GREEN

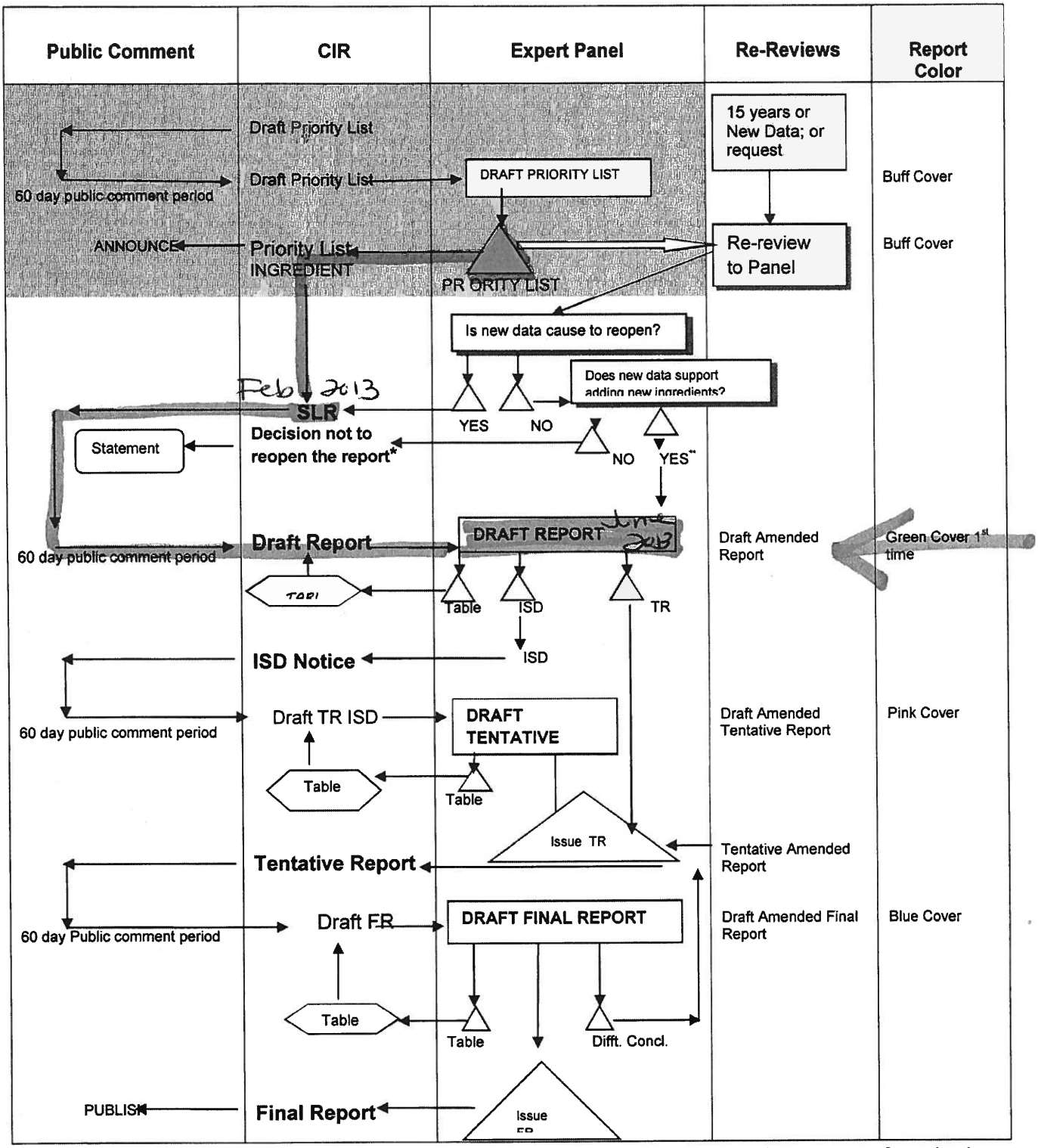
Safety Assessment of Alumina as Used in Cosmetics

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

Alumina June 2013

SAFETY ASSESSMENT FLOW CHART



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Expert Panel Decision

Document for Panel Review

Option for Re-review

Cosmetic Ingredient Review

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May 10, 2013

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Draft Safety Assessment For Alumina and Aluminum Hydroxide As Used In Cosmetics

This is the first time the Panel is seeing this report. A scientific literature review was issued in February 2013. Comments from industry have been addressed. Attached is the draft report of alumina and aluminum hydroxide for your consideration.

CIR reasoned that FDA's safety assessment of alumina in its use in medical devices (i.e., artificial hips and dentition) as well as the use of aluminum hydroxide in OTC antacids provides support for the safety of these ingredients as used in cosmetics. To augment the FDA's findings, data on clinical trials of medical devices using alumina are included along with data on the safety of aluminum hydroxide.

The Panel should review the information as presented and determine whether there are enough data for the Panel to come to a conclusion on safety. If this approach and data are sufficient, the Panel is to issue an insufficient data announcement listing the data needs.

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History of Alumina and Aluminum Hydroxide

February, 2013 - SLR is posted for public comment.

June, 2013 – Panel examines the draft report.

Alumina and Aluminum Hydroxide Data Profile for June, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitiza-tion					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Alumina																		
Aluminum Hydroxide							X				X				X			

Since CIR is depending on FDA's assessments of these ingredients, only data that augments the information has been included in this report.

Search Strategy for
Alumina and Aluminum Hydroxide

Names and CAS Nos. in **SciFinder –** Discovered multiple patents for medical devices using alumina. Also discovered multiple patents and references to aluminum hydroxide and antacids.

Searched **FDA website** for alumina and for the types of medical devices found in SciFinder. Also searched for aluminum hydroxide in pharmacuticals.

Mined report on aluminum for data on aluminum hydroxide.

Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 17, 2013
Panel Meeting Date: June 10-11, 2013

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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INTRODUCTION

This is a draft report on the safety of alumina and aluminum hydroxide as used in cosmetics. 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 U. S. Food and Drug Administration (FDA) for various medical devices and over the counter (OTC) drug uses. The Cosmetic Ingredient Review (CIR) believes that the cosmetic ingredient alumina chemically equivalent to the alumina used in medical devices as a device color additive for bone cements and sutures and in the construction of dental and hip implants. The FDA found the safety information for those medical devices and to be adequate to support safety and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs.

CIR also believes aluminum hydroxide used in cosmetics is chemically equivalent to that used in OTC drugs. The FDA found the safety information for those drugs to be adequate to support safety. Based on the adequacy of those data, the FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) as a food substance and may be used as an antacid and as a direct food additive.

The evaluation of the FDA, along with the data below on aluminum hydroxide, is believed to be sufficient for an evaluation of safety of alumina and aluminum hydroxide.

CIR has reviewed several cosmetic ingredients that contain an aluminum component (Table 2). All are safe as used.

CHEMISTRY

Overview

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

Alumina, also known as aluminum oxide (Al_2O_3), is dehydrated (or calcined) aluminum hydroxide.[1] 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, the most common phase of naturally occurring alumina. This water insoluble, but amphoteric, 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 the rate of acid/base reactions. When synthetically dehydrated from aluminum hydroxide, a mixture of alumina phases typically forms, unless specific controls are applied. While Figure 1 shows both amorphic and crystalline alumina, data on which form is used in cosmetics were not available.

Aluminum hydroxide, also known as hydrated alumina, is most commonly found as the polymorph mineral gibbsite (a component of the aluminum ore known as bauxite).[1,2] This inorganic, amphoteric, solid, can also form three other polymorphs. However, the chemical formula of $Al(OH)_3$ remains the same for all four polymorphs and each one only differs by interlayer spacing and the consequential relative rates of acid/base reactions.

There are four known polymorphs of crystalline aluminum hydroxide: gibbsite, bayerite, nordstrandite, and doyleite that can have different chemical/physical properties.[3] The properties of the starting materials (pH, presence of anions or salt, and mineral surfaces) are what influence the formation of aluminum hydroxide ($Al(OH)_3$) 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 that hydrogen bond the layers together with the difference being the stacking sequences of the layers. Of the possible configurations, gibbsite and bayerite represent the two 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 between sources.[3] The categorization is made according to their crystallographic structures found under environmental conditions and most cited in the literature. 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 instances of polymorphism and cases of alteration or dehydration (originally to all other aluminum hydroxides and hydrolyzed aluminas). The γ-phase has cubic close-packed lattices or related structures. Comparisons of nomenclature are presented in Table 3.

Physical and Chemical Properties

Physical and chemical properties of alumina and aluminum hydroxide are provided in Table 4. Alumina and aluminum hydroxide are white, insoluble solids. Alumina is the third hardest naturally occurring substance after diamond and carbonundum (SiC).[4] The presence of trace amounts of chromium or cobalt creates ruby and sapphire, respectively.

Aluminum compounds cannot easily be oxidized and atmospheric transformations would not be expected to occur.[5]

Aluminum hydroxide compounds are considered amphoteric (e.g., they can act as both acids and bases in solution).[6] Because of this property, aluminum hydroxides can act as buffers and resist pH changes within the narrow pH range of 4–5.[7] Aqueous aluminum hydroxide gel has a pH of ~6.[8]

Method of Manufacture

Aluminum hydroxide is most commonly produced by aqueous alkaline extraction from bauxite ore, a method known as the Bayer process.[1] Alumina is then produced from the resultant aluminum hydroxide simply by strong heating to drive off the water.[9]

Impurities

Alumina balls used in artificial hips must meet the following specifications: grain size, < 5 microns and purity, > 99.7% aluminum oxide).[10] The maximum percentages for trace elements 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 (dried aluminum hydroxide) should contain no more than 0.5% insoluble matter in dilute hydrochloric acid. The following are the limits of impurities: lead (as Pb) ≤ 10 ppm, arsenic (as As) ≤ 1 ppm, mercury (as Hg), ≤ 1 ppm, and aluminum oxide (Al2O3), ≥ 50% (21CFR 73.1010)

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 5).[11] A survey has been conducted by the Personal Care Products Council (Council) of the maximum use concentrations.[12,13]

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

Non-Cosmetic

Use in medical devices will be addressed below.

Aluminum salts are incorporated into some vaccine formulations as an adjuvant to enhance the immune response in the vaccinated individual.[14] The aluminum compounds used in some U.S. licensed vaccines are aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts. Aluminum hydroxide may be used in vaccines in amounts up to 25 µg/L in large volume parenteral drug products (21 CFR 201.323) and up to 1.25 µg/single dose, depending on calculation method (Table 6; 21 CFR 610.15).

The FDA considered the safety of aluminum hydroxide in OTC drugs (Table 6). The FDA recommended the oral maximum daily dose of an antacid containing aluminum hydroxide dried gel to be 8 g (21 CFR 331.11). Chewable tablet of aluminum hydroxide;magnesium trisilicate (80:20 mg) was approved by FDA.[15] Two other chewable tablets were approved with doses of 80:20 mg and 160:40 mg.[16]

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

The safety and effectiveness of aluminum hydroxide in OTC drugs has not been established for: topical acne drug products and antidiarrheal drugs. It has been approved for digestive aid drug products and diaper rash drugs (21 CFR 310.545).

Alumina is used as an adsorbent, desiccant, and abrasive.[17] 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, etc. and as a catalyst for organic reactions.

Aluminum hydroxide is considered GRAS as a food substance by the FDA.[18]

The National Institute for Occupational Safety and Health placed a limit of 15 α-alumina mg/m^3 total time weighted average exposure in the workplace air and 5 α-alumina mg/m^3 for total respirable fraction.[19]

There are many regulations have to do with aluminum or other aluminum compounds. Regulations with regards to aluminum and related compounds that are informative to 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”.[20]

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

- Color additive for PMMA bone cement and sutures,
- Endosseous dental implant abutments, and
- Femoral bearing head of artificial hips.

Color Additives

Colors that contain alumina (i.e., FD&C Blue #1 Aluminum Lake) are approved by the FDA to be used to color cosmetics, food, dietary supplements, drugs for internal and external use, and medical devices (i.e., bone cement, surgical sutures). These colors are created by applying the color to an alumina substrate. All lakes are subject to certification. The term lake is formed from combining the name of the color additive with the name of the basic radical and adding the word "Lake". For example, by extending the aluminum salt of FD&C Blue No. 1 upon alumina produces FD&C Blue No. 1 - Aluminum Lake. If a lake is prepared by extending an FD&C color additive on a substratum other than alumina, the symbol "FD&C" will be replaced by "D&C". For example, lake prepared by extending the aluminum salt of FD&C Blue No. 1 upon a substratum other than alumina would be D&C Blue No. 1- Aluminum Lake. A list of lake colors and their associated regulations are listed in Table 5.[21]

Alumina has been approved as a color additive for OTC drugs (Table 8) (21 CFR 73.1010).

Ceramic Hip

The use of ceramic femoral heads (i.e., Ceramtec™ Alumina Heads, Alumina V40 Head) made up of an alumina/ceramic composite have been approved for use for hip joint replacement in humans. The material follows FDA's guideline "Guidance Document For The Preparation Of Premarket Notifications For Ceramic Ball Hip Systems".[10,22,23]

One hip replacement product was reported to be ~75% alumina, ~25% zirconia, and < 1% chromium oxide.[24]

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 stenting for treatment of traceomalacia.[25] These stents are implanted within the trachea.

TOXICOKINETICS

Overview

Most available toxicokinetic and toxicity data are based on aluminum.

Aluminum is poorly absorbed through either oral or inhalation routes and is essentially not absorbed dermally in healthy humans.[26] Orally, ~0.1% – 0.6% of aluminum is usually absorbed; the less bioavailable form of aluminum hydroxide is absorbed at ~0.1%. Unabsorbed aluminum is excreted in the feces. The bioavailability of aluminum is strongly influenced by the type of aluminum compound and the presence of dietary constituents which can form a complex with aluminum and thereby enhance or inhibit absorption. The main mechanism of absorption is thought to be passive diffusion through paracellular pathways. Aluminum binds to various ligands in the blood and distributes to every organ, but mostly to bone and lung tissues. Absorbed aluminum is excreted mostly in the urine and, to a lesser extent, in the bile. Studies on aluminum uptake and elimination rates 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 the lifespan. High levels of aluminum, such as those associated with long-term use of antacids, will cause levels to increase in the blood and tissue. The levels return to normal upon cessation of exposure. Under certain atypical conditions (e.g., poor renal function with increased aluminum load), levels of aluminum in the body may raise high enough to cause toxicity in humans. The main target organs under these conditions appear to be the central nervous system and bone. The molecular mechanism of aluminum bone and neurotoxicity has not been established.

Blood and tissue (liver, spleen, kidney, brain, bone) levels of aluminum from oral aluminum hydroxide were increased by concurrent administration of citric, lactic, malic, oxalic, and tartaric acids in rats.[27-29]

Dermal

Aluminum salts used in antiperspirants form a hydroxide precipitate of denatured keratin in the cornified layer that surrounds and occludes the opening of sweat ducts.[30] The authors concluded that these mechanisms suggest that there is little or no dermal absorption of aluminum hydroxide, or any other form of aluminum.

Oral

ALUMINUM HYDROXIDE

Bioavailability of orally administered ^{26}aluminum hydroxide (in 2 ml water; pH 7) to male Wistar rats (n = 9) was 0.1%.[31] After administration, the rats were placed in metabolic cages and blood sampled at 20, 45, 60, 90, 150, and 300 min. 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.[32] 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 in necropsied at the end of the test period and at 7 and 21 days. The treatment group had increased aluminum in the tibiae-fibulae, ulnae-radii, leg muscles, and kidneys. At day 21, all aluminum content values were similar to controls.

This experiment was repeated with 9 (control) and 1070 Al µg /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.[33] Renally impaired rabbits absorbed 0.36 ± 0.30%.

Orally administered aluminum hydroxide is poorly absorbed at <0.01% in humans.[34,35]

Using ^{26}Al, the estimated aluminum absorption rates were 0.523%, 0.0104%, and 0.136% in two subjects receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in an aqueous citrate solution, respectively.[36] The test materials were delivered to the stomach by a pediatric feeding tube. Blood was collected at 1, 4, and 14 h. Feces and urine were collected for 6 days. The uptake of aluminum was greatest in the citrate form and least as aluminum hydroxide. The addition of citrate to the aluminum hydroxide increased the ^{26}Al uptake in both subjects.

There was no appreciable increase in the amount of aluminum absorbed in subjects (n = 8, 10, 7) administered aluminum hydroxide (equal to 244, 976, or 1952 mg Al in the form of antacid tablets; pH 9.2).[37] By measuring the amount of aluminum in the urine, the amount of aluminum absorbed was 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 1000 ml distilled water; pH 2.4), absorption increased to 0.03% and 0.2%.

Intravenous

ALUMINUM HYDROXIDE

The half-life of i.v. administered aluminum hydroxide (100 µmol/kg as concentrated aluminum hydroxide gel) to renally intact rabbits (n = 10) was 27 ± 13 h.[33] For renally impaired rabbits, the half-life was 14 ± 5 h. Blood was sampled at 24 and immediately prior to treatment and at ~5, 10, 20, 30, 45, and 60 min and 2, 4, 8, 12 24, and 48 h.

TOXICITY

Repeated Dose

Oral – Animal

ALUMINUM HYDROXIDE

When aluminum hydroxide (average 2400 mg/kg/k in drinking water) was administered to Long Evans male hooded rat weanlings (n = 7, 8) for 60 days, there was no reduction in cognitive abilities.[38] At necropsy, the highest concentration of aluminum in the brain was in the hippocampus. The test group had reduced 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 in with each of the rats. Only one treated rat exhibited the behavior.

When aluminum hydroxide (300 mg/kg in carboxylmethyl 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 when measured using a four-T shaped labyrinth.[39] Controls learned the way to the goal in an average of 5.1 ± 2.88 times vs. 16.0 ± 2.98 and 13.2 ± 5.39 times, respectively. The amount of aluminum content of the brains of the control rats at necropsy was 6.6 ± 3.01 ppm compared to 18.0 ± 10.20 and 11.0 ± 4.80 ppm, 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 reduced weight gain and initial feed efficiency when administered i.p. aluminum hydroxide (80 mg/kg) 3 times/week for 6 months.[40] There were no differences in feed intake. Aluminum hydroxide did not affect the peak growth rate or the time to reach maturity. The calcium balance in the treated rats was reduced and there was an increase in the amount of calcium excreted in the feces. The rate of skeletal Ca^{++} accretion was decreased with changes in the bone calcium resorption.

Oral – Human

ALUMINUM HYDROXIDE

There were no adverse effects observed when subjects (n = 9 females, 4 males) were administered aluminum hydroxide (equal to 59 mg Al) three times daily for 6 weeks.[41] When compared to the control group (n = 3 females, 2 males) urinary Al was ~ 10- to 20-fold greater during treatment. The authors state 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* Ig and IL production. There were

similar time-dependent changes before as well as during the test period. There were no differences observed between groups regarding the immune parameters, 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 – 15 to Swiss mice (n = 20), there were no effects attributed to the test substance.[42] There were no differences in maternal weight, feed consumption, appearance, or behavior. There were no differences in 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 (1064 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 – 15), there were no differences among group with regards to pre- or post-implantation loss, number of live fetuses per litter, or sex ration.[43] Fetal body weight was reduced and skeletal variations (delayed ossification or occipital and sternebrae; absence of xiphoides) were increased in the aluminum hydroxide plus citric acid group. The absence of xiphoides was also observed in the aluminum citrate group. The dams had reduced weight gain in the aluminum hydroxide plus citric acid group during treatment but recovered and caught up to the other groups post treatment. There was increased aluminum in the livers, bones, and placentas of the aluminum citrate group. There was no difference in aluminum content in the kidneys and brains. Aluminum was not detected in whole fetuses. The control group (n = 17) was administered water.

IRRITATION

ALUMINUM HYDROXIDE

Aluminum hydroxide (10% w/v in 0.2% Tween-80) was not irritating when applied to the shaved backs of female TF1 strains 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.[44] 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 alumina-on-alumina or alumina ceramic hips, alumina/ceramic composite stents, and dental implants. There were no adverse reactions reported. None of the failures reported were due to adverse effects of the alumina but were related to mechanical or technique issues (Table 9).

In a review of four case studies of alumina ceramic hip implant failures, it was determined that all problems were due to design issues, implementation issues, or surgical issues.[45] None of the failures were attributed to any negative 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.

CIR believes that the alumina and aluminum hydroxide produced for cosmetics is chemically equivalent to the materials used to color surgical sutures and in other commercial medical devices made of alumina as well as that used in OTC drugs and vaccines. The safety information for those medical devices and drugs was provided to the FDA in medical device and drug applications including: acute and long-term biocompatibility testing for cytotoxicity, irritation or intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility. The FDA found those data to be adequate and determined that alumina and was safe and effective for use in hip and dental implants as well as to color PMMA bone cement and surgical sutures. Aluminum hydroxide is GRAS as a food additive and safe in OTC drugs and vaccines.

Hydroxyaluminum compounds are considered amphoteric.

Aluminum hydroxide is most commonly produced by the Bayer process.

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 up to 25%. Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% (in eye products) and 6 rinse-off products up to 8.8% (in oral hygiene products).

Alumina is used in color additives for PMMA bone cement and sutures, endosseous dental implant abutments, and femoral bearing head of artificial hips.

In clinical trials of artificial hips, dental implants, and esophageal stents, all adverse effects were from mechanical or installation problems, not due to exposure to alumina.

Orally administered aluminum from aluminum hydroxide has low bioavailability and is excreted in the urine.

Aluminum hydroxide orally administered to rats at 2400 mg/kg had no effect on cognitive abilities but when 100

mg/kg was administered to rats with citric acid, reduced learning ability was demonstrated.

Rats exhibited reduced weight gain and initial feed efficiency when administered i.p. aluminum hydroxide at 80 mg/kg 3 times/week for 6 months.

There were no effects to immunity parameters in humans orally administered aluminum hydroxide (equal to 59 mg Al) three times daily for 6 weeks.

There were no reproductive effects to mice when orally administered aluminum hydroxide at 266 mg/kg during gestation days 6 – 15 or to rats at 384 mg/kg. However, when administered with citric acid, there was reduced weight gain in the dams and an increase is skeletal abnormalities in the pups.

Aluminum hydroxide at 10% was not dermally irritating to mice, rabbits, and pigs (n = 2; 1.0 ml).

DISCUSSION

Discussion to be developed at the June, 2013 Panel meeting.

CONCLUSION

Conclusion will be developed at the June, 2013 Panel meeting.

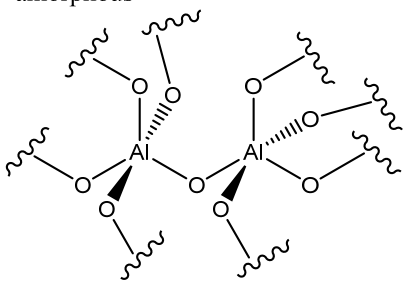
TABLES AND FIGURES

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

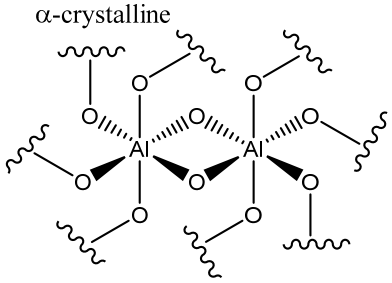
Alumina

aluminum oxide

amorphous



α-crystalline



Aluminum hydroxide

aluminum hydroxide

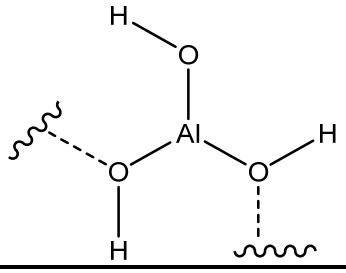


Table 1. Definitions and functions of the ingredients in this safety assessment.[46]
(The *italicized* text below represents additions made by CIR staff.)

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 (i.e., 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 $Al(OH)_3 \cdot xH_2O$. *Alumina hydrates are true hydroxides (meaning they do not contain water of hydration; are often called hydrated alumina or aluminum hydroxide) and are naturally occurring as minerals including bauxite or gibbsite.*	Opacifying agent, skin protectant

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 non-respirable.	44	47
Aluminum citrate	Safe as used.	80	48
Aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum myristates/palmitates	Safe as used.	82	49,50
Aluminum silicate, magnesium aluminum silicate	Safe as used.	100	51
Aluminum starch octenylsuccinate	Safe as used with limitations on heavy metal content	30	52
Aluminum distearate, aluminum stearate, aluminum tristearate	Safe as used.	25	53,54
Calcium aluminum borosilicate	Safe as used.	97	55
Potassium aluminum polyacrylate	Safe as used when formulated to be nonirritating	25	56

Table 3. Comparison of nomenclatures for alumina and aluminum hydroxide.[3]

Mineral Name	Chemical composition	Common crystallographic designation	Past accepted crystallographic designation
Gibbsite (hydrargillite[1])[2]	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

[1] Hydrargillite is a mineral that was named after the Greek hyder (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.
[2] The terms in parenthesis refer to possible forms.

Table 4. Chemical and physical properties of alumina and aluminum hydroxide.

Property	Value	Reference
Alumina		
Physical Form	Solid, crystalline powder	[17,57]
Color	White	[17]
Odor	None	[57]
Molecular Weight g/mol	101.96	[17]
Density/Specific Gravity @ 20°C	4.0	[17]
Viscosity kg/(s m)@ 20°C	Solid	[57]
Vapor pressure mmHg@ 20°C	Negligible	[57]
Melting Point °C	~2000	[17]
Boiling Point °C	2980	[17]
Water Solubility g/L @ °C & pH	Insoluble	[17]
Aluminum hydroxide		
Physical Form	Amorphous powder	[17]
Color	White	[17]
Molecular Weight g/mol	78.00	[17]
Density/Specific Gravity @ °C	2.42	[17]
Melting Point °C	300	[17]
Water Solubility	Practically insoluble	[17]

Table 5. Frequency of use according to duration and exposure of alumina and aluminum hydroxide.[11-13]

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	NS0.0022-8.8
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[a]
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

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

[a] The Council reports that the skin care preparations and suntan preparations in their survey are not sprays.

Note: 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.

Table 6. 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 is a premanufactured prosthetic component directly connected to the endosseous dental implant and is intended for use as an aid in prosthetic rehabilitation. 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. (See 872.1(e) for the availability of this guidance document.)	21 CFR 872.3630
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 one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. The two-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 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. (b)*Classification.* Class II.	21 CFR 888.3353
	(a) A hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis is a two-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 one 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). (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 semiconstrained 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 semiconstrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976. Any other hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis must have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.	21 CFR 888.3410
Injections		
	Sec. 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition. (a) The aluminum content of LVP) drug products used in TPN therapy must not exceed 25 µg/L. WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/L/kg/d accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. (f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under 314.60 or 314.96 of this chapter.	21 CFR 201.323
	(a)*Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed: (1) 0.85 milligrams if determined by assay; (2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum	21 CFR 610.15

Table 6. Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
	compound added; or (3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter). (b)*Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000. (c)*Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines. (d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.	
OTC Drugs		
	(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 for the specified uses: (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.*	21CFR310.545
	(a) Aluminum-containing active ingredients: (1) Basic aluminum carbonate gel. (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried 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 percent of the total acid neutralizing capacity; maximum daily dosage limit is 8 grams	21CFR331.11
	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 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. 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 codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).	
	Permitted combinations of active ingredients. (a)*Combinations of skin protectant active ingredients.* (1) Any two 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 two 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 percent aluminum acetate solution when the powder or tablet is dissolved in the volume of water specified in "Directions."	21 CRF 347.10

Table 6. Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
Food Packaging		
	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.	21CFR177.2600

LVP - large volume parenteral; PBP – pharmacy bulk packages; SVP - small volume parenteral; TPN - total parenteral nutrition

Table 7. Government regulations with regard to aluminum and related compounds.[26]

Agency	Regulation	Reference
INTERNATIONAL		
IARC	Group 1: aluminum production carcinogenic to humans	[58]
WHO	Drinking water quality guidelines for aluminum ≤0.1 mg/L in large water treatment facilities ≤0.2 mg/L in small water treatment facilities	[59]
NATIONAL		
Air		
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al) 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	[60]
EPA	AEGL-1 for aluminum phosphide[b] - Not recommended due to insufficient data AEGL-2 for aluminum phosphide[b] 10 minutes - 4.0 ppm 30 minutes - 4.0 ppm 60 minutes - 2.0 ppm 4 hours - 0.50 ppm 8 hours - 0.25 ppm AEGL-3 for aluminum phosphide[b] 10 minutes - 7.2 ppm 30 minutes - 7.2 ppm 60 minutes - 3.6 ppm 4 hours - 0.90 ppm 8 hours - 0.45 ppm	[61]
NIOSH	REL (10-hour TWA) 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)	[19]
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide 15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	29 CFR 1910.10000
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
EPA	Drinking water standards and health advisories - 0.05–0.2 mg/L	[62]
EPA	National primary drinking water Standards - No data	[63]
EPA	National secondary drinking water standards for aluminum - 0.05–0.2 mg/	40 CFR 143.3
EPA	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
EPA	Water quality criteria for human health for aluminum Freshwater CMC - 750 µg/L Freshwater CCC - 87 µg/L	[64]

Table 7. Government regulations with regard to aluminum and related compounds.[26]

Agency	Regulation	Reference
Food		
FDA	Bottled drinking water for aluminum - 0.2 mg/L	21 CFR 165.110
Other		
EPA	RfD for aluminum phosphide - $4x10^{-4}$ mg/kg/day	[64]
	Pesticide exemptions from the requirement of a tolerance Aluminum hydroxide (for use as a diluent and carrier)[c] Aluminum oxide (for use as a diluent)[g]	40 CFR 180.910

[a] TWA: the value is for particulate matter containing no asbestos and <1% crystalline silica.
[b] AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[c] 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.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; 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; IRIS = Integrated Risk Information System; 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; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

Table 8. Code of Federal Regulations concerning Lake colors and other colors containing alumina.[65]

Color	Rule	Reference
FOOD, DRUGS AND COSMETICS		
FD&C Blue #1 Aluminum Lake	Color additive mixtures for food use (including dietary supplements) made with FD+C Blue No. 1 may contain only those diluents that are suitable (listed in part 73) as safe for use in color additive mixtures for coloring foods. FD+C Blue No. 1 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by current good manufacturing practice: • Sum of volatile matter (at 135 deg. C) and chlorides and sulfates (calculated as sodium salts) ≤ 15.0%. • Water-insoluble matter ≤ 0.2%. • Leuco base ≤ 5% percent. • Sum of *o* -,*m* -, and *p* -sulfobenzaldehydes ≤1.5%. • *N* -Ethyl, *N* -(*m* -sulfobenzyl)sulfanilic acid ≤ 0.3%. • Subsidiary colors ≤ 6.0%. • Chromium (as Cr) ≤ 50 ppm. • Manganese (as Mn) ≤ 100 ppm. • Arsenic (as As) ≤ 3 ppm. • Lead (as Pb) ≤ 10 ppm. • Total color ≥ 85.0%. FD+C Blue No. 1 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards. All batches of FD+C Blue No. 1 shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.101
	For ingested drugs, the color additive FD+C Blue No. 1 shall conform in identity to the requirements of 74.101(a)(1). For externally applied drugs, the color additive FD+C Blue No. 1 shall conform in identity to the requirements of 74.2101(a). Color additive mixtures for drug use made with FD+C Blue No. 1 may contain only those diluents that are suitable (listed in part 73) and generally shall conform in specifications to the requirements of 74.101(b). It shall be prepared in accordance with the requirements of 82.51 of this chapter and may be safely used for coloring drugs, including drugs intended for use in the area of the eye, in amounts consistent with current good manufacturing practice subject to the restrictions on the use of color additives in 70.5(b) and (c). All batches of FD+C Blue No. 1 shall be certified in accordance with regulations in part 80.	21 CFR 74.1101

Table 8. Code of Federal Regulations concerning Lake colors and other colors containing alumina.[65]

Color	Rule	Reference
	FD+C Blue No. 1 shall conform in specifications to the requirements of 74.101(b) and shall be prepared in accordance with the requirements of 82.51 of this chapter. It may be safely used for coloring cosmetics generally, including cosmetics intended for use in the area of the eye, in amounts consistent with current good manufacturing practice.	21 CFR 74.2101,
	The color additive FD+C Blue No. 1 shall conform in identity and specifications to the requirements of 74.101(a)(1) and (b).	21 CFR 82.101
	Any lake made by extending on a substratum of alumina, a salt prepared from one of the certified water-soluble straight colors hereinbefore listed in this subpart by combining such color with the basic radical aluminum or calcium. Specifications: • Soluble chlorides and sulfates (as sodium salts) ≤ 2.0%. • Inorganic matter, insoluble HCl ≤ 0.5%.	21 CFR 82.51
FD&C Blue #2 Aluminum Lake on alumina	Color additive mixtures for food use (including dietary supplements) made with FD+C Blue No. 2 may contain only those diluents that are suitable and that are listed in part 73 of this chapter as safe for use in color additive mixtures for coloring foods. The color additive FD+C Blue No. 2 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by current good manufacturing practice: • Sum of volatile matter at 135 deg. C (275 deg. F) and chlorides and sulfates (calculated as sodium salts), ≤15 percent. • Water insoluble matter ≤0.4%. • Isatin-5-sulfonic acid ≤ 0.4% percent. • 5-Sulfoanthranilic acid ≤ 0.2%. • Disodium salt of 2-(1,3-dihydro-3-oxo-7-sulfo-2*H* -indol-2-ylidene)-2,3-dihydro-3-oxo-1*H* -indole-5-sulfonic acid ≤ 18%. • Sodium salt of 2-(1,3-dihydro-3-oxo-2*H* -indol-2-ylidene)-2,3-dihydro-3-oxo-1*H* -indole-5-sulfonic acid ≤ 2%. • Lead (as Pb) ≤10 ppm. • Arsenic (as As) ≤ 3 ppm. • Mercury (as Hg) ≤ 1% ppm. • Total color ≥ 85%. The color additive FD+C Blue No. 2 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with current good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the Federal Food, Drug, and Cosmetic Act unless added color is authorized by such standards. All batches of FD+C Blue No. 2 shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.102
	The color additive FD+C Blue No. 2 for use in coloring surgical sutures shall conform to the specifications of this sectionand shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice. The color additive FD+C Blue No. 2-Aluminum Lake on alumina for use in bone cement shall be prepared in accordance with the requirements of 82.51. The color additive FD+C Blue No. 2 may be safely used for coloring nylon (the copolymer of adipic acid and hexamethylene diamine) surgical sutures for use in general surgery subject to the restriction in this section. The color additive FD+C Blue No. 2-Aluminum Lake on alumina may be safely used for coloring bone cement at a level ≤ 0.1% by weight of the bone cement. All batches of FD+C Blue No. 2 and its lake shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.3102
	The color additive FD+C Blue No. 2 shall conform in identity and specifications to the requirements of 74.102(a)(1) and (b).	21 CFR 82.102
FD&C Red #40 and its Aluminum Lake	*Color additives for use in the area of the eye.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use in the area of the eye unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use in the area of the eye, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses. *Color additives for use in injections.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use in injections unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use in injections, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses. *Color additives for use in surgical sutures.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use as a surgical suture unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use as a surgical suture, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses.	21 CFR 70.5
	The listing of this color additive includes lakes prepared as described in 82.51 of this chapter, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 of this chapter. FD+C Red No. 40 shall conform to the following specifications and shall be free from impurities other than	21 CFR 74.340

Table 8. Code of Federal Regulations concerning Lake colors and other colors containing alumina.[65]

Color	Rule	Reference
	those named to the extent that such other impurities may be avoided by good manufacturing practice: • Sum of volatile matter (at 135 deg. C.) and chlorides and sulfates (calculated as sodium salts) ≤ 14.0%. • Water-insoluble matter ≤ 0.2%. • Higher sulfonated subsidiary colors (as sodium salts) ≤ than 1.0%. • Lower sulfonated subsidiary colors (as sodium salts) ≤ 1.0%. • Disodium salt of 6-hydroxy-5-[(2-methoxy-5-methyl-4-sulfophenyl) azo] -8-(2-methoxy-5-methyl-4-sulfophenoxy)-2-naphthalenesulfonic acid ≤ 1.0%. • Sodium salt of 6-hydroxy-2-naphthalenesulfonic acid (Schaeffer's salt) ≤ 0.3%. • 4-Amino-5-methoxy-*o*- toluenesulfonic acid ≤ 0.2%. • Disodium salt of 6,6'-oxybis (2-naphthalene-sulfonic acid) ≤ 1.0%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 3 parts ppm. • Total color ≥ 85.0%. FD+C Red No. 40 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards. All batches of FD+C Red No. 40 and lakes thereof shall be certified in accordance with regulations in part 80 of this chapter.	
	Color additive mixtures for drug use made with FD+C Red No. 40 may contain only those diluents that are suitable and that are listed in part 73 of this chapter as safe for use in color additive mixtures for coloring drugs. The listing of this color additive includes lakes prepared as described in 82.51 and 82.1051 of this chapter, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 or 82.1051. FD+C Red No. 40 and FD+C Red No. 40 Aluminum Lake may be safely used in coloring drugs, including those intended for use in the area of the eye, subject to the restrictions on the use of color additives in 70.5(b) and (c), in amounts consistent with current good manufacturing practice. Other lakes of FD+C Red No. 40 may be safely used in coloring drugs, subject to the restrictions on the use of color additives in 70.5, in amounts consistent with current good manufacturing practice. All batches of FD+C Red No. 40 and lakes thereof shall be certified in accordance with regulations, in part 80.	21 CFR 74.1340
	The listing of this color additive includes lakes prepared as described in 82.51 and 82.1051, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 or 82.1051. FD+C Red No. 40 may be safely used in coloring cosmetics generally, except that only FD+C Red No. 40 and FD+C Red No. 40 Aluminum Lake may be safely used in coloring cosmetics intended for use in the area of the eye. These uses are subject to the following restrictions: • The color additive may be used in amounts consistent with current good manufacturing practice. • The color additive shall not be exposed to oxidizing or reducing agents that may affect the integrity of the color additives or any other condition that may affect their integrity. All batches of FD+C Red No. 40 shall be certified in accordance with regulations in part 80.	21 CFR 74.2340
FD&C Yellow #5 Aluminum Lake	FD+C Yellow No. 5 Aluminum Lake shall be prepared in accordance with the requirements of 82.51. FD+C Yellow No. 5 Aluminum Lake may be safely used for coloring drugs intended for use in the area of the eye, when prepared in accordance with 82.51 of this chapter.	21 CFR 74.1705
	FD+C Yellow No. 5 Aluminum Lake shall be prepared in accordance with the requirements of 82.51. FD+C Yellow No. 5 Aluminum Lake may be safely used for coloring cosmetics intended for use in the area of the eye, subject to the restrictions on use of color additives in 70.5(b) and (c), in amounts consistent with current good manufacturing practice.	21 CFR 74.2705
	The color additive FD+C Yellow No. 5 shall conform in identity and specifications to the requirements of 74.705 (a)(1) and (b).	21 CFR 82.705
EXTERNALLY APPLIED DRUGS AND COSMETICS (None of these colors may be used in products that are for use in the area of the eye)		
Ext. D&C Lakes	The Commissioner of Food and Drugs finds that the following lists of color additives are provisionally listed under section 203(b) of the Color Additive Amendments of 1960 (sec. 203(b), 74 Stat. 405 (21 U.S.C. 379e note)). Except for color additives for which petitions have been filed, progress reports are required by January 1, 1968, and at 6-month intervals thereafter. Specifications for color additives listed in paragraphs (a), (b), and (c) of this section appear in the respective designated sections. The listing of color additives in this section is not to be construed as a listing for surgical suture use unless color additive petitions have been submitted for such use or the Commissioner has been notified of studies underway to establish the safety of the color additive for such use. The color additives listed in paragraphs (a), (b), and (c) of this section may not be used in products which are intended to be used in the area of the eye. The color additives listed in paragraphs (a), (b), and (c) of this section are provisionally listed until the closing dates set forth therein. • Lakes (FD+C) (sec. 82.51) • Lakes (D+C) (Sec. 82.2051) • Lakes (Ext. D+C) (sec. 82.105(1))	21 CFR 81.1
	Any lake made by extending on a substratum of alumina, blanc fixe, gloss white, clay, titanium dioxide, zinc oxide, talc, rosin, aluminum benzoate, calcium carbonate, or on any combination of two or more of these: • one of the straight colors hereinbefore listed in this subpart, which color is a salt in which is	21 CFR 82.2051

Table 8. Code of Federal Regulations concerning Lake colors and other colors containing alumina.[65]

Color	Rule	Reference
	combined the basic radical sodium, potassium, barium, or calcium; or • (ii) a salt prepared from one of the straight colors hereinbefore listed in this subpart by combining such color with the basic radical sodium, potassium, aluminum, barium, calcium, strontium, or zirconium. Specifications: • Ether extracts ≤ 0.5%. • Soluble chlorides and sulfates (as sodium salts) ≤ 3.0%. • Intermediates ≤ 0.2%. Each lake made as prescribed in this section shall be considered to be a straight color and to be listed therein under the name which is formed as follows: • The listed name of the color from which the lake is prepared; • The name of the basic radical combined in such color; and • The word "Lake." (For example, the name of a lake prepared by extending the color Ext. D+C Yellow No. 2 upon a substratum is "Ext. D+C Yellow No. 2--Calcium Lake," and a lake prepared by extending the barium salt prepared from Ext. D+C Red No. 2 upon the substratum is "Ext. D+C Red No. 2--Barium Lake.")	
	The color additive Ext. D+C Yellow No. 7 shall conform in identity with specifications to the requirements of 74.1707a(a)(1) and (b) of this chapter. Ext. D+C Yellow No. 7 is restricted to use in externally applied drugs and cosmetics.	21 CFR 82.2707
DRUGS (None of these color additives may be used in products that are for use in the area of the eye, unless otherwise indicated.).		
Alumina	Color additive mixtures for drug use made with alumina (dried aluminum hydroxide) may contain only those diluents listed in this subpart as safe and suitable for use in color additive mixtures for coloring drugs. Alumina (dried aluminum hydroxide) shall conform to the following specifications: • Acidity or alkalinity: Agitate 1 gram of the color additive with 25 milliliters of water and filter. The filtrate shall be neutral to litmus paper. • Matter insoluble in dilute hydrochloric acid ≤ 0.5%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 1 ppm. • Mercury (as Hg) ≤ 1 ppm. • Aluminum oxide (Al_2O_3) ≥ 50%. Alumina (dried aluminum hydroxide) may be safely used in amounts consistent with good manufacturing practice to color drugs generally. Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.	21 CFR 73.1010
Aluminum hydroxide	Aluminum hydroxide gel is approved for OTC skin protectant drug products as an active ingredient at 0.15% - 5% with caution to consult a doctor for children under 6 months.	21 CFR 247.10; 21 CFR 347.50
MEDICAL DEVICES		
FD&C Blue #2 Aluminum lake on alumina	The color additive FD+C Blue No. 2 shall conform in identity to the requirements of 74.102(a)(1). The color additive FD+C Blue No. 2 for use in coloring surgical sutures shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice: • Sum of volatile matter at 135 deg. C (275 deg. F) and chlorides and sulfates (calculated as sodium salts) ≤ 15%. • Water insoluble matter ≤ 0.4%. • Isatin-5-sulfonic acid ≤ 0.4%. • Isomeric colors ≤ 18%. • Lower sulfonated subsidiary colors ≤ 5%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 3 ppm. • Total color ≥ 85%. The color additive FD+C Blue No. 2-Aluminum Lake on alumina for use in bone cement shall be prepared in accordance with the requirements of 82.51. The color additive FD+C Blue No. 2 may be safely used for coloring nylon (the copolymer of adipic acid and hexamethylene diamine) surgical sutures for use in general surgery subject to the following restrictions: • The quantity of color additive does not exceed 1% by weight of the suture; • The dyed suture shall conform in all respects to the requirements of the United States Pharmacopeia XX (1980); and • When the sutures are used for the purposes specified in their labeling, the color additive does not migrate to the surrounding tissues. The color additive FD+C Blue No. 2-Aluminum Lake on alumina may be safely used for coloring bone cement at a level not to exceed 0.1% by weight of the bone cement. All batches of FD+C Blue No. 2 and its lake shall be certified in accordance with regulations in part 80.	21 CFR 74.3102

Table 9. Clinical trials of medical devices containing alumina.

Study	Results	Reference
Artificial Hips		
Alumina-on-alumina (n = 88 subjects; 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.	[66]
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 has a histologically observable impact on surrounding tissues and leads to surface wear in vivo, This was considered mechanical and not a reaction to alumina.	[67]
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[1] of the hips at 10 years was 96.8%.	[68]
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.	[24]
Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.	8 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.	[69]
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.	[70]
Two alumina ceramic hips compared (n=27, 23) comparing an alumina and a polyethylene liner followed for 2 years.	No adverse effects from either form of hip.	[71]
Dental Implants		
Alumina ceramic attachment (> 95% alumina) to hold dentures (n = 20) were followed for 1 year.	No adverse effects from exposure to alumina.	[72]
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.	[73]
Single crystal alumina endosteal dental implants (n = 23; 15 subjects) followed for 10 years. 6 weeks after implantation, the implants served as abutments for fixed prostheses.	After 10 years 2l baseline implants were still in place, I7 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.	[74]
Glass infiltrated alumina crowns (n = 5a; 21 subjects) followed for 5 years.	All adverse events were mechanical and not related to exposure to alumina.	[75]
Other Devices		
Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for treatment of traceomalacia 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	[25]

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

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Cosmetic Ingredient Review

Commitment & Credibility since 1976

May 10, 2013

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Unpublished Data for the Safety Assessment of Alumina and Aluminum Hydroxide As Used In Cosmetics

Unpublished data for the draft report of alumina and aluminum hydroxide include:

1. Concentration of use data for Alumina and Sodium Aluminate (which was removed from the report and replaced with Aluminum Hydroxide).

2. VCRP data for Alumina and Aluminum Hydroxide.

3. Concentration of use data for Aluminum Hydroxide.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 23, 2013

SUBJECT: Concentration of Use by FDA Product Category: Alumina and Sodium Aluminate

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Concentration of Use by FDA Product Category*
Alumina
Sodium Aluminate

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Alumina	01B	Baby products powder	0.0023%
Alumina	03A	Eyebrow pencil	0.14-5.5%
Alumina	03B	Eyeliner	0.01-0.05%
Alumina	03C	Eye shadow	4.9-22.8%
Alumina	03D	Eye lotion	0.012-30%
Alumina	03F	Mascara	0.00075-0.02%
Alumina	04C	Powders (dusting and talcum)	0.0023%
Alumina	04E	Other fragrance preparations	6%
Alumina	06H	Other hair dye preparations	1%
Alumina	07A	Blushers (all types)	0.014-12%
Alumina	07B	Face powders	0.22-5%
Alumina	07C	Foundations	0.025-6.2%
Alumina	07D	Leg and body paints	0.24%
Alumina	07E	Lipstick	0.0004-6.7%
Alumina	07F	Makeup bases	1.9-5%
Alumina	07G	Rouges	0.032%
Alumina	07I	Other makeup preparations	0.0037-0.4%
Alumina	08A	Basecoats and undercoats (manicuring preparations)	0.16%
Alumina	08E	Nail polish and enamel	0.0048-2%
Alumina	08G	Other manicuring preparations powder	60%
Alumina	09A	Dentifrices (aerosol, liquid, pastes and powders)	1-5%
Alumina	10A	Bath soaps and detergents	0.0046-0.06%

Alumina	10B	Deodorant not spray	0.004-0.01%
Alumina	10E	Other personal cleanliness products	0.003%
Alumina	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0034-25%
Alumina	12C	Face and neck produucts not spray	0.06-20%
Alumina	12D	Body and hand products not spray	0.05-1%
Alumina	12F	Moisturizing products not spray	0.05-0.36%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.
†Product category codes used by FDA

Information collected in 2012
Table prepared January 23, 2013

VCRP Data for Alumina

03A - Eyebrow Pencil	1344281	ALUMINA	1
03B - Eyeliner	1344281	ALUMINA	6
03C - Eye Shadow	1344281	ALUMINA	57
03D - Eye Lotion	1344281	ALUMINA	5
03F - Mascara	1344281	ALUMINA	3
03G - Other Eye Makeup Preparations	1344281	ALUMINA	12
04B - Perfumes	1344281	ALUMINA	1
04C - Powders (dusting and talcum, excluding aftershave talc)	1344281	ALUMINA	1
04E - Other Fragrance Preparation	1344281	ALUMINA	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1344281	ALUMINA	1
07A - Blushers (all types)	1344281	ALUMINA	16
07B - Face Powders	1344281	ALUMINA	41
07C - Foundations	1344281	ALUMINA	128
07D - Leg and Body Paints	1344281	ALUMINA	1
07E - Lipstick	1344281	ALUMINA	87
07F - Makeup Bases	1344281	ALUMINA	10
07G - Rouges	1344281	ALUMINA	2
07I - Other Makeup Preparations	1344281	ALUMINA	32
08A - Basecoats and Undercoats	1344281	ALUMINA	2
08E - Nail Polish and Enamel	1344281	ALUMINA	25
08G - Other Manicuring Preparations	1344281	ALUMINA	3
09A - Dentifrices	1344281	ALUMINA	1
10A - Bath Soaps and Detergents	1344281	ALUMINA	6
10E - Other Personal Cleanliness Products	1344281	ALUMINA	13
12A - Cleansing	1344281	ALUMINA	18
12C - Face and Neck (exc shave)	1344281	ALUMINA	36
12D - Body and Hand (exc shave)	1344281	ALUMINA	6
12F - Moisturizing	1344281	ALUMINA	27
12G - Night	1344281	ALUMINA	1
12H - Paste Masks (mud packs)	1344281	ALUMINA	2
12J - Other Skin Care Preps	1344281	ALUMINA	14
13A - Suntan Gels, Creams, and Liquids	1344281	ALUMINA	2
13B - Indoor Tanning Preparations	1344281	ALUMINA	3
13C - Other Suntan Preparations	1344281	ALUMINA	1
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03B - Eyeliner	21645512	ALUMINUM HYDROXIDE	4
03C - Eye Shadow	21645512	ALUMINUM HYDROXIDE	40
03D - Eye Lotion	21645512	ALUMINUM HYDROXIDE	5
03F - Mascara	21645512	ALUMINUM HYDROXIDE	7
03G - Other Eye Makeup Preparations	21645512	ALUMINUM HYDROXIDE	24
07A - Blushers (all types)	21645512	ALUMINUM HYDROXIDE	16
07B - Face Powders	21645512	ALUMINUM HYDROXIDE	40
07C - Foundations	21645512	ALUMINUM HYDROXIDE	133
07D - Leg and Body Paints	21645512	ALUMINUM HYDROXIDE	1
07E - Lipstick	21645512	ALUMINUM HYDROXIDE	154
07F - Makeup Bases	21645512	ALUMINUM HYDROXIDE	13
07G - Rouges	21645512	ALUMINUM HYDROXIDE	24
07H - Makeup Fixatives	21645512	ALUMINUM HYDROXIDE	9
07I - Other Makeup Preparations	21645512	ALUMINUM HYDROXIDE	36
08A - Basecoats and Undercoats	21645512	ALUMINUM HYDROXIDE	2
08E - Nail Polish and Enamel	21645512	ALUMINUM HYDROXIDE	5
09C - Other Oral Hygiene Products	21645512	ALUMINUM HYDROXIDE	1
10A - Bath Soaps and Detergents	21645512	ALUMINUM HYDROXIDE	2
11G - Other Shaving Preparation Products	21645512	ALUMINUM HYDROXIDE	1
12A - Cleansing	21645512	ALUMINUM HYDROXIDE	2
12C - Face and Neck (exc shave)	21645512	ALUMINUM HYDROXIDE	24
12D - Body and Hand (exc shave)	21645512	ALUMINUM HYDROXIDE	1
12F - Moisturizing	21645512	ALUMINUM HYDROXIDE	16
12G - Night	21645512	ALUMINUM HYDROXIDE	2
12I - Skin Fresheners	21645512	ALUMINUM HYDROXIDE	1
12J - Other Skin Care Preps	21645512	ALUMINUM HYDROXIDE	9
13A - Suntan Gels, Creams, and Liquids	21645512	ALUMINUM HYDROXIDE	5
13B - Indoor Tanning Preparations	21645512	ALUMINUM HYDROXIDE	1
			578

Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: May 2, 2013

SUBJECT: Concentration of Use by FDA Product Category: Aluminum Hydroxide, March 2013 Survey

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Concentration of Use by FDA Product Category - Aluminum Hydroxide

FDA Code†	Product Category	Maximum Concentration of Use
03A	Eyebrow pencil	0.51%
03B	Eye liner	0.05-0.6%
03C	Eye shadow	0.78-10.1%
03D	Eye lotion	0.025-0.46%
03F	Mascara	0.009-4%
03G	Other eye makeup preparations	0.02%
05A	Hair conditioners	0.004%
05G	Tonics, dressings and other hair grooming aids	0.016%
06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.1%
07A	Blushers (all types)	0.2-0.9%
07B	Face powders	0.029-1.5%
07C	Foundations	0.02-3%
07E	Lipstick	0.01-7%
07F	Makeup bases	0.0023-2%
07H	Makeup fixatives	0.63%
07I	Other makeup preparations	0.002%
08E	Nail polish and enamel	0.016-1%
09A	Dentifrices (aerosol, liquid, pastes and powders)	0.0022%
09C	Other oral hygiene products	8.8%
12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.009-0.011%
12C	Face and neck products not spray	0.12-4%
12D	Body and hand products not spray	0.2-2%
12F	Moisturizing products	

	not spray	1%
12G	Night products not spray	0.0003-0.014%
12H	Paste masks and mud packs	0.06-0.45%
12J	Other skin care preparations	0.0000008-5%
13A	Suntan products not spray	0.66-0.9%

†Product category codes used by FDA

Information collected in 2013
Table prepared: May 2, 2013

Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 21, 2013

SUBJECT: Comments on the Scientific Literature Review on Alumina and Aluminum Hydroxide as Used in Cosmetics

Key Issues

It is not at all clear why safety data on aluminum (especially studies on Alumina and Aluminum Hydroxide) are not even mentioned in this report. The CIR Expert Panel should be given the opportunity to review the available safety and kinetic data on Alumina and Alumina Hydroxide. At a minimum, this report should mention other reviews of aluminum such as the ATSDR profile on aluminum (found at http://www.atsdr.cdc.gov/ToxProfiles/tp22.pdf), which does include some studies on Aluminum Hydroxide. Information on the potential dermal penetration of aluminum compounds would also be especially helpful. In this case, relying on FDA reviews for other uses does not seem appropriate when there are published safety data available. If the report does not include safety or kinetic studies on aluminum compounds, the report should acknowledge that safety studies on aluminum compounds exist and provide a clearer rational as to why the studies were not included.

Additional Comments

p.2 - In the Non-Cosmetic Use section, it is not correct to call Aluminum Hydroxide an aluminum salt.

p.2 - Please include the use for which FDA considers Aluminum Hydroxide GRAS.

p.2 - In the Color Additives section the statement "(with and without certification for use around the eyes)" is not correct. As stated later in the paragraph, "All lakes are subject to certification." There are a few cosmetic colors that are not subject to certification, but they have nothing to do with Alumina or Aluminum Hydroxide.

p.3 - The Summary states that the following data have been provided to FDA: "acute and long-term biocompatibility testing for cytotoxicity, irritation or intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility". Where are those data? The CIR Expert Panel should review at least some data on the safety of these ingredients.

p.6, Table 4 - The title of Table 4 needs to be corrected as Sodium Aluminate is not included in this report.

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p.6-10, Table 5 - The specifications for the various certified colors are not relevant to a safety review of Alumina and Aluminum Hydroxide. A list of the colors that can used as aluminum lakes would be sufficient. Alumina (a drug color) is not a lake color and should not be included in a table titled: "Code of Federal Regulations concerning Lake colors containing alumina". Aluminum Hydroxide (under drugs) is not a color and should not be included in this table.

p.10-12, Table 6 - There is very little information in this table that is relevant to a safety review of Alumina and Aluminum Hydroxide as they are used in cosmetics. Table 6 is titled "Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide". 21CFR 201.323 does not describe a "regulated use" of Alumina or Aluminum Hydroxide. This CIR citation sets limits on the amount of aluminum that can be in parenteral nutrition. This is the only place in the report that suggests that too much aluminum can be toxic.

p.13, Table 7 - It is not clear why the clinical trials of medical devices containing Alumina are relevant to the safety of these ingredients as used in cosmetics when other studies of Aluminum Hydroxide are not even included in the report.