Final Report of the Cosmetic Ingredient Review Expert Panel

Safety Assessment of Fumaric Acid And Related Salts and Esters as Used in Cosmetics

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The 2009 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Valerie C. Robinson, Scientific Analyst/Writer.

Final Report of the Safety Assessment of Fumaric Acid and Related Salts and Esters as Used in Cosmetics

Abstract: Fumaric Acid, Dibehenyl Fumarate, Di-C12-15 Alkyl Fumarate, Diethylhexyl Fumarate, Diisostearyl Fumarate, Disodium Fumarate, Ferrous Fumarate, Sodium Fumarate, and Sodium Stearyl Fumarate are used in cosmetics. Salts of dimethyl fumarate are used as antipsoriatic pharmaceuticals, but not in cosmetics. Fumarate metabolism occurs in the citric acid cycle to produce water and carbon dioxide. Most animal studies demonstrate no significant single or repeated dose toxicity, including genotoxicity and carcinogenicity assays. One repeated dose animal study did report gonadotropic and estrogenic activity, and progressive testicular atrophy, but a comparable study reported that spermatogenesis and testicular structure were unaffected. In pre-clinical studies, dimethyl fumarate, at doses approaching maternal toxicity levels, was not a developmental toxicant; embryo-fetal toxicity was only observed at maternally toxic doses. These ingredients are not irritants or sensitizers. The CIR Expert Panel considered that the available data were adequate to support the safety of these ingredients as used in cosmetics.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel has considered the information in this report to assess the safety of Fumaric Acid, Dibehenyl Fumarate, Di-C12-15 Alkyl Fumarate, Diethylhexyl Fumarate, Diisostearyl Fumarate, Disodium Fumarate, Ferrous Fumarate, Sodium Fumarate, and Sodium Stearyl Fumarate as used in cosmetics as binders, bulking agents, buffering agents, emollient skin conditioning agents, nonaqueous viscosity increasing agents, pH adjusters, and slip modifiers.

Fumaric Acid is a trans dicarboxylic acid. The corresponding cis dicarboxylic acid is Maleic Acid. Previously, the CIR Expert Panel had reviewed the safety of Maleic Acid (Andersen 2007) with the conclusion of safe for use in cosmetic formulations as a pH adjustor in the practices of use as described in that safety assessment; i.e., up to 0.0004%. These two isomers are not considered readily interconverted and have different chemical and physical properties.

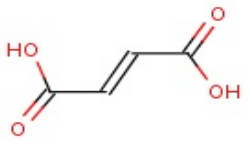
CHEMISTRY

Definition and Structure

Fumaric Acid

As listed in the *International Cosmetic Ingredient Dictionary and Handbook* (G ıric Acid (CAS Nos.110-17-8 c acid shown in **Figure 1a**.

(a)



(b)

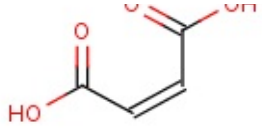


Figure 1. (a) Fumaric Acid and (b) Maleic Acid (ChemIDplus Lite 2008).

The difference in structure of the cis dicarboxylic acid form of Maleic Acid may be seen in the structure shown in Figure 1b.

Technical names for Fumaric Acid include: Allomaqleic Acid, Boletic Acid, 2-Butenedioic Acid; trans-1,2-Ethylenedicarboxylic Acid, and Lichenic Acid. Trade name mixtures include: Lipoderma - Shield BG, Lipoderma - Shield PG, and Unicontrozon C-49 (Gottschalck and Bailey 2008).

According to Hansson and Thorneby-Andersson (2003), Fumaric Acid is an endogenous compound formed mainly in the citric acid cycle. Fumaric Acid is also a fruit acid, ubiquitous in plants.

Dibehenyl Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Dibehenyl Fumarate (CAS No. not listed) is the diester of behenyl alcohol and Fumaric Acid with the chemical structure shown in **Figure 2.**

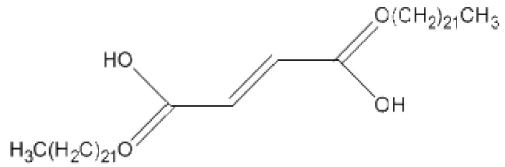


Figure 2. Dibehenyl Fumarate (Gottschalck and Bailey 2008).

A synonym for Dibehenyl Fumarate is 1,4-Bis-Docosanyl Butenedioate. A trade name is listed as Marrix 222 (Gottschalck and Bailey 2008).

Di-C12-15 Alkyl Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Di-C12-15 Alkyl Fumarate (CAS No. not listed) is the diester of C12-15 Alcohols (q.v.) and Fumaric Acid. It has the chemical structure shown in **Figure 3.**

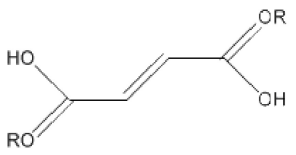


Figure 3. Di-C12-15 Alkyl Fumarate, where R represents the C12-15 alkyl group (Gottschalck and Bailey 2008).

A trade name for Di-C12-15 Alkyl Fumarate is Marrix S.F. (Gottschalck and Bailey 2008).

Diethylhexyl Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Diethylhexyl Fumarate (CAS Nos. 141-02-6; 128111-61-5) is the diester of 2-ethylhexanol and Fumaric Acid. It has the chemical structure shown in Figure 4.

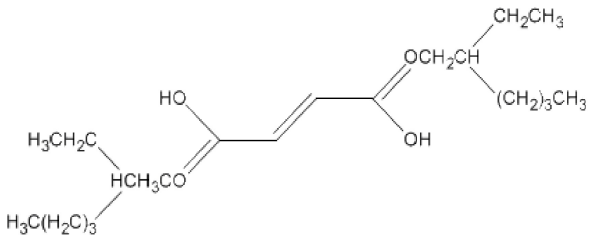


Figure 4. Diethylhexyl Fumarate (Gottschalck and Bailey 2008).

Synonyms for Diethylhexyl Fumarate include: Bis(2-Ethylhexyl) 2-Butenedioate; 2-Butenedioic Acid, Bis(2-Ethylhexyl) Ester; and Dioctyl Fumarate. A trade name for this chemical is Bernel Ester 284 (Gottschalck and Bailey 2008).

Diisostearyl Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Diisostearyl Fumarate (CAS Nos. 112385-09-8; 113431-53-1) is the diester of isostearyl alcohol and Fumaric Acid (q.v.). It has the chemical structure shown in Figure 5.

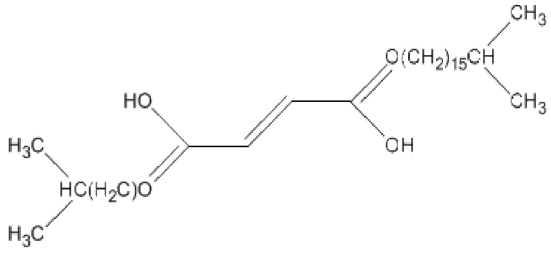


Figure 5. Diisostearyl Fumarate (Gottschalck and Bailey 2008).

Synonyms for Diisostearyl Fumarate include 2-Butenedioic Acid, Diisooctodecyl Ester and Diisooctadecyl 2-Butendioate. A trade name is Schercemol DISF Ester (Gottschalck and Bailey 2008).

Disodium Fumarate

As listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Disodium Fumarate (CAS No. 17013-01-3) is the disodium salt of Fumaric Acid (q.v.). It has the chemical structure shown in Figure 6.

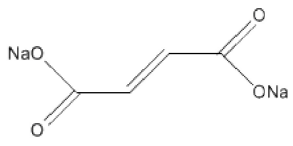


Figure 6. Disodium Fumarate (Gottschalck and Bailey 2008).

Another name for Disodium Fumarate is Fumaric Acid, Disodium Salt. A trade name mixture is listed as Extrapone Apple 2/033317 (Gottschalck and Bailey 2008).

Ferrous Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Ferrous Fumarate (CAS No. 40770-80-8) is the salt in the chemical structure shown in Figure 7.

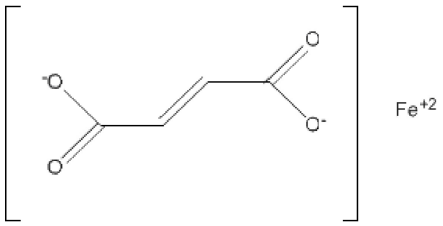


Figure 7. Ferrous Fumarate (Gottschalck and Bailey 2008).

A synonym for Ferrous Fumarate is 2-Butenedioic Acid (2E1-, Iron (2^+) Salt (1:1).

Sodium Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Sodium Fumarate (CAS Nos. 5873-57-4; 7704-73-6) is the mono-sodium salt of Fumaric Acid (q.v.). It has the chemical structure shown in Figure 8.

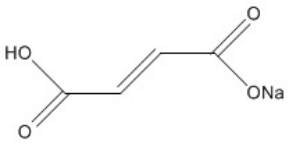


Figure 8. Sodium Fumarate (Gottschalck and Bailey 2008).

Synonyms for Sodium Fumarate include: 2-Butenedioic Acid, Monosodium Salt; Fumaric Acid, Monosodium Salt; and Monosodium Fumarate (Gottschalck and Bailey 2008).

Sodium Stearyl Fumarate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008), Sodium Stearyl Fumarate (CAS No. 1120-04-3) is the organic compound shown in the structure shown in Figure 9.

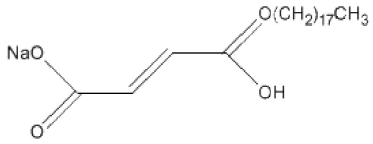


Figure 9. Sodium Stearyl Fumarate (Gottschalck and Bailey 2008).

A trade name for Sodium Stearyl Fumarate is Covafluid FS (Gottschalck and Bailey 2008).

Physical and Chemical Properties

Table 1 presents physical and chemical properties of Fumaric Acid, Disodium Fumarate, Diisostearyl Fumarate, Sodium Stearyl Fumarate, and Ferrous Fumarate; and chemical class information on all ingredients in this safety assessment.

Reactivity

Hansson and Thorneby-Andersson (2003) reported that maleic acid and Fumaric Acid have several chemical reactions in common, particularly those based on their electrophilic properties. Their electrophilic character is displayed in their reactions with

Table 1. Physical and Chemical Properties of Fumaric Acid, its salts and esters.

Property	Description	Reference
	Fumaric Acid	
Chemical Class	Carboxylic Acids	Gottschalck and Bailey (2008)
Appearance	White crystals or clear, crystalline powder, solid	Bartek Ingredients, Inc. (2007); and Food Chemicals Codex (2008)
Odor/Taste	None/fruit-like	Bartek Ingredients, Inc. (2007)
pH (1:30 aqueous solution)	2.0 - 2.5	Food Chemicals Codex (2008)
Molecular Weight:	116.07	Bartek Ingredients, Inc. (2007)
Acid Equivalent Weight	58.04	Bartek Ingredients, Inc. (2007)
Specific Gravity (20°C/4°C)	1.635	Bartek Ingredients, Inc. (2007)
Melting Point (°C)	286	Bartek Ingredients, Inc. (2007)
Flash Point (°C)	282	Bartek Ingredients, Inc. (2007)
Solubility	Soluble in alcohol, slightly soluble in water and ether, very slightly soluble in chloroform.	Food Chemicals Codex (2008)
log P_{ow}	0.33	European Chemicals Bureau (2000)
	Disodium Fumarate	
Chemical Class	Organic Salts	Gottschalck and Bailey (2008)
Molecular Weight:	160	Bimax Ingredients, Inc. (2007)
Appearance	White powder	Bimax Ingredients, Inc. (2007)
pH (10% in water):	6.8	Bimax Ingredients, Inc. (2007)
	Sodium Fumarate	
Chemical Class	Organic Salts	Gottschalck and Bailey (2008)
	Dibehenyl Fumarate	
Chemical Class	Esters	Gottschalck and Bailey (2008)
	Di-C12-15 Alkyl Fumarate	
Chemical Class	Esters	Gottschalck and Bailey (2008)
	Diethylhexyl Fumarate	
Chemical Class	Esters	Gottschalck and Bailey (2008)
	Diisostearyl Fumarate	
Chemical Class	Esters	Gottschalck and Bailey (2008)
Appearance @ 25°C	Clear to slightly hazy viscous liquid	Lubrizol (2007)
Color, Gardner	1 max	Lubrizol (2007)
Odor	Slight, characteristic	Lubrizol (2007)
Specific Gravity @ 25°C	0.890 - 0.910	Lubrizol (2007)
Refractive Index @ 25°C	1.461 - 1.464	Lubrizol (2007)
Acid Value, mg KOH/g	2.0 max	Lubrizol (2007)
Saponification Value, mg KOH/g	160 - 180	Lubrizol (2007)
IR (neat)	Conforms to reference	Lubrizol (2007)
Solubility	Solubile in most hydrophobic solvents such as esters, vegetable oils, mineral oils, alcohols, aliphatic, aromatic and chlorinated hydrocarbons; partly soluble in glycols; dispersible in triols and polyols; and insoluble in water.	Lubrizol (2007)
	Sodium Stearyl Fumarate	
Molecular weight	390.54	Science Lab (2007a)
Melting Point	decomposes	Science Lab (2007a)
Appearance	Fine, white powder	Food Chemicals Codex (2008)
Solubility	Slightly soluble in methanol, but practically insoluble in water	Food Chemicals Codex (2008)
	Ferrous Fumarate	
Appearance	red-orange to red-brown powder; may contain soft lumps that produce a yellow streak when crushed	Food Chemicals Codex (2008)
Solubility	Soluble in water and alcohol	Food Chemicals Codex (2008)
Molecular weight	169.9	Science Lab (2007b)
Melting Point	decomposes	Science Lab (2007b)

thiols, such as cysteine and glutathione. The reaction of endogenous Fumaric Acid with glutathione and with cysteine give S-(1,2-dicarboxylethyl)glutathione and S-(1,2-dicarboxylethyl)cysteine, respectively, as products.

Method of Manufacture

According to Gottschalck and Bailey (2008), Disodium Fumarate, Sodium Fumarate, Di-C12-15 Alkyl Fumarate, and Diethylhexyl Fumarate are derived solely from a synthetic source. Dibehenyl Fumarate is derived from plant and synthetic sources, and Diisostearyl Fumarate is derived from animal and synthetic sources.

The *Merck Index* stated that Fumaric Acid is prepared industrially from glucose by the action of fungi (i.e., *Rhizopus nigricans*) and that laboratory preparation of Fumaric Acid is performed by the oxidation of furfural with sodium chlorate in the presence of vanadium pentoxide (O'Neill 2006).

Natural Occurrence

Haviv et al. (1999) reported that fumarates are derived from succinates by succinate dehydrogenase, an enzyme that is unique because it is an integral part of the inner mitochondrial membrane, and directly linked to the electron transport chain. Human skin naturally produces Fumaric Acid when exposed to sunlight.

The Merck Index (O'Neil et al. 2006) stated that Fumaric Acid naturally occurs in many plants, including *Fumaria officinalis* L.

Analytical Methods

Kim and Karasek (1981) compared the negative ions observed by plasma chromatography (PC) and atmospheric pressure ionization mass spectrometry (APIMS) for maleic acid, Fumaric Acid, and the isomeric phthalic acids. All 3 isomers of phthalic acid (phthalic acid, isophthalic acid, and terephthalic acid) showed the identical species of (M-18)- and (M + O)- in APIMS, whereas phthalic acid and isophthalic acid showed a single ionic species with different ion mobilities in PC. Maleic acid and Fumaric Acid showed the same patterns of negative production ions in either PC or APIMS. The authors concluded that if the ion survival time from a compound is longer than the time of PC detection, then the ion can be observed by both techniques; if the ion survival time is $\leq 10^{-5}$ sec then the ion can be observed only by APIMS.

Impurities

Lonza (2006) provided the specifications for Fumaric Acid (in the trade name mixture, Unicontrozon C-49) shown in **Table 2**.

UV Absorption

European Chemicals Bureau (2000) stated that Fumaric Acid does not absorb UV light above 290 nm in methanol, acidic methanol or basic methanol solution.

Table 2. Specifications for Fumaric Acid in the trade name mixture, Unicontrozon C-49 as given by Lonza (2006).

Characteristics	Guaranteed
Purity (%)	99.7 min.
Moisture (%)	0.25 max.
Color in alcohol (sol. 5%) (Hazen)	10 max.
Ash (ppm)	50 max.
Iron (ppm)	5 max.
Arsenic (ppm)	1 max.
Heavy Metals (as Pb) (ppm)	10 max.
Lead (ppm)	1 max.
Mercury (ppm)	1 max.
Maleic Acid (%)	0.1 max.
Granulometric Analysis	
Granular form	
on 30 mesh sieve (%)	0.5 max.
on 140 mesh sieve (%)	90 min.
Granular FF form	
on 30 mesh sieve (%)	2.5 max.
on 140 mesh sieve (%)	60 min.
Powder form	
through 80 mesh sieve (%)	100 min.
through 100 mesh sieve (%)	95 min.
Microbiology Data[1]	
Bacteria (CFU/g)	<10
Molds and Yeasts (CFU/g)	<10
Total Coliforms (CFU/g)	<10
Fecal Coliforms (CFU.g)	<10
Salmonella (CFU/g)	Absent

[1] This is a statistical control realized in a external laboratory and did not appear on the Certificate of Quality.

USE

Cosmetic

The functions of Fumaric Acid and its salts in cosmetics as given in the International Cosmetic Ingredient Dictionary and Handbook are shown in **Table 3**.

Industry provided reports of ingredient usage to the Food and Drug Administration (FDA) through the Voluntary Cosmetic Registration Program (VCRP) and the Cosmetic, Toiletry and Fragrance Association (CTFA - now the Personal Care Products Council) conducted a survey of current use concentrations. These data are given in **Table 4**.

As provided to the VCRP, both Fumaric Acid an Di-C12-15 Alkyl Fumarate have 4 uses and Diisostearyl Fumarate has 1 use in cosmetics (FDA 2006). Based on industry survey data, Fumaric Acid, Di-C12-15 Alkyl Fumarate, Diisostearyl Fumarate, and Ferrous Fumarate are used at concentrations of 0.0008% - 5%, 0.4% - 5%, 1% - 20%, and 0.0003%, respectively (CTFA 2007).

No current uses or use concentrations were available for Disodium Fumarate, Sodium Fumarate, Dibehenyl Fumarate, Diethylhexyl Fumarate, or Sodium Stearyl Fumarate.

According to Lubrizol (2007), Diisostearyl Fumarate is a high shine emollient with good conditioning properties. In lip care products, it helps to disperse pigments and is used to decrease feathering and bleeding. It provides a rich skin feel in creams and lotions. With its high contact angle, Diisostearyl Fumarate is ideal for applications requiring target delivery.

Certain uses of these ingredients as given in **Table 4** suggested that the product type could be aerosolized or sprayed.

Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 ± 1.5 µm for respirable particles that could result in lung exposure (Jensen and O'Brien, 1993).

Bower (1999), reported diameters of anhydrous hair spray particles of 60 - 80 µm and pump hair sprays with particle diameters of ≥80 µm. Johnsen (2004) reported that the mean particle diameter is around 38 µm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 - 110 µm range.

Non-Cosmetic

According to Davidson and Juneja (1990), Fumaric Acid is used to prevent the occurrence of malolactic fermentation in wines and as an antimicrobial agent in wines.

According to Hansson and Thorneby-Andersson (2003), Fumaric Acid is used as an additive to food for acidification purposes. It is also used in the plastics industry in the form of its dicarboxylic esters, especially in the production of polyesters. Esters of Fumaric Acid are also used as pharmacological tools in the depletion of glutathione.

FDA (2007), established by regulation (21CFR172.350) that Fumaric Acid and its calcium, ferrous, magnesium, potassium, and sodium salts may be safely used as food additives: (a) if the additives meet the following specifications: (1) Fumaric Acid contains a minimum of 99.5 percent by weight of Fumaric Acid, calculated on the anhydrous basis, and (2) the calcium, magnesium, potassium, and sodium salts contain a minimum of 99 percent by weight of the respective salt, calculated on the anhydrous basis, and Ferrous Fumarate contains a minimum of 31.3 percent total iron and not more than 2 percent ferric iron; (b) with the exception of Ferrous Fumarate, Fumaric Acid and the named salts are used singly or in combination in food at a level not in excess of the amount reasonably required to accomplish the intended effect; and (c) Ferrous Fumarate is used as a source of iron in foods for special dietary use, when the use is consistent with good nutrition practice.

FDA (2007) also established by regulation (21CFR172.826) that Sodium Stearyl Fumarate may be safely used as a food additive if: (a) it contains not less than 99 percent Sodium Stearyl Fumarate calculated on the anhydrous basis, and not more than 0.25 percent sodium stearyl maleate; and (b) The additive is used or intended for use: (1) as a dough conditioner in yeast-leavened bakery products in an amount not to exceed 0.5 percent by weight of the flour used, (2) as a conditioning agent in dehydrated potatoes in an amount not to exceed 1 percent by weight thereof, (3) as a stabilizing agent in non-yeast-leavened bakery products in an amount not to exceed 1 percent by weight of the flour used, (4) as a conditioning agent in processed cereals for cooking in an amount not to exceed 1 percent by weight of the dry cereal, except for foods for which standards of identity preclude such use, or (5) as a conditioning agent in starch-thickened or flour-thickened foods in an amount not to exceed 0.2 percent by weight of the food.

European Chemicals Bureau (2000) described Fumaric Acid as being used in paints, lacquers, varnishes, paper, pulp and wood fixing agents, food and foodstuff additives, intermediates, pH-regulating agents, and stabilizers.

Table 3. Functions of Fumaric Acid and its Salts and Esters in Cosmetics (Gottschalck and Bailey 2008).

Ingredient	Function
Fumaric Acid	Fragrance Ingredient; pH Adjuster
Disodium Fumarate	Buffering Agent; pH Adjuster
Sodium Fumarate	Buffering Agent; pH Adjuster
Dibehenyl Fumarate	Viscosity Increasing Agent - Nonaqueous
Di-C12-15 Alkyl Fumarate	Skin-Conditioning Agent - Emollient
Diethylhexyl Fumarate	Skin-Conditioning Agent - Emollient
Diisostearyl Fumarate	Skin-Conditioning Agent - Emollient
Sodium Stearyl Fumarate	Binder; Bulking Agent; Slip Modifier
Ferrous Fumarate	Not Reported

Table 4. Current uses and concentrations of Fumaric Acid and its salts and esters in cosmetics.

Product Category	2005 uses (FDA 2006)	2007 concentrations (CTFA 2007)
Fumaric Acid		
Bath Preparations		
Oils, tablets and salts	-	5%
Capsules	-	2%
Other bath preparations	-	0.08%
Non-coloring Hair Preparations		
Hair conditioners	-	0.2%
Skin Care Preparations		
Face and neck skin care preparations	-	0.2%
Body and hand skin care preparations	1	0.008%
Foot powders and sprays	1	
Moisturizers	-	0.02%
Night skin care preparations	-	0.2%
Paste masks (mud packs)	2	0.2%
Other skin care preparations	-	0.0008%
Total uses/ranges for Fumaric Acid	**4**	**0.0008% - 5%**
Ferrous Fumarate		
Personal Hygiene Products		
Other personal cleanliness products[1]	-	0.0003%
Skin Care Preparations		
Body and hand creams, lotions and powders	-	0.0003%
Total uses/ranges for Ferrous Fumarate	**-**	**0.0003%**
Di-C12-15 Alkyl Fumarate		
Baby Products		
Lotions, oils, powders and creams	-	5%
Non-coloring Hair Preparations		
Hair conditioners	-	0.4%
Makeup Preparations		
Face powders	-	1%
Foundations	-	2%
Lipsticks	1	5%
Skin Care Preparations		
Face and neck skin care preparations	-	1% -2%
Body and hand skin care preparations	1	1%
Foot powders and sprays	-	
Moisturizers	2	4%
Night skin care preparations	-	3%
Total uses/ranges for Di-C12-15 Alkyl Fumarate	**4**	**0.4% - 5%**
Diisostearyl Fumarate		
Eye Makeup Preparations		
Other eye makeup preparations	1	-
Non-coloring Hair Preparations		
Hair conditioners	-	1%
Hair sprays/aerosol fixatives	-	1%
Shampoos	-	1%
Other non-coloring hair preparations	-	1%
Makeup Preparations		
Blushers	-	3%
Lipsticks	-	20%
Total uses/ranges for Diisostearyl Fumarate	**1**	**1% - 20%**

GENERAL BIOLOGY

Citric Acid Cycle

According to Haviv et al. (1999), succinate and fumarate are readily oxidized by the kidneys. Succinate, fumarate and malate enhance cellular respiration catalytically, rather than stoichiochemically. Hydration of fumarate occurs via fumarase, which catalyzes a stereospecific trans addition of H^+ and OH^- to form L-malate, the only isomer that occurs naturally. Fumarate is an intermediate in the citric acid cycle used by cells to produce energy in the form of ATP from food. Fumarate is formed in the citric acid cycle via the oxidation of adenylsuccinate by the enzyme succinate dehydrogenase. Fumarate is then converted by the enzyme fumarase to malate.

Absorption, Distribution, Metabolism, Excretion

Fumaric Acid is a normal constituent of tissues as an intermediate in the tricarboxylic acid cycle. Distribution of Fumaric Acid in rat tissue has been studied by partition chromatography and it was found that blood contained 3 mg/l, brain tissue 150 mg/kg, kidney tissue 95 mg/kg, liver 78 mg/kg and muscle 23 mg/kg (Marshall et al. 1949).

According to Mrowietz et al. (1999), Fumaric Acid is poorly absorbed after oral intake. However, Fumaric Acid esters are almost completely absorbed in the small intestine. Dimethylfumarate (DMF) is rapidly hydrolyzed by esterases to monoethylfumarate (MEF), which is regarded as the active metabolite. MEF is further metabolized in the citrate cycle into water and carbon dioxide. The authors noted that there is no evidence for a cytochrome P450-dependent metabolism of Fumaric Acid esters. Excretion of metabolites is mainly through breathing, with only small amounts being excreted via urine and feces. DMF has a half-life of about 12 min, and MEF has a half-life of 36 h. Peak concentrations of monomethylfumarate are seen between 5 h and 6 h. DMF and free Fumaric Acid do not bind to serum proteins. Monomethylfumarate shows a protein binding of about 50%. The oral absorption of the esters refers to smaller esters (methyl and ethyl) than those used in cosmetics.

According to Hansson and Thorneby-Andersson (2003), the Fumaric Acid concentration in normal human plasma is about 2 µM, with the total body content in a adult human ranging from 8 to 80 g.

Membrane Effects

Butterfield et al. (1986) studied of the effect of various dicarboxylic acid compounds on the physical state of membrane proteins in human erythrocytes. Fumaric Acid, produced highly significant alteration in the physical state of membrane proteins.

Enzyme Effects

Spencer et al. (1990) reported that dimethyl fumarate and dimethyl maleate are potent inducers of cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) oxidoreductase activity in Hepa 1c1c7 murine hepatoma cells in culture, whereas Fumaric Acid and maleic acids are much less potent. Dimethyl fumarate in the diet (0.2 - 0.5%) of female CD-1 mice and female Sprague-Dawley rats elevated cytosolic glutathione transferases and quinine reductase activities in a variety of organs. The widespread induction of such detoxification enzymes by dimethyl fumarate suggested to these authors the potential value of this compound as a protective agent against chemical carcinogenesis and other forms of electrophile toxicity. The authors concluded that this study supports the finding that the concentrations of dimethyl fumarate required to obtain substantial enzyme induction were well-tolerated by rodents.

Hepatoprotective Effects

Rao and Mishra (1997) assessed the hepatoprotective activity of Fumaric Acid in the aqueous extract of the whole plants of *Sida cordifolia* Linn. (*Malvaceae*), commonly known as Bala.

Table 5 describes the effect of Fumaric Acid from this source on the viability of isolated rat hepatocytes exposed to galactosamine and thioacetamide. Fumaric Acid was found to be non-hepatotoxic at the maximum dose of 1000 µg/ml in vitro and hepatoprotective of thioacetamide at all concentrations and of galactosamine at the two highest concentration levels.

The authors also stated that Fumaric Acid from this source was non-hepatotoxic at 20 mg/kg p.o. in vivo. The compound had significant protection against thioacetamide induced hepatic cytotoxicity at all the tested concentration levels. It also had significant protection against galactosamine induced hepatic cytotoxicity at 100 and 1000 µg/ml, but it did not show any protection at 10 µg/ml (Rao and Mishra 1997).

Antiproliferative Effects

Hagedorn et al. (1975) reported on the effect of Fumaric Acid monoethylester (MEF) on DNA-synthesis. The incorporation of ^{14}C-thymidine into the DNA of cultured human lymphocytes was depressed by added MEF depending on the dosage of MEF. Decreasing incorporation was due to a lower number of DNA synthesizing cells. No selective inhibition of proliferation during one of the cell cycle phases was observed.

The effect of Fumaric Acid was examined on DNA synthesis in hepatocytes or hepatoma cells from rats treated with toxic agents (Kuroda et al. 1986).

Table 5. Effect of Fumaric Acid on viability of isolated rat hepatocytes exposed to galactosamine and thioacetamide (Rao and Mishra 1997).

Group		% Viability, Mean ± SEM (% Protection)			
		Galactosamine		Thioacetamide	
		% Viable Cells	Oxygen Uptake (µl/hr/mg protein)	% Viable Cells	Oxygen Uptake (µl/hr/mg protein)
Control		98.05 ± 0.56	4.13 ± 0.13	98.05 ± 0.56	4.13 ± 0.13
Toxicant		50.01 ± 0.11	1.98 ± 0.02	24.73 ± 1.14	0.98 ± 0.01
Fumaric Acid	10 µg/ml	32.50 ± 0.94	NU[a]	70.59 ± 1.31[b]	NU[a]
	100 µg/ml	98.10 ± 1.03[b]	NU[a]	92.96 ± 0.54[b]	NU[a]
	1000 µg/ml	99.10 ± 1.12[b]	4.28 ± 0.05[b]	90.01 ± 1.15[b]	3.91 ± 0.07[b]

[a] NU = Not undertaken
[b] Significant reduction compared to toxicant ($P < 0.01$).

Male Donryu rats were injected with mitomycin C or aflatoxin B1, singly or in combination with Fumaric Acid. After a specified period, hepatocytes were isolated from the liver by the collagenase perfusion method and placed in culture, and their activities for DNA synthesis were measured. Mitomycin C (0.5 mg/kg) reduced the semiconservative DNA synthesis, but simultaneous dosing of Fumaric Acid (40 mg/kg) enhanced the recovery. DNA synthesis in hepatoma cells was also reduced with mitomycin C but, in contrast to that of the hepatocytes, was little influenced by the simultaneous dosing of Fumaric Acid. The i.p. injection of Fumaric Acid also reduced the toxicity of aflatoxin B1 (0.25 mg/kg, ip), preventing the reduction of DNA synthesis as well as the occurrence of nuclear degenerative changes in the aflatoxin B1-exposed hepatocytes.

Sebok (1993), as part of an effort to study antipsoriatic effects, examined the antiproliferative and cytotoxic profile of Fumaric Acid in keratinocyte cultures. Hyperproliferative HaCaT keratinocytes in monolayer cultures were exposed to Fumaric Acid at concentrations between 0.4 µM and 960 µM for 48 h. Cell proliferation was studied by [^{3}H]thymidine incorporation. In addition ^{14}C-labelled amino acid uptake and total protein content were measured. Direct cytotoxicity was determined by the release of cytoplasmic lactate dehydrogenase (LDH) into the culture medium. The corresponding 50% inhibition concentration (IC_{50}) was calculated for DNA/protein synthesis: > 960 µM (Fumaric Acid), respectively. The total protein content was less sensitive. The authors concluded that there was no association between the cytotoxic and antiproliferative potential of Fumaric Acid.

Vandermeeren et al. (1997) reported that Western blots of normal human dermal fibroblast cytoplasmic extracts showed that dimethylfumarate had minor effects on the I kappa B alpha, beta and epsilon proteins: their cytokine-induced degradation and synthesis was only slowed down, an effect most prominently observed for I kappa B beta. No inhibitory effect of dimethylfumarate was observed on cytokine-induced RelA/p65 or c-Rel accumulation in nuclear extracts of cytokine-treated normal human dermal fibroblast cells. In contrast, cytokine-induced nuclear factor kappa B1/p50 nuclear accumulation was specifically inhibited by dimethylfumarate. This inhibitory effect was sufficient to inhibit nuclear factor kappa B1-RelA binding to nuclear factor kappa B consensus oligonucleotides in DNA binding assays. Likewise, cytokine-induced activation of a pNF kappa B:luciferase reporter construct in transiently transfected normal human dermal fibroblasts was inhibited by dimethylfumarate. The authors stated that the observations supported a mechanistic model for the oral antipsoriatic dimethylfumarate in which lowering of nuclear factor kappa B1 leads to changes in the nuclear factor kappa B1-RelA nuclear balance and inhibition of cytokine-induced adhesion molecule expression in normal human dermal fibroblasts.

ANIMAL TOXICOLOGY

Acute Toxicity

Table 6 summarizes acute animal toxicity studies involving Fumaric Acid, Sodium Fumarate, Disodium Fumarate, Diisostearyl Fumarate, and Di-C12-15 Alkyl Fumarate. Overall, these ingredients exhibited little acute toxicity. In some instances, the number of animals used were not provided by the study authors.

Short-term Oral Toxicity

Disodium Fumarate

Fourteen rabbits were fed 320-2080 mg/kg bw of Disodium Fumarate daily for 28 days without any deaths. An additional 6 rabbits received 2880-3680 mg/kg bw for 17 days with 3 deaths. Two rabbits were fed a daily diet containing 640 mg/kg bw Disodium Fumarate for 36 days without consistent adverse effect on body weight, hematology, non-protein nitrogen or creatinine levels, or histopathological findings (Locke et al. 1942).

Short-term Parenteral Toxicity

Sodium Fumarate

Each of 5 rabbits received i.v. injections of 50-500 mg/kg Sodium Fumarate every 2nd or 3rd day for 10-32 days without any injurious effect on blood levels of non-protein nitrogen or creatinine, phensulfolphthalein excretion, or kidney and liver histology (Bodansky et al. 1942).

Six rabbits received twice weekly i.p. injections of 60 mg/kg bw of Sodium Fumarate over 17-29 weeks. Swelling and congestion of the thyroids and atrophy of testes, with low hyaluronidase content, were found (Arai and Suchiro 1953).

Subchronic Oral Toxicity

Sodium Fumarate

In a study by Packman et al. (1963), 4 groups of 15 rabbits were fed diets containing 0 or 6.9% Sodium Fumarate (equivalent to 5% Fumaric Acid) for 150 days. There were no significant differences from controls in body weight gain, feed consumption, mortality rate, blood counts, blood sugar, non-protein nitrogen level and urine. Organ weights were not significantly different between the groups and histologic examination showed no adverse findings attributable to the diet. In particular, spermatogenesis and testicular structure were unaffected.

Chronic Oral Toxicity

Fumaric Acid

Levey et al. (1946) reported a study in which rats (14/group) were maintained on daily diets containing 0.1% or 1.0% Fumaric Acid for 2 years. The control group received 0.2% acetic acid. After 6 months, 7 of the animals were necropsied and examined grossly and histologically. The remaining 7 animals were continued on the experiment for the remainder of the 2-year period. Because of respiratory infections, survival in all groups (including control) was reduced significantly during the second half of the study: 0/7 control, 1/7 0.1% Fumaric Acid treated, and 2/7 1.0% Fumaric Acid treated animals survived until the end of the study. This reduction was not attributed to the test material. No clinical or pathological effects attributed to dosing were observed in rats fed 0.1% or 1.0% Fumaric Acid.

Eight groups of 14 weanling rats were kept on diets containing 0, 0.1 or 1.0% Fumaric Acid or 1.38% Sodium Fumarate for one year (half the groups) or 2 years. No adverse effect was noted on rate of weight gain, hemoglobin, blood picture, calcium balance as shown by bone histology, or on the histology of liver, kidney, spleen and stomach (Levey et al. 1946).

Fitzhugh and Nelson (1947) reported that 5 groups of 12 male and 12 female rats were fed diets containing 0, 0.1, 0.5, 0.8 or 1.2% Fumaric Acid for 2 years without toxic effects on growth or feed consumption. A further 4 groups of 12 male rats were kept for 2 years on diets containing 0, 0.5, 1.0 or 1.5% Fumaric Acid. At the 1.5% level was there a very slight increase in mortality rate and some testicular atrophy. Gross and microscopic examination of major organs revealed no abnormalities and tumor incidence was not significantly different between the groups.

Arai et al. (1955) reported a study in which 9 male rabbits received 60 mg/kg Sodium Fumarate every second day by i.p. injection, for 150 days. By the end of the test period, serum gonadotropic activity and estrogenic activity were detected. There was progressive testicular atrophy in all animals, resulting in disappearance of seminiferous epithelium and survival of Sertoli cells only. Chromophobe cells were increased in the pituitary.

Table 6. Acute animal toxicity studies with Fumaric Acid, Sodium Fumarate, Disodium Fumarate, Diisostearyl Fumarate, and Di-C12-15 Alkyl Fumarate.

Animal	Route	LD_{50} (mg/kg b.w.)/Results	Reference
		Fumaric Acid	
Rat	Oral	10,000	Ullmann's Encyclopedia of Industrial Chemistry (1996)
Rat	Oral	Female: 9,300; range: 6,300 - 13,800 Male: 10,700; range: 7,200 -15,800	Vernot et al. (1977)
Rat	Oral	10,700	Lewis (1991)
Rabbit	Oral	5,000	National Institute for Occupational Safety and Health (NIOSH 1986)
Rabbit	Dermal	> 20,000	Vernot (1977)
Mouse	i.p.	100	NIOSH (1986)
Mouse	i.p.	200	Smith et al. (1963)
Rat	i.p.	< 587 [a]	Levey et al. (1946)
		Sodium Fumarate	
Rat	Oral	~8,000	Levey et al. (1946)
		Disodium Fumarate	
Rabbit	Oral	~3,600	Locke et al. (1942)
Not specified	Not specified	~4,800	Weiss et al. (1923)
		Diisostearyl Fumarate	
Ten (5 males, 5 females) albino rats, 200 - 288 g	Oral	>5000	Consumer Product Testing (1993)
		Di-C12-15 Alkyl Fumarate	
3 male and 3 female HanBri:WIST (SPF) rats	oral gavage	>2000	RCC (2001)
5 male and 5 female rabbits	Acute dermal toxicity limit test	>2000	LebercoCelsis Testing (1996)

[a] necropsy showed hemorrhagic spots on the intestine near the site of injection; the surface of the liver appeared to be seared; and there was engorgement of the intestine and liver.

Fumaric Acid was fed to 4 groups of 6 young dogs at 0, 1, 3 and 5% of the diet for 2 years without adverse effect on body weight gain, development, hematology, blood sugar and urea levels, hemoglobin or urine analysis. Organ weights and gross and histopathological examination of all principal organs and tissues revealed no effects attributable to the treatment (Harrisson and Abbott 1962).

Ocular Irritation

Table 7 lists ocular irritation studies regarding the use of Fumaric Acid, Di-C12-15 Alkyl Fumarate, and Diisostearyl Fumarate in rabbits. Overall, Fumaric Acid was irritating and the esters were not significant ocular irritants. In some instances, the number of animals used were not provided by the study authors.

Table 7. Ocular Irritation Studies with Fumaric Acid, Di-C12-15 Alkyl Fumarate,and Diisostearyl Fumarate.

Animal	Method	Result	Reference
	Fumaric Acid		
Rabbit	100 mg/ 24h	Moderately irritating	NIOSH (1986); Sax-Lewis (1991)
Rabbit	No details provided	Irritating	European Chemicals Bureau (2000)
	Di-C12-15 Alkyl Fumarate		
6 New Zealand White Rabbits	0.1 mL placed on the everted lower lid of one eye; the upper and lower lids were gently held together for 1 second; lesions evaluated at 24, 48 and 72 h.	Non-irritating	AMA Laboratories (1991)
	Diisostearyl Fumarate		
6 New Zealand White Rabbits	0.1 mL intraocular 1 eye; eyes unwashed for 24 h; lesions evaluated at 24, 48, and 72 h.	Mild ocular irritant	Consumer Product Testing (1993)

Dermal Irritation

Table 8 lists dermal irritation studies regarding the use of Fumaric Acid, Di-C12-15 Alkyl Fumarate, and Diisostearyl Fumarate in rabbits. Overall these ingredients were not significant dermal irritants. In some instances, the number of animals used were not provided by the study authors.

Dermal Sensitization

Di-C12-15 Alkyl Fumarate

RCC (2002) reported on the contact hypersensitivity in 15 male albino guinea pigs (10 test, 5 control) in a maximization test using Di-C12-15 Alkyl Fumarate. The intradermal induction of sensitization in the test group was performed in the nuchal region with a 50% dilution of the test material in corn oil and in an emulsion of FCA/physiological saline. The induction of sensitization was conducted for 48 h under occlusion with the test item at 75% in corn oil 1 week after the intradermal induction and following pre-treatment of the test areas with 10% Sodium Lauryl Sulfate (SLS) approximately 24 h prior to application of the test item.

The animals of the control group were intradermally induced with corn oil under occlusion following pre-treatment with 10% SLS. Two weeks after epidermal induction, the control and test animals were challenged by epidermal application of the test item at 75% and 15% in corn oil and corn oil alone under occlusive dressing. Cutaneous reactions were evaluated at 24 h and 48 h after removal of the dressing. No toxic symptoms were evident in the guinea pigs of the control or test group. No deaths occurred. None of the control or test animals had skin reactions after the challenge treatment with Di-C12-15 Alkyl Fumarate at 75% and 15% (w/w/) in corn oil. Based on the findings, Di-C12-15 Alkyl Fumarate was determined to be a non-sensitizer under the conditions of this study.

Diisostearyl Malate

According to Research and Development (1988), Diisostearyl Malate was tested for contact allergy in the guinea pig (no details were provided on number of animals). The induction concentration was 0.05% in propylene glycol and FCA. The challenge concentration was 0.50% (100% in petrolatum). There were no reactions to the test material. Diisostearyl Malate was determined to be a non-sensitizer.

Other Fumarates

Dimethylfumarate (DMF) and monoethylfumarate (MEF) are Fumaric Acid derivatives used in psoriasis treatment, primarily in Europe, and have been studied to identify potential adverse effects. DMF and MEF are not cosmetic ingredients.

In order to determine the irritating and sensitizing properties of DMF and MEF, De Haan et al. (1994) used a cytotoxicity, flank irritation, ear swelling and guinea pig maximization test. Twenty guinea pigs were used for immunization: 10 with DMF and 10 with MEF. Each guinea pig received 1 ml of a compound dissolved in 6 ml phosphate buffer saline and mixed with 6 ml Freund's complete adjuvant (FCA): in the nucha (0.4 ml), in front and hind legs (each 0.1 ml), and in both ears (0.1ml).

Another 10 guinea pigs were injected with FCA and served as the control animals. The results of the cytotoxicity test demonstrated that DMF was the most toxic derivative. DMF induced contact-urticarial reactions in contrast to MEF. Challenge experiments 21 days after immunization (open epicutaneous) with Fumaric Acid (400 mM), MEF (100 mM) and DMF (20 mM) in MEF- and DMF-sensitized guinea pigs demonstrated that both MEF and DMF are moderate contact sensitizers. Readings were done after 20 min, 24, 48, and 72 h. In DMF-sensitized animals cross-reactions with MEF were found. As DMF and MEF have cytotoxic, contact-urticarial and/or sensitizing properties, topical application should be avoided. Fumaric Acid was not found to be a sensitizer. No further study details were provided.

REPRODUCTIVE and DEVELOPMENTAL TOXICITY

Fumaric Acid

Levey et al. (1946) reported a study in which 12 guinea pigs (male and female) were used to determine whether Fumaric Acid might have an effect on reproduction and lactation. The animals received 1% Fumaric Acid in the diet (~400 mg/kg b.w./day). The exposure period was not reported. There were no detectable toxic effects on growth, reproduction or lactation of the Fumaric Acid-treated guinea pigs.

Table 8. Dermal Irritation Studies with Fumaric Acid, Di-C12-15 Alkyl Fumarate, and Diisostearyl Fumarate.

Animal	Method	Result	Reference
	Fumaric Acid		
Rabbit	500 mg/ 24 h	Slightly irritating	NIOSH (1986); Sax-Lewis (1991)
Rabbit	no details provided	Non-irritating	European Chemicals Bureau (2000)
	Di-C12-15 Alkyl Fumarate		
6 New Zealand Albino Rabbits	Trunks of the rabbits were clipped free of hair; patches were placed over intact and abraded skin; 0.5 g test material was place under each patch; the trunk animal was wrapped to retard evaporation and maintain test patch position; skin lesions were evaluated at 24 and 72 h	Non-primary irritant	AMA Laboratories, Inc. (1991)
	Diisostearyl Fumarate		
6 New Zealand White Rabbits	single dermal application of 0.5 mL of the test material on 2 occluded test sites (1 abraded, 1 non-abraded); observed at 24 and 72 h	Primary Irritation Index: 1.35 Non-primary irritant	Consumer Product Testing (1993)

Other Fumarates

According to BiogenIdec (2008), the drugs, Fumaderm® and Fumaderm® initial, are approved for use in Germany in the treatment of plaque psoriasis. These drugs contain 120 mg of dimethyl fumarate (aka DMF), 87 mg of ethyl hydrogen fumarate (calcium salt), 5 mg ethyl hydrogen fumarate (magnesium salt), and 3 mg ethyl hydrogen fumarate (zinc salt), in the case of Fumaderm®; or 30 mg of dimethyl fumarate, 67 mg of ethyl hydrogen fumarate (calcium salt), 5 mg ethyl hydrogen fumarate (magnesium salt), and 3 mg ethyl hydrogen fumarate (zinc salt) in the case of Fumaderm® initial.

While the studies provided to support approval of these pharmaceuticals were not available, a summary of preclinical data is provided in the package insert. This summary stated that studies on rats and rabbits exposed to doses approaching levels causing maternal toxicity, yielded no evidence of any teratogenic effect. Embryo-fetal toxicity (growth retardation, mortality) was only observed at doses known to cause maternal toxicity. In one reproduction study on rats, there was no evidence to indicate any effect on fertility (BiogenIdec 2008).

GENOTOXICITY

Fumaric Acid

Table 9 describes in vitro genotoxicity studies of Fumaric Acid. Fumaric Acid was not mutagenic in several Ames tests and in CHO cells in culture, but was mutagenic in one assay using L5178Y cells in culture.

Diisostearyl Fumarate

SafePharm Laboratories (2008) reported on a reverse mutation assay (Ames Test) using *S. typhimurium* and *Escherichia coli*. *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *E. coli* strain WP2uvrA were treated with Diisostearyl Fumarate at 5 dose levels, in triplicate, both with and without the addition of metabolic activation. In experiment 1, the dose range was determined in a preliminary toxicity assay and was 50 to 5000 µg/plate. The experiment was repeated on a separate day using the same dose range as Experiment 1, fresh cultures of the bacterial strains and fresh material formulations.

The vehicle (acetone) control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation. Therefore, the sensitivity of the assay and the efficacy of the S9-mix were validated. The test material caused no visible reduction in the growth of the bacteria at any dose level. The test material was therefore tested up to the maximum recommended dose level of 5000 µg/plate. A precipitate (oily in appearance) was observed at and above 1500 µg/plate; this did not prevent the scoring of revertant colonies.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation. Diisostearyl Fumarate was considered to be non-mutagenic under the test conditions (SafePharm Laboratories 2008).

Di-C12-15 Alkyl Fumarate

According to Sitek Research Laboratories (1995), Di-C12-15 Alkyl Fumarate was tested for its potential to cause mutation at the histidine operon of *S. typhimurium* strains TA98, TA100, TA1537, and TA1538 and at the tryptophan operon of *E. coli* strain WP2uvrA. The test article, dissolved in acetone, was tested for toxicity to strains TA100 and WP2uvrA in a range finding test at test article concentrations ranging from 5.0 to 5000 µg/plate. The tester strains were exposed to the test article in the absence of exogenous activation and in the presence of Aroclor 1254-induced rat liver S-9 plus cofactors.

Based on the results of the range finding test, the first mutation assay was performed with the 5 *S. typhimurium* tester strains and *E. coli* strain WP2uvrA using concentrations of 100, 250, 500, 750 and 1000 µg/plate in the presence and absence of S-9 activation. The second mutation assay was performed with the preincubation method to confirm the results of the first assay, using the same concentrations. The results of both mutation assays indicated that the test article did not induce any positive increase in the number of revertant colonies for any of the tester strains in the presence or absence of Aroclor 1254-induced rat liver S-9. Under the conditions of this study, Di-C12-15 Alkyl Fumarate is negative in the *S. typhimurium/E. coli* plate incorporation/preincubation mutation assay.

Table 9. Fumaric Acid Genotoxicity Studies.

System	Concentration	Result	Reference
S. typhimurium - TA100	10000, 1000, 100, and 10 µg/plate	not mutagenic	Rapson (1980)
S. typhimurium - TA92, TA94, TA98, TA100, TA1535, and TA1537 with and without metabolic activation	Up to 10 µg/plate	not mutagenic	Ishidate et al. (1984)
S. typhimurium - TA97, TA98, TA100, TA1535 with and without metabolic activation	33, 100, 333, 1000, and 2000 µg/plate	not mutagenic	Ishidate et al. (1984)
S. typhimurium - TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation	10 - 5000 µg/plate	not mutagenic	European Chemicals Bureau (2000)
Chinese hamster lung fibroblast (CHL) with and without metabolic activation	0.125, 0.25, and 0.5 µg/mL	incidence of polyploidy or structural aberrations of treated cells did not differ from the negative controls.	Ishidate et al. (1984)
L5178Y cells (TK+/-) with and without metabolic activation.	2856 - 8000 µg/mL	mutagenic with and without metabolic activation	Saffioti and Shubik (1963)

CARCINOGENICITY

According to Levey et al. (1946), Fumaric Acid was not carcinogenic in male and female Osborne-Mendel rats. The rats received Fumaric Acid in the diet daily at 0.1, 0.5, 0.8, 1.0, 1.2, and 1.5% (~750 mg/kg/day). The exposure period was not reported. In the highest dose group, there was a low level of survival (2 out of 12) at the end of the experiment, while in the lower dose groups, mortality did not differ significantly from the controls (details not given). The gross and microscopic findings showed no difference between the control and treated animals. Tumors showed no difference in incidence among the animal groups.

According to Saffioti & Shubik (1963), Fumaric Acid was found to induce moderate focal hyperplasia of the epidermis, but not tumors in female Swiss mice. The animals were initially treated once a week to the clipped dorsal skin with 7, 12-dimethylbenz(a)anthracene (1.5% in mineral oil), then with Fumaric Acid twice a week (1% in acetone). The entire treatment period was 76 weeks with Fumaric Acid alone.

Antitumor Activity

Kuroda and Akao (1981) studied the antitumor and anti-intoxication activities of Fumaric Acid in cultured cells. The Ehrlich, MH-134, and L1210 cell lines were grown in the peritoneal cavity of ICR/JCL, C2H/He, and DBA/2 male mice, respectively. Fumaric Acid was isolated as the active component of Capsella bursa-pastoris herb for inhibiting the solid growth of Ehrlich tumors in mice, and was found to significantly reduce the growth and viability of Ehrlich, MH134, and L1210 mouse tumor cells in culture at concentrations of 0.3 ~ 1.2 mg/mL. Also, at these concentrations, Fumaric Acid in the culture medium had no deleterious effect on monolayer development of mouse and chick embryo cells, but exhibited activity to enhance the recovery of cells from the toxic effects of mitomycin C, aflatoxin B_1, N-methyl-N'-nitro-N-nitrosoguanidine, and potassium 1-methyl-7-[2-(5-nitro-2-furyl) vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (NFN).

The inhibitory effect of Fumaric Acid on carcinogenesis by NFN was examined histologically with male ICR/JCL mice (Kuroda et al. 1982). NFN was fed to 62 mice at a dose level of 0.012% in the diet for 14 weeks. These mice were then divided into 2 groups. One group was given a basal diet, and the other group was given a diet containing 1% Fumaric Acid in the subsequent 39 weeks. In the group of 30 mice fed NFN alone, squamous cell carcinomas were found in the stomachs of 7 mice, multiple papillomas in the stomachs of 13 mice, and multiple and large papillary adenocarcinomas in the lungs of 27 animals. The administration of Fumaric Acid suppressed the NFN-induced stomach and lung carcinogenesis. In the group of 32 mice fed NFN and Fumaric Acid, no stomach tumors developed except 1 early-stage squamous cell carcinoma. In the lungs, only a small focus of mild atypical hyperplasia and a few early-stage adenocarcinomas were noted in 7 and 11 animals in the group of 32 mice, respectively.

In a study by Kuroda et al. (1983), Fumaric Acid was examined for its effect on hepatocarcinogenesis in rats fed 3-methyl-4'-(dimethylamino)azobenzene (3-Me-DAB). Male Donryu rats received approximately 0.5 g 3-Me-DAB in a diet containing 0.06% 3-Me-DAB for 50 days; they then received a diet containing 1% Fumaric Acid and drinking water containing 0.025% Fumaric Acid for 51 weeks. The administration of Fumaric Acid effectively suppressed the development of hepatocellular carcinoma, hyperplastic nodules, and hyperplastic areas in the livers of rats fed 3-Me-DAB.

Pereira et al. (1994) examined the use of azoxymethane (AOM)-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. Foci of aberrant and/or hexosaminidase-negative crypts in rat colon are putative precancerous lesions that have been proposed as biomarkers for short-term bioassays for chemical carcinogens and chemopreventive agents. The ability of a substance to reduce the yield of AOM-induced foci in the colon of male Fischer 344 rats was evaluated as a screening assay for chemopreventive agents. Twenty-eight test agents were administered continuously in the diet from the start of the experiments until the animals were killed 35 days later. Calcium salts of carbonate, chloride and glucarate decreased the yield of AOM-induced foci while the acidic salts of lactate and phosphate did not inhibit the formation of foci. Dimethyl fumarate, Fumaric Acid, genistein, piroxicam, simethicone, sodium suramin and sulindac reduced the yield of AOM-induced foci of aberrant crypts, with genistein being the most potent.

Kuroda et al. (1987) examined the inhibitory effect of Fumaric Acid on hepatocarcinogenesis in mice fed thioacetamide (TAA). A group of male ICR mice was fed TAA at a level of 0.035% in the diet for 40 weeks and then fed a basal diet for 48 weeks. Hepatic tumors developed in 11 of the 24 animals of this group and they were diagnosed as hepatocellular carcinomas. However, cirrhotic lesions and the enlargement of hepatocyte nucleoli were not as marked in mice as in previous findings in rats fed TAA. The effect of Fumaric Acid on carcinogenesis was examined in a group of mice fed this compound at a level of 1% in a basal diet after ingestion of TAA. The inhibitory effect of Fumaric Acid on TAA carcinogenesis was so marked that no hepatic carcinomas were found in any of the 15 animals fed Fumaric Acid in combination with TAA.

According to Kuroda and Akao (1989), Fumaric Acid suppressed the carcinogenesis in the liver of rats fed 3'-Me-DAB, and a study was performed to examine the effect of Fumaric Acid on DNA synthesis and subcellular structures of hepatocytes under the anticarcinogenic regimen. Male Donryu strain rats were given 3'-Me-DAB by being fed a diet containing 0.06% 3'-Me-DAB for 50 d. They then received a diet containing 1% Fumaric Acid and drinking water containing 0.025% Fumaric Acid for 53 to 69 weeks. Hepatocytes were isolated from the liver by the collagenase perfusion method and placed in culture, and their activity for DNA synthesis was measured in terms of the incorporation of [^{3}H]dThd into DNA. An enhanced DNA synthesis of hepatocytes was noted in the rats given Fumaric Acid, indicating that Fumaric Acid enhanced the proliferation of hepatocytes to counteract the carcinogenic effect of 3'-Me-DAB. An electron microscopic examination indicated that the distribution of subcellular organella was almost normal in the Fumaric Acid-treated hepatocytes.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation/Sensitization

Fumaric Acid

De Haan et al. (1994) reported that topical therapy for psoriasis with Fumaric Acid and its derivatives in the treatment of psoriasis can produce perilesional skin irritation, macular papular rashes and urticarial reactions.

Dermtest (1997) studied the primary skin irritation and allergic hypersensitivity potential in humans patch tested with 20% aqueous solution of the trade name mixture Unicotrozon C-49 containing 5% Fumaric Acid and 17.5% Fumaris Officinalis Extract that also contains some Fumaric Acid. This trade name mixture also included water, citrus medica limonum (lemon) fruit extract and propylene glycol. Fifty subjects (male and female) were used in the study. No evidence of primary irritation or

allergic hypersensitivity was seen in any of the subjects. No positive reactions were found in any of the subjects after 24, 48, and 72 h. The authors of this study concluded that under the test conditions, 20% aqueous Unicontrozon C-49 was not an irritant or sensitizer.

Di-C12-15 Alkyl Fumarate

Stephens & Associates (1997) conducted a 14-day cumulative irritation study using 5% Di-C12-15 Alkyl Fumarate. Twenty-seven subjects completed the study. Subjects were patched with test and control materials daily for 14 days. Subjects wore the patches for approximately 24 h and removed them approximately 2 h before grading of the test sites. There was no experimental irritation demonstrated with the test material.

Stephens & Associates (1998) evaluated the safety, effectiveness, comedogenicity, and acnegenicity of 5% Di-C12-15 Alkyl Fumarate, a topically applied cosmetic product designed to improve skin moisturization in women. Thirty-nine female subjects (50% Japanese, 50% Caucasian) completed the 8-week controlled usage study. Results indicated that the test material was non-acnegenic and non-comedogenic.

In another study by Stephens & Associates (1998), a human repeat insult patch test using 5% Di-C12-15 Alkyl Fumarate was performed. Ninety-eight subjects completed the study. During the induction phase, patches containing the test material were applied 9 times at approximately 48 to 72 h intervals. Reactions at the application sites were graded approximately 48 to 72 h after each application. Twelve to twenty-four (12-24) days after application of the last induction patches, challenge patches were applied to original and alternate sites, and reactions were graded at approximately 48 and 96 h post-application. No edema, vesicles, bullae, spreading, or weeping were observed during the study. The test material did not induce allergic contact dermatitis in any of the subjects.

Clinical Research Laboratories, Inc. (2004) determined the dermal irritation and sensitization potential of a leave-on product containing 1% Di-C12-15 Alkyl Fumarate. A total of 112 subjects, male and female, between the ages of 18 - 70, enrolled in the study, of which 108 subjects completed the study - 4 subjects discontinued participation for reasons unrelated to the testing. Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material was applied under a semi-occlusive patch to the upper back and was allowed to remain in direct skin contact for a 24 h period.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the induction period. The sites were graded for dermal irritation and sensitization 24 h after removal of the patches by the subjects on Tuesday and Thursday and 48 h after the removal of the patches on Saturday. The sites were graded according to the following scoring system: 0, no visible skin reaction; ±, barely perceptible erythema (minimal); 1+, mild erythema (diffuse); 2+, well-defined erythema; 3+, erythema and edema; and 4+, erythema and edema with vesiculation.

After a 2-week rest period, challenge patches were applied to previously untreated areas on the back. After 24 h, the patches were removed and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 h and 72 h. Based on the conditions of this study, the test material containing 1% Di-C12-15 Alkyl Fumarate did not demonstrate a potential for eliciting dermal irritation or sensitization (Clinical Research Laboratories 2004).

Clinical Research Laboratories, Inc. (2005), determined the dermal irritation and sensitization potential of a leave-on product containing 1% Di-C12-15 Alkyl Fumarate. A total of 112 subjects, male and female, between the ages of 18 - 70, were enrolled in the study, of which 104 subjects completed the study - 8 subjects discontinued participation for reasons unrelated to the testing. Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material was applied under a semi-occlusive patch to the upper back (between the scalpulae) and was allowed to remain in direct skin contact for a 24 h period. Patches were applied to the same site according to the protocol described previously for a total of 9 applications during the induction period. Based on the conditions of this study, the test material did not demonstrate a potential for eliciting dermal irritation or sensitization (Clinical Research Laboratories 2005).

Diisostearyl Fumarate

KGL, Inc. (2006) evaluated the contact-sensitization potential of a lip gloss containing 20% Diisostearyl Fumarate to human skin by means of maximization assay. A total of 26 healthy adults (23 females, 3 males) participated in the study; of which 25 completed the study. Approximately 0.05 mL of aqueous SLS (0.25%) was applied to a designated site under a 15 mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24-h. After 24-h, the SLS patch was removed and 0.05 mL of the test material (SPF-15 lip gloss) was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48-h (or for 72-h when placed over the weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was reapplied to the same site for 24-h, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence was continued for a total of 5 induction exposures. If irritation developed at any time-point during the induction phase, the 24-h SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-h rest period during which no patch was applied.

After a 10-day rest period which followed the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed. Pre-treatment with SLS was performed prior to challenge. Approximately 0.05 mL of a 5.0% aqueous solution was applied to a fresh skin site under a 15 mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for 1-h. It was then removed and the test material was applied to the same site. The challenge patch was left in place for 48-h. After that period, the patch was removed and the site graded 15-30 min later and again 24-h later for any reaction. No adverse or unexpected reactions were seen in any of the subjects during the induction phase and no instances of contact allergy were recorded during the challenge phase at either 48 or 72-h (KGL, Inc. 2006).

KGL, Inc. (2007) evaluated the contact-sensitization potential of a lip gloss containing 17.41% Diisostearyl Fumarate to human skin by means of maximization assay. A total of 26 healthy adults (20 - 61 years old) participated in the study; 25 completed the study. Approximately 0.05 mL of aqueous SLS (0.25%) was applied to a designated site under a 15 mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24-h. After 24-h, the SLS patch was removed and 0.05 mL of the test material (SPF-15 lip gloss) was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48-h (or for 72-h when placed over the weekend) following which it was removed and the site again examined for irritation. If no

irritation was present, a 0.25% aqueous SLS patch was reapplied to the same site for 24-h, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence was continued for a total of 5 induction exposures. If irritation developed at any time-point during the induction phase, the 24-h SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-h rest period during which no patch was applied.

After a 10-day rest period which followed the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed. Pre-treatment with SLS was performed prior to challenge. Approximately 0.05 mL of a 5.0% aqueous solution was applied to a fresh skin site under a 15 mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for 1-h. It was then removed and the test material was applied to the same site. The challenge patch was left in place for 48-h. After that period, the patch was removed and the site graded 15-30 min later and again 24-h later for any reaction. Under the conditions of this test, the lipgloss containing 17.4% Diisostearyl Fumarate did not possess a detectable contact-sensitizing potential and is not likely to cause contact sensitivity reactions under normal use conditions (KGL, Inc. 2007).

Dimethyl Fumarate

Rantanen (2008) reported on an epidemic of severe contact dermatitis cases related to newly acquired Chinese sofas and chairs. Five patients were studied. Furniture samples were analyzed by gas chromatography-mass spectrometry. Compounds were identified using a mass spectrum library and measured semiquantitatively. Patch tests were performed with commercial standard allergens, furniture upholstery and chemicals found in the analysis. Patch tests with commercial allergens did not solve the problem. Up to 470 µg/kg of DMF was found in chairs (kg refers to the upholstery). The patients showed strong positive patch test reactions to upholstery fabric samples and to DMF, down to a level of 1 ppm in the most severe case. It was concluded by the author that the cause of the Chinese sofa/chair dermatitis epidemic is likely to be contact allergy to DMF, a novel potent contact sensitizer. As noted earlier, DMF is not a cosmetic ingredient.

Psoriasis Treatment

Fumaric Acid and its derivatives have been studied as anti-psoriatic agents, primarily the salts of the dimethyl and monoethyl forms which are not used as cosmetic ingredients.

The drugs, Fumaderm® and Fumaderm® initial, are approved for use in Germany in the treatment of plaque psoriasis (BiogenIdec 2008). Raab (1984) expressed the view that MEF is anti-psoriatic, but is too toxic for clinical use, while Fumaric Acid itself may produce secondary changes that have beneficial effects on psoriatic lesions, but is not itself an anti-psoriatic. Raschka and Koch (1999) reported that Fumaric Acid preparations can be used as long-term and effective treatment of psoriasis, but that gastrointestinal, dermatological and hematological side-effects, and transient renal damage may be present during treatment with Fumaric Acid.

Table 10 briefly summarizes published studies related to Fumaric Acid and its derivatives in the treatment of psoriasis.

Table 10. Psoriasis Treatment using Fumaric Acid and its derivatives.

Study Description	Reference
Fumaric Acid compound therapy (FACT) consists of the oral intake of dimethylfumaric acid ester (DMFAE) and several salts of monoethylfumaric acid ester (MEFAE) in combination with topical Fumaric Acid therapy (1% to 3% MEFAE in an ointment or Fumaric Acid in bathing oils) and a diet. An open pilot study was conducted using 36 patients in which FACT therapy was effective. Thereafter, several controlled studies with MEFAE sodium in 2 different dosages versus placebo, and DMFAE versus placebo, were done. The results indicated that MEFAE sodium in dosages up to 240 mg daily was ineffective, whereas daily dosages of 720 mg resulted in a significant decrease in scaling and itching but did not affect extension of the eruption. DMFAE, 240 mg daily, produced a significant amelioration and prevented extension. Side effects of Fumaric Acid treatment were nausea, diarrhea, general malaise, and severe stomach ache. Mild disturbances of liver and kidney function during treatment were observed with the 720 mg dosage of MEFAE and with the 240 mg dosage of DMFAE. Moreover, a relative lymphopenia with a selective decrease of suppressor T lymphocytes occurred in about 50% of the patients treated with DMFAE.	Neiboer et al. (1989)
in a 4-month double-blind study, the effects of dimethylfumaric acid esters (DMFAE-EC) and DMFAE (120 mg per tablet) plus salts of monoethylfumaric acid esters (Fumaric Acid combination, FAC-EC) in enteric-coated tablets were compared in 22 and 23 patients, respectively, with psoriasis. In both groups about 50% showed a considerable improvement, i.e. the initial score was more than halved. The therapeutic effects showed no significant differences in both groups with respect to the total psoriasis score or the different parameters. In the FAC-EC (120 mg per tablet) group the effects were obtained more rapidly. Most frequently observed side effects in both groups were flushings, stomach ache and diarrhea. Due to these complaints, patients discontinued therapy. Eosinophilia, leukopenia and lymphopenia were the most frequently observed differences in lab tests. It was concluded that FAC-EC had no significantly better effect than monotherapy with DMFAE-EC. Moreover, enteric coating of the tablets did not prevent stomach complaints.	Nieboer et al. (1990)
196 patients, 18 years of age and older with nummular and plaque-type psoriasis over at least 10% of the body surface, were given one of two reatments: dimethyl Fumaric Acid ester (DMFAE, monotherapy) and Fumaric Acid combination (FAC) therapy. The DMFAE group was treated with capsules filled with 60 mg of semienteric coated granulate of DMFAE. In the first week, the dosage was 60 mg/day. This was increased weekly by 60 mg to a maximum of 240 mg/day. The FAC group was treated with 2 types of enteric-coated tablets: (1) mite tablet, containing 30 mg of DMFAE, 5 mg Mg-, 3 mg Zn-, and 56 mg Ca-MEFAE; or (2) forte tablet, containing 120 mg of DMFAE, 5 mg Mg-, 3 mg Zn-, and 87 mg Ca-MEFAE. Medication started with 1 mite tablet per day. In the 4th week, medication was switched to 1 forte tablet per day and this was increased weekly to a maximum of 4 tablets per day, in 2 divided doses after meals. Topical treatment consisted of the application of a bland cream or ointment or a mild topical corticosteroid. Therapeutic evaluation was done in the periods of 3 to 6 months, 6 to 12 months, 12 to 18 months, and 18 to 24 months. No significant differences could be found between DMFAE monotherapy and FACT therapy when equivalent doses of DMFAE were taken. Several side effects were observed (gastrointestinal complaints, general malaise, mild liver and kidney disturbances (seen in 3 and 1 patient), and leukocytopenia (in 4% of the patients). The symptoms disappeared immediately after discontinuation of treatment. Recurrent psoriasis after discontinuation varied, but in most cases complete healing occurred.	Kolbach and Nieboer (1992)

Table 10 (continued). Psoriasis Treatment using Fumaric Acid and its derivatives.

Study Description	Reference
a randomized double-blind study in 100 patients (male and female, 18-70 years old) with psoriasis, comparing Fumaric Acid derivatives with placebo. Patients were treated with either drug or placebo in tablet form. The drug consisted of a mixture of dimethylfumarate and monoethyl-hydrogenfumarates. The low dose contained 105 mg of ester mixture up to a maximum dose of 1290 mg by week 16. The results indicated statistically significant superiority of the Fumaric Acid derivatives over placebo. Adverse events (flush, gastrointestinal disturbances) were initially relatively frequent, but decreased thereafter. Fumaric Acid derivatives were reported to be effective and safe in the treatment of psoriasis.	Altmeyer et al. (1994)
2041 psoriatic patients over a 9-yr period using Fumaric Acid preparations (Fu-P-mite; 105 mg ester mixture, Fu-P-forte; 215 mg ester mixture). Many of the patients exhibited side effects when first being introduced to the forte tablets and when reaching the dosage of 4 to 6 tablets daily. For this reason, the protocol was altered as follows: mite tablets were increased daily for 6 days, then for 2 to 3 days a dose of 6 mite tablets were given as maintenance, and subsequently every 2 to 3 days two mite tablets were replaced by 1 forte tablet. The forte tablets were increased to consider body weight and side effects up to a maximum of 3 to 4 tablets per day. The maximum dose was obtained for 3 to 6 months. Thereafter, the dose was reduced continuously by 1 forte tablet per month until signs of deterioration disappeared. At this time, dosage was again increased with mite tablets. Many of the patients improved after only 2 to 6 months of treatment. No serious side effects were noted.	Skaria and Schmid (1996)
the safety of Fumaric Acid esters (Fumaderm initial, 215 mg; Fumaderm, 105 mg) was evaluated in the oral long-term therapy of severe psoriasis vulgaris. A total of 83 patients with severe psoriasis were investigated in a 12-month clinical trial. The antipsoriatic effect of Fumaric Acid derivatives was clear, with a mean reduction of 76% in psoriasis area and severity index (PASI). Adverse events were noted in 62% of the patients – mainly gastrointestinal complaints. These were dose-dependent and decreased in frequency throughout the course of the study. No severe adverse effects occurred. The authors concluded that Fumaric Acid derivatives are indicated in cases of severe therapy-resistant psoriasis and can be used even for long-term application.	Altmeyer and Nuchel (1996)
based on the premise that psoriasis is not primarily a skin disorder, but an immunological disturbance under the skin and that the skin manifestations are a result of overstimulation of superficial skin cells (Langerhans cells) due to increased production of interleukin 2, 6 and 8, as well as transforming growth-factor-alpha. Interleukin-10 production is diminished, this study addressed the immunotherapeutic effect of Fumaric Acid in combination with thymus extract and selenium - 54 patients were treated with Fumaric Acid in addition to intravenous thymus extract and selenium (no concentrations were provided). They showed a faster healing rate than with Fumaric Acid alone. The author determined that Fumaric Acid, thymus extract and selenium have a synergistic effect.	Christ (1999)
in this randomized, double-blind, vehicle-controlled study, 143 patients were treated for up to 13 weeks. Group A received Fumaric Acid tablets with an increasing daily dosing from 105 to 1075 mg + ointment vehicle. Group B received Fumaric Acid tablets + calcipotriol ointment (50 µg/g). Ointments were applied twice daily. Clinical response was assessed using percentage changes in the PASI, from baseline to treatment end. The mean percentage change in the PASI was -76.1% in group B and -51.9% in group A, the difference between treatments was -24.2% (95% Cl from -34.2 to -14.2%; $P < 0.001$). Group B responded more rapidly to treatment. Investigators' and patients' overall efficacy assessments were significantly more favorable for Group B ($P < 0.001$). Group B was prescribed less Fumaric Acid esters than group A. This difference was greatest at the last visit (mean daily dose 529 and 685 mg, respectively; $P = 0.006$). Overall, adverse events in the 2 groups were similar. The authors concluded that the combination of calcipotriol and Fumaric Acid esters is significantly more effective and faster acting than Fumaric Acid ester monotherapy in the treatment of severe plaque psoriasis.	Gollnick et al. (2002)
12 patients received Fumaric Acid esters for severe psoriasis. The mean duration of the psoriasis was 24 years (range 8 – 42). All of the patients failed to respond to topical therapy and/or phototherapy alone. The existing regimen of each patient was substituted with Fumaric Acid esters produced in tablets containing 2 dose levels. Low strength tablets contained 30 mg dimethylfumarate, 67 mg ethylhydrogenfumarate Ca salt, 5 mg ethylhydrogenfumarate Mg salt, and 3 mg ethylhydrogenfumarate Zn salt. The high-dose tablets contained 120 mg dimethylfumarate, 87 mg ethylhydrogenfumarate Ca salt, 5 mg ethylhydrogenfumarate Mg salt, and 3 mg ethylhydrogenfumarate Zn salt. Doses were taken at intervals of 2 weeks or longer and 1 – 3 times a day. Patients were examined every 2 weeks until improvement was noted and then every month. One out of 12 patients discontinued treatment early due to flushing while on the low-dose tablets. The other 11 patients all demonstrated improvement in psoriasis after starting treatment with Fumaric Acid esters. Nine patients received Fumaric Acid esters in combination with other systemic agents and generally enabled the doses of the more hazardous drugs to be reduced. The authors recommended that careful monitoring be used when using Fumaric Acid esters in such combined regimens.	Balasubramaniam et al. (2003)
while ~⅔ of patients treated with Fumaric Acid experienced gastrointestinal symptoms, and ⅓ developed flushing, these authors reported that long-term administration of Fumaric Acid has been associated with a transient increase in liver enzyme levels and with kidney damage.	Hoefnagel et al. (2003)
oral treatment of psoriasis on an outpatient basis, using a preparation containing Fumaric Acid derivatives, was evaluated as initial monotherapy (3 months) and as long-term basic therapy (12-14 months) in 13 and 11 patients, respectively. The course of the disease was analyzed in each individual case. After completion of both parts of the trial, half of the patients that had only responded poorly to conventional antipsoriatic therapy showed a significant improvement which occurred after several weeks of treatment. In 4 patients the medication had to be stopped because of abdominal pain. No severe side effects, particularly of a renal, hepatic or hematological nature, could be established.	Bayard et al. (2004)
clinical experience in Italy; >80% of patients achieved complete remission following 6 months of treatment with dimethylfumarate.	Carboni et al. (2004)

Laxative Effects

Twenty-six constipated patients suffering from a variety of chronic diseases not involving the gastrointestinal tract were given oral doses of 5-30 g Sodium Fumarate; a satisfactory bowel motion resulted in 18 patients. There was much variability of response to a given dose between patients and in the same individual. Doses above 15 g caused unpleasant side effects. No abnormalities were noted in the urine or serum non-protein nitrogen level (Bodansky et al. 1942).

Other Clinical Treatment

Kreuter et al. (2005) investigated Fumaric Acid esters in the treatment of necrobiosis lipoidica (NL). NL is an uncommon granulomatous skin disease with association to diabetes mellitus. Eighteen patients with histopathologically proven NL were used in this non-controlled study. Fumaric Acid esters dosages were given as a standard therapy regimen for psoriasis for at least 6 months. The results were evaluated by clinical and histological scoring, as well as ultrasound assessments. Three patients discontinued therapy with Fumaric Acid esters, while the remaining 15 completed the study. After a mean ± SD treatment period of 7.7 ± 2.9 months, a significant ($p < 0.001$) decrease in the mean ± SD clinical score, from 7.4 ± 1.8 at the beginning to 2.2 ± 1.3 at the end of the therapy, was observed. Significant clinical improvement of NL was accompanied by significant ($P = 0.019$) increase of dermal density as assessed by means of 20-MHZ ultrasound, and significant ($P = 0.011$) reduction of the histological score. Adverse effects were moderate and consisted mainly of gastrointestinal complaints and flushing. During follow-up of at least 6 months, clinical outcome remained stable in all patients. The authors therefore concluded that the study demonstrates that Fumaric Acid esters are beneficial and safe in the treatment of patients with NL.

CASE REPORTS

Stuhlinger et al. (1990) reported on a case where 2 sisters, aged 25 and 29 years, with generalized psoriasis guttata since childhood, developed nausea, upper-abdominal pain, loss of appetite, palpitations and flushes in the course of local and oral administration of Fumaric Acid. Because of these side effects the treatment was discontinued after about 2 weeks, and the symptoms disappeared. But proteinuria and haematuria were subsequently noted, creatinine concentration rose to 2.2 and 2.5 mg/dl, respectively, while creatinine clearance fell to 44 and 27 ml/min, respectively. Examination of urinary sediments and analysis of urinary proteins gave results compatible with tubular-interstitial renal damage. The abnormal renal functions and urinary findings proved reversible within 3 weeks.

Fliegner and Spiegel (1992) reported on a case of fully reversible tubular toxicity with consecutive metabolic osteopathy following systemic Fumaric Acid therapy. A 46-yr-old female patient with a long history of recurrent palmoplantar psoriasis underwent oral treatment with Fumaric Acid in accordance with the Schafer method, preceding attempts at curative treatment with conventional antipsoriatic agents having proved unsatisfactory.

Two months later, the patient began experiencing arthralgia, back pain in the early hours of the morning and myalgia with increasing frequency, progressing to disablement in moving and walking, and finally, to total immobility. Nine months later, it was determined that the reason for these severe disabilities stemmed from hypophophataemic osteomalacia as a result of a complex disturbance of the renal tubular system. The clinical symptoms and the results of laboratory chemistry tests returned to normal as soon as Fumaric Acid medication was discontinued. Two re-exposure attempts confirmed the causal relationship. The authors therefore concluded that Fumaric Acid medication should never be administered without clinical and chemical controls (Fliegner and Spiegel 1992).

Raschka and Koch (1999) reported on the case of a 38 year old woman who was treated with Fumaric Acid (420 mg) for 5 years before she complained of excessive fatigue and weakness. According to the clinical laboratory, she had developed severe proximal tubular damage. Hypophosphatemia, glycosuria and proteinuria persisted although medication was stopped immediately.

Haviv et al. (1999) described a case of a 48-yr old Caucasian female admitted with respiratory distress. Previous medical history was positive for only psoriatic arthritis mutilans beginning at the age of 30-yrs. Medical treatments with glucocorticoids, methotrexate and indomethacin had failed, and the patient underwent bilateral total hip replacement at age 40. Since the age of 39, the patient had been restricted to her home, became a strict vegetarian, and began taking Fumaric Acid tablets 3 times a day. The skin and joint lesions responded to the treatment.

During this period, the patient's physical state gradually deteriorated, and she lost the ability to walk. The patient also experienced loss in weight and height. She eventually developed dyspnoea and was hospitalized. Upon physical examination, it was found that the patient was cachectic. The vital signs were normal, except for tachypnoea, and there was maximum jugular venous distention. The skeletal examination revealed miniature pigeon test, normal size limbs, rosaries of the lower ribs, and extremely fragile bones. Laboratory data disclosed megaloblastic anemia, secondary to B_{12} deficiency, normal liver function tests, normal glucose and electrolytes except for chloride of 116 mmol/L, and normal serum creatinine level. The patient was treated by phosphate loading, and her respiratory capacity improved. However, during a gastrostomy performed for enteral hyperailmentation, she died suddenly. The authors proposed that administration of maleic acid anologue esters in pharmacological doses may have induced a diffuse tubular mitichondrial injury leading to Fanconi syndrome and vitamin D-resistant osteomalacia (Haviv 1999).

Hansson and Thorneby-Andersson (2003) reported a case of a 30-year old healthy male with no history of allergy or skin disease who developed an acute dermatitis. In his profession as an organic chemist, he was exposed to different esters of small organic molecules, among other esters of maleic acid and of Fumaric Acid. Accidentally, his hands had been exposed to a reaction mixture containing dimethyl maleate. He developed a bullous dermatitis on 1 hand and on his left wrist, an erythematous dermatitis with large bullae was noted. After treatment with a topical corticosteroid, the lesions healed. Two weeks later, he again developed an eczematous reaction, displaying erythematous scaling maculae on his left wrist, as well eczema with erythema and a large number of vesicles on the back of his left hand and fingers. These lesions healed after a second treatment with a steroid cream. Two weeks later, he was patch tested with the TRUE test standard series and with the chemicals the patient brought in from his own laboratory. Since the diethyl esters of maleic acid and of Fumaric Acid were available among the patient's chemicals, they were chosen for a comparison of the esters of the 2 acids. The patch tests in the standard series were negative. There were strong reactions to esters of both acids, whereas the free acids as well as maleic anhydride gave negative results. The sensitivity to Fumaric Acid diethyl esters was stronger than that to maleic acid diethyl ester. The patch tests were evaluated after 72 hours, and the reactions were scored.

Guenther et al. (2003) reported on a case of a 68-year-old Caucasian woman who was treated with Fumaric Acid esters (FAE) for 4 days for lichen planus and then developed

generalized pruritic exanthema. This was suspected to be an allergic drug reaction to FAE, and the treatment was discontinued. After 48-72 hours, the exanthema resolved completely. An objective causality assessment revealed that the adverse drug event was probable. As skin testing for diagnostic purposes is not feasible with FAE, the drug-related origin of the exanthema was confirmed by oral rechallenge with FAE. The effectiveness of FAE in the systemic treatment of psoriasis vulgaris has been proven by controlled clinical trials. The compound has been shown to be tolerable and safe even during prolonged treatment. The most frequent adverse effects are gastrointestinal symptoms and flushing, which typically occur 4-6 hours after administration of the drug. Allergic reactions to FAE have not yet been reported. Since the patient was rechallenged with the suspected drug, the authors could confirm the allergic origin of the exanthema. The occurrence of allergic skin reaction should be considered in patients receiving treatment with FAE.

SUMMARY

This report presents available information pertinent to the safety of Fumaric Acid, and its salts and esters as used in cosmetics. Not all Fumaric Acid esters are cosmetic ingredients. For example, salts of dimethyl fumarate and monoethyl fumarate are used in psoriasis treatment, but are not cosmetic ingredients. The salts and esters included in this safety assessment are Disodium Fumarate, Sodium Fumarate, Dibehenyl Fumarate, Di-C12-15 Alkyl Fumarate, Diethylhexyl Fumarate, Diisostearyl Fumarate, Sodium Stearyl Fumarate, and Ferrous Fumarate.

Fumaric Acid is an endogenous compound formed mainly in the citric acid cycle. Fumaric Acid is also a fruit acid, ubiquitous in plants. Human skin naturally produces Fumaric Acid when exposed to sunlight. The salts and esters of Fumaric Acid are known as fumarates and may be derived from succinate by succinate dehydrogenase. Fumarates are then converted by the enzyme fumarase to malates.

Fumaric Acid does not absorb UV light above 290 nm in methanol, acidic methanol or basic methanol solution. Fumaric Acid functions in cosmetics as a fragrance ingredient and pH adjuster; Disodium and Sodium Fumarate are described as buffering agents/ pH adjusters; Dibehenyl Fumarate functions as a nonaqueous viscosity increasing agent; Di-C12-15 Alkyl Fumarate, Diethylhexyl Fumarate, and Diisostearyl Fumarate function as emollient skin-conditioning agents; Sodium Stearyl Fumarate is a binder, bulking agent, and slip modifier; and no function in cosmetics was reported for Ferrous Fumarate.

Fumaric Acid has 4 reported uses at concentrations of 0.0008% - 5%. Di-C12-15 Alkyl Fumarate also has 4 reported uses at concentrations of 0.4% - 5%. In each case specific use concentrations were reported in product categories for which no uses were reported to FDA. Diisostearyl Fumarate has 1 reported use in eye preparations, but no concentration data were available; other uses at concentrations between 1% - 20% were reported in non-coloring hair care and makeup products. Use concentrations were reported for Ferrous Fumarate at 0.0003%.

Fumaric Acid is poorly absorbed after oral intake. However, Fumaric Acid esters are almost completely absorbed in the small intestine. Dimethylfumarate is rapidly hydrolyzed by esterases to monoethylfumarate, which is regarded as the active metabolite. Monomethylfumarate is further metabolized in the citrate cycle into water and carbon dioxide. There is no evidence for a cytochrome P450-dependent metabolism of Fumaric Acid esters. Excretion of metabolites is mainly through breathing, with only small amounts being excreted via urine and feces. Dimethylfumarate has a half-life of about 12 min, and monoethylfumarate has a half-life of 36 h. Peak concentrations of monomethylfumarate in blood are seen between 5 h and 6 h. Dimethylfumarate and free Fumaric Acid do not bind to serum proteins. Monomethylfumarate shows a protein binding of about 50%. The Fumaric Acid concentration in normal human plasma is about 2 µM, with the total body content in a adult human ranging from 8 to 80 g.

Fumaric Acid and dimethyl fumarate have cytotoxic and antiproliferative effects in vitro. Dimethyl fumarate and dimethyl maleate are potent inducers of cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) oxidoreductase activity in Hepa 1c1c7 murine hepatoma cells in culture, whereas Fumaric Acid and maleic acids are much less potent. The addition of dimethyl fumarate into the diet of female CD-1 mice and female Sprague-Dawley rats at 0.2% - 0.5% concentrations elevated cytosolic glutathione transferases and quinine reductase activities in a variety of organs, whereas much higher concentrations of Fumaric Acid were only marginally active.

Fumaric Acid has a low chronic toxicity and is a naturally-occurring metabolic intermediate that is already in the food chain as an additive.

Fumaric Acid is hepatoprotective in rat hepatocytes in vitro and in albino rats in vivo.

In short-term animal studies using rabbits, up to 2080 mg/kg bw of Disodium Fumarate daily for 28 days did not result in any mortality. Of 6 rabbits that received up to 3680 mg/kg bw for 17 days, 3 animals died.

Rabbits that received i.v. injections of 50-500 mg/kg Sodium Fumarate every second or third day for 10-32 days had no injurious effect on blood levels of non-protein nitrogen or creatinine, phenosulfolphthalein excretion, or kidney and liver histology. Rabbits that received twice weekly i.p. injections of 60 mg/kg bw of Sodium Fumarate over 17-29 weeks had swelling and congestion of the thyroid gland and atrophy of testes, with low hyaluronidase content. Male rabbits that received 60 mg/kg bw Sodium Fumarate every second day by i.p. injection for 150 days had gonadotropic activity, as well as estrogenic activity, detected in the serum. There was progressive testicular atrophy in all animals.

Rats (14/group) maintained on daily diets containing 0.1% and 1.0% Fumaric Acid for 2 years had no clinical or pathological effects. Eight groups of 14 weanling rats kept on diets containing 0, 0.1 and 1.0% Fumaric Acid and 1.38% Sodium Fumarate for one year (half the groups) or two years had no adverse effects (e.g., rate of weight gain, hemoglobin, blood picture, calcium balance as shown by bone histology, or on the histology of liver, kidney, spleen and stomach). Five groups of 12 male and 12 female rats fed diets containing 0, 0.1, 0.5, 0.8 and 1.2% of Fumaric Acid for 2 years had no effects on growth or food consumption; at the 1.5% level there was a slight increase in mortality rate and some testicular atrophy. Fumaric Acid fed to dogs at 0, 1, 3 and 5% of the diet for 2 years produced no adverse effect on body weight gain, development, hematology, blood sugar and urea levels, organ weights, and gross and histopathological examination of all principal organs and tissues. Rabbits fed diets containing 0 or 6.9% Sodium Fumarate for 150 days had no significant differences from controls in body weight gain, feed consumption, mortality rate, blood counts, blood sugar, non-protein nitrogen level and urine; and organ weights were not significantly different between the groups and histologic examination showed no adverse findings attributable to the diet. In particular, spermatogenesis and testicular structure were unaffected.

Systemic and topical therapies with Fumaric Acid and its derivatives are used in the treatment of psoriasis. Topical application was accompanied by perilesional skin irritation,

macular papular rashes and urticarial reactions. In a guinea pig maximization study, 20 animals were used for immunization: 10 with dimethylfumarate (DMF) and 10 with monoethylfumarate (MEF). Each guinea pig received 1 ml of a compound dissolved in 6 ml phosphate buffer saline and mixed with 6 ml Freund's complete adjuvant: in the nucha (0.4 ml), in front and hind legs (each 0.1 ml), and in both ears (0.1 ml). Another 10 guinea pigs were injected with Freund's complete adjuvant and served as the control animals. The results of the cytotoxicity test demonstrated that DMF was the most toxic derivative. DMF also induced contact-urticarial reactions in contrast to MEF. Challenge experiments 21 days after immunization (open epicutaneous) with Fumaric Acid (400 mM), MEF (100 mM) and DMF (20 mM) in MEF- and DMF-sensitized guinea pigs demonstrated that both MEF and DMF are moderate contact sensitizers. In DMF-sensitized animals cross-reactions with MEF were found. Fumaric Acid was not found to be a sensitizer.

Twelve guinea pigs (male and female) were bred in order to determine whether Fumaric Acid might have an effect on reproduction and lactation. The animals received 1% Fumaric Acid in the diet (~400 mg/kg b.w./day). The exposure period was not reported. There were no detectable toxic effects on growth, reproduction or lactation of the Fumaric Acid-treated guinea pigs.

The drugs, Fumaderm® and Fumaderm® initial, are approved for use in Germany in the treatment of plaque psoriasis. Studies on rats and rabbits exposed to doses approaching levels causing maternal toxicity, yielded no evidence of any teratogenic effect. Embryo-fetal toxicity (growth retardation, mortality) was only observed at doses known to cause maternal toxicity. In one reproduction study on rats, there was no evidence to indicate any effect on fertility.

Fumaric Acid was not mutagenic in several Ames tests and in CHO cells in culture, but was mutagenic in one assay using L5178Y cells in culture. Neither Di-C12-15 Alkyl Fumarate nor Diisostearyl Fumarate were mutagenic in Ames tests.

Fumaric Acid in the diet up to 1.5% was not carcinogenic in male and female Osborne-Mendel rats. Fumaric Acid was found to induce moderate focal hyperplasia of the epidermis. No tumors were formed in female Swiss mice treated once a week with 7,12-dimethylbenz(a)anthracene (1.5% in mineral oil), then with Fumaric Acid twice a week (1% in acetone), for a total of 76 weeks. Fumaric Acid, isolated as the active component of Capsella bursa-pastoris herb, inhibited the solid growth of Ehrlich tumors in mice, and was found to significantly reduce the growth and viability of Ehrlich, MH134, and L1210 mouse tumor cells in culture at concentrations of 0.3 ~ 1.2 mg/mL, with no deleterious effect on monolayer development of mouse and chick embryo cells, but with activity to enhance the recovery of cells from the toxic effects of mitomycin C, aflatoxin B_1, N-methyl-N'-nitro-N-nitrosoguanidine, and potassium 1-methyl-7-[2-(5-nitro-2-furyl) vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate. Fumaric Acid inhibited carcinogenesis by potassium 1-methyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (NFN) in male ICR/JCL mice. The administration of Fumaric Acid suppressed the NFN-induced stomach and lung carcinogenesis. The administration of Fumaric Acid effectively suppressed the development of hepatocellular carcinoma, hyperplastic nodules, and hyperplastic areas in the livers of rats fed 3-methyl-4'-(dimethylamino)azobenzene.

No evidence of primary irritation or allergic hypersensitivity was seen in any of the subjects patch tested with 20% aqueous solution of the trade name mixture Unicotrozon C-49 containing 5% Fumaric Acid and 17.5% Fumaris Officinalis Extract that also contains some Fumaric Acid. A leave-on product containing 1% Di-C12-15 Alkyl Fumarate did not demonstrate a potential for eliciting dermal irritation or sensitization.

Diisostearyl Fumarate is a high shine emollient with good conditioning properties. In lip care products, it helps to disperse pigments and is used to decrease feathering and bleeding.

The contact-sensitization potential of a lip gloss containing 20% Diisostearyl Fumarate to human skin by means of maximization assay was evaluated. A total of 26 healthy adults (23 females, 3 males) participated in the study; of which 25 completed the study. No adverse or unexpected reactions were seen in any of the subjects during the induction phase and no instances of contact allergy were recorded during the challenge phase at either 48 or 72-h.

The contact-sensitization potential of a lip gloss containing 17.41% Diisostearyl Fumarate to human skin by means of maximization assay was evaluated. A total of 26 healthy adults (20 - 61 years old) participated in the study; 25 completed the study. The lipgloss containing 17.4% Diisostearyl Fumarate did not possess a detectable contact-sensitizing potential and is not likely to cause contact sensitivity reactions under normal use conditions.

Fumaric Acid and its esters are used in psoriasis treatment, primarily in Europe.

Case reports include reports of nausea, upper-abdominal pain, loss of appetite, palpitations and flushes consistent with those seen in clinical testing; abnormal renal functions and urinary findings appeared generally reversible.

The cis isomer of Fumaric Acid, Maleic Acid, was found safe for use in cosmetics as a pH adjustor.

DISCUSSION

Overall, the CIR Expert Panel considered that the available data, including the role of Fumaric Acid in normal metabolism, animal toxicity data, and clinical experience were adequate to assess the safety of these ingredients as used in cosmetics.

While salts of dimethyl fumarate and monoethyl fumarate are not cosmetic ingredients, they are approved pharmaceuticals in Europe for treatment of psoriasis. As a consequence, they have been evaluated for both sensitization (published) and reproductive and developmental toxicity (unpublished). In both cases, no concern regarding sensitization potential were raised about these compounds.

The CIR Expert Panel recognized that certain ingredients in this group are reportedly used in a given product category, but the concentration of use was not available. For other ingredients in this group, information regarding use concentration for specific product categories was provided, but the number of such products was unknown. In still other cases, an ingredient was not in current use, but may be used in the future. The information available on the types of products and at what concentration indicate a pattern of use, within which some of these ingredients likely would be used.

The available safety test data support that these ingredients can be used safely at concentrations up to 20%.

In the absence of inhalation toxicity data, the Panel determined that these ingredients can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (≤10 μm).

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concluded that Fumaric Acid, Disodium Fumarate, Sodium Fumarate, Dibehenyl Fumarate, Di-C12-15 Alkyl Fumarate,

Diethylhexyl Fumarate, Diisostearyl Fumarate, Sodium Stearyl Fumarate, and Ferrous Fumarate are safe as used in cosmetic formulations in the practices of use given in this Final safety assessment.[1]

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