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Final Report on the Safety Assessment of Benzophenones-1, -3, -4, -5, -9, and -11

Benzophenones-1 to -12 are substituted derivatives of 2-hydroxybenzophenone. They are used as photostabilizers in cosmetics and have a photoprotective effect on the skin.

When ingested and absorbed, Benzophenones were primarily conjugated and excreted in the urine. Benzophenones were practically nontoxic when chronically administered orally to rats, and Benzophenones-3 and -4 were nontoxic when applied to the skin of rabbits at doses of > 5 g/kg. Subchronic oral ingestion of Benzophenone-3 at 1% was nontoxic to rats; however, another study showed Benzophenone-3 at 0.5% was toxic. Benzophenone-1 elicited toxic effects in rats at 0.6 g/kg.

Benzophenones were nonirritating or mildly irritating to rabbit skin at concentrations of up to 100% and practically nonirritating to the eyes of rabbits. A subchronic skin irritation test indicated that Benzophenone-4 was capable of causing minimal irritation in rabbits at a concentration of 10%. Benzophenone-3 was reported to be nonsensitizing and nonphototoxic in guinea pigs and rabbits.

Benzophenones-1, -3, -4, -5, and -9 were nonmutagenic both with and without metabolic activation in the Ames test.

Skin irritation and sensitization in humans indicated that Benzophenones were mildly irritating and sensitizing at concentrations greater than those used in cosmetics.

On the basis of the available animal data and clinical human experience, it is concluded that Benzophenone-1, -3, -4, -5, -9, and -11 are safe for topical application to humans in the present practices of use and concentration in cosmetics.

INTRODUCTION

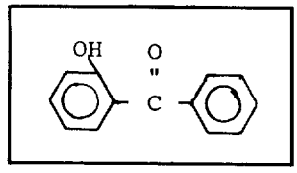
This document reviews the published and unpublished information on Benzophenones-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, and -12. On the basis of

the information within this report, a safety assessment has been made concerning Benzophenones-1, -3, -4, -5, -9, and -11. Relevant chemical, use, toxicological, and clinical data on the other Benzophenones have been included. Benzophenones-7, -10, and -12 are not used in cosmetics; therefore, a safety recommendation is not included on these three ingredients. A separate determination of safety was made for Benzophenones-2, -6, and -8.

CHEMISTRY

General Structure

Benzophenones-1 to -12 are substituted derivatives of 2-hydroxybenzophenone, which conforms to the structure:



Substituents include hydroxy, methoxy, octyloxy, sulfonyl, methyl, and chloride groups. Benzophenones* may be mono- di-, tri-, or tetra-substituted.

Among the many preparative methods for individual Benzophenones, the most common is the Friedel–Crafts reaction.[1-4]

Benzophenones-3, -6, and -8 are components of and can be extracted from certain flower pigments.[5]

General Properties

The most important property of the Benzophenones is their ability to absorb and dissipate ultraviolet (UV) radiation. When UV light passes through a Benzophenone solution, certain frequencies or wavelengths are selectively absorbed. Electromagnetic energy is transferred to the Benzophenone molecule; as a result, outer electrons are promoted from their lowest-energy ground state to higher-energy excited states. Since only certain states are possible in any given molecule, and since the energy difference between any ground state and excited state must equal the energy added by the quantum, only certain frequencies of radiation can be absorbed by a particular Benzophenone. Excited molecules are relatively short-lived and tend to return to their ground states after approximately

*Throughout this report the term "Benzophenone(s)" is used although all compounds reviewed are 2-hydroxybenzophenones.

10^{-8} seconds. Under usual circumstances, the excited molecule loses its energy and returns to the ground state through a series of collisions with other molecules in the system; the net effect of this process is that the absorbed energy is converted to heat. If an excited molecule is slow to lose its excess energy through collision, it may return to the ground state by emitting radiation of lower frequency than the absorbed radiation. The net effect of this process is fluorescence. Benzophenones are used to protect photodegradable compounds. The Benzophenones form intermolecular hydrogen bonds with the photodegradable molecules; these bonds serve as bridges to transfer energy from the electronically excited, vulnerable molecules to the Benzophenone molecule.[6-8]

In a study that determined the effect of substituent addition and substitution on the photostabilizing property of Benzophenones, alkylation of the hydroxyl group at the para position reduced the photostabilizing potential of the molecule. Addition of a methoxy group to the second benzene nucleus also reduced the molecule's photoprotecting effect.[9]

Most Benzophenones are solid at room temperature, soluble in organic solvents, and insoluble in water.

General Reactions

Owing to the variety of substituents in these ingredients, many Benzophenone derivatives can be prepared. Benzophenones can undergo etherification and reactions typical of ketones. Via the Grignard reaction, alcohols can be prepared from Benzophenones.[10] Benzophenones can take part in photopinacolization reactions in which a reduction of two ketones produces a bond between the carbons.[11] Benzophenones are reduced by sodium hydroborates.[12]

Although Benzophenones are frequently incorporated into plastics and films, normally they do not react with the polymer itself. However, Kamogawa[13] described an acid-catalyzed reaction between N-(hydroxymethyl)-acrylamide and Benzophenones. The resulting product was a polymeric phenolic UV absorber.

General Analysis

Thin-layer chromatography and gas chromatography are frequently employed to determine the Benzophenone content in plastics, polymers, and films.[14-21] Spectroscopic methods including mass spectroscopy, spectrofluorometry, phosphorimetry, nuclear magnetic resonance (NMR), and infrared (IR) spectroscopy are also used to identify Benzophenones.[22-27]

Since 1978, reverse phase high performance liquid chromotography (HPLC) has been recommended for the analysis of Benzophenones. In the case of the Benzophenone sulfonic acids (Benzophenone-4, -5, and -9), a μ Bondapak CN column and water-methanol (95:5) mobile phase are used; in the case of the other Benzophenones, a μ Bondapak C_{18} column and a water-methanol (40:60) plus 1 to 2 volumes acetic acid mobile phase are used.[28]

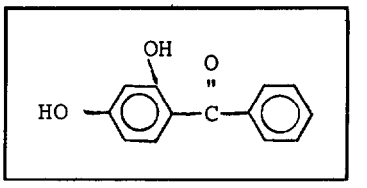
Infrared spectra for the individual Benzophenones have been reported by CTFA.[29]

Individual Benzophenone Ingredients

Benzophenone-1

Structure

Benzophenone-1 is a dihydroxy Benzophenone conforming to the structure:[3]



Other names include:

2,4-Dihydroxybenzophenone
Benzoresorcinol
4-Benzoyl Resorcinol
(2,4-Dihydroxyphenyl) phenylmethanone
Resbenzophenone

Three methods of Benzophenone-1 preparation from resorcinol are reported. Stephen[30] and Zilberman and Rybakova[31] prepared Benzophenone-1 from the Hoesch reaction of resorcinol and either a substituted imido chloride (to form an imido-ester intermediate) or a corresponding aromatic nitrile and a metal halide catalyst. Shaw and Mehta[32] described the condensation of benzamide with resorcinol in the presence of phosphorous oxychloride and zinc chloride to Benzophenone-1. Additionally, Benzophenone-1 can be prepared in low yield by the Fries rearrangement from phenyl-2-methoxy-benzoate.[1]

Properties

Benzophenone-1 (MW 214.21) is a light-yellow powder with a melting point of 144°C. It is soluble in methanol, ethanol, ethyl acetate, methyl ethyl ketone, acetone, ether, and acetic acid; slightly soluble in benzene; and insoluble in water.[3,29] Tables 1 and 2 describe other physical and chemical data for this compound.

Reactivity

Benzophenone-1 reacts with a variety of organic and inorganic compounds. Head[33] reported an etherification of the 4-hydroxy group of Benzophenone-1 to 4-(β-aryioxymethyl), 4-(β-arylethoxymethyl), and 4-[β-(aryloxymethoxy)ethyl] derivatives. In the presence of bromide, phenyl nitrate, or nitric acid, Benzophenone-1 can react to form a number of bromo-and nitrobenzenes.[34] Benzophenone-1 and methyl acrylate can combine to form a product that can polymerize with other compounds to form a photostable polymer.[35] Benzophenone-1 is highly reactive with diphenylpicrylhydrazyl.[36]

TABLE 1. Chemical and Physical Properties.[a]

Ingredient	Specific gravity (at 25°C)	pH (10%/25°C)	Moisture (% max.)	Impurities (ppm max.) Pb	As
Benzophenone-1	1.2743	2.0–3.0	2	18	1
Benzophenone-2	–[b]	4.0	5.0	8	1
Benzophenone-3	–	–	2	13	1
Benzophenone-4	–	2.0 (1%)	10–16 (trihydrate)	18	1
Benzophenone-6	1.3448	4.0–5.0	0.5	13	1
Benzophenone-8	–	–	2	–	–
Benzophenone-9	–	6.8–7.2	5.0	8	1
Benzophenone-11	1.3843	3.0–4.0	5.0	13	1

[a]Data from Refs. 3, 6, and 29.
[b]No data available.

Impurities

The maximum recommended levels of arsenic and lead in Benzophenone-1 are reported in Table 1.[3]

Benzophenone-2

Structure

Benzophenone-2 is a tetrahydroxy-substituted derivative of Benzophenone conforming to the structure:[3]

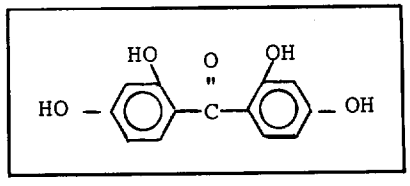


TABLE 2. UV Absorption Spectra Data for Benzophenones.

Benzophenone	λ max (nm)	log ε	λ max (nm)	log ε	λ max (nm)	log ε	Ref.
–1	242	3.94	290	3.96	338	4.12	37
–2	242	3.80	283	3.96	352	4.17	37
–3	–	–	289	4.13	322	3.96	37
–4	242	4.11[a]	288	4.14[a]	333	3.92[a]	38
–6	–	–	281	4.11	339	4.12	3,29
–8	242	4.18[b]	285	4.31[b]	330	4.18[b]	38
–9	–	–	284	3.85	333	–	3,29
–10	250	3.89	300	4.27	–	–	37
–11	–	–	285	4.10	341	4.12[c]	3,29

[a]Assuming cell path length = 1 cm.
[b]Assuming cell path length = 10 cm.
[c]Assuming average molecular wt. of BP-11 is approx. that of BP-6.

Other names include:

2,2', 4, 4'-Tetrahydroxybenzophenone

Benzophenone-2 is prepared either by the reaction of hydroxybenzenes with benzyl hydroxide in the presence of a metal halide catalyst,or by the condensation of resorcinol with 2,4-dihydroxybenzoic acid in the presence of $POCl_3$ and $ZnCl_2$.[2,3,39,40]

Properties

Benzophenone-2 (MW 302.33) is a yellow crystalline solid with a melting point of 195°C. It is soluble in methanol, ethanol, methyl ethyl ketone, and only slightly soluble in water and toluene.[29,41] Tables 1 and 2 list other physicochemical data of Benzophenone-2.

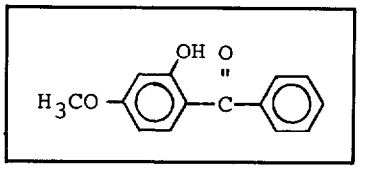
Impurities

The maximum recommended levels of lead and arsenic in Benzophenone-2 are listed in Table 1.[3]

Benzophenone-3

Structure

Benzophenone-3 is a monomethoxylated derivative of the parent compound, and it conforms to the structure:[3]



Other names include:

2-Hydroxy-4-methoxybenzophenone
Oxybenzone

Benzophenone-3 is prepared by the Friedel-Crafts reaction of benzoyl chloride with 3-hydroxyanisole. The product is then recrystallized from water/methanol and dried.[3]

Properties

Benzophenone-3 (MW 228.26) is a light cream-colored powder that melts at 66°C and has low volatility. It is soluble in most organic solvents and insoluble in water.[3,42] Tables 1 and 2 list other physical and chemical data for this compound.[3,6]

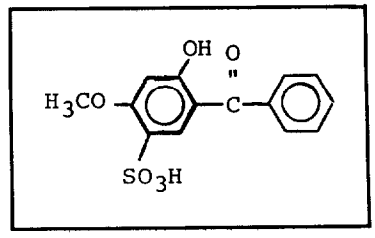
Impurities

The maximum recommended levels of lead and arsenic impurities in Benzophenone-3 are listed in Table 1.[3]

Benzophenone-4

Structure

Benzophenone-4 is a sulfonic acid derivative of Benzophenone-3. It conforms to the structure:[3]



Other names include:

2-Hydroxy-4-Methoxybenzophenone-5-Sulfonic Acid
Sulisobenzone

Benzophenone-4 is prepared via sulfonation of Benzophenone-3. The product is purified by precipitation from aqueous HCl, isolated by centrifugation, washed with acidic water, and dried.[3]

Properties

Benzophenone-4 (MW 318.39) is a pale ivory-colored powder that is soluble in water (33.4 g/100 ml H_2O), methanol, and ethanol.[43] It has a melting point of 147°C.[44,45] Tables 1 and 2 list other data for Benzophenone-4.[3,6]

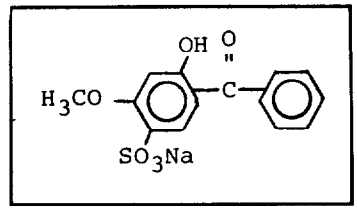
Impurities

The maximum recommended levels of lead and arsenic impurities in Benzophenone-4 are reported in Table 1.[3]

Benzophenone-5

Structure

Benzophenone-5 is the sodium salt of Benzophenone-4. It conforms to the structure:[3]



Other names include:

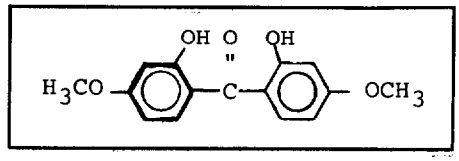
2-Hydroxy-4-Methoxybenzophenone-5-Sodium Sulfonate

No data on properties, reactivity, or impurities of Benzophenone-5 were available.

Benzophenone-6

Structure

Benzophenone-6 is a tetra-substituted Benzophenone conforming to the structure:[3]



Other names include:

2,2'-Dihydroxy-4,4'-Dimethoxybenzophenone
Bis (2-Hydroxy-4-Methoxyphenyl)-Methanone

For the synthesis of Benzophenone-6, 1,3-dimethoxybenzene is reacted with oxalyl chloride. The resulting 2,2',4,4'-tetramethoxy-benzophenone is demethylated to Benzophenone-6 with $AlCl_3$.[46] The same compound is also formed by the condensation of 3-methoxyphenol with 2-hydroxy-4-methoxybenzoic acid in the presence of phosphorous oxychloride and zinc chloride.[2] A proprietary method has been reported in which the Friedel-Crafts reaction is used.[3]

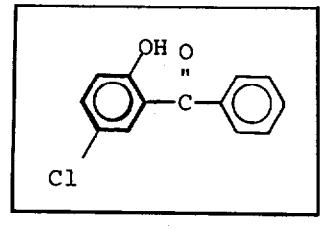
Properties

Benzophenone-6 (MW 274.26) is a light yellow solid with a melting point of 124°C. It is soluble in methanol, ethanol, ethyl acetate, methyl ethyl ketone, and toluene, but is insoluble in water.[3,29] Tables 1 and 2 contain additional information regarding Benzophenone-6.

Benzophenone-7

Structure

Benzophenone-7 is a chlorinated derivative of hydroxybenzophenone. It conforms to the structure:[3]



Other names include:

5-Chloro-2-Hydroxybenzophenone
2-Hydroxy-5-Chlorobenzophenone

Benzophenone-7 is prepared via the Friedel-Crafts reaction of chloromethoxybenzene with benzoyl chloride in the presence of aluminum chloride.[4]

Reactivity

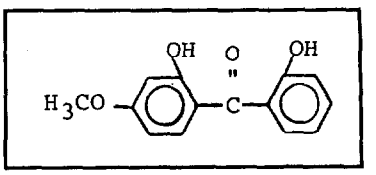
Benzophenone-7 reacts with phosphorous pentachloride to give 4-chloro-2-

$(C_6H_5CCl_2)$-$C_6H_3OPOCl_2$. It will also combine with salicylaldehyde and cobalt to form a series of cobalt (II) complexes of cyclic ligands.[47,48] Benzophenone-7 is reactive in the presence of diphenylpicrylhydrazyl.[36]

Benzophenone-8

Structure

Benzophenone-8 is the 2'-hydroxy derivative of Benzophenone-3, and it conforms to the structure:[3]



Other names include:

2,2'-Dihydroxy-4-Methoxybenzophenone
Dioxybenzone

No information regarding the manufacturing process of Benzophenone-8 was available.

Properties

Benzophenone-8 (MW 244.24) is a yellow crystalline solid. A product of 93% purity had a melting range of 73.5°–74.5°C and a boiling point at 1 mm Hg of 164°–166°C.[49] It is soluble in methanol, ethanol, ethyl acetate, isopropanol, ether, and acetone, and slightly soluble in water. Benzophenone-8 is stable to moisture at temperatures up to 200°C.[3,29,41,50] Tables 1 and 2 list other physical and chemical data for this compound.[3,6]

Reactivity

Ismail[51] reported that Benzophenone-8 reacts with organometallic compounds to give preparations which, when used in polyvinyl chloride, stabilize this polymer against ultraviolet radiation damage.

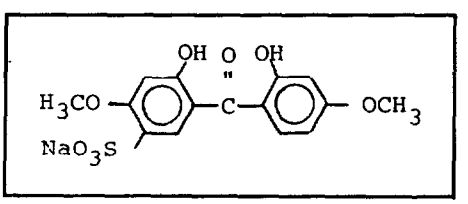
Impurities

The starting materials used or the by-products formed in the preparation of Benzophenone-8 may be present at a total concentration of up to 7% in the final product. These materials include: resorcinol dimethyl ether, resorcinol monomethyl ether, trihydroxybenzophenone, xanthone, free sulfur, or sulfur compounds.[52]

Benzophenone-9

Structure

Benzophenone-9 conforms to the structure:[3]



Other names include:

Sodium 2,2'-Dihydroxy-4,4'-Dimethoxy-5-Sulfobenzophenone

Benzophenone-9 is prepared by the sulfonation of Benzophenone-6.[3]

Properties

Benzophenone-9 is a light yellow powder with a melting point of 350°C. It is soluble in water and slightly soluble in methanol and ethanol, and insoluble in ethyl acetate and benzene. Benzophenone-9 is diluted with sodium sulfate to 67% when supplied from the manufacturer.[3,29] Tables 1 and 2 list other physiochemical data for this compound.

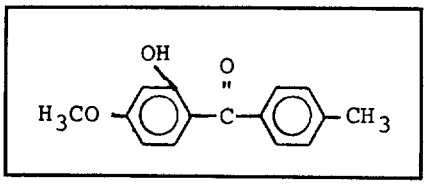
Impurities

The maximum recommended levels of lead and arsenic impurities in Benzophenone-9 are reported in Table 1.[3]

Benzophenone-10

Structure

Benzophenone-10 is a 4'-methyl derivative of Benzophenone-3. It conforms to the structure:[3]



Other names for Benzophenone-10 include:

2-Hydroxy-4-Methoxy-4'-Methylbenzophenone

Mexenone

No other chemical data regarding Benzophenone-10 were available.

Benzophenone-11

Structure

Benzophenone-11 is a mixture of 2,2'-Dihydroxy-4,4'-dimethoxybenzophenone (Benzohenone-6) and other tetra-substituted benzophenones.[3] Benzophenone-11 is manufactured by a proprietary Friedel-Crafts reaction.[3]

Properties

Benzophenone-11 is a yellow or tan powder that has a melting range of 85°–105°C.[3] It is soluble in methanol, ethanol, ethyl acetate, and methyl ethyl ketone, and insoluble in water.[45] Other properties of Benzophenone-11 are listed in Tables 1 and 2.[3,6]

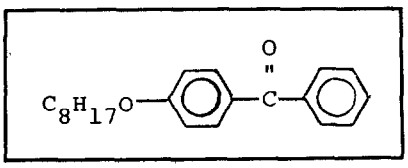
Impurities

The maximum recommended levels of lead and arsenic impurities in Benzophenone-11 are reported in Table 1.[3]

Benzophenone-12

Structure

Benzophenone-12 conforms to the structure:[3]



Other names include:

2-Hydroxy-4-(octyloxy)benzophenone
2-Hydroxy-4-(octyloxy)phenyl phenylmethanone
Octabenzone

Properties

Benzophenone-12 (MW 326.42) has a melting point of 46°C.[3] In a study of the volatility at 200°C of various antioxidants used in polymers, this ingredient was one of the least volatile.[53]

USE

Cosmetic

Benzophenones are used in cosmetics as ultraviolet light absorbers (photostabilizers). Each Benzophenone has its own characteristic absorption spectrum (Table 2). Benzophenones-2, -3, -4, -6, -8, and -9 are used in suntan lotions and hair sprays because they protect the skin and hair from the harmful effects of the sun.[54-63] These ingredients also photostabilize cosmetic dyes, creams, and lotions.[61,64-66] Although most Benzophenones are water insoluble, the presence of the sulfonic acid group in Benzophenones-4, -5, and -9 makes these ingredients soluble in water.[3]

According to the industry's voluntary submission to the Food and Drug Administration (FDA) in 1976, Benzophenones are used in over a thousand cosmetic formulations, typically in concentrations up to 1%. Benzophenones are supplied undiluted from the manufacturer, with the exceptions of Benzophenone-9, which is diluted with sodium sulfate to 67%, and Benzophenone-8, which is supplied as 93% active. The following are the maximum reported product concentrations for each Benzophenone: Benzophenone-1, 1%; Benzophenone-2, 5%; Benzophenone-3, 1%; Benzophenone-4, 10%; Benzophenone-5, $\leq$0.1%; Benzophenone-6, 1%; Benzophenone-8, 1%; Benzophenone-9, 1%; Benzophenone-11, 5%. Benzophenones-7, -10, and -12 have no current cosmetic use. Product formulation data for Benzophenones are listed in Table 3.[67,68]

The cosmetic product formulation computer printout, which is made available by the FDA, is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are

TABLE 3. Product Formulation Data.[a]

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Benzophenone-1						
Bath oils, tablets, and salts	1	–	–	–	–	1
Bubble baths	2	–	–	–	–	2
Colognes and toilet waters	3	–	–	–	–	3
Other fragrance preparations	5	–	–	–	–	5
Hair shampoos (noncoloring)	7	–	–	–	–	7
Tonics, dressings, and other hair grooming aids	2	–	–	–	1	1
Wave sets	4	–	–	–	–	4
Other hair preparations (noncoloring)	1	–	–	–	–	1
Blushers (all types)	1	–	–	–	1	–
Lipstick	7	–	–	–	7	–
Nail basecoats and undercoats	5	–	–	–	3	2
Nail polish and enamel	87	–	–	–	2	85
Other manicuring preparations	4	–	–	–	1	3
Aftershave lotions	6	–	–	–	–	6
Beard softeners	2	–	–	–	–	2
Face, body, and hand skin care preparations (excluding shaving preparations)	2	–	–	–	–	2
Moisturizing skin care preparations	3	–	–	–	–	3
1976 TOTALS	142	–	–	0	15	127
1979 TOTALS[c]	113	–	–	1	21	91
Benzophenone-2						
Bath oils, tablets, and salts	3	–	–	–	–	3
Bubble baths	5	–	–	–	1	4
Other bath preparations	6	–	–	–	–	6
Colognes and toilet waters	120	–	–	1	27	92
Perfumes	22	–	–	–	1	21
Sachets	4	–	–	–	–	4
Other fragrance preparations	15	–	–	–	5	10
Hair conditioners	2	–	–	–	–	2
Hair rinses (noncoloring)	4	–	–	–	–	4
Hair shampoos (noncoloring)	14	–	–	–	2	12
Tonics, dressings, and other hair grooming aids	2	–	–	–	–	2
Wave sets	3	–	–	–	3	–
Blushers (all types)	3	–	–	–	–	3
Rouges	1	–	–	–	–	1

TABLE 3. (Continued.)

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Makeup fixatives	1	–	–	–	–	1
Other makeup preparations (not eye)	4	–	–	–	–	4
Feminine hygiene deodorants	1	–	–	–	–	1
Aftershave lotions	30	–	–	–	6	24
Preshave lotions (all types)	1	–	–	–	–	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	6	–	–	–	2	4
Face, body, and hand skin care preparations (excluding shaving preparations)	7	–	–	–	–	7
Moisturizing skin care preparations	8	–	–	–	–	8
Paste masks (mud packs)	1	–	–	–	–	1
Skin lighteners	1	–	–	–	–	1
Skin fresheners	27	–	–	–	–	27
Wrinkle smoothers (removers)	1	–	–	–	–	1
Skin care preparations	5	–	–	–	1	4
Suntan gels, creams, and liquids	1	–	–	–	–	1
Other suntan preparations	1	–	–	–	–	1
1976 TOTALS	299	–	–	1	48	250
1979 TOTALS[c]	321	80	–	2	32	207
Benzophenone-3						
Bath oils, tablets, and salts	1	–	–	–	–	1
Colognes and toilet waters	1	–	–	–	1	–
Perfumes	1	–	–	–	–	1
Hair shampoos (noncoloring)	1	–	–	–	–	1
Makeup preparations (not eye)	1	–	–	–	1	–
Nail polish and enamel	36	–	–	–	36	–
Aftershave lotions	3	–	–	–	3	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	2	–	–	–	–	2
Skin fresheners	1	–	–	–	–	1
1976 TOTALS	47	–	–	–	41	6
1979 TOTALS[c]	62	–	–	10	45	7
Benzophenone-4						
Baby shampoos	2	–	–	–	–	2
Bath oils, tablets, and salts	11	–	–	–	–	11

TABLE 3. (Continued.)

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Bubble baths	2	–	–	–	–	2
Other bath preparations	4	–	–	–	–	4
Eye shadow	1	–	–	–	1	–
Colognes and toilet waters	8	–	–	–	–	8
Other fragrance preparations	11	–	–	–	–	11
Hair conditioners	29	–	–	1	2	26
Hair sprays (aerosol fixatives)	1	–	–	–	–	1
Permanent waves	2	–	–	–	–	2
Hair rinses (noncoloring)	7	–	–	–	–	7
Hair shampoos (noncoloring)	45	–	–	1	16	28
Tonics, dressings, and other hair grooming aids	7	–	–	–	1	6
Wave sets	27	–	–	–	1	26
Other hair preparations (noncoloring)	13	–	–	–	–	13
Hair shampoos (coloring)	1	–	–	–	1	–
Blushers (all types)	6	–	–	–	2	4
Makeup foundations	1	–	–	–	–	1
Leg and body paints	1	–	–	–	–	1
Makeup bases	1	–	–	–	1	–
Other makeup preparations (not eye)	2	–	–	–	2	–
Cuticle softeners	2	–	–	–	–	2
Bath soaps and detergents	2	–	–	–	2	–
Aftershave lotions	2	–	–	–	–	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	6	–	–	–	1	5
Face, body, and hand skin care preparations (excluding shaving preparations)	9	–	–	–	–	9
Moisturizing skin care preparations	21	–	–	–	–	21
Skin fresheners	5	–	–	–	–	5
Other skin care preparations	9	–	–	–	2	7
Suntan gels, creams, and liquids	2	–	1	–	–	1
1976 TOTALS	240	–	1	2	32	205
1979 TOTALS[c]	251	67	1	1	19	163
Benzophenone-5						
Face, body, and hand skin care preparations (excluding shaving preparations)	7	–	–	–	–	7

TABLE 3. (Continued.)

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Night skin care preparations	3	–	–	–	–	3
1976 TOTALS	10	–	–	–	–	10
1979 TOTALS[c]	11	–	–	–	–	11
Benzophenone-6						
Bath oils, tablets, and salts	2	–	–	–	–	2
Colognes and toilet waters	1	–	–	–	–	1
Perfumes	2	–	–	–	1	1
Hair shampoos (noncoloring)	1	–	–	–	–	1
Tonics, dressings, and other hair grooming aids	1	–	–	–	–	1
Wave sets	2	–	–	–	–	2
Cuticle softeners	1	–	–	–	–	1
Nail polish and enamel	77	–	–	–	77	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	1	–	–	–	–	1
Moisturizing skin care preparations	2	–	–	–	1	1
1976 TOTALS	90	–	–	–	79	11
1979 TOTALS[c]	106	–	–	–	93	13
Benezophenone-8						
Bath oils, tablets and salts	1	–	–	–	1	–
Hair conditioners	2	–	–	–	2	–
Moisturizing skin care preparations	1	–	–	–	–	1
1976 TOTALS	4	–	–	–	–	4
1979 TOTALS[c]	3	–	–	1	1	1
Benzophenone-9[d]						
Bubble baths	20	–	–	–	–	20
Bath capsules	1	–	–	–	–	1
Other bath preparations	34	–	–	–	–	34
Colognes and toilet waters	2	–	–	–	1	1
Perfumes	1	–	–	–	1	–
Other fragrance preparations	1	–	–	–	–	1
Hair conditioners	9	–	–	–	1	8
Hair rinses (noncoloring)	3	–	–	–	–	3
Hair shampoos (noncoloring)	8	–	–	–	3	5
Tonics, dressings, and other hair grooming aids	1	–	–	–	–	1
Wave sets	2	–	–	–	–	2

TABLE 3. (Continued.)

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Other hair preparations (noncoloring)	1	–	–	–	–	1
Blushers (all types)	1	–	–	–	–	1
Makeup bases	1	–	–	–	1	–
Rouges	1	–	–	–	–	1
Nail basecoats and undercoats	1	–	–	–	–	1
Cuticle softeners	1	–	–	–	–	1
Nail creams and lotions	1	–	–	–	–	1
Aftershave lotions	3	–	–	–	1	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	4	–	–	–	2	2
Face, body, and hand skin care preparations (excluding shaving preparations)	14	–	–	–	1	13
Moisturizing skin care preparations	2	–	–	–	–	2
Skin fresheners	9	–	–	–	1	8
Other skin care preparations	1	–	–	–	–	1
Suntan and sunscreen preparations	1	–	–	–	1	–
1976 TOTALS	123	–	–	–	13	110
1979 TOTALS[c]	85	38	–	–	9	38
Benzophenone-11						
Bath oils, tablets, and salts	4	–	–	–	2	2
Bubble baths	4	–	–	–	–	4
Other bath preparations	1	–	–	–	–	1
Colognes and toilet waters	59	–	–	–	6	53
Perfumes	14	–	–	–	–	14
Sachets	7	–	–	–	–	7
Other fragrance preparations	8	–	–	–	–	8
Hair sprays (aerosol fixatives)	4	–	–	1	2	1
Hair shampoos (noncoloring)	13	–	–	–	–	13
Tonics, dressings, and other hair grooming aids	2	–	–	–	2	–
Wave sets	2	–	–	–	–	2
Blushers (all types)	1	–	–	–	–	1
Nail polish and enamel	3	–	–	–	–	3
Bath soaps and detergents	3	–	–	–	–	3
Aftershave lotions	16	–	–	–	–	16
Preshave lotions (all types)	1	–	–	–	–	1

TABLE 3. (Continued.)

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]				
		Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Face, body, and hand skin care preparations (excluding shaving preparations)	2	–	–	–	–	2
Moisturizing skin care preparations	12	–	–	–	–	12
Skin fresheners	11	–	–	–	–	11
Other skin care preparations	1	–	–	–	–	1
1976 TOTALS	168	–	–	1	12	155
1979 TOTALS[c]	103	65	–	1	10	27

[a]Data from Ref. 67.

[b]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4); see Scope and Extent of Use in Cosmetics.

[c]Data from Ref. 73.

[d]Benzophenone-9 is supplied as a 67% solution; use concentration values may or may not have been adjusted accordingly by manufacturers when submited to the FDA.

listed in prescribed concentration ranges under specific product-type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration.

Benzophenones-1, -3, and -6 are most frequently found in nail polishes (in concentrations up to 1%); Benzophenones-2 and -11 are most frequently used in fragrance preparations (in concentrations up to 1%); and Benzophenones-4, -5, and -9 are generally used in hair, skin, and bath preparations, respectively (in concentrations up to 1%).

Benzophenones are used in at least nine major cosmetic categories. Formulations containing Benzophenones may come into contact with the face, hair and scalp, nails, lips, mucosa, and skin. Products containing Benzophenones are used daily or occasionally; their use may extend over a period of years. Frequency and duration of application may be continuous.

Certain Benzophenones reduce the harmful effects of UV radiation on the skin. The maximum absorption wavelengths for specific Benzophenones are

listed in Table 2. Ultraviolet light is divided into three distinct bands: UV-A (320–400 nm), UV-B (280–320 nm), and UV-C (200–280 nm). Exposing unprotected skin to UV light (primarily in the UV-B range) can induce sunburn and, over a long period of time, promote premature aging of the skin and skin cancer. The harmful effects of UV radiation on the skin have been reviewed.[44,56,69]

Benzophenone sunscreens, applied topically, protect the skin from these harmful effects of ultraviolet light by chemically absorbing light energy (photons). As this occurs, the Benzophenone molecule becomes excited to higher energy levels. As the excited molecule returns to its ground state, the energy is released in the form of thermal energy. The hydroxyl group in the ortho position to the carbonyl group is believed to be a structural requirement for the Benzophenones' absorption of UV light. This structural arrangement also contributes to the electronic stability of the molecule. Thus, a surface coating of Benzophenones decreases the amount of UV radiation absorbed by the skin by limiting the total amount of energy that reaches the skin. Benzophenones absorb energy throughout the UV range, though maximum absorbance is between 284 and 287 nm for the 2-hydroxybenzophenones and between 333 and 345 nm for the 2,2'-dihydroxybenzophenones. The effectiveness of any Benzophenone as a sunscreen is determined by its concentration on the skin, the pH of the skin and chemical environment, and the solvent system; a change in either of the latter two conditions can cause the peak absorbance of the Benzophenone to vary.[6,56,69]

Benzophenones also protect patients using drugs that have the side effect of eliciting from the individual a photosensitization reaction either phototoxic or photoallergic in nature. A phototoxic reaction occurs when a drug absorbs UV light and transfers energy from it to the vulnerable cell organelles; the damage caused is characterized by a sunburn-like reaction. Photoallergic reactions, on the other hand, involve an immunologic mechanism between the photosensitizing drug and skin proteins. The reaction is characterized by eczematous or polymorphic dermatitis of delayed onset, which will recur with each subsequent exposure to UV light.[56] Phototoxic reactions to long-wavelength UV radiation (320–380 nm) occur in patients who used topically applied psoralen for the treatment of vitiligo, a condition in which pigment is lost. Topical application of Benzophenone-4 or Benzophenone-8 (10%) controlled photosensitivity in these individuals.[70] Chlorpromazine, a drug frequently used to treat schizophrenia, often produces photosensitivity. Topically applied Benzophenone-4 (10% in a cream base) protected ten such chlorpromazine photosensitized individuals.[71] In addition, photosensitivity resulting from the use of chlortetracycline was effectively controlled when patients applied a skin cream containing 10% Benzophenone-4.[56] Oleniacz et al.[72] reported photosensitivity to UV light in the 300–425 nm range in individuals who used the topical antibacterial agent 3,3',4',5-tetrachlorosalicylanilide (TCSA). A TCSA in vitro study revealed the disruption of lysosomal and mast cell membranes as a primary photosensitizing event, and that TCSA enhanced the light sensitivity of lysosomes, resulting in concomitant edema and erythema. Benzophenone-4 protected TCSA-treated cells from UV radiation. Emmett et al.[74] reported that workers who handled absorbers used in the production of UV-cured inks became sensitized to UV light. This reaction induced pruritic dermatitis on sun-exposed surfaces of the body. Topical use of a

cream containing 10% Benzophenone-4 was effective in controlling this sensitization.

Benzophenones are also used as topical agents for the treatment of photodermatoses such as solar urticaria (a vascular reaction of the skin marked by wheals) and polymorphous light eruption (a skin eruption confined to sun-exposed surfaces and not attributable to medications or systemic disease).[75]

The FDA Panel on Review of Topical Analgesics has proposed that Benzophenones-3, -4, and -8 are safe and effective as active ingredients in sunscreens for over-the-counter (OTC) use at the following concentrations: Benzophenone-3, 2%–6%; Benzophenone-4, 5%–10%; and Benzophenone-8, 3%. The Panel proposed these concentration limits on a combined safety and efficacy basis (a concentration limit may reflect maximum efficacy and not necessarily an indication of toxicity at a higher concentration).[69]

Noncosmetic

Owing to their photostabilizing properties, Benzophenones are used in food and agricultural products, as well as in packaging materials. At maximum concentrations of 0.01% and 0.05%, respectively, Benzophenone-12 is a food stabilizer in petroleum wax and an antioxidant/stabilizer in olefin polymers.[76,77] Benzophenone-7 is a commercial grain fungicide, whereas Benzophenone-9 protects the insect pathogens, *Bacillus thuringensis* (spores) and spruce budworm nuclear polyhedrosis virus, from sunlight's harmful effects.[78,79] Benzophenone-2 is used in herbicides, and Benzophenone-3 is added to agricultural films (such as polyvinyl chloride), where it serves as a photostabilizer.[20,80,81] When used in packaging materials, Benzophenone-12 prevents UV radiation from reaching the stored product and increases the stability of the container.[82-84] Table 4 lists other noncosmetic uses of Benzophenones.

When studying Benzophenones as light stabilizers in packaging, Marcincin and Pikler[85] reported that an increase in the number of hydroxyl groups and a decrease in the carbon chain length of the Benzophenone substituents resulted in increased diffusion and extraction of the Benzophenone from the polymer. It was reported that when Benzophenone photostabilizers are used in packaging material, they migrate into aqueous, acidic, or dilute alkaline media, including food.[86]

BIOLOGICAL PROPERTIES

General Effects

Benzophenone-2 had an insignificant effect when tested for antitumor and antimicrobial activity. When assayed with Sarcoma 180 tumor cell cultures, this ingredient had an ID50 (dose for 50% inhibition of growth) of 17 μg/ml; tumor inhibition was considered to be insignificant. Antimicrobial activity of Benzophenone-2 against *Esherichia coli* and *Streptococcus fecalis* was also reported to be insignificant (Median inhibitory dose [ID50] = $>10^3$ *M*/l).[93]

Benzophenone-7 is a grain fungicide and was detected in starlings throughout the U.S. at concentrations up to 3.33 ppm.[78]

TABLE 4. Noncosmetic Use of Benzophenones as Light Stabilizers.

Benzophenone	*Substances used in*	*Product use*	*Ref.*
−3	Polyethylene tereptithalate	Fabrics, films, magnetic tape	87,88
−3	Polyvinyl butyral	Interlayer safety glass in autos and airplanes	89
−1, −3	Cellulose acetate	Rubber and celluloid subst., films, varnish, lacquer, fabric, records	9
−3, −6, −8	General	Adhesives, lacquers, plastics	5
−1, −3, −6	Polyvinyl chloride	Rubber subst., films, textile finishes, shoe soles, raincoats, insulation, tubing	90
−1, −2, −3, −6, −7, −11	Toluidene Red	Dye	91
−1, −2, −3, −6, −7, −11	Polyester	Tires, rubber subst., clothing, protective coatings, magnetic tapes	92
−1, −2, −3, −6, −7, −11	Acrylic acid resin	In plastics	92
−1, −2, −3, −6, −7, −11	Nitrocellulose	Celluloids, textile fibers, lacquers, rocket propellant	92
−1, −2, −3, −6, −7, −11	Polyvinyl chloride	Celluloids, textile fibers, lacquers, rocket propellant	92
−1, −2, −3, −6, −7, −11	Polystyrene	Packaging, cabinets, containers, refrigerator doors, toys	92

Absorption, Metabolism, and Excretion

Patel et al.[94] studied absorption and excretion of Benzophenone-12 incorporated in the rat diet. Preliminary short-term feeding studies indicated that most of the compound was unabsorbed and passed in the feces; the remainder was absorbed, conjugated, and excreted as a glucuronide in the urine. Long-term absorption and excretion of Benzophenone-12 was studied in 18 male albino rabbits that were maintained on diets containing 0%, 1.25%, or 5.0% Benzophenone-12 for 35 days. Daily food consumption was measured for each animal, and the individual intake of Benzophenone-12 was calculated. Daily samples of the animals' feces and urine were analyzed by paper chromatography for Benzophenone-12 or the glucuronic acid. Two animals from each dietary level were sacrificed for liver and kidney examination after 11, 22, and 35 days of feeding. Urinary excretion of Benzophenone-12 as a glucuronide in animals at both dietary levels of Benzophenone-12 was approximately 10% of the daily dose, whereas the recovery of unchanged Benzophenone-12 from the feces was about 90%. These results indicated that the animals did not retain measurable amounts of Benzophenone-12 even when the compound was ingested over a long period of time.

Patel et al.[94] conducted limited metabolism studies on Benzophenone-3 (in which a methoxy group replaces the octyloxy chain of Benzophenone-12). Preliminary results suggested that Benzophenone-3 was absorbed and conjugated to a greater extent than Benzophenone-12, indicating that the length of the alkoxy side-chain influences the degrees to which these compounds are absorbed from the intestine.

Animal Toxicology

Acute Toxicity

Oral

The Benzophenones have been tested for acute oral toxicity in rats. The animals were weighed and dosed after a one-week observation; the test material was then administered by gastric intubation. Rats were observed daily for 7 to 14 days, during which time food and water were allowed ad libitum; in some instances, animals were sacrificed and autopsied for gross pathology. Results, listed in Table 5, indicate that in acute oral toxicity tests, Benzophenones-1, -3, -6, -8, -9, and -12 are practically nontoxic, whereas Benzophenones-2, -4, and -11 are slightly toxic.

Dermal

The acute dermal toxicity of Benzophenones-3, -4, -8, and -12 was tested in albino rabbits. The test substance was applied at various dosages to the epilated skin of the back or flanks and held in contact for 18–24 hours; it was then washed off. Observations were made daily for signs of toxicity and irritation. Animals were autopsied following the 5- to 7-day observation period. Benzophenone-3 had an acute dermal LD50 >16.0 g/kg when applied to rabbits in doses of 2.0–16.0 g/kg. Local skin reactions, consisting of mild to moderate erythema, were observed in two animals at the 2.0 g/kg dose 24 and 48 hours following the exposure period. No significant pathology was revealed upon autopsy.[95] Ten rabbits dosed at 5 g/kg Benzophenone-4 had an acute dermal LD50 >5 g/kg. There were no gross signs of toxicity or irritation throughout the observation period; autopsy revealed one animal with congested kidneys.[96] The acute dermal LD50 of Benzophenone-8 was determined to be >10 g/kg; ten rabbits dosed at 10 g/kg developed no systemic toxicity, skin irritation, or pathology attributable to dermal application of this compound.[49] Benzophenone-12 had an acute dermal LD50 of >10 g/kg when tested on five rabbits; animals developed no systemic toxicity or skin irritation.[94] Results of these tests indicate that Benzophenone-8 is relatively harmless and causes no systemic toxicity when applied dermally.

Subchronic Oral Toxicity

Benzophenones-1, -3, -8, and -12 were tested for subchronic oral toxicity, the results of which appear in Table 6. Benzophenone-1, fed to 40 rats at doses of 0–1.9 g/kg for 90 days, produced depressed growth and liver and kidney lesions in animals at doses of 0.6 and 1.9 g/kg.[97] Benzophenone-3 caused no toxic effect in rats when incorporated into their diets (up to 1%) for 27 days; however, in a 90-day study, rats fed 0.5% or 1.0% Benzophenone-3 displayed depressed growth, leucocytosis, anemia, reduced organ weights, and degenerative nephrosis.[95,98] When Benzophenone-8 was fed to rats at dietary concentrations of 0%–10%, gross hematuria was occasionally noted at the two highest dose levels (5% and 10%). Upon autopsy, kidney discoloration and liver enlargement (in direct proportion to dose levels of Benzophenone-8) were observed. Hematuria

TABLE 5. Acute oral toxicity.

Benzophenone	*No. of rats*	*Conc. (%)*	*Vehicle*	*Dose*	*LD50*	*Comments*[a]	*Ref.*
−1	50	25	Corn oil	8–32 ml/kg	24.4 ml/kg	Relatively harmless	99
−1		–[b]	Olive oil	–	8.8 g/kg	Practically nontoxic	97
−2	100	5	Corn oil	1–3.5 g/kg	1.22 g/kg	Slightly toxic (convulsion and immediate death at highest dosage)	100
−2		–	Olive oil	–	7.0g/kg	Practically nontoxic	97
−3	25	25	Corn oil	6.25–16 g/kg	11.6 g/kg	Practically nontoxic	100
−3	14	15	Methyl Cellulose	4.5–6 g/kg	>6 g/kg	Pale livers and kidneys, gastrointestinal irritation	101
−3		–	Olive oil	–	7.4 g/kg	Practically nontoxic	97
−3		–	–	–	>12.8 g/kg	Practically nontoxic	98
−4	30	5	Water	0.2–6.4 g/kg	>6.4 g/kg	Practically nontoxic	102
−4	15	0.2 g/ml	Water/agar/tween	2.5–10 g/kg	6.15 g/kg	Practically nontoxic	96
−4	20	20	Agar/tween	1.25–10 g/kg	3.53 g/kg	Slightly toxic (ataxia)	96
−6	25	25	Corn oil	1–16 g/kg	>16 g/kg	Practically nontoxic	103
−8	10	0.2 g/ml	Water	10 g/kg	>10 g/kg	Practically nontoxic	49
−9	25	26.8	Water	6.14–16 g/kg	9.0 g/kg	Practically nontoxic	104
−11	100	5	Corn oil	1.5–3.75 g/kg	3 g/kg	Slightly toxic	103
−12[c]		–	Olive oil	–	>12 g/kg	Practically nontoxic	97
−12[c]	10	20	Water	10 g/kg	>10 g/kg	Practically nontoxic	94

[a]According to Hodge and Sterner.
[b]No data available.
[c]BP-12 has no reported use in cosmetics.

TABLE 6. Subchronic and chronic oral toxicity data.

Benzophenone	*No. animals/ Species*	*Dose*	*No. days on diet*	*No. deaths*	*No effect level*	*Comments*	*Ref.*
−1	40 albino rats	0, 0.19, 0.6, 1.9 g/kg	90	0	0.19 g/kg	Depressed growth, liver and kidney lesions at 0.6 and 1.9 g/kg	97
−3	40 albino rats	0%, 0.01%, 0.1%, 1%	27	0	>1.0%	No toxic effect	95
−3	120 albino rats	0%, 0.02%, 0.1%, 0.5%, 1.0%	90	0	0.1%	Depressed growth, leucocytosis, anemia, reduced organ weight, nephrosis at 0.5% and 1.0%	98
−8	40 albino rats	0%, 2.5%, 5.0%, 10%	36	0	2.5%	Gross hematuria at 5% and 10%	49
−12	40 albino rats	0, 0.19, 0.6, 1.9 g/kg	90	0	0.6 g/kg	Depressed growth, liver and kidney lesions at 1.9 g/kg	97
−12	160 albino rats	0%, 0.2%, 0.6%, 1.8%	90	2[a]	>1.8%	Nontoxic	94
−12	16 beagle dogs	0%, 0.2%, 0.4%, 0.6%	120	0	>0.6%	Nontoxic	94

[a]Unrelated to ingestion of BP-12.

was explained by the deposition of an insoluble glucuronic acid conjugate of Benzophenone-8 in the kidney tubules.[49] Benzophenone-12, fed to 160 rats at concentrations up to 1.8% (approximately 0.9 g/kg) for 90 days, was practically nontoxic at all dose levels.[94] In another 90-day study, however, rats dosed at 1.9 g/kg Benzophenone-12 exhibited depressed growth as well as liver and kidney lesions; in this study, 0.6 g/kg was reported to be the "no-effect" level.[97]

Chronic Oral Toxicity

Four groups of beagle dogs, consisting of two males and two females each, were placed on 120-day diets containing 0%, 0.2%, 0.6%, or 1.8% Benzophenone-12 (Table 6). The highest dietary concentration of Benzophenone-12 was lowered from 1.8% to 0.4% after the 14th day because the dogs rejected their food. No significant differences were observed between control and test animals in body and organ weights, hemoglobin, hematocrit, leucocyte counts, and plasma levels of urea nitrogen and alkaline phosphatase. Benzophenone-12 was considered to be nontoxic when ingested as 0.6% in the diet over a period of four months.[94]

Acute Irritation

Skin

Irritation: Procedures outlined by the Federal Hazardous Substances Labeling Act (FHSLA) were used to test Benzophenones for acute skin irritation. An occlusive patch containing 0.5 ml or 0.5 mg of the test ingredient was applied to the intact and abraded skin of albino rabbits. Patches remained in place for 24 hours and were then removed and scored for irritation according to the Draize method. Sites were again scored 24 hours after patch removal. Benzophenones-2, -3, -9, and -11 were nonirritating to intact and abraded skin when tested at concentrations from 4% to 100%. Benzophenones-1, -4, and -6 were minimally irritating (PII = 0.25–0.50) when applied as 16% solutions in dimethyl phthalate (DMP). However, these ingredients were nonirritating at 8% in DMP and at 16% in petrolatum.[96,104-107] Table 7 summarizes the results of Benzophenone skin irritation studies.

Phototoxicity and Photosensitization

A sunscreen containing 3% Benzophenone-8 was tested for potential phototoxicity in guinea pigs. A 0.1 ml dose of the undiluted lotion was applied to four areas of skin on each of three animals. Fifteen to 20 minutes later, two of the sites were exposed to UV-A light (maximum at 360 nm) from four F40BL bulbs at a distance of 12 inches for 60 minutes. The other two sites were nonirradiated controls. All sites were scored 24 hours after application of the test material. The sunscreen containing 3% Benzophenone-8 did not induce erythema at control or irradiated sites indicating a lack of phototoxicity.[113]

A sunscreen containing 6% Benzophenone-3 was tested for photosensitization in six albino rabbits. A 0.4 ml dose of the lotion was applied to the clipped dorsal skin of each animal. Skin sites were then irradiated with UV light from a sunlamp. This procedure was repeated five times weekly for two weeks (ten applications total). Sites were scored 24 hours following each irradiation. Mild

TABLE 7. Primary Skin Irritation (FHSLA Procedures).

Benzophenone	No. of albino rabbits	Conc. (%) Vehicle	Primary Irritation Index(PII)[a]	Comments	Ref.
-1	6	16,8,4/Petrolatum	0.00	Nonirritating	107
-1	6	16,8,4/DMP[b]	0.25 (16%)	Minimally irritating (16%)	107
-2	6	100	0.00	Nonirritating	105
-2	6	16,8,4/Petrolatum	0.00	Nonirritating	107
-2	6	16,8,4/DMP	0.00	Nonirritating	107
-3	6	100	0.00	Nonirritating	106
-3	6	100	0.00	Nonirritating	108
-4	6	16,8,4/Petrolatum	0.00	Nonirritating	107
-4	6	16,8,4/DMP	0.50 (16%)	Minimally irritating (16%)	107
-6	6	16,8,4/Petrolatum	0.00	Nonirritating	107
-6	6	16,8,4/DMP	0.25 (16%)	Minimally irritating (16%)	107
-9	6	10.72,5.36,2.68/ Petrolatum	0.00	Nonirritating	107
-9	6	10.72,5.36,2.68/DMP	0.00	Nonirritating	107
-9	6	5.36/Water	0.00	Nonirritating	104,106,109-112
-11	6	16,8,4/Petrolatum	0.00	Nonirritating	107
-11	6	16,8,4/DMP	0.00	Nonirritating	107

[a]Maximum score = 8.
[b]Dimethyl Phthalate.

erythema, mild edema, and desquamation were observed in both test and irradiated control animals; however, no photosensitization occurred in any of the test animals.[69]

Eye

A number of studies have determined the potential irritancy of Benzophenones to the eyes of rabbits. The test material (0.1 ml or 0.1 g) was instilled into one eye of each rabbit; the other eye served as an untreated control. Eyes were examined and scored for irritation daily for a period of three to ten days. Some test procedures included washing of the treated eyes with water four seconds after instillation of the test material. Results of eye irritation tests revealed that most Benzophenones at concentrations of 5%-100% were nonirritating when instilled into the eyes of rabbits. Benzophenones-1, -2, and -4 were slightly to moderately irritating at 100% concentration; however, Benzophenones-1 and -2 were nonirritating when tested at 16% in dimethyl phthalate (DMP) or petrolatum. Although Benzophenone-4 was irritating at concentrations of 8 and 16% in DMP or petrolatum, it was nonirritating when tested as a 5% solution in water. Whereas one study indicated that Benzophenone-11 (5% in DMP) was slightly irritating, another revealed that 16% Benzophenone-11 in DMP was nonirritating. Table 8 summarizes eye irritation data for the Benzophenones.

Subchronic Skin Irritation and Sensitization

Irritation

Marzulli and Maibach[114] used a 16-day cumulative test on rabbits to study the irritation potential of Benzophenone-4. An alcohol solution containing either

TABLE 8. Primary Eye Irritation.

Benzophenone	Method	No. of albino rabbits	Eye wash Y/N	Test Conc. (%)	Dose	Average score per day[a] 1	2	3	4	5	6	7	Comments	Ref.
−1	Draize	6	N	100	100 mg	20	7.00	0	–	–	–	–	Mildly irritating (conjunctiva and cornea)	115
−1	FHSLA	6	N	16,8,4/DMP[b]	0.1 ml	0	0	0	–	–	–	–	Nonirritating	107
−1	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	0	0	0	–	–	–	–	Nonirritating	107
−2	Draize	6	N	100	100 mg	17	15	10.3	3.0	0	–	–	Moderately irritating (conjunctiva and cornea)	110
−2	FHSLA	6	N	16,8,4/DMP	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−2	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−3	FHSLA	6	N	16,8,4/DMP	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−3	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−3	Draize	6	N	100	100 mg	0	0	0	0	–	–	0	Nonirritating	111
−3	Mod. FHSLA	3	N	100	3 mg	0	0	0	0	0	0	–	Nonirritating	101
−3	Mod. FHSLA	6	N	100	100 mg	0	0	0	–	–	–	0	Nonirritating	108
−4	FHSLA	6	N	16,8,4/DMP	0.1 ml	–	–	–	–	–	–	–	Irritating (Cornea, conjunctiva−16%; conjunctiva−8%)	107
−4	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	–	–	–	–	–	–	–	Irritating (Cornea, conjunctiva−16%; conjunctiva−8%)	107

−4	Draize	9	Y−3 rabbits	5/water	0.1 ml	0	0	0	0	–	–	0	Nonirritating	116
−4	Draize	6	N	100	100 mg	2.58	2.38	2.05	–	–	–	–	Irritating to iris and conjunctiva	96
−6	FHSLA	6	N	16,8,4/DMP	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−6	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−6	Draize	6	N	100	100 mg	0	0	0	0	–	–	0	Nonirritating	109
−8	–	5	N	100	100 mg	0	0	0	–	–	–	0	Nonirritating	49
−9	FHSLA	6	N	10.72,5.36,2.68/DMP	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−9	FHSLA	6	N	10.72,5.36,2.68/Petrolatum	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−9	Draize	6	N	5.36/water	0.1 ml	0	0	0	0	–	–	0	Nonirritating	112
−11	FHSLA	6	N	16,8,4/DMP	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−11	FHSLA	6	N	16,8,4/Petrolatum	0.1 ml	0	0	0	–	–	–	0	Nonirritating	107
−11	Draize	9	N	5/DMP	0.1 ml	2.89	0.67	0	0	0	0	0	Slightly irritating to conjunctiva in all rabbits	104
−12	Draize	5	N	100	100 mg	0	0	0	0	0	0	0	Nonirritating	94

[a]Maximum score = 110.
[b]Dimethyl phthalate.

10% or 1% Benzophenone-4 was applied uncovered to the depilated backs of six New Zealand albino rabbits. Twenty-four hours later the sites were scored for irritation, and the solution was reapplied. This procedure was repeated every other day for five weeks, until a total of 16 applications of Benzophenone-4 had been made. The average cumulative irritation score was then calculated (maximum score = 64); applications of Benzophenone-4 (10%) and Benzophenone-4 (1%) produced scores of 3.6 and 0.3, respectively.

Sensitization

Benzophenone-3 was tested for sensitizing potential using the Kligman Maximization Procedure. A 0.05 ml intradermal injection of 5% Benzophenone-3 in corn oil or 50% Benzophenone-3 in aqueous Freund's Adjuvant was administered to the shaved back of each of ten female albino guinea pigs per solution. Seven days following injection, a topical booster patch containing 10% Benzophenone-3 in petrolatum was applied for 48 hours. Two weeks later, a challenge test of 0.1 ml of 2.5% Benzophenone-3 in petrolatum was applied under an occlusive patch to a virgin site for 24 hours. Sites were scored 24 and 48 hours after patch removal. Results of this test indicated that Benzophenone-3 was not a skin sensitizer.[117]

Special Studies

Mutagenesis

The Ames *Salmonella*/Mammalian-Microsomal Assay was used to test Benzophenones-1, -2, -3, -4, -6, -8, -9, and -11 for mutagenicity. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were used; all tests were performed in the presence and absence of Aroclor-induced rat liver microsomal S-9 cell fraction to observe the mutagenic effect of each compound following metabolic activation. Preliminary cytotoxicity studies determined the dose range of each compound to be used. The results of these tests appear in Table 9. All Benzophenones were nonmutagenic when assayed directly. All but three Benzophenones (-2, -6, and -8) were nonmutagenic with metabolic activation. Benzophenone-8 was weakly mutagenic in *Salmonella* strain TA1537; whereas, Benzophenone-6 was determined to be mutagenic at three doses in the same strain (TA1537). Benzophenone-2, in the presence of rat liver microsomes, induced a "small but fairly consistent increase in the number of mutants" in four *Salmonella* strains tested. At doses of 100–300 μg, Benzophenone-2 induced mutant increases of 50–100% in TA100 and 200%–500% in TA1537. A mutant increase of 50% was observed in strains TA98 and TA1535, but these strains had not been tested enough times to provide conclusive results. The investigator suggested that "the small and somewhat erratic nature of the (mutagenic) response we have seen raises the possibility that the observed effect may be due to the presence of an impurity." The purity of the test sample was 99% (lab-grade) and was assumed to be purer than that of the cosmetic-grade. Additional tests using lab-grade Benzophenone-2 found this ingredient to be mutagenic in TA1537 at doses of 200 and 750 μg when activated by Aroclor-induced hamster liver enzymes. Preliminary assays of cosmetic-grade Benzophenone-2 revealed mutagenic activity not differing significantly from that of the purer lab-grade.[118-122]

TABLE 9. Ames *Salmonella* Mutagenesis Assay.[a]

Benzophenone	Dose range (μg) (Solvent)	Results[b] without S-9 metabolic activation					Results[b] with S-9 metabolic activation					Comment
		TA98	TA100	TA1535	TA1537	TA1538	TA98	TA100	TA1535	TA1537	TA1538	
−1	0.1–500 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation
−2	0.1–10,000 (DMSO)	(−)	(−)	(−)	(−)	−[c]	(+)	(+)	(+)	(+)	−[c]	Mutagenic with S-9 activation in all strains (see text)
−2	10–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation
−3	1.0–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation
−4	1.0–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation
−6	1.0–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(+)	(−)	Mutagenic only in TA1537 with S-9 activation at 10 and 100 μg. Toxic to TA1537 at 500 and 1000 μg with S-9
−8	7.0–700 (ETOH)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(+)	(−)	Dose-dependent, weak but significant mutagen in TA1537 with S-9 activation only
−9	1.0–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation
−11	10–1000 (DMSO)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Nonmutagenic with and without S-9 activation

[a]Data from Refs. 118–122.
[b](−) = Nonmutagenic; (+) = mutagenic.
[c]No data.

An in vitro cytogenic assay was used to evaluate the ability of Benzophenone-2 to induce sister chromatid exchange (SCE) and chromosome aberrations (CA) in L5178Y mouse lymphoma cells. Assays were performed in the presence and absence of Aroclor-induced rat liver microsomal enzymes (S-9). The solubility of Benzophenone-2 in DMSO and its cytotoxicity were first determined. For the mutagenesis assays, doses of 6.250–200.00 μg Benzophenone-2 per plate were used. When assayed in the absence of S-9, Benzophenone-2 induced small but "biologically insignificant" increases in SCE frequency at 100 and 200 μg; CA frequencies were not elevated at any dose. With metabolic activation, however, Benzophenone-2 produced "statistically and biologically significant" increases in SCE frequency at the three highest dose levels, indicating a dose-response relationship. The author noted that Benzophenone-2 was more toxic to cells under the activation system; only 17 scorable cells were located at the 100 μg dose. The investigator reported that 10 CAs (including a quadriradial, a translocation, and two triradials) were observed among the 67 cells scored at the two highest doses with activation. He concluded that Benzophenone-2 does not directly induce significant SCE or CA increases but does, under metabolic activation, induce these changes.[123]

A Mouse Lymphoma Forward Mutation Assay was used to test Benzophenones-2 and -8 for mutagenesis. The L5178Y TK+/− cell line was used; assays were performed in the presence and absence of an Aroclor-induced rat liver microsomal preparation (S-9). Materials were dissolved in DMSO and tested for preliminary cytotoxicity to determine doses to be used in the assays.

Without activation, Benzophenone-2 was mutagenic at "highly toxic" doses. In the presence of S-9, Benzophenone-2 became more toxic. An increase in the mutant frequency (3.0–6.8 times) was observed with the three most toxic doses. A dose-response relationship was not demonstrated. The investigator suggested that Benzophenone-2 "appears to react with microsomal system to yield a mutagenic product that induces mutants at lower applied concentrations and toxicities than under nonactivation conditions." It was concluded that Benzophenone-2 induced an increase in mutations at the TK locus in L5178Y mouse lymphoma cells only for highly toxic doses with or without metabolic activation and that this material is weakly mutagenic under the conditions of the test.[123] These findings need to be reconfirmed since there was no dose-response pattern of toxicities over the preferred relative growth range in any of the trials; increases in mutant frequency in the assays occurred only at levels bordering total lethality; and the lethal dose was poorly reproduced from one trial to another with metabolic activation.

When assayed directly, Benzophenone-8 did not induce mutant frequencies significantly greater than those of controls. With metabolic activation, however, Benzophenone-8 induced dose-dependant mutant frequency increases of 3.8 and 2.0 times for the two highest doses (32 and 24 μg, respectively). The investigator concluded that, under the test conditions, Benzophenone-8 is nonmutagenic when assayed directly, but under metabolic activation it induces a significant, dose-dependent increase in mutant frequency.[118]

Other

No information was available on any of the Benzophenones with respect to teratogenesis and carcinogenesis.

Clinical Assessment of Safety

Skin Irritation and Sensitization

Benzophenones were tested for potential irritation and sensitization to human skin. In general, these ingredients were reported to be nonirritating and nonsensitizing at concentrations higher than those found in cosmetics. Table 10 summarizes the results of these studies.

Four studies reported irritation and/or sensitization to Benzophenones. Benzophenone-2 was applied to 50 subjects in a Shelanski repeated insult patch test (RIPT). Induction patches were applied to the subject's skin for 24 hours every other day for a total of 15 patches. The initial nine patches contained a 4.9% Benzophenone-2 solution; the remaining six patches contained a 2.45% Benzophenone-2 solution. Two weeks after removal of the last induction patch, a challenge patch containing 2.45% Benzophenone-2 was applied to the original test site. All sites were scored upon patch removal. Sixteen of 50 subjects reacted to one or more of the induction patches; responses of 1+ to 3+ (maximum score = 4+) were observed. Four subjects reacted to the challenge patch with responses of 1+ and one with 2+. The investigators concluded that at 4.5%, Benzophenone-2 is not a primary irritant but is a "fatiguing agent" and possibly a sensitizer.[124]

A Modified Draize/Shelanski RIPT was used to study the irritancy and sensitizing potential of a sunscreen containing a 3.0% Benzophenone-3 in 57 subjects. One subject displayed erythema (1+ response) to the final induction and challenge patches; no reaction was elicited by a challenge patch on a virgin site. This subject was repatched 11 months later with each component of the sunscreen. Benzophenone-3 in ethyl alcohol was applied under occlusion to her upper arm for 24 hours. The site was scored at 48 and 72 hours. Spreading erythema and mild edema (2+ response) was elicited at 48 hours; by 72 hours only erythema (1+ response) was observed. It was concluded that this test subject was sensitized to Benzophenone-3. The investigators concluded that the product containing 3% Benzophenone-3 may have a "minimum potential for inducing sensitization under the exaggerated conditions of the test."[125]

Benzophenone-8 was tested for irritation and sensitization using a Modified Draize/Shelanski RIPT. Ten induction patches containing 25% Benzophenone-8 in petrolatum were applied to each of 100 subjects. Following a one-week rest, a challenge patch containing 10% Benzophenone-8 in petrolatum was applied to a fresh skin site. Seven subjects reacted to both induction and challenge patches; these results indicated contact sensitivity. Moreover, one subject exhibited 2+ reactions for induction patches 8–10 and a 4+ reaction to the challenge patch. The authors concluded that Benzophenone-8 (25%) is a moderate sensitizer.[50]

Benzophenones-4 and -11 were tested for potential skin irritation in separate single insult patch tests. Each ingredient was applied at concentrations of 16, 8, and 4% in DMP and in petrolatum to the skin of each of 14 subjects. At a concentration of 16% in either base, Benzophenones-4 and -11 were irritating to four and two subjects, respectively. Neither ingredient was irritating at concentrations of 4% or 8% in either vehicle.[107]

Marzulli and Maibach[114] tested the potential irritancy of Benzophenone-4 on six adult white humans. Patches containing 1% or 10% Benzophenone-4 in

TABLE 10. Human Patch Test Data.

Benzophenone	*Test method*[a]	*No. of subjects*	*Effective conc. (%)*	*No. of reactions*	*Comments*	*Ref.*
−1	Shelanski RIPT	100	1 in butyl carbitol	0	Nonirritating/nonsensitizing	126
−1	SIPT	14	16,8,4/DMP			
			16,8,4/Petrolatum	0	Nonirritating	107
−2	Shelanski RIPT	50	2.45 and 4.9/H_2O	17/50−induction 5/50−challenge	Evidence of fatiguing and possible sensitization at 5%; none at 2.5%	124
−2	SIPT	14	16,8,4/DMP			
			16,8,4/Petrolatum	"Mild reactions similar to toilet soap"	Nonirritating	107
−3	SIPT	14	16,8,4/DMP			
			16,8,4/Petrolatum	0	Nonirritating	107
−3	Mod. D/S RIPT	100	25−induction in petrolatum			
			10−challenge in petrolatum	0	Nonirritating/nonsensitizing	50
−3(3% in a lotion)	Mod. Draize RIPT	203	3.0	0	Nonirritating/nonsensitizing	113
−3(3% in a sunscreen)	SIPT (48 hr)	100	3.0	0	Nonirritating	69
−3(3% in a sunscreen)	Mod. D/S RIPT	150	3.0	"several nonspecific reactions"	"Not a primary irritant"; nonsensitizing	69
−3(3% in a sunscreen)	Mod. Draize RIPT	150	3.0	Mild irritation (but no sensitization) challenge patches	Nonsensitizing	69
−3(3% in a sunscreen)	Mod. D/S RIPT	57	3.0	1 sensitized reaction	Minimum sensitizing potential	125
−4	SIPT	14	16,8,4/DMP	Four subjects reacted to 16% BP-4 in DMP and petrolatum.	Irritating at 16% in DMP and petrolatum	107
			16,8,4/Petrolatum	One subject reacted to 8% BP-4 in DMP and Petrolatum.		

−4	Shelanski RIPT	50	5−in H_2O	0	Nonirritating/nonsensitizing	127
−4	Mod. D/S RIPT	100	25−induction/ Petrolatum 10−challenge/ Petrolatum	0	Nonirritating/nonsensitizing	50
−6	SIPT	14	16,8,4/DMP 16,8,4/Petrolatum	0	Nonirritating	107
−6	Shelanski RIPT	50	100	0	Nonirritating/nonsensitizing	109
−8	Mod. D/S RIPT	100	25−induction/ Petrolatum 10−challenge/ Petrolatum	Seven cases of irritation to induction and challenge patches	Contact sensitizing	50
−8(2% in a lotion)	Mod. Draize RIPT	205	2	0	Nonirritating/nonsensitizing	113
−9	SIPT	14	10.72,5.36,2.68/ DMP 10.72,5.36,2.68/ Petrolatum	0	Nonirritating	107
−11	SIPT	14	16,8,4/DMP 16,8,4/Petrolatum	Two subjects reacted to 16% BP-11 in DMP and petrolatum.	Nonirritating at 8 and 4%	107
−11	Shelanski RIPT	50	20−in butyl carbitol acetate	0	Nonirritating/nonsensitizing	128
−12	Mod. D/S RIPT	50	25−induction/ Petrolatum 10−challenge/ Petrolatum	0	Nonirritating/nonsensitizing	94

[a]Shelanski double insult patch test−120-hr patch/3 wk rest/48-hr patch (challenge) to original site.
Single Insult Patch Test (SIPT)−24-hr patch.
Shelanski repeated insult patch test (RIPT)−15 (24-hr patch/24-hr rest)/2-wk rest/24-hr patch (challenge) to original site.
Modified Draize/Shelanski RIPT−10 (21-hr patch/24-hr rest)/1-wk rest/24-hr patch (challenge) to virgin site.
Modified Draize RIPT−10 (24 hr-patch/24 hr-rest)/2-wk rest/72-hr patch (challenge) to virgin site.

alcohol were applied to the subjects for 24 hours, after which time the patches were removed, the sites scored, and fresh patches applied. This procedure was repeated every other day, three days per week for seven weeks, until a total of 21 patches had been made. The mean cumulative irritation scores for 1% and 10% solutions were 8.6 and 53.1, respectively (maximum score = 84). The latter value is indicative of a primary irritant.

Fisher[129] reported that "in the past ten years of patch testing on hundreds of patients [at his practice], only two patients have been allergic to Benzophenone-4." He concluded that this indicates "very low sensitivity" in the population, and that this ingredient is safe for general use.

No data were available regarding the clinical assessment of Benzophenone-5.

The scientific literature generally confirms the clinical safety of topically used Benzophenones; however, several cases of contact sensitivity to these ingredients have been reported. Pariser[130] reported contact dermatitis caused by topical use of a sunscreen containing 3% Benzophenone-3 and 3% Benzophenone-8. "Standard" patch tests of the sunscreen lotion, 2% Benzophenone-8 (in petrolatum), or 2% Benzophenone-3 (in petrolatum), revealed irritation at 48 and 72 hours to the first two and mild irritation at 72 hours to the last. Ramsey et al.[131] reported a case of contact sensitivity resulting from topical use of a suntan lotion containing 10% Benzophenone-4. A scratch test of a 1% Benzophenone-4 solution resulted in a 2+ response; a 1% Benzophenone-3 solution also elicited a 2+ reaction. A single 24-hour patch test of a 5% Benzophenone-4 solution (aqueous) revealed a 2+ papular reaction at 24 and 48 hours. Thompson et al.[132] reported that a 62-year-old man with a history of photosensitivity developed contact dermatitis after he used a sunscreen containing Benzophenones-3 and -8 (no concentrations given). Patch tests of the lotion or of the individual Benzophenones at product concentrations resulted in 2+ reactions at 48 hours.

Photosensitivity

Phototoxicity

Cosmetic products containing Benzophenones-2, -3, or -4 (0.1%–3.5%) were tested for phototoxicity in humans (Table 11). In each study, the test material was applied under occlusion to the subject's skin for 24 hours. Sites were then scored, exposed to UV radiation, and then scored daily for up to seven days. Nonirradiated/treated and nontreated/irradiated controls were frequently used. Products containing Benzophenones-2, -3, and -4 were nonphototoxic in all studies; however, a number of subjects experienced slight irritation (usually a 1+ response) to the test material.

Photoallergenicity

Cosmetic products containing up to 3.5% Benzophenone-3 were tested for photoallergenicity potential in humans (Table 11). In each study, the protocol was similar to that for phototoxicity except that the procedure was repeated three times weekly until 10 or 12 induction applications had been made. Following a 10- to 14-day rest, 24-hour challenge patches were applied to the original site

TABLE 11. Clinical Photosensitivity.

Benzophenone (Product)	*Benzophenone Test conc. (%)*	*Test*	*No. of subjects*	*UV-light source*[a]	*Reactors*[b]*/ Photosens.*	*Conclusion/Comments*	*Ref.*
−2(bath prep)	0.0005	Phototox.[c]	22	Sunlight	9(1+;c,i)/0	Nonphototoxic (reactions due to primary irritation)	134
−2(bath prep)	0.0005	Phototox.[c]	22	Sunlight	6(1+;c,i)/0	Nonphototoxic (reactions due to primary irritation)	134
−2(bath prep)	0.0005	Phototox.[c]	22	Sunlight	5(1+;c,i)/0	Nonphototoxic (reactions due to primary irritation)	134
−3(face lotion)	2	Phototox.	10	BL	0/0	Nonphototoxic	125
−3(suntan lotion)	3.5	Phototox.	10	BL	0/0	Nonphototoxic	125
−3(eye cream)	2	Phototox.	10	BL	0/0	Nonphototoxic	133
−3(lotion)	3.5	Phototox.	28	BL/HQML	0/0	Nonphototoxic	40
−3(sunscreen)	1	Phototox.	10	XASS	10/0	Nonphototoxic (minimal irritation due to presence of UV-B light)	135
−3(sunscreen)	3	Phototox.	12	BL	1(1+;c,i)/0	Nonphototoxic (slightly irritating to 1 subject)	125
−3(sunscreen)	3	Phototox.	26	–	0/0	Nonphototoxic	69
−4(skin prep)	0.1	Phototox.	25	Sunlight	0/0	Nonphototoxic	136
−3(suntan lotion)	3.5	Photoall.	27	BL	3(1+;c,i−induct)/ 1(1+;c,i,o,v)/0	Nonphotoallergenic (primary irritation/1 subject sensitized)	125
−3(face lotion)	2	Photoall.	27	BL	2(1+;i) 1(1+;c)	Nonphotoallergenic (primary irritation)	125
−3(eye cream)	2	Photoall.	28	BL	1(c,i,o)/0	Nonphotoallergenic (1 subject sensitized)	133
−3(lotion)	3.5	Photoall.	28	BL	0/0	Nonphotoallergenic	40
−3(sunscreen)	3	Photoall.	30	BL	1(2+;c,i,o)/0	Nonphotoallergenic (1 subject sensitized to BP-3)	125
−3(sunscreen)	3	Photoall.	25	–	0/0	Nonphotoallergenic	69

[a]sunlight (UV-A, UV-B); XASS−Xenon arc solar simulator (UV-A); BL−F40 black lights (UV-A); HQML−Hot quartz mercury lamp (UV-B).
[b]c = control site; i = irradiated site; o = original site (challenge); v = virgin site (challenge).
[c]Procedure repeated daily for five consecutive days.

and/or a fresh site. Sites were scored upon patch removal and daily for up to four days. The products containing Benzophenone-3 were nonphotoallergenic in all studies; however a number of subjects experienced irritation or sensitization to the test material. One of 30 subjects reacted (2+ response) to one induction patch and the challenge patches, each containing 3.0% Benzophenone-3 sunscreen. Irritation persisted throughout the 72-hour observation period. When this subject was rechallenged six weeks later, similar reactions were observed at original and virgin sites. Eleven months later, the subject was patched with each component of the sunscreen. Benzophenone-3 induced sensitization in this individual. The investigators concluded, however, that the product containing 3% Benzophenone-3 is nonphotoallergenic.[125]

One subject with a history of contact sensitivity to cosmetics reacted to a challenge patch containing 2% Benzophenone-3 applied to the original site. The reaction occurred at both control and irradiated sites. However, no irritation resulted from patches applied to a fresh site.[133] Three of ten subjects reacted to a total of five induction patches containing 2% Benzophenone-3 in a face lotion. No irritation resulted from challenge patch application.[133] The suntan lotion (3.5% Benzophenone-3) caused several reactions to induction patches concurrently at control and irradiated sites. Although one subject developed irritation (1+) to the challenge patches at original and virgin sites, the response occurred at both control and irradiated sites.[125]

Other Clinical Experience

Benzophenones-3 (2%–10%); -4 (1%–10%); -8 (2%–10%); and -10 (0.5%–10%) have been tested for sunscreen efficacy in more than 121, 167, 130, and 295 human subjects, respectively, and under various sources of UV radiation (Table 12). In all tests combined, there was no report of irritancy or phototoxic reaction to these ingredients.

SUMMARY

Benzophenones-1 to -12 are substituted derivatives of 2-hydroxybenzophenone. These ingredients have similar chemical and physical properties. Benzophenones-7, -10, and -12 have no current use in cosmetics; however, they are used noncosmetically as fungicides, pharmaceutical sunscreens, and antioxidant/photostabilizers. In addition to their widespread use as photostabilizers in cosmetics, Benzophenones, have a photoprotective effect on the skin. Benzophenones are typically used in cosmetic formulations at concentrations up to 1%; however, concentrations of up to 5 or 10% are reported for certain Benzophenones.

Benzophenones-3, -4, and -8 are registered with the FDA as safe and effective sunscreen ingredients (at concentrations up to 10%) for OTC use and as indirect food additives (Benzophenone-12, up to 0.01%). These sunscreens play an active role in protecting individuals who have photodermatoses, especially drug-mediated.

When ingested, absorbed Benzophenones were primarily conjugated and

TABLE 12. Benzophenone Sunscreen Efficacy Tests.

Benzophenone	*Conc. tested (%)*	*No. of subjects*	*UV radiation source*	*Ref.*
−3	3	9–17	Solar simulator	69
	3	18	Solar simulator	69
	3	20	Sunlight	55
	2	10	Xenon arc solar simulator	63
	5	10	Xenon arc solar simulator	63
	10	10	Xenon arc solar simulator	63
	3	12	Germicidal mercury lamp	38
	3	23	Prism grating monchrom.	45
	3	9	Sunlight	137
−4	1–3	10	Solar simulator	69
	10	5	Sunlight	69
	10	10	Ultraviolet lamp	71
	10	10	Hot quartz lamp	62
	10	20	Sunlight	55
	5	10	Xenon arc solar simulator	63
	5	12	Germicidal mercury lamp	38
	10	12	Germicidal mercury lamp	38
	10	16 normal 10 photosens.	Quartz mercury lamp	138
	10	30	Sunlight	139
	10	6	Mercury UV lamp	45
	10	16	Prism grating monochrom.	45
−8	3	9	Sunlight	69
	3	33	Sunlight	69
	3	20	Sunlight	55
	2	10	Xenon arc solar simulator	63
	5	10	Xenon arc solar simulator	63
	10	10	Xenon arc solar simulator	63
	3	12	Germicidal mercury lamp	38
	3	17	Prism grating monochrom.	45
	3	9	Sunlight	137
−10	10	86	Sunlight	140
	0.5	104 normal 28 photosens.	Xenon arc monochromator	57
	–	77	–	58

excreted in the urine, while the unabsorbed material passed out with the feces. Benzophenones were practically nontoxic when administered orally to rats, and Benzophenones-3, -4, -8, and -12 were nontoxic when applied to the skin of rabbits at doses of > 5 g/kg. In subchronic oral toxicity studies, Benzophenones-3 and -12, at 1% and 1.8% in the diet, respectively, were nontoxic to rats. Benzophenones-1 and -12 elicited toxic effects in rats at 0.6 and 1.9 g/kg, respectively, when fed for 90 days. In the same time period, Benzophenone-3, fed at 0.5% in the diet, and Benzophenone-8, fed at 5%, produced toxic effects. In a 120-day feeding study, Benzophenone-12 was nontoxic to dogs at a concentration of 0.6% in the diet.

Benzophenones were nonirritating or mildly irritating when applied to rabbit skin at concentrations of up to 100%. Benzophenones were practically nonirritating to the eyes of rabbits, even when instilled undiluted. A subchronic skin irritation test revealed that Benzophenone-4 was capable of causing minimal irritation (in rabbits) at a concentration of 10%. When Benzophenone-3 was tested for potential sensitization through the Kligman Guinea Pig Maximization procedures, it was reported to be nonsensitizing. Benzophenone-8 (3%) and Benzophenone-3 (6%) were nonphototoxic in guinea pigs and rabbits, respectively.

Benzophenones-2, -6, and -8 were reported to be weakly mutagenic with metabolic activation in the Ames test. Benzophenones-6 and -8 were mutagenic in one *Salmonella* strain only. In a Mouse Lymphoma Forward Mutation Assay and a cytogenic assay, Benzophenone-2 was weakly mutagenic at high concentrations and with metabolic activation. All other Benzophenones were nonmutagenic both with and without metabolic activation in the Ames test.

Benzophenones were tested for skin irritation and sensitization in humans. In general, these ingredients were mildly irritating and sensitizing at concentrations greater than those used in cosmetics. The published scientific literature reports isolated incidences of contact sensitization to Benzophenones-3, -4, and -8.

Sunscreens and other cosmetic products containing Benzophenones-2, -3 and -4 (at concentrations of 0.1%–3.5%) were tested for phototoxicity and/or photosensitivity in a number of studies. All products were reported to be nonphototoxic and nonphotoallergenic, although instances of primary irritation and contact sensitization to these products were observed.

Benzophenones-3, -4, -8, and -10 were tested extensively for sunscreen efficacy; no instances of irritation or phototoxicity were reported.

DISCUSSION

Benzophenones-1, -2, -3, -4, -5, -6, -8, -9, and -11 are photostabilizers in cosmetics. Benzophenones-7, -10, and -12 have no reported cosmetic use, yet they are used noncosmetically as fungicides, pharmaceutical sunscreens, and antioxidant/photostabilizers, respectively. Relevant chemical, use, toxicological, and clinical data on Benzophenones-2, -6, and -8 have been included in this report. The mutagenicity data on these three ingredients are available in a subsequent Addendum to the Final Report.

Benzophenones-3, -4, and -8 are approved by the FDA for use as safe and effective OTC sunscreen ingredients at concentrations equal to or greater than those used in cosmetics.

Although there are no animal toxicology or clinical data for Benzophenone-5, this ingredient is simply the sodium salt of Benzophenone-4. It would be expected that Benzophenones-4 and -5 have similar biological properties (i.e., toxicity, irritancy potential, etc.). At high concentrations, Benzophenone-5 may be an eye irritant; however, it would not be expected to induce significant ocular irritation at cosmetic use concentration ($\leq$0.1%).

All Benzophenones were tested for mutagenesis under the Ames *Salmonella* test. All Benzophenones were nonmutagenic when assayed directly, and all but

Benzophenones-2, -6, and -8 were nonmutagenic following metabolic activation. Benzophenones-6 and -8 were weakly mutagenic at high doses in only one strain (TA1537). Benzophenone-2 was nonmutagenic with and without activation in one Ames test, but in another test it was mutagenic under activation in four *Salmonella* strains. Benzophenone-2 was also reported to be weakly mutagenic under activation conditions in a cytogenic assay and in a forward mutation assay.

Benzophenones-1, -5, -6, -9, and -11 lack photosensitivity data, but because of their conditions of use, as well as similarities in chemical structure and UV-absorption spectra to other Benzophenones, these five ingredients would not be expected to induce phototoxicity or photoallergenicity.

CONCLUSION

On the basis of the available animal data and clinical human experience presented in this report, the Panel concludes that Benzophenones -1, -3, -4, -5, -9, and -11 are safe for topical application to humans in the present practices of use and concentration in cosmetics.

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