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Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

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Abstract

This is a safety assessment of alumina and aluminum hydroxide as used in cosmetics. Alumina functions as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent. Aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster. The Food and Drug Administration (FDA) evaluated the safe use of alumina in several medical devices and aluminum hydroxide in over-the-counter drugs, which included a review of human and animal safety data. The Cosmetic Ingredient Review (CIR) Expert Panel considered the FDA evaluations as part of the basis for determining the safety of these ingredients as used in cosmetics. Alumina used in cosmetics is essentially the same as that used in medical devices. This safety assessment does not include metallic or elemental aluminum as a cosmetic ingredient. The CIR Expert Panel concluded that alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

Keywords

alumina, aluminum hydroxide, safety, cosmetics

Introduction

This report addresses the safety of alumina and aluminum hydroxide as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook*,[1] alumina is reported to function in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide is reported to function as a buffering agent, corrosion inhibitor, and pH adjuster (Table 1).

These ingredients have been approved by the US Food and Drug Administration (FDA) for use in medical devices and over-the-counter (OTC) drugs (21 CFR 247.10; 21 CFR 331.11; 21 CFR 347.50).[2-4] The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that the cosmetic ingredient alumina is chemically equivalent to the alumina used as part of color additives in medical devices such as bone cements and sutures. Alumina is also a material used in the construction of dental and hip implants. The FDA found that the information submitted for the approval of medical devices containing alumina was adequate and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs.[2] Additionally, alumina is approved by the FDA as an indirect food additive.[5] The Panel concluded that the FDA's evaluations of alumina in medical devices, coupled with the Panel's review of information on aluminum hydroxide, were sufficient to support the safety assessment of alumina.

The Panel also concluded that the aluminum hydroxide used in cosmetics is chemically equivalent to that used in OTC antacid products. The FDA found that the information submitted for the approval of those drugs was adequate to support safe use (21 CFR 247.10; 21 CFR 331.11; 21 CFR 347.50). The FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) as a direct food additive (21 CFR 176.210, 177.1200, 177.2600).[6] The Panel concluded that FDA's evaluations of aluminum hydroxide as a food additive and OTC drug, coupled with the Panel's review of primary scientific toxicity data, were sufficient to support the safety assessment of this ingredient as used in cosmetics.

The CIR has reviewed several cosmetic ingredients that consist of molecules containing aluminum atoms (Table 2). The conclusions were safe as used or safe with qualifications for all of these ingredients.

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Table 1. Definitions and Functions of the Ingredients in This Safety Assessment.[a]

Ingredient CAS No.	Definition	Function
Alumina 1333-84-2 (hydrate *("hydrate" in reference to alumina often means aluminum hydroxide or something between alumina and aluminum hydroxide; alternative CAS No. for 21645-51-2*) 1344-28-1	Alumina is an inorganic compound that conforms to the formula—Al_2O_3. *Aluminum oxide, also known as alumina, is a mineral found as corundum, emery, ruby, sapphire, and in hydrated form (ie, aluminum hydroxide) as bauxite or gibbsite*	Abrasive, absorbent, anticaking agent, bulking agent, opacifying agent
Aluminum hydroxide 1333-84-2 21645-51-2	Aluminum hydroxide is an inorganic compound that conforms to the formula—$Al(OH)_3.xH_2O$. *Alumina hydrates are true hydroxides (meaning they do not contain water of hydration; they are often called hydrated alumina or aluminum hydroxide) and are naturally occurring as minerals including bauxite or gibbsite*	Opacifying agent, skin protectant

Abbreviation: CIR, cosmetic ingredient review.
[a]The italicized text represents additions made by CIR staff.

The cosmetic ingredients alumina (aluminum oxide) and aluminum hydroxide are stable, oxidized aluminum compounds that differ substantially from aluminum (elemental or metallic) in chemical and physical properties, functions, and potential for toxicity. There has been substantial speculation in the literature that exposure to elemental aluminum or aluminum compounds could play a role in the etiology of Alzheimer's disease, breast cancer, and other health problems. Overall, scientific research has failed to find cause and effect relationships.[7-56] Furthermore, systemic exposure to aluminum from the use of alumina and aluminum hydroxide in cosmetics is expected to be negligible because it is poorly absorbed.[7,40,57-69] The Panel considered the toxicological literature on aluminum and was satisfied that much of the speculation about aluminum toxicity is not relevant to the assessment of the safety of alumina and alumina hydroxide as used in cosmetics. A brief overview of aluminum toxicity studies is attached (Appendix A) to provide supplementary information reflecting the Panel's consideration of these issues.

Chemistry

Overview

Definitions, CAS numbers, and functions are provided in Table 1. The structures of alumina and aluminum hydroxide are presented in Figure 1.

Alumina, also known as aluminum oxide (Al_2O_3), is dehydrated (or calcined) aluminum hydroxide.[70] Alumina is also the primary constituent of emerald, ruby, and sapphire (the colors of which come from small impurities of heavy metals). The most common naturally occurring form of alumina is corundum. Corundum is primarily composed of α-alumina, which is crystalline. This water-insoluble, inorganic solid can form a number of other crystalline phases, and an amorphous form as well. Each phase has a unique crystal structure and varies in chemical properties, such as its acid–base reaction rate. When synthetically dehydrated from aluminum hydroxide, a mixture of alumina phases typically forms, unless specific controls are applied. Figure 1 schematically depicts both amorphous and crystalline alumina.

Aluminum hydroxide, also known as hydrated alumina, is most commonly found as the polymorphic mineral gibbsite (a component of the aluminum ore known as bauxite).[70,71] This inorganic, amphoteric solid can also form 3 other polymorphs. However, the chemical formula of $Al(OH)_3$ is the same for all polymorphs, each of which differs from the others only by interlayer spacing and, consequently, by relative acid/base reaction rates.

There are 4 known polymorphs of crystalline aluminum hydroxide: gibbsite, bayerite, nordstrandite, and doyleite, which can have different chemical/physical properties.[72] The properties of the starting materials (pH, presence of anions or salt and mineral surfaces) influence the formation of particular polymorphs from aluminum interlayers and/or hydroxyl aluminum polymers. All the polymorphs of aluminum hydroxide consist of layers of aluminum octahedra with hydroxyl groups on either side, which hydrogen bond the layers together, and differences arising from variations in the stacking sequences of the layers. Of the possible configurations, gibbsite and bayerite represent the 2 ends of the spectrum of types of stacking sequences. Nordstrandite and doyleite have intermediate structures.

There is no universal standard nomenclature for aluminum oxides and hydroxides; thus, there may be inconsistencies in the use of these names among sources.[72] Categorization is based on crystallographic structures found under environmental conditions and cited most often in the literature (Table 3). The α prefix is generally applied to hexagonal, close-packed, and related structures; these are aluminum minerals abundantly found in nature. The γ prefix is generally applied to designate polymorphism, structural alteration, or dehydration of these minerals (originally applied to all aluminum hydroxides and hydrolyzed aluminas other than the α-phase minerals). The γ-phase has cubic close-packed lattices or other related structures.

Table 2. Cosmetic Ingredients Containing Aluminum That Have Been Reviewed by CIR.

Ingredients	Conclusion	Maximum concentration (%)	Reference
Alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicate, sodium potassium aluminum silicate	Safe as used when formulated to be nonrespirable	44	108
Aluminum citrate	Safe as used	80	109
Aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum myristates/palmitates	Safe as used	82	110,111
Aluminum silicate, magnesium aluminum silicate	Safe as used	100	112
Aluminum starch octenylsuccinate	Safe as used with limitations on heavy metal content	30	113
Aluminum distearate, aluminum stearate, aluminum tristearate	Safe as used	25	114,115
Calcium aluminum borosilicate	Safe as used	97	116
Potassium aluminum polyacrylate	Safe as used when formulated to be nonirritating	25	117

Abbreviation: CIR, cosmetic ingredient review.

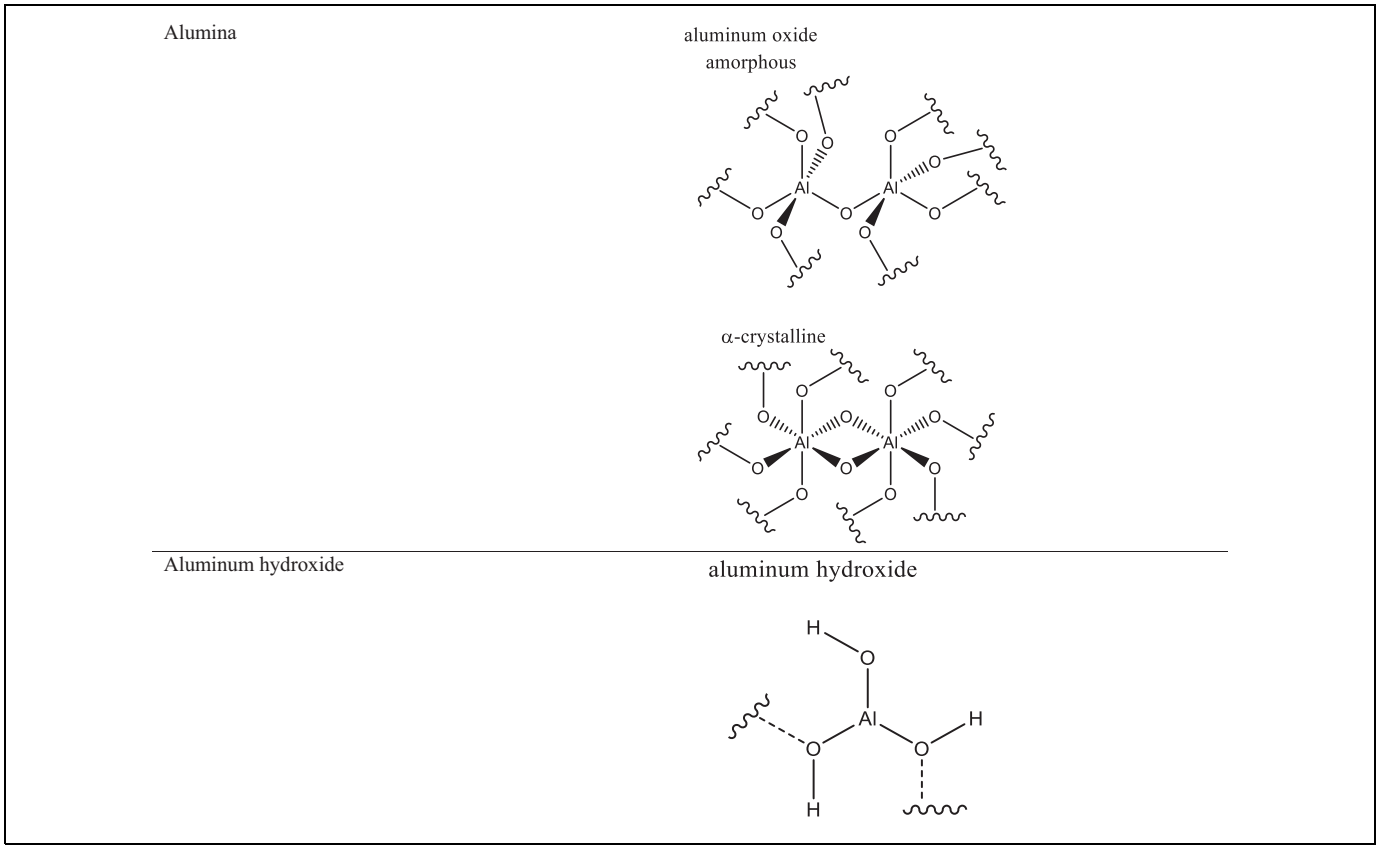

Figure 1. Formulas and idealized structures of the ingredients in this safety assessment.

Physical and Chemical Properties

Alumina and aluminum hydroxide are white, insoluble solids (Table 4). Alumina is the third hardest naturally occurring substance after diamond and carborundum (SiC).[55] The presence of trace amounts of chromium and cobalt creates ruby and sapphire, respectively.

Aluminum compounds cannot easily be oxidized, and thus, atmospheric oxidations generally are not expected to occur.[73] All forms of aluminum hydroxide are amphoteric (eg, they can act as both acids and bases in solution).[74] Accordingly, aluminum hydroxides can serve as buffers to resist pH changes within the narrow pH range of 4 to 5.[75] Aqueous aluminum hydroxide gel has an effective pH of ~6.[76]

Method of Manufacture

Aluminum hydroxide is most commonly produced by aqueous alkaline extraction from bauxite ore, a method known as the

Table 3. Comparison of Nomenclature for Alumina and Aluminum Hydroxide.[72]

Mineral name	Chemical composition	Common crystallographic designation	Past accepted crystallographic designation
Gibbsite (hydrargillite[a])[b]	Aluminum trihydroxide	α-$Al(OH)_3$	γ-$Al(OH)_3$
Bayerite	Aluminum trihydroxide	β-$Al(OH)_3$	α-$Al(OH)_3$
Nordstrandite	Aluminum trihydroxide	$Al(OH)_3$	$Al(OH)_3$
Doyleite	Aluminum trihydroxide	$Al(OH)_3$	-
Boehmite	Aluminum oxyhydroxide	γ-AlOOH	γ-AlOOH
Diaspore	Aluminum oxyhydroxide	α-AlOOH	α-AlOOH
Corundum (α-alumina)	Aluminum oxide	α-Al_2O_3	α-Al_2O_3

[a]Hydrargillite is a mineral that was named after the Greek hydor (water) and argylles (clay). The name hydrargillite was mistakenly given to describe aluminum hydroxide but later was proven to be aluminum phosphate. However, both names are still used to describe aluminum hydroxide—gibbsite is preferred in the United States and hydrargillite is used more often in Europe.
[b]The terms in parentheses refer to possible forms.

Table 4. Chemical and Physical Properties of Alumina and Aluminum Hydroxide.

Property	Value	Reference
Alumina		
Physical form	Solid, crystalline powder	84,118
Color	White	84
Odor	None	118
Gram formula weight, g/mol	101.96	84
Density/specific gravity at 20°C	4.0	84
Viscosity (kg/[s·m]) at 20°C	Solid	118
Vapor pressure (mm Hg) at 20°C	Negligible	118
Melting point, °C	~2,000	84
Boiling point, °C	2,980	84
Water solubility	Insoluble	84
Aluminum hydroxide		
Physical form	Amorphous powder	84
Color	White	84
Gram formula weight, g/mol	78.00	84
Density/specific gravity	2.42	84
Melting point, °C	300	84
Water solubility	Practically insoluble	84

Bayer process.[70] Alumina is then produced from the resultant aluminum hydroxide simply by vigorous heating to drive off water.[77]

Impurities

Alumina balls used in artificial hips must meet the following specifications: grain size <5 μm and purity >99.7% aluminum oxide.[78] The maximum percentages for trace substances permitted are MgO, 0.2%; SiO_2, 0.01%; CaO, 0.03%; Na_2O, 0.02%; Fe_2O_3, 0.03%; and TiO_2, 0.01%.

When used in OTC drugs as a color additive, alumina should contain no more than 0.5% insoluble matter in dilute hydrochloric acid. The following are the limits of impurities: lead (as Pb) $\leq$10 ppm, arsenic (as As) $\leq$1 ppm, mercury (as Hg) $\leq$1 ppm, and aluminum oxide (Al_2O_3) $\geq$50% (21 CFR 73.1010).

Table 5. Frequency of Use According to Duration and Exposure of Alumina and Aluminum Hydroxide.[a,b,79-81]

Use type	Uses	Maximum concentration (%)	Uses	Maximum concentration (%)
	Alumina		Aluminum hydroxide	
Total/range	563	0.0004-60	578	0.0000008-10.1
Duration of use				
Leave on	523	0.0004-60	572	0.0000008-10.1
Rinse off	40	0.003-25	6	0.0022-8.8
Diluted for (bath) use	NR	NR	NR	NR
Exposure type				
Eye area	84	0.00075-30	80	0.009-10.1
Incidental ingestion	88	0.0004-6.7	155	0.0022-8.8
Incidental inhalation—sprays	7	6	6	NR[c]
Incidental inhalation—powders	41	0.0023-5	40	0.029-1.5
Dermal contact	441	0.0023-30	409	0.0000008-10.1
Deodorant (underarm)	NR	0.004-0.01	NR	NR
Hair—noncoloring	1	NR	NR	0.004-0.016
Hair—coloring	NR	1	NR	0.1
Nail	30	0.0048-60	7	0.016-1
Mucous membrane	107	0.0004-6.7	157	0.0022-8.8
Baby	NR	0.0023	NR	NR

Abbreviation: NR, not reported.
[a]Totals = rinse-off + leave-on product uses.
[b]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
[c]The Council reports that the skin care preparations and suntan preparations in their survey are not sprays.

Use

Cosmetic

Data on ingredient usage are provided to the FDA Voluntary Cosmetic Registration Program (Table 5).[79] A survey of the maximum use concentrations has been conducted by the Personal Care Products Council.[80,81]

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products. Formulations include 84 products used around the eye at concentrations up to 30%, 87 lipsticks up to 6.7%, and 104 skin care preparations up to 25%.

Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% and 6 rinse-off products up to 8.8%. Formulations include 80 products used around the eye at up to

10.1%, 154 lipsticks up to 7%, oral hygiene products up to 8.8%, and 6 suntan preparations up to 0.9%.

Noncosmetic

Aluminum salts are incorporated into some vaccine formulations as an adjuvant to enhance the immune response to vaccination.[82] The aluminum compounds used in some US licensed vaccines are aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts. Aluminum hydroxide may be used in vaccines up to 25 μg/L in large-volume parenteral drug products (21 CFR 201.323) and up to 1.25 μg in single-dose products (21 CFR 610.15), depending on the calculation method (Table 6).

The FDA evaluated the safety of aluminum hydroxide in OTC drugs (Table 6). The FDA stated that the oral maximum daily dose of an antacid containing aluminum hydroxide dried gel is 8 g (21 CFR 331.11). A chewable tablet of aluminum hydroxide:magnesium trisilicate (80:20 mg) was approved by the FDA.[3] Two other chewable tablets were approved with aluminum hydroxide:magnesium trisilicate doses of 80:20 mg and 160:40 mg.[4] Liquid suspensions of aluminum hydroxide are also used as antacids.[83]

Aluminum hydroxide gel is approved for use in OTC skin protectant drug products as an active ingredient at 0.15% to 5%, with caution to consult a doctor for children younger than 6 months of age (Table 6; 21 CFR 247.10; 21 CFR 347.50).

The safety and effectiveness of aluminum hydroxide for use in OTC drugs has not been established for the treatment of diarrhea or the topical treatment of acne. Aluminum hydroxide has been approved for use in digestive aid drug products and preparations for treating diaper rash (21 CFR 346.14).

Alumina is used as an adsorbent, desiccant, and abrasive.[84] It is used as filler for paints and varnishes. It is also used in the manufacture of alloys, ceramic materials, electrical insulators and resistors, dental cements, glass, steel, and artificial gems. It is used in coatings for metals and other surfaces and as a catalyst or catalyst substrate for organic chemical reactions.

Alumina is approved as an indirect food additive by the FDA.[5] Aluminum hydroxide is considered GRAS as a direct food ingredient by the FDA (21 CFR 176.210, 177.1200, 177.2600).[6]

There are many regulations and recommendations for aluminum compounds. Those that are informative for the purpose of this safety assessment are listed in Table 7.

Alumina in Medical Devices

Alumina has been approved by the FDA for use in medical devices. The alumina used in these devices must comply with ASTMF603-12, ''Standard Specification for High-Purity Dense Aluminum Oxide for Medical Application.''[2]

The FDA considered the safety of alumina when approving the following medical devices that contain this material:

- Color additives for polymethyl methacrylate (PMMA) bone cement and sutures.
- Endosseous dental implant abutments.
- Femoral bearing head of artificial hips.

Color Additives

Colors that contain alumina (eg, FD&C Blue #1 aluminum lake) are approved by the FDA to be used in color cosmetics, food, dietary supplements, drugs for internal and external use, and medical devices (ie, bone cement, surgical sutures).[85] The colors are created by applying the coloring material to an alumina substrate. Alumina has been approved as a color additive for OTC drugs (21 CFR 73.1010).

Ceramic Hip

The use of ceramic femoral heads (ie, CeramTec Alumina Heads, Alumina V40 Head) made of alumina/ceramic composites has been approved for use in hip joint replacements in humans. The materials conform to FDA's ''Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Hip Systems.''[78,86,87] One of these hip replacement products was reported to consist of ~75% alumina, ~25% zirconia, and <1% chromium oxide.[88]

Other Devices

Alumina has been approved for use in endosseous dental implant abutments (Table 6; 21 CFR 872.3630). Alumina/ceramic composite is used to make internal stents for treating tracheomalacia.[89] These stents are implanted inside the trachea.

Toxicokinetics

Overview

Aluminum hydroxide, as measured by aluminum content, is poorly absorbed through either oral or inhalation routes and is essentially not absorbed dermally in healthy humans.[90] Orally, the bioavailable forms of aluminum hydroxide are absorbed at only approximately 0.1%. Ingested aluminum hydroxide is excreted as aluminum in the feces. Studies on uptake and elimination rates of aluminum hydroxide indicate that a near steady state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over a lifespan. High-level, long-term use of antacids containing aluminum hydroxide will cause levels of aluminum to increase in the blood and other tissues. The levels return to normal upon cessation of high-level exposure. Under certain atypical conditions (eg, poor renal function with increased aluminum load), levels of aluminum in the body may rise high enough to cause toxicity in humans.

Blood and tissue (liver, spleen, kidney, brain, bone) levels of aluminum from the ingestion of aluminum hydroxide

Table 6. US Government Regulations for Medical Devices, Drugs, and Other Regulated Uses of Alumina and Aluminum Hydroxide.

Device/drug	Rule	Reference
Endosseous dental implant abutment	An endosseous dental implant abutment (made of alumina) is a premanufactured prosthetic component directly connected to the endosseous dental implant and is intended for use as an aid in prosthetic rehabilitation.	21 CFR 872.3630
	Class II (special controls). The guidance document entitled "Class II Special Controls Guidance Document: Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments" will serve as the special control.	
Hip joint metal/ceramic/ polymer semi-constrained cemented or nonporous uncemented prosthesis	(a) A hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis is a device intended to be implanted to replace a hip joint. This device limits translation and rotation in 1 or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. The 2-part femoral component consists of a femoral stem made of alloys to be fixed in the intramedullary canal of the femur by impaction with or without the use of bone cement. The proximal end of the femoral stem is tapered with a surface that ensures positive locking with the spherical ceramic (aluminum oxide, $A1_20_3$) head of the femoral component. The acetabular component is made of ultra-high-molecular-weight polyethylene or ultra-high-molecular-weight polyethylene reinforced with nonporous metal alloys and used with or without bone cement.	21 CFR 888.3353
	(b) Classification*:* class II.	
	(a) A hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis is a 2-part device intended to be implanted to replace the articulating surfaces of the hip while preserving the femoral head and neck. The device limits translation 888.3410 and rotation in 1 or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. This generic type of device includes prostheses that consist of a femoral cap component made of a metal alloy, such as cobalt–chromium–molybdenum, or a ceramic material, that is placed over a surgically prepared femoral head and an acetabular resurfacing polymer component. Both components are intended for use with bone cement (888.3027).	21 CFR 888.3410
	(b) Classification: class III.	
	(c) *Date PMA or notice of completion of a PDP is required*. A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before January 3, 2005, for any hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before January 3, 2005, been found to be substantially equivalent to a hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976. Any other hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis must have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.	
OTC drugs	Section 350.50. Labeling of antiperspirant drug products.	21 CFR350.50
	(c) *Warnings*: The labeling of the product contains the following statements under the heading "Warnings":	
	(1) "Do not use on broken skin."	
	(2) "Stop use if rash or irritation occurs."	
	(3) "Ask a doctor before use if you have kidney disease."	
	(4) *For products in an aerosolized dosage form.* (i) "When using this product, keep away from face and mouth to avoid breathing it."	
	(a) Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of aluminum hydroxide ingredients for the specified uses:	21CFR310.545
	(1) *Topical acne drug products.*	
	(3) *Antidiarrheal drug products*—(i) *Approved as of May 7, 1991.*	
	(8) *Digestive aid drug products*—(i) *Approved as of May 7, 1991.*	
	(iii) *Diaper rash drug products.*	
	(a) Aluminum-containing active ingredients:	21CFR331.11
	(1) Basic aluminum carbonate gel.	
	(2) Aluminum hydroxide (or as aluminum hydroxide–hexitol stabilized polymer, aluminum hydroxide–magnesium carbonate co-dried gel, aluminum hydroxide–magnesium trisilicate co-dried gel, aluminum hydroxide sucrose powder hydrated).	
	(3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.	
	(4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25% of the total acid neutralizing capacity; maximum daily dosage limit is 8 g.	

(continued)

Table 6. (continued)

Device/drug	Rule	Reference
	Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. (a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients (aluminum hydroxide) for the specified uses: topical acne drug products and antidiarrheal drugs.	21 CFR 310.545
	The labeling of the product contains the following information for anorectal ingredients identified in 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20 and for combinations of anorectal ingredients identified in 346.22 (up to 50%). Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use. (H) Temporarily relieves the symptoms of perianal skin irritation. (iv) *For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "For the temporary relief of itching associated with moist anorectal conditions." *For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."	21 CFR 346.14
	Listing of specific active ingredients (a) Aluminum-containing active ingredients: (2) Aluminum hydroxide (or as aluminum hydroxide–hexitol stabilized polymer, aluminum hydroxide–magnesium carbonate co-dried gel, aluminum hydroxide–magnesium trisilicate co-dried gel, aluminum hydroxide–sucrose powder hydrated).	21 CFR 331.11
	Permitted combinations of active ingredients. (a) *Combinations of skin protectant active ingredients.* (1) Any 2 or more of the ingredients identified in 347.10(a), (d), (e), (i), (k), (l), (m), and (r) may be combined, provided the combination is labeled according to 347.50(b)(1) and provided each ingredient in the combination is within the concentration specified in 347.10. (2) Any 2 or more of the ingredients identified in 347.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) may be combined, provided the combination is labeled according to 347.50(b)(2) and provided each ingredient in the combination is within the concentration specified in 347.10. (b) *Combination of ingredients to prepare an aluminum acetate solution*. Aluminum sulfate tetradecahydrate may be combined with calcium acetate monohydrate in powder or tablet form to provide a 0.13% to 0.5% aluminum acetate solution when the powder or tablet is dissolved in the volume of water specified in "Directions."	21 CRF 347.10
Food packaging	Aluminum hydroxide is among the list of defoaming agents that may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food.	21 CFR 176.210
	Aluminum hydroxide is among the list of substances that may be a component of cellophane as a food packaging substance.	21 CFR 177.1200
	Aluminum hydroxide is included in the list of fillers of rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2600
Indirect food additive	Aluminum hydroxide is among the list of substances that may be safely used as colorants used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions and definitions set forth in this section. (a) The term *colorant* means a dye, pigment, or other substance that is used to impart color to or to alter the color of a food-contact material but that does not migrate to food in amounts that will contribute to that food any color apparent to the naked eye. (b) The colorant must be used in accordance with current good manufacturing practice, including use levels that are not in excess of those reasonably required to accomplish the intended coloring effect. (c) Colorants in this section must conform to the description and specifications indicated. (d) Color additives and their lakes listed for direct use in foods, under the provisions of the color additive regulations in parts 73, 74, 81, and 82 of this chapter, may also be used as colorants for food contact polymers.	21 CFR 178.3297

Abbreviations: PBP, pharmacy bulk packages; PDP, product development protocol.

Table 7. Organizational Findings and Government Regulations With Regard to Aluminum and Related Compounds.[90]

Agency	Findings/regulation	Reference
International		
IARC	Group 1: Aluminum production carcinogenic to humans	119
WHO	Drinking water quality guidelines for aluminum	120
	≤0.1 mg/L in large water treatment facilities	
	≤0.2 mg/L in small water treatment facilities	
United States		
Air		
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al)	121
	Metal dust—10 mg/m^3	
	Pyro powders—5 mg/m^3	
	Soluble salts—2 mg/m^3	
	Alkyls (NOS)—2 mg/m^3	
	TLV (8-hour TWA) for aluminum oxide[a]—10 mg/m^3	
NIOSH	REL (10-hour TWA)	122
	Aluminum	
	10 mg/m^3 (total dust)	
	5 mg/m^3 (respirable fraction)	
	Aluminum oxide	
	15 mg/m^3 (total dust)	
	5 mg/m^3 (respirable fraction)	
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide	29 CFR 1910.10000
	15 mg/m^3 (total dust)	
	5 mg/m^3 (respirable fraction)	
Water		
EPA	Designated as hazardous substances in accordance with section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate	40 CFR 116.4
	Drinking water standards and health advisories—0.05 to 0.2 mg/L	123
	National primary drinking water standards—no data	124
	National secondary drinking water standards for aluminum—0.05 to 0.2 mg/	40 CFR 143.3
	Reportable quantities of hazardous substances designated pursuant to section 311 of the Clean Water Act for aluminum sulfate—5,000 pounds	40 CFR 117.3
	Water quality criteria for human health for aluminum	125
	Freshwater CMC—750 μg/L	
	Freshwater CCC—87 μg/L	
Food		
FDA	Bottled drinking water for aluminum—0.2 mg/L	21 CFR 165.110
Other		
EPA	Pesticide exemptions from the requirement of a tolerance	40 CFR 180.910
	Aluminum hydroxide (for use as a diluent and carrier)[b]	
	Aluminum oxide (for use as a diluent)	

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; Al, aluminum; CCC, criterion continuous concentration; CMC, criteria maximum concentration; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; NOS, not otherwise specified; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit values; TWA, time-weighted average; WHO, World Health Organization.
[a]TWA: The value is for particulate matter containing no asbestos and <1% crystalline silica.
[b]Pesticide exemptions from the requirement of a tolerance: residues of the following materials are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

(100, 281, 1,500, 2,000 mg/kg/d) were increased by concurrent oral administration of citric, lactic, malic, oxalic, or tartaric acids in rats.[91-93]

Dermal. Aluminum salts used in antiperspirants form hydroxide precipitates of denatured keratin in the cornified layer that surrounds and occludes the opening of sweat ducts.[94] This mechanism suggests that there is little or no dermal absorption of aluminum hydroxide or any other form of aluminum.

Oral—Nonhuman

Aluminum hydroxide. Bioavailability of orally administered [^{26}Al]aluminum hydroxide (in 2 mL water; pH 7) to male Wistar rats (n = 9) was 0.1%.[95] After administration, the rats were placed in metabolic cages and blood sampled at 20, 45, 60, 90, 150, and 300 minutes. The rats were then killed and necropsied.

The aluminum content returned to normal levels in the tissues of Sprague Dawley rats within 21 days after oral administration of aluminum hydroxide.[96] In the first study, the rats were fed a

control diet containing 26 μg Al/g (n = 5) or 989 μg Al/g (n = 15) for 16 days. All rats were then fed the control diet. Five rats were killed and necropsied at the end of the test period and 7 and 21 days thereafter. The treatment group had increased aluminum in the tibiae–fibulae, ulnae–radii, leg muscles, and kidneys. At day 21, all aluminum content measurements were similar to controls.

This experiment was repeated with 9 additional rats (control) and 1,070 μg Al/g in the diet, and the rats were killed and necropsied at 0, 3, and 7 days after treatment. The increase in aluminum content in the test group returned to control levels by day 7. Ingestion of aluminum hydroxide had no effect on the levels of phosphorus, calcium, magnesium, zinc, and iron in the tissues examined.

Only 0.45% ± 0.47% of orally administered aluminum hydroxide (10,000 μmol/kg as concentrated aluminum hydroxide gel with 4 mL water by stomach tube) to renally intact rabbits (n = 10) was absorbed.[97] Renally impaired rabbits absorbed 0.36% ± 0.30%.

Oral—Human

Aluminum hydroxide. Orally administered aluminum hydroxide is poorly absorbed (<0.01%) in humans.[57,63] Using 26Al, the estimated aluminum absorption rates were 0.523%, 0.0104%, and 0.136% in 2 participants receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in an aqueous citrate solution, respectively.[98] The test materials were delivered to the stomach through a pediatric feeding tube. Blood was collected at 1, 4, and 14 hours. Feces and urine were collected for 6 days. The uptake of aluminum was greatest for the citrate form and least for aluminum hydroxide. The addition of citrate to aluminum hydroxide increased the 26Al uptake in both participants.

There was no appreciable increase in the amount of aluminum absorbed in participants (n = 8, 10, 7) administered with aluminum hydroxide (equal to 244, 976, or 1,952 mg Al in the form of antacid tablets; pH 9.2).[99] By measuring the amount of aluminum in the urine, the amount of aluminum absorbed was estimated to be 0.001%, 0.004%, and 0.007%, respectively. When the high dose was combined with orange juice (70 mL; pH 4.2) or citric acid (70 g in 1,000 mL distilled water; pH 2.4), absorption increased to 0.03% and 0.2%, respectively.

Intravenous

Aluminum hydroxide. The half-life of intravenously (IV) administered aluminum hydroxide (100 μmol/kg as concentrated aluminum hydroxide gel) in renally intact rabbits (n = 10) was 27 ± 13 hours.[97] In renally impaired rabbits, the half-life was 14 ± 5 hours. Blood was sampled at 24 hours and immediately prior to treatment and at approximately 5, 10, 20, 30, 45, and 60 minutes and 2, 4, 8, 12, 24, and 48 hours after treatment.

Toxicity

Repeated Dose

Oral—Animal

Aluminum hydroxide. When aluminum hydroxide (average 2,400 mg/kg/d in drinking water) was administered to Long Evans male hooded rat weanlings (n = 7 or 8) for 60 days, there was no reduction in cognitive abilities.[100] At necropsy, the highest concentration of aluminum in the brain was in the hippocampus. The test group had decreased weight gain compared to controls, possibly reflecting reduced water intake at the beginning of the test period. The rats were assessed with an open-field activity test biweekly. At the end of the test period, the rats were tested for muricidal behavior by placing an albino mouse with each of the rats. Only 1 treated rat exhibited the behavior.

When aluminum hydroxide (300 mg/kg in carboxymethyl cellulose) and aluminum hydroxide (100 mg/kg) plus citric acid (30 mg/kg) were orally administered to Long Evans rats (n = 10/sex), their learning ability was reduced as measured using a 4-T shaped labyrinth.[101] Control rats learned the way to the goal in an average of 5.1 ± 2.88 times versus 16.0 ± 2.98 and 13.2 ± 5.39 times for the 2 treatment groups, respectively. The aluminum content of the brains of the control rats at necropsy was 6.6 ± 3.01 ppm compared to 18.0 ± 10.20 ppm and 11.0 ± 4.80 ppm in the 2 treatment groups, respectively. There was also increased acetylcholinesterase activity in the aluminum hydroxide plus citric acid group. There was no increase in choline acetyltransferase activity in the brains of either group. No other clinical signs or abnormalities were reported.

Intraperitoneal—Animal

Aluminum hydroxide. Male Wistar rats (n = 12) exhibited decreased weight gain and initial feed efficiency when administered intraperitoneal (IP) aluminum hydroxide (80 mg/kg) 3 times/week for 6 months.[102] However, there were no differences in total feed intake. Aluminum hydroxide did not affect the peak growth rate or the time to reach maturity. The systemic calcium balance in the treated rats was altered, and there was an increase in the amount of calcium excreted in the feces. The rate of skeletal Ca^{++} accretion was decreased without changes in the bone calcium resorption.

Oral—Human

Aluminum hydroxide. There were no adverse effects observed when participants (n = 9 females, 4 males) were administered aluminum hydroxide (equal to 59 mg Al) 3 times daily for 6 weeks.[103] When compared to the control group (n = 3 females, 2 males), urinary Al was ~10- to 20-fold greater during treatment. The authors stated that this indicated that ingestion of an Al-containing antacid is associated with Al absorption above that originating from food and drinking water. There were no differences in the lymphocyte subpopulations, lymphocyte proliferation, and in vitro immunoglobulin and interleukin production. There were no differences between groups in the immune parameters examined, except for a slightly smaller $CD8^{+}CD45R0^{+}$ population (primed cytotoxic T cells) in the test group compared to the referents.

Reproductive and Developmental Toxicity

Aluminum Hydroxide

When aluminum hydroxide (0, 66.5, 133, or 266 mg/kg in distilled water) was administered by gavage on gestation days

6 to 15 to Swiss mice (n = 20), there were no effects attributed to the test substance.[104] There were no differences in maternal weights, feed consumption, appearance, or behavior. There were no differences in the number of total implants, resorptions, number of live or dead fetuses, fetal size parameters, or sex distribution observed at necropsy. There were no differences observed at gross external, soft tissue, and skeletal examinations.

When aluminum hydroxide (384 mg/kg/d; n = 18), aluminum citrate (1,064 mg/kg/d; n = 15), or aluminum hydroxide (384 mg/kg/d; n = 19) plus citric acid (62 mg/kg/d) was orally administered to Sprague Dawley rats (during gestation day 6 to 15), there were no differences among the groups in pre- or postimplantation loss, number of live fetuses per litter, or sex ratio.[105] Fetal body weight was reduced and skeletal variations (delayed ossification of occipital bone and sternebrae; absence of xiphoids) were increased in the aluminum hydroxide plus citric acid group. The absence of xiphoids was also observed in the aluminum citrate group. The dams exhibited decreased weight gain in the aluminum hydroxide plus citric acid group during treatment but recovered and caught up to the other groups posttreatment. There was increased aluminum in the livers, bones, and placentas of the dams in the aluminum citrate group; there were no differences in aluminum content in the kidneys and brains. Aluminum accumulation was not detected in whole fetuses of the treated mice compared with those in the control group (n = 17), which were administered water.

Irritation

Aluminum Hydroxide

Aluminum hydroxide (10% wt/vol in 0.2% Tween-80) was not irritating when applied to the shaved backs of female TF1 strain albino mice (n = 5; 0.5 mL), New Zealand white rabbits (n = 3; 0.5 mL), and large white strain pigs (n = 2; 1.0 mL) for 5 consecutive days.[106] The test substance was applied uncovered. The animals were restrained until the substance was dry.

Clinical Use

Clinical Trials

There are multiple clinical trials of artificial hips (with alumina-on-alumina ball and socket contact or alumina ceramic hips), alumina/ceramic composite stents, and dental implants. There were no adverse reactions reported. None of the failures reported were attributable to adverse health effects of the alumina but were related to mechanical or implantation technical issues (Table 8).

In a review of 4 case studies of alumina ceramic hip implant failures, it was determined that all problems were due to design issues, implementation issues, or surgical issues.[107] None of the failures were attributed to adverse reactions to the alumina.

Summary

Alumina functions in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster.

The alumina and aluminum hydroxide produced for cosmetics are chemically equivalent to the materials used in color surgical sutures and to the alumina in other medical devices, as well as to the alumina in OTC drugs. The safety information submitted for those medical devices and drugs was reviewed by the FDA, including the results of acute and long-term biocompatibility testing for cytotoxicity, irritation and intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility studies. The FDA found the data to be adequate and determined that alumina was safe and effective for use in hip and dental implants, as well as for coloring PMMA bone cement and surgical sutures. Alumina is approved as an indirect food additive. Aluminum hydroxide is GRAS as a direct food additive and safe for use in OTC drugs.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products at concentrations up to 25%. Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% (in eye products) and in 6 rinse-off products up to 8.8% (in oral hygiene products).

Alumina is used in color additives for sutures and is a material used in the construction of endosseous dental implant abutments and femoral bearing heads of artificial hips. In clinical trials of artificial hips, dental implants, and esophageal stents, all adverse effects were from mechanical or installation problems, not attributable to exposure to alumina.

Orally administered aluminum in aluminum hydroxide has low bioavailability and is excreted primarily in the feces; the systemically absorbed aluminum in aluminum hydroxide is excreted primarily in the urine.

Aluminum hydroxide orally administered to rats at 2,400 mg/kg had no effect on cognitive abilities, but 100 mg/kg administered with citric acid reduced the rat's learning ability. Rats exhibited decreased weight gain and decreased initial feed efficiency when administered with aluminum hydroxide IP at 80 mg/kg 3 times/week for 6 months.

There were no effects on immunological parameters in humans when orally administered with aluminum hydroxide (equal to 59 mg Al) 3 times daily for 6 weeks. There were no reproductive effects in mice when orally administered with 266 mg/kg aluminum hydroxide during gestation days 6 to 15. There were also no reproductive effects in rats at 384 mg/kg aluminum hydroxide orally administered during gestation days 6 to 15. However, when administered to rats with citric acid, there was reduced weight gain in the dams and increased skeletal abnormalities in the pups. Aluminum hydroxide at 10% was not dermally irritating to mice, rabbits, or pigs (n = 2; 1.0 mL).

Table 8. Clinical Trials of Medical Devices Containing Alumina.

Study	Results	Reference
Artificial hips		
Alumina-on-alumina (n = 88 participants; 107 hips) and alumina ceramic bearing (n = 65; 71 hips) followed for an average of 6.84 ± 1.49 years and 7.73 ± 1.60 years.	No adverse effects from exposure to alumina.	126
Two alumina hips compared with and without alumina grit-blasted finish (n = 14, 18) followed for 12 months and compared for complications.	Alumina particles on the surface of prostheses had a histologically observable impact on surrounding tissues and leads to surface wear in vivo. This was considered mechanical and not a reaction to alumina.	127
Alumina-on-alumina (n = 849; 930 hips) followed for an average of 5.9 years for adverse events, 10 years for survivorship.	All adverse event/complications were of mechanical origin, not from exposure to alumina. Survival[a] of the hips at 10 years was 96.8%.	128
Fine-grained alumina ceramic hips, with and without zirconium oxide added (n = 29 women, 35 men and 21 women, 24 men) followed for an average of 73 (26-108) and 72 (31-98) months.	Survivorship was 95% and 93% at 6 years, respectively. There were no cases of osteolysis in the first group and 1 case in the second. No adverse effects attributed to alumina were reported.	88
Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.	Eight-year survival was 90.7% with no revisions, 94.4% with revisions. All issues were attributed to mechanical issues and not from exposure to alumina.	129
Alumina ceramic hips (n = 301) were followed for at least 10 years.	Survival was 98% (confidence interval 94.2%-99.6%) at 10 years. All adverse effects were due to mechanical issues.	130
Two alumina ceramic hips (n = 27, 23) comparing an alumina and a polyethylene liner followed for 2 years.	No adverse effects from either form of hip.	131
Dental implants		
Alumina ceramic attachment (> 95% alumina) to hold dentures (n = 20) were followed for 1 year.	No adverse effects from exposure to alumina.	132
Single crystal alumina endosteal dental implants (n = 29) followed for 5 years.	5 implants removed from study due to mechanical issues, infection, or patient discomfort. No adverse effects from exposure to alumina.	133
Single crystal alumina endosteal dental implants (n = 23; 15 participants) followed for 10 years. Six weeks after implantation, the implants served as abutments for fixed prostheses.	After 10 years, 21 baseline implants were still in place and 17 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.	134
Glass infiltrated alumina crowns (n = 5[a]; 21 participants) followed for 5 years.	All adverse events were mechanical and not related to exposure to alumina.	135
Other devices		
Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for the treatment of tracheomalacia were followed.	None of the complications were due to the materials. In an assessment of biocompatibility, the authors concluded that there were no foreign body reactions, the inserts were stable, and were a long-term solution with proper suturing technique.	89

[a]Survival refers to how long the prosthesis is functional.

Discussion

The CIR Panel emphasized that this is a safety assessment of alumina and aluminum hydroxide and that these ingredients are not to be confused with elemental aluminum. The Panel noted that the scientific literature provides no plausible evidence linking Alzheimer disease or breast cancer to the use of these ingredients.

The Panel was not concerned with the potential for incidental ingestion of alumina when used in lipsticks or oral hygiene formulations. The amounts of aluminum ion that could be released in the digestive tract through the incidental ingestion of such cosmetic products are far below the levels of toxicological concern. There was no concern about dermal penetration or cosmetic application around the eye because these ingredients are practically insoluble and are not irritating to the skin.

The Panel discussed the issue of incidental inhalation exposure to alumina and aluminum hydroxide in cosmetic powders and fragrance preparations. These ingredients are reportedly used at concentrations up to 6% in cosmetic products that may be sprayed and up to 5% in other products that may become airborne. The Panel noted that 95% to 99% of droplets/particles would not be respirable in any appreciable amounts. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for alumina and aluminum

hydroxide to cause dermal irritation and systemic toxicity in multiple clinical trials of medical devices consisting of alumina. Alumina and aluminum hydroxide are insoluble in water, thus not systemically available. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The CIR Panel concluded that alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

Appendix A

Overview of Aluminum Toxicity Studies

Absorption. Aluminum in cosmetics and in antiperspirants is not systemically absorbed to any appreciable extent through the skin.[56,136,137] Aluminum is poorly absorbed in both the respiratory tract and the gastrointestinal tract.[7]

Gastrointestinal absorption of dietary aluminum generally ranges from 0.01% to 0.6% in humans, although absorption of large bolus doses (up to 0.5 g) of aluminum hydroxide, ingested as antacids throughout the day, and other insoluble aluminum compounds is normally $\leq$0.01%.[40,57,58,60-63,65-69] In contrast, the absorption of water-soluble aluminum compounds can range from 0.5% to 5%.[7] Accordingly, dietary constituents can enhance or inhibit aluminum absorption in the digestive tract by forming absorbable, usually water-soluble, complexes (eg, citric, lactic, or other carboxylic acids) or by forming unabsorbable, generally insoluble compounds (eg, phosphate or dissolved silicate).[7,59,64]

Osteomalacia. There are many case reports of osteomalacia in otherwise healthy children and adults after long-term ingestion of aluminum-containing antacids (eg, aluminum hydroxide given with buffered citrate) for gastrointestinal problems.[7,18,22,24,138-140] Skeletal effects in these cases are attributable to impaired phosphate absorption through the formation of insoluble complexes between aluminum and dietary phosphorous in the gut, which leads to hypophosphatemia and phosphate depletion in the bone.

Dialysis encephalopathy. Most human studies on the toxicity of aluminum are reports of osteomalacia, microcytic anemia, and neurological effects in hemodialysis patients with chronic renal failure.[7,13,14,16,19,36,40,46,49,52,55,56,64,139,141-148] Many of these patients developed signs of central nervous system toxicity, sometimes progressing to dialysis encephalopathy syndrome and even death. These effects are attributable to the accumulation of aluminum in the brain from long-term IV hemodialysis with aluminum-contaminated dialysis fluid and, often, concurrent high oral doses of aluminum hydroxide.[7,33,40,139,149] However, these studies have limited usefulness for predicting toxicity in the general population because kidney failure, coupled with very large aluminum exposures, causes atypical aluminum accumulation and risk of aluminum-induced effects in these patients.[7]

Alzheimer disease. The hypothesis that aluminum could be involved in the pathogenesis of Alzheimer disease stems from an early report that aluminum was detected in senile plaques and neurofibrillary tangles in brain tissue from patients with Alzheimer disease.[27] Since then, several authors reported increased aluminum concentrations in brain tissue from patients with Alzheimer disease compared to that from adults without Alzheimer disease.[26,43,139,150-152] However, others found no increase in aluminum levels in brain tissues of patients with Alzheimer disease.[23,139,143,153-155] Further, other researchers found patients with elevated brain aluminum levels but with no clinical signs of Alzheimer disease.[12,17,139] In a study of brains taken at autopsy (n = 50), signs of dialysis encephalopathy were found in 10 hemodialysis patients with a history of high-dose aluminum ingestion (total doses up to 2,478 g), but no evidence of Alzheimer disease morphology was found in any of them.[156] In contrast, Alzheimer disease morphology was found in 6 patients who had ingested little or no aluminum-containing drugs. The authors concluded that there was no link between the total amount of ingested, bioavailable aluminum administered medically and the appearance of Alzheimer disease-associated aluminum inclusions in glial and neuronal cells.

Several epidemiological studies have examined the possible association between Alzheimer disease and exposure to aluminum in drinking water.[7,34,37-39,41,53,54,157-166] These studies report conflicting results and have been criticized for flawed participant selection, small sample sizes, poor exposure assessment, inaccurate diagnosis of Alzheimer disease, weak statistical correlations, and failure to adjust for important confounding factors.[7,32,40,42,56,65,139]

Other epidemiological studies have associated total dietary aluminum consumption with an increased risk of Alzheimer disease.[139,167] However, no significant association was found between Alzheimer disease and the ingestion of aluminum from tea (typically 2 to 6 mg/L aluminum or 10 to 50 times higher than in drinking water).[39,40,167,168] In addition, no significant association was found with the use of antacids (typically 300 to 600 mg aluminum hydroxide per tablet, capsule, or 5 mL liquid dose).[7,15,21,25,39,44,51,56,139,169] Likewise, no significant association was found between Alzheimer disease and inhalation exposure to aluminum dusts and fumes in the workplace.[7,45,47,139,170,171] Overall, the available studies have not substantiated a causal link between aluminum exposure and Alzheimer disease.[7-9,35,40,48,65,139,172-174]

Breast cancer. A number of aluminum-containing compounds are used as active ingredients in underarm antiperspirant products (21 CFR 350.10).[7,11,20,175,176] Compounds approved for this purpose do not include alumina or aluminum hydroxide. However, compounds such as aluminum zirconium octachlorohydrate and aluminum chlorohydrate can be used at

concentrations up to 20% and 25% by weight, respectively, in the United States and in Europe, and aluminum chloride has been used in antiperspirant products up to 15% in Europe (21 CFR 350.10).[31,177]

Darbre and coworkers have suggested that long-term, regular underarm and breast-area application of products containing potential endocrine disruptors may promote the development of breast cancer.[28-31,50,177-179] Furthermore, these authors have suggested that aluminum chloride and aluminum chlorohydrate have the potential to disrupt endocrine function in human breast cancer cells by interfering with the binding of estrogens to estrogen receptors and inducing estrogen-regulated gene expression, based on the results of in vitro experiments using the estrogen-sensitive MCF-7 breast cancer cell line.[30,31,177]

High concentrations of aluminum salts perturbed estrogen receptor signaling in MCF-7 cells.[31,177] The results of these experiments indicate that aluminum compounds, particularly water-soluble aluminum compounds at high concentrations, can perturb estrogen receptor-mediated activities in MCF-7 breast cancer cells. However, these observations cannot be considered relevant to the use of alumina and aluminum hydroxide in cosmetics, which are insoluble and are not absorbed through the skin to any significant extent.

Furthermore, there was no association between underarm antiperspirant or deodorant use and breast cancer in a population-based case-controlled epidemiological study conducted in the United States.[180] Briefly, patients with breast cancer (n = 813) were compared with control participants (n = 793) from the same population; the control participants were frequency matched to the patients with cancer by 5-year age-groups. Measures of antiperspirant or deodorant use included self-reported regular use (ever), exclusive use of antiperspirant versus deodorant (or vice versa), and regular use within 1 hour of underarm shaving. Odds ratios ranged from 0.9 to 1.2, and *P* values from 0.12 to 0.40. The assessment of both antiperspirant and deodorant use in this study helped address the possibility that some of the participants may have reported deodorant use when they actually used an antiperspirant (or vice versa) or may have used a combination of the 2. Overall, the scientific literature provides no plausible evidence linking breast cancer to the use of underarm antiperspirant or deodorant products.[10]

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, Washington, DC.

Author Contributions

Lillian C. Becker contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted the manuscript. Ivan Boyer contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. Lillian J. Gill, F. Alan Andersen, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, James G. Marks, Ronald C. Shank, Thomas J. Slaga, and Paul W. Snyder contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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