse effects.

In multiple retrospective studies, there were few or no positive reactions to Hydrogen Peroxide in subjects with occupational dermatitis or occupational allergic dermatoses. In a retrospective study of Hydrogen Peroxide (6%) in tooth-whitening strips, oral irritation occurred in an average of 22% of the subjects. In virtually all circumstances, adverse events were transient.

In a clinical trial, the local skin reaction of a mixture of Hydrogen Peroxide (40% w/w) in an aqueous solution of isopropyl alcohol and water administered to subjects seborrheic keratoses included erythema, stinging, edema, scaling, and crusting. In a clinical trial of tooth-whitening strips containing Hydrogen Peroxide (9 mg/strip), irritation was observed in 25.0% of the subjects; there were no serious adverse events. In a clinical trial of Hydrogen Peroxide (0.75% or 1.5%) as an oral rinse, mucosal abnormalities were observed and subjective complaints included discoloration of the mucosal surfaces and the tongue.

DISCUSSION

The Panel determined that the available genotoxicity, dermal, inhalation, carcinogenicity, and reproductive/developmental toxicity data were sufficient to issue the conclusion that Hydrogen Peroxide is safe in the present practices of use and concentration. The potential for dermal absorption of Hydrogen Peroxide was noted, but was considered negligible due to the low concentrations used for cosmetic products. In addition, Hydrogen Peroxide is reactive, and degrades rapidly, due to reactions with all classes of organic biomolecules. The rapid degradation upon contact with skin explains the absence of systemic effects from dermal exposure to Hydrogen Peroxide. The Panel also noted the positive genotoxicity studies, but determined the results are not relevant to cosmetic use due to rapid consumption of Hydrogen Peroxide by reaction with the proteins on the skin surface.

Generally, the toxic potency of Hydrogen Peroxide is positively correlated with the concentration used. Hydrogen Peroxide comes in a variety of grades for different uses. For example, the 3% grade is commonly used topically and for pharmaceutical purposes, while a 90% grade is used as an oxygen source for rocket fuel. For cosmetics, the maximum concentration of Hydrogen Peroxide in leave-on hair products is reported to be relatively low (4%), and the maximum reported concentration of use for Hydrogen Peroxide is 15% in a professional hair coloring formulation.

The Panel noted the positive irritation studies in rabbits dermally exposed to concentrations of 35-70% Hydrogen Peroxide. However, the concentrations used in these studies are higher than the concentrations used in cosmetics. Hydrogen Peroxide was non-irritating in rabbits and non-sensitizing in guinea pigs at concentrations of 10% and 6%, respectively. Due to these factors, the concern of dermal irritation and sensitization resulting from dermal cosmetic application is considered negligible.

In addition, Hydrogen Peroxide is inevitably synthesized in the body (e.g., oral cavity, urinary tract, respiratory system). When 16 urine samples were examined in healthy human volunteers from the ages of 18 - 49, an average of 16.9 μ M Hydrogen Peroxide was detected. The robust natural production and clearance of Hydrogen Peroxide in the body further mitigates any concern of toxic potential resulting from cosmetic use.

Hydrogen Peroxide is an oxidizer in permanent hair coloring formulations and hair bleaches. The highest maximum concentration of use in hair dyes and colors is 12.4%; however, Hydrogen Peroxide is commonly reacted (e.g., 1:1 with an oxidative hair dye or hair dye ingredient) in preparation of the hair dye formulation to be applied. Accordingly, it should be noted that FDA has issued certain safety precautions to be followed when using permanent hair dye formulations, <https://www.fda.gov/Cosmetics/ResourcesForYou/Consumers/ucm167436.htm>.

The Panel noted the potential for incidental inhalation exposure with aerosol hair sprays (4%). The available inhalation data suggest little potential for respiratory effects at relevant doses. It should also be noted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range and long exposure durations to ensure that the potential for pulmonary or systemic toxicity will be detected. In contrast, however, the concentrations of respirable droplets/particles and the inhalation exposure durations from the use of cosmetic products will be much less than those of the animal studies. Thus, the adverse effects reported in such studies may have little or no relevance for evaluating the inhalation safety of cosmetic ingredients. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

CONCLUSION

The CIR Expert Panel concluded that Hydrogen Peroxide is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical and physical properties of Hydrogen Peroxide (100%).

Property	Value	Reference
Physical Form	Liquid	5,136,137
Color	Colorless	5,136,137
Odor	Sharp	5,137
Taste	Bitter	9
Molecular Weight (g/mol)	34.02	2
Density (g/mL) @ -20°C	1.17	2
@ 25 °C	1.4425	11
Viscosity (kg/(s*m) @ 20°C)	0.001249	2
Vapor pressure (mmHg @ 30°C)	5	9
Melting Point (°C)	-11.11	9
Boiling Point (°C)	150.2	2
	150 – 152	11
	141	9
Water Solubility (g/l @ 20°C & pH 7)	100	2
	Miscible	11,13
log P _{ow}	-1.57 est.	2
Disassociation constants pKa (@ 25°C)	11.62 est.	2,11

est. = estimated

Table 2. Chemicals used to stabilize aqueous Hydrogen Peroxide.¹¹

Phosphoric acid	Sodium phosphate	Sodium stannate
Ammonium sulfate	Sodium silicate	Acetanilide
8-Hydroxyquinoline	Pyridine carboxylic acid	Benzoic acids
Nitrate salts		

Table 3. Frequency of use according to duration and exposure of Hydrogen Peroxide.^{15,16}

Use type	Uses	Maximum Concentration (%)
Total/range	390	0.000002-15
<i>Duration of use</i>		
Leave-on	18	0.000002-4
Rinse-off	372	0.000003-15
Diluted for (bath) use	NR	NR
<i>Exposure type</i>		
Eye area	NR	0.000002
Incidental ingestion	93	1.5-4.6 (in oral hygiene products)
Incidental Inhalation-sprays	2; 5 ^a	4; 0.01-2 ^a
Incidental inhalation-powders	NR	0.000002 ^b
Dermal contact	11	0.000002-3
Deodorant (underarm)	NR	NR
Hair-noncoloring	33	0.00008-4
Hair-coloring	250	3.5-15 ^c
Nail	3	NR
Mucous Membrane	93	0.00009-4.6
Baby	NR	0.0019

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

Note: Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

^a It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

^b It is possible these products may be powders, but it is not specified whether the reported uses are powders.

^c The 15% hair-coloring product is a professional developer that is diluted as needed. The next highest maximum concentration of use in this category is 12.4% in hair dyes and colors.

Table 4. EU Restrictions for Hydrogen Peroxide in cosmetic products.^{23,24}

Product type	Label Instructions/ Warnings	Maximum concentration
Hair	Wear suitable gloves. Contains Hydrogen Peroxide. Avoid contact with eyes. Rinse eyes immediately if product comes into contact with them.	12% present or released
Skin	Contains Hydrogen Peroxide. Avoid contact with eyes. Rinse eyes immediately if product comes into contact with them.	4% present or released
Nail hardening	Contains Hydrogen Peroxide. Avoid contact with eyes. Rinse eyes immediately if product comes into contact with them.	2% present or released
Oral products including mouth rinse, tooth paste, and tooth whitening/bleaching products		≤ 0.1% present or released
Tooth whitening or bleaching (to be only sold to dental practitioners)	Contains Hydrogen Peroxide. Avoid contact with eyes. Rinse eyes immediately if product comes into contact with them. Concentration of Hydrogen Peroxide. Not to be used on a person under 18 years of age. To be sold only to dental practitioners. For each cycle of use, the first use to be only done by dental practitioners or under their direct supervision if an equivalent level of safety is ensured. Afterwards to be provided to the consumer to complete the cycle of use.	> 0.1% to ≤6%
Eye lashes; professional use only	Wear suitable gloves. For professional use only. Avoid contact with eyes. Rinse eyes immediately if product comes into contact with them. Contains Hydrogen Peroxide.	2% present or released

Table 5. U.S. FDA and EPA regulation on Hydrogen Peroxide in food preparation.

Permitted use	Regulation
Up to 23 mg/kg may be used in a silver nitrate solution as an antimicrobial agent in bottled water	21CFR172.167
As part of a solution to make acetone peroxides to use as bleaching agents in flour or a dough conditioning agent in rolls and breads	21CFR172.182
With lecithin, as hydroxylated lecithin, as an emulsifier in foods	21CFR172.814
Food starch may be bleached with Hydrogen Peroxide if active oxygen from Hydrogen Peroxide does not exceed 0.45% all active oxygen	21CFR172.892
With acetic acid to form peroxyacetic acid up to 59 ppm may be used in wash water on fruits and vegetables that are not raw in combination	21CFR173.315
Epoxidize soybean oil by reacting soybean oil in toluene with hydrogen peroxide and formic acid	21CFR172.723
Used in adhesives that come in contact with food	21CFR175.105
The sterilization of polymeric food-contact surfaces (e.g., food packaging materials)	21CFR178.1005
An aqueous solution containing Hydrogen Peroxide, peracetic acid, acetic acid, and 1-hydroxyethylidene-1,1-diphosphonic acid may be safely used on food-processing equipment and utensils, and on other food-contact articles to control the growth of micro-organisms	21CFR178.1010
Used as ingredients in an antimicrobial pesticide formulation, may be applied to food-contact surfaces in public eating places, dairy-processing equipment, and food-processing equipment and utensils; when it is ready for use, the end-use concentration is not to exceed 91 ppm Hydrogen Peroxide	40CFR180.940

EPA = Environmental Protection Agency; FDA = Food and Drug Administration

Table 6. Acute toxicity studies.

Animal (n)	Concentration	Dose/Concentration	Procedure	Results	Reference
Dermal					
Mice (strain and n not specified)	10% and 28% aq.	1400 and 8000 mg/kg	Not specified	Clinical signs: excitation and inhibition, ataxia, tremors and paresis of the limbs, and increased respiration rate developed 5 to 10 min after dermal application at 1400 mg/kg. Death of some mice was observed on application of 28% Hydrogen Peroxide in doses > 8000 mg/kg	11
White rats (12)	90% aq.	4899 and 5520 mg/kg	No details provided	Four of 12 died in the low-dose group and 9 of 12 died in the high-dose group	33
Black rats (6)	Not specified	6900 and 8280 mg/kg	No details provided	None of the rats died in the low-dose group and 2 of 6 rats died in the high-dose group	33
Rats (strain and n not specified)	Not specified	4060 mg/kg	No details provided	50% of the rats died	33
New Zealand White rabbits (10/sex)	35% w/w aq.	2000 mg/kg	OECD GL 402 (Acute Dermal Toxicity) Under occlusion for 24 h. Rabbits were observed at 0.5, 1, 2, 3, 4 and 6 h, twice daily for 13 days, and once on day 14 The rabbits were then killed and necropsied.	There were no deaths. Nasal discharge in one rabbit and lacrimation in another rabbit were observed on day 4 and 5, respectively. Seven rabbits gained weight and three rabbits lost weight. No gross lesions were observed at necropsy. LD ₅₀ > 2000 mg/kg	2,33
Male rabbits (4)	70% aq. w/w	6500 and 13,000 mg/kg	OECD GL 402	None of the rabbits died in the low-dose group; all rabbits in the high-dose group died. LD ₅₀ = 9200 mg/kg	2,33
Rabbits (12)	90% aq.	690 mg/kg	No details provided	Six of 12 rabbits died.	33
Cats (2)	90% aq.	4361 mg/kg	No details provided	None of the cats died	33
Pigs (5)	Not specified	2760 mg/kg	No details provided	Two of 5 pigs died	33
Oral					
Mice (strain and n not specified)	90% aq.	Not specified	No detail provided	LD ₅₀ = 2000 mg/kg	33
Wistar rats (10/sex)	9.6% aq.	Males: 847 to 2529 mg/kg Females: 886 to 2646 mg/kg	Gavage	All deaths occurred within 24 h. Surviving rats recovered within 4 to 24 h. Dose-dependent inhibition of autonomic behavior was observed immediately after dosing. At 3801.6 mg/kg or higher in males and 3974.4 mg/kg or higher in females, rats remained in a strongly inhibited state until their deaths, which occurred within 1 to 3 h. Necropsy of the rats that died showed a dose-dependent dilation of capillaries of the stomach and intestines starting at the lowest doses. No changes were observed in other organs. Males: LD ₅₀ = 1520 mg/kg Females: LD ₅₀ = 1620 mg/kg	2
Wistar-JCL rats	9.6% aq.	Oral administration not specified	7-day observation period.	Males: LD ₅₀ = 1571 mg/kg Females: LD ₅₀ = 1671 mg/kg	33
Sprague-Dawley rats (5/sex)	10% aq.	5000 mg/kg	OECD GL 401 (Acute Oral Toxicity) Rats were observed at 0.5, 1, 2, 3, 4 and 6 h, twice daily for 13 days, and once on day 14 The rats were then killed and necropsied.	No deaths occurred after dosing. One female rat died at day one after dosing, but no other mortality occurred during the observation period. Clinical signs included decreased locomotion, ataxia, and nasal discharge. Necropsy showed hemorrhagic, blood filled stomachs and intestines and reddened lungs. LD ₅₀ > 5000 mg/kg	2

Table 6. Acute toxicity studies.

Animal (n)	Concentration	Dose/Concentration	Procedure	Results	Reference
Sprague-Dawley rats (10/sex)	35% w/w aq.	Males: 630, 794, 1000, 1260, 1588, and 2000 mg/kg Females: 794, 1000, 1260, and 1588 mg/kg	Administered by gavage. Rats were observed at 0.5, 1, 2, 3, 4 and 6 h, twice daily for 13 days, and once on day 14. The rats were then killed and necropsied.	Mortality was observed at all doses; none survived in the 2000 mg/kg group. Most deaths occurred within 24 h of dosing. Clinical signs included tremors, decreased motility, prostration, and oral, ocular, and nasal discharge. Necropsy of rats found dead revealed hemorrhagic stomachs and intestines filled with blood. Reddened lungs and white tongues were observed. Less frequently, blood-filled bladders and stomach and livers containing white foci were observed. All surviving rats appeared normal at necropsy. Males: LD ₅₀ = 1193 mg/kg Females: LD ₅₀ = 1270 mg/kg	2,33
Sprague-Dawley rats (n not specified)	50% aq.	Not specified	Observed for 14 days.	LD ₅₀ > 225 and < 1200 mg/kg No deaths among female rats, 1 of 5 male rat died on day one	11
Wistar rats (n not specified)	60% aq.	Males: 0, 0.351, 0.535, 0.734, 1.019 or 1.296 mL/kg Females: 0, 0.213, 0.323, 0.426, 0.659, 0.879, 1.236 or 1.647 mL/kg	Observed for 14 days.	Males: LD ₅₀ = 872 mg/kg Females: LD ₅₀ = 801 mg/kg	11
CrI:CD BR rats (5/sex)	70% w/w aq.	Males: 500, 1000 and 1500 mg/kg Females: 500, 750 and 1000 mg/kg	OECD GL 401 Observed for 14 days.	Two males in the 1000 mg/kg group, 1 female in the 500 mg/kg group, and 2 females in the 750 mg/kg group died. All males in 1500 mg/kg group and females in 1000 mg/kg group died; most were found dead on day of administration. Compound-related gross changes of the tongue, esophagus, stomach, and duodenum and adhesions in the peritoneal cavity were observed in male and female rats that died. Degenerative ulceration and regenerative hyperplasia of pyloric antrum of the stomach were observed at all dose levels. Ulcerative necrosis penetrated into the gastric epithelium (muscularis mucosa); severity of the ulcerations was rated minimal to mild. Males: LD ₅₀ = 1026 mg/kg (no confidence interval available) Females: LD ₅₀ = 693.7 mg/kg (95% confidence interval 427 – 960 mg/kg) Combined: LD ₅₀ = 805 mg/kg (no confidence interval available)	2
Rats (strain and n not specified)	70% aq.	50, 75 or 100 mg/kg	No details provided	Males: LD ₅₀ = 75 mg/kg	11
Dogs (6 treatment, 1 control)	3% aq.	2 ml/kg (not more than 45 ml) Control was administered apomorphine in the conjunctival sac.	Oral administration (method not specified) was repeated 10 min later if emesis had not occurred.	Emesis was successfully induced in 5 out of 6 dogs after one dose and on second dose with remaining dog. Mean time to emesis was 4.5 min and 2 min for apomorphine. Most severe lesions identified were gastric ulcers and gastric degeneration and necrosis, evident at 4 and 24 h following treatment. Most gastroduodenal lesions were present for up to 1 week, with resolution by 2 weeks. Duodenum was less affected grossly than esophagus or stomach, and was less affected than stomach histologically. Esophagus was not evaluated histologically.	37
Inhalation					
Male Swiss mice (4)	70% w/w aq.	300, 616, 1135 and 1856 mg/m ³	Nose-only exposure for a single 30 min period. Respiratory movements were recorded before, during and after exposure. After exposure, mice were observed for clinical signs and body weight changes up to 1 day after exposure. Mice were killed and gross pathology examinations were conducted, including a histopathological study of livers.	No mice died during the exposure. Respiratory RD ₅₀ was 665 mg/m ³ (95% CI: 280 - 1139 mg/m ³) and the exposure concentration at which a 50% reduction of the minute volume was observed was 696 mg/m ³ (95% CI: 360 - 1137 mg/m ³). Two mice in the 616 mg/m ³ group and all mice in high-dose group had swollen white spots on the tip of the nose between 1 to 4 h after exposure. No other signs were observed. Two mice in 300 and 1856 mg/m ³ groups (one each) had local degenerative changes of the liver.	2

Table 6. Acute toxicity studies.

Animal (n)	Concentration	Dose/Concentration	Procedure	Results	Reference
Male OF1 mice (8)	Not specified	25, 39, 103, or 212 ppm (calculated as 35, 54, 143, or 295 mg/m ³)	Head-only exposure for 60 min. Respiration was measured during exposure and recovery.	The onset of decrease in respiration started almost immediately at all concentrations and was steady through treatment period. Recovery was rapid, starting at 15 min, with respiration returning to 74% to 98% of pre-exposure. RD ₅₀ = 113 ppm (calculated as 157 mg/m ³)	³⁸
Mice (strain not specified; 10)	Not specified	3600 to 19,000 mg/m ³	Exposed for 5, 10 or 15 min. Average mass median droplet size was approximately 3.5 µm.	There were no deaths up to 5000 mg/m ³ . Reported mortalities: 9462 mg/m ³ for 5 min, no mortality; 13,287 mg/m ³ for 10 min, 5 of 10 died; 11,877 mg/m ³ for 15 min, 5 of 10 died; 16,809 mg/m ³ , 9 of 10 died. Exposures up to 5000 mg/m ³ for 5 min caused nasal irritation, blinking, and slight gasping. At necropsy, lung congestion was observed. Four of 20 mice in the 5200 mg/m ³ had necrosis of bronchial epithelium. At 9400 mg/m ³ and higher for 5 to 15 min, mice had more severe signs and 10% to 15% of mice died within 1 h after convulsions. Necropsy showed pulmonary congestion. Mice that survived for several days to 8 weeks had necrosis of bronchial epithelium. Mice surviving 9400 mg/m ³ or more had slowly developing corneal damage, which appeared 5 weeks after exposure.	³³
Mice (strain and n not specified)	70% aq.	920 to 2000 mg/m ³ and 12,000 to 13,000 mg/m ³	2 h full-body exposure	Half of the mice died after 10 to 15 min of exposure at 12,000 to 13,000 mg/m ³ Hydrogen Peroxide aerosol. Exposures at 920 to 2000 mg/m ³ were lethal to at least some mice. Macroscopic examination of dead mice showed swelling and/or discoloration of skin of head, tongue, neck, forepaws, and nose; subcutaneous emphysema and hemorrhages; red lymph nodes; and diffuse red lungs. Effects were attributed to bleaching and corrosive nature of test substance.	¹¹
Swiss-Webster Mice (4)	70% aq.	880 to 4960 mg/m ³	7.5 to 120 min to aerosolized test material in nose-only apparatus. Surviving mice were observed for 14 days before necropsy.	No treatment-related mortalities were observed up to 3220 mg/m ³ for up to 30 min. Longer exposure to 3130 mg/m ³ (1 h) and 880 mg/m ³ (2 h) was lethal. Clinical signs (not specified) were almost immediate. Time to recovery increased with time of exposure and concentration, but did not exceed 1 week. Effects at necropsy were attributed to bleaching or corrosiveness of test material. No changes in lung weights were observed. Macroscopic examination of surviving mice at end of recovery period showed no effects except bald area between eyes, suggesting that no permanent damage was caused by exposure to test material.	³³
Swiss mice (10)	90% aq.	16.1 ppm (23 mg/m ³)	4 h exposure followed by 2 weeks observation.	There were no mortalities. Lethal dose > 16.1 ppm	³⁹
Male mice (strain not specified; 4)	90% aq.	3600 to 19,000 mg/m ³	Exposed for 5 to 15 min	At concentrations from 3600 to 5200 mg/m ³ , there were no deaths, but congestion of lungs and necrosis of bronchial epithelium were observed. At 9400 mg/m ³ , lethal range was reached with death occurring 6 days following exposure. At 12,000 to 19,000 mg/m ³ for 10 to 15 min, survival time was reduced in majority of mice to less than 1 h. Clinical signs during exposure to low concentrations consisted of mild nasal irritation, blinking eyes, slight gasping, and loss of muscular coordination, which resolved within 30 min. Pulmonary congestion was noted, and surviving mice had necrosis of bronchial epithelium. LC ₁₀ = 9400 mg/m ³	²
Sprague-Dawley rats (5/sex)	50% aq. w/w	170 mg/m ³ (122 ppm)	US EPA Guideline Vol 50 (§798.1150) (Acute Inhalation Toxicity) Atmosphere was generated by bubbling air flow through a reservoir containing 1000 ml of 50% aq. Full body exposure for 4 h followed by observation for 14 days. Rats were then killed and necropsied.	Signs of treatment were minimal during exposure (decreased activity and eye closure) but a few responses such as nasal discharge were noted during 14-day observation period. A minimal, transient adverse effect upon body weight was produced by treatment. Otherwise, body weight gain was considered unremarkable. At necropsy, observations and lung weights were considered unremarkable. No LD ₅₀ value for acute inhalation toxicity could be established and must be greater than the maximum attainable vapor concentration of 170 mg/m ³ .	^{2,33}

Table 6. Acute toxicity studies.

Animal (n)	Concentration	Dose/Concentration	Procedure	Results	Reference
Male Wistar rats (18)	90% aq.	Not specified	Rats were exposed to vapor in glass chamber for 8 h. Rats were killed and necropsied periodically over next 14 days.	No rats died and there were no clinical signs observed. Only abnormal signs noted were rats scratching and licking themselves. Pathological examination showed congestion in trachea and lungs. Small, localized areas of pulmonary edema without hemorrhage and areas of alveolar emphysema were present among rats killed during first 3 days after exposure. Most lungs exhibited many areas of alveolar emphysema in addition to severe congestion. All other organs examined appeared normal.	40
Male Wistar rats (10, 20)	90% aq.	338 to 427 mg/m ³	Rats were exposed to vapor in glass chamber for 4 h (n = 10) or 2 8-h (n = 20) exposures.	There were no deaths reported from either single 4-h exposure or two 8-h exposures. Only abnormal signs noted were rats scratching and licking themselves. Pathological examination showed congestion in trachea and lungs. Small, localized areas of pulmonary edema without hemorrhage and areas of alveolar emphysema were present among rats killed during first 3 days after exposure. Most lungs exhibited many areas of alveolar emphysema in addition to severe congestion. All other organs examined appeared normal.	40
Male Wistar rats (5)	90% aq.	16.1 ppm (23 mg/m ³)	4 h exposure followed by 2 weeks observation.	There were no mortalities Lethal dose > 16.1 ppm (22.52 mg/m ³)	39
Sprague-Dawley rats (4, 6, 13)	Not specified	0, 0.01, 0.02, 0.1 ppm (calculated as 0, 0.014, 0.025, or 0.14 mg/m ³)	Rats were exposed for 2h in a nose-only apparatus. Rats were killed and lungs were examined immediately (n = 4 or 6) or 24 h (n = 4 or 13) after exposure.	There were no changes observed in light microscopy at 0.014 and 0.025 mg/m ³ ; electron microscopy revealed an increase in number of neutrophils in capillary spaces adjacent to terminal respiratory bronchioles and in alveolar ducts in lungs from rats after inhalation of 0.025 mg/m ³ (not observed at 0.14 mg/m ³). There were no changes in cell number, cell viability, and BAL fluid LDH at any concentration or time period when compared to controls. There was an increase in serum LDH only at 0.025 mg/m ³ at 24 h. There was an increase in TNF- α at both time periods and reactive oxygen intermediates (superoxide anion) at 24 h. Nitric oxide production was decreased at all concentrations. The authors suggest that vapor-phase Hydrogen Peroxide reaches the lower lung and modulates macrophage function.	41
Rats (strain not specified; 3)	Not specified	Not specified	4 h exposure	Threshold concentration of Hydrogen Peroxide vapors for increase of NAD-diaphorase in rat bronchial epithelium was 60 mg/m ³ . Threshold for skin effects (moderate hyperemia and transient thickening because of oxygen bubbles in skin) was 110 mg/m ³ . Authors concluded that primary cause of death was gas embolus. LC ₅₀ = 2000 (1690 - 2360) mg/m ³ LOEC for respiratory mucosa = 60 mg/m ³ LOEC for skin effects = 110 mg/m ³	2
Male and female New Zealand White rabbits (8)	Not specified	0.75, 7.5, or 37 mg/m ³ in saline (total inhaled dose = 0, 0.1, 1.4, 7.1 mg, respectively) Controls exposed to aerosolized saline.	4 h using a nebulizer	Exposure to Hydrogen Peroxide aerosols did not alter baseline airway resistance, dynamic elastance, slope of inspiratory pressure generation, or arterial blood pressure and blood gas measurements.	42

BAL = bronchoalveolar lavage; LC₅₀ = median lethal concentration; LDH = lactate dehydrogenase; LOEC = lowest observed effective concentration; NAD = nicotinamide adenine dinucleotide; RD₅₀ = 50% reduction of the respiratory rate

Table 7. Oral repeated dose studies of Hydrogen Peroxide.

Animal (n)	Concentration of Hydrogen Peroxide	Dose or Drinking Water Concentration	Duration	Methods/Procedure	Results	Reference
Short-Term Toxicity Studies						
Male dd mice (n not specified)	Not specified	0.3%, 0.6%, or >1%	2 weeks	Administered in drinking water	There was a decrease in body weight gains in 0.6% group but not 0.3% group. There was a decrease in body weight gains and death within 2 weeks at >1%.	33
C57BL/6NCrIBR mice (10/sex)	Not specified	0, 200, 1000, 3000, or 6000 mg/l (w/v)	14 days	Administered in drinking water	No toxic signs were observed in 0 to 3000 mg/l groups. Water consumption was reduced in a dose-dependent manner in the 1000 mg/l and greater groups. Body weight gains were reduced in the 3000 and 6000 mg/l group first 3 days, which was thought to be due to dehydration. Decreased body weights and feed consumption were observed in high-dose group throughout study. Gross pathological examination was unremarkable. Histopathology showed degenerative (minimal to mild erosions) and regenerative (minimal to mild) hyperplasia changes in mucosa of the stomach and/or duodenum in the 3000 and 6000 mg/l groups in both sexes. Overall NOAEL for pathology was 1000 mg/l for both sexes (males = 164 mg/kg, females = 198 mg/kg)	33
Male Osborne-Mendel rats (n not specified)	Not specified	0 or 0.45%	3 weeks	Administered in drinking water	There was a decreased intake of liquid, which was reflected in total body weight of treated rats (average weight 108 g) compared to controls (156 g). Control rats consumed tap water at an average of 544 ml/day, whereas the treated rats consumed an average of 282 ml/day. There were no differences in relative weights in testes, kidneys, spleen, or heart.	45
Male Osborne-Mendel rats (n not specified; 3)	Not specified	0 or 0.45%	3 weeks	Administered in drinking water; control group was limited to the amount of water consumed by the test group. Older rats with an average weight of 600 g were administered Hydrogen Peroxide in drinking water for 3 weeks and weighed. they were then administered tap water for 3 weeks and weighted	Rats in control group continued to seek water after their allotment was consumed; the test group did not. Average body weight for the test group was 116 g vs. 104 g in the control group. There were no differences in relative or dry weights in testes, kidneys, spleen, or heart. Weight decreased to an average of 511 g. The rats regained the lost weight by the end of 3 weeks on tap water.	45
Wistar rats (n = 10/sex)	Not specified	0, 0.6, 1, 2, 3, or 6 mg/100g bw (0, 6, 10, 20,30 or 60 mg/kg/d)	40 days	Administered by oral catheter. Controls received water.	No deaths were reported. No toxic effects were observed at doses < 30 mg/kg/day. Body weight decreased (5%) at and after 20 days of administration in high-dose group. At highest dose, hematocrit values and blood plasma protein concentrations were lower; in 30 and 60 mg/kg groups, plasma catalase activity was lower. Gross pathology: There were slightly higher spleen weights at 40 days. (60 mg/kg/day). LOAEL = 30 mg/kg/day	46
Rats (n not specified)	Not specified	1/5 and 1/10 LD ₅₀ (actual dose not specified)	45 days	Gavage	Both doses caused decreased body weight gain, increased blood peroxidase activity, decreased liver catalase activity, increased circulating reticulocytes, and increased urinary albumin. Stomach walls showed inflammatory responses at both doses with severity in a dose-dependent manner.	33

Table 7. Oral repeated dose studies of Hydrogen Peroxide.

Animal (n)	Concentration of Hydrogen Peroxide	Dose or Drinking Water Concentration	Duration	Methods/Procedure	Results	Reference
Holtzman rats (24)	Not specified	0, 0.5%, 1.0%, and 1.5%	8 weeks	In drinking water	Mortality: 7 of 24 in the high-dose group died. Dose-dependent extensive carious lesions and pathological changes in the periodontium. Body weight gain was reduced in a concentration-dependent manner in all treatment groups.	⁴⁷
Male Wistar JCL rats (n not specified)	5% aq.	56.2, 168.7, or 506.0 mg/kg	12 weeks	6 days/week by gavage	High-dose group had reduced body weight gain and reduced hemoglobin concentration, erythrocyte count, blood corpuscle volume, serum SGOT, SGPT, and alkaline phosphatase activity. Mid-dose group had abnormalities in kidney function. Kidney, liver, and heart weights were decreased and adrenal and testes weights were increased in the high-dose group. Erosion and scars of gastric mucosa was observed in high-dose group.	^{3,33}
Subchronic Toxicity Studies						
C57BL/6NCrIBR mice (n = 15/sex)	35% w/w aq. Hydrogen Peroxide added to water	0, 100, 300, 1000, or 3000 ppm	~ 90 days	OECD GL 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) Administered in drinking water. After dosing period, 10 mice/group were killed and necropsied and remainder were allowed a 6-week recovery period. This strain of mice was chosen due to particular sensitivity to Hydrogen Peroxide because of a deficient detoxification pathway and, therefore, be regarded as a very sensitive animal model for this particular substance.	No treatment-related deaths occurred and no treatment-related clinical signs were observed at any time. Male and females exhibited significant reductions in body weight at 3000 ppm. Feed and water consumption were reduced in the 3000 ppm group but not in 1000 and 300 ppm groups. Males in the 3000 ppm group displayed reductions in total protein and globulin levels in blood, possibly caused by mucosal hyperplasia occurring in their duodenums. Necropsy revealed no treatment-related gross lesions. Microscopic examination showed an increase in cross-sectional diameter and wall thickness of the duodenum. Subsequent microscopic evaluations revealed mild mucosal hyperplasia in 8 of 9 males in 3000 ppm group and in 7 of 10 males in the 1000 ppm group. Minimal mucosal hyperplasia was observed in 1 of 10 males in 300 ppm group. Minimal to mild mucosal hyperplasia was also observed in 10 of 10 females in 3000 ppm group and in 8 of 10 females in 1000 ppm group. No other areas of the gastrointestinal tract were affected. No evidence of cellular atypia or architectural disruptions or any other indications of neoplastic changes were observed; therefore, treatment-related mucosal hyperplasia noted was not considered as a neoplastic lesion. Based on dose-related reductions in feed and water consumption and observation of duodenal mucosal hyperplasia, LOEL = 300 ppm and NOEL = 100 ppm (26 and 37 mg/kg/day for males and females). Clinical pathologic effects (decreased total protein and globulin blood levels) were limited to 3000 ppm level. All effects noted during treatment period were reversible; mice necropsied following recovery period were considered biologically normal.	²
Male Wistar rats (n = 10/sex)	Not specified	0, 0.6, 1, 2, 3, or 6 mg/100g (0, 6, 10, 20, 30 or 60 mg/kg)	100 days	Administered in feed.	No deaths were reported. There were no significant effects to body weights, organ weights, or blood chemistry observed at all doses	⁴⁶

Table 7. Oral repeated dose studies of Hydrogen Peroxide.

Animal (n)	Concentration of Hydrogen Peroxide	Dose or Drinking Water Concentration	Duration	Methods/Procedure	Results	Reference
Chronic Toxicity Studies						
C57BL/6J mice (50/sex)	Not specified	~ 300 or 1200 mg/kg/day; 0.1% or 0.4%	100 weeks	In drinking water	Erosion and ulcers in the glandular stomach and hyperplasia, adenomas and carcinomas in the duodenum were observed. Erosion in the stomach occurred after 40 weeks. No metastases or other treatment-related tumors were observed. Body weights were significantly reduced in the high dose females after 15 months.	49,50
Male and female rabbits (n not specified)	Not specified	0.005, 0.05, 0.5, 5, or 50 mg/kg/day; 0.00001%, 0.0001%, 0.001%, 0.01%, or 0.1%	6 Months	Administered by gavage daily	High-dose group had decreased body weights and blood lymphocyte concentrations; increased numbers of reticulocytes and hemolysis, albuminuria; decreased hepatic catalase activity, increase hepatic succinyl-dehydrogenase activity, changes in enzyme activity of stomach, duodenum, cerebrum; structural changes of gastrointestinal mucosa; and focal fatty changes in hepatocytes. Low-dose groups only had changes in hematology and enzyme activities. NOAEL = 0.005 mg/kg/day [Study appears to not be included in DFG safety evaluation due to insufficient documentation.]	2,113

DFG = Deutsche Forschungsgemeinschaft; LOAEL = lowest observed adverse effects level; LOEL = lowest observed effects level; NOEL = no observed effects level; NOAEL = no observed adverse effects level; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Table 8. Inhalation repeated dose studies of Hydrogen Peroxide.

Animal (n)	Concentration of Hydrogen Peroxide	Air Concentration	Duration	Methods/Procedure	Results	Reference
Short-Term Toxicity Studies						
Mice (10)	90%	79 or 107 mg/m ³	up to 4 weeks	79 mg/m ³ : 6 h/day for 2 to 3 days/week (8 exposures) or 107 mg/m ³ : 6 h/day; 3 days/week during week 1; 5 days/week for weeks 2-4 (18 exposures)	After week 2: both groups had nasal discharge, edematous feet, irritation of skin in the groin region After week 5: both groups had hair loss around the nose, probably due to scratching due to irritation 7 of 9 mice died after 8 exposures in the low-dose group; 5 of 10 mice died after 8 exposures in the high-dose group, 8 of 10 mice died after 18 exposures. LOAEL = 79 mg/m ³	40
Alpk:ApfSD Wistar rats (n = 5/sex)	50% aq.	2.88, 14.6, 33.0 mg/m ³ 82.4 mg/m ³ then 38.7 mg/m ³	28 days	OECD GL 412 (Subacute Inhalation Toxicity: 28-Day Study) Whole body chambers for 5 days per week, 6 h per day. A fourth group of rats was exposed to 82.4 mg/m ³ on days 1, 4, 5 and 6. Exposure level was reduced to 38.7 mg/m ³ on days 11 and 12. Treatment was terminated on day 13 and rats were euthanized due to toxicity.	Clinical signs were observed in rats exposed to 14.6 mg/m ³ and greater. In general, number and severity of these clinical signs increased with repeated exposure at low doses, whereas the onset of clinical signs was earlier at higher doses but also a certain degree of recovery from symptoms was seen at higher doses. Clinical signs included reddened nose, stains around snout and mouth, salivation, signs of respiratory tract irritation, irregular breathing, urinary incontinence, piloerection, chromodacryorrhea, hunched posture, increased response to touch, and thin appearance. Some evidence of recovery was observed after treatment ended. Body weights gradually decreased in males in 33.0 mg/m ³ group and in males and females in 82.4/38.7 mg/m ³ group. Feed consumption was reduced in males in 33.0 mg/m ³ group and in males and females in 82.4/38.7 mg/m ³ group. Minor effects on hematology in 33.0 mg/m ³ group, which were not considered biologically and toxicologically significant. In both sexes, there was a minimal decrease in albumin and total protein levels in 33.0 mg/m ³ group. Kidney weights increased in females in 33.0 mg/m ³ group. Relative lung weights in males and relative kidney weights in females in 33.0 mg/m ³ group were increased. Treatment-related findings were observed in nasal and oral cavities of rats at necropsy at end of study. Staining of nares was observed at 14.6mg/m ³ and above and mouth staining was at 33.0 mg/m ³ ; in both cases, no dose-response could be found. Increased findings, including necrosis, inflammation and perivascular neutrophil infiltration, in exposed rats over controls during the microscopic examinations were observed in the nasal cavity, larynx, and lung. Clinical observations were consistent with test material being a respiratory tract irritant (reddened noses, stains around nose, and abnormal respiratory noise); in general, time to onset, incidence and severity of clinical signs increased with exposure concentration and repeated exposure. Males exposed to 33.0 mg/m ³ had lower feed consumption and body weight gain compared to controls. Minimal changes in albumin and total protein blood levels were observed in males and females in 33.0 mg/m ³ group. Histopathological, treatment-related changes were observed in anterior-most regions of nasal cavity lined with squamous epithelium, where minimal to slight necrosis (with associated inflammation) and rhinitis were observed in rats in 10.3 and 33.0 mg/m ³ groups. Inflammation and epithelial erosion in larynx and increased perivascular neutrophil infiltration in lungs were considered unlikely to be related to treatment due to absence of a clear dose response relationship. NOEL was 2.9 mg/m ³ and LOAEL was 14.6 mg/m ³ .	2
Rats (strain not specified; 23; 10 for mortality studies and 13 for pathology)	90%	0 or 93 mg/m ³	7 weeks	6 h/day, 2 or 3 days/week for weeks, 1 and 2, respectively, 5 days/week during weeks 3-7, for 30 exposures 1-2 pathology group rats were killed each week for necropsy	There were signs of nasal irritation and profuse nasal discharge after 2 weeks exposure. Lung congestion (primarily slight congestion) was observed in all rats killed throughout study, and tracheal congestion was observed at weeks 5 and 7. Hair loss around the nose, probably due to scratching due to irritation, was observed after week 5. One rat died. No significant microscopic changes were observed at necropsy.	40
Black rabbits (Strain not specified; 8)	90%	30 mg/m ³ (22 ppm) vapor	12 weeks	6 h/day, 5 days/week. Whole body exposure.	No effects were observed except for bleaching of fur and some nasal irritation.	40

Table 8. Inhalation repeated dose studies of Hydrogen Peroxide.

Animal (n)	Concentration of Hydrogen Peroxide	Air Concentration	Duration	Methods/Procedure	Results	Reference
Subchronic Toxicity Studies						
Rats (strain and n not specified)	Not specified	0.1, 1.0, or 10.1 mg/m ³	Up to 4 months	5 h per day, 5 day per week for up to 4 months for whole body exposures. Some of the mice were shaved for dermal exposure [See Subchronic Toxicity Studies for dermal results]	Threshold concentration for lung effects was 10 mg/m ³ . At 2 and 3 months in 10 mg/m ³ group, there was an increase in serum epoxidase activity (2.50 and 2.63, respectively; controls, 2.16 and 2.20, respectively). After 4 months lungs showed a decrease of SDH (0.26 versus 0.34 in controls). Studies of lungs showed a decrease in activities of SDH, MAO, acid phosphatase, diesterase, and an increase in activity of alkaline phosphatase. NOEL = 1 mg/m ³ LOEL = 10 mg/m ³	2,33
Wistar rats (n = 10/sex)	50% aq.	1.5, 3.6, 10.3 mg/m ³	13 weeks	OECD GL 413 (Subchronic Inhalation Toxicity: 90-Day Study) Nose-only apparatus for 6 h per day, 5 days per week	There were no mortalities during study. No treatment-related clinical abnormalities or ocular changes were observed. No significant treatment-related effects were observed for body weight gains or feed consumption. At necropsy, no treatment-related effects were observed on any hematology or white blood cell parameters tested. Of clinical chemistry parameters tested, there was an increase in alkaline phosphatase concentrations in male rats in high-concentration group, which was not considered an adverse effect when compared to historical control data. Liver and thymus weights (both absolute and relative to body weight) of male rats in high-concentration group were decreased. However, this weight change was not accompanied by microscopic abnormalities in these organs and values were consistent with historical control data. No effects were observed on weights of any of other organs or tissues of rats (male or female). No treatment-related effects were observed at microscopic examination of any organ or tissue, including respiratory tract. NOAEL = 10.3 mg/m ³ for male and female rats.	2
Rabbits (n and strain not specified)	90% aq.	22 ppm (calculated as 30.77 mg/m ³)	3 months	Daily; no other details provided	Irritation was noted around nose	29
Chronic Toxicity Studies						
Dogs (2)	90%	10 mg/m ³	26 weeks	6 h/day, 4 to 5 days/week	At 14 weeks, there were no effects observed except for fur bleaching and loss. After 23 weeks, sporadic sneezing and lacrimation were observed. There were no weight changes or changes in clinical chemistry and hematology. Lungs had areas of atelectasis and emphysema and there were some hyperplasia in bronchial musculature.	40

LOAEL = lowest observed adverse effect level; MAO = monoamine oxidase; NOAEL = no observed adverse effects level; NOEL = no observed effects level; OECD = Organisation for Economic Co-operation and Development; SDH = succinate dehydrogenase activity

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
In vitro			
Ames assay	3% in 0.067 M potassium or sodium phosphate buffer, pH 7 <i>S. typhimurium</i> (TA98, TA1535, and TA1538) Without metabolic activation: 0.0033 to 0.67 mg/plate With metabolic activation: 0.01 to 3.3 mg/plate <i>S. typhimurium</i> (TA100 and TA1537) Without metabolic activation: 0.001 to 0.33 mg/plate With metabolic activation: 0.01 to 3.3 mg/plate <i>E. coli</i> (WP2) With metabolic activation: 0.033 to 3.3 mg per plate With metabolic activation: 0.01 to 3.3 mg/plate Positive controls Without S9 mix: 2-nitrofluoren (TA98, TA1538), sodium azide (TA100, TA1535), 9-aminoacridine (TA1537), furylfuramide or <i>N</i> -methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine (<i>E. coli</i>); With S9 mix: 2-Anthramine (all tested strains)	<i>S. typhimurium</i> (TA100): There were increased numbers of revertant colonies with and without metabolic activation starting at 0.033 mg/plate. Hydrogen Peroxide was not mutagenic in all other strains tested.	58
Ames assay	3% aq. <i>S. typhimurium</i> (TA98) 100 µl/plate with and without metabolic activation	Not mutagenic with or without metabolic activation	60
Ames assay	30.0% in phosphate buffer <i>S. typhimurium</i> (TA92, TA94, TA98, TA100, TA1535, and TA1537) 0.2 mg/plate	Positive for genotoxicity. 107 his ⁺ revertant colonies/plate at 0.2 mg/plate in TA100 without metabolic activation.	71
Ames assay	30% aq. <i>S. typhimurium</i> (TA97, TA102, TA104, SB1106, SB1106p, and SB1111) 0 to 4 µmol/plate	Very mutagenic: SB1106p (4x control) and TA97 (2x) Weakly mutagenic: TA102, TA104, SB1106, and SB1111	53
Ames assay	30% aq. Preincubation <i>S. typhimurium</i> (TA97, TA102, TA104, SB1106, SB1106p, and SB1111) 0 to 1.2 µmol/plate	Very mutagenic: SB1106p (4x) and TA97 (4x) Weakly mutagenic: TA102, TA104, SB1106, and SB1111	53
Ames assay	Concentration not specified <i>S. typhimurium</i> (TA102 and TA2638) 100 µg/plate in water without metabolic activation	Positive for genotoxicity TA102-746 revertants per plate vs 240 in controls. TA2638-91 revertants per plate vs 38 in controls.	57
Ames assay	Concentration not specified <i>S. typhimurium</i> (TA97, TA98, TA100, TA102, TA1537, and TA1538) 0 to 6000 µmol/plate	Weakly mutagenic: TA97, TA98, TA102, TA1537 Not mutagenic: TA100 and TA1538	56
Ames assay	Concentration not specified Preincubation <i>S. typhimurium</i> (TA97, TA98, TA100, TA102, TA1537, and TA1538) 0 to 340 µmol/plate	Weakly mutagenic: all strains (2 to 6x)	56
Ames assay	Concentration not specified Preincubation with metabolic activation <i>S. typhimurium</i> (TA97, TA102, TA1537, and TA1538) 0 to 340 µmol/plate	Not mutagenic: all strains	56

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
Ames assay	Concentration not specified Liquid incubation <i>S. typhimurium</i> (TA97, TA98, TA100, TA102, TA1537, and TA1538) 0 to 6 µmol/plate with catalase or SOD superoxide dismutase or without metabolic activation	Weakly mutagenic: TA1537 without metabolic activation and TA97 with SOD Remaining are not mutagenic:	56
Ames assay	Concentration not specified Preincubation <i>S. typhimurium</i> (TA92, TA97, TA100, TA102, TA104, TA1535, and TA1537) 0 to 2.4 µmol/plate without metabolic activation	Mutagenic: TA100 (2.5x), pronounced mutagenic effects on TA102 (2.8x) and TA104 (4.4x) Not mutagenic: TA92, TA97, TA1535, and TA1537 (weakly)	55
Ames assay	Concentration not specified <i>S. typhimurium</i> (TA102) 0 to 50 µmol/plate (with sulfide) and 400 µmol/plate (without sulfide)	Positive for genotoxicity. Highly positive with sulfide.	54
Ames assay	Concentration not specified <i>S. typhimurium</i> (TA97 and TA102) without metabolic activation <i>S. typhimurium</i> (TA102) with metabolic activation	Negative for genotoxicity: TA97 Weakly positive for genotoxicity: TA102 without metabolic activation, less genotoxic with metabolic activation	33,59
Modified Ames assay (WP2 Mutoxitest)	Concentration not specified <i>E. coli</i> (Strain IC203, deficient in OxyR, and its <i>oxyRq</i> parent WP2 <i>uArpKM101</i> (IC188)) 0, 25, 50, 100 mg/plate in water with and without metabolic activation	Reverted IC203 more efficiently than IC188, thus classed as an oxidative mutagen at 50 and 100 mg/plate without metabolic activation. Not mutagenic with metabolic activation.	62
Ames assay	Concentration not specified <i>E. coli</i> (trp-) (WP2uvrA(pKM101) and WP2(pKM101)) 0 to 300 µg/plate without metabolic activation	Mutagenic in both strains (x2.7)	61
Modified Ames assay (multigene sporulation assay)	Concentration not specified <i>B. subtilis</i> (Exc-) 0 to 0.003% without metabolic activation	Mutagenic	64
Gene mutation assays (Auxotroph reversion, forward mutation, and gene conversion)	Concentration not specified Auxotroph reversion: <i>S. typhimurium</i> (G.46), <i>E. coli</i> (trp-) (WP2uvrA+ and WP2uvrA-) Forward mutation: <i>E. coli</i> (caca-) (WP2uvrA) Gene conversion: <i>S. cerevisiae</i> 5% on filter paper without metabolic activation	Not mutagenic: (trp-) (WP2uvrA+ and WP2uvrA-), <i>S. cerevisiae</i> Questionable: (caca-) (WP2uvrA)	63
Nuclear gene mutation assay	Concentration not specified <i>S. cerevisiae</i> 100 µg/plate	Mutagenic for forward mutations	65
Bacterial forward mutation assay	Concentration not specified <i>E. coli</i> (DB2; amp-) 0 to 80 µg/ml without metabolic activation	Mutagenic at 24 to 80 µg/ml (x5)	67
Bacterial forward mutation assay	30% aq. <i>E. coli</i> (K12 strains lacking catalase activity due to mutations in <i>katG</i> , <i>katE</i> and <i>katF</i> genes, and catalase-proficient strains; L-arabinose resistance) Up to 900 nmol/ml Preincubation and plate incorporation assays without metabolic activation	<i>kat</i> (-)-strains gave maximum level mutagenesis at 75 nmol/ml and <i>kat</i> (+)-strain at 600 nmol/ml. Both strains showed a threefold maximum increase in induced colonies, compared to spontaneous levels.	66
Bacterial forward mutation assay	Concentration not specified <i>B. subtilis</i> (168DB) 0.0005%, 0.001%, 0.002% or 0.003% without metabolic activation	Number of mutants increased from background level of 1.8/104 colonies to a maximum of 60.2 at 0.002%. All tested concentrations were greater than in controls.	64
Bacterial forward mutation assay	Concentration not specified <i>S. typhimurium</i> (TA100) Pretreatment: 0, 25, 50 or 100 µM; Incubation: 0.5, 1.0, 1.5, 3.0, 4.5 or 7.5 µmol/plate without metabolic activation	Ambiguous	69

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
Bacterial forward mutation assay	Concentration not specified <i>S. typhimurium</i> (TA102) Two runs with 0, 50, 75, 100, 150, 175, 200 or 300 µg/plate without metabolic activation Pretreatment of cells	Run 1: Increased revertant counts were 2.3-fold, compared to control, in a dose-dependent manner. < 2-fold increase was observed in run 2, although a dose-response was noted. Increases over controls were observed at 75 µg/plate and higher, corresponding to 1.4-fold and higher increases in first test, and 1.5-fold and higher increases over controls in run 2.	61
Forward mutation assay	Concentration not specified 100 to 300 µmol without metabolic activation V79 cells	Not mutagenic. No increase in frequency of 8-azaguanine or quabain-resistant mutation. Cytotoxicity starts at < 100 µmol.	68
L-Arabinose Bacterial forward mutation assay (l-arabinose resistance test)	Concentration not specified <i>S. typhimurium</i> (BA9 and BA13) 2941, 5882, 11765 or 17647 nmol/ml without metabolic activation	Maximum induction of AraR/108 viable cells was 11.7-fold compared to control with strain BA9. Maximum absolute number of AraR/plate was 11.1-fold in BA13.	70
Chromosome aberration test	Concentration not specified OECD GL 473 (In Vitro Mammalian Chromosome Aberration Test) CHO cells Without metabolic activation: 25.31, 33.75, and 45.0 nl/ml With metabolic activation: 10, 50, 100 nl/ml	Hydrogen Peroxide caused an increase in number of chromosomal aberrations per cell and in percentage of cells with aberration. A definite dose response trend was observed in activated system. Cytotoxic at 10 nl/ml with metabolic activation.	2
Chromosome aberration test	Concentration not specified 100, 200, or 300 µM without metabolic activation CHO-K1 and V79 cells 100, 200, or 300 µM without metabolic activation Syrian hamster cells 10, 20, and 50 µM BALB/c mouse cells 0 or 500 µM with and without metabolic activation CHO-K1	CHO, V79, and Syrian hamster Cells - Concentration-dependent increase in the amount of chromosomal aberrations including gaps, breaks, exchanges, and minutes (chromatid- and chromosome-type aberrations). As the dose increased, the mitotic index decreased and damages to metaphase chromosomes increased. BALB/c mouse cells - Chromosome aberrations were induced at 10 to 100 µM. CHO-K1 - There were an increased number of abnormal metaphases without metabolic activation; number of abnormal metaphases was similar to controls with metabolic activation.	68
Chromosome aberration test	30.0% in saline 0 to 0.25 mg/ml for 24 and 48 h without metabolic activation Chinese hamster fibroblast cells	2.0% polyploid Structural aberrations 46.0% at 24 h. D ₂₀ = 0.13; TR = 1.44 Positive at : 0.063 mg/ml at 48 h (10.0% cells with structural chromosomal aberrations), 0.125 mg/ml at 24 h (15.0% cells with structural chromosomal aberrations) and at 48 h (31.0% cells with structural chromosomal aberrations), 0.25 mg/ml at 24 h (46% cells with structural chromosomal aberrations).	71
Chromosome aberration test	Concentration not specified 10 and 20 µM (time not specified) without metabolic activation 20 µM (time not specified) with ferrous ions Murine splenocytes	Mutagenic: Synergistic enhancement of micronucleus frequency with ferrous ions Not mutagenic: without metabolic activation, no increase in frequency of micronucleated splenocytes	72
Chromosome aberration test	Concentration not specified 10 to 20 µM for 1 h without metabolic activation V79 cells	Concentration-dependent increase of micronuclei starting at 10 µM in PBS but not in MEM	73
Chromosome aberration test	Concentration not specified 0, 150, 300, or 450 µM SHE cells	Mutagenic at 300 and 450 µM	74

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
Chromosome aberration test	Concentration not specified 10 to 20 μM for 10 min without metabolic activation Human embryonic fibroblasts	Concentration-dependent increase of chromosomal and chromatid aberrations starting at 20 μM	⁷⁵
Chromosome aberration test	Concentration not specified 15 and 20 μM for 24 h without metabolic activation Human leukocytes	Mutagenic: 6-fold increase of chromosomal aberrations at 20 μM	³³
Mouse lymphoma assay	30% w/w aq. TK locus mouse lymphoma L5178Y cells 0.075, 0.1, 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, and 1.0 $\mu\text{g}/\text{ml}$ with and without metabolic activation Positive control: ethylmethanesulphonate, <i>N</i> -dimethylnitrosamine	Hydrogen Peroxide increased mutation frequency in absence of metabolic activation, but not in present of metabolic activation. It is concluded that the substance induces mutation at TK locus in L5178Y mouse lymphoma cells.	²
Mouse lymphoma assay	30% w/w aq. TK locus mouse lymphoma L5178Y cells 0.0018 - 0.1 $\mu\text{g}/\text{ml}$ without metabolic activation 2.3 - 30 $\mu\text{g}/\text{ml}$ without metabolic activation Positive control: ethylmethanesulphonate, <i>N</i> -dimethylnitrosamine	Hydrogen Peroxide increased mutation frequency in absence of metabolic activation, but not in present of metabolic activation. It is concluded that the substance induces mutation at TK locus in L5178Y mouse lymphoma cells.	²
Mouse lymphoma assay	Concentration not specified 18.6 to 496 μmol without metabolic activation L5178Y mouse lymphoma cells	Concentration-dependent increase of mutation at thymidine kinase locus starting at 18.6 μmol . Cytotoxicity starts at 37.2 to 79.5 μmol .	⁷⁶
Mammalian cell gene mutation assay	Concentration not specified 10 μmol without metabolic activation V79 cells	Induced mutations at the HGPRT locus	⁷⁷
Mammalian cell gene mutation assay	Concentration not specified 500 to 4000 μmol without metabolic activation V79 cells	Concentration-dependent increase in the 6-thioguanine-frequency resistant clones starting at 500 μmol . Cytotoxicity > 4000 μmol .	⁸⁷
Mammalian cell gene mutation assay	Concentration not specified 100 to 585 μmol without metabolic activation Mutagenicity V79 cells	No mutations at HGPRT locus. Cytotoxicity starts at approximately 100 μmol .	⁷⁹
SCE	Concentration not specified 10 to 80 μmol without metabolic activation V79 cells	No mutations at HGPRT locus Cytotoxicity starts at 20 to 40 μmol .	⁷⁸
SCE	Concentration not specified 353 μM without metabolic activation V79 cells	No mutations at HGPRT locus. Cytotoxicity: 20% survival	⁸⁰
SCE	Concentration not specified 5 to 20 μM in MEM or PBS for 1 h without metabolic activation V79 cells	Not mutagenic in MEM. Increased SCE at 10 μM in PBS Cytotoxicity: > 20 μM in MEM; 5 to 10 μM in PBS	⁷³
SCE	Concentration not specified 10 to 80 μM for 3 h without metabolic activation V79 cells	Mutagenic: SCE at 20 μM Cytotoxicity: 20 to 40 μM	⁷⁸
SCE	Concentration not specified 1 to 800 μM for 1 or 9 h without metabolic activation 100 to 800 μM for 9 h with catalase V79 cells	Mutagenic without catalase. Not mutagenic with catalase.	⁸²
SCE	Concentration not specified 10 to 40 μM for 1 or 24 h without metabolic activation 10 to 40 μM for 1 h with metabolic activation V79 and CHO cells	Mutagenic without metabolic activation at 10 to 20 μM Not mutagenic with metabolic activation	⁸¹

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
SCE	Concentration not specified 0, 40, 80, 120, 160, 200, or 240 μM in phosphate-buffered saline for 15 and 20 to 22 h CHO AUXB1 cells	Mutagenic. Increased SCE and endoreduplicated cells starting at 40 μM . Cytotoxicity: 40 μM	85
SCE	Concentration not specified 0.1 to 100 μM for 2 h without metabolic activation CHO cells	Slight increase in SCE at 0.5 μM Cytotoxicity: 10 μM	86
SCE	Concentration not specified 100 to 100,000 μM for 2 h without metabolic activation CHO cells	Slight increase in SCE frequency at 500 μM	86
SCE	Concentration not specified 0.3 to 7.8 μM for 24 h without metabolic activation 5 to 100 μM (time not specified) with catalase CHO cells	Mutagenic without metabolic activation at 3.9 μM Not mutagenic: with catalase	83
SCE	Concentration not specified 0, 90, or 300 μM SHE cells	Increased frequencies of SCEs at 300 μM Mutagenic	88
SCE	Concentration not specified 20 to 2000 μM in for 24 h without metabolic activation 80 to 200 μM in for 2 h without metabolic activation Whole human blood or human purified lymphocytes 80 to 200 μM in for 2 h with catalase, peroxidase, or S9 mix Human purified lymphocytes	24 h: Mutagenic in lymphocytes at 20 μM . Not mutagenic in whole blood culture. 2 h: Mutagenic in lymphocytes at 80 μM . Not mutagenic in whole blood culture. Metabolic activation reduced Hydrogen Peroxide-induced SCEs	84
SCE	Concentration not specified 15 to 60 μM in for 24 h without metabolic activation D98/AH2 human cells	Mutagenic: 3-fold SCE induction at 60 μM	89
Endo-reduplicated cells	Concentration not specified 0, 40, 80, 120, 160, 200, or 240 μM in phosphate-buffered saline for 15 and 20 to 22 h CHO AUXB1 cells	Mutagenic starting a 160 μM in a dose-dependent manner	85
DNA Damage and Repair/ Unscheduled DNA Synthesis	35.7 % aq. OECD GL 482 Rat hepatocytes Run 1: 0, 10, 30, 100, 300, 1000, and 3000 $\mu\text{g}/\text{ml}$ Run 2: 0.78125, 1.5625, 3.125, 6.25, 12.5, 25, 50, and 100 $\mu\text{g}/\text{ml}$ Positive control: 2-acetylaminofluorene	Run 1 (10 to 3000 $\mu\text{g}/\text{ml}$): marked reductions in nuclear and cytoplasmic counts at nearly all dose levels indicated a generalized toxic effect. Run 2 (0.78125 to 100 $\mu\text{g}/\text{ml}$): 100 $\mu\text{g}/\text{ml}$ was completely toxic and signs of toxicity were also observed at 50 $\mu\text{g}/\text{ml}$. Clear increase in NNG counts and also in the percentage of cells in repair were observed at 25 and 50 $\mu\text{g}/\text{ml}$. A dose-dependent increase in NNG values was observed at 6.25 to 25 $\mu\text{g}/\text{ml}$. Overall: Results demonstrate a positive result at concentrations of 6.25 to 50 $\mu\text{g}/\text{ml}$. Cytotoxicity was observed at 50 $\mu\text{g}/\text{ml}$ and greater.	2
Comet assay	Concentration not specified 0, 0.8, 4, 20, 100, and 500 μM L5178Y <i>tk</i> [±] mouse lymphoma cells	Genotoxic at 500 μM . Calculated concentration to double tail DNA = 190 μM	90
Comet assay	Concentration not specified 0, 1, 10 μM for 24 or 48 h Fresh rat hepatocytes	Genotoxic at both concentrations	91
Comet assay	Concentration not specified 0, 10, 20, 50, 100 μM <i>S. cerevisiae</i>	Mutagenic at 20 μM and greater	92

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
Comet assay	0.3 M 25 and 50 μ M in DMEM HepG2 cells. Pre-incubated for 5, 30, or 40 min, 1 or 24 h.	DNA damage increased after 1h of incubation with 25 μ M and 50 μ M and decreased at 24 h, likely due to metabolism of test material and DNA repair mechanisms. Cells were susceptible to DNA damage by low doses of the test substance.	98
Comet assay	Concentration not specified 0, 10, 50, 100, and 200 μ M Exposed for 15 min MCF-7 and MCF-10A breast cancer cells	Increased DNA strand breakage at 200 μ M	94
Comet assay	Concentration not specified 0 or 10 μ M Human lymphocytes	Mutagenic	95
Comet assay	37% aq. 0 to 60 μ M Human fibroblasts (cell lines GM 5757, GM 5856, GM 5659)	Mutagenic at 30 μ M and greater	96
Comet assay	Concentration not specified 0 to 30 μ M HeLa cells	Mutagenic at 30 μ M	97
Comet assay	37% aq. 0 to 70 μ M V79 cells; 0 to 50 μ M Human Fibroblasts; 0 to 50 μ M Human lymphocytes; 0 to 60 μ M HeLa cells; 0 to 70 μ M Hep G2 cells	V79 cells: mutagenic at 40 μ M and greater Human fibroblasts: mutagenic at 20 μ M and greater Human lymphocytes: mutagenic at 20 μ M and greater HeLa cells: mutagenic at 40 μ M and greater Hep G2 cells: mutagenic at 40 μ M and greater	93
Comet assay/ micronucleus assay	Concentration not specified Comet assay: 50 μ M; micronucleus assay: 100 μ M V79 cells	Genotoxic in both assays	99
Comet assay/ micronucleus assay	Concentration not specified 0, 20, 40, 80, 160, or 320 μ M (0, 2.5, 5, 10, 20, or 30 μ g/ml) for 4 h Human lymphoblastoid TK6 cells	There was a positive response in the micronucleus assay starting at 40 μ M, and starting at 80 μ M in the comet assay. Cytotoxicity on Day 0 remained at 100% at up to the highest dose; all cytostatic parameters decreased to cytotoxic level ($55 \pm 5\%$ of these parameters) at 40 μ M and greater.	100
Micronucleus test	Concentration not specified 0, 0.8, 4, 20, 100, and 500 μ M L5178Y <i>tk</i> ^{+/−} mouse lymphoma cells	Genotoxic at 20 μ M. and greater Calculated concentration to micronuclei-containing bi-nucleated cells = 20 μ M	90
DNA adducts	Concentration not specified 0, 0.8, 4, 20, 100, and 500 μ M L5178Y <i>tk</i> ^{+/−} mouse lymphoma cells 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) measured by LC-MS/MS	Not mutagenic	90
DNA adducts	Concentration not specified 0, 0.8, 4, 20, 100, and 500 μ M L5178Y <i>tk</i> ^{+/−} mouse lymphoma cells 8-oxo-1,N ⁶ -etheno-2'-deoxyadenosine (ϵ dAdo) measured by LC-MS/MS	Not mutagenic	90
<i>Tk</i> ^{−/−} Gene mutation assay	Concentration not specified 0, 0.8, 4, 20, 100, and 500 μ M L5178Y <i>tk</i> ^{+/−} mouse lymphoma cells	Genotoxic at 100 μ M and greater. Calculated concentration to double number of mutants = 28 μ M	90

Table 9. Genotoxicity studies of Hydrogen Peroxide.

Assay	Test Details	Results	Reference
HPRT assay	37% aq. 0, 70, or 110 µM V79 cells	Not mutagenic.	96
In vivo			
Mammalian erythrocyte micronucleus test	OECD GL 474 (mammalian erythrocyte micronucleus test) 35% w/w aq. Swiss OF1/ICO:OF1 (IOPS Caw) mice (n = 5/sex) Run 1: 0, 500, 1000, 2000 mg/kg Run 2: 0, 250, 500, 1000 mg/kg Test substance was administered once by i.p. route using a dose volume of 25 ml/kg. Vehicle control mice received vehicle alone, under same conditions. Positive control mice received cyclophosphamide, by oral route, at a volume of 10 ml/kg. Mice were killed at 24 or 48 h and cytogenetic damage in bone marrow was evaluated. PE to NE erythrocyte ratio was established by scoring 1000 erythrocytes (PE + NE).	Two vehicle control groups had mean values of MPEs in the range of historical controls. Cyclophosphamide induced a large increase in number of MPEs and decreased PE/NE ratio, indicating cytotoxicity of control substance. In all treated groups, mean MPE values were similar to those of their respective vehicle controls. A slight increase in MPEs in low-dose group after 24 h was deemed biologically insignificant. A decrease in the PE/NE ratio in most treated groups after 24 and 48 h showed that Hydrogen Peroxide effectively affected bone marrow cells. It was concluded that Hydrogen Peroxide did not induce cytogenetic damage in bone marrow cells of mice when administered i.p.	2
Mammalian erythrocyte micronucleus test	OECD GL 474 35% w/w aq. C57BL/6Ncr1BR mice (10/sex) 0, 200, 1000, 3000 or 6000 ppm (males: 0, 42.4, 164, 415 or 536 mg/kg/day; females: 0, 48.5, 198, 485 or 774 mg/kg/day) administered in drinking water for 14 days. Controls: 5/sex were taken from control group and treated with 20 mg/kg cyclophosphamide by a single i.p. injection on day 13.	No specific gross findings were attributable to exposure to Hydrogen Peroxide. Microscopic findings of degenerative and regenerative alterations in mucosa of stomach and/or duodenum were observed in 3000 and 6000 ppm groups and considered to be test substance related. No increases in frequency of micronucleated PEs were observed in 6000 ppm dose group; no decrease in polychromatic/normochromatic erythrocytes ratio observed. Mice receiving cyclophosphamide responded as expected. Hydrogen Peroxide did not show any genotoxic effects at tested concentrations.	2
UDS Test with Mammalian Liver Cells in vivo	OECD GL 486 (Unscheduled DNA synthesis test with mammalian liver cells in vivo) 35% w/w aq. Male Wistar rats (n = 5 - 6) 0, 25, or 50 mg/kg 2 - 4 or 12 - 14 h 1 or 2 mg/ml (dose rate 0.2 ml/min for final doses of 25 mg/kg or 50 mg/kg) administered i.v. Rats were killed at 2 - 4 h or 12 - 14 h. DMN was positive control in 2 - 4-h experiment, and 2 -AAF was positive control in 12 - 14-h experiment. Water was negative control. Hepatocytes were treated with 3H-thymidine and put onto slides. Slides were examined and number of grains present in the nucleus minus mean number of grains in three equivalent areas of cytoplasm was determined for NNG.	Negative vehicle controls gave a group mean NNG value of less than zero with 0 to 0.3% cells in repair. Group mean NNG values were increased by 2-AAF and DMN treatment to at least 9.4 and more than 80 % of cells were found to be in repair. Treatment with 25 or 50 mg/kg Hydrogen Peroxide did not produce a group mean NNG greater than zero (-2.1 - -2.7 respectively) nor were any more than 0.7% cells found in repair at either dose or time point. Hydrogen Peroxide did not induce unscheduled DNA synthesis following treatment in vivo.	2
Dermal genotoxicity assay	70% aq. Hydrogen Peroxide 10, 100, 200 mmol in 200 ml of ethanol was dermally applied to the skin of female Sencar mice (n not specified) for 4 weeks. Further details were not provided.	Negative for genotoxicity	2

2 - AAF = acetamidfluorene; CHL = Chinese hamster lung; CHO = Chinese hamster ovary; DMEM = Dulbecco's modified Eagle's medium; DMN = dimethylnitrosamine; ER = erythrocyte ratio; HPRT = hypoxanthine-guanine phosphoribosyltransferase; i.p. = intraperitoneal; LC-MS/MS = liquid chromatography-tandem mass spectrometry; MEM = minimal essential medium; MPE = micronucleated polychromatic erythrocytes; NE = normochromatic erythrocyte; NNG = net nuclear grain count; OECD GL = Organisation of Economic Co-operation and Development Guideline; PBS = phosphate buffered saline; PE = polychromatic erythrocyte; SCE = sister chromatid exchange; SHE = Syrian hamster embryo; SOD = superoxide dismutase; UDS = Unscheduled DNA Synthesis

Table 10. Dermal, oral, and mucosal carcinogenicity studies.

Animal (n)	Test Material	Concentration	Procedure/Details	Results	Reference
Dermal					
Swiss mice (50/sex)	Three hair dye formulations each mixed 1:1 with Hydrogen Peroxide (6% aq.); 0.05 ml in acetone	6% aq. Hydrogen Peroxide:hair dye (1:1)	Three hair dye mixtures were applied to shaved skin of mid-scapular region. Controls were administered acetone or were left untreated. For each formulation and for vehicle control, one group was treated once weekly and another group once every other week for 18 months.	Survival at 18 months varied from 58% to 80%. No sign of systemic toxicity was observed in any dye-treated groups. Average body weights were comparable in all groups throughout the study. Incidence of lung tumors was similar between treated and control groups. No skin tumors were observed at the site of application.	103
Sencar mice (60)	Hydrogen Peroxide (30% aq.); diluted 1:1 in 0.2 ml acetone	30% aq. Hydrogen Peroxide:acetone (1:1)	Mice were administered twice-weekly topical applications of Hydrogen Peroxide mixture for 25 weeks.	Papillomas were observed in 3 of 57 of the treated mice. No squamous-cell carcinoma was observed at up to 50 weeks	105
Wistar rats (10/sex)	Hydrogen Peroxide (6% aq.) mixed 1:1 with oxidized <i>p</i> -phenylenediamine (5% <i>p</i> -phenylenediamine in 2% ammonium hydroxide)	6% aq. Hydrogen Peroxide: oxidized <i>p</i> -phenylenediamine (1:1)	Mixture was administered to shaved dorsal skin once per week for 18 months. Control rats were shaved and treated with the aqueous vehicle. All surviving rats were killed and examined after 21 months.	Treated and control groups were similar in body weight gain and survival. 4 of 10 males developed tumors (1 cholangiocarcinoma and 1 adenoma of the liver, 1 nephroblastoma with lung and pancreas metastasis, 1 cortical adenoma of adrenal gland) and 6 of 10 females developed tumors (1 fibromatosis and 5 mammary gland tumors which include fibrosarcoma, fibroadenoma and adenoma). No skin tumors were observed at the application site. No tumors were found in male control rats; 1 tumor (uterine stromal cell sarcoma) was found in female control rats.	60
Sprague-Dawley rats (50/sex; controls = 25/sex and 50/sex)	Permanent hair dye formulation or a colorless jelly mixed 1:1 with Hydrogen Peroxide (6% aq.); 0.5 g	6% aq. Hydrogen Peroxide:hair dye (1:1), 6% aq. Hydrogen Peroxide:colorless jelly (1:1), or no treatment	Mixture was administered to a 3-cm ² area of shaved dorsal skin for 30 min twice per week for 2 years. Rats were then observed for an additional 6 months. Control groups received 0.5 g vehicle alone, to which Hydrogen Peroxide was added immediately before application. Another group served as untreated controls. Skin at application site, liver, kidney, lung and gross lesions were studied histologically.	No difference in survival was observed between treated, vehicle, and untreated control groups. No skin tumors were observed at site of application, and there was no difference in incidence of tumors, including those of the skin, between treated, vehicle control and untreated control groups.	104
Sprague-Dawley rats (60/sex; controls 30/sex)	Six oxidative hair dye formulations each mixed 1:1 with Hydrogen Peroxide 6% aq.; 0.5 ml	6% aq. Hydrogen Peroxide:hair dye (1:1)	Administered to shaved areas of back (approximately 2.5 cm in diameter) twice per week up to week 117. Three separate, untreated, concurrent control groups received applications of vehicle alone.	Mean body weights and survival were similar in treated and control groups. No skin tumors were observed and no increase in the incidence of tumors at any site was observed in treated as compared with controls.	51
Oral					
C57BL/6N mice (15/sex)	Hydrogen Peroxide (concentration not specified)	0, 100, 300, 1000, or 3000 ppm in distilled water	Administered in drinking water for 13 weeks followed by 6-week recovery period	Mild to minimal duodenal mucosal hyperplasia was observed in mice in 1000 and 3000 ppm groups and in 1 male in the 300 ppm group. All effects noted during treatment period, including the duodenal hyperplasia, were reversible during recovery period. The NOAEL was 100 ppm (26 and 37 mg/kg/day for males and females, respectively).	4
C57BL/6J mice of both sexes (98, 101 and 99)	Hydrogen Peroxide (30% aq.; for food-additive use)	0, 0.1%, and 0.4% in distilled water	Administered as drinking water for 100 weeks	One adenoma of the duodenum was observed in controls; 6 adenomas and one carcinoma of duodenum were observed in mice in low-dose group; and 2 adenomas and 5 carcinomas of duodenum were observed in mice in high-dose group (p > 0.05 compared with controls).	49

Table 10. Dermal, oral, and mucosal carcinogenicity studies.

Animal (n)	Test Material	Concentration	Procedure/Details	Results	Reference
Male and female C57BL/6N mice (138)	Hydrogen Peroxide (30% aq.; for food-additive use)	0.4% in drinking-water	Groups of 5 to 17 mice were killed and necropsied at 30-day intervals up to 210 days, and then every 60, 70 or 90 days up to 630 days. At end of experiment, 29 mice were killed and necropsied on day 700. Reversibility of lesions was investigated in groups of mice treated with Hydrogen Peroxide (0.4%) for 120, 140, 150 or 180 days followed by a treatment-free period of 10 to 30 days.	Gastric erosions and duodenal plaques (round, flat, avillous areas) were observed at 30 days and were present consistently at each subsequent time period. Nodules (hyperplastic lesions, adenomas, and carcinomas) were observed in both duodenum and stomach from 90 days until end of experiment, with exception of days 210 and 360. These lesions did not appear to increase in frequency, but atypical hyperplasia appeared late in experiment and 5% of mice developed duodenal adenocarcinoma. None of these lesions were observed in controls. Stomach lesions regressed completely, irrespective of length of treatment, but some duodenal lesions persisted.	⁵⁰
DBA/2N (22), BALB/cAnN (39) and C57BL/6N (34) mice of both sexes	Hydrogen Peroxide (30% aq.; for food-additive use)	0.4% in drinking-water	Mice were examined sequentially from 90 to 210 days of treatment for strain differences in development of gastric and duodenal 'nodules' (hyperplastic lesions, adenomas, and carcinomas).	Incidences of gastric nodules were 2 of 22, 1 of 39, and 12 of 34, and duodenal nodules were 14 of 22, 7 of 39, and 22 of 34 in DBA/2N, BALB/cAnN, and C57BL/6N mice, respectively. Duodenal nodules appeared at 90 days in all three strains.	⁵⁰
Female C3H/HeN, B6C3F1, C57BL/6N and C3H/Cbs mice (18 to 24)	Hydrogen Peroxide (source concentration not specified; food grade)	0.4% in distilled water as drinking water	Mice with different levels of catalase activities in duodenal mucosa (5.3, 1.7, 0.7 and 0.4×10^{-4} k/mg protein, respectively) were administered Hydrogen Peroxide in distilled water as drinking water for 6 or 7 months.	Incidences of duodenal 'nodules' (hyperplastic lesions, adenomas and carcinomas) were 2 out of 18, 7 out of 22, 21 out of 21, and 22 out of 24 in C3H/HeN, B6C3F1, C57BL/6N and C3H/Cbs mice, respectively.	³⁴
Fischer F344 rats (50)	Hydrogen Peroxide (source concentration not specified)	0, 0.3%, or 0.6% in drinking water	Administered in drinking water for 78 weeks followed by a 6-month recovery.	Survival of treatment groups was similar to controls except for males in 0.3% group (36 vs 41 out of 50 survival). There was no difference in number of tumors in rats that died, rats that survived to end of experiment, and control group in testes, mammary glands, and skin.	^{4,52}
Mucosal					
Syrian golden hamsters (25/sex)	Hydrogen Peroxide (source concentration not specified)	0.75% in a dentifrice	Administered into buccal cheek pouches 5 times per week for 20 weeks	No neoplasms were observed in the surviving 37 hamsters	¹⁰⁶
Co-Carcinogenicity					
Syrian hamsters (5 to 11)	Hydrogen Peroxide (source concentration not specified)	3% or 30% aq.	Administered into buccal cheek pouches, with and without DMBA, twice weekly for 19 or 22 weeks. Hamsters were then killed and necropsied, including histopathological examination.	All hamsters treated with Hydrogen Peroxide alone had hyperkeratosis and hyperplasia, with hyperchromatic cells and mild dysplasia in 4 out of 9 hamsters; no tumors were observed. In hamsters treated with DMBA alone, 3 out of 7 (43%) developed epidermoid carcinoma. Six of 11 hamsters (55%) treated with DMBA and 3% Hydrogen Peroxide developed epidermoid carcinomas by 22 weeks; all 5 hamsters treated with DMBA and 30% Hydrogen Peroxide developed epidermoid carcinomas by 22 weeks. In all hamsters, chronic inflammation, hyperchromatic cells and dysplasia were observed at 19 weeks. No carcinomas were observed in hamsters treated with 30% Hydrogen Peroxide alone. Hydrogen Peroxide can, by itself, induce pathologic/inflammatory changes, but not cause pathologic changes associated with preneoplastic lesions at 3%. Hydrogen Peroxide augmented the oral carcinogenesis of DMBA at 30% aq.	⁵²

Table 10. Dermal, oral, and mucosal carcinogenicity studies.

Animal (n)	Test Material	Concentration	Procedure/Details	Results	Reference
Tumor Promotion					
Sencar mice (60)	Hydrogen Peroxide (30% aq.) diluted 1:1 in 0.2 ml acetone	30% aq. Hydrogen Peroxide:acetone (1:1)	Mice were administered a single topical application of Hydrogen Peroxide. Control group was administered acetone alone. One week later, twice-weekly applications of TPA (2 µg in acetone; a tumor promoter) were administered for 25 weeks.	Papillomas were observed in 3 of 56 in control group and 6 of 58 in Hydrogen Peroxide-treated group. Hydrogen Peroxide did not induce tumor formation when administered in conjunction with TPA.	¹⁰⁵
Female 8-week-old ICR Swiss mice (30)	Hydrogen Peroxide (3% aq.)	3% aq.; 0.2 ml in water	Single dermal application of DMBA (125 µg in 0.25 ml acetone; a tumor promoter) was administered to the dorsal skin of the mice. Three weeks later, mice were administered dermal applications of Hydrogen Peroxide 5 times weekly for 56 weeks.	No skin tumors were found at necropsy at weeks 10, 26, 52, or 58	¹⁰⁸
Sencar mice (60)	Hydrogen Peroxide (30% aq.)	30% aq. Hydrogen Peroxide:acetone (1:0, 1:1, 1:2, or 1:5 in acetone; 0.2 ml)	Single topical application of DMBA (10 nmol in 0.2 ml acetone), followed 1 week later by applications of 30% aq. Hydrogen Peroxide diluted 1:1 in acetone (once and twice weekly), 1:2 (twice weekly), or 1:5 (twice weekly) for 25 weeks. Controls received acetone alone.	The proportions of mice with papillomas at 25 weeks were: 30% aq. Hydrogen Peroxide (twice/week) – 6 of 58 30% aq. Hydrogen Peroxide:acetone (1:1; once /week) – 5 of 59 30% aq. Hydrogen Peroxide:acetone (1:1; twice /week) – 8 of 59 30% aq. Hydrogen Peroxide:acetone (1:2; twice /week) – 10 of 59 30% aq. Hydrogen Peroxide:acetone (1:5; twice /week) – 10 of 60 Acetone (twice/week) – 0 of 60 Hydrogen Peroxide was found to be ineffective as a tumor promoter.	¹⁰⁵
Wistar rats (30, 21, 10)	Hydrogen Peroxide (source concentration not specified)	1% in drinking water	Two groups were administered MNNG (a carcinogen) in drinking water for 8 weeks followed by either 1% Hydrogen Peroxide in drinking water or tap water for 32 weeks. A third group was not administered MNNG but did have 1% Hydrogen Peroxide in drinking water for 32 weeks. Rats were then killed and necropsied.	Hydrogen Peroxide did not increase number of gastrointestinal tumors. All treated rats had forestomach papillomas, including those only treated with Hydrogen Peroxide. No carcinoma development was observed in the stomach or duodenum. Erosions and ulcerations also occurred in the fundic mucosa of the stomach of the Hydrogen Peroxide treated rats.	^{33,109}

Table 10. Dermal, oral, and mucosal carcinogenicity studies.

Animal (n)	Test Material	Concentration	Procedure/Details	Results	Reference
Syrian golden hamsters (30 to 40 of both sexes)	Hydrogen Peroxide (30% aq.)	20 µl	Two groups were administered an initiating dose of NNK (10 mg; 1 mg twice per day until full dose; a carcinogen) to cheek pouch. One group received no further treatment; other group and a control group were then topically administered Hydrogen Peroxide to cheek pouch 5 days per week for 24 weeks. A fourth group was administered NNK (20 mg; 1 mg/day) and Hydrogen Peroxide (20 µl) at the same time. The hamsters were then maintained for up to 16 months. A few of the hamsters in each group were killed (at 8 – 11 and 12 – 16 months, or if found moribund) and necropsied. Controls were an untreated group and a group treated with NNK (120 mg) alone and these were maintained for 22 months.	NNK alone – 0 of 14 and 0 of 16 incidences of tumors at 11 and 16 months, respectively. NNK followed by Hydrogen Peroxide – 8 of 14 and 15 of 18 incidences of tumors at 11 and 16 months, respectively. 1 out of 32 hamsters developed a cheek pouch adenoma. A total of 3 liver, 6 stomach, and 7 lung tumors were also found. Hydrogen Peroxide alone – 0 of 7 and 0 of 19 incidences of tumors at 11 and 16 months, respectively. NNK and Hydrogen Peroxide simultaneously – 8 of 14 and 15 of 18 incidences of tumors at 11 and 16 months, respectively. 8 out of 32 hamsters developed a cheek pouch adenoma. A total of 1 liver, 12 stomach, and 11 lung tumors were also found. There were no tumors in the untreated controls group. The extended NNK-treated control group – 1 of 7, 3 of 8, and 5 of 9 incidences of tumors at 11, 16, 22 months, respectively. A total of 1 liver, 7 stomach, and 2 lung tumors were also found. Histologic examination showed lung tumors to be adenomas, stomach nodules to be forestomach papillomas, liver tumors to be hepatomas, and cheek pouch tumors to be papillomas of the cheek pouch epithelium.	¹¹⁰

DMBA = 7,12-dimethylbenz(a)anthracene; MNNG = N-methyl-N'-nitro-N-nitrosoguanidine; NNK = 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone; TPA = 12-O-tetradecanoylphorbol 13-acetate

Table 11. Dermal irritation studies of Hydrogen Peroxide in animals.

Animal (n)	Concentration	Procedure	Results	Reference
New Zealand White rabbits (6)	3% aq. (volume not specified)	Administered to intact and abraded skin under occlusion for 24 h.	PII = 0.125 out of 8 Not irritating	²
Rabbits (not specified)	3% aq. (volume not specified)	24 h exposure under occlusion. Observation at 24 and 72 h.	PII = 0 at both observations. Non-irritant	³³
Albino rabbits (6)	6% aq. (89% water, 5% not specified; 0.5 ml)	Administered to intact and abraded skin under occlusion for 24 h.	Erythema and edema were observed at 24 and 72 h. PII at 24 h = 0.75 out of 8 PII at 48 h = 0.70. Classified as not irritating.	²
Rabbits (not specified)	6% aq. (volume not specified)	24 h exposure under occlusion. Observation at 24 and 72 h.	PII = 0 at both observations. Non-irritant	³³
Rabbits (6)	8% aq. (0.5 ml)	Administered to intact and abraded skin under occlusion for 24 h.	Erythema and edema were observed at 24 and 72 h after administration. PII = 0.04 out of 8.	²
Rabbits (not specified)	8% aq. (volume not specified)	24 h exposure under occlusion. Observation at 24 and 72 h.	PII = 0 at both observations. Non-irritant	³³
New Zealand White rabbits (3/sex)	10% aq. (0.5 ml)	OECD GL 404 (Acute Irritation and Corrosion) Under semi-occlusion to shaved skin for 4 h. Rabbits were observed at 30 min and 24, 48, and 72 h after removal.	Slight erythema was observed in 2 rabbits up to 24 h post-dosing, which was resolved at 48 h. PII = 0.08 out of 8 Not irritating.	²
Rabbits (not specified)	10% aq. (volume not specified)	24 h exposure. Observation at 4.5, 24, 48, and 72 h. (further details not provided)	PII = 0.3, 0.2, 0, and 0 out of 8 at 4.5, 24, 48, and 72 h, respectively. Non-irritant	³³
New Zealand White	35% aq. (0.5 ml)	Under occlusion to shaved skin for 4 h.	Scores for erythema/eschar were not higher than 2 for individual rabbits at any	²

Table 11. Dermal irritation studies of Hydrogen Peroxide in animals.

Animal (n)	Concentration	Procedure	Results	Reference
rabbits (3/sex)		Rabbits were observed at removal and daily for 2 weeks.	time. Mean scores were 1, 1.75, 0.58 and 0.58 out of 8 at 4, 24, 48 and 72 h. Scores for edema were not higher than two for individual rabbits at any time. Mean scores were 1.83, 0.83, 0 and 0 at 4, 24, 48 and 72 h. After 14 days, 2 rabbits had brown areas with desquamation at the test sites. Test material was judged to be moderately irritating to the rabbit's skin and was non-corrosive within 48 h of dosing. PII = 1.6 out of 8	
Rabbits (not specified)	35% aq. (volume not specified)	4 h exposure to intact skin under occlusion. Observed at 4, 24, 48, 72, and 96 h.	PII = 2.8, 2.6, 0.58, 0.58, and 0.42 out of 8 at 4, 24, 48, 72, and 96 h, respectively. Non-irritant	³³
New Zealand White rabbits (10/sex)	35% w/w aq. (2000 mg/kg; volume not specified)	OECD GL 402 (Acute Dermal Toxicity) Under occlusion for 24 h. Observed at 0.5, 1, 2, 3, 4 and 6 h, twice daily for 13 days, and once on day 14. Rabbits were then killed and necropsied.	Erythema, edema, and blanching of the test sites were observed in all rabbits 24 h after administration. By day 4, all rabbits had necrosis which developed into eschar on day 7. At termination of the study, eschar and exfoliation were present in all rabbits.	²
Rabbits (6)	35% w/w aq. (volume not specified)	Administered for 24 h (further details not provided)	Mild erythema with moderate to slight edema in all 6 rabbits at 24 h, and severe to moderate erythema with slight to very slight edema in all 6 rabbits at 48 h. <u>Irritating</u>	²
Female New Zealand White rabbits (1)	49.2 % aq. (0.5 ml)	OECD GL 404 Rabbit was anesthetized prior to dosing. Under semi-occlusion to 2 sites for 4 h then observed at 30 min and 24 and 48 h.	Severe erythema, moderate edema, and gray areas were observed on both test sites at 24 h. Moderate erythema, slight edema, gray areas, and ataxia were present at 48 h. Histopathologic examination showed severe irritation that would have resulted in ulceration and necrosis. PII = 5 out of 8	²
Rabbit (1)	50% or 70% aq.	Draize Assay Exposure of 70% for 3 min and 50% for 3 min and 1 and 4 h.	Exposure to 50% Hydrogen Peroxide for 3 min caused moderate erythema and mild edema. Mild erythema and no to mild edema were observed at 24, 48, and 72 h after treatment. No dermal irritation was observed at 7 or 14 days. Blanching was observed at time of dosing in test site of rabbit treated with 70% Hydrogen Peroxide. After 3 min, mild erythema and severe edema were observed around area of blanching. Moderate or mild erythema and moderate or mild edema were observed at 24, 48, and 72 h. Sloughing and fissuring were also observed. Superficial necrosis was observed at 24, 48, and 72 h after treatment; necrosis was observed at 7 days. Scar tissue was observed at 14 days. Exposure to 50% Hydrogen Peroxide for 1 h produced slight erythema, severe edema, and blanching. Mild erythema with mild, slight or no edema was observed through day 7 of observation. No erythema or edema was observed on day 14 after treatment. Superficial necrosis was observed in test site at 72 h after treatment, and necrosis and sloughing were observed at 7 days. Scar tissue was observed at 14 days. Exposure to 50% Hydrogen Peroxide for 4 h produced mild erythema, moderate edema, and blanching by end of exposure period. Blanching was observed through 48 h. Moderate, mild, or slight erythema and mild, slight, or no edema was observed through day 7 after treatment. No erythema or edema was observed at day 14. Superficial necrosis was observed at 72 h and necrosis and sloughing were observed at day 7. Scar tissue and sloughing were observed at day 14. 70% Hydrogen Peroxide, 3 min exposure was corrosive 50% Hydrogen Peroxide, 1 or 4 h exposure was corrosive	²
Male rabbits (4)	70% w/w aq. (6500 and 13,000 mg/kg; volume not specified)	OECD GL 402 (further details not provided)	Observation of the skin revealed redness, massive edema, eschar formation, and sloughing off at application sites.	²
Rabbit (1)	70% aq. (volume not specified)	OECD GL 404 Exposure for 1 h (further details not provided)	Test site had slight erythema, severe edema and white bubbles under the skin. At 24 h there was still mild erythema, edema, and white bubbles under the skin accompanied by several 1 to 2-mm brown spots. At 48 h, findings were similar but brown spots had enlarged to spotted areas. Corresponding Draize scores at 30 min	²

Table 11. Dermal irritation studies of Hydrogen Peroxide in animals.

Animal (n)	Concentration	Procedure	Results	Reference
			and 24 and 48 h were 0.4, 0.3, and 0.3 out of 8, respectively. Histopathological lesions were consistent with those occurring in third degree burns. Test material was judged to have caused extensive damage to dermis, epidermis, blood vessels, connective tissue, and adnexa. Corrosive	
Mice (strain and n not specified)	15% or 30% aq.	Single application to the dorsal skin	Extensive epidermolysis, inflammation and vascular injury, similar to that produced by tumor promoters, followed by quick regeneration and epidermal hyperplasia, with a temporary increase in number of dark basal keratinocytes. Extensive endothelial damage to dermal blood vessels also occurred.	¹⁰⁵
Wistar WBN/Kob-Ht rats (5)	0, 3%, 6%, or 10% aq.; 0.04 ml	Each concentration was administered to 1 of 4 sites on the shaved dorsal skin for 7 consecutive days. Another group of untreated rats acted as additional controls. Rats were killed and skin examined 1 day after last application.	Skin exposed to 3% Hydrogen Peroxide had mild focal epidermal thickening, which had keratinocytes with signs of pyknosis. Intracytoplasmic edema was sporadically observed at and around thickened skin, especially in basal layer. Mild infiltration of mononuclear cells was sporadically observed in the superficial dermis. Deeper dermis layers had an increase in number of mast cells. At 6%, changes observed at 3% progressed and border between the epidermis and dermis became irregular. There were portions where epidermis was partially detached from dermis, leaving a space filled with fluid. At 10%, focal trans-epidermal necrosis was observed in some sites. Skin lesions were observed. At all concentrations, necrotic keratinocytes were observed scattered in spinous and basal layers, and necrotic keratinocytes were occasionally ingested by macrophages. Basal layer contained clusters of keratinocytes with signs of shrinking cell bodies and/or intracytoplasmic edema and occasional infiltration of basement membrane. Marked degenerative changes were detected occasionally in capillary endothelial cells in superficial dermis.	¹¹²
Guinea pigs (not specified)	9 solutions of Hydrogen Peroxide at 3% and 6% aq. (volume not specified)	Administered to intact and abraded skin (further details not provided).	None of 9 solutions was more than mildly irritating when applied to intact skin (initial patch reactions). When applied to abraded skin, 2 of 9 solutions (one at 3% and one at 6%) were strongly irritating, while other preparations were at most only mildly irritating.	²

OECD GL = Organisation of Economic Co-operation and Development Guide Lines; PII = primary irritation index

Table 12. Ocular irritation studies for Hydrogen Peroxide.

Animal (n)	Concentration	Method/Assay	Results	Reference
Rabbits (strain and n not specified)	0.5% aq. (drop)	Dropped onto cornea of eye	Caused disturbances of epithelium, but eyes returned to normal within 24 h	¹¹⁶
Albino rabbits (6)	3% aq. (0.1 ml)	Test substance was instilled once and not washed out. Eyes were examined with a bright artificial light and hand-slit lamp at 24, 48, and 72 h after treatment.	No irritant response was observed within 72 h after instillation.	²
Female New Zealand White rabbits (4)	5% aq. (0.1 ml)	OECD GL 405 (Acute Eye Irritation/Corrosion) 0.5 % Tetracaine Hydrochloride was used to minimize pain. Eyes of 2 of 4 rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, and 72 h.	1 h after instillation, all treated eyes had slight conjunctivitis. At 24 h, slight to mild conjunctival redness was noted in all treated eyes. Three treated eyes had slight redness 48 h after instillation. At 72 h, all irritation was resolved. Slightly irritating	²

Table 12. Ocular irritation studies for Hydrogen Peroxide.

Animal (n)	Concentration	Method/Assay	Results	Reference
Rabbits (strain and n not specified)	5% aq. (0.1 ml)	Eyes of some rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, and 72 h.	Draize score: ^a Unwashed: 8.0, 3.0, 2.0, and 0 and washed: 6.0, 3.0, 1.0, and 0 at 1, 24, 48, and 72 h, respectively. Irritation scores: ^b C = 0; I = 0; R = 0.83; H = 0. Non-irritant	³³
New Zealand White rabbits (6)	6% aq. (0.1 ml)	OECD GL 405 Eyes of 3 rabbits were unwashed; eyes of 3 rabbits were washed for 1 min with water 20 sec after instillation. Eyes were examined at 1, 24, 48, and 72 h after instillation; 2 rabbits of each treatment group were examined after 7 days and 1 was examined 14 and 21 days following treatment.	Slight to severe irritating effects in both unwashed and washed eyes were observed, which were reversible in most cases within 72 h following treatment. Treated eye in 1 rabbit was normal after 7 days. Moderate to severe corneal damage was observed in 1 rabbit. Corneal vascularization, which may be interpreted as a sign of healing, was still present in this rabbit after 21 days. Serious eye irritant	²
Rabbits (strain and n not specified)	6% aq. (0.1 ml)	Eyes of some rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, and 72 h and 14 and 21 days.	Draize score: ^a unwashed at 1, 24, 48, and 72 h and 7 days: 19.0, 5.2, 3.3, 0.7, and 0, respectively, and at 1, 24, 48, and 72 h washed: 27.0, 15.0, 19.7, and 5 respectively; < 4 and < 7 for 1 rabbit evaluated at 14 and 21 days, respectively. Irritation scores: ^b Unwashed: C = 0; I = 0; R = 1.33; H = 0.2 and washed: C = 0.4; I = 0.22; R = 1.33; H = 0.78. Non-irritant.	³³
Male New Zealand White rabbits (4)	8% aq. (0.1 ml)	OECD GL 405 0.5 % Tetracaine hydrochloride was used to minimize pain. Treated eyes of 2 rabbits remained unwashed, while the eyes of the 2 remaining rabbits were washed 20 to 30 sec following instillation. Eyes were examined at 1, 24, 48, and 72 h and days 4, 7, 10, 13, 16, 19, and 22.	Moderate conjunctivitis was observed in all eyes 1 h after dosing. Irritation worsened by 24 h at which time unwashed eyes had slight corneal opacities, iritis, and severe conjunctivitis. Washed eyes had severe corneal opacities, severe iritis and conjunctivitis. Irritation gradually resolved in unwashed eyes; washed eyes developed corneal vascularization on day 7 and bulging of the cornea (1 rabbit) on day 13. At day 22, 1 unwashed eye had a slight corneal opacity and eye of the remaining rabbit in the group with washed eyes had a slight corneal opacity, mild conjunctivitis and vascularization. Washing eyes with tap water shortly after exposure increased severity of irritation observed. One rabbit of the group with washed eyes died on Day 21 of the study due to enteritis (possibly stress-related) and was not considered to be directly related to treatment. Ocular irritant	²
Rabbits (strain and n not specified)	8% aq. (0.1 ml)	Eyes of some rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, 72, and 96 h and 7, 16, and 21 days.	Draize score: ^a Unwashed: 13.0, 31.0, 11.0, 5.0, 4.0, 2.0, 2.5, and 2.5; washed: 12.0, 84.5, 77.5, 71.0, 57.0, 47.0, 22.0, and 16.0 at 1, 24, 48, 72, and 96 h and 7, 16, and 21 days, respectively. Irritation scores: ^b C = 1.66; I = 0.50; R = 2.50; H = 1.58. Irritant	³³
Female New Zealand White rabbits (4)	10% aq. (0.1 ml)	OECD GL 405 Treated eyes of 2 rabbits remained unwashed, while eyes of 2 remaining rabbits were washed 20 to 30 sec following instillation. Eyes were examined up to 7 days after instillation.	1 h after instillation, moderate to severe conjunctivitis was observed in all eyes; 1 washed eye had a hemorrhagic conjunctiva. Within 24 h, severe corneal opacities, iritis, and conjunctivitis were observed in all eyes. Three rabbits had conjunctival hemorrhages. Eyes gradually improved until day 7, at which time corneal opacities were present in all eyes; iritis was observed in 1 unwashed and 1 washed eye, and conjunctivitis was observed in all treated eyes. Washing eyes with tap water shortly after exposure increased severity of irritation observed. Irritation scores at 24 and 72 h: Cornea opacity = 4 and 2.75; Iris = 2 and 1; conjunctivae = 3 and 3, respectively. Extremely irritating	²
Rabbits (strain and n not specified)	10% aq. (0.1 ml)	Eyes of some rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, 72, and 96 h and 7 days.	Draize score: ^a Unwashed: 11.0, 107, 107, 71.0, 44.5, and 40.5; washed: 15.0, 108, 108, 81.0, 65.5, and 49.0 at 1, 24, 48, 72, and 96 h and 7 days, respectively. Irritation scores: ^b C = 3.5; I = 1.67; R = 3.0; H = 2.8. Irritant	³³

Table 12. Ocular irritation studies for Hydrogen Peroxide.

Animal (n)	Concentration	Method/Assay	Results	Reference
Male New Zealand albino rabbits (12)	10% and 15% aq.	Applied directly to cornea of right eye of each rabbit. Macroscopic assessments for irritation were made 3 h, and 1, 3, and 35 days after dosing. Light microscopic examinations were conducted. In vivo confocal microscopy and measurements of dead corneal epithelial cells and keratocytes at 3 h and 1 day were used to characterize quantitatively initial corneal injury. In vivo confocal microscopy performed at 3 h and 1, 3, 7, 14, and 35 days was used to characterize corneal changes over time.	Changes with 10% and 15% Hydrogen Peroxide were consistent with severe irritation. Both concentrations affected the epithelium and deep stroma. High concentration also, at times, affected endothelium. However, there was an incongruity between extent of epithelial and stromal injury, with stromal injury being more extensive than epithelial injury.	¹¹⁷
Rabbits (strain and n not specified)	35% aq. (0.1 ml)	Eyes of some rabbits were washed 20 to 30 sec after instillation and scored after 1, 24, 48, 72, and 96 h and 7, 14, and 22 days.	Draize score: ^a Unwashed: 39.2, 62.5, 69.5, 69.5, 63.7, 79.3, 74.8, and 72.7; washed: 41.3, 49.0, 69.7, 59.7, 48.7, 76.7, 76.0, and 74.3 at 1, 24, 48, 72, and 96 h and 7, 14, and 22 days, respectively. Irritation scores: ^b C = 2.33; I = 1.72; R = 1.27; H = 2.28. Irritant	³³
Female New Zealand White rabbits (8)	70% aq. (0.1 ml)	Draize test The rabbits were observed for 72 h after dosing.	There was extreme irritation with maximum corneal, iridial, and conjunctival effects. One rabbit died 10 min after instillation. Draize score was not determined. Corrosive; risk of serious damage to eyes	^{2,33}
Black rabbits (Strain not specified; 8)	30 mg/m ³ (22 ppm) vapor; concentration not specified	6 h/day, 5 days/week. Whole body exposure for 12 week (60 exposures).	Ophthalmologic examination showed no changes due to exposure to test material.	⁴⁰
Male mice (strain not specified; 4)	3.6 - 19 mg/l aerosolized; 90% aq.	Exposed for 5 to 15 min	Gross opacities were present in eyes of 4 mice exposed to 19 mg/l (highest concentration) at 8 weeks after exposure. Microscopic lesions were observed in eyes of mice exposed to 9.4 mg/l 8 weeks after exposure, while those necropsied at 5 weeks after exposure showed no significant changes. Authors concluded that these findings indicate that there is an insidious and slowly developing corneal damage subsequent to exposure to high aerosol concentrations of Hydrogen Peroxide.	²

OECD GL = Organisation of Economic Co-operation and Development

^a Scores determined by the Draize method with a maximum score of 110

^b Irritation scores based on separate calculation of the mean 24, 48, and 72 h scores for cornea damage (C); iris damage (I), redness (R), and chemosis (H) for all rabbits tested.

Table 13. Case reports on exposure to Hydrogen Peroxide

Dose, Concentration, and vehicle (if known)	Report	Reference
Dermal		
3% aq. Hydrogen Peroxide in commercial hair dye	Two women had been exposed to Hydrogen Peroxide as an ingredient in commercial hair dyes. Both women tested positively to 3% Hydrogen Peroxide and numerous other ingredients in the hair dyes. The author reported that 156 other hairdresser patch tested with hairdresser series tested negatively to 3% Hydrogen Peroxide.	4
30% aq. Hydrogen Peroxide	A 31-year-old man presented with right knee pain after industrial-strength Hydrogen Peroxide (30%) splashed onto his pants while he was working in a leather factory. He denied any trauma. Physical examination showed 2% of total body surface area with second- to third-degree degree chemical burns with yellowish leathery skin covered with air-filled bullae and tenderness with subcutaneous crepitation over the right knee. He had a white cell count of 9200/mm ³ with predominance of neutrophil (85.1%); radiography disclosed subcutaneous air around the right knee soft tissue. Under the diagnosis of chemical burn injury of the right knee, the patient received debridement and wound management.	138
Oral		
Approximately 230 g of 3% aq. Hydrogen Peroxide solution (dose estimated at 600 mg/kg)	A 16-month-old boy died 10 hours after ingestion. On postmortem examination there was frothy blood in the right ventricle and in the portal venous system. The gastric mucosa was red and the brain was edematous. Histopathology showed edema in the lungs, diffuse interstitial emphysema and gas emboli within the pulmonary vasculature and gastrointestinal lymphatics. Clear vacuoles were also found within the spleen, kidneys and myocardium	139
3% aq. Hydrogen Peroxide 2 to 4 oz	A previously healthy 3-year-old boy ingested 3% Hydrogen Peroxide. Approximately 30 min later, foam was noted in his mouth and he began to vomit. He experienced blood streaked emesis 15 min after drinking water. A radiograph of the abdomen for air embolization was negative. Upper GI endoscopy showed a normal esophagus, but there were multiple ulcers located in the gastric antrum, and multiple erosions were noted in the duodenal bulb. Repeat endoscopy 1 week later showed healing gastric and duodenal ulcers with no active bleeding or evidence of stricture formation.	140
A mouthful of 3% aq. Hydrogen Peroxide	A healthy 21-year-old male presented with vomiting and pain in his mouth, throat, and epigastrium. He was tachycardic and mildly hypertensive but not hypoxic. Clinical examination revealed dysphonia with mild erythema and edema of the oropharynx and uvula. CT scan showed pneumatosis and mucosal thickening throughout the stomach and proximal duodenum, as well as extensive portal venous gas. An upper endoscopy performed 3 days after the ingestion was normal, with no evidence of mucosal injury. A repeat CT scan showed interval partial resolution of the bowel wall thickening and complete resolution of the pneumatosis and portal venous gas.	141
3% aq. Hydrogen Peroxide (dose estimated at 40 ml)	A 25-year-old woman who had ingested Hydrogen Peroxide presented with epigastric pain and persistent vomiting with a small amount of blood. She had mild tenderness in the epigastric area. Numerous symptoms were found in the gastric tract including multiple large round mucosal erosions in the distal esophagus and diffuse hemorrhagic gastritis involving the entire gastric mucosa. Two days after admission, the hemoglobin concentration decreased and test result for occult blood in the stool was positive. The patient showed erythematous gastritis and resolution of the esophageal lesion on day 14.	142
One swallow of 30% aq. Hydrogen Peroxide	A 5-year-old presented with vomiting and epigastric pain. Radiographic evaluation showed portal venous gas embolism. Upper gastrointestinal endoscopy showed diffuse hemorrhagic gastritis. He was observed for 12 days and discharged. Follow-up endoscopy, 9 days later, showed erythematous gastritis.	143
Approximately 50 ml of 33% aq. Hydrogen Peroxide solution	Five persons who accidentally drank the solution experienced stomach and chest pain, retention of breath, foaming at the mouth and loss of consciousness. Later, they experienced motor and sensory disorders, fever, micro-hemorrhages and moderate leukocytosis. One subject developed pneumonia. All recovered completely within 2 to 3 weeks.	8
113 to 170 g of 35% aq. Hydrogen Peroxide (dose estimated at 3800 mg/kg)	A 2-year-old boy ingested the solution. He had gas in the heart and in the portal venous system, together with severe hemorrhagic gastritis without perforation. After death on day 4, autopsy showed marked diffused cerebral edema.	144
1 pint bottle of 35% aq. Hydrogen Peroxide	A 33-yr-old woman vomited, collapsed, and experienced a brief tonic-clonic seizure within minutes of ingestion. The patient was intermittently seizing and markedly cyanotic and had copious white foam emanating from her mouth. Within 30 sec after nasotracheal intubation, the patient became apneic and dependent on mechanical ventilation. She had mild erythema of the distal esophagus and diffuse hemorrhages and edema of the gastric mucosa. Bilateral cerebral hemisphere swelling was followed by patchy areas of weakness in the upper and lower extremities and truncal ataxia with inability to maintain a sitting position.	145
120 ml of 35% aq. solution Hydrogen Peroxide (dose estimated at 600 mg/kg)	A 63-year-old man who ingested the solution vomited three times and complained of general malaise. Laparotomy 5 h after ingestion showed severe erythema, edema, and emphysema of the gastric serosa; a visible perforation was not detected. Multiple brain embolisms were observed by MRI. On the fifth hospital day, the patient became alert and complained of numbness of the extremities. Neurologic examination demonstrated a left hemiparesis predominantly affecting the lower limb while sparing the face and a mild weakness of right lower limb. Abdominal symptoms rapidly improved, but recovery from the neurologic deficits was only partial.	146

Table 13. Case reports on exposure to Hydrogen Peroxide

Dose, Concentration, and vehicle (if known)	Report	Reference
30 ml of 35% aq. Hydrogen Peroxide (dose estimated at 150 mg/kg)	Ingestion of Hydrogen Peroxide resulted in brain injury presumed to be due to cerebral oxygen embolism in an 84-year-old man. Multiple cerebral infarctions (detected with MRI) occurring immediately after ingestion. Authors suggested that pathophysiologic mechanism was a patent foramen ovale of the heart (not said to be involved in the case), some unmetabolized Hydrogen Peroxide crossing the pulmonary capillary bed into the arterial circulation, or aspiration and absorption of Hydrogen Peroxide from the pulmonary capillaries.	147
Approximately 2 tablespoons of 35% aq. Hydrogen Peroxide	An elderly woman drank Hydrogen Peroxide and developed respiratory distress within a few min. She had a frothy mouth and soon became unresponsive. A CAT scan of the chest/abdomen/pelvis showed air in the heart, spleen, and splenic and portal veins. She exhibited an altered mental status. She was treated with phenytoin, midazolam for seizure prophylaxis and hyperbaric oxygen for the air embolism without improvement.	148
Mucosal		
3% aq. Hydrogen Peroxide	A 35-year-old man presented with severe pain and erythema of the lower labial mucosa. He had self-medicated for halitosis and gingivitis by applying 3% Hydrogen Peroxide to the region with a cotton swab. A few hours later, he experienced painful oral ulcerations at the site of application. There was an extensive area of ulceration and erythema involving the alveolar mucosa and the marginal and attached gingival region. Focal areas of ulceration and sloughing with necrosis of surface layers of the epithelium were also observed. The patient discontinued use of Hydrogen Peroxide, and the area was gently rinsed with saline to remove necrotic tissue. The 1-week follow-up examination showed complete healing.	149
Ocular		
3% aq. Hydrogen Peroxide disinfectant solution	A woman who had inadvertently stored a contact lens in a 3% Hydrogen Peroxide disinfectant solution had an immediate painful reaction with hyperemia, tearing, and eyelid spasm. Her eye became increasingly inflamed over the next 48 h (despite anti-inflammatory drops), the cornea began to show punctate staining, and the conjunctiva was edematous. Her cornea began to clear after 48 h and the pain reduced. Visual acuity had dropped to 20/40 and recovered to 20/20. Several days later, there seemed to be no residual effects, except minimal punctate keratopathy and mild discomfort.	150
Inhalation		
12 to 41 mg/m ³	Workers who operated a machine that used Hydrogen Peroxide to sanitize cardboard packaging were exposed to aerosolized Hydrogen Peroxide. Workers reported eye and throat irritation and gradual bleaching of hair. One worker developed interstitial pulmonary disease and impaired gas exchange, but since he was a heavy smoker, the cause could not be ascertained.	151
1.7 to 3.4 mg/m ³ and 0.2 to 0.6 TWA (highest reading 11.3 mg/m ³ for 1.5 h every morning)	Six workers who operated a machine for which Hydrogen Peroxide was used to sanitize the equipment were exposed to aerosolized Hydrogen Peroxide and its vapors for almost 3 years. Workers reported redness and burning in the eyes, blocked nose, itching and dryness in the throat, cough, and asthma symptoms. Most symptoms were worse at work and at the end of the work week. Additional symptoms included headache, protracted dry cough, and temporary loss of olfaction. Skin effects included burning and pricking of the fingers, drying of the hands and face, decrease in skin elasticity, and color change. Hair blanched and felt dry and rough. Two workers developed bronchoconstriction. Effects continued after the levels of Hydrogen Peroxide were reduced.	152
Hydrogen Peroxide (concentration and amount not specified)	A 51-year-old man was in the presence of a broken bottle fully filled with Hydrogen Peroxide. He inhaled fumes for 15 min. He experienced burning and watery eyes, and blurred vision developed (could see only shadows) over 2 h. He presented 3 days later with bilateral visual loss and reported that he was only able to see shadows in both eyes. Neuro-ophthalmological examination revealed visual acuity of 2/10 in both eyes. Direct and consensual pupillary light reflexes were decreased, extrinsic ocular motility was normal, and color perception was impaired. There was swelling of the optic discs. Other neurological examination findings were normal. The patient underwent pulse therapy of methylprednisolone and maintenance therapy of prednisone. He showed visual improvement in 6 days, but showed similar visual acuity findings and bilateral optic atrophy in 30 days.	153
90% aq. Hydrogen Peroxide vapor	Men accidentally exposed to 90% Hydrogen Peroxide vapor experienced an increased flow of saliva, scratchy feeling of the throat, and respiratory passage inflammation.	116

Table 13. Case reports on exposure to Hydrogen Peroxide

Dose, Concentration, and vehicle (if known)	Report	Reference
Other		
5 x 20 ml 3% aq. Hydrogen Peroxide	An obese 54-year-old male underwent irrigation of an infected and fistulous herniorrhaphy wound with Hydrogen Peroxide. Not all irrigating volume seemed to have drained from the wound. On the fifth irrigation the patient suddenly lost consciousness, showed cardiac shock and fell into coma which lasted for 15 min. ECG showed signs of transient myocardial ischemia. The patient made a full recovery within 3 days. The authors attributed this occurrence to widespread embolization of oxygen microbubbles, especially to the cerebral and coronary arteries	154

ECG = electrocardiogram; MRI – magnetic resonance imaging

REFERENCES

1. Nikitakis, J and Lange B (eds). Web-Based Ingredient Dictionary (wINCI). <http://webdictionary.personalcarecouncil.org/jsp/Home.jsp>. Washington, DC. Last Updated 2017. Date Accessed 10-30-2017.
2. European Chemicals Agency (ECHA). Hydrogen peroxide, EC number 231-765-0/CAS number 7722-84-1. <http://echa.europa.eu/registration-dossier/-/registered-dossier/15701/1>. European Chemicals Agency (ECHA). Last Updated 2017. Date Accessed 11-21-2017.
3. Scientific Committee on Consumer Products (SCCP). Hydrogen peroxide, in its free form or when released, in oral hygiene products and tooth whitening products. Brussels, Belgium: European Commission. 2007. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_122.pdf. Date Accessed 1-11-2018. Report No. SCCP/1129/07. pp. 1-107.
4. Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers concerning hydrogen (carbamide, zinc) peroxide in tooth bleaching/whitening products. Brussels, Belgium: European Commission. 2002. http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out180_en.pdf. Date Accessed 11-3-2018. Report No. SCCNFP/0602/02, final. pp. 1-42.
5. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Human health Tier II assessment for hydrogen peroxide (H₂O₂). http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1404#cas-A_7722-84-1. Sydney, Australia. Last Updated 2014.
6. Biocidal Products Committee. Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products; Evaluation of active substances assessment report; Hydrogen peroxide; Product types 1-6. Finland: 2015. http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/1315-01/1315-01_Assessment_Report.pdf. Date Accessed 2-1-2018. pp. 1-88.
7. Human & Environmental Risk Assessment (HERA). Human & environmental risk assessment on ingredients of household cleaning products: hydrogen peroxide CAS No. 7722-84-1. Human & Environmental Risk Assessment (HERA). 2005. http://www.heraproject.com/files/36-f-05-shor_h2o2_version1.pdf. Date Accessed 12-1-2017. pp. 1-13.
8. International Agency for Research on Cancer (IARC). Hydrogen peroxide. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans; Ally Compounds, Aldehydes, Epoxides and Peroxides*. Vol. 36. Lyon, France: IARC; 1985:285-314.
9. Agency for Toxic Substances and Disease Registry. Hydrogen peroxide (H₂O₂); CAS 7722-84-1; UN 2984 (8%-20%), UN 2014 (20%-52%), UN 2015 (>52%). Atlanta, GA: Agency for Toxic Substances and Disease Registry Division of Toxicology and Human Health Sciences. 2017. <http://www.atsdr.cdc.gov/MMG/MMG.asp?id=304&tid=55>. Date Accessed 11-3-2017.
10. International Programme on Chemical Safety (IPCS) International Programme on Chemical Safety (INCHEM). Hydrogen peroxide. <http://www.inchem.org/documents/pims/chemical/pim946.htm>. Inter-organization Programme for the Sound Management of Chemicals (IOMC). Last Updated 1998. Date Accessed 11-3-2017.
11. European Chemicals Bureau. European Union Risk Assessment Report; hydrogen peroxide; CAS No: 7722-84-1; EINECS No: 231-765-0. Helsinki, Finland: European Commission Joint Research Centre; Institute for Health and Consumer Protection; European Chemicals Bureau. 2003. <http://publications.jrc.ec.europa.eu/repository/handle/JRC26024>. Date Accessed 11-10-2017. Report No. 38. pp. 1-243.
12. USP Technologies. What are H₂O₂ stabilizers and will they affect my application? *USP Technologies*. 2011. Danaher Corporation. <http://www.h2o2.com/faqs/FaqDetail.aspx?fid=11Date> Accessed 12-15-2017
13. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Hydrogen peroxide. Food and Agricultural Organization of the United Nations. 2004. http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-229.pdf. Date Accessed 11-1-2017. pp. 1-3.
14. United States Pharmacopeial Convention. Food Chemicals Codes. 10 ed. Rockville, MD: United States Pharmacopeial Convention, 2016.
15. U.S. Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD: 2018. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2018; received February 5 2018).
16. Personal Care Products Council. 9-28-2017. Concentration of Use by FDA Product Category: Hydrogen Peroxide. Unpublished data submitted by Personal Care Products Council.
17. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC Monogr Eval Carcinog Risks Hum*. 1993;57(1):43-118.

18. U.S. Food and Drug Administration (FDA). Hair dye and hair relaxers. <http://www.fda.gov/forconsumers/byaudience/forwomen/ucm118527.htm>. Silver Spring, MD. Last Updated 1-19-2018. Date Accessed 4-12-2018.
19. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.
20. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.
21. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. <http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf>. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.
22. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 8-28-2011;205(2):97-104. PM:21669261.
23. European Commission (EC). Annex III; List of substances which cosmetic products must not contain except subject to the restrictions laid down. http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20III_v2.pdf. Last Updated 2017. Date Accessed 2-13-0018.
24. Scientific Committee on Safety (SCCS). Opinion on oxidative hair dye substances and hydrogen peroxide used in products to colour eyelashes. Brussels, Belgium: European Commission. 2012. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_111.pdf. Date Accessed 1-24-0018. Report No. SCCS/1475/12. pp. 1-21.
25. The Council of the European Union. Council Directive 2011/84/EU of 20 September 2011 amending Directive 76/768/EEC, concerning cosmetic products, for the purpose of adapting Annex III thereto to technical progress. *Official Journal of the European Union*. 2011; <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:283:0036:0038:en:PDF>.
26. Department of Health, Australian Government. Poisons Standard March 2018. 2014. <https://www.legislation.gov.au/Details/F2018L00168/Html/Text>. Report No. F2018L00168. pp. 1-681.
27. U.S. Food and Drug Administration (FDA). Oral health care drug products for over-the-counter human use; antigingivitis/antiplaque drug products; establishment of a monograph. *Federal Register*. 2003;68(103):32232-32287.
28. Lineaweaver W HRSD. Topical Antimicrobial Toxicity. *The Archives of Surgery*. 1985;120(3):267-270.
29. National Institutes of Health (NIH) National Center for Biotechnology. Open Chemistry Database; Compound summary for CID 784; hydrogen peroxide. http://pubchem.ncbi.nlm.nih.gov/compound/hydrogen_peroxide. Bethesda, MD. Last Updated 2004. Date Accessed 2-13-0018.
30. U.S. Food and Drug Administration (FDA). Drugs@FDA Approved Drug Products: Approval Dates and History, Letters, Labels, Reviews for NDA 209305. <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209305>. Last Updated 12-14-2017. Date Accessed 4-5-2018.
31. U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). M7(R1) assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk: guidance for industry. Silver Spring, USA: U.S. Department of Health and Human Services. 2018. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>. Date Accessed 3-14-2018. pp. 1-129.
32. Khan SA, McLean MK, and Slater M. Effectiveness and adverse effects of the use of apomorphine and 3% hydrogen peroxide solution to induce emesis in dogs. *Journal of the American Veterinary Medical Association*. 2012;241(9):1179-1184.
33. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Hydrogen peroxide OEL criteria document; CAS No. 7722-84-1. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1996. <http://www.ecetoc.org/wp-content/uploads/2014/08/SR-10.pdf>. Date Accessed 11-10-2017. Report No. Special Report No. 10. pp. 1-152.
34. Ito A, Watanabe H, Naito M, et al. Correlation between induction of duodenal tumor by hydrogen peroxide and catalase activity in mice. *Gann Japanese Journal of Cancer Research*. 1984;75(1):17-21.
35. Halliwell B. Superoxide dismutase, catalase and glutathione peroxidase: solutions to the problems of living with oxygen. *New Phytologist*. 1974;73(6):1075-1086.
36. Halliwell B and Gutteridge J. Review article: oxygen toxicity, oxygen radicals, transition metals and disease. *Biochemical Journal*. 1984;219(1):1-14.
37. Niedzwecki A, Book B, Lewis K, et al. Effects of oral 3% hydrogen peroxide used as an emetic on the gastroduodenal mucosa of healthy dogs. *Journal of Veterinary Emergency and Critical Care*. 2017;27(2):178-184.

38. Gagnaire F, Marignac B, Hecht G, et al. Sensory irritation of acetic acid, hydrogen peroxide, peroxyacetic acid and their mixture in mice. *Annals of Occupational Hygiene*. 2002;46(1):97-102.
39. Svrbely J, Dobrogorski O, and Stokinger H. Enhanced toxicity of ozone-hydrogen peroxide mixtures. *American Industrial Hygiene Association Journal*. 1961;22(1):21-26.
40. Oberst F, Comstock C, and Hackley E. Inhalation toxicity of ninety percent hydrogen peroxide vapor. *A.M.A. Archives of Industrial Health*. 1954;10(4):319-327.
41. Laskin DL, Morio L, Hooper K, et al. Peroxides and macrophages in the toxicity of fine particulate matter in rats. Section 3. Acute effects of inhaled (NH₄)₂SO₄ and H₂O₂ on lung tissues. Boston, MA: Health Effects Institute. 2003. Report No. 117. pp. 20-43.
42. Mensing T, Marek W, Raulf-Heimsoth M, et al. Acute exposure to hair bleach causes airway hyperresponsiveness in a rabbit model. *European Respiratory Journal*. 1998;12(6):1371-1374.
43. Chan H and Maibach H. Hydrogen peroxide, bleaching, and skin; an overview. *Cutaneous and Ocular Toxicology*. 2008;27(4):307-309.
44. Ernstgård L, Sjögren B, and Johanson G. Acute effects of exposure to vapors of hydrogen peroxide in humans. *Toxicology Letters*. 2012;212(2):222-227.
45. Hankin L. Hydrogen peroxide ingestion and the growth of rats. *Nature*. 1958;182(4647):1453
46. Kawasaki C, Kondo M, and Nagayama T. Effect of hydrogen peroxide on the growth of rats. *Food Hygiene and Safety Science (Shokuhin Eiseigaku Zasshi)*. 1969;10(2):68-72.
47. Shapiro M, Brat V, and Ershoff B. Induction of dental caries and pathological changes in periodontium of rat with hydrogen peroxide and other oxidizing agents. *Journal of Dental Research*. 1960;39(2):332-343.
48. Burnett C, Goldenthal E, Harris S, et al. Teratology and percutaneous toxicity studies on hair dyes. *Journal of Toxicology and Environmental Health, Part A Current Issues*. 1976;1(6):1027-1040.
49. Ito A, Watanabe H, Maito M, et al. Induction of duodenal tumors in mice by oral administration of hydrogen peroxide. *Gann Japanese Journal of Cancer Research*. 1981;72(1):174-175.
50. Ito A, Naito M, Maito Y, et al. Induction and characterization of gastro-duodenal lesions in mice given continuous oral administration of hydrogen peroxide. *Gann Japanese Journal of Cancer Research*. 1982;73(2):315-322.
51. Burnett C and Goldenthal E. Multigenerational reproduction and carcinogenicity studies in Sprague-Dawley rats exposed topically to oxidative hair-colouring formulations containing *p*-phenylenediamine and other aromatic amines. *Food and Chemical Toxicology*. 1988;26(5):267-274.
52. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Joint assessment of commodity chemicals no. 22; Hydrogen peroxide CAS No. 7722-84-1. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1992. pp. 1-150.
53. Abu-Shakra A and Zeiger E. Effects of Salmonella genotypes and testing protocols on H₂O₂-induced mutation. *Mutagenesis*. 1990;5(5):469-473.
54. Carlsson J, Berglin E, Claesson R, et al. Catalase inhibition by sulfide and hydrogen peroxide-induced mutagenicity in *Salmonella typhimurium* strain TA102. *Mutation Research*. 1988;202(1):59-64.
55. Glatt H. Mutagenicity spectra in *Salmonella typhimurium* strains of glutathione, L-cysteine and active oxygen species. *Mutagenesis*. 1989;4(3):221-227.
56. Kensese S and Smith L. Hydrogen peroxide mutagenicity towards *Salmonella typhimurium*. *Teratogenesis, Carcinogenesis, and Mutagenesis*. 2018;9(4):211-218.
57. Levin D, Hollstein M, Christman M, et al. A new *Salmonella* tester strain (TA102) with A-T base pairs at the site of mutation detects oxidative mutagens. *Proceedings of the National Academy of Sciences*. 1982;79(23):7445-7449.
58. Prival M, Simmon V, and Mortelmans K. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. *Mutation Research*. 1991;260(4):321-329.
59. De Flora S, Camoirano A, Zancacchi P, et al. Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other *Salmonella* strains. *Mutation Research*. 1984;134(2-3):159-165.
60. Rojanapo W, Kupradinun P, Tepsuwan A, et al. Carcinogenicity of an oxidation product of *p*-phenylenediamine. *Carcinogenesis*. 1986;7(12):1997-2002.

61. Wilcox P, Naidoo A, Wedd D, et al. Comparison of *Salmonella typhimurium* TA102 with *Escherichia coli* WP2 tester strains. *Mutagenesis*. 1990;5(3):285-291.
62. Martínez A, Urios A, and Blanco M. Mutagenicity of 80 chemicals in *Escherichia coli* tester strains IC203, deficient in OxyR, and its *oxyR*⁺ parents WP2 *uvrA*pKM101: detection of 31 oxidative mutagens. *Mutation Research*. 2000;467(1):41-53.
63. Mitchell IdG. A comparison of the sensitivity and specificity of microbial systems for assessing genetic damage. *Agents and Actions*. 1974;4(4):286-294.
64. Sacks L and MacGregor J. The *B. subtilis* multigene sporulation test for mutagens: detection of mutagens inactive in the somonella *his*. *Mutation Research*. 1982;95(2-3):191-202.
65. Thacker J and Parker W. The induction of mutation in yeast by hydrogen peroxide. *Mutation Research*. 1976;38(1):43-52.
66. Abril N and Pueyo C. Mutagenesis in *Escherichia coli* lacking catalase. *Environmental and Molecular Mutagenesis*. 1990;15(4):184-189.
67. Bosworth D, Crofton-Sleigh C, and Venitt S. A forward mutation assay using ampicillin-resistance in *Escherichia coli* designed for investigating the mutagenicity of biological samples. *Mutagenesis*. 1987;2(6):455-467.
68. Tsuda H. Chromosomal aberrations induced by hydrogen peroxide in cultured mammalian cells. *Japanese Journal of Genetics*. 1981;56(1):1-8.
69. Winquist L, Rannug U, Rannug A, et al. Protection from toxic and mutagenic effects of H₂O₂ by catalase induction in *Salmonella typhimurium*. *Mutation Research*. 1984;141(3-4):145-147.
70. Ruiz-Rubio M, Alejandre-Durán E, and Pueyo C. Oxidative mutagens specific for A • T base pairs induce forward mutations to L-arabinose resistance in *Slamonella typhimurium*. *Mutation Research*. 1985;147(4):153-163.
71. Ishidate Jr M, Sofuni T, Yoshikawa K, et al. Primary mutagenicity screening of food additives currently used in Japan. *Food and Chemical Toxicology*. 1984;22(8):623-636.
72. Dreosti I, Baghurst P, Partick E, et al. Induction of micronuclei in cultured murine splenocytes exposed to elevated levels of ferrous ions, hydrogen peroxide and ultraviolet irradiation. *Mutation Research*. 1990;244(4):337-343.
73. Tachon P and Giacomoni P. Histidine modulates the clastogenic effect of oxidative stress. *Mutation Research*. 1989;211(1):103-109.
74. Hikiba H, Watanabe E, Barrett J, et al. Ability of fourteen chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells. *Journal of Pharmacological Sciences*. 2005;97(1):146-152.
75. Oya Y, Yamamoto K, and Tomomura A. The biological activity of hydrogen peroxide. I. induction of chromosome-type aberrations susceptible to inhibition by scavengers of hydroxyl radicals in human embryonic fibroblasts. *Mutation Research*. 1986;172(3):245-253.
76. Wangenheim J and Bolcsfoldi G. Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. *Mutagenesis*. 1988;3(3):193-205.
77. Nassi-Calò L, Mello-Filho C, and Meneghini R. *o*-Phenanthroline protects mammalian cells from hydrogen peroxide-induced gene mutation and morphological transformation. *Carcinogenesis*. 1989;10(6):1055-1057.
78. Speit G. The relationship between the induction of SCEs and mutations in Chinese hamster cells. I. Experiments with hydrogen peroxide and caffeine. *Mutation Research Letters*. 1986;174(1):21-26.
79. Bradley M and Erickson L. Comparison of the effects of hydrogen peroxide and x-ray irradiation on toxicity, mutation, and DNA damage/repair in mammalian cells (V-79). *Biochimica et Biophysica Acta*. 1981;654(1):135-141.
80. Bradley M, Hsu I, and Harris C. Relationships between sister chromatid exchange and mutagenicity, toxicity and DNA damage. *Nature*. 1979;282(5736):318-320.
81. Mehnert K, Vogel W, Benz R, et al. Different effects of mutagens on sister chromatid exchange induction in three Chinese hamster cell lines. *Environmental Mutagenesis*. 1984;6(4):573-583.
82. Speit G, Vogel W, and Wolf M. Characterization of sister chromatid exchange induction by hydrogen peroxide. *Environmental Mutagenesis*. 1982;4(2):135-142.
83. MacRae W and Stich H. Induction of sister-chromatid exchanges in Chinese hamster ovary cells by thiol and hydrazine compounds. *Mutation Research*. 1979;68(4):351-365.
84. Mehnert K, Düring R, Vogel W, et al. Differences in the induction of SCEs between human whole blood cultures and purified lymphocyte cultures and the effect of an S9 mix. *Mutation Research*. 1984;130(6):403-410.
85. Tucker J, Taylor R, Christensen M, et al. Cytogenetic response to 1,2-dicarbonyls and hydrogen peroxide in Chinese hamster ovary AUXB1 cells and human peripheral lymphocytes. *Mutation Research*. 1989;224(2):269-279.

86. Wilmer J and Natarajan A. Induction of sister-chromatid exchanges and chromosome aberrations by γ -irradiated nucleic acid constituents in CHO cells. *Mutation Research*. 1981;88(4):99-107.
87. Ziegler-Skylakakis K and Andrae U. Mutagenicity of hydrogen peroxide in V79 Chinese hamster cells. *Mutation Research*. 1987;192(1):65-67.
88. Miyachi T and Tsutsui T. Ability of 13 chemical agents used in dental practice to induce sister-chromatid exchanges in Syrian hamster embryo cells. *Odontology*. 2005;93(1):24-29.
89. Estervig D and Wang R. Sister chromatid exchanges and chromosome aberrations in human cells induced by H₂O₂ and other photoproducts generated in fluorescent light-exposed medium. *Photochemistry and Photobiology*. 1984;40(3):333-336.
90. Brink A, Richter I, Lutz U, et al. Biological significance of DNA adducts: comparison of increments over background for various biomarkers of genotoxicity in L5178Y tk(+/-) mouse lymphoma cells treated with hydrogen peroxide and cumene hydroperoxide. *Mutation Research*. 2009;678(2):123-128.
91. Horváthová E, Eckl P, Bresgen N, et al. Evaluation of genotoxic and cytotoxic effects of H₂O₂ and DMNQ on freshly isolated rat hepatocytes; protective effects of carboxymethyl chitin-glucan. *Neuroendocrinology Letters*. 2008;29(5):644-648.
92. Rank J, Syberg K, and Jensen K. Comet assay on tetraploid yeast cells. *Mutation Research*. 2009;673(1):53-58.
93. Stang A and Witte I. Mutation research/genetic toxicology and environmental mutagenesis. *Mutation Research*. 2010;701(2):103-106.
94. Djuric Z, Everett C, and Luongo D. Toxicity, single-strand breaks, and 5-hydroxymethyl-2'-deoxyuridine formation in human breast epithelial cells treated with hydrogen peroxide. *Free Radical Biology & Medicine*. 1993;14(5):541-547.
95. Razo-Aguilera G, Baez-Reyes R, Álvarez-González L, et al. Inhibitory effect of grapefruit juice on the genotoxicity induced by hydrogen peroxide in human lymphocytes. *Food and Chemical Toxicology*. 2011;49(11):2947-2953.
96. Purschke M, Jacobi H, and Witte I. Differences in genotoxicity of H₂O₂ and tetrachlorohydroquinone in human fibroblasts. *Mutation Research*. 2002;513(1-2):159-167.
97. Pligina K, Ródina I, Shevchenko T, et al. DNA-damaging effects of dental bleaching agents. *Bulletin of Experimental Biology and Medicine-Pharmacology and Toxicology*. 2012;153(1):65-69.
98. Benhusein G, Mutch E, Aburawi S, et al. Genotoxic effect induced by hydrogen peroxide in human hepatoma cells using comet assay. *Libyan Journal of Medicine*. 2010;5(1):4637
99. de Oliveira P, Leandro L, Montanheiro G, et al. Baccharin prevents genotoxic effects induced by methyl methanesulfonate and hydrogen peroxide in V79 cells. *Journal of Food Science*. 2012;77(8):T138-T142.
100. Kimura A, Miyata A, and Honma M. A combination of *in vitro* comet assay and micronucleus test using human lymphoblastoid TK6 cells. *Mutagenesis*. 2013;28(5):583-590.
101. Rezende M, DeGeus J, Loguercio A, et al. Clinical evaluation of genotoxicity of in-office bleaching. *Operative Dentistry*. 2016;41(6):578-586.
102. Turanitz K, Kovac R, Tuschl H, et al. Investigations on the effect of repeated hair dyeing on sister chromatid exchanges. *Food and Chemical Toxicology*. 1983;21(6):791-793.
103. Burnett C, Lanman B, Biovacchini R, et al. Long-term toxicity studies on oxidation hair dyes. *Food and Chemical Toxicology*. 1975;13(3):353-357.
104. Kinkel H and Holzmann S. Study of long-term percutaneous toxicity and carcinogenicity of hair dyes (oxidizing dyes) in rats. *Food and Cosmetic Toxicology*. 1973;11(4):641-648.
105. Klein-Szanto A and Slaga T. Effects of peroxides on rodent skin: Epidermal Hyperplasia and tumor promotion. *Journal of Investigative Dermatology*. 1982;79(1):30-34.
106. Marshall M, Kuhn J, Torrey C, et al. Hamster cheek pouch bioassay of dentifrices containing hydrogen peroxide and baking soda. *Journal of the American College of Toxicology*. 1996;15(1):45-61.
107. International Agency for Research on Cancer (IARC). Hydrogen peroxide. In: *IARC Monographs on the Evaluations of Carcinogenic Risks to Humans; Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. Vol. 71. WHO Press; 1999:671-689.
108. Bock F, Myers H, and Fox H. Cocarcinogenic activity of peroxy compounds. *Journal of the National Cancer Institute*. 1975;55(6):1359-1361.
109. Takahashi, M, Hasegawa, R, Furukawa, F, Toyoda, K, Sato, H, and Hayashi, Y. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *Japanese Journal of Cancer Research*. 1986. 77:(2): pp.118-24.

110. Padma P, Lalitha V, Amonkar A, et al. Carcinogenicity studies on the two tobacco-specific *N*-nitrosamine, *N'*-nitrososornicotine and 4-(methylnitrosamino)-1(3-pyridyl)-1-butanone. *Carcinogenesis*. 1997;10(11):1997-2002.
111. Seo J-A, Bae I-H, Jang W-H, et al. Hydrogen peroxide and monoethanolamine are the key causative ingredients for hair dye-induced dermatitis and hair loss. *Journal of Dermatological Science*. 2012;66(1):12-19.
112. Iwamoto S, Nakayama H, Yasoshima A, et al. Hydrogen peroxide-induced dermatitis in WBN/Kob-Ht rats. *Experimental Animals*. 1997;46(2):147-151.
113. Deutsche Forschungsgemeinschaft (DFG). The MAK-Collection Part I: MAK Value Documentations. Weinheim, Germany: WILEY-VCH Verlag GmbH & Co., 2011.
114. Deutsche Forschungsgemeinschaft (DFG). Establishment of MAK Values. http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/structure/working_groups/derivation_mak/index.html. Last Updated 2018. Date Accessed 10-15-2018.
115. Donahue D, Avalos J, Kaufman L, et al. Ocular irritation reversibility assessment for personal care products using a porcine corneal culture assay. *Toxicology in Vitro*. 2011;25(3):708-714.
116. Grant, M and Schuman JS. Toxicology of the eye: Effects on the eyes and visual system from chemicals, drugs, metals and minerals, plants, toxins, and venoms; Also, systemic side effects from eye medications. 4 ed. Springfield, IL: Charles C. Thomas, 1993.
117. Maurer J, Malai A, Parker R, et al. Pathology of ocular irritation with bleaching agents in Rabbit; Low-volume eye test. *Toxicological Pathology*. 2001;29(3):308-319.
118. McNally J. Clinical aspects of topical application of dilute hydrogen peroxide solution. *CLAO Journal*. 1990;16(1):S46-S52.
119. Rotstein I, Wesselink P, and Bab I. Catalase protection against hydrogen peroxide-induced injury in rat oral mucosa. *Oral Surgery Oral Medicine ORal Pathology*. 1993;75(6):744-750.
120. Carl, W, Daly, C, Andreana, S, Ciancio, S, Cohen, RE, and Nisengard, RJ. Article Summary: Clinical evaluation of the effect of a hydrogen peroxide mouth rinse, Toothette-Plus® swab containing sodium bicarbonate, and a water-based mouth moisturizer on oral health in medically compromised patients. *Periodontal Insights*. 1999. pp.1-1.
121. Niwano Y, Konno K, Matayoshi T, et al. Oral mucosal irritation study in hamster to evaluate a therapeutic apparatus using hydrogen peroxide photolysis for periodontitis treatment. *Regulatory Toxicology and Pharmacology*. 2017;90(Nov):206-213.
122. Wang M, Farmer S, Richardson D, et al. Patch-testing with hairdressing chemicals. *Dermatitis*. 2011;22(1):16-26.
123. Kiec-Swierczynska M, Krecisz B, and Chomiczewska D. Results of patch test in hairdressers examined in the Institute of Occupational Medicine in Lodz. *Medycyna, Pracy*. 2009;60(6):459-467.
124. Kanerva L, Jolanki R, Riihimäki V, et al. Patch test reactions and occupational dermatoses caused by hydrogen peroxide. *Contact Dermatitis*. 1998;39(3):146
125. Leino T, Estlander T, and Kanerva L. Occupational allergic dermatoses in hairdressers. *Contact Dermatitis*. 1998;38(3):166-167.
126. Aclaris Therapeutics, Inc. ESKATA™ (hydrogen peroxide) topical solution; Initial U.S. Approval: 2017 [pamphlet]. Blairstown, NJ: James Alexander Corp.; 2017.
127. Farrell S, Barker M, McMillan D, et al. Placebo-controlled trial evaluating safety with 12-month continuous use of 6% hydrogen peroxide whitening strips. *Journal of Dentistry*. 2008;36(9):726-730.
128. Gerlach R, Barker M, Karpinia K, et al. Single site meta-analysis of 6% hydrogen peroxide whitening strip effectiveness and safety over 2 weeks. *Journal of Dentistry*. 2009;37(5):360-365.
129. Tombes, MB and Gallucci, B. The effects of hydrogen peroxide on the normal oral mucosa. *Nursing Research*. 1993. 42:(6): pp.332-337.
130. Leino T, Tammilehto L, Hytönen M, et al. Occupational skin and respiratory diseases among hairdressers. *Scandinavian Journal of Work, Environment & Health*. 1998;24(5):398-406.
131. Lyons G, Roberst H, Palmer A, et al. Hairdressers presenting to an occupational dermatology clinic in Melbourne, Australia. *Contact Dermatitis*. 2012;68(5):300-306.
132. Tresukosol P and Swasdivanich C. Hand contact dermatitis in hairdressers: clinical and casuative allergens, experience in Bangkok. *Journal of Allergy and Immunology*. 2012;701(2):103-106.
133. National Institute for Occupational Safety and Health. Dangerous to life or health (IDLH) values table of IDLH values. Washington, DC: 2014. <http://www.cdc.gov/niosh/idlh/772841.html>. Date Accessed 11-3-2017.

134. Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation of the Scientific Committee on Occupational Exposure Limits for hydrogen peroxide. <https://www.ser.nl/documents/43426.pdf>. Brussels, Belgium. Last Updated 2008. Date Accessed 1-25-2018.
135. Hofer H, Bornatowicz N, and Reindl E. Analysis of human chromosomes after repeated hair dyeing. *Food and Chemical Toxicology*. 1983;21(6):785-789.
136. International Agency for Research on Cancer (IARC). Hydrogen peroxide. Vol. 71. World Health Organization; 2015:671-689.
137. National Institute for Occupational Safety and Health (NIOSH). NIOSH International Chemical Safety Cards (ICSC); Hydrogen peroxide (>60% solution in water) [pamphlet]. Atlanta, GA: U.S. Department of Health & Human Services; 2014.
138. Shih S-Y and Lai C-C. Dermal injury caused by hydrogen peroxide. *Journal of Emergency Medicine*. 2017;53(6):e141-e142.
139. Cina S, Downs J, and Conradi S. Hydrogen peroxide: A source of lethal oxygen embolism. *The American Journal of Forensic Medicine and Pathology*. 1994;15(1):44-50.
140. Henry M, Wheeler J, mofenson H, et al. Hydrogen peroxide 3% exposures. *Journal of Clinical Toxicology*. 1996;34(3):323-327.
141. Arnfield E, Bhardwaj H, Brown N, et al. Hydrogen peroxide poisoning: an unusual cause of portal venous gas. *BJR Case Report*. 2016;2(1):2015283
142. Moon J, Chun B, and Min Y. Hemorrhagic gastritis and gas emboli after ingesting hydrogen peroxide. *Journal of Emergency Medicine*. 2005;30(4):403-406.
143. Mihál V, Klásková E, and Karásková E. Vzduchová embolie v portálním recisti po náhodném pozití koncentrovaného peroxidu vodíku. *Pediatric Pro Praxi*. 2017;18(3):192-194.
144. Christensen D, Faught W, Black R, et al. Fatal oxygen embolization after hydrogen peroxide ingestion. *Critical Care Medicine*. 1992;20(4):543-544.
145. Giberson T, Kern J, Pettigrew III D, et al. Near-fatal hydrogen peroxide ingestion. *Annals of Emergency Medicine*. 1989;18(7):778-779.
146. Ijichi T, Itoh T, Sakai R, et al. Multiple brain gas embolism after ingestion of concentrated hydrogen peroxide. *American Academy of Neurology*. 1997;48(1):277-279.
147. Sherman S, Boyer L, and Sibley W. Cerebral infarction immediately after ingestion of hydrogen peroxide solution. *Stroke*. 1994;25(5):1065-1067.
148. Afzal M, Dar S, Sarwar T, et al. An ingestion of industrial strength hydrogen peroxide resulting in cerebral embolism and death. *American Journal of Medical Case Report*. 2017;5(9):234-236.
149. Shetty K. Hydrogen peroxide burn of the oral mucosa. *Annals of Pharmacotherapy*. 2006;40(2):351
150. Knopf H. Reaction to hydrogen peroxide in a contact-lens wearer. *American Journal of Ophthalmology*. 1984;97(6):796
151. Kaelin R, Kapanci Y, and Tschopp J. Diffuse interstitial lung disease associated with hydrogen peroxide inhalation in a dairy worker. *American Review of Respiratory Disease*. 1988;137(5):1233-1235.
152. Riihimäki V, Toppila A, Pirrila A, et al. Respiratory health in aseptic packaging with hydrogen peroxide. A report of two cases. *Journal or Occupational Health*. 2002;44(6):433-438.
153. Domaç F, Koçer A, and Tanidir R. Optic neuropathy related to hydrogen peroxide inhalation. *Clinical Neuropharmacology*. 2007;30(1):55-57.
154. Bassan M, Dudai M, and Shalev O. Near-fatal systemic oxygen embolism due to wound irrigation with hydrogen peroxide. *Postgraduate Medical Journal*. 1982;58(July):488-450.