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Review

Evaluation of the health aspects of methyl paraben: a review of the published literature

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Abstract

Methyl paraben (CAS No. 99-76-3) is a methyl ester of *p*-hydroxybenzoic acid. It is a stable, non-volatile compound used as an antimicrobial preservative in foods, drugs and cosmetics for over 50 years. Methyl paraben is readily and completely absorbed through the skin and from the gastrointestinal tract. It is hydrolyzed to *p*-hydroxybenzoic acid, conjugated, and the conjugates are rapidly excreted in the urine. There is no evidence of accumulation. Acute toxicity studies in animals indicate that methyl paraben is practically non-toxic by both oral and parenteral routes. In a population with normal skin, methyl paraben is practically non-irritating and non-sensitizing. In chronic administration studies, no-observed-effect levels (NOEL) as high as 1050 mg/kg have been reported and a no-observed-adverse-effect level (NOAEL) in the rat of 5700 mg/kg is posited. Methyl paraben is not carcinogenic or mutagenic. It is not teratogenic or embryotoxic and is negative in the uterotrophic assay. The mechanism of cytotoxic action of parabens may be linked to mitochondrial failure dependent on induction of membrane permeability transition accompanied by the mitochondrial depolarization and depletion of cellular ATP through uncoupling of oxidative phosphorylation. Parabens are reported to cause contact dermatitis reactions in some individuals on cutaneousl exposure. Parabens have been implicated in numerous cases of contact sensitivity associated with cutaneous exposure; however, the mechanism of this sensitivity is unknown. Sensitization has occurred when medications containing parabens have been applied to damaged or broken skin. Allergic reactions to ingested parabens have been reported, although rigorous evidence of the allergenicity of ingested paraben is lacking.

Keywords: Methyl paraben; Preservative; Food ingredient; Food additive; Cosmetic; Drug; Excipient; Antimicrobial; Safety

Contents

Abbreviations: Ach, acetylcholine; ADI, acceptable daily intake; CAM, chorioallantoic membrane; CAM–TB, CAM–trypan blue staining; CVS, crystal violet staining; DBP, dibenzo[*a,i*]pyrene; DNCB, dinitrochlorobenzene; DRG, dorsal root ganglion; FEMA, Flavor and Extract Manufacturers' Association; GRAS, generally recognized as safe; 2HBC, 2-hydroxypropyl-β-cyclodextrin; HET–CAM, hen's egg test–CAM; LISS, low-ionic-strength salt; LPS, lipopolysaccharide; MIC, minimum inhibitory concentration; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; NRU, neutral red uptake; OTC, over-the-counter; PADI, possible average daily intake; PCB, polychlorinated biphenyls; PII, primary irritation index; RIPT, repeated insult patch test; SCOGS, Select Committee on GRAS Substances; SLS, sodium lauryl sulfate; SRBC, anti-sheep red blood cell.

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1. Introduction

Methyl paraben (Fig. 1) is one of a homologous series of parabens (including methyl, ethyl, butyl, heptyl and benzyl parabens), used singly or in combination to exert the intended antimicrobial affect. Parabens are particularly useful against molds and yeasts. These substances can have multiple biological effects, but it is generally considered that their inhibitory effects on membrane transport and mitochondrial function processes are key for their actions. The parabens meet several of the criteria of an ideal preservative, in that they have a broad spectrum

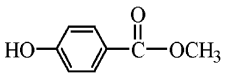

Fig. 1. Structure of methyl paraben.

of antimicrobial activity, are safe to use (i.e. relatively non-irritating, non-sensitizing, and of low toxicity), are stable over the pH range, and are sufficiently soluble in water to produce the effective concentration in aqueous phase. Antimicrobial activity of paraben increases as the chain length of the ester group increases, but since solubility decreases with increasing chain length, the lower esters (methyl and propyl) are the practical choices for use in foods. Methyl paraben has been used as an antimicrobial preservative in foods, drugs and cosmetics for over 50 years. There have been several previous safety assessments undertaken on this substance by several agencies, including FAO/WHO, FDA and FEMA. The purpose of this review is to examine the scientific literature describing the safety of methyl paraben in order to set an acceptable daily intake (AID).

1.1. Description, specification, occurrence and sources

Pure methyl paraben is a colorless crystalline or white powder. It is odorless or has a faint characteristic odor and a slight burning taste. Methyl paraben is resistant to hydrolysis in hot and cold water but hydrolyzes in alkaline solutions. It is stable in air. Aqueous solutions of methyl paraben buffered at pH 3 and 6 showed no decomposition when heated for 2 h at 100 °C or for 30 min at 120 °C.

Methyl paraben is an ester of *p*-hydroxybenzoic acid. It is produced by the methanol esterification of *p*-hydroxybenzoic acid in the presence of sulfuric acid. The materials are heated for distillation in a glass-lined reactor under reflux. The acid is then neutralized with caustic soda and the product is crystallized by cooling. The crystallized product is centrifuged, washed, dried under vacuum, milled and blended, all in corrosion-resistant equipment to avoid metallic contamination. Some published specifications for methyl paraben are summarized in Table 1.

Aqueous solutions of methyl paraben, at pH 36, may be sterilized by autoclaving at 120 °C for 20 min, without decomposition (Kibbe, 2000; Raval and Parrott, 1967). Aqueous solutions at pH 3–6 are stable (less than 10% decomposition) for up to about 4 years at room temperature. Aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days of storage at room temperature). McCarthy (1970) reported that storage of methyl paraben (0.1%) in polyethylene bottles or in rigid polyvinyl chloride containers at 25 °C for 12 weeks did not result in any loss of methyl paraben.

Natural occurrence of methyl paraben has been reported in cloudberry, yellow passion fruit juice, white wine, botrytised wine and Bourbon vanilla. The amount of methyl paraben detected in cloudberry is around 0.15 ppm (TNO, 2000). Goodwin et al. (1979) identified methyl paraben as a component of vaginal secretions of female dogs in estrus. Analysis of secretions at other points of their estrous cycle revealed no presence of methyl paraben. The authors of this study suggested that methyl paraben is a sex pheromone of dogs.

1.2. Economic uses

Methyl paraben is widely used as an antimicrobial preservative in cosmetics, food products and pharmaceutical formulations. It may be used either alone, in combination with other parabens, or with other antimicrobial agents. In cosmetics, methyl paraben is the most frequently used antimicrobial preservative (Decker and Wenninger, 1987).

Table 1
Methyl paraben specifications (published values)

	SCOGS[a] (1972)	Burdock (1997)	Elder (1984)	FCC[b] (1996)
Physical form	Small crystals or white powder	White needles	Colorless crystals	Small crystals
Odor	Faint, characteristic	Odorless	No odor	Faint, characteristic
Solubility	0.25 g/100 ml water at 25 °C	Slightly soluble	Slightly soluble	1 g/400 ml water at 25 °C
Melting point (°C)	125–128	131	131	125–128
Molecular weight	152.14	152.15	152.16	152.15
Inorganic impurities				
Arsenic	3 ppm	–	1 ppm	–
Heavy metals (Pb)	10 ppm	–	10 ppm	10 mg/kg
Residue on ignition	0.05%	–	−0.05%	0.05%

[a] SCOGS, Subcommittee on GRAS Substances.
[b] FCC, Food Chemical Codex.

1.3. Cosmetic uses

Parabens are widely used cosmetic preservatives present in a large variety of products, including face, body and hand creams, lotions and moisturizers; eye makeup products; foundation and other makeup products; night creams and lotions; cleansing products; hair conditioners; bubble baths; shampoos; mud packs; underarm deodorants; skin lighteners; and sachets (Nikitakis, 1988). Methyl paraben and propyl paraben are the most commonly used preservatives in cosmetics (Berke et al., 1982; Gruvberger et al., 1998; Soni et al., 2001). Parabens are found in all types of formulations and have a use in over 13,200 formulations (Elder, 1984). Concentrations of parabens are usually less than 0.3%, with the most common preservative system containing 0.3% methyl paraben and 0.1% propyl paraben but may range up to 1%. Parabens formulate well because they have no perceptible odor or taste, are practically neutral, do not produce discoloration, and do not cause hardening or "muddying" (Neidig and Burrell, 1944).

The popular use of paraben preservatives in cosmetics and toiletries arises from their low toxicity, broad spectrum of activity, worldwide regulatory acceptance, biodegradability, and low cost. Moreover, parabens have excellent chemical stability in relation to pH (effective between pH 4.5 and 7.5) and temperature (Blaug and Grant, 1974; Alexander et al., 1978). Consequently, products containing parabens can be autoclaved safely without significant loss of antimicrobial activity from hydrolysis (Maddox, 1982). Other advantages of parabens are found in their low tendency towards absorption in commonly used plastics of primary packaging material. The percent decomposition of a methyl paraben solution in an autoclave for 30 min at pH 6 and 9 was 5.5 and 49% of the initial concentration, respectively. Sunderland and Watts (1984) reported that the time taken for a 10% loss of the initial methyl ester concentration at 130.5 °C and pHs of 10.59, 8.9 and 6.58 are approximately 4 s, 3 min and 40 min, respectively. This ester is therefore unable to adequately withstand a normal sterilization procedure unless the solution is within a pH range of 3–6 at the sterilization temperature.

As the carbon number of the alkyl chain of parabens increases, antimicrobial activity increases, but water solubility decreases and oil solubility increases. Since microbial replication generally occurs in the water phase of oil/water bases, the amount of paraben dissolved in the water phase generally determines the preservative efficiency. Taking advantage of each paraben's solubility characteristics, various concentrations of methyl paraben and propyl paraben can be added to the base's water and oil phases, respectively. These favorable characteristics make the combination of methyl paraben and propyl paraben the most frequently used preservative system (Jackson, 1992; Soni et al., 2001).

Chemburkar and Jostlin (1975) studied the partitioning of parabens, including methyl paraben, in flavoring oils from aqueous systems. The partitioning was dependent on the concentration of flavoring oil, the pH of the aqueous medium, and the nature and concentration of additives to the aqueous medium.

According to the industry's voluntary submissions to the FDA in 1981, the number of product formulations and maximum use concentrations for methyl paraben was 6606 and 25%, respectively (FDA, 1981). Commonly, formulations contain parabens in concentrations up to 1%. Methyl paraben individually or with other parabens is used in all 13 product formulation categories. Products containing these ingredients may contact the skin, hair and scalp, lips, mucosae (oral, ocular and vaginal), axillae and nails. Products containing parabens may be used on an occasional or daily basis and their use may extend over a period of years. Frequency of application and duration of exposure may be continuous. Methyl paraben is the most used preservative in cosmetics (Mowad, 2000).

Rastogi et al. (1995) determined the contents of parabens in cosmetic products to elucidate the concentration and frequency of use of different parabens to monitor whether the products complied with the Danish and EEC regulations. In an investigation of 215 cosmetic products, a maximum of 0.32% methyl paraben was present in paraben positive cosmetics. Of all paraben-containing cosmetics tested, 98% contained methyl paraben. A preferential use of methyl→ethyl→propyl→butyl→benzyl paraben in various groups of cosmetic products was reported.

1.4. Uses in food

Because of their low toxicity and effective antimicrobial activity, parabens, including methyl paraben, have been used in food for more than 50 years. Under FDA regulation, methyl paraben is generally recognized as safe (GRAS) when used as chemical preservative in foods, with a use limit of 0.1% (21 CFR 184.1490; Table 2). Types of food that may contain parabens include alcoholic beverages, frozen dairy products, gelatins, grain products, jams, jellies, marmalades, mincemeat, olives, pickles, relishes, preserves, processed fruits and vegetables, tomato pulp, tomato puree, catsup, fruit juices, soft drinks, puddings, seasonings, soft candy, sugar substitutes, syrups and sweet sauces (Smolinske, 1992). Parabens are used in coffee extracts, fruit juices, pickles, sauces, soft drinks, processed vegetables, baked goods, seasonings, sugar substitutes and frozen dairy products at concentrations of between 450 and 2000 ppm (Daniel, 1986). In a

Table 2
CFR and FEMA[a] approved methyl paraben uses

Source	Citation number	Food category	Permitted functionality	Use limits
FDA	21 CFR 150.141 Food Standards. Artificially sweetened fruit jelly. Optional ingredient	Artificially sweetened fruit jelly	Preservative	Not to exceed 0.1%
FDA	21 CFR 150.161 Food Standards. Artificially sweetened fruit jams. Optional ingredient	Artificially sweetened fruit preserves and jams	Preservative	Not to exceed 0.1%
FDA	21 CFR 172.515 Food additives. Permitted for direct addition to agents and food for human consumption. Subpart F- Flavoring agents and related substances. Synthetic flavoring substances and adjuvants	No restriction	(12) Flavoring agents and adjuvants	CGMP[a]
FDA	21 CFR 181.23 Prior sanctioned ingredients. Certain substances employed in the manufacture of food-packaging materials. Antimycotics	No restriction	(2) Antimicrobial	CGMP[a]
FDA	21 CFR 184.1490 Direct food substances affirmed GRAS.	No restriction	(2) Antimicrobial agent	CGMP[b] 0.1%
FEMA	FEMA GRAS No. 2710		Preservative	0.1%

[a] FEMA, Flavor and Extract Manufacturers' Association.
[b] CGMP, current good manufacturing practice.

LSRO/FASEB (1972) report it is stated that methyl paraben is not reported to be used in fats and oils, processed fruits, or alcoholic beverages. Higuera-Ciapara and Nieblas (1995) reported the use of hydrogen peroxide-methyl paraben for preservation and stability of corn tortillas held at room temperature.

Methyl paraben is also permitted for use in certain standardized foods including artificially sweetened fruit jelly (21 CFR 150.141) and artificially sweetened fruit preserves and jams (21 CFR 150.161) at a level not to exceed 0.1% by weight of the finished food. Methyl paraben, propyl paraben and butyl paraben are permitted as direct food additives for use in synthetic flavoring substances and adjuvants in the minimum quantities required to produce their intended effects (21 CFR 172.515). As indirect food additives, methyl paraben and propyl paraben are permitted by prior sanction as antimycotics in food packaging materials with no limit or restriction (21 CFR 181.23).

1.5. Pharmaceutical uses

Parabens have a long history of use in drug products. They were first employed as preservatives in pharmaceutical products in the mid-1920s (Sabalitschka, 1930). Parabens have been incorporated as preservatives in a variety of drug formulations. Combinations of parabens are more active than individual parabens (Boehm and Maddox, 1972). Parabens are or have been used in suppositories, anesthetics, eyewashes, pills, syrups, weight gaining solutions, injectable solutions, and contraceptives. Use concentration varies from product to product but seldom exceeds 1% (Neidig and Burrell, 1944; Hassler, 1954; Boehm and Maddox, 1972; Orth, 1980a). Methyl paraben is used in injections (0.065–0.25%), ophthalmic preparations (0.015–0.05%), oral solutions and suspensions (0.015–0.2%), topical preparations (0.02–0.3%) and vaginal preparations (0.1–0.18%) (Anonymous, 1998). Golomb and Shipigelman (1991) described the advantages of using parabens, which make them suitable for imparting antibacterial properties to implanted biomaterials.

Methyl paraben and propyl paraben are used in a number of over-the-counter (OTC) drugs (21 CFR 310.545). The Ophthalmic Drug Panel of FDA's Bureau of Drugs has determined that these two ingredients, if used alone, are unsuitable as preservatives in OTC ophthalmic products because they are irritating to eyes if used at concentrations effective against micro-organisms. However, eye irritation by parabens could not be confirmed by the references cited in the OTC ophthalmic report. It was suggested that further formulation studies and safety testing be done on these two ingredients (FDA, 1980a). Other OTC panels have concluded that methyl paraben is a safe and effective preservative in concentrations of 0.1–0.2% in products for anorectal application and other antimicrobial uses (FDA, 1978, 1980a,b).

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