International Journal of Toxicology
30(Supplement 1) 54S-65S

DOI: 10.1177/1091581811407352
http://ijt.sagepub.com
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Final Report of the Cosmetic Ingredient Review Expert Panel Safety Assessment of Polymethyl Methacrylate (PMMA), Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer

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Abstract

Polymethyl methacrylate (PMMA) and related cosmetic ingredients methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer are polymers that function as film formers and viscosity-increasing agents in cosmetics. The Food and Drug Administration (FDA) determination of safety of PMMA use in several medical devices, which included human and animal safety data, was used as the basis of safety of PMMA and related polymers in cosmetics by the Cosmetic Ingredient Review (CIR) Expert Panel. The PMMA used in cosmetics is substantially the same as in medical devices. The Panel concluded that these ingredients are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Keywords

cosmetics, methyl methacrylate/glycol dimethacrylate crosspolymer, polymethyl methacrylate, safety

Introduction

This is the final report of the safety assessment of polymethyl methacrylate (PMMA) as used in cosmetics by Cosmetic Ingredient Review (CIR). Based on chemical similarity, the CIR considers that 2 other cosmetic ingredients should be considered in this safety assessment: methyl methacrylate crosspolymer and methyl methacrylate/glycol.

Polymethyl methacrylate is the polymer of methyl methacrylate (MMA). In commercial medical devices, PMMA is available in its components for mixing and formation in situ or preformed into beads or other shapes. Polymethyl methacrylate produced for cosmetics is similar to the PMMA in certain medical device categories in that it is already formed into beads or powder. The safety information for those medical devices has been provided to the Food and Drug Administration (FDA) in medical device applications of PMMA in intraocular lenses (IOLs), bone cement, dental fillers, and dermal fillers. The FDA has found those data to be adequate and has determined the safety (and efficacy) of PMMA for use in these devices. Several of these devices have been approved as implants, resulting in systemic exposures that far exceed that expected for PMMA use in cosmetics.

The CIR considers that the assessment of PMMA safety as used in medical devices by the FDA provides the basis to establish the safety of PMMA in cosmetics because the PMMA is substantially the same as that used in approved medical devices and is used in a manner that presents less exposure risk. Given the chemical similarity, it follows that such data could be extrapolated to support the safety of methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer.

Below is a summary of the information available from the FDA to assess the safe use of PMMA, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer in cosmetics as well as supplemental information from the cosmetic industry.

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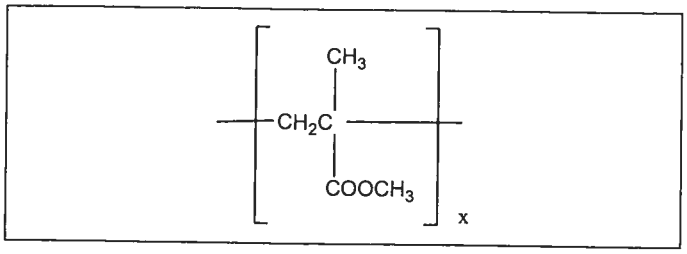

Figure 1. The monomer structure of PMMA.[30] PMMA indicates polymethyl methacrylate.

Chemical Description

Polymethyl methacrylate (CAS No. 9011-14-7) is the polymer of methyl methacrylate that conforms to the formula in Figure 1.[1] Its chemical class is synthetic polymers and it functions as a film former and it has only synthetic sources. Another technical name is 2-propenoic acid, 2-methyl, methyl ester, homopolymer.

Methyl methacrylate crosspolymer (CAS No. 25777-71-3) is a copolymer of methyl methacrylate crosslinked with glycol dimethacrylate (Figure 2). Its chemical class is synthetic polymers and it functions as a film former and a viscosity-increasing agent—nonaqueous. It has only synthetic sources. Other technical names include:

- methyl 2-methyl-2-propenoate, polymer with 2-methyl-2-propenoic acid, 1,2-ethanediyl ester;
- 2-methyl-2-propenoic acid, 1,2-ethanediyl ester, polymer with methyl 2-methyl-2-propenoate; and
- 2-propenoic acid, 2-methyl, 1,2-ethanediyl ester, polymer with methyl 2-methyl-2-propenoate.

The International Nomenclature of Cosmetic Ingredients (INCI) defines methyl methacrylate/glycol dimethacrylate crosspolymer (no CAS No.) as a cross-linked copolymer of methyl methacrylate and ethylene glycol dimethacrylate monomers (Figure 2). Its chemical class is synthetic polymers and it functions as a film former.

Material Characterization

Data provided by industry include a sufficient description of PMMA to conclude that it is similar to the PMMA medical devices approved by the FDA. Table 1 compares the physical properties of PMMA beads used in cosmetics and dermal fillers.

Polymethyl methacrylate. Ingredients in this safety assessment are polymers. In a linear polymer (eg, PMMA), the structural units are connected in a long, linear chain arrangement and thus need to be only bifunctional, that is, have 2 bonding sites. When the structural unit is trifunctional (3 bonding sites) and is polymerized, a nonlinear branched polymer results. Ethylene, styrene, and ethylene glycol are examples of bifunctional monomers, while glycerin and divinyl benzene are both polyfunctional. A crosspolymer has multiple polymer chains that are linked together with a compound called a crosslinking agent (eg, methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer). Polymers containing a single repeating unit, such as PMMA, are called homopolymers. Polymers containing 2 or more different structural units (monomers), such as phenol-formaldehyde resin, are called copolymers. Polymers can be classified as either addition polymers or condensation polymers. An addition polymer is one in which the molecular formula of the repeating structural unit is identical to that of the monomer, for example, polyethylene and polystyrene. A condensation polymer is one in which the repeating structural unit contains fewer atoms than that of the monomer or monomers because of the splitting of water or some other substance, for example, polyesters and polycarbonates. Accordingly, PMMA is an addition type of homopolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer is an addition type of copolymer.

A comparison of PMMA beads used in dermal fillers with different sources revealed a wide variation in quality and conformity.[6] One source reported size ranges from 30 to 50 μm with negligible small sizes. The surfaces were smooth with scant, if any, sediment. The beads from another source were characterized as having a wide variety of particle sizes (0.2-70 μm), with

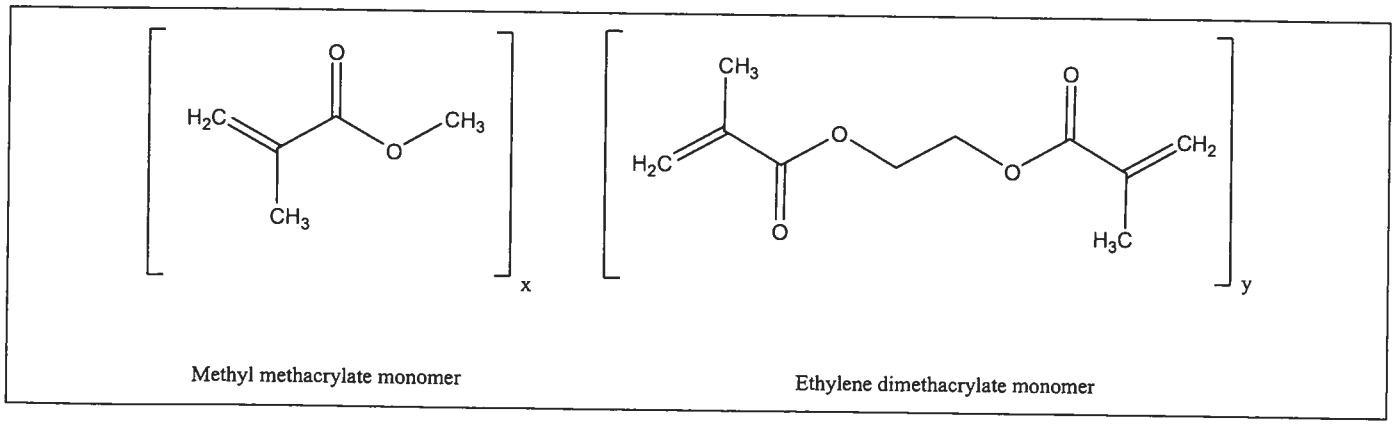

Figure 2. Methyl methacrylate monomers and ethylene dimethacrylate monomers are polymerized to make up methyl methacrylate/glycol dimethacrylate crosspolymer and methyl methacrylate crosspolymer—more detailed structures are not available because the connectivity is not given and the values for x and y are not known.

Table 1. Comparison of PMMA Beads Used in Cosmetic and Dermal Fillers

Property	Cosmetics	Dermal Fillers
Form	Beads	Beads
Appearance	Fine white powder	Fine white powder
Diameter (μm)	5-10, 6-10, 6.5-10.5, 5-16[2]; 4-8, 6-10, 20[3]; <2-35[4]; 4.5-8.5[5,6]; 60-80[7]	30-50[8]; .2-70[8]; 30-42[9]; 4-40[10]; 4.3-72[10]; 30-42[9]
Molecular weight of monomer	PMMA—88.11	PMMA—88.11
Molecular weight of polymer (d)	> 250,000[7]	Not available
Residual monomer (ppm)	< 100, < 50, < 10[2]; < 20 on surface, < 100 total[2]; < 100[2,11,6]	10.3 μg/kg[2,10]

some oversized and very small spheres. Some of the particles were not round and/or were conjoined.

The molecular weight of the PMMA monomer is 88.11. Polymethyl methacrylate made by emulsion polymerization can have a molecular weight of several million. The glass transition temperature (Tg), where the polymer changes between the crystal state and glass state, of PMMA is 105°C. Polymethyl methacrylate is rigid at room temperature and is highly stable.[12] The surface of PMMA is dominated by methyl ester groups and when exposed to water demonstrate no detectable surface restructuring.[13] Visible light transmits through PMMA up to 92% and transmits into the ultraviolet range. Emulsion-made polymers of methacrylates that are copolymers (mixed with other polymer components) have physical properties that vary widely depending on the composition and morphology of the emulsion particles.[14]

Polymethyl Methacrylate in Cosmetics. The PMMA used in cosmetics are in the form of fine powders or beads.[2] The diameter of the beads supplied to cosmetic companies were reported to be 5 to 10 μm, 6 to 10 μm, 6.5 to 10.5 μm, 5 to 16 μm, or having an average diameter of 6 μm, depending on product. One product information sheet for PMMA for cosmetic use identified the form as highly porous spherical beads. Size range and tolerance, porosity, or any chemical property information were not provided.[15] Another product information[3] sheet described the PMMA product (for use in cosmetics) as low-micron materials with an appearance of white fine powders with an average particle size of 4 to 8 μm. At 10% in water, the pH is 5.0 to 8.0 and the oil absorbance is 64 mL/100 g.

A product information sheet of several PMMA bead products (for use in cosmetics) described the products as a white fine powder.[11] Diameters were reported to be 4 to 8, 6 to 10, or 20 μm with a pH in the range of 5.0 to 8.0. The oil absorbance ranges from 64 to 73 mL/100 g.

An analysis of the diameters of beads in a sample of PMMA (for use in cosmetics) shows a peak at just under 5 μm with the highest range of ~3.5 to 10 μm.[4] The entire bead diameter size range is < 2 to ~35 μm.

Another analysis of PMMA beads confirms that the sample is a white powder with an average particle size of 6.3 μm (specifications 4.5-8.5 μm), a pH of 6.5 (5-8), 0.07% residue at ignition (≤0.1%), and 0.4% loss on drying (≤2%).[5]

In artificial nail-enhancement products, the molecular weights of PMMA particles are, >250 000 Da.[7] The particle size ranges between 60 and 80 μm.

Methyl Methacrylate Crosspolymer

On a product data sheet, methyl methacrylate crosspolymer beads have an average size of 8 μm and the spheres are hollow.[16]

Methyl methacrylate crosspolymer products are also described as a white fine powder with diameters reported to be 8.5, 4 to 8, or 6 to 10 μm.[17] The pH ranges from 5.0 to 8.0 and the oil absorbance is from 70 to 75 mL/100 g with one reported to be 170.

Methods of Manufacture

Industry has stated that the manufacturing process for PMMA beads used in medical devices and cosmetic products is the same. The only difference is the size of the PMMA spheres, which are provided according to the specifications of the purchaser.

Polymethyl methacrylate beads or powders in cosmetics are precipitated out from a polymerization reaction.[2] The average bead size can be controlled within the 4 to 50 μm specifications. Furthermore, the chemical resistance and the compositions of submicron polymers can be altered.[16]

Polymethyl methacrylate can be polymerized, then crushed and pelletized.[18] Suspension and bulk polymerization are generally used for injection molding and extrusion applications. Variation in the diameter of commercial PMMA beads was achieved by changing the time the stabilizing agent was added to the reaction; delay in the addition of the stabilizing agent resulted in larger beads.

Several methods of PMMA manufacture have been described.[14] Bulk casting employs a mold of glass to create sheets, rods, and blocks. Suspension and bulk polymerization are generally used for injection molding and extrusion applications. Suspension polymerization uses beads of the monomer to form beads of the polymer that may be used as produced or extruded to yield pellets. Continuous bulk polymerization can be carried out using PMMA as both the reactant and the solvent. Emulsion polymerization is used to create submicron-sized (50-1000 nm) particles in an aqueous medium, which has the advantages of easy heat dispersion, low polymerization medium viscosity, ability to achieve high-molecular weight, and high monomer conversion.[14]

Table 2. Methods of Physical and Chemical Analysis of PMMA Used as a Bone Cement[23]

Characterization	Suggested Testing	Examples of Testing Methods
Mixing and application	Mix liquid and powder components	ASTM F451-95; ISO 5833-92
	Dough time	ASTM F451-95; ISO 5833-92
	Setting time	ASTM F451-95; ISO 5833-92
	Viscosity: pre-dough stage extrusion	ASTM F451-95; ISO 5833-92
	Dough stage extrusion	ASTM F451-95; ISO 5833-92
Chemical composition	Ingredients: chemical formula, structure, additives, etc	Liquid-NMR, FTIR, HPLC/MS
	Type of radiopacifier	TGA/gross pyrolysis
	Purity or trace elements	ICP/MS, GC/FTIR/MS, titration
	Residue low-mw molecules	GC, HPLC/GPC, liquid-NMR
	Leachables (ie, low MW molecules)	GC, HPLC/GPC
Molecular weight and polymer structure	MW by viscosity flow	Viscosity measurements (ie, solution)
	MW: polydispersity, M_n, M_w	GPC with refractive index detector using polystyrene as standard material
	Branched, linear, or cross-linked	Solubility, swelling, liquid NMR
	% Crystallinity, if applicable	X-ray diffraction, DSC
	Crystallization temperature, if applicable	DSC, DMA
	Glass transition temperature (Tg), if applicable	DSC, DMA
Physical properties	Powder's morphology, size characterization, and dispersion of polymer and additives	Light microscopy, SEM of powder and cured cement
	Porosity characterization	Scanning acoustical microscopy of bulk cement (ie, SLAM, C-SAM) and serial sectioning of the cured cement
	Dimensional changes during curing (shrinkage)	Volume measurement
	% Water absorption (swelling)	Saturation testing
	Aging due to fluid absorption and polymerization	Mechanical testing
Stability of components	Change in monomer viscosity due to artificial aging	ASTM 451-95
	Change in benzoyl peroxide levels	Titration method, FTIR, GC
Thermal properties	Maximum polymerization temperature	ASTM F451-95; ISO 5833-92

Abbreviations: TM, American Standard for Testing Materials; C-SAM, C-mode scanning acoustical microscopy; MDA, dynamic mechanical analysis; DSC, differential scanning calorimetry; FTIR, Fourier transform infrared; GC, Gas chromatography; GPC, gel permeation chromatography; HPLC, High performance liquid chromatography; ICP, Inductively coupled plasma; ISO, International Standards Organization; MS, mass spectroscopy; MW, molecular weight; NMR, nuclear magnetic resonance; SEM, scanning electron microscope; SLAM, scanning laser acoustical microscopy; TGA, thermogravimetric analysis.

In nail products, polymer powders are made from methyl or ethyl methacrylate or their copolymers.[7]

The methods of manufacture, where available, are included with the description of the FDA-approved medical devices below. Manufacture of PMMA for medical devices requires compliance with good manufacturing practices.[19]

Analytical Methods

To test for residual monomer, beads of PMMA for cosmetics are soaked in methanol with supersonic dispersion. The sample is then centrifuged, and the solution on the upper side is analyzed by high-pressure liquid chromatography.[20] A fluorine limit test is used to test for the fluorine, and a lead limit test is used to test for lead contained in a sample of PMMA.[21]

During manufacture, infrared spectroscopy is used to monitor the polymerization of MMA to PMMA.[22] Table 2 shows the methods of physical and chemical analysis of PMMA used as bone cement.

Raman spectroscopic identification was used to identify PMMA IOLs implanted in human eyes.[24]

The amount of the residual monomer MMA on PMMA denture material was measured by removing the monomer with tetrahydrofuran and analyzing using HPLC.[25] A light microscopic technique with polarized light was used to measure the thickness of the unpolymerized surface layer of PMMA.

Impurities

The monomer levels in PMMA used in cosmetics were reported as <100, <50, and <10 ppm, depending on the product.[2] One supplier reported a monomer level of <20 ppm on the surface and <100 ppm total. Analysis showed <5 ppm on the surface and <25 ppm total.

The Nail Manufacturers Council reported that the residual monomer is typically <1.5%; averages of 0.7% and 1.2% have been reported.[7]

The PMMA in an eyebrow pencil contained <20 ppm monomer.[26]

A 2-year-old PMMA sample was found to have <1 ppm arsenic and <10 ppm heavy metal (specifications were <3 ppm and <10 ppm, respectively). The surface had <5 ppm residual monomer and there was <25 ppm total, below specifications of <20 ppm and <100 ppm.[5]

A supplier reported that residual MMA in methyl methacrylate crosspolymer is similar to that of PMMA, <100 ppm.[2]

Cosmetic Use

According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), PMMA was used in a total of 892 cosmetic products (Table 3).[29] Use concentrations ranged from 0.01% to 45%, according to a survey of current use concentrations conducted by the Personal Care Products Council (Council).[30] Polymethyl methacrylate was reported to be used in 304 eye products, 369 makeup products (including 60 lipsticks), and 198 other types of leave-on products.

Methyl methacrylate crosspolymer was reported to be used in 144 cosmetic products at 0.1% to 14%. Methyl methacrylate crosspolymer was used in 15 eye products, 79 makeup products (including 15 lipsticks), and 47 other types of leave-on products. It was used in at least 1 spray product.

Methyl methacrylate/glycol dimethacrylate crosspolymer was reported to be used in 7 leave-on cosmetic products at 0.1% to 3%.

The number of uses within concentration ranges as reported by Health Canada is presented in Table 4.

A product data sheet stated that PMMA beads are used as a delivery system in cosmetic applications, commonly for sodium hyaluronate, folic acid, vitamin E, Fomblin, and a-hydroxy acid. The beads may also be used to deliver colorants. The beads provide a ball-bearing effect that contributes to product feel.[15]

Both PMMA and methyl methacrylate crosspolymer are used in color sprays. For ingredients used in cosmetic sprays and aerosols, it is important to consider inhalation safety. Safety of inhaled aerosols depends on the ingredient, the concentration, the duration of the exposure, and where they are deposited within the respiratory system.[30] The site of deposition is associated most with the particle size and density of the particle being inhaled.

Absorption of gases and vapors by inhalation is determined by the partitioning of the compound between the blood and the gas phase along with its solubility and tissue reactivity. The important characteristics that affect absorption after exposure to aerosols are the aerosol size and water solubility of any chemical present in the aerosol. In general, the smaller the particle, the further the particle will deposit into the respiratory tree and the greater the impact on the respiratory system.

The parameter most closely associated with this regional deposition is the aerodynamic diameter, d_a, defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. In humans, particles with an aerodynamic diameter of ≤ 10 μm are respirable. Particles with a d_a from 0.1 to 10 μm settle in the upper respiratory tract and particles with a d_a <0.1 μm settle in the lower respiratory tract.[32,33] Nanoparticles have the potential to deliver high amounts of particulates to the lung.[34]

As noted earlier, PMMA is supplied as a fine powder with an average particle size between 4 and 8 μm, in the respirable size range. The current technology for producing cosmetic aerosols for the mixture of all ingredients cannot deliver particles that small. Particle diameters of 60 to 80 μm and ≥ 80 μm have been reported for anhydrous hair sprays and pump hairsprays, respectively.[35] In practice, aerosols should have at least 99% of their particle diameters in the 10 to 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm.[36] Therefore, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

A search of the Environmental Working Group's database of cosmetic ingredients revealed 4 uses of PMMA in nail glues that were not reported to the FDA or the Council.[37] Additional input from the Personal Care Products Council (Council) and the Nail Manufacturer's Council revealed that the PMMA was used in final form in nail glues and was not mixed in situ, as with bone cement.[38]

In artificial nail-enhancement systems, PMMA is used as an inert carrier for the curing agent, benzoyl peroxide (BPO), and FD&C and D&C coloring agents.[7] It also serves as a thickening agent for placement and shaping of liquid and powder slurry on the nail plate in nail products. Polymethyl methacrylate beads are a reinforcing agent to prevent crack propagation in the cured polymer matrix.

Polymethyl Methacrylate Use in Medical Devices

The FDA has considered the safety of PMMA when approving medical devices made of this material.

Intraocular lenses (ie, Tecnis, Advanced Medical Optics, Inc., Irvine, CA and SENSAR Soft Acrylic UV Light-absorbing Posterior Chamber Intraocular Lens, Allergan, Inc., Santa Ana, CA) are made of PMMA. Premarket applications have been approved since 1976.[39,40]

Polymethyl methacrylate bone cement has been approved by the FDA as a class II (special controls) medical device that requires premarket notification and adherence to standards. The FDA-cleared bone cements have been marketed since 1999.[41,42]

Polymethyl methacrylate beads are incorporated into collagen as dermal fillers (ie, Artecoll PMMA/Collagen Implant, Artes Medical, Inc., San Diego, CA and Artefill, Artes Medical, Inc., San Diego, CA). A premarket application was approved in 2006.[43,44]

Temporary (provisional) PMMA crown and bridge materials (ie, Artegral ImCrown, Merz Dental, Lutjenberg, Germany) have been cleared for marketing since before 1976 and comply with class II special controls.[45]

Polymethyl methacrylate membranes also have been used in dialyzers for hemodialysis.[46,47] Polymethyl methacrylate has been used in other medical applications.[48-62]

Safety Data Submitted to the FDA on PMMA Medical Devices

The FDA has reviewed extensive data on several medical devices; that review was considered to support the safety of use of PMMA and the associated ingredients in cosmetics. Data on the safety of implanted PMMA obviates the need for absorption, distribution, metabolism, and excretion (ADME) or

Table 3. Cosmetic Product Uses and Concentrations for PMMA, Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer

Product Category (Total Products in Category—FDA 2008)	2008 Uses (FDA 2010)[27]	2009 Concentrations (%) Council 2009)[28]
Polymethyl methacrylate		
Bath products		
Soaps and detergents (1329)	2	6
Eye products		
Eyebrow pencil (153)	13	5-15
Eyeliner (834)	59	0.1-17
Shadow (1343)	173	5-45
Lotion (260)	20	0.5-3
Makeup remover (133)	–	–
Mascara (528)	9	0.5-2
Other (412)	30	0.9[a]
Fragrance products		
Colognes and toilet waters (1426)	–	15
Perfumes (742)	2	20
Powders (237)	2	10
Other (641)	3	0.5-11
Noncoloring hair care products		
Rinses (34)	2	0.3
34 Tonics, dressings, etc (1321)	–	1
Hair-coloring products		
Tints (6)	–	2
Color sprays/aerosol (7)	1	–
Makeup		
Blushers (471)	70	0.1-16
Face powders (724)	91	2-30
Foundations (624)	99	3-25
Lipstick (2045)	60	3-20
Makeup bases (126)	13	1-26
Rouges (107)	9	–
Fixatives (49)	14	5
Other (536)	13	2-23
Nail care products		
Polish and enamel (351)	2	0.7-20
Other (137)	12	30
Personal hygiene products		
Underarm deodorants (623)	–	4
Shaving products		
Aftershave lotions (381)	4	0.4-2
Shaving cream (128)	2	–
Other (126)	3	–
Skin care products		
Cleansing creams, lotions, liquids, and pads (1528)	2	–
Face and neck creams, lotions, etc (1652)	62	1-16
Body and hand creams, lotions, etc (1875)	17	0.3-5
Moisturizers (2750)	50	0.3-3
Night creams, lotions, powder and sprays (386)	15	0.2-2
Paste masks/mud packs (462)	2	0.5-2
Fresheners (267)	2	–
Other (1446)	27	0.2-3
Suntan products		
Suntan gels, creams, liquids, and sprays (106)	3	0.01-15
Indoor tanning preparations (247)	1	–
Other (61)	3	3
Total uses/ranges for PMMA	892	0.01-30
Methyl methacrylate crosspolymer		
Eye products		
Eyebrow pencil (153)	–	10
Eyeliner (834)	1	10
Shadow (1343)	7	1-10
Lotion (260)	3	0.5
Mascara (528)	1	1-2
Other (412)	3	–
Fragrance products		
Powders (237)	1	8
Noncoloring hair care products		
Sprays/aerosol fixatives (321)	–	0.1
Makeup		
Blushers (471)	6	0.8-1
Face powders (724)	16	0.5-12
Foundations (624)	33	0.5-10
Lipstick (2045)	15	1-10
Makeup bases (126)	–	4
Fixatives (49)	4	–
Other (536)	5	4-10
Nail care products		
Basecoats and undercoats (69)	–	1
Nail polish and enamel (351)	1	–
Personal hygiene products		
Underarm deodorants (623)	–	0.9
Shaving products		
Other (126)	1	–
Skin care products		–
Skin cleansing creams, lotions, liquids, and pads (1528)	1	–
Face and neck creams, lotions, etc (1652)	13	1-3
Body and hand creams, lotions, etc (1875)	3	0.1-0.5
Moisturizers (2750)	17	0.8-3
Night creams, lotions, powder, and sprays (386)	5	–
Fresheners (267)	1	0.6
Other (1446)	5	3-14
Suntan products		
Indoor tanning preparations (247)	2	–
Total uses/ranges for methyl methacrylate crosspolymer	144	0.1-14
Methyl methacrylate/glycol dimethacrylate crosspolymer		
Fragrance products		
Powders (237)	–	3
Makeup		
Other (536)	4	0.6
Skin care products		–
Face and neck creams, lotions, etc (1652)	–	0.1-0.2
Moisturizers (2750)	1	0.5
Paste masks/mud packs (462)	–	0.1
Other (1446)	2	–
Total uses/ranges for Methyl methacrylate/glycol dimethacrylate crosspolymer	7	0.1-3

Abbreviations: FDA, Food and Drug Administration; PMMA, polymethyl methacrylate.

[a] 0.9% in an eye makeup fixative.

Table 4. Use and Concentration of Use Reported by Health Canada[31]

Ingredient Name	Range							
	>30%-100%	>10%-30%	>3%-10%	>1%-3%	>0.3%-1%	>0.1%-0.3%	0.1% or Less	Total
Polymethyl methacrylate	57	180	543	595	542	143	156	2216
Methyl methacrylate crosspolymer	6	41	154	185	106	19	15	526
Methyl methacrylate /glycol dimethacrylate crosspolymer	0	0	5	17	16	9	8	55

other safety data. Relevant safety issues, such as microbial adhesion and monomer issues, have been addressed by the FDA in the course of its safety review.

Intraocular Lenses

Intraocular lenses are considered permanent implants. They replace the natural occluded lens following lens removal in cataract surgery. A battery of in vivo and in vitro acute and chronic toxicity tests established the biocompatibility of the PMMA IOL material. Based on these studies and data from chemistry and engineering analyses, the suitability of the material for use as IOL material was established. Physiochemical tests include tests for exhaustive extraction, leachables, hydrolytic stability, photostability against ultraviolet and visible irradiation, stability against neodymium yttrium-aluminum-garnet (Nd-YAG) laser exposure, and insoluble inorganics. The FDA also requires biocompatibility testing according to the FDA-modified use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation, and Testing for blood-contacting, long-term devices.[63] Biological testing must conform to International Standard ISO-10993-5, Biological Evaluation of Medical Devices Part 5: Tests for in vitro cytotoxicity.[64] Testing for effects on cell growth and cell damage, genotoxicity, local effects after implantation, and sensitization potential is required.

Postoperative follow-up of patients (n = 335) implanted with acrylic IOLs with PMMA haptics (SENSAR Soft Acrylic UV Light-Absorbing Posterior Chamber Intraocular Lens, Model AR40) implants was performed for 12 months. The FDA concluded that the clinical performance of the IOL compared favorably with 1983 historical data including adverse events reported to the FDA.[40]

Nonclinical and clinical testing of PMMA IOLs was conducted (Model AC21B Ultraviolet-Absorbing PMMA Anterior Chamber Intraocular Lens). Patients (n = 722) were followed for 12 to 24 months. No adverse events were reported. A battery of in vivo and in vitro and chronic toxicity tests established biocompatibility in this application.[65]

Manufacturing information on PMMA was provided to the FDA. Quality control procedures, purity, and other tests are required. The FDA requires that <1% free monomer be present in the PMMA used in IOLs (Don Calogero, personal communication, September 2009).

Bone Cement

The FDA has issued a class II special controls guidance document for PMMA bone cement for the allowance of new commercial bone cement products to be deemed "substantially equivalent to legally marketed predicate devices."[23] The guidance stipulates that the cement be PMMA. The FDA also requires biocompatibility testing according to the FDA-modified Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation, and Testing for blood-contacting, long-term devices.[66] The ISO standard also states that the identified risks of bone cement implantation syndrome, polymerization setting problems, loosening or migration of the device, infection and fever, adverse tissue reaction, pain and/or loss of function, and revision be mitigated by material and performance characterization (physical and chemical characterization, mechanical testing, shelf-life, product expiration dating, and storage conditions), sterility, and labeling. Bone cement labeling must include cautions about inhalation of monomer vapors, exothermic reaction, inadequate fixation, and the dissolving of rubber or latex gloves or tissue during mixing and setting. None of these possible adverse events pertain to cosmetic use since PMMA used in cosmetics is used only in its final, fully polymerized form.

The FDA has approved a number of PMMA bone cements for market, including Cemex ISOPLASTIC Bone Cement, SmartSet GH Gentamicin, Cobalt HV Bone Cement, Spine-Fix Biomimetic Bone Cement, and SmartSet MV Bone Cement.[65,23,67-70]

Polymethyl methacrylate bone cement consists of methyl methacrylate (97.4% w/w) added to *N,N*-dimethyl-*para*-toluidine (2.6% w/w) and hydroquinone (75 ± 15 ppm). This is then added to PMMA (15% w/w) and methyl methacrylate-styrene copolymer (75% w/w) with barium sulfate USP (10% w/w) to make the cement radiopaque.[71]

Polymethyl methacrylate bone cement is polymerized by radical-initiated addition reaction. The 2 components are a powder containing prepolymerized beads of PMMA (or PMMA/styrene copolymer) and a liquid containing MMA monomers. The BPO initiator is incorporated into the powder, and the chemical activator is incorporated into the liquid. Peroxide cleavage and polymerization begins when the 2 are mixed. Growing polymer chains encapsulate the PMMA beads. The liquid-to-powder ratio affects the strength of the cement and temperature. The initiator-to-activator ratio affects

polymerization times. Polymethyl methacrylate beads act as heat sinks; their concentration and size affect overall temperature and setting times but have little impact on strength.[57]

Artecoll Dermal Filler

Safety and effectiveness data for approval by the FDA of Artecoll, a dermal filler made up of collagen and PMMA beads, are summarized in the summary of safety and effectiveness (SSE).[10]

Testing for cytotoxicity was done according to the ISO-10993-5 guidelines.[64] There was no evidence of cell toxicity observed. Artecoll was found to be less cytotoxic than a grade 2 (mild reactivity) material.

Testing for mutagenicity was done in a reverse mutation assay. Artecoll was nonmutagenic to *Salmonella typhimurium* and *Escherichia coli*.

A guinea pig (n = 10) maximization test was performed. Artecoll did not cause a delayed dermal contact sensitization reaction.

Artecoll was studied in implantation studies in rabbits and did not cause a significant reaction compared to controls. Microscopic evaluation found the test substance to be nonirritating. Implantation studies of cross-linked collagen, hyaluronic acid, silicone oil, PMMA microspheres (4-40 μm), PMMA microspheres in hyaluronic acid (40 μm), polylactic acid microspheres (40 μm), dextran microspheres (40 μm), trisacryl-gelatin microspheres, silicone particles, ZrO-coated parrolytic carbon beads (212-500 μm) suspended in 3% β-glucan and polyacrylamide were also done in humans or mice. Polymethyl methacrylate microspheres were well tolerated and stable over 9 months.

Phagocytosis of PMMA microspheres (4.3-72 μm) was determined by incubation with U-937 macrophage, XS 106, and SX 52 Langerhans cells as well as HaCaT keratinocytes. U-937 macrophages, keratinocytes, and Langerhans cells phagocytosized PMMA microspheres <20 μm; larger microspheres were not ingested. There was no tumor necrosis factor-alpha (TNF-α) secreted.

The FDA concluded that PMMA microspheres are safe and approved for dermal implantation due to the above data and the evidence that MMA has been removed by the bead processing (use could result in dose of MMA of 10.3 μg/kg).[10]

The PMMA beads range in size from 30 to 42 μm.[9]

The trade name for this product in the United States is now Artefil.[72] Artecoll is the name used outside the United States.

Dental Material

The FDA has issued a class II special controls guidance document for PMMA provisional dental crowns and bridges for new commercial dental material products to be deemed substantially equivalent to legally marketed predicate devices. Manufacturers are required to test for mechanical failure; toxicity and adverse tissue reaction, and identification of improper use. Physical properties to be tested are compressive strength (MPa), flexural strength (MPa), elastic modulus (GPs), intensity (mW/cm^2) for curing (for photo-initiated resins), wavelength (nm) for curing (for photo-initiated resins), depth of cure (mm; for photo-initiated resins), filler particle size distribution (μ), surface hardness (KHN), radiopacity (mm of Al), water sorption ($\mu g/mm^3$), solubility ($\mu g/mm^3$), release profile ($\mu g/mm^3$; if the device contains a releasable agent such as fluoride or nitrate ions), working time (seconds), curing time (seconds; for photo-initiated resins), and setting time (minutes). Biocompatibility is tested according to ISO-10993-5.[45,64,73]

Nonmedical Device Assessment

Acute Oral Toxicity

Polymethyl methacrylate (500 mg/kg in water and carboxymethylcellulose) was orally administered to male ICO:OF1 IFFA CREDO mice (n = 6) after overnight fasting.[74] The mice were observed for 8 days then necropsied. In the first 24 hours, the mice had short time periods of prostration and diarrhea. From day 2 on, there were no clinical signs and all mice survived the observation period. The necropsies were unremarkable.

Ocular Irritation

In an ocular irritation study of a PMMA (0.1 mL; 4.5-8.5 μm) sample using New Zealand rabbits (n = 6), the test sample was placed in the right eye and the untreated left eye was the control.[75] After 24 hours, the eyes were rinsed with sterile water and scored. There were slight signs of irritation on the conjunctiva (redness, swelling, and lacrimation) at 24 hours. Only lacrimation was observed at 48 hours. At 72 hours, 3 of the 6 had recovered and all had recovered by 96 hours. The general behavior of the rabbits was not modified by the test substance. The mean ocular irritation scores were 6.7, 3.7, 1.0, 0, and 0 at 24, 48, 72, and 96 hours, respectively. The authors concluded that PMMA is a slight ocular irritant.

Dermal Irritancy

A dermal patch test was performed on a PMMA (0.5 mL) sample using male New Zealand rabbits (n = 6).[76] The test material was applied to the intact and scarified clipped skin and was left for 24 hours. There was no edema up to 72 hours after patch removal. Five of the rabbits had slight redness on both application sites. The primary irritation score was 0.46 and PMMA was rated a nonirritant.

Clinical Assessment of Safety

A modified Draize human repeat insult patch test (HRIPT) was conducted on the bulk material of a brow pencil (9.723% PMMA) diluted to 70% in water. The test material was applied to the upper arm of the participants (n = 52) and removed after 24 hours under semiocclusion for 9 consecutive applications. The challenge application was applied after a 2-week rest. No skin reactivity was observed in any test participant during

sensitization. The authors[26] concluded that there was no indication of cumulative skin irritation or sensitization of PMMA at 6.8%.

An HRIPT was conducted on a mascara (0.2 g) containing methyl methacrylate crosspolymer (2.0%).[77] The test material was applied to the backs of the participants (n = 106). There was no dermal reactivity during induction or challenge.

In an EpiOcular test of a mascara containing methyl methacrylate crosspolymer (2.0%) diluted to 20% in distilled water, tissue was exposed to the test material for 20 minutes, 1 hour, and 4 hours.[78] The Draize ocular irritation score of 100% methyl methacrylate crosspolymer was calculated to be 0 and classified as nonirritating.

Monomer Sensitivity

After the polymerization process, there is the possibility of unreacted monomer being present within and on the final product. The monomer has been examined and some of the data considered are summarized here.[79] Methyl methacrylate is the residual monomer from the polymerization process in making PMMA. Methyl methacrylate was found to be sensitizing at 25% in guinea pigs.[80] The minimum induction concentration in a guinea pig maximization test was 1 mol/L (100 and 120 ppm).[81] In a local lymph node assay, MMA had an EC3 (stimulation index [SI] of 3 relative to concurrent vehicle-treated controls) of 60% w/v in acetone and 90% w/v in olive oil. Methyl methacrylate was rated as a weak contact allergen.[82]

Sensitization data also were reviewed in the safety assessment of ethyl methacrylate used in the formulation of artificial nail-enhancement products. Ethyl methacrylate was found to be "... safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of ethyl methacrylate."[79] The frequency of positive reactions among all patients tested with ethyl methacrylate was 14 (64%) of 22. The frequency of positive reactions among patients with artificial nails was 7 (64%) of 11, suggesting that the use of artificial nail-enhancement products presented no additional risk. More to the point of considering the potential sensitization of the MMA monomer, the frequency of positive reactions to MMA among all patients was 7 (32%) of 22 and among patients with artificial nails was 1 (10%) of 10. Combining the low frequency of sensitization to MMA with the low level of the monomer in PMMA, the risk of sensitization may be considered low.

Cross- or co-reactivity of ethyl methacrylate and MMA was another concern addressed in the safety assessment of ethyl methacrylate, specifically because of the use of MMA in PMMA bone cements and the possibility that an individual sensitized to ethyl methacrylate might then have an allergic reaction to the bone cement in a necessary medical procedure. The Panel concluded that there were no data supporting any sensitization reactions in patients receiving implants cemented with MMA and that adverse consequences of cross-reactivity of ethyl methacrylate and MMA are not a concern.

Summary

The FDA has already reviewed the safety of PMMA for the use in several medical devices that are implanted into the human body, (IOLs, bone cement, dental fillers, and dermal fillers) that result in far greater systematic exposure than any use in cosmetics. Presuming that the PMMA used in cosmetics is not substantially different (eg, same or lower monomer levels) from PMMA used in medical devices, then the data available to the FDA in support of medical device safety have relevance to safety in cosmetics.

These ingredients are polymers with synthetic sources that are used as film formers, viscosity-increasing agents, binders, and emulsion stabilizers. Commonly used analytical techniques can determine monomer and polymer levels.

The impurity of concern is the monomer MMA. Analysis of PMMA beads used in cosmetic formulations found MMA to be present at <100 ppm. Arsenic and heavy metals are found at low levels.

Polymethyl methacrylate is reported to be used in 892 cosmetic products at 0.01% to 45%; methyl methacrylate crosspolymer in 144 cosmetic products at 0.1% to 14%; and methyl methacrylate/glycol dimethacrylate crosspolymer in 7 products at 0.1% to 3%.

Safety data for use of PMMA in IOLs included monomer levels (< 1%), other leachables, hydrolytic stability, photostability, biocompatibility, in vitro cytotoxicity, local effects at site of implantation, cell damage, genotoxicity, and sensitization. Extensive postimplantation follow-up did not uncover any material-related safety concerns.

Safety data for use of PMMA in bone cements reviewed by the FDA included monomer levels, polymer setting process, and biocompatibility. Other safety data developed for bone cements related to polymerization at the site of use were not relevant to cosmetic use where PMMA is used in its fully polymerized form.

Of the medical devices, the safety data for dermal fillers may be the most relevant to cosmetic use because both use PMMA beads. The FDA reviewed cytotoxicity, mutagenicity, sensitization, irritation, biocompatibility, and TNF-α stimulation data, leading to the approval of dermal fillers with PMMA in the market.

While biocompatibility testing of PMMA in dental material was required by the FDA to support that approval, most of the data requirements related to physical performance.

Additional data indicated that PMMA was not orally toxic to mice at 500 mg/kg. Polymethyl methacrylate was mildly irritating in an eye test and was not a dermal irritant to rabbits. Polymethyl methacrylate was not irritating or sensitizing at 6.8% in an HRIPT test using 52 participants. The same result was obtained in another HRIPT test of PMMA at 2.0% using 106 participants. In an EpiOcular test, PMMA had a Draize ocular irritation score of 0.

Methyl methacrylate, the monomer of PMMA, was sensitizing at 25% in guinea pigs. Methyl methacrylate was a weak contact allergen in a local lymph node assay (LLNA); MMA had an

EC3 of 60% w/v in acetone and 90% w/v in olive oil. Ethyl methacrylate was sensitizing in 64% of participants tested.

Discussion

The CIR Expert Panel used a different approach (compared to past safety assessments) to the assessment of PMMA, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer. The FDA had already reviewed the safety of PMMA for use in several medical devices that are implanted into the human body (IOLs, bone cement, dental fillers, and dermal fillers), which result in far greater systemic exposure than any use in cosmetics. The Panel considered that the PMMA used in cosmetics to be substantially the same as PMMA used in medical devices. Thus, the data available to the FDA in support of medical device safety has relevance to cosmetics. Data made available by industry confirmed that there are no significant differences in the material or in the monomer levels that may be related to PMMA and the other ingredients used in cosmetic products.

The CIR Expert Panel saw no need to review systemic toxicity data on PMMA and related polymers applied to the skin as the safety of this route of exposure can be extrapolated from data on use of these polymers as medical devices, which had already been reviewed and found safe by the FDA. Several of these devices have been approved as implants, resulting in systemic exposures that far exceed the exposure expected for PMMA use in cosmetics.

Polymethyl methacrylate-based cosmetic ingredients are large molecules and remain in particulate form (dispersed) in final preparations and thus will not likely cross the stratum corneum to induce systemic toxicity.

While the residual monomer methyl methacrylate (MMA) has the potential to induce sensitization, the levels in these ingredients were reported to be well below the levels that would induce sensitization to MMA, thus resolving the Panel's concern about sensitization.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure, and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 to 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of $\leq$10μm are respirable. The smallest diameter of PMMA in cosmetics is 4 μm. However, in aerosols, the particles will not be isolated but in formulation, so the aerosol spray containing PMMA will be of a diameter that will not be respirable. In the absence of inhalation toxicity data, the Panel determined that PMMA and the associated ingredients can be used safely in hair sprays, because the product particle size is not respirable.

Conclusion

Polymethyl methacrylate, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Author's Note

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

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St., Suite 412, Washington, DC 20036, USA.

Acknowledgment

The Cosmetic Ingredient Review Program is financially supported by the Personal Care Products Council. F. Alan Andersen, PhD, and Lillian C. Becker are employed by Cosmetic Ingredient Review.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*. 13th ed. Washington, DC: Personal Care Products Council (formerly the Cosmetic, Toiletry, and Fragrance Association); 2010.
2. Personal Care Products Council. *Description of Polymethyl Methacrylate Used in Cosmetics*. Washington, DC: Council; 2009:1–1.
3. Presperse, Inc. *Technical Data Sheet GanzPearl [pamphlet]*. Somerset, NJ: Presperse, Incorporated; 2010.
4. Particle Sizing Systems, Inc. *Test [pamphlet]*. Santa Barbara, CA: Particle Sizing Systems,Inc; 2001.
5. Presperse LLC. *Certificate of Analysis Ganzpearl GM-0600 [pamphlet]*. Somerset, NJ: Presperse, LLC; 2010.
6. Presperse, Inc. *Specification Sheet [pamphlet]*. Somerset, NJ: Presperse, Incorporated; 2003.
7. Schoon D. *A brief overview of polymer powders used in artificial nail enhancement systems*. 3-31-2010.
8. Piacquadio D, Smith S, Anderson R. A comparison of commercially available polymethylmethacrylate-based soft tissue fillers. *Dermatol Surg*. 2008;34(supp 1):S48–S52.
9. U.S.Food and Drug Administration. General and plastic surgery devices panel of the Medical Devices Advisory Committee. U.S. Food and Drug Administration. 2003. www.fda.gov/ohms/dockets/ac/03/transcripts/3934t1-am%20serssion.doc. 1–196. Accessed February 8, 2010.

10. U.S.Food and Drug Administration. *Artecoll PMMA/Collagen Implant, P020012; Preclinical Review.* Washington, DC. Report No. P020012. 2009:1–4.
11. Presperse, Inc. *Technical Data Sheet GanzPearl [pamphlet].* Somerset, NJ: Presperse Incorporated; 2004.
12. Sugaya H, Sakai Y. Polymethylmethacrylate: from polymer to dialyzer. *Contrib Nephrol.* 1999;125:1–8.
13. Woodcock SE, Johnson WC, Chen Z. Collagen adsorption and structure on polymer surfaces observed by atomic force microscopy. *J Colloid Interface Sci.* 2005;292(1):99–107.
14. Cholod MS, Parker H-Y. Poly(Methyl Methacrylate) (Overview) In Salamone JC, ed. *Polymeric Materials Encyclopedia.* Boca Raton: CRC Press; 1996:6385–6390.
15. Cardre Inc. *PMMA polymethyl methacrylate.* www.cardre.com. Accessed April 15, 2010.
16. Ganz Chemical Co.LTD. GanzPearl: Spherical fine polymer beads. 1–6. Date Accessed 2-9-2010.
17. Ganz Chemical Co.LTD. GanzPearl: Spherical fine polymer beads [pamphlet]. 13–27, Minami Senba 1 Chome, Chuo-Ku, 542-0081 Osaka, Japan: Ganz Chemical Co, Ltd; 2001.
18. Gonçalves OH, Nogueira AL, Schilischting R, Coan T, Sanches AAF, Machado RAF. Methyl methacrylate suspension polymerization: Strategies on particle size distribution. 2nd Mercosur Congress on Chemical Engineering and 4th Mercosur Congress on Process Systems Engineering. 2005. Rio de Janeiro, Brazil.
19. U.S.Food and Drug Administration. Quality system regulation. 2009. pp.CFR 820.1-820.250. Code of Federal Regulations:
20. Cosmetic GANZPEARL. Standard analytical method (cosmetic GANZPEARL): Residual monomer (MMA, EGDM, and i-BMA) [pamphlet]. GANZ Chemical Co, Ltd; 5-27-2005.
21. Nippo Y. *Japnese Stadard for Cosmetic Ingredients (JSCI).* 2nd ed. Tokyo, Japan: Yakuji Nippo, Ltd; 1985.
22. Kaczmarczyk B, Morejko-Buz B, Stolarzewicz A. Investigation of infrared calibration methods for application to the study of methyl methacrylate polymerization. *Fresenius J Anal Chem.* 2001;370(7):899–903.
23. U.S.Food and Drug Administration. *Class II Special Controls Guidance Document: Polymethylmathacrylate (PMMA) Bone Cement; Guidance for Industry and FDA.* 7-17-2002. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072795.htm#bio. Accessed June 19, 2009.
24. Erckens RJ, March WF, Jongsma FH, et al. Noninvasive Raman spectroscopic identification of intraocular lens material in the living human eye. *J Cataract Refract.Surg.* 2001;27(7):1065–1070.
25. Vallittu PK, Miettinen V, Alakuijala P. Residual monomer content and its release into water from denture base materials. *Dent.Mater.* 1995;11(6):338–342.
26. proDERM Institute for Applied Dermatological Research. Polymethyl methacrylate–Summary of clincial study. 2001;1–1.
27. US Food and Drug Administration. Submitted by FDA in response to FOI request. *VCRP total number of products in each product category, May 2010.* 2010:1–2.
28. Personal Care Products Council. *Concentration of Use Polymethyl Methacrylate, Methyl Methacrylate Crosspolymer, Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer and Sodium Polymethacrylate.* Washington DC, 2009:1–3.
29. U.S.Food and Drug Administration. *FDA database. Cosmetic Production Fomulation and Frequency of Use Data.* Washington, DC: FDA; 2009.
30. Personal Care Products Council. *Concentration of Use Polymethyl Methacrylate, Methyl Methacrylate Crosspolymer, Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer and Sodium Polymethacrylate.* Washington, DC; 2010:1–3.
31. Health Canada. Use data for PMMA and related ingredients. 2010.
32. James AC, Stahlhofen W, Rudolf G, et al. Deposition of inhaled particles. *Ann ICRP.* 1994;24(1-3):231–232.
33. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect.* 2005;113(7):823–839.
34. Lehman-McKeeman LD. Absorption, distribution, and excretion of toxicants. In: Klassen CD, ed. *Casarett and Doull's Toxicology: The Basic Science of Poisons.* 7th ed. New York, NY: McGraw-Hill Companies, Inc; 2008:131–159.
35. Bower D. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting in Washington, DC; 1999.
36. Johnson MA. The influence of particle size. *Spray Technol Market.* 2004;24–27.
37. Environmental Working Group. Browse products containing polymethyl methacrylate. http://www.cosmeticsdatabase.com/browse.php?containing=705070&&showmore=products&atatime=500. Accessed February 15, 2010.
38. Personal Care Products Council. *Use of polymethyl methacrylate in artificial nail products.* 3-9-2010:1-1.
39. US Food and Drug Administration. *Summary of Safety and Effectiveness Data: Tecnis Multifocal Intraocular Lens, Models ZM900 and ZMA00.* Washington, DC. Report No. P080010. 2009: 1-37.
40. US Food and Drug Administration. *Summary of Safety and Effectiveness Data: Premarket Approval Application (PMA) Number P980040.* Washington, DC. Report No. P980040. 2000: 1-9.
41. US Food and Drug Administration. 7-17-2002. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072795.htm. Accessed June 19, 2009.
42. US Food and Drug Administration. *Polymethylmethacrylate (PMMA) bone cement.* 7-17-2002. 21CFR888.3027:
43. US Food and Drug Administration. *Artecoll PMMA/Collagen Implant, P020012; Preclincal Review.* Washington, DC, 9. Report No. P020012. 1-4.
44. US Food and Drug Administration. *Summary of Safety and Effectiveness Data: ArteFill.* Washington, DC. Report No. P020012. 2006:8-25.
45. US Food and Drug Administration. *Premarket Notification: Temporary Crown and Bridge Material.* Washington, DC. Report No. K091548. 2007:1-4.
46. Brendolan A, Ronco C, Ghezzi PM, Scabardi M, La Greca G. Hydraulic and flow dynamic characteristics of PMMA dialyzers. *Contrib Nephrol.* 1999;125:41–52.
47. Di Filippo S, Manzoni C, Locatelli F. Efficiency parameters and treatment adequacy of hemodialysis and hemodiafiltration using

polymethylmethacrylate membranes. *Contrib Nephrol.* 1999;125: 86–95.
48. Sarnoff DS, Saini R, Gotkin RH. Comparison of filling agents for lip augmentation. *Aesthet Surg J.* 2008;28(5):556–563.
49. Dayan SH, Bassichis BA. Facial dermal fillers: selection of appropriate products and techniques. *Aesthet Surg J.* 2008; 28(3):335–347.
50. Decoster TA, Bozorgnia S. Antibiotic beads. *J Am Acad Orthop Surg.* 2008;16(11):674–678.
51. Cheng YK, Weng HH, Yang JT, Lee MH, Wang TC, Chang CN. Factors affecting graft infection after cranioplasty. *J Clin Neurosci.* 2008;15(10):1115–1119.
52. Arevalo-Silva CA, Eavey RD, Cao Y, Vacanti M, Weng Y, Vacanti CA. Internal support of tissue-engineered cartilage. *Arch Otolaryngol Head Neck Surg.* 2000;126(12):1448–1452.
53. Tao S, Young C, Redenti S, Zhang Y, Klassen H, Desai T, Young MJ. Survival, migration and differentiation of retinal progenitor cells transplanted on micro-machined poly(methyl methacrylate) scaffolds to the subretinal space. *Lab Chip.* 2007;7(6):695–701.
54. Al-Qattan MM. Late artecoll granulomas aggravated by pregnancy. *Ann Plast Surg.* 2007;58(5):592.
55. Broder KW, Cohen SR. ArteFill: a permanent skin filler. *Expert Rev Med Devices.* 2006;3(3):281–289.
56. Sanna V, Gavini E, Giunchedi P. Bilayer tablets based on poly (epsilon-caprolactone) and polymethylmethacrilates as controlled-release systems for ruminants. *Pharm Dev Technol.* 2004;9(3):321–328.
57. Nussbaum DA, Gailloud P, Murphy K. The chemistry of acrylic bone cements and implications for clinical use in image-guided therapy. *J Vasc Interv Radiol.* 2004;15(2 Pt 1):121–126.
58. Karademir K, Senkul T, Demir S, Erden D, Iseri C, Baykal K. A new testis prosthesis material: polymethylmethacrylate. *Urol Int.* 2004;72(1):71–75.
59. Booth TM, Butson RJ, Clegg PD, Schramme MC, Smith RK. Treatment of sepsis in the small tarsal joints of 11 horses with gentamicin-impregnated polymethylmethacrylate beads. *Vet Rec.* 2001;148(12):376–380.
60. Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implantation of Plexiglas (PMMA) microspheres for the treatment of GERD. *Gastrointest Endosc.* 2001;53(4):423–426.
61. Radhakrishnan VV, Saraswathy A, Rao VR, Rout D, Jayakrishnan A. Histopathological evaluation of polymethyl methacrylate as an embolic agent. *Acta Neurochir (Wien).* 1992;117(1-2):30–33.
62. Batmanabane M, Malathi S, Ekandem GJ. Polymethyl methacrylate dissolved in chloroform as treatment for superficial digital injuries. *Am J Surg.* 1982;144(5):527.
63. International Organization for Standards. *Ophthalmic Implants–Intraocular lenses–Part 5: Biocompatibility.* Switzerland, International Organization for Standards. Date Accessed 9-22-2009. Report No. ISO 11979-5:2006(E). 2006:1-32.
64. International Organization for Standards. *Biological Evaluation of Medical Devices–Part 5: Tests for in Vitro Cytotoxicity.* Switzerland: International Organization for Standards. 2009:1–42.
65. US Food and Drug Administration. *510(k) Summary; Cobalt™ HV Bone Cement.* Washington, DC: U.S. Food and Drug Administration. Report No. K051496. 2005:1-5.
66. International Organization for Standards. *Biological Evaluation of Medical Devices–Part 1: Evaluation and Testing.* Switzerland: International organization for Statndards. 2003. Report No. ISO 10993-1:2003.
67. US Food and Drug Administration. Exactech, Inc. *Tecres Cemex® System Bone Cement; Special 510(k) Summary of Safety and Effectiveness.* Washington, DC: U.S. Food and Drug Administration. Report No. K021715. 2002:1-5.
68. US Food and Drug Administration. *510(k) Summary; SmarSet GHV Gentamicin Bone Cement.* Washington, DC: U.S. Food and Drug Administration. Report No. K033563. 2004:1-5.
69. US Food and Drug Administration. *510(k) Summary; Spine-Fix® Biomimetic Bone Cement.* Washington, DC: U.S. Food and Drug Administration. Report No. K043593. 2006:1-4.
70. US Food and Drug Administration. *510(K) Summary DePuy Orthopaedics, Inc.* Washington, DC: U.S. Food and Drug Administration. Report No. K081155. 2008:1-5.
71. Bigatti MP, Lamberti L, Cannas M, Rossi E. Lack of sister-chromatid exchange induction by polymethyl methacrylate bone cement in human lymphocytes cultured in vitro. *Mutat Res.* 1989; 227(1):21–24.
72. Phillips MK. Comment on Draft Report on PMMA 12-9-09. 2010.
73. US Food and Drug Administration. *Guidance for Industry and FDA Staff: Dental Composite Resin Devices–Premarket Notification [510(k)] Submissions.* Washington, DC: FDA. 2005:1–10.
74. BIO-TOX SARL. *Oral Acute Toxicity Study of a Chemical Batch or Pharmaceutical Formulation in Male Mice: GANZ PEARL GM 0600. Not Clear.* Report No. BT 8225. 1996:1–6.
75. BIO-TOX SARL. *Determination of the Acute Ocular Irritation or Corrosion in Male Rabbits. Not Clear.* Report No. BT 8224. 1996; 1–6.
76. Laboratoire BIO-TOX SARL. *Determination of the Acute Dermal Irritation or Corrosion in Male Rabbits. Not Clear.* Report No. BT 8223. 1996:1–7.
77. Consumer Product Testing Co. *Summary of an HRIPT on a mascara containing 2.0% methyl methacrylate crosspolymer.* 2008.
78. Consumer Product Testing Co. *Summary of an EpiOcular test on a mascara contianing 2.0% methyl methacrylate crosspolymer.* 2008.
79. Andersen FA. Amended final report on the safety assessment of ethyl methacrylate. *Int J Toxicol.* 2002;21(suppl 1):63–79.
80. Rustemeyer T, de Groot J, von Blomberg BME, Frosch PJ, Scheper RJ. Cross-reactivity patterns of contact-sensitizing methacrylates. *Toxicol Appl Pharmacol.* 1998;148(1):83–90.
81. Kanazawa Y, Yoshida T, Kojima K. Structure-activity relationships in allergic contact dermatitis induced by methacrylates. *Contact Dermatitis.* 1999;40(1):19–23.
82. Betts CJ, Dearman RJ, Heylings JR, Kimber I, Basketer DA. Skin sensitization potency of methyl methacrylate in the local lymph node assay: comparisons with guinea-pig data and human experience. *Contact Dermatitis.* 2006;55(3):140–147.