Safety Assessment of Silicates as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: May 23, 2018
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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Analyst/Writer
Date: May 23, 2018
Subject: Silicate-Related Ingredients Re-Review

Enclosed is the Re-Review of the Safety Assessment of Silicate-Related Ingredients as Used in Cosmetics. (It is identified as *silica06208rep* in the pdf document).

The CIR Final Report on the Safety Assessment of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite was published in 2003. Based on the available data at the time, the Panel concluded that the 17 silicates named in that report are safe for use in cosmetic products. Because it has been 15+ years since this document was published, it is time for a re-review.

In addition to the ingredients that were included in the 2003 review, there are 16 possible "add-ons" that have not yet been looked at by CIR. Further, the related safety assessment on Potassium Silicate, Sodium Metasilicate, and Sodium Silicate was published in 2005. These would be additional ingredients for consideration for inclusion: a re-review of this safety assessment would be due soon. The Panel may also consider adding the ingredients from the 2009 safety assessment on Silica and Related Cosmetic Ingredient. This safety assessment was never published in the *International Journal of Toxicology* and will be due for a re-review in approximately 6 years.

In a cursory review of the literature available on PubMed and SciFinder, minimal new pertinent data was found on the original ingredients and those reviewed in 2005 and 2009. There were no pertinent data on the proposed add-on ingredients that have not been previously reviewed. Because of time constraints, a partial review of certain databases, such as ECHA, was performed, but a full review would be conducted if the Panel decides to re-open the original silicates report to include the proposed add-on ingredients. Most of the data that was included in the re-review did not seem to indicate any new toxicological concerns.

According to 2018 VCRP data, Silica has the most reported uses in cosmetic products, with a total of 8024; the majority of the uses are in leave-on eye makeup preparations and makeup preparations. Kaolin has the second most reported uses in cosmetic products, with a total of 1794; the majority of the uses are also in leave-on eye makeup preparations and makeup preparations. The reported numbers of uses for the remaining ingredients in this report are much lower. The uses for both of these ingredients have greatly increased since the original safety assessments were finalized: in 2009, Silica was reported to have 3276 uses and in 1998, Kaolin was reported to have 509 uses. The results of the concentration of use survey conducted in 2018 by the Council indicate Kaolin has the highest reported maximum concentration of use; it is used at up to 53% in "other" manicuring products and up to 35% in rinse-off "other" skin care preparations (*silica062018data1* and *silica062018data2*). Zeolite is used at up to 37.8% in in paste masks and mud packs and up to 35.7% in hair tonics, dressings and other hair grooming aids. According to the original safety assessments, the maximum use concentration for Kaolin was 100% in leave-on "other" skin care preparations and the maximum use concentration for Hectorite was 100% in rinse-off skin cleansing preparations (the maximum leave-on concentration was 15% in makeup foundations). Silica was reported to be used at up to 44% in eye shadows. Several proposed add-on ingredients have not been surveyed by the Council yet.

The previous reports are attached for your use:

- Final Report on the Safety Assessment of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite (2003) [*silica062018origrep*]
- Final Report on the Safety Assessment of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate (2005) [*silica062018_silicates2005*]

- Final Report on the Safety Assessment of Silica and Related Cosmetic Ingredients (2009) [*silica062018_silica2009*]

Minutes from the original deliberations of the original review, and from the other reports named above, have been included:

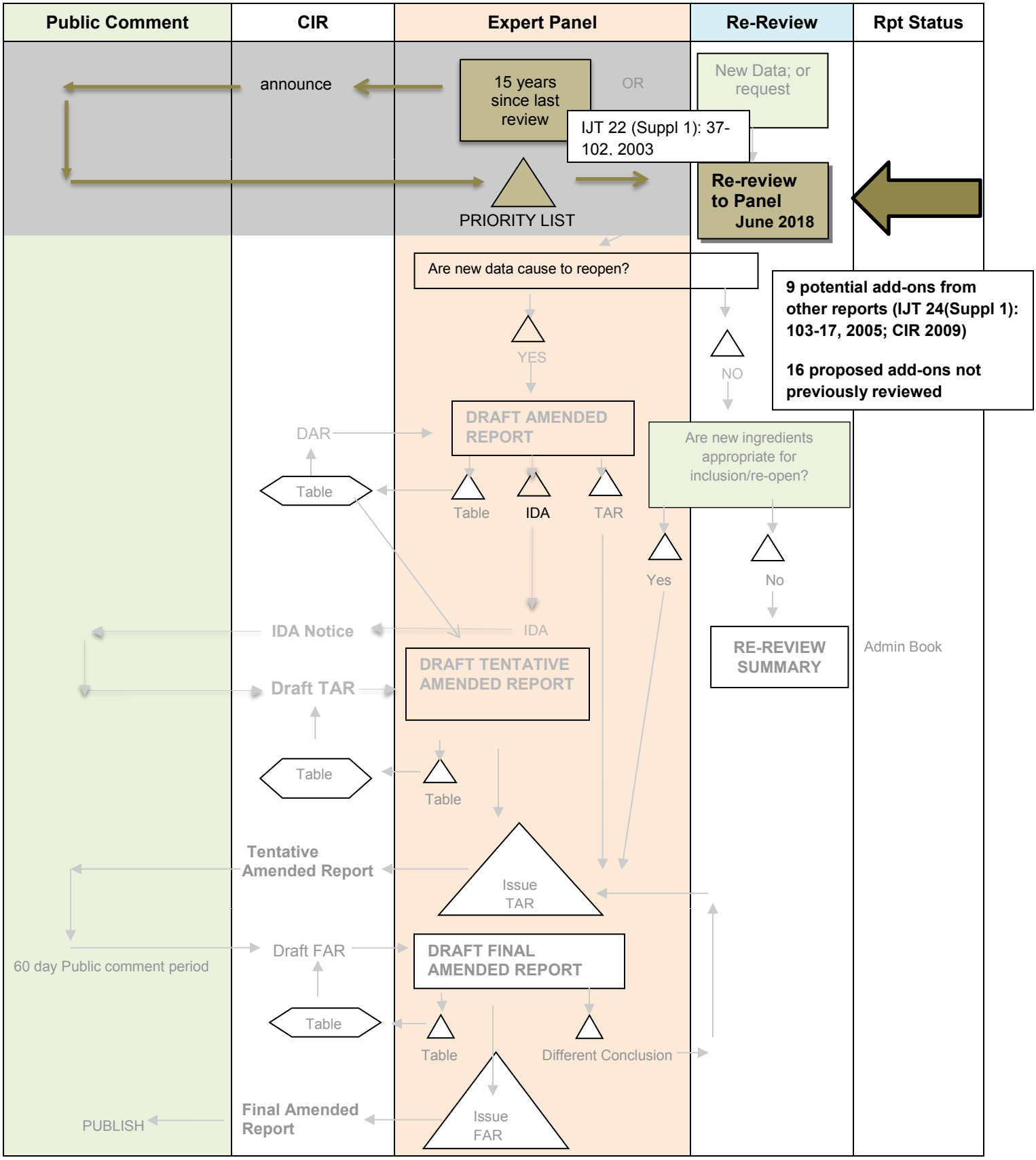
- September 1999 and February 2000 - Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite [*silica062018min1_origsilicates*]
- December 1999, May 2000, December 2000 and June 2001 - Potassium Silicate, Sodium Metasilicate, and Sodium Silicate [*silica062018min2_saltsilicates*]
- June 2009 and September 2009 - Silica and Related Cosmetic Ingredients [*silica062018min3_silica*]

Based on the similarity of the proposed add-on ingredients to those in the original report and on the topics of discussion from the previous deliberations of all of these ingredients, the Panel may want to re-open the original report to include all of the proposed add-on ingredients in one report on Silica and Silicate ingredients.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Silicates

MEETING June 2018



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

Silicates History

2003– The CIR's Final Report on the Safety Assessment of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite in the *IJT* after the report was finalized by the Panel in 2000. Based on the available animal and clinical data available at that time, the Panel concluded that these ingredients are safe as cosmetic ingredients in the practices of use and concentrations as described in the safety assessment.

2005 – The CIR's Final Report on the Safety Assessment of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate in the IJT after the report was finalized by the Panel in 2001. Based on the available animal and clinical data available at that time, the Panel concluded that these ingredients are safe for use in cosmetic products in the practices of use and concentration described in the safety assessment when formulated to avoid irritation.

2009 – The CIR issued a Final Report on the Safety Assessment of Silica and Related Cosmetic Ingredients, which has not been published in the IJT. Based on the available animal and clinical data available at that time, the Panel concluded that Silica, Alumina Magnesium Metasilicate (now called Magnesium Aluminometasilicate), Aluminum Calcium Sodium Silicate, Aluminum Iron Silicates, Hydrated Silica, and Sodium Potassium Aluminum Silicate are safe as cosmetic ingredients in the practices of use and concentrations as described in the safety assessment.

April/May 2018 – Review of the available published literature since 2000 was conducted in accordance to CIR Procedure regarding re-review of ingredients after ~15 years.

Silica and Silicates Data Profile –June 2018 – Writer, Christina Burnett

	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Clinical Studies/Case Reports	Toxicokinetics
Original Report – Aluminum Silicates et. Al																
Aluminum Silicate	X	X	X	X	X				X						X	
Calcium Silicate	X	X			X	X	X	X	X						X	
Magnesium Aluminum Silicate	X	X	X	X	X	X	X	X			X	X	X			
Magnesium Silicate		X				X										
Magnesium Trisilicate		X				X									X	X
Sodium Magnesium Silicate	X	X									X		X			
Zirconium Silicate		X			X								X		X	
Attapulgite	X	X	X	X	X	X	X		X							
Bentonite	X	X	X	X	X	X							X		X	
Fuller's Earth	X			X											X	
Hectorite	X	X		X	X		X				X		X			
Kaolin	X	X	X	X	X	X		X							X	
Lithium Magnesium Silicate																
Lithium Magnesium Sodium Silicate																
Montmorillonite				X	X										X	X
Pyrophyllite																
Zeolite			X	X	X	X	X	X	X				X		X	X
Re-Review – Aluminum Silicates et. al																
Aluminum Silicate	X	X			X		X				X		X			
Calcium Silicate	X	X			X											
Magnesium Aluminum Silicate	X															
Magnesium Silicate	X															
Magnesium Trisilicate	X															
Sodium Magnesium Silicate	X															
Zirconium Silicate																
Attapulgite	X															
Bentonite	X				X										X	

Silica and Silicates Data Profile –June 2018 – Writer, Christina Burnett

	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Clinical Studies/Case Reports	Toxicokinetics
Fuller's Earth	X															
Hectorite	X															
Kaolin	X															
Lithium Magnesium Silicate	X															
Lithium Magnesium Sodium Silicate	X															
Montmorillonite	X					X	X			X					X	
Pyrophyllite																
Zeolite	X				X										X	
Original Report - Previously Reviewed Potential Add-on Ingredients																
Potassium Silicate	X	X	X								X		X			
Sodium Metasilicate	X	X	X		X	X	X				X	X	X		X	
Sodium Silicate	X	X	X	X	X	X	X	X			X	X	X		X	X
Silica		X	X	X	X	X	X	X	X	X	X		X		X	X
Hydrated Silica					X	X	X		X	X	X	X	X		X	X
Aluminum Calcium Sodium Silicate			X		X											
Aluminum Iron Silicates																
Magnesium Aluminometasilicate																
Sodium Potassium Aluminum Silicate			X							X						
Re-Review – Previously Reviewed Potential Add-on Ingredients																
Potassium Silicate		X			X						X		X			
Sodium Metasilicate		X					X				X		X		X	
Sodium Silicate		X			X		X									
Silica																
Hydrated Silica																
Aluminum Calcium Sodium Silicate	X															
Aluminum Iron Silicates																
Magnesium Aluminometasilicate	X															

Silica and Silicates Data Profile –June 2018 – Writer, Christina Burnett

	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Clinical Studies/Case Reports	Toxicokinetics
Sodium Potassium Aluminum Silicate	X															
Re-Review – New Add-on Ingredients																
Activated Clay																
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates																
Aluminum Iron Calcium Magnesium Germanium Silicates																
Aluminum Iron Calcium Magnesium Zirconium Silicates																
Ammonium Silver Zeolite																
Ammonium Silver Zinc Aluminum Silicate	X															
Calcium Magnesium Silicate																
Gold Zeolite																
Silver Copper Zeolite																
Silver Zinc Zeolite																
Sodium Magnesium Aluminum Silicate		X			X											
Sodium Silver Aluminum Silicate																
Titanium Zeolite																
Tromethamine Magnesium Aluminum Silicate																
Zinc Silicate		X					X				X		X			
Zinc Zeolite	X															

"X" indicates that data were available in the category for that ingredient.

Silicates

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Re-Review Ingredients																				
Aluminum Silicate	1327-36-2	√	√	√		CFRs	√	√		√			√		√					
Aluminum Calcium Sodium Silicate	1344-01-1	√	√	√			√	√					√							
Aluminum Iron Silicates		√	√	√			√	√					√							
Attapulgite	12174-11-7; 1337-76-4	√	√	√	IARC 1987	CFRs	√	√		√			√		√					
Bentonite	1302-78-9	√	√	√		CFRs	√	√		√			√		√					
Calcium Silicate	1344-95-2	√	√	√		CFRs	√	TBC		YES			√		√					
Fuller's Earth	8031-18-3	√	√	√			√	√		√			√		√					
Hectorite	12173-47-6; 68084-71-9	√	√	√		CFRs	√	√		√			√		√					
Hydrated Silica	10279-57-9; 112926-00-8; 1343-98-2; 63231-67-4; 7631-86-9	√	√	√		CFRs	√						√							
Kaolin	1332-58-7	√	√	√		CFRs OTC	√	√		√			√		√					
Lithium Magnesium Silicate	37220-90-9	√	√	√			√	√		√			√		√					
Lithium Magnesium Sodium Silicate	53320-86-8	√	√	√			√	TBC		√			√		√					
Magnesium Aluminometasilicate	12408-47-8	√	√	√			√						√							
Magnesium Aluminum Silicate	12199-37-0; 12511-31-8	√	√	√		CFRs OTC	√	TBC		√			√		√					
Magnesium Silicate	1343-88-0	√	√	√		CFRs	√	TBC		√			√		√					
Magnesium Trisilicate	14987-04-3	√	√	√		CFRs OTC	√	√		√			√		√					
Montmorillonite	1318-93-0	√	√	√			√	√		√			√		√					

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Pyrophyllite	11349-10-3; 113349-11-4; 113349-12-5; 12269-78-2; 141040-73-5; 141040-74-6	√	√	√		CFRs	√	√		√			√		√					
Silica	112945-52-5; 60676-86-0; 7631-86-9	√	√	√	IARC?	CFRs	√	TBC					√							
Sodium Magnesium Silicate		√	√	√			√	√		√			√		√					
Sodium Potassium Aluminum Silicate	12736-96-8; 66402-68-4	√	√	√			√	TBC					√I							
Zeolite	1318-02-1	√	√	√	IARC 1997		√	TBC		YES HERA			√		√					
Zirconium Silicate	10101-52-7; 1344-21-4	√	√	√		CFRs	√	√		√			√		√					
Sodium Silicate	1344-09-8	√	√	√		CFRs	√	√		YES			√		√					
Sodium Metasilicate	6834-92-0	√	√	√		CFRs	√	√		YES			√		YES					
Potassium Silicate	1312-76-1	√	√	√		CFRs	√	√		YES			√		√					
Potential Add-ons																				
Sodium Silver Aluminum Silicate		√	√	√			√	√		√			√		√					
Tromethamine Magnesium Aluminum Silicate		√	√	√			√	√		√			√		√					
Activated Clay		√	√	√			√	√		√			√		√					
Ammonium Silver Zinc Aluminum Silicate		√	√	√			√	√		√			√		√					
Ammonium Silver Zeolite		√	√	√			√	√					√							
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates		√	√	√			√	√		√			√		√					

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Aluminum Iron Calcium Magnesium Germanium Silicates		√	√	√			√	√		√			√		√					
Aluminum Iron Calcium Magnesium Zirconium Silicates		√	√	√			√	√		√			√		√					
Calcium Magnesium Silicate	12765-06-9	√	√	√			√	√					√							
Silver Copper Zeolite	130328-19-7; 168042-42-0	√	√	√	IARC?		√	√					√							
Silver Zinc Zeolite	under development	under development	√	√	IARC?		√	√					√							
Sodium Magnesium Aluminum Silicate	12040-43-6	√	√	√			√	√		√			√		√					
Zinc Silicate	13597-65-4	√	√	√			√	√		√			√		√					
Gold Zeolite		√	√	√			√	√		√			√		√					
Zinc Zeolite		√	√	√			√	√		√			√		√					
Titanium Zeolite		√	√	√	IARC?		√	√					√							

TBC = To be completed upon re-opening

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

Total references ordered/downloaded from initial searches = 45 (some relevant hits were duplicates)

Search Strategy: Re-review ingredients limited time frame from 2000-2018, except where noted

PubMed

Re-review ingredients

Aluminum Silicate – 11825 hits, limited with toxicity = 770 hits, limited with irritation = 14 hits (4 relevant), limited with sensitization = 9 (0 relevant), limited with dermal = 20 hits (5 relevant)
Aluminum Calcium Sodium Silicate – 6 hits (0 relevant)
Aluminum Iron Silicates - 281 hits, limited with toxicity = 27 hits, limited with irritation = 0 hits, limited with sensitization = 0 hits, limited with dermal = 0 hits
Attapulgite – 231 hits, limited with toxicity = 13 hits (3 relevant), limited with irritation = 0 hits, limited with sensitization = 0 hits, limited with dermal = 0 hits
Bentonite – 2155 hits, limited with toxicity = 161 hits, limited with irritation = 3 hits (1 revelant), limited with sensitization = 0 hits, limited with dermal = 7 hits (1 relevant)
Calcium Silicate – 1181 hits, limited with toxicity = 79 hits, limited with irritation = 0 hits, limited with sensitization = 0 hits, limited with dermal = 1 hit (0 relevant)
Fuller's Earth – 50 hits (12 relevant)
Hectorite – 89 hits (0 relevant)
Hydrated Silica (limited to 2009-2018) – 12440 hits, limited with toxicity = 1764 hits, limited with irritation = 14 hits (4 relevant), limited with sensitization = 9 hits (0 relevant), limited with dermal = 28 hits (6 relevant)
Kaolin – 1964 hits, limited with toxicity = 160 hits (4 relevant), limited with irritation = 2 hits (0 relevant), limited with sensitization = 17 hits (0 relevant), limited with dermal = 1 hit (0 relevant)
Lithium Magnesium Silicate – 3 hits (0 relevant)
Lithium Magnesium Sodium Silicate – 2 hits (1 relevant)
Magnesium Aluminometasilicate – 24 hits (0 relevant)
Magnesium Aluminum Silicate – 80 hits (1 relevant)
Magnesium Silicate – 776 hits, limited with toxicity = 31 hits (3 relevant), limited with irritation (0 relevant), limited with sensitization = 1 hit (0 relevant), limited with dermal =1 hit (0 relevant)
Magnesium Trisilicate – 198 hits (2 relevant)
Montmorillonite – 3385 hits, limited with toxicity = 214 hits (8 relevant), limited with irritation = 6 hits (1 relevant), limited with sensitization = 0 hits, limited with dermal = 8 hits (1 relevant)
Pyrophyllite – 946 hits, limited with toxicity = 60 hits (0 relevant), limited with irritation = 3 hits (0 relevant), limited with senstitzation = 0 hits, limited with dermal = 0 hits
Silica (limited to 2009-2018) – 47,440 hits, limited with toxicity = 3342 hits, limited with irritation = 30 hits (2 relevant), limited with sensitization = 41 hits (0 relevant), limited with dermal = 84 hits (3 relevant)
Sodium Magnesium Silicate – 66 hits (1 relevant)
Sodium Potassium Aluminum Silicate – 8 hits (0 relevant)
Zeolite – 6699 hits, limited with toxicity = 193 hits (1 relevant), limited with irritation = 4 hits (1 relevant), limited with sensitization = 6 hits (0 relevant), limited with dermal = 5 hits (1 relevant)
Zirconium Silicate – 350 hits (0 relevant)
Sodium Silicate – 338 hits (3 relevant)
Sodium Metasilicate – 84 hits (5 relevant)
Potassium Silicate – 912 hits, limited with toxicity = 25 hits (1 relevant), limited with irritation = 4 hits (0 relevant), limited with sensitization = 0 hits, limited with dermal = 0 hits

Add-on ingredients

Sodium Silver Aluminum Silicate - 18 hits (0 relevant)
Tromethamine Magnesium Aluminum Silicate – 0 hits
Activated Clay – 383 hits (0 relevant)
Ammonium Silver Zinc Aluminum Silicate – 1 hit (0 relevant)

Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates - 2 hits (0 relevant)
Aluminum Iron Calcium Magnesium Germanium Silicates – 0 hits
Aluminum Iron Calcium Magnesium Zirconium Silicates – 0 hits
Sodium Magnesium Aluminum Silicate – 19 hits (0 relevant)
Zinc Silicate - 70 hits (0 relevant)
Ammonium Silver Silcate – 4 hits (0 relevant)
Gold Zeolite - 62 hits (0 relevant)
Zinc Zeolite – 222 hits (0 relevant)

SciFinder: Re-review ingredients limited time from from 2000-2018, except where noted, and to Adverse Effects and English
Re-review ingredients
Aluminum Silicate – 10 hits, 0 relevant (CAS#1335-30-4), 25 hits, 0 relevant (CAS#1327-36-2)
Aluminum Calcium Sodium Silicate (from 2005-2018) – 15 hits, 2 relevant
Aluminum Iron Silicates (from 2005-2018)
Attapulgite – 11 hits, 5 relevant
Bentonite – 119 hits, 7 relevant
Calcium Silicate - 5 hits, 1 relevant (CAS# 10034-77-2), 60 hits, 4 relevant (CAS#1344-95-2)
Fuller's Earth – 13 hits, 0 relevant
Hectorite – 4 hits (CAS# 12173-47-6)
Hydrated Silica (from 2005-2018) - 0 hits (CAS#870616-37-8), 0 hits (CAS#68918-35-4), 1 hit, 1 relevant (CAS#112926-00-8), 18 hits, 0 relevant (CAS#63231-67-4), 2 hits, 0 relevant (CAS#10279-57-9), 54 hits, 1 relevant (CAS#1343-98-2)
Kaolin – 132 hits, 1 relevant
Lithium Magnesium Silicate – 0 hits
Lithium Magnesium Sodium Silicate – 1 hit, 1 relevant
Magnesium Aluminometasilicate – 0 hits
Magnesium Aluminum Silicate – 4 hits, 1 relevant (CAS#1327-43-1), 0 hits (CAS#12511-31-8), 20 hits, 0 relevant (CAS#12199-37-0)
Magnesium Silicate – 11 hits, 1 relevant
Magnesium Trisilicate – 7 hits, 1 relevant
Montmorillonite – 47 hits, 7 relevant
Pyrophyllite – 0 hits (CAS#141040-74-6), 0 hits (CAS#141040-73-5), 0 hits (CAS#13349-12-5), 0 hits (CAS#113349-11-4), 0 hits (CAS#113349-10-3), 0 hits (CAS #12269-78-2)
Silica (from 2005-2018) – 3606 hits, further limited by dermal OR irritation OR sensitization OR cosmetic = 6 hits, 0 relevant;
Sodium Magnesium Silicate – 0 hits
Sodium Potassium Aluminum Silicate (from 2005-2018) – 0 hits
Zeolite – 140 hits, 1 relevant
Zirconium Silicate – 5 hits, 0 relevant (CAS#10101-52-7), 5 hits, 0 relevant (CAS#1344-21-4)
Sodium Silicate – 16 hits, 1 relevant
Sodium Metasilicate – 13hits, 5 relevant
Potassium Silicate – 0 hits (CAS#10006-28-7), 5 hits, 0 relevant (CAS#1312-76-1)

Add-on ingredients
Sodium Silver Aluminum Silicate – 0 hits
Tromethamine Magnesium Aluminum Silicate – 0 hits

Activated Clay- 0 hits
Ammonium Silver Zinc Aluminum Silicate – 0 hits
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates – 0 hits
Aluminum Iron Calcium Magnesium Germanium Silicates – 0 hits
Aluminum Iron Calcium Magnesium Zirconium Silicates - 0 hits
Ammonium Silver Zeolite – 0 hits
Sodium Magnesium Aluminum Silicate – 0 hits
Zinc Silicate – 0 hits (CAS #127734-84-3), 0 hits (CAS#126755-25-7), 0 hits (CAS#13814-85-2), 1 hit, 0 relevant (CAS#13597-65-4) 0 hits (CAS#11126-29-7)
Ammonium Silver Silcate – 0 hits
Gold Zeolite – 0 hits
Calcium Magnesium Silicate – 1 hit, 0 relevant
Silver Copper Zeolite – 0 hits
Silver Zinc Zeolite – 0 hits
Zinc Zeolite – 0 hits
Titanium Zeolite – 0 hits

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Potassium Silicate, Sodium Magnesium Silicate, Sodium Metasilicate, Sodium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite

September 9-10, 1999

Dr. Belsito noted that this group of ingredients consists mostly of clay-like materials, but that salts (i.e., Potassium Silicate, Sodium Metasilicate, Sodium Silicate, and, possibly, Zirconium Silicate) are also included. He also recalled studies indicating that the salts, but not the clays, were irritants, and that his Team recommended that these four salts should be included in a separate report. The Belsito Team also concluded that the remaining ingredients are safe as used in cosmetic products. Dr. Belsito said that his Team will make a decision on specific data requests after the current report has been divided into two separate reports.

Dr. Schroeter said that his Team agreed that the ingredients in this review could be separated into two groups, soluble salts, which may be active (Sodium Metasilicate, Potassium Silicate, and Sodium Silicate) and minerals of solids (or clays) within the same report. He noted that the clays have no absorption and are basically safe, except for the possibility of irritation. Dr. Schroeter also noted that cosmetic use includes sprays and that the issue of inhalation exposure could be addressed in the report discussion as a cautionary item. Furthermore, he said that the irritation potential of clays could be addressed in the report discussion by stating that concentrations in formulation that induce irritation should be avoided.

Dr. Andersen said that according to yesterday's Team discussions, the principal issue concerning the soluble salts relates to irritation. Therefore, he said that if the conclusion on this group of ingredients could reflect the need to formulate so that products are not irritating, then that concern could be eliminated.

Dr. Andersen also said that it may be possible for the Panel to issue a tentative conclusion on this group of ingredients. He recalled that, except for the issue of inhalation exposure to clays, there are no other safety issues and, thus, the clays could be considered safe as used.

Dr. Belsito agreed that a safe as used conclusion could be issued on the clays. He also said that it could be stated in the report discussion that data on the use of clays in aerosolized products are insufficient.

Dr. Shank expressed concern over the possibility of silicosis following inhalation exposure to dust particles.

Dr. McEwen said that silicosis is not a concern because these ingredients are not composed of crystalline silicone. However, he noted that pneumoconiosis may be a concern.

Dr. Andersen noted that crystalline forms do exist.

Dr. Belsito proposed dividing the current document into two reports. One of the reports will contain a safe as used conclusion on the clays and the other report on the salts will be re-reviewed as a separate document. Dr. Belsito speculated that the issue of irritation will be the only safety issue relating to the salts.

The Panel agreed with Dr. Belsito's proposal.

Dr. Schroeter confirmed that the issue of inhalation relating to the clays will be addressed in the report discussion.

The Panel voted unanimously in favor of issuing a Tentative Report with a safe as used conclusion (and appropriate report discussion) on the clays.

The Panel also voted unanimously in favor of incorporating the data on the soluble salts from the current report into a separate document that will be reviewed by the Panel.

Dr. Bergfeld stated that the report on the soluble salts will be reviewed at the next Team meeting.

February 14-15, 2000

Dr. Schroeter stated that a Tentative Report with a safe as used conclusion was issued at the September 9-10, 1999 Panel meeting. He then noted that one of the ingredients included in this review, Magnesium Silicate, had been considered talc, and that FDA informed the Panel that there is a considerable amount of data indicating that talc may have carcinogenic potential and that this issue is being addressed. Dr. Schroeter pointed out that the structure and CAS number of Magnesium Silicate are different from those associated with talc, and that this should be clarified in the CIR report.

Dr. Belsito said that the fact that talc is not one of the ingredients in this review should be stated in the report introduction and discussion, and also noted that talc will be the subject of another review by the CIR Expert Panel. The Panel voted unanimously in favor of issuing a Final Report with a safe as used conclusion on the Aluminum Silicate ingredient family.

Because of the number of ingredients to date for which the issue of particle size (relating to inhalation or aerosol exposure) has been raised, Dr. Bergfeld asked Dr. Belsito to review the caveat relating to particle size that has been included in CIR reports. Dr. Bergfeld informed the Panel that this caveat will be discussed at the upcoming Panel meeting.

Dr. Bergfeld also noted that because it is likely that the Panel will review talc at some point, the Panel's prioritization of this ingredient for review should be considered.

Dr. Belsito added that it is his understanding that FDA has reviewed talc and has not found that the data warrant any immediate action. He said that talc should be added to the CIR Priority List, but should not necessarily be added at the top of the list.

Dr. Bailey said that there are some aspects of talc that would be of interest, more so from the perspective of setting standards or specifications for talc in terms of particle size. He noted that the results of an NTP inhalation study (animals) on talc indicated exposure-related carcinogenic effects that were attributed to particle size. In this study, the particle size of the talc was smaller than that used in cosmetics. Dr. Bailey added that he has not reviewed any comprehensive data that address the particle size of talc that is used in cosmetics (i.e., the particle size distribution). In light of the NTP finding, he also said that in order for one to have a higher level of confidence relative to inhalation exposure, data on particle size distribution (in cosmetics) would be very useful.

Dr. McEwen said that the NTP study results were not linked directly to the talc, but to the overload and a secondary mechanism. He also said that the effects of talc in miners and millers of this chemical have been studied over a period of 50 to 60 years. The magnitude of the lung effects seen in a specific talcosis is basically pneumoconiosis, which can be identified by the crystalline structure in X-rays. Dr. McEwen added that lung cancer has never resulted from exposure to talc itself. However, talc that is mined from asbestiform-containing mineral deposits has been implicated in cancer, specifically, the asbestiform particulate. According to Dr. McEwen, the specification for cosmetic grade talc indicates that it contains no asbestiform particulate.

Dr. Bailey wanted to know the extent of industry compliance with the CTFA specification for cosmetic grade talc. He said that it would be nice to have some assurance that the standard is being implemented.

Dr. McEwen said that relevant sampling would have to be done in order to insure this.

Dr. Bailey said that the Expert Panel could request these data, and that the Panel's efforts may be more successful than those of FDA.

Dr. Bailey also said that another issue relates to perineal use of talc and ovarian cancer, and that, based on the available data, FDA has not arrived at any conclusion relative to this issue.

Dr. Bergfeld said that information relating to particle size will be retrieved from CIR reports for review. She noted that the Panel has been faced with issues relating to aerosol exposure to cosmetic ingredients, and that previous statements regarding particle size need to be captured for future use in safety assessments.

Potassium Silicate, Sodium Metasilicate, and Sodium Silicate

December 20-21, 1999
Dr. Schroeter recalled that at the September 9-10, 1999 Panel meeting, these three silicate salts were removed from the CIR report on these ingredients and Silicate Minerals and Clays.

The Panel issued the following informal data request:

(1) Physical and chemical properties, including octanol/water partition coefficient and impurities data
(2) UV absorption (while these ingredients are not expected to have significant UV absorption, the Panel believes the report would be improved if these data were available rather than assumed)
(3) Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures; and, if these data are suggestive, reproductive and developmental toxicity data may be needed
(4) Dermal irritation and sensitization (what is the highest non-irritating dose?)
(5) Mammalian genotoxicity data
(6) Ocular irritation, if available; with the view of establishing the highest non- irritating dose

May 18-19, 2000
Dr. Schroeter noted that no response to the following informal data request issued at the December 20-21, 1999 Panel meeting was received:

(1) Physical and chemical properties, including octanol/water partition coefficient and impurities data
(2) UV absorption (while these ingredients are not expected to have significant UV absorption, the Panel believes the report would be improved if these data were available rather than assumed)
(3) Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures; and, if these data are suggestive, reproductive and developmental toxicity data may be needed
(4) Dermal irritation and sensitization (what is the highest non-irritating dose?)
(5) Mammalian genotoxicity data
(6) Ocular irritation, if available; with the view of establishing the highest non-irritating dose

He also stated that his Team determined that item 6 above is unnecessary and should be deleted from the list of data requests.

Dr. Schroeter also noted that the hypersensitivity test on Sodium Metasilicate that is being conducted by the National Toxicology Program study is nearing completion and that the preliminary data appear to be negative.

Concerning item 5 above, Dr. Belsito noted that the Panel has negative Ames test data on the silicate, but no test data on the metasilicate. Thus, the Belsito Team determined that Ames test data on the metasilicate and mammalian genotoxicity data on the silicate and metasilicate are needed.

Dr. Slaga recalled that Ames mutagenicity test data on Sodium Silicate are included in the CIR report.

Dr. McEwen did not see the need for another non-mammalian mutagenicity assay, considering that assays of this type are included in the report.

Dr. Klaassen noted that bacterial mutagenicity data on Sodium Metasilicate are not included in the CIR report and need to be requested.

Dr. McEwen said that based on the negative Ames test data on Sodium Silicate, it is expected that the other two ingredients also are not mutagenic. He did not see the need for additional mutagenicity tests on either of the three ingredients.

Dr. Belsito noted that his Team did not mention specific ingredients in any of the other data requests and asked whether this should be done because of differences in chemical structure.

Dr. Slaga noted that the three chemicals in this review are very similar and it is possible that data on one chemical may be used to evaluate the safety of another.

The Panel voted unanimously in favor of issuing an insufficient data announcement with the following data requests:

(1) Physical and chemical properties, including the octanol/water partition coefficient and impurities data
(2) Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures; and if these data are suggestive, reproductive and developmental toxicity data may be needed
(3) Human dermal irritation and sensitization (specifically, the Panel wants to know the highest non-irritating dose)
(4) Two genotoxicity studies for Sodium Metasilicate, one of which should be in a mammalian system; and one mammalian genotoxicity study for either Potassium or Sodium Silicate
(5) Ocular irritation data, if available (again with the view of establishing a non-irritating dose)

December 4-5, 2000

At the May 18-19, 2000 Panel meeting, the Panel voted unanimously in favor of issuing an insufficient data announcement with the following data requests:

(1) Physical and chemical properties, including the octanol/water partition coefficient and impurities data
(2) Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures; and if these data are suggestive, reproductive and developmental toxicity data may be needed
(3) Human dermal irritation and sensitization (specifically, the Panel wants to know the highest non-irritating dose)
(4) Two genotoxicity studies for Sodium Metasilicate, one of which should be in a mammalian system, and one mammalian genotoxicity study for either Potassium or Sodium Silicate
(5) Ocular irritation data, if available (again, with the view of establishing a non-irritating dose)

Dr. Schroeter stated that unpublished data from industry were received in response to the preceding announcement and that the Panel also received additional published studies. He then noted that his Team concluded that the available data on Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are no longer insufficient for the following reasons, addressing each item on the list of data requests:

(1) Data on chemical and physical properties (Item 1) are available and further information is not needed. The octanol/water partition coefficient (Item 1) is not needed because these ingredients are probably poorly absorbed through the skin.
(2) Item 2 above is not needed because there was no evidence of developmental toxicity and these ingredients are probably poorly absorbed through the skin.
(3) Item 3 is not needed. Irritancy may be a problem, but appropriate formulations should decrease the likelihood of skin irritation.
(4) Item 4 is not needed. On the basis of limited skin absorption, mutagenicity and genotoxicity data are not necessary.
(5) Item 5 is not needed. Ocular irritation may be avoided by formulation in rinse-off products to create a non-irritating product. Leave-on product cautionary statements may also be developed.

Dr. Schroeter said that, based on the preceding comments, the reasons why the data originally requested are no longer needed should be stated in the report discussion.

Dr. Belsito noted that Sodium Silicate is used in skin cleansing products, which include cleansing lotions, liquids, and pads (which may be considered rinse-off products) and cold creams (which may be considered leave-on products). He also noted that Sodium Silicate is used in skin cleansing products at concentrations up to 10.0%, and that any leave-on product containing 10.0% Sodium Silicate may be irritating to the skin. Dr. Belsito added that a safe as used conclusion for ingredient use at this concentration in a cold cream would probably be inappropriate, given the uncertainty as to whether or not the skin cleansing cold creams are classified as leave-on products.

The possibility of concentration limits for Sodium Silicate (up to 4.0%, based on available data) as well as Sodium Metasilicate in leave-on products was also mentioned, taking into consideration that Sodium Metasilicate has a different type of irritation potential when compared to Sodium Silicate. Dr. Belsito said that a concentration limit for Sodium Metasilicate needs to be determined.

Dr. Shank noted that Sodium Metasilicate is used only in rinse-off products.

Dr. Schroeter said that the irritation potential of Sodium Silicate should be addressed by indicating in the report discussion that products containing this ingredient should be formulated to avoid skin irritation. He did not feel that a concentration limit should be established for this ingredient.

Dr. Belsito agreed that Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are safe as used in cosmetic products when formulated to avoid skin irritation, and proposed this statement for the report conclusion.
The Panel voted unanimously in favor of issuing a Tentative Report with the following conclusion: Based on the animal and clinical data included in this report, the CIR Expert Panel concludes that Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are safe as used in cosmetic products when formulated to avoid skin irritation.

June 4-5, 2001
Dr. Schroeter recalled that a Tentative Report with the following conclusion was issued at the December 4-5, 2000 Panel meeting: The CIR Expert Panel concludes that Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are safe as used in cosmetic products when formulated to avoid skin irritation.

Dr. Schroeter also noted that unpublished data (clinical skin irritation studies on Sodium Silicate and Sodium Metasilicate) considered by the Panel at its December 2000 meeting have been incorporated into the report text, and that these data do not warrant any change in the Panel's tentative conclusion.

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: Based on the available data contained within this report, the CIR Expert Panel concluded that Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are safe when formulated to avoid irritation in cosmetic formulations.

Silica and Silicates

June 29-30, 2009

Presentation:

DR. ANDERSEN: The next item on the agenda is to hear from the folks from SASSI which is the Synthetic Amorphous Silica and Silicate Industry Association. Dave Pavlich is the association manager and has a PowerPoint presentation for us. There are limited numbers of copies, but certainly enough for the panel to look at. The rest of you can take notes on what Dave is saying. We're going to try and get this up onto the screen. Dave, take a deep breath and let's see what we can do.

MR. PAVLICH: As for the acronym, when I reserved the domain name I thought for sure I'd get some interesting calls from people to buy it, but that didn't happen. I'm also sure that there are people who go to that website and they're disappointed by what they found, and amorphous silica is probably not what they had intended to see.

The Synthetic Amorphous Silica and Silicate Industry Association is an association that has been around for a number of years but was actually incorporated and formed in July 2007. The eight founding companies that are listed here, J.M. Huber, Evonik, Wacker Chemical, Cabot Corporation, Rhodia, PPG Industries, PQ Corp. and W.R. Grace, you may or may not recognize them as being the major global producers of synthetic amorphous silica, but they are. We are also associated with a group that's a subgroup called the Amorphous Silica and Silicate Producers, so we've done some work with them in doing research, that's a group that we're associated with and we meet with them every year. I'm also here with two other representatives from SASSI companies, Dr. Jim Hathaway from Rhodia, and Dr. Gregg Daum from W.R. Grace. Dr. Hathaway is going to come up here in a little bit and go through some of the details of our comments, but at this point I'll give an introduction of why we're here.

The basic reason is that the circumstance of CIR's review of silica fits our mission particularly well, and our association's mission is to further the understanding of synthetic amorphous silica and silicate health and safety within the industry, to monitor the regulation of synthetic amorphous silica and silicates by government, to educate the public and government on the views of the industry, and to consult and cooperate with state officials and state agencies on matters having industry-wide significance, and I would add other groups like CIR. That's our purpose here.

We'd like to thank Dr. Andersen for working with us. He did attend our spring meeting in March and gave us an overview of the CIR process for reviewing silica, and then gave us the opportunity to review the March 25 scientific literature review. We did send comments in on May 12 on that review and a number of those were incorporated into the latest version of the scientific literature review, but there were a number of things that we felt were not addressed, and those are the comments that we're going to make today. I'll highlight here seven issues that we'd like to address, and then I'll introduce Dr. Hathaway to go through those in detail.

First of all, obviously a reason for our existence is to differentiate synthetic amorphous silica from other forms of silica. In the SLR we definitely feel that there is a need to have fair and accurate differentiation of SAS from other forms of silica. Also the SLR we feel needed to focus more on just synthetic amorphous silica since that's the form used in cosmetics and limit the discussion in reference to other forms of silica. This is a document that's published and is going to be available, and obviously SASSI members are concerned about misinterpretation of information.

Similarly, there are a number of manufacturing processes that are mentioned in the summary that are not contemporary and do not reflect the processes that are used for commercial manufacturing of synthetic amorphous silica, and we feel that there is too much emphasis on those noncommercial processes and the composition of the materials from those processes. Along the same lines, those references also give some information about the impurity levels which we feel incorrectly represent synthetic amorphous silica. In the toxicological studies that are referenced, there are a number of factors that Dr. Hathaway will emphasize that are important in interpreting the judging the applicability of the studies on synthetic amorphous silica. The bibliography of the SLR is very lengthy. We feel that it's relatively comprehensive but that because of the number of studies that are referenced that there is little effort to identify the more current information that's available and to emphasize the importance of that data. Finally, we were relatively surprised that in the summary, the information quoted was there were 3,276 products that contain synthetic amorphous silica and the only specific reference was to hair spray with little identification of other

cosmetic products of routes of exposure that are suspected for those products. I'll now introduce Dr. Hathaway to go through those comments in detail. Thank you.

DR. HATHAWAY: I appreciate the opportunity to provide additional comments to the CIR expert panel. I think the thing that we're most concerned about is having a very clear and accurate differentiation from synthetic amorphous silica and other forms of silica particularly crystalline silica or products that contain crystalline silica.

Unfortunately, there's a tremendous amount of confusion between these that is occurring all the time. Just a couple of years ago the insurance carriers for all of the member companies wanted to have an exclusion against any product liability for silica. Part of the problem is there's one cast number for all forms of silica and a lot of people don't understand the difference. Companies had to have extensive discussions with their insurance carriers. Once they understood the difference they limited it to crystalline silica, but to the extent that the document which will be available publicly has some confusion in it, we'd very much appreciate it if those things could be corrected so that we don't get something else out there that misinforms or confuses the public.

Instead of using the term silica, we would prefer that every time that you're referring to synthetic amorphous silica, that either that full term be used or that it be abbreviated SAS and be very clear that the abbreviation stands for synthetic amorphous silica.

Also the document contains a lot of references to the other forms of silica which I don't think adds anything of benefit to the review, and we would prefer that you have something that I'll show you in a couple more slides, a very limited discussion of the other forms of silica, and then following that strictly limiting the rest of it to synthetic amorphous silica.

Hopefully you can read it a little bit better in the document that you have. There are some things here that are not quite as clear as I had hoped they would be. If you look right here, that's the form of amorphous silica, it's called fused silica. It's essentially made by melting crystalline silica to a molten form. You form a kind of glass. In the document this was listed as if it were the major form of production of synthetic amorphous silica. I guess it's a synthetic amorphous silica, but it's not what goes into cosmetics. It would be a hunk of glass and it's not ground up and put into synthetic amorphous silica at all.

Over here in this group here, that's natural diatomaceous earth from diatoms. In nature it contains about 2 to 3 percent crystalline silica and the rest is amorphous silica. The ones that are further down that list are calcined, and when you calcine diatomaceous earth, a lot of this is used as a filter aid for filtering various products in their manufacturing processes, you form up to 70 percent crystalline silica. There are a lot of problems with the epidemiology studies that are talking about amorphous silica because in some cases they found cases of silicosis, but these are ones where there was exposure to the calcine diatomaceous earth which is up to 70 crystalline silica, and so it's very important to make a very clear distinction between what we're calling synthetic amorphous silica and these other forms that can actually contain crystalline silica themselves.

Right here, this particular area is what we think should be the focus of the document. These are the synthetic amorphous silicas that would be used in cosmetics. There are two essential processes here. One is the way process that produces precipitated silica and also silica gel, and the other one is a thermal process that produces pyrogenic silica. Unfortunately, the historic name for pyrogenic silica was fumed silica and this has the potential for tremendous confusion. Let me just show you. Over there there's a thing called silica fume. It sounds a lot like fumed silica. Unfortunately, silica fume contains crystalline silica. I think the person who drafted the document had some confusion between these two and we would of course like that cleared up as well and we would strongly prefer that the thermal process, synthetic amorphous silica, always be called pyrogenic to help avoid this confusion in terms of terminology.

As I mentioned before on that fused silica where they essentially melt crystalline silica, this is really not a commercial process that's used in anything that goes into there. It would probably be best that it be taken out of the document. You can show the kind of table that we presented in the previous slide and then after that limit the discussion to the true synthetic amorphous silicas that are used in cosmetics.

I think I've pretty much discussed both of these things already, the confusion with heating the crystalline silica to form a type of glass, and the confusion between silica fume and pyrogenic silica.

In some of the discussion of pyrogenic silica which in the document is referred to as fumed silica, they have a reference saying that it may contain up to 6 to 8 percent crystalline silica. We're pretty sure that was confusion with silica fume. Then it follows immediately after that reference with a reference from Cabot saying that their stuff is 99.8 percent pure as if there's maybe some discrepancy in which one do you want to believe. The pyrogenic silica from Cabot Corporation is indeed 99.8 percent, and any of the producers of the pyrogenic form have a very high level of purity. The precipitated silica is less pure mostly because it contains a certain amount of water and the pyrogenic is very dry. It appears to call into question the claims about Cabot Corporation about the purity and we think the way these things are juxtaposed they are potentially very misleading to reader.

In terms of the toxicology studies, I think the ones that discuss oral toxicity and dermal toxicity are pretty much fine. This is a compound that is considered safe to use in food products. In terms of skin exposure there is very little in the way of issues. Synthetic amorphous silica can absorb water, so if you put the powder directly on your skin it may cause some drying of the skin and some irritation. I don't imagine that this would be an issue the way it's used as ingredients within cosmetics, however. It could be an issue in the workplace. But there is a very key thing when we're considering inhalation or intratracheal injection studies. One of the things that creates an anomaly here is that these products as they're produced are about 100 microns in diameter and for some applications they are milled down into the maybe the 10 or 20 micron range, and that's actually a relatively smaller percentage of the total. Most of the material is actually in 100 micron range or at least about 30 or 40 microns in diameter as it would be used in most cosmetic ingredients. But if you're going to do an inhalation study and you have material that's big, anything above 10 microns is not going to get down into the lungs. So the various groups like OECD that do the toxicology protocols require that these things be broken up into something that averages 4 microns in diameter, and indeed all of the toxicology studies have had to do this in order to comply with these protocols. So you get an artificial situation where this material can now be inhaled or it can be injected down into the trachea. What happens when this is done is you have the smaller particles that have a higher surface area and although synthetic amorphous silica if you look up some of the references on solubility, they will say it's insoluble; everything is relative. Crystalline silica for example is pretty much insoluble. Synthetic amorphous silica is relatively insoluble. As you get to a larger surface area for the mass of material, you do get some of this material dissolved and it dissolves to form silicic acid. If you do break up these particles either by dispersion or by milling or by whatever means and you have an inhalation toxicology study, you're going to get some silicic formed on the alveoli of the experimental animals and you're going to get some corrosive effects from the acidic silicic acid. This is not something that you would see from even inhalation of cosmetic products or from the manufacture of these things in the protocols that workers might be exposed to during the manufacturing process because they're just not respirable in the form that they're being used. In a sense it's almost an artificial situation, and they do cause inhalation toxicity if they are broken up to those smaller sizes. One of the interesting things is though that because they are somewhat soluble under these circumstances, there are a number of clearance studies that show that this material is completely cleared from the lungs and that the reason that the studies don't find fibrosis that you would find with crystalline silica. It's something that we would recommend that before they go into the animal inhalation studies that they talk about this particle size and the fact that it's an artificial situation with all of the inhalation and intratracheal toxicology studies that were done and that you would not see this with the larger particles that are used commercially.

As Dave mentioned, the review covers an enormous number of studies. Unfortunately, there's not a lot of I guess what you'd call interpretation of weighing of which of the studies are most significant. We would like to see a little bit more of this done and perhaps more emphasis be given to some of the newer or more credible studies rather than just simply listing them all and leaving it up to the reader to try to judge which ones are most important. Most of the older inhalation toxicity studies did not discuss this particle size difference in terms of the materials being dispersed or milled down to a small particle size, that's unfortunate, and so the abstracts don't discuss that at all, but the reader is going to wonder which ones of these are really the correct situation. If you want, we would be willing to go and try to give some assistance here in terms of pointing out what we think are the more reliable and credible studies.

As Dave mentioned, we were surprised that there wasn't more discussion of the actual applications in cosmetics. That really is not a big issue with us, but it's something that you might want to consider in terms of improving the document. Here we have the spelling of our names and our website and so forth.

I'd be happy to address any questions that any of the panel members have.

DR. SLAGA: Just to have it straight, the 100 percent that is supplied to the cosmetic industry is between 10 and 100 microns?

DR. HATHAWAY: Correct.

DR. SLAGA: And only in some of the studies did an inhalation was it at 4 micron?

DR. HATHAWAY: Correct. They either break it up and disperse it some form or mill it down to that smaller diameter so it can get in there. In fact, in order to comply with the testing protocols they have to do this even though it's not representative of the material that would be involved in worker exposure or consumer exposure.

DR. LIEBLER: I appreciate the silica family tree that you provided us. I think it's helpful in organizing our thinking about this. I have two questions that relate to this. One is are there any sort of milestone dates in terms of synthetic amorphous silica manufacturing processes that would be useful in helping us interpret some of the older literature? In other words, in the 1970s or 1980s or sometime were there any changes in manufacturing processes that yielded the materials that are used in cosmetics now?

DR. HATHAWAY: I'm going to go out on a limb and make some guesses. I'm thinking that these processes probably were introduced in the 1950s or earlier. There is certainly much more production now than there was in that timeframe. But many of these articles that are from the 1950s to the 1970s still are talking about older processes and maybe there was some use of this glass that was formed from melting crystalline silica and I'm not sure what it would be today. I think a relatively small amount of these materials go into the cosmetic field. I know of the stuff that our company produces probably 80 percent goes into tires to reduce rolling friction and most of the other 20 percent goes into toothpaste, so relatively small amounts go into the cosmetic industry, but it's probably widely used in a lot of products.

DR. LIEBLER: It doesn't sound like there's a clear dividing line of any sort in the manufacturing process that would be helpful to us.

DR. HATHAWAY: Unfortunately not, but I would say the studies that would have dates after 1990 certainly would be probably more credible than ones that had dates before that.

DR. LIEBLER: I have one other question. What is the analytical method that's used to determine the content of crystalline silica in a background of synthetic amorphous silica?

DR. HATHAWAY: Usually this would be a microscopic thing. I was recently at our plant that manufactures this and even though we expected to find no crystalline silica, we went ahead and had some industrial hygiene sampling done at the site to reassure our own employees, and they do a microscopic analysis for the three forms of crystalline silica and they found nondetectable levels at extremely low levels, whereas when they measured total particulates which would include the larger particles, indeed there was a certain amount of dust exposure during the manufacturing process.

DR. LIEBLER: So the analytical methodology then probably would have been the same for a long time if you say it's microscopic evaluation?

DR. HATHAWAY: I believe so, yes.

DR. LIEBLER: So you're counting particles in microscopic fields. Right?

DR. HATHAWAY: I believe so, yes.

DR. BELSITO: As you may or may not be aware, and I guess that's my question, we're already issued two prior reports on silicates and this is the third to capture all of the ingredients that we failed to capture before. Did you have the opportunity to review those two prior published reports?

DR. HATHAWAY: This would have been before the one that came out in March?

DR. BELSITO: Yes. This is before this SLR.

DR. HATHAWAY: I don't think we were aware of that. Dave, were you aware of anything?

MR. PAVLICH: No, we haven't seen that.

DR. MARKS: In the manufacturing of the cosmetics, are there any physical changes that would occur as with a natural amorphous silica where there would be more crystalline silica produced in the end product or the use?

DR. HATHAWAY: I'm not familiar with how they're done in cosmetics. I would assume these are simply blendings, and unless you have a process that introduces very high heat, I don't believe you'd form any crystalline silica.

DR. HILL: I want to get clarification in that regard. So if they were truly amorphous rather than crystalline and they were inhaled because it was in some powdered product or some spray, what we would expect is dissolution to silicic acid and the lung is able to clear that and you'd probably talking about small amounts where there wouldn't be a toxicity issue. Is that what I heard you to say?

DR. HATHAWAY: I have a hard time imagining very much is going to be inhaled from any cosmetic use.

DR. HILL: Clearly not toothpaste.

DR. HATHAWAY: But even hair spray I have a hard time imagining.

DR. HILL: Because of the particles produced by the spray.

DR. HATHAWAY: There was one reference in the review that talked about hair spray and I believe that they said that the particles were in the 30 to 50 micron range for that particular product which is way above the respirable size and I would imagine that the proportion that might be below 10 would be very, very small. Most of the things that we've looked at have been at least 99 percent above 10 in terms of total mass of the dust. So these the amount of fines that might be below 10 is going to be below 1 percent and I would suspect considerably below 1 percent.

DR. HILL: And what is produced under those circumstances you're telling us that the lungs should be able to clear?

DR. HATHAWAY: Even when they used very large amounts of the dispersed material, this clears in the lungs. I think the half-life is less than 30 days even with a significant amount. Between SASSI and ASAP, the European equivalent of ours, we've done these dissolution studies to demonstrate this. There is also a study of three German manufacturing for synthetic amorphous silica in terms of epidemiology studies where they're looking both at pulmonary function and chest X-rays and I believe this is in the process of being written up for publication and they've found no evidence of any fibrosis.

DR. MARKS: There was one reference in which Epstein in the early 1960s injected colloidal silica subcutaneously and developed granuloma formation. Is this an example where we don't really know what was in that colloidal silica that was not synthetic amorphous silica?

DR. HATHAWAY: I'm really not sure. Colloidal sounds like it would probably be amorphous, but I have a hard time knowing. I'm not familiar with that particular article.

DR. MARKS: Can you comment about granuloma formation?

DR. HATHAWAY: There are an awful lot of things that can cause granulomas. If you implant a diamond in a rat you're going to get granulomas forming. I'm not sure it's directly related to any kind of an inhalation type of toxicity or exposure to the exterior of the skin. There are lots of things just because of their geometric shape and so forth

will cause granulomas in experimental animals especially rats. When I was in the Army and we were looking at issues with the safety of Kevlar for bulletproof vests, they implanted some Kevlar in the rats and you form granulomas around them.

DR. MARKS: I was thinking more in terms of application to damaged skin.

DR. SNYDER: Related to slide 7, the reliability of the studies, do you have additional data that you could provide us that are not in the reports?

DR. HATHAWAY: We provided two documents that are relatively recent and I think pretty thorough reviews of the issue. One of these is called the Jack Report that was produced in Europe. It's a very, very large document. Then we recently produced another document that I think is around 50 pages long that's maybe a condensed summary of a lot of that information and we did this as a voluntary effort with the Environmental Protection Agency because they're concerned about nanoparticle issues. In the manufacturing process, you start off with nanosized amorphous silica and it forms aggregates and then agglomerates to get up to the 100 micron size so the primary particles are nanosized and this was the reason that we provided that summary. It's a shorter summary but I think it covers the manufacturing processes very well. There are pretty good summaries on the epidemiology and the toxicology studies. It also talks about the bonding of the agglomerates. These things do not break up under normal circumstances. You have to go to pretty significant mechanical forces to get these things to break up into smaller particles. Thank you very much.

Belsito's Team Meeting:

DR. BELSITO: Okay, Silica and Silicates. Now, folks, we've really got to concentrate on this because the Marks Group report's in public session, and we got to get ready to attack them.

Okay, so this is -- we got some pages here, information that was not in the book, unpublished data, and basically it was two human studies, 27 individuals each, exposed to 17 percent concentration of hydrated silica with negative sensitization.

And then we got a guinea pig sensitization study on hydrated silica -- the shortest study I've ever seen, or at least the shortest summary -- and this was 10 percent in distilled water with a challenge that induction from 1 to 20 percent, and that was on 10 animals, and that was negative.

And then we got a summary from the FDA on line just lots of data that I didn't think had added anything to the report.

And then we had a rather SASSI talk this morning, so hopefully you've heard more than you need to hear already today on silicates.

And so the question here is, what are we -- where are we going with this? And I thought probably, you know, safe as used, I sort of did agree with the comments this morning that we need to be very careful about the amorphous silica because I got like really confused reading the document as to where we're going.

And I guess the other questions I have are, how do we handle these prior reports from 2003 and 2005? Do we want to lump them now? Do we want to wait till 2018 when the first 2003 report comes up for re-review, and then lump them all together? Or where do we go with those? And table 10 was missing from my document.

SPEAKER: (off mike)

DR. BELSITO: Table 12 was where -- table 12 continued was where Table 10 was supposed to be, so --

MS. BECKER: Right. So table 12 continues -- started a page early.

B - SPEAKER: Microphone.

DR. BELSITO: Oh, so table 12 on page 78 is really table 10.

MS. BECKER: Correct.

DR. BELSITO: And table 12 continued belongs after belongs after table 12? Okay. Or is table 12 continued -- really Table 10? Which one is table --

SPEAKER: The first table 12 continued on page 78, the table --(off mike).

DR. BELSITO: Oh. So it's really not table 12 continued. Oh, okay, good. Well, that helped me out there. (Inaudible chatter) I thought I was Hebrew reading from right to left.

Okay, those are my comments. Curt and Paul?

DR. SNYDER: So all of that data, that other data has been added in?

MS. BECKER: Everything's in.

DR. SNYDER: That's everything?

MS. BECKER: That I have except for what just this little bit you got handed.

DR. LIEBLER: I would quite agree with the revision suggested in the staff, the presentation this morning, on clarifying the definition of the form to use and minimizing the emphasis on crystalline silica.

DR. BERGFELD: Minimizing or deleting?

DR. LIEBLER: Excuse me?

DR. BERGFELD: Minimizing or deleting.

DR. LIEBLER: Minimizing.

DR. BERGFELD: Do you think leaving it in leads to confusion?

DR. LIEBLER: No, I -- well, I got the impression that it's good to know that what is being discussed is not crystalline silica.

DR. BERGFELD: That will be really a very great delete.

DR. LIEBLER: Very brief, right, minimizing.

DR. BELSITO: And probably just summarizing that a) we're not talking about crystalline silica, and so that means things in the nature of silicosis, pneumoconiosis, those types of issues that people associate with silica are going away.

DR. LIEBLER: Exactly. But if you don't mention that, if you don't mention it's not crystalline silica, then people are going to get confused and asked why you're ignoring all that stuff.

DR. BERGFELD: But there are a lot of citations here that --(off mike).

DR. LIEBLER: Yeah. And I guess I had a question, in the older literature where it may not have been clear what form of silica was actually used in some of these older studies, and what effects are valuated? Should those studies be included?

That's why I asked the question this morning, was there any milestone or change in manufacturing process that would have sort of invalidated earlier studies, because the material that was tested was no longer applicable to current cosmetic use. And it sounds like it's not that straightforward.

But where it's not clear that the material study was the material that is used in current cosmetic use, I think that stuff should be deleted.

MS. BECKER: Whenever I was unclear on whether it's crystalline or amorphous, I left it out. I only did thinks I could definitely say were amorphous from the test to this paper.

DR. BERGFELD: You have the fume silica. Fume silica, that would be one of --

MS. BECKER: If they called it fumed silica. If it says silica fume, I never saw that.

DR. BERGFELD: Okay, but --

MS. BECKER: But I saw fumed silica.

DR. SNYDER: That's all the tox data, is fumed siliar.

DR. BERGFELD: But that's different from the crystalline form, then.

MS. BECKER: I guess.

DR. BAILEY: I would recommend taking from the presentation this morning that in some detail the characterization and definition and so forth, and put that into the appropriate part of this report, because there is a huge amount of confusion. And your assessment will be for the synthetic amorphous silica. And I think you need to, in the discussion, strongly make that distinction and separate from the crystalline silica, because this is an area where there's so much confusion, and the terms used and, you know, questions about silicosis and, you know, being related to silicos used in cosmetics. That really needs to be clarified.

And your expectations need to be clarified that we're talking about, you know, that we're talking about the, you know, synthetic amorphous silica in the process.

DR. BELSITO: Right. But as Paul pointed out, you know, a lot of the studies, and I guess what really threw, you know, a monkey wrench into -- and again I think it's safe as used -- but I mean I think you want to present the correct data and not incorrect data that you have to argue against: Was the fumed silica versus silica fumed, and one is actually crystalline and not amorphous, and the other is amorphous.

DR. BAILEY: Right. Right, exactly.

DR. BELSITO: And so when we're referring a lot of the studies in here is a fumed silica which -- is that silica fumed or fumed silica? Is it amorphous, or is it crystalline?

And, you know, I don't -- you know, based upon that, I don't know how to proceed with this. Should we --

DR. HATHAWAY: Can I make a --

DR. BELSITO: Yeah. (Chatter -- inaudible)

DR. HATHAWAY: Unfortunately, there's different categories of amorphous silica. What's used in the cosmetics are synthetic amorphous silica, and there is the two processes, you know, the wet and the thermal that was described. There is also a whole bunch of other things that are called amorphous silica that typically contain a certain amount of crystalline silica. And so that adds to additional confusion. You have the diatomaceousers which contain a little bit to start with.

When they're calcine they contain a lot. And then you have on the other side of the other amorphous ones is silica fume, which is usually called an amorphous silica, but it contains a certain amount of crystalline silica.

So it presents a potential point of confusion, and we offered to work with -- I forget your name --

MS. BECKER: Lillian.

DR. HATHAWAY: Lillian -- you know, to try to come up with some, you know, perhaps a better way of presenting the characterization of the material, you know, early on in the report.

DR. SNYDER: I think that's a good idea.

DR. BELSITO: So should we table this --

DR. BERGFELD: Yeah.

DR. BELSITO: -- and ask Lillian to work with the SASSI -- but we don't want to get too sassy in the process, Lillian -- and go through and look at each of the references that are here and make sure that a) that when they're talking about fume silica, it's the amorphous and not the crystalline.

And then spoof up the document and have it come back to us with the notion that at least I'm comfortable, Paul and Curt, with the idea that this is going to be safe as used, but we want the information in the document to be what is actually used in cosmetics and not what is not used in cosmetics or --

Lillian, do you feel that you've already done that --

MS. BECKER: I --

DR. BELSITO: -- or were you confused by their presentation?

MS. BECKER: I was. That's one of the things that took me so long in getting started on this particular -- was going through and combing through all of that and figuring out what was amorphous and what was not.

DR. BELSITO: Okay.

MS. BECKER: And all I have to go on is what, you know, the writers wrote. And what the writers wrote I did quote in there. If they say colloidal, I put it in there; if they say silica so I'll put it in there so that I did not interpretation other than its amorphous or not.

So unless they know something I don't know about the papers, I don't think I can -- you know.

DR. BELSITO: Okay.

DR. BAILEY: (off mike) -- these are really editorial changes. I mean they may be more editorial than we're maybe used to, but I think if you feel comfortable with the, you know, conclusion, and working with SASSI folks to make these corrections and editorial changes, that, you know, we would -- I would recommend going ahead and giving your conclusion and moving the documents forward.

DR. BELSITO: Okay.

DR. BAILEY: With the idea that you'll have a chance to look at it, you know, with those editorials when corrected.

MS. BECKER: And then when we get through, it might be more clear –

DR. BELSITO: Okay.

MS. BECKER: -- without the --

DR. BELSITO: So, then, why don't -- well, then, the suggestion is we move forward, tentative final, safe as used.

Lillian will get together with the SASSI people for editorial corrections, and I guess I would like to see done what was done for the cyclomethicone report where there are comments that we should delete something that is currently in here. If they could keep it, then just underline that whole paragraph with a comment that, yeah, in review we're recommending this be deleted because in reality it was not amorphous silica, and then we can say, oh, okay. You know, rather than just having a whole bunch of material disappear from this document and us now knowing why it disappeared.

DR. BERGFELD: Well, can I offer another suggestion that maybe, when they're working on their draft, that they do that? But then they give us the second draft of deleting all of that, because I think it's going to be confusing with all that fume stuff in there. It's everywhere.

DR. SNYDER: But isn't the fume silica the pyrogenic silica which is one of the forms of a --

DR. BERGFELD: Well, maybe. You did say, Dr. Hathaway, that some of that had a high crystalline level.

DR. SNYDER: That's silica fume.

DR. BERGFELD: I know. I know. I know, but --

DR. HATHAWAY: Unfortunately, the two terms are very similar. That's why, you know, and the editorial changes we would strongly recommend that you use the term "pyrogenic" instead of fume silica. We're trying to do that in the industry to, you know, avoid that confusion.

DR. ANDERSEN: Don, I think with due respect to the industry input that we've received today, I'm not prepared to turn this report over to industry for writing it.

DR. BELSITO: Well, I don't think for writing, but for comment that we can review.

DR. ANDERSEN: Comment can be made by any interested party when the tentative document is issued for public review. If we get some further input, I'd love to receive that.

DR. BELSITO: Okay.

DR. ANDERSEN: But there is nothing that I've heard in terms of fundamental flaws that says this should stop. Should we include up front maybe a further glossary that explains to the reader that some of the terminology you're going to be seeing may look strange, and, in fact, the current preferred term for fume silica is pyrogenic silica. We can put that up front so that the explanation is provided.

But if the author of the published study called it fume silica, we can't recreate what was said in that published study. The fact that we think that's pyrogenic silica, you can in fact state positively that we think it is.

DR. BELSITO: Okay.

DR. ANDERSEN: That's a fine way to deal with it. But I don't -- I'm not hearing anything that says that there is a fundamental flaw in this document. The data that are there don't raise particularly any safety issues. It is axiomatic that we must be clear that this is not a safety assessment of crystalline silica.

DR. BELSITO: Mm-hmm.

DR. ANDERSEN: So however we do that, you know, it's going to be like teaching high school history: Tell 'em what you're going to tell 'em; tell 'em and tell 'em what you told 'em. If we don't say it that many times, we will not have done our job. So we can look at it from that point of emphasis, but unless there is a study that's included in here that is known to be crystalline silica and shouldn't be in there, there's nothing to deal with here.

DR. BELSITO: Okay. So then we're not going to make any changes, except to perhaps a little stronger emphasis in the --

DR. SNYDER: Prologue.

DR. ANDERSEN: Except to be responsive to Dan Liebler's --

DR. BELSITO: Right.

DR. ANDERSEN: -- point about minimizing the crystalline silica part, that I don't have a problem with that.

DR. BELSITO: Mm-hmm.

DR. ANDERSEN: But that is indeed, as John pointed out, it's editorial. And that's just a level of finessing this that is important. I mean I think we heard clearly this morning that to any reader they better see clearly the focus of this is away from crystalline silica.

DR. BELSITO: Okay.

DR. ANDERSEN: I think we're very close to that anyway, but a little more emphasis can't hurt.

DR. BAILEY: I mean I -- from the industry's perspective, I would like to see this document, you know, set sort of a framework for future use of terms, and understanding of what is what. A glossary would certainly do that.

DR. BELSITO: Okay, sure.

DR. ANDERSEN: It could help.

DR. LIEBLER: You had a figure 1 that's sort of like what I called the silica family tree –

DR. ANDERSEN: Right.

DR. LIEBLER: -- earlier in this morning's presentation. And I think, you know, maybe sitting here with a couple cups of coffee and listening to it here to get off to the second time made it more clear to me that there were some nice distinctions that emerged from this morning's presentation that I just didn't get first time reading it. And that might have been me, not you, but I think it's worth making the point about pyrogenic silica being -- also being called in the literature "fumed silica," and how that can lead to confusion of that material with "silica fume."

And if that can be briefly explained in the introductory material so that it allows, then, the reader to go to the original language in the literature report and not be baffled.

DR. BELSITO: Right. Okay.

DR. ANDERSEN: That works.

SPEAKER: That we know how to do.

DR. BELSITO: Okay. And then just to get back to my prior point about we have two prior reports out, the 2003, 2005, do we want to collapse all of those ingredients into this report? And then a final point is in one of those two our conclusion was when formulated not to be irritating. In this series of reports we really don't have any data to suggest that these materials are in fact irritating when used.

But now this will be the third silica document. One I think was safe as used, and one had a conclusion that -- that potassium, sodium, and silicate is the one that says "when formulated to avoid irritation." And then the other one was just "are safe as used in cosmetic products."

DR. BERGFELD: You could -- you could handle that with "should not be irritating in the product." I mean like we did before.

DR. BELSITO: I understand that, but my point, Wilma, is that in this current document --

DR. BERGFELD: Yeah.

DR. BELSITO: -- with these current ingredients, we have no data to suggest that irritation is, in fact, the problem. And, in fact, the irritation that we had --

MS. BECKER: Was only with the potassium study only.

DR. SNYDER: Sodium potassium.

DR. BELSITO: -- was only with potassium, sodium --

DR. BERGFELD: Silica.

DR. BELSITO: -- metasilicate and sodium silicate.

DR. BERGFELD: Which was the --

DR. BELSITO: And that was, you know, I think because we had data as in all cases where, you know, 100 percent there was some irritation or something, and this was back when we -- I don't know what we were doing -- but so if we don't combine these documents, then we're going to have two reports on silicates that say safe as used, and one that says safe as used when formulated not to be irritating.

And it's just, to me, if I were not on this panel, and I'm looking, okay, so what's the difference between calcium and sodium silicate, and why can one be safe as used and one only be safe as used when it's formulated not to be irritating?

DR. ANDERSEN: Well, I think that the answer is not in this report, but the answer is in fixing the other report. The only data that suggested a concern was actually sodium metasilicate.

DR. BELSITO: Right.

DR. ANDERSEN: And the conclusion could have focused on that ingredient in the earlier report; we just didn't do that. But all of the other simple salts were not irritating, continuing the pattern. So I don't think that you lose anything by not perpetuating the problem here but rather when we come back to the previous report fixing it. Or if industry is particularly concerned, they can suggest an amendment as needed to the earlier safety assessment.

DR. BELSITO: Okay.

DR. HATHAWAY: I might be able to add a little bit of clarification. The sodium metasilicate is a very alkaline material, and that may be the reason why in some formulations, if it's not very careful to adjust the overall pH of the product, you could end up with an irritating situation. We really didn't comment on that; we focused really only on the synthetic amorphous silica things, but that's probably why it was there in the older ones.

DR. BERGFELD: And our summary from the older document mentions that.

DR. BELSITO: Okay, so we're going ahead with the safe as used. We're going to do -- clean just as little bit, strengthen the introduction to clarify exactly what we're looking at, the fume versus fumed silicate -- silicate fumes, and, I gather from what Alan said, we're not going to add in the ingredients from the reports we previously did, we're worry for the 2018 people.

So you'll remember this discussion, Wilma, in 2018.

DR. BERGFELD: Me, too.

Marks' Team Meeting:

DR. MARKS: Okay. Let's move on. We've got another non-contentious ingredient named silica.

SPEAKER: Lillian will come up.

DR. SLAGA: I recommend we table this.

DR. MARKS: Okay.

DR. HILL: And I second that.

DR. MARKS: Let me see -- and I'm the one that --

DR. SLAGA: It's too complicated. Unless all these things are changed and number two, I would like to see us relook at -- even if informal -- the other two that we -- has been approved in the past.

DR. MARKS: Well, one of --

MS. BECKER: (off mike)

DR. MARKS: Go ahead, Lillian.

DR. SLAGA: Why?

MS. BECKER: I'm just trying to catch up, so I think I'm just going to sit in while I listen here.

DR. SLAGA: Because I think somewhere (off mike).

DR. SHANK: But they're already finished.

DR. MARKS: No. Not -- actually nothing was said. Basically the suggestion was made that this be tabled so we can go ahead and integrate the presentation we heard this morning. Thank you. And then also look at the two previous safety assessments that were done and, in fact, one of the -- the potential suggestion --

DR. SLAGA: Well, even Belsito wanted them to look at those two. I mean --

DR. MARKS: Yeah.

DR. SLAGA: -- because that'll be brought out tomorrow, I'm sure.

DR. MARKS: Well, one of the potential tacts I thought was we just reopen the old safety assessments and group all of this together.

DR. SLAGA: That could be wise.

DR. MARKS: And that could be -- so it could be tabled with that idea also as to consider do we group all -- all of the safety assessments.

DR. SLAGA: Who's presenting this one?

DR. MARKS: I'm tomorrow. So it will be easy if it's tabled. But I should think we need to know what we want other than obviously integrating the data we've heard today.

MS. BECKER: Well, of the data you heard today, the papers that they talked about are already integrated into the report. I got the information in time to integrate it for you guys. So you've already read everything they've given us.

DR. SLAGA: Oh, okay. It's been changed over what they were --

MS. BECKER: Right, right.

DR. SLAGA: Oh, okay.

MS. BECKER: Yes. They gave me the stuff -- I already -- I stayed up late at night putting all this stuff in so you guys could have it. You have it.

DR. SHANK: You made it clear about the crystalline versus amorphous. Is that what you're talking about?

MS. BECKER: Um.

DR. SLAGA: I didn't think that was --

DR. MARKS: Yeah, it's in the introduction -- the second paragraph. It's very clear. There are two categories -- crystalline and amorphous -- and only the amorphous ones are used in cosmetics. That's page one.

DR. HATHAWAY: Part of the problem is that a lot of amorphous forms are not used. It's really only the synthetic amorphous forms. And -- you know -- we would appreciate it if even though the data is in there, particularly the section on the silicas -- you know -- I think it could be clarified so that it would be a lot less confusing to other people. It may not affect your safety assessment, but since it would be a public document -- you know -- we would like it to be -- you know -- as straight forward and easy for -- you know -- someone else to read and understand it.

MS. BECKER: When I was going through all the papers in many papers it is very difficult to figure out which type of silica it was and I gave their -- the author's description of the silica as given and that is clear as I can make it. If you know something I don't as in -- you know -- we know this guy only worked on this type of silica, which is never used, we could -- you know --

DR. SLAGA: We probably don't know that.

MS. BECKER: We don't as far as I know.

DR. SLAGA: I would based on the (off mike).

DR. MARKS: (off mike)

MS. BECKER: But, I used the description of the authors provided.

DR. HATHAWAY: No, I understand that. The confusion comes as I mentioned this morning. This one amorphous silica that's formed by melting crystalline silica -- you know -- ends up forming a solid object, you know. Maybe it doesn't become a glass like this, but it's a type of glass. So it's not really relevant to this and then the confusion between silica fume, which is considered another amorphous form but has a certain amount of crystalline silica in it and the pyrogenic silica -- that a synonym is fumed silica -- you know there's a problem there. You know we would just like -- we would very much appreciate it if -- you know -- all of these terminologies were clarified so there would be not confusion on the part of an outsider reader and -- you know -- we're willing to work with you to try to get that squared away.

SPEAKER: We can do that. We can help.

MS. BECKER: Yeah, because as far as -- my information -- with the information I have, it's as clear as I can make it. So if you've got better information --

DR. SLAGA: Some of the publications won't be clear. That's -- I think that's the point you make.

MS. BECKER: Yes.

DR. ANSELL: Well, a lot of them do have scriptors -- precipitated study, aerosols, silica, undescribed, (off mike) silica. Perhaps we could clarify --

DR. HATHAWAY: No. There's no question the revision is a lot better than the -- than the initial draft, but there's still, we feel, could be improved to avoid -- you know -- confusion by people reading it.

SPEAKER: Well, I --

DR. ANSELL: Could you identify which of these are the cosmetic silicas as opposed to the (off mike) silicas?

DR. HATHAWAY: Correct. Yeah.

DR. SHANK: Inclusion of that flow sheet that you gave us this morning would be helpful.

DR. MARKS: It is actually in there.

MS. BECKER: It is in there.

DR. MARKS: Page 62. Yeah. It's page 62.

DR. SHANK: I forgot that.

DR. MARKS: Yeah. It's in there which -- so I think we're -- if we decide to issue a tentative report, that gives the opportunity for you to comment and do some of this suggestions you have.

DR. HATHAWAY: I mean -- yeah. I mean if you'd be willing to -- you know -- have us work with you --

MS. BECKER: Um-hmm. Sure.

DR. HATHAWAY: I think the section on describing the forms of silica is an area that we would like to see changed.

DR. MARKS: Sure.

DR. HATHAWAY: And maybe some introduction on the inhalation intratracheal thing on particle size -- you know -- just to clarify. I mean you have it in there, but it was right at the very beginning -- you know -- that kind of prefacing all of these studies, even though many of the studies may not have specifically referenced particle size -- particularly some of the older ones.

DR. MARKS: And sometimes that appears in the discussion and the discussion at this point hasn't actually been written, so these nuances are often included in the discussion to put it in perspective. So that can -- all that can be done.

MS. BECKER: Yeah. The inhalation boilerplate is in there.

DR. MARKS: Yeah.

DR. HATHAWAY: On the form (off mike) size?

DR. MARKS: Yes.

DR. HATHAWAY: Okay.

SPEAKER: Let's help through the discussion focus on the most relevant studies versus (off mike).

SPEAKER: Dr. Marks?

DR. MARKS: Yes.

SPEAKER: May I make an administrative request here --

DR. MARKS: Sure.

SPEAKER: -- which is that we do have an administrative process which includes a time period during which comments are solicited and welcome and we really would like people to submit valuable comments -- to submit them during that time frame, not afterwards. Because that really messes up our process and it doesn't allow us to incorporate the changes in a timely way so that you can see them before the panel meeting and the panel can see them.

DR. MARKS: Right. And that's a 60 day time period, so we'll have plenty of --

SPEAKER: Well, okay -- wait -- yeah -- we --

DR. MARKS: -- plenty of time to add these wording. We haven't even seen the discussion on this. We are basically today to decide --

SPEAKER: Okay.

DR. MARKS: -- one, do we want to issue a tentative safety assessment.

DR. PAVLICH: As we understood the process when Dr. Andersen visited, we were given the opportunity to look at the first draft of the scientific review and we sent in our comments and then he told me that we probably wouldn't have a chance to get those comments incorporated into the review before this meeting and therefore just to come and give our presentation. So that was our -- that's how we understood the process. So -- I mean -- we had these prepared last week, but we -- our understanding was that it wouldn't make it any difference if we sent them in early or not.

SPEAKER: Not the case (off mike).

DR. PAVLICH: Not the case.

DR. MARKS: Okay.

DR. PAVLICH: We stand corrected.

DR. MARKS: So, Ron, Ron and Tom -- Ron, Tom and Ron -- whichever way I want to go is -- do you want to move this forward to make a conclusion on these ingredients as a cosmetic ingredient and keep it as such? Do you want to group this with the other reviews (off mike)?

DR. SLAGA: Well, based on a lot of changes have already made, there's -- we can do it with the others later. We don't have to deal with them (off mike).

SPEAKER: She can't hear you.

DR. SLAGA: I think we have to deal with this --

DR. MARKS: Okay.

DR. SLAGA: -- and right now, I don't think we have to based on what we have already heard that we have to deal with the other two that have been already out in literature.

DR. MARKS: Is there -- so can the conclusion be safe?

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. SHANK: With one question. The iron -- the which is it called -- aluminum iron silicate. We have almost no data on any of the metal silicates. But calcium silicate, sodium silicate -- that doesn't bother me. But the adding aluminum iron -- especially if it's inhaled with a high oxygen content of the lung -- the iron atom could produce oxidative damage which would not be expected by any of the other silicates. So I would not include aluminum iron silicate without data. The others I can add. That's the only change.

DR. MARKS: So that would be insufficient?

DR. SHANK: Insufficient for -- well, these are add- ons, aren't they or whatever?

DR. MARKS: No.

SPEAKER: No. It's the original assessment.

DR. SHANK: So it would be insufficient for the aluminum iron silicate and you'd need inhalation data unless -- you could say since it's not respirable.

DR. HATHAWAY: Well, I don't think any of our member companies produce that compound, so I don't have any information.

DR. SHANK: Okay. We had no data on it. But if it's -- if it's not respirable, then it's not a problem.

SPEAKER: I have no idea what the (off mike) for that is.

DR. SHANK: But, since we have no data on it, we would need some data.

SPEAKER: That's a good compromise.

DR. MARKS: So we'll move that this be a tentative safety assessment and it's these ingredients are safe with the exception of aluminum iron silicates, which would be insufficient data --

DR. SHANK: Inhalation needed.

DR. MARKS: Yeah. We need the inhalation.

DR. SLAGA: Unless that can be shown --

DR. SHANK: Well --

DR. MARKS: Yeah.

DR. SHANK: -- if it can show it's not inhaled then --

SPEAKER: Unless someone shows (off mike).

DR. MARKS: So we'll issue a tentative safety --

DR. HILL: And I'm answering a question while you're writing sort of from this morning is -- and I'm thinking in particular of hairspray formulations where there -- the amounts are small anyway. I understood you to say that as manufactured -- according to your knowledge -- there are large enough aggregates that even assuming that whatever

liquid accompanied the droplets evaporated before somebody inhales this, that the particle sizes are still too large to go any farther than the trachea. So I --

DR. HATHAWAY: Correct. When they're -- when they're in a solution -- whether it's aqueous or a combination of other solvents or whatever -- it's not going to disaggregate.

DR. HILL: So then my question became at least based on your knowledge of the companies that are manufacturing this stuff, that are in products available to Americans at least, that there are no nanosize particles -- anything smaller than four microns that are fines -- what we always called fines working with silica in the lab -- in products as they are manufactured, but the finished products -- the hairsprays and such.
DR. HATHAWAY: We ran it by -- you know -- the companies on both sides of the Atlantic. Initially we had down there 16 to 100 microns because that's pretty much what all the people on this side had and they recommended we drop it to 10, because I guess they must have some products that are down closer to 10.

DR. HILL: Okay. Okay.

DR. HATHAWAY: But -- you know -- we checked with -- you know -- the eight companies are the same companies on both sides of the Atlantic. They may have different plants and have -- you know -- slightly different product mix, so we certainly checked with all of the European and the North American manufacturers.

MS. BECKER: Could we get a letter or memo saying that so I can put it in the document?

DR. PAVLICH: It's in the -- it's in our summary. Ten to 100 was quoted in that summary.

MS. BECKER: Okay. Thank you.

DR. MARKS: Okay. Any other comments? We'll issue -- we will move -- I will move since I'm the one that will be presenting this -- issue a tentative safety assessment with a finding that aluminum magnesium (off mike) aluminum calcium, sodium silicate, hydrated silica and a sodium potassium aluminum silicate are safe for use in cosmetic ingredients. And that the aluminum iron silicates -- there's insufficient data and we need the inhalation data to decide whether that's safe. And, Ron, if there's any discussion --

DR. SHANK: Unless it's in the 10 to the 100 --

DR. MARKS: Well, that would be essentially the --

DR. ANSELL: Yeah, that would be formulated to be nonrespirable.

SPEAKER: Do we have anything you want in the discussion other than inhalation?

DR. SHANK: Did Lillian catch what we just said?

DR. ANSELL: And formulated to be nonrespirable.

MS. BECKER: Yes. Writing it down.

DR. MARKS: And we can use the same words as they used in the 2004 report.

SPEAKER: Just finishing silica.

MS. BECKER: For which?

DR. SHANK: In the discussion for this document, you can just use the discussion on inhalation with cosmetic sprays --

MS. BECKER: Okay.

DR. SHANK: -- that we used in 2004 --

MS. BECKER: Okay.

DR. SHANK: -- which was the potassium and (off mike).

MS. BECKER: Alright. That works for me.

DR. MARKS: Okay. Any other?

SPEAKER: Anything else?

DR. HATHAWAY: Just to say that although I mentioned hairspray, face powders is in here. So this is a totally theoretical question.

SPEAKER: Alright.

DR. MARKS: Not really. Thank you very much for your patience and comments.

SPEAKER: Thank you.

SPEAKER: Thank you.

MS. BECKER: Thank you.

SPEAKER: Very helpful.

DR. MARKS: This morning and also right now. Thank you.

DR. PAVLICH: Good. Well thank you for having us.

Full Panel Meeting:

DR. BERGFELD: We're going to move forward then. This (off mike) this table to answer the questions that have been so stated, and we'll be moving on to the next group, Dr. Marks presenting on silica and silicates.

DR. MARKS: In the March meeting of the CIR Panel, a scientific literature review was announced, and we're now seeing the draft report on silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, alumino-iron silicates, hydrated silica, sodium potassium aluminosilicate. And we had the presentation yesterday by the SASSI group clarifying the difference between synthetic amorphous silica, which is used in cosmetics and other forms of silica, and based on the information that we reviewed, we move to issue a tentative safety assessment that has the ingredients safe with the exception of aluminum iron silicates. We move that that be insufficient data, because of concern about inhalation toxicity.

DR. SLAGA: Unless it's (off mike).

DR. MARKS: Ron can -- well, that would be the inhalation data. If it's not respirable, then it's not an issue.

DR. BERGFELD: Any other -- that's a motion?

DR. MARKS: Yes.

DR. BERGFELD: And there's no other comment on the motion? Second? Second, Ron? Discussion?

DR. BELSITO: Respirable? We have that boilerplate. How would it be respirable?

DR. MARKS: We don't know. We can consider that it's not.

DR. SHANK: I worry about the -- or I have concern about the iron atom going into the lung, high-oxygen environment. There could be oxidative damage, which would not expect that the other silicates –

DR. BELSITO: But I –

DR. SHANK: If not, we can say this is formulated (off mike). That takes care of the issue. But we don't have that information.

DR. BELSITO: I thought the information we have was that cosmetic formulations -- the particle size was such that it's in a pump or a spray it's not respirable.

DR. SHANK: Okay, but this one doesn't have a stated use, does it?

DR. BELSITO: But how would it be used as an aerosol other than as a hairspray?

DR. SHANK: Don't know. Lack of information is not proof of safety.

DR. BELSITO: But -- then I just –

DR. BERGFELD: Alan?

DR. ANDERSEN: We did have the information yesterday from the synthetic amorphous silica group that said the particle size of the amorphous silica material is between 10 and 100 microns in diameter, so independent of what happens to it after that, the particle size as produced by the suppliers is already of a size to be not respirable.

DR. BELSITO: Correct.

DR. ANDERSEN: From that point, it doesn't matter what formulation it goes into. Not much can happen beyond that, and in order to conduct the inhalation toxicity studies that were described, further unnatural reduction particle size had to be done, but that doesn't represent what's actually on the market from the suppliers. So, we could rely on that information that was presented to make the assertion that in fact the panel does not expect that these particles are respirable and put that burden on the industry for all of the amorphous silica, including the iron one. So, it would be a way to assert the panel's expectation of non-respirable.

DR. BERGFELD: So, you're going to amend?

DR. MARKS: I'll retract the previous motion with that clarification, and that being captured in the discussion so that all these silica cosmetic ingredients would be safe and that we issue a tentative safety assessment of that conclusion.

DR. BELSITO: Second.

DR. BERGFELD: Second. And with the assumption that the discussion will take the place or support your worry.

DR. MARKS: Yeah.

DR. BERGFELD: Okay. Any other discussion? John?

DR. BAILEY: Yeah, at yesterday's team meeting I emphasized the importance of stating clearly in this document the synthetic amorphous silica as the material that's used in cosmetics, because we have a lot of confusion inquiries coming in that rather it's crystal and we're amorphous and we'd like to be able to use this document to clear that up both for people who have concerns in the public but also for the users of the ingredients so that that's clearly communicated to them what they're supposed to do.

DR. BERGFELD: I think that I sat on Don Belsito's team and he discussed that and which to do with that, did you not?

DR. BELSITO: Yeah, a very strong statement up front in the introduction going over basically that slide of silica production and where we are and that this is not crystal and then the amorphous, so I think Dan had -- Did you actually beef up your introduction, or --

DR. LIEBLER: I provided comments.

DR. BELSITO: Right.

DR. LIEBLER: But I think it's most important to -- because some of the original literature refers to silica forms -- for example, as fume silica -- and that there's a preferred term now, pyrogenic silica, for that, but there needs to be a very clear sort of glossary in the introduction section to provide the reader with some guidance as they go forward in the report, because we did have some discussion about whether to change in the body of the report reference to fume silica -- change that to pyrogenic -- but that would be essentially, as Alan pointed out, replacing -- revising the literature inappropriately, and I agree with that, so a glossary up front that clarifies the terminology for names and points out where you're going to have confusion between silica fume and fume silica, for example.

DR. BERGFELD: Paul, any comment? Greg? Coming over here. Don? Ron? Rob? Jim? Is there any other comments? Okay. Motion has been placed that this ingredient is safe and discussant points have been added, so all those in favor please raise your hand for a safe review. Thank you very much. It's a unanimous vote.

September 24-25, 2009
Belsito's Team Meeting:

DR. BELSITO: So now we get into the silica and the silicates (off mike). Okay, so where are we here? Silicates. Okay. So, we got -- is this a handout from today from Sassi?

MS. BECKER: You got that in the e-mail.

DR. BELSITO: In the e-mail. Oh, I printed out an e-mail. Okay.

MS. BECKER: Yes.

DR. BELSITO: I must have addressed it. Okay. I thought, Lillian, you did a great job and I really thought that Figure 1 and 2 were really great in this report. And I think it really addressed concerns of our team, at least particularly Dan's concern of getting everything up front and making it clear. I like the way you've boxed that out in Figure 1.

DR. LIEBLER: Yeah.

DR. BELSITO: It was really a superb way of handling that to show exactly where we're focusing.

DR. LIEBLER: One little note on that on Figure 1 -- so I completely echo Don's praise for your work on this -- but one little thing I would change is under the box where you've got – where it says the types of silica in this safety assessment, and it's got a little box around that -- that that actually kind of hides that because everything else in the figure has a box around it. And that's actually a message that you want to stand out and putting the box around it makes it blend in. So what I would say is take the box out of it and then use a bigger font and italicize it just so it --

DR. BELSITO: And put it into the box maybe even.

DR. LIEBLER: Or right under the box or, yeah, lower the box a little bit and stick that in the box. Yeah, that's a good idea.

MS. BECKER: Yeah. That's what I'm drawing right now actually.

DR. LIEBLER: Okay. But that's just a tweak. It's very nice. Huge improvement.

DR. BELSITO: On page 17, under parenteral silica one, two, three, four, five, six lines down, it says lymphocytes were less numerous and new.

MS. BECKER: Okay, few. Probably -- yeah, few. Probably something (off mike) said.

DR. BELSITO: So if it's less numerous and few, then you don't even need few.

MS. BECKER: Yeah.

DR. BELSITO: Just less numerous.

MS. BECKER: So we will check that.

DR. KLAASSEN: Probably don't need numerous either. There were lots of lymphocytes.

MS. BECKER: There's some pretty weird wording on some of these.

DR. BELSITO: Page 29. Things were moved around so perhaps I missed it, but in the prior document there was an ECETOC 2006 report of two subchronic oral and toxicity studies that I couldn't find again.

MS. BECKER: If I remember correctly, a couple of short-term -- I'm sorry, long-term and chronic got moved around just because of dates, but I don't -- did you check to see if it's just in a different time section?

DR. BELSITO: I tried to do that and I couldn't find it, but, I mean, it's entirely possible. The reference though is gone, at least as an ECETOC 2006 reference, so I'm wondering if someone recommended it be deleted or was it, in fact, maybe published under a different title?

DR. BRESLAWEC: Here's ECETOC 2006 on 31.

MS. BECKER: There was also a couple that were thought to be duplicates of the other large document I had and we picked one or the other.

DR. BELSITO: Okay.

MS. BECKER: So that might be --

DR. BELSITO: So it may be --

MS. BECKER: It might be under UNEP instead.

DR. BELSITO: Okay. But then that ECETOC 2006 reference doesn't occur in your references.

MS. BECKER: I see what you're saying.

DR. BRESLAWEC: If you look at the reference there's nothing that says ECETOC.

DR. BELSITO: And there are some ECETOC on page 31 that refers to some 2006 unpublished studies, which are different from the studies that I was talking about.

MS. BECKER: European Centre for Ecotoxicology and Toxicology of Chemicals.

DR. BELSITO: Okay.

MS. BECKER: On page 57. It's in the references.

DR. BELSITO: There it is. ECETOC 2006. Sorry, I stand corrected.

Okay. On page 35, the fifth line up the bottom, starting from the line above that it says although there was a trend of more frequent incidence in those exposed to pyrogenic silica, it was obscured in some control animals. Interstitial fibrosis was associated with yadda, yadda, yadda. And some of the rats of the control treatment groups, although there was a trend to more frequent incidence in those exposed, but was obscured in some control animals. I'm assuming it wasn't significant because it was seen in control animals or --

MS. BECKER: If I remember correctly, yes.

DR. BELSITO: I just think that needs to be stated a little bit more clearly.

MS. BECKER: You got it.

DR. BELSITO: Page 54, the third paragraph, silica subcutaneously instilled in humans. Next sentence, the cells --

MS. BECKER: I'm sorry?

DR. BELSITO: -- invested blood vessels. Invaded blood vessels?

MS. BECKER: Page 54?

DR. BELSITO: Page 54.

MS. BECKER: Third paragraph?

DR. BELSITO: From the bottom.

MS. BECKER: Oh, sorry.

DR. BELSITO: Silica subcutaneouslyinstilled in humans caused granulomatous inflammation with seven days and persisted for months. The cells invested blood vessels?

MS. BECKER: That was --

DR. BELSITO: Invaded blood vessels?

MS. BECKER: Something like that would have been stolen wording. Yes, that was wording from Epstein 63. That's 47 and that would have been his wording. That's not something I would have picked up, but I try not to interpret too much. Is that 47? Epstein 63.

DR. LIEBLER: Just strike the whole sentence. It doesn't add anything.

MS. BECKER: Okay.

DR. BELSITO: Okay. In our conclusion, do we really need to isolate aluminum iron silicates?

MS. BECKER: That was Dr. Shank and his concern about the iron.

DR. BELSITO: I understand and I remember the discussion, but we decided that it wasn't going to be (off mike) even in the current form that it was used. So do we need to put that in the conclusion or just the discussion? I mean, I think, you know, its ingredients and practice of use in concentration as described in the safety assessment is sufficient. If there's any concern that could go in the discussion that the size of these particles, irrespective of how they would be used that was captured in the minutes, would not be respirable.

Beyond that, we know that the way pumps and sprays are formulated it wouldn't be respirable either. But as Alan pointed out at the last meeting, you literally would have to break down the silicates in order to make them of a size where they would be respirable. So, taking that out and putting it into the conclusion I think is a bit much.

MS. BECKER: Okay.

DR. BELSITO: I would just move that to the discussion if there's any concern at all.

DR. LIEBLER: So simply in the conclusion --

MS. BECKER: Just the first sentence.

DR. LIEBLER: -- just use the first sentence and then add aluminum iron silicates to the first sentence.

DR. BELSITO: Exactly.

MS. BECKER: Got it.

DR. BELSITO: The last thing that I couldn't find and maybe you can tell me where it was is -- and maybe it was decided to get rid of it -- but in the old document there was a statement about natural silica levels in rabbits. And I couldn't find where that was moved to, but the reference was retained.

MS. BECKER: Do you have the reference offhand?

DR. BELSITO: Yes, Ammon and Moan, 1959.

MS. BECKER: Ammon with an A?

DR. BELSITO: A-M-M-O-N.

MS. BECKER: I think that was marked as not necessary.

DR. BELSITO: I would agree that it's not necessary. Then we just need to delete the reference if it's not in the document. I mean, just check because -- I mean, you could just do a quick word search and see if it pops up someplace in the document other than the references.

MS. BECKER: Okay. That's going to be my major task this weekend actually.

DR. BELSITO: I hope not this weekend.

MS. BECKER: Oh, yeah.

DR. BELSITO: I think that's all that I had. So before we address the Sassi comments, any other comments?

DR. LIEBLER: Page 2 and 3, I recommend a couple of additional tweaks. Just moving sections to make the presentation more logical in terms of the flow.

So, on top of page 2, you have Chemistry, major heading, then subhead Definition and Structure, and then Amorphous versus Crystalline Silica. You have two paragraphs. Then you've got Silica, which is really the very most introductory information about silica. And I suggested moving that stuff there that's subtitled Silica, beginning with the CAS Number 7631, all the way through the top of the next page where it says, "The current terminology for silicon dioxide fumed is pyrogenic silica." That whole chunk, move it up between Definition and Structure and Amorphous versus Crystalline Silica. And I pointed -- I drew it on my copy for you.

MS. BECKER: Okay. All right. We're changing a lot of things as CIR, but normally we keep all of the definitions of all the ingredients together. Would that -- I'm just asking if that -- separating silica out separately from the aluminum magnesium, metasilicate, et cetera, would that be confusing?

DR. LIEBLER: I don't think so because the way you have it now you begin by talking about amorphous versus crystalline silica. And then at the bottom of page 2, you start out by explaining what silica is. It seems like you should start out by explaining what silica is and then get into the distinction between amorphous versus crystalline. It just seems more logical to me.

MS. BECKER: Okay.

DR. LIEBLER: And so you can move that section up to the top. And then you also have, at the bottom of page 3, you have the section on hydrated silica. That can go right after amorphous versus crystalline silica. And then you get into the aluminum magnesium salts and the silicates.

MS. BECKER: Okay.

DR. LIEBLER: And so that way you're doing pure silica first, then the salts, to just introduce the chemistry.

MS. BECKER: Okay.

DR. BELSITO: Except I guess the only issue that I'd have with that, Dan, is that we're doing -- you know, we're looking only at the amorphous. So then you would have amorphous and then you'd mix in amorphous with crystalline and then go back to the amorphous forms. That could be confusing. So that I guess if you wanted to move things around would be to move the amorphous and crystalline to the end of the whole thing and list the things that we're discussing first and then making the point of the difference between amorphous and crystalline at the end.

MS. BECKER: That would be more my inclination, but.

DR. LIEBLER: So, instead of moving the things I moved, just take amorphous versus crystalline and move it to the end?

DR. BELSITO: Yes.

DR. LIEBLER: I'm fine with that. That accomplishes the same thing. I just thought that you have amorphous versus crystalline at the top of the description of all the silica and silicates and it was premature to address that at that point. So, Don's suggestion takes care of that as well and I agree with it.

MS. BECKER: Okay.

DR. SNYDER: I had some issues with the nomenclature again. It's just really confusing because on page 5 we introduce silica gel and precipitated silica for the first time. And then on page 6 we introduce colloidal silica. And on page 8 we bring in the sodium metasilicate, hydrated silica, and silica solution. So I was a little confused as to where those all --

DR. LIEBLER: So under hydrated silica, Lillian has these bullets of synonyms, and silica gel and precipitated silica are listed there. So the reader will have encountered those definitions before they got to where you're concerned about.

MS. BECKER: Right.

DR. LIEBLER: And colloidal silica, is that one here?

DR. SNYDER: Yeah, page 6.

DR. LIEBLER: Page 6.

DR. SNYDER: On the third paragraph on down, silica sols, colloidal silica.

DR. LIEBLER: Does colloidal fall under one of these? Lillian, do you know?

MS. BECKER: I thought it was under hydrate.

DR. LIEBLER: I want to double-check that. If it can be defined there, that's a good place to put it if that's correct.

MS. BECKER: The issue was that through the literature the naming conventions are not consistent. And unless they gave me something that said I can identify it as exactly what we have as our definition, I used the terminology of the author.

DR. LIEBLER: So in Table 1 with the box around the forms that are defined in the safety assessment on page 61, you have silica gel or colloidal silica.

MS. BECKER: Right.

DR. LIEBLER: So the reader will have seen this figure at that point. It's just that colloidal silica isn't listed under the bullets that you have on pages 2 and 3.

MS. BECKER: Right. Yeah, and what I just explained is also in the introduction that I did not guess what the authors were trying to say.

DR. LIEBLER: Okay.

MS. BECKER: Unless they gave me real evidence.

DR. LIEBLER: Right.

DR. BELSITO: So colloidal silica is silica gel?

MS. BECKER: Yes.

DR. BELSITO: And silica gel is hydrated silica?

MS. BECKER: Pretty much.

DR. LIEBLER: Right.

DR. BRESLAWEC: So on page 3, you said include that in the bullets there?

DR. BELSITO: Under hydrated silica.

DR. LIEBLER: And colloidal silica.

MS. BECKER: So that -- well, okay, but that's another reference, so that would be slightly different.

DR. BELSITO: But you could add it just so it's clear and just put that reference so we know where each of them falls.

DR. LIEBLER: I mean, there must have been a basis for in Figure 1 including colloidal silica with silica gel.

MS. BECKER: Right. Right.

DR. LIEBLER: So that would presumably be the same reference.

MS. BECKER: Yes. That's what ARTS did. Yes.

DR. LIEBLER: Okay.

DR. SNYDER: And then there's in the nomenclature you get all the way to page 19 and we start talking about ultra fine and then fine silica. And we haven't defined that (off mike).

MS. BECKER: And neither did the authors.

DR. LIEBLER: I'm sure it's just particle sizing.

DR. SNYDER: So then for this use, does this have an aerosol use?

DR. LIEBLER: You know what? I'm sorry, just to -- fine versus ultra fine, on page 5, under Particle Size and Form, we've got amorphous silicas are composed of very fine particles, average 20 microns. Very fine, ultra fine, fine.

SPEAKER: Super fine.

DR. LIEBLER: Super fine.

SPEAKER: The point comes into question that we do have data here that says that the sum of the particles are respirable size, certainly the.01 to.1 micron diameter particles.

DR. LIEBLER: I don't know if there's a standard nomenclature of, you know, fine, ultra fine, very fine, that actually corresponds to giant particle diameter ranges. It might be something to look for and see because you list very fine in a way that just might mean it's sort of a kind of ordinary colloquia descriptor as opposed to whether or not very fine

means a particular size range. And if there is any definition in the literature that assigns the term "fine," "very fine," "ultra fine," the size range, this would be a good place to put it. This would be the ideal place to put it. So if there is any additional information you could find that would put it there, that would be useful there.

MS. BECKER: Okay.

DR. LIEBLER: I mean, I realize this whole area is a mess, but, you know.

MS. BECKER: Right. And it's a 1961 reference, so.

DR. LIEBLER: Yeah. I'm not sure where you could ask, but someone might be able to point you in the right direction. I forget who was here last time that made -- the Sassi people, I guess, you know, provided some input on – some clarification on the nomenclature and forms. They may know something or be able to point you in the direction on sizing nomenclature. If there is any and if it's referred to in the types of particle study, it probably should be up front in this report.

MS. BECKER: Okay.

DR. KLAASSEN: On page 5, about the fifth or sixth line, it says there that very fine particles had an average of 20 micrometers.

DR. LIEBLER: Yeah, that's what I was pointing to. Yeah. Yeah. So I'm assuming fine is more than 20 micrometers and ultra fine is less.

MS. BECKER: Well, I think the phrase that might solve all of it, is right after the 20, is "which tends to aggregate loosely in the air." So something that size doesn't exist very long. It adheres onto others and makes larger particles.

DR. BELSITO: And I think that's what we were told before.

MS. BECKER: Yes.

DR. BELSITO: And then going on it says aggregates assemble in chains, fumed or clusters precipitated in gel. Agglomerates are assembled -- assemblies of aggregates held together by strong physical adhesion forces and not in a dispersible nano-size less than 100 nanometers.

MS. BECKER: I think that kind of solves it.

DR. BELSITO: So the concept of very fine is a laboratory concept, not a real concept in nature?

MS. BECKER: At least not in the air.

DR. BELSITO: At least not as it would be formulated into a cosmetic product. I seem to remember them telling us that, too. They rapidly sort of adhere together.

DR. LIEBLER: I was just looking for a way to address Paul's question about whether --

DR. SNYDER: I mean, it was deep in the document and all of a sudden this popped up. And I thought if we could pop in appropriate information to define that, that would be useful. If any of the subsequent literature refers to particle size and distinguishes effects on the basis of anything having to do with particle size, then I think we need to deal with it.

DR. BELSITO: But then we could put -- we could move that issue of the aggregation of these very fine particles into the discussion as well since there is a hairspray use. And I see that the panel noted data on the use of very fine, fine molecular structures, average of 20 microns.

SPEAKER: (off mike) they are in respirable range of diameter.

DR. BELSITO: Right. But it is our understanding that these aggregate into chains, fumed or clusters, precipitated in gel to particle sizes that would not be respirable in cosmetic formulations.

DR. KLAASSEN: In general, to get things down into the alveoli you want to have it between 1 and 10. Larger than 10 they don't get to the alveoli very well and if they're smaller than 1 they don't settle in the alveoli. They just blow them back out again. So, even at this 20 microns here they're relatively safe as far as getting them into the alveoli. You still have them in the bronchi, et cetera. So, what Don said I agree with. This just gives us even further protection.

DR. SNYDER: We have a statement on page 53 in the fourth paragraph, the last sentence, related to -- in relation to monkey status, it says the frequency and the size of the cell aggregates vary with the type of silica precipitated in greater (off mike) and greater than gel. So that's what we should capture there.

DR. HOWARD: It is in the discussion -- I mean, the summary. So you want that clearly in the discussion?

DR. SNYDER: Well, I mean, I think that's just some more data --

DR. BELSITO: Well, I think we did, particularly now that we've moved the aluminum iron silicates out of the conclusion. We're going to make mention about it in the discussion anyway. So then we could just expand upon it a little bit if the panel noted data on use of very fine silicas, average molecular size 20 microns. However, we noted that these tend to aggregate into -- help me.

DR. SNYDER: Tend to form aggregates.

DR. BELSITO: Tend to form aggregates of a size that would not be respirable.

DR. LIEBLER: But is the passage you're referring to, Paul, is that referring to the silica particles or cells aggregating? Because it says the frequency and size of the cells aggregates.

DR. BELSITO: Oh, oh.

DR. LIEBLER: That's why I'm reading.

DR. SNYDER: Oh, I see. Yeah.

DR. LIEBLER: I'm trying to see if there's anything that's being said about clumps or aggregates of, like, lymphocytes.

DR. SNYDER: No, I mean, to me (off mike) the other way. I read it that it was the aggregates as in aggregates of silica. I mean, I guess there's nothing in that paragraph to suggest otherwise, is there?

DR. LIEBLER: So I'm just wondering what that actually refers to. Because the preceding paragraph refers to considerable cellular infiltration of the alveoli and the alveolar septa.

DR. SNYDER: There's nothing about aggregation there.

DR. LIEBLER: And with the extension and accumulation of acetate and macrophages. See, that could easily be referring to clumps of macrophages, perhaps. That's how I would read that. So maybe check that language there.

DR. KLAASSEN: And if true, then this sentence should go up in the other paragraph.

DR. LIEBLER: Yeah.

DR. BELSITO: So where are you moving this, Curt?

DR. KLAASSEN: Well, into the previous paragraph. It really has to do with macrophage. If it really has to do with cells and the aggregation of cells, then it probably is more appropriate in the previous paragraph. But we, first of all, need to make sure what's going on here.

MS. BECKER: It's the study on page -- it starts at the very bottom of 35.

DR. SNYDER: Yeah. It's macrophage and (off mike) aggregate. So just change that to "Frequency and size of the inflammatory cell aggregates varied with the type of silica," and move it up to the previous paragraph, to the paragraph that begins, "Rabbits and (off mike)."

DR. BELSITO: But these weren't rabbits; these were monkeys.

DR. SNYDER: Oh, so the monkeys then.

DR. BELSITO: So that's the paragraph above it?

DR. SNYDER: Yes.

MS. BECKER: These are two different experiments. I'm sorry. Say what you want to change again.

DR. BELSITO: The paragraph above is a different study.

MS. BECKER: Right.

DR. BELSITO: These are two different studies in monkeys. So that paragraph has to – I mean, you can't move it anywhere.

DR. SNYDER: Okay. All right.

DR. BELSITO: The monkeys were exposed to different types of silica. The precipitated silica had lower lung volumes. No change in parameters, ventillary performance, mechanical parameters, dynamic lung compliance and FEP. When exposed to silica gel, the frequency and size of cellular aggregates varied with the type of silica.

DR. SNYDER: I would just change that sentence. So the frequency and size of inflammatory cell aggregates varied with the type of silica.

DR. BELSITO: Okay.

MS. BECKER: Okay.

DR. BELSITO: So the frequency and size of inflammatory cell aggregates varied with the type of silica. Okay.

DR. SNYDER: That'll do it.

DR. BELSITO: Okay. Industry comments from Sassi, page 53. It says: In our opinion the following statement on page 53 does not accurately describe the commercial pyrogenic process used to manufacture synthetic amorphous silica. Amorphous silica is the product of a high heat process applied to crystalline silica. The contemporary pyrogenic process is accurately described on page 6 of the report and should be substituted for the description on page 53.

I'm just reading what was sent out to us.

DR. SNYDER: I can't make it out.

MS. BECKER: Maybe 6 and 3?

DR. SNYDER: It's on page 50, actually.

MS. BECKER: Page 50.

DR. BELSITO: They may be referring to the old report. I don't know.

DR. SNYDER: Here it is on page 50, the second paragraph. (off mike) pyrogenic silica is a product of high heat process applied to crystalline and silica.

MS. BECKER: You're on 50?

DR. SNYDER: Page 50.

DR. BELSITO: Fifty, the first and second paragraph.

DR. SNYDER: Second paragraph, first line.

DR. BELSITO: So --

MS. BECKER: You want to get rid of that sentence?

DR. BELSITO: Well, no. They're saying that it's not the way it's produced. The way it's produced is --

DR. SNYDER: On page 6.

DR. BELSITO: What we said on page 6: Precipitated silica and silica gels are produced from an alkaline metal silicate dissolved in water and then acid, usually sulfuric.

DR. LIEBLER: No, they are actually probably referring to the bottom of page 5 on the current report, amorphous pyrogenic silica.

DR. BELSITO: Yes. Okay.

DR. LIEBLER: So here it says, on page 5, the bottom of our current report, it says, "Amorphous pyrogenic silica is manufactured by the hydrolysis of volatile silanes, usually silica and tetrachloride, in the flame of an oxygen hydrogen burner."

And then page 50, second paragraph of our second report, it says, "Amorphous pyrogenic silica is the product of a high heat process applied to crystalline silica."

MS. BECKER: Right. Which is of that.

DR. BELSITO: Right. So what they're saying is that's not -- the contemporary pyrogenic process is the process currently described on page 5.

MS. BECKER: Right. The rest of the paragraph, I think --

DR. LIEBLER: We agreed.

MS. BECKER: So we just want to get rid of the --

DR. BELSITO: You want the amorphous pyrogenic silica, you just want to --

DR. SNYDER: Capture from page 6.

DR. BELSITO: -- capture from page -- no, 5.

DR. LIEBLER: Yeah, right. So the sentence on page 50, the first sentence of the second paragraph, amorphous pyrogenic silica through -- applied to crystalline silica, delete that sentence and in its place copy the sentence from the bottom of page 5, "Amorphous pyrogenic silica through oxygen hydrogen burner." It's the same definition word for word from the bottom of page 5 instead.

MS. BECKER: Thank you.

DR. BELSITO: Okay. The next comment from Sassi is we noted in our earlier comments the lack of differentiation between silica fumes and the commercial product called fumed silica, i.e., pyrogenic silica, leads to a clear misunderstanding of the significance of the statement on page 8 -- may be different -- regarding the high level of crystalline silica impurity 6 to 8 percent noted in the Swensson 1971 study.

DR. SNYDER: On page 7, first sentence.

DR. BELSITO: Since silica fume is a commercial product not classified as synthetic amorphous silica, we recommend deleting this reference on the basis of irrelevance. So, that's now on page 7.

DR. SNYDER: First sentence, (off mike) composition of the fumes.

DR. KLAASSEN: So you want to eliminate the first paragraph? Is that what we're talking about?

DR. LIEBLER: Maybe the first sentence.

DR. BELSITO: The first sentence.

DR. LIEBLER: Swensson, et al., through courts.

DR. BELSITO: You have the Cabot Corporation. They're not saying anything about --

DR. LIEBLER: So that's two (off mike).

DR. BELSITO: So it would just be, "Cabot Corporation 2004 states that its silicate products are greater than 99.8 percent pure." The moisture content, yeah, treated silicas are susceptible to.

Okay. Next comment from Sassi. On page 3, two references to Spiron as a technical name for silica are noted. Our members are not aware of this technical name and suspect it is a trade name.

MS. BECKER: For silica?

DR. BELSITO: That may have already been removed because I'm not seeing Spiron here anywhere.

SPEAKER: I don't see it.

MS. BECKER: You have that little table somewhere (off mike)?

DR. BELSITO: No, it would have just -- it would have been on the page. I mean, maybe it was in the old report and it's already been deleted. Again, this letter seems to be addressing the old report and not --

MS. BECKER: Yeah, because they would have got the version that I produced right after the last panel meeting.

DR. BELSITO: Okay.

MS. BECKER: It's been edited since then one more time before you got it.

DR. BELSITO: Okay. What you may want to do, Lillian, again, just do a word search for "Spiron." Make sure that it's been deleted.

Okay. Page 24, a reference to a UNEP 2004 study mentioned the LC50 of.69 1 milligrams per liter. We believe the greater than symbol was omitted in error on the LC50, so.

SPEAKER: On page 21? Under inhalation, third paragraph?

DR. BELSITO: Okay. So you need to check and be certain that they're correct, that the LC50 was greater than.691.

MS. BECKER: Sure.

DR. BELSITO: Okay. In the discussion we noted that the last sentence to the paragraph was incomplete. It appears a word may have been omitted. I didn't notice a word omitted, so this may again --

DR. LIEBLER: Last sentence of which paragraph?

DR. BELSITO: It just says, "in the discussion session section on page 50A." Well, it's not relevant anymore. We noted that the last sentence of the paragraph was incomplete.

MS. BECKER: Okay. Okay, it wasn't quite the last sentence. My guess is that the whole section was completely removed.

DR. BELSITO: Right. Okay. That was it from the silica council.

DR. SNYDER: They changed that sentence anyway. So instead of saying no pursuant silica is used -- to the panel determined that silicosis is not an issue since crystalline silica is not an ingredient used in cosmetics.

MS. BECKER: Okay.

DR. BELSITO: Okay.

DR. LIEBLER: I had a -- again, in the front on pages 4 and 5 of our current document, the use of subheads under, for example, Physical and Chemical Properties and then Properties.

MS. BECKER: I'm sorry. Where?

DR. LIEBLER: On page 4, Physical and Chemical Properties. And then you hove Properties and then you have the subhead Silica. And then there's no other compound like silicates referred to.

I think when you don't have any other compound referred to, you can just delete the Silica subheading. I made a few notes like that, but then I stopped. I think it's a question if there's going to be silica and then you're going to do aluminum magnesium silicate, then you have the subheads for each. Otherwise, you just delete silica subheads.

MS. BECKER: Okay.

DR. BELSITO: Except that I find it helpful because then you know exactly what information you have under that particular heading. You can quickly, very visually see it rather than -- I know what you're saying.

DR. LIEBLER: Yeah.

DR. BELSITO: It's like you look at properties and the only properties we're going to get are on silica. It's not going to be on something else.

DR. LIEBLER: Okay. I'm an editorial slasher by nature, so.

DR. KLAASSEN: You can have silica property.

DR. BRESLAWEC: May I suggest that we do whatever the JAMA format requires us to do in terms of the IJT publication on that?

DR. BELSITO: Okay.

DR. BRESLAWEC: We'll follow the guidance there.

DR. BELSITO: Sure. Okay, good. That sounds reasonable. Anything else on this silica?

DR. LIEBLER: When judgment fails, fall back on policy.

SPEAKER: What?

DR. LIEBLER: When judgment fails, fall back on policy.

DR. BELSITO: Okay. So no other comments. We'll move to sodium and potassium bromate.

MS. BECKER: So we're going final?

DR. BELSITO: We're going final. And I think the change moving the aluminum iron out of the conclusion is really editorial. I mean, it's not substantive so I don't think we need to send it out again.

Marks' Team Meeting:

DR. MARKS: You're welcome. Next is silica and silicates. We have in front of us a "Tentative Report of Silica and Related Ingredients." There were comments from industry. There's a September 3 letter from SASSI, the Synthetic Amorphous Silica and Silicate Industry Association, who characterized their comments as being relatively minor. The conclusion is that these ingredients are safe as cosmetic ingredients, that aluminum iron silicate is safe as a cosmetic ingredient in the practices and uses described in the safety assessment when formulated to be nonrespirable, and I think there are some potential comments about that. Ron Shank?

DR. SHANK: I think the conclusion is okay. The SASSI suggestions I agree with to put in as they have requested. There is a UNEP report of 2004. On page 21 SASSI refers to the LC50, we say 0.691 and SASSI says it should be less than 0.691. That can be checked by going to the UNEP report. On page 45 under "Clinical Assessment of Safety," it says that the oral lethal dose is 15 grams per kilogram. That would be over 1 kilo per person, so that there is something wrong there, and it really doesn't add anything. I would just throw it out. It's an FDA comment or something. With due respect to FDA, I don't think that could possibly be correct that the oral lethal dose is 15 grams per kilo. It would be pretty hard to take a kilogram for an adult. Those are my only comments.

DR. MARKS: Lillian will capture those then. I'm not sure we need to mention that tomorrow unless you feel we need to.

DR. SLAGA: Right.

DR. MARKS: Are there any other comments? Ron Hill?

DR. BERGFELD: I'd like to make a comment that I thought it was nicely reorganized and redefined so that we were not as confused in reading it. Thank you.

DR. MARKS: I suspect tomorrow that our team will be seconding a motion that a final report be issued with the conclusions as stated on page 55, that these are safe and with the proviso that aluminum iron silicates are not respirable. Let's take a break for 5 minutes. You have more comments? After your comments, Jay.

DR. ANSELL: Just on the wording, this is the first report we hit where we put in this "were ingredients in this group not currently to be used in the future. The expectation is that they be used in product categories and concentrations comparable to others in the group," is a little tortured.

DR. MARKS: We've discussed that at some time in the past, Jay. Do you have a proposal to make it clear and less tortured?

DR. ANSELL: No, not right now.

DR. MARKS: When you come up with the proposed change, let us look at it. I know we all worked on it, and Alan particularly.

Full Panel Meeting:

DR. BERGFELD: We're moving on to "Silica," Dr. Belsito.

DR. BELSITO: Yes, at the last meeting we issued a tentative safety assessment that these ingredients -- silica, aluminum magnesium metasilicate, aluminum calcium sodium silicate, hydrated silica, sodium potassium aluminum silicate -- are safe as cosmetic ingredients in the practice of use in concentrations as described in the safety assessment, and put a caveat in that conclusion that aluminum ion silicate is safe as a cosmetic ingredient, the practice of use in concentration as described in the safety assessment when formulated to be non-respirable.

We thought that we would like to make a minor editorial change in that conclusion and just put aluminum ion silicate into the list of other silica products that are safe as used and move the discussion of the ability of these particles to be inhaled, which essentially they cannot be because of their size -- they tend to aggregate into large molecular sizes -- into the discussion rather than putting it into the conclusion.

DR. BERGFELD: And that's a motion.

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there a second? Second, Paul? Discussion? Ron?

DR. SHANK: That's okay.

DR. BERGFELD: It's okay? Any other discussion?

DR. BELSITO: Yeah, in the discussion itself just putting -- stressing that these do tend to aggregate into larger molecular weight particles in formulation, stressing that a little bit more.

DR. BERGFELD: Any other discussion? Seeing none, I call the question. All those in favor of this conclusion please indicate by raising your hands. Unanimous. No abstainers. Okay.

Safety Assessment of Silicates as Used in Cosmetics

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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INTRODUCTION

The CIR Expert Panel (Panel) previously reviewed the safety of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite in a report that was published in 2003.[1] The Panel concluded that these ingredients were safe as used in cosmetic products. In accordance with its procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued.

The Panel also previously reviewed Potassium Silicate, Sodium Metasilicate, and Sodium Silicate in a report that was published in 2005 and concluded that these ingredients were safe for use in cosmetic products in the practices of use and concentration described in the safety assessment when formulated to avoid irritation.[2] In 2009, the Panel issued a final report on the safety of Silica, Alumina Magnesium Metasilicate (now called Magnesium Aluminometasilicate), Aluminum Calcium Sodium Silicate, Aluminum Iron Silicates, Hydrated Silica, and Sodium Potassium Aluminum Silicate with the conclusion that these ingredients are safe as cosmetic ingredients in the practices of use and concentrations as described in the safety assessment. Because of the similarity of these 9 ingredients to those of the original 2003 assessment, the Panel may be consider adding on these ingredients and 16 other related silicate ingredients, that were not previously reviewed, to this assessment. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1), the majority of these ingredients function as abrasives, absorbents, bulking agents, and/or deodorant agents in cosmetic products.[3]

Related ingredients that were previously reviewed by the Panel but are not up for consideration as add-ons include ammonium hectorites (Disteardiomonium Hectorite, Dihydrogenated Tallow Benzylmonium Hectorite, Stearlkonium Hectorite, and Quaternium -18 Hectorite) and silylates and surface-modified siloxysilicates (Silica Silylate, Silica Dimethyl Silylate, Trimethylsiloxysilicate, and Trifluoropropyldimethyl/Trimethylsiloxysilicate).[4,5] The conclusion of the former report was safe as used in cosmetic ingredients and the conclusion of the latter report was safe as used in cosmetics when formulated and delivered in the final product not to be irritating or sensitizing to the respiratory tract.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summary of the 2003 report, as well as the 2005 and 2009 reports of the potential add-ons, are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information, except for chemical and physical properties, is not included in the tables or the summary section.) The original reports that were published in 2003, 2005, and 2009 are available on the CIR website (http://www.cir-safety.org/ingredients).

CHEMISTRY

Definition

The definitions and functions of the silicate ingredients included in this re-review are provided in Table 1.

Physical and Chemical Properties

Physical and chemical properties of the silicate ingredients are provided in Table 2. These ingredients generally are not soluble in water.

Method of Manufacturing

No published methods of manufacturing were discovered, and no unpublished data were submitted for the proposed, not previously reviewed add-on ingredients.

Composition/Impurities

No composition/impurities data were discovered, and no unpublished data were submitted for the proposed, not previously reviewed add-on ingredients.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2018 VCRP data, Silica has the most reported uses in cosmetic products, with a total of 8024; the majority of the uses are in leave-on eye makeup preparations and makeup preparations (Table 3 and Table 4).[6] Kaolin has the second most reported uses in cosmetic products, with a total of 1794; the majority of the uses are also in leave-on eye makeup preparations and makeup preparations. The reported numbers of uses for the remaining ingredients in this report are much lower. The uses for both of these ingredients have greatly increased since the original safety assessments were finalized: in 2009, Silica was reported to have 3276 uses and in 1998, Kaolin was reported to have 509 uses.[1,2,7] The results of the concentration of use survey conducted in 2018 by the Council indicate Kaolin has the highest reported maximum concentration of use; it is used at up to 53% in "other" manicuring products and up to 35% in rinse-off "other" skin care preparations.[8] Zeolite is used at up to 37.8% in in paste masks and mud packs and up to 35.7% in hair tonics, dressings and other hair grooming aids. According to the original safety assessments, the maximum use concentration for Kaolin was 100% in leave-on "other" skin care preparations and the maximum use concentration for Hectorite was 100% in rinse-off skin cleansing preparations (the maximum leave-on concentration was 15% in makeup foundations).[1] Silica was reported to be used at up to 44% in eye shadows.[7] Cosmetic ingredients with no reported uses in the VCRP database are listed in Table 5. The Council is currently performing a concentration of use survey on Aluminum Calcium Sodium Silicate, Aluminum Iron Silicate, Aluminum Silicate, Calcium Magnesium Silicate, Hydrated Silica, Magnesium Aluimnometasilicate (previously Alumina Magnesium Metasilicate), Silica, Silver Copper Zeolite, Silver Zinc Zeolite, Sodium Potassium Aluminum Silicate, and Titanium Zeolite.

Many of the silicate ingredients described in this safety assessment may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, use is reported in lipsticks and oral hygiene products.[6] In the 2009 report, Hydrated Silica was reported to be in dentifrices at up to 34%.[7] Additionally, these ingredients have been reported to be used in products that may come into contact with the eyes, such as eye shadows, eye liners, and mascaras. In the 2003 report, Kaolin was reported to be used at up to 48% in eyeliner.[1] Moreover, these ingredients are reported to be used in spray products and powders that could possibly be inhaled, like hair sprays and face powders. In the original reports, Silica was reported to be used at up to 6% in a fragrance product and Kaolin was reported to be used at up to 30% in face powders.[1,7] In practice, 95% to 99% of the droplets/ particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump spray.[9-12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[9,11] Silicates are also used in powders, and these products could possibly be inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[13-15]

In regulations on cosmetic products in the European Union, zirconium and its compounds (including Zirconium Silicate) are listed under Annex II-substances prohibited in cosmetic products, with the exception of the substances listed under reference number 50 in Annex III, and the zirconium lakes, pigments or salts of the coloring agents when listed in Annex IV.[16] Aluminum Silicate, Bentonite, and Kaolin are listed under Annex IV – colorants allowed in cosmetic products. The remaining silicate-related ingredients listed in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.

According to Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS), the following ingredients are Tier I chemicals (not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment): Aluminum Silicate, Bentonite, Calcium Silicate, Fuller's Earth, Kaolin, Magnesium Silicate, Magnesium Trisilicate, Montmorillonite, Sodium Potassium Aluminum Silicate, Zeolite, and Silica (as amorphous, fumed, crystalline-free; gel; gel-precipated, crystalline-free; and vitreous).[17] Attapulgite, Potassium Silicate, Sodium Silicate, Sodium Metasilicate, and Silica (crystalline) are Tier II chemicals (require risk management measures to be instituted for safe use for human health or the environment). The remaining silicates have no NICNAS determination.

Non-Cosmetic

Aluminum Silicate is approved as an indirect food additive in the Code of Federal Regulations (CFR).[1] Bentonite is considered GRAS as a direct food additive and Kaolin is considered GRAS as an indirect food additive. Pyrophyllite is listed as a naturally occurring color additive in the CFR. Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Trisilicate, Attapulgite, Hectorite, and Kaolin are all used in over-the-counter drug products.

Potassium Silicate and Sodium Silicate were reported as being used in industrial cleaners and detergents.[2] Sodium Metasilicate is a GRAS food ingredient.

Hydrated Aluminum Calcium Sodium Silicate countered the effects of aflatoxin in animal feed.[7] Silica is used in food preparation as an anticaking agent, dispersion agent, suspending agent, and thickening agent. It is a defoaming and conditioning agent in malt beverages. Silica is a thickener in pastes and ointments.

Calcium Silicate

Calcium Silicate is used in endodontics in root canal sealer preparations and dental cements.[18-20]

Fuller's Earth

Fuller's Earth is reported to be used as military decontaminant for removal of hazardous materials from the skin.[21]

Sodium Magnesium Aluminum Silicate

Sodium Magnesium Aluminum Silicate is reported to be used in print enhancement (imparting high brightness and opacity), paper filer, and carbonless copy intensifier.[22]

Zeolite

The use of Zeolite has been investigated for use in oral drug delivery of acidic medications, such as aspirin.[23]

Zinc Silicate

Zinc Silicate is reported to be used as phosphors (in television screens), in spray ingredients, and to remove traces of copper from gasoline.[22,24]

TOXICOKINETICS

Absorption, Distribution, Metabolism, Distribution

All silicates have the great ability to absorb, especially the clays.[1] Reports describe drugs, bacteria, viruses, and toxins absorbed to clays due to the physical structure of clays and their cationic nature.

No statistically significant absorption of aluminum and elevated levels of silicon were recorded in assayed plasma samples given Magnesium Trisilicate and Zeolite orally.[1] The urinary excretion of silica was 5.2% in males given 20 g of Magnesium Trisilicate. Ten percent Bentonite in the diets of rats overcame T-2 toxicosis completely. Various Zeolites were added to the diets of pigs. No adverse effects were noted by the supplementation.

A sample of Aluminum Silicate was toxic to pulmonary alveolar macrophages and LDH activity and β-GAL release were increased.[1] Aluminum Silicate had relatively no effect on the hemolysis of rat RBCs. Synthetic Calcium Silicate samples and higher concentrations of Calcium Silicate caused increased hemolysis of human RBCs; a greater fibrous character of Calcium Silicate samples caused increased LDH and β-Gal release. Many clays (Attapulgite, Bentonite, Hectorite, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite) demonstrated cytotoxicity to several macrophage type cell lines and have hemolytic activity towards seceral species' RBCs. Particle size, fibrogenicity, concentration, and mineral composition had the greatest effect on toxicity. Larger particle size and longer and wider fibers cause more adverse effects. In most of the studies, a dose-dependent effect on cytotoxicity or lysis was observed. Most mineral samples were not 100% pure and many samples already contained toxic dusts or minerals like quartz or cristobalite.

Sodium Silicate administered orally acts as a mild alkali and was readily absorbed from the alimentary canal and excreted in the urine.[2] Urinary excretion of Sodium Silicate given orally to rats at 40 and 1000 mg/kg was 18.9% and 2.8%, respectively.

Orally administered Silica was mostly excreted through the urine in guinea pigs.[7] Some studies showed accumulation of Silica from oral exposure whereas others did not. Silica intraperitoneally injected

into guinea pigs was mostly excreted through the urine. When Silica is inhaled by rats, it accumulates in the lungs and lymph nodes initially. The accumulated amount remains at a steady state with continued treatment. When treatment ceases, the Silica decreases. When subcutaneously injected into rats, Silica is absorbed over a few months. When Silica is inhaled or intratracheally instilled into rats, mice, and rabbits, there is a transient inflammatory response that resolves in days. Incubated macrophages ingested fewer Silica particles than C. albicans or S. cerevisiae. Ultra-fine Silica (14 nm) did more damage to the lungs during the inflammation than did fine Silica (213 nm).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The following are a list of acute oral LD_{50} determinations: Calcium Silicate, 3400 mg/kg in rats; Magnesium Aluminum Silicate, 50,000 mg/kg in mice; Zirconium Silicate, > 200 g/kg in mice; Hectorite, > 5 g/kg in rats; Kaolin, 149 g/kg in rats (death due to bowel obstruction); 15 natural Zeolites, 10 g/kg in rats.[1] *The acute dermal LD_{50} was > 3.5 g/kg of r rabbits exposed to Magnesium Aluminum Silicate.*

The toxicity of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate has been related to the molar ratio of SiO_2/Na_2O and the concentration.[2] *The acute oral LD_{50} of Sodium Metasilicate ranged from 847 mg/kg in male ras to 1349.3 mg/kg in female rats, and from 770 mg/kg in female mice to 820 mg/kg in male mice. Gross lesions of variable severity were found in the oral cavity, pharynx, esophagus, stomach, larynx, lungs, and kidneys of dogs receiving 0.25 g/kg or more of a commercial detergent containing Sodium Metasilicate. Similar lesions were seen in pigs given the same detergent and dose as in the previous study. Male Sprague-Dawley rats orally administered 464 mg/kg of a 20% solution containing either 2.0 or 2.4 ratio to 1.0 ratio of sodium oxide showed no signs of toxicity, whereas doses of 1000 and 2150 mg/kg produced gasping, dyspnea, and acute depression. Acute intraperitoneal injections of a neutralized 2% solution of Sodium Metasilicate in white rats resulted in a decrease in spleen weight and relative enlargement of the kidneys.*

Silica was reported to have an oral LD_{50} of > 40,000 mg/kg in rats and > 8000 mg/kg in mice.[7] *The oral lethal dose of pyrogenic silica in humans is 15 g/kg. Orally administered Aluminum Calcium Sodium Silicate had no adverse effects up to 800 mg/kg in mice. The acute dermal NOEL for silica is > 2000 mg/kg for rabbits. When applied as an aqueous paste, there were no adverse effects. The LD_{50} was > 5000 mg/kg for precipitated (hydrated) Silica and > 2000 mg/kg for silica gel on intact and abraded rabbit skin. Mild erythema was observed. The acute inhalation of silica at 477 mg/m^3 by rats resulted in restlessness, droopy eyelids, lethargy, and dyspnea during treatment. Clinical signs resolved quickly after treatment and necropsies were unremarkable.*

Acute dermal, oral, and inhalation data from recent literature searches are summarized in Table 6. Potassium Silicate (30%) had a dermal LD_{50} greater than 5 g/kg in rats. [25] In oral rat studies, the LD_{50} for Aluminum Silicate (concentration not reported), Calcium Silicate (20%), Potassium Silicate (concentration not reported), Sodium Magnesium Aluminum Silicate (concentration not reported), and Sodium Silicate were > 2 g/kg, > 10g/kg, > 5 g/kg, > 2 g/kg, and up to 8.65 g/kg, respectively.[25-30] An oral LD_{50} for Sodium Silicate in mice was 6.60 g/kg.[27] In an inhalation study, the LC_{50} for 30% Potassium Silicate in rats was > 2.06 mg/l.[25]

Short-Term and Subchronic Toxicity Studies

In short-term oral toxicity studies, no adverse effects were seen in mice or rabbits dosed up to 5 g/kg Magnesium Aluminum Silicate; beagle does and rats fed Aluminum Silicate had no renal lesions.[1] *Dogs and rats fed Magnesium Trisilicate for 4 weeks had polydipsia and polyuria, and all dogs had renal cortical lesions. Guinea pigs had renal lesions after 4 months of drinking Magnesium Trisilicate in their tap water. Rats fed 10% Magnesium Aluminum Silicate had slightly elevated silicon levels of the spleen and dogs and rats fed 10% Magnesium Aluminum Silicate had no negative responses in 90-day feeding studies.*

Beagle dogs fed 2.4 g/kg/day of Sodium Silicate for 4 weeks had gross renal lesions but no impairment of renal function. In an oral subchronic study (drinking water containing 600 and 1200 ppm of added silica), there were body weight gains in male rats, but decreases in female rats. No apparent effect of the treatment in the drinking water was found on the longevity in rats having started treatment after weaning.

Short-term oral doses of silica at 8000 mg/kg/d produced no clinical effects in dogs. Short-term oral doses of silica produced no clinical effects for rats; [highest no effect levels] (*HNELS*) *were up to 1000 mg/kg/d. At 16,000 mg/kg, clinical signs observed were shyness, dirty fur, reduced activity, cachexia,*

hemorrhages of mucous membranes of the eyes and nose. Short-term dermal application of silica to intact and abraded skin resulted in no dermal toxicity in rabbits.

Short-term inhalation of silica up to 668 mg/m3 resulted in respiratory distress during treatment and a short-term inflammation response in the lungs, which resolved quickly when treatment ceased in rats. The lung clearance half-life was ~50 day for 50.5 and 154 mg/m3. The NOAEL was 10.1 mg/m3 in one study. In other studies, the NOEL was 1 and 46 mg/m^3.

The oral subchronic HNEL was 5000 mg/kg/d, the NOEL was 500 mg/kg/d and the lowest effect level was 500 mg/kg/d for rats. There were no clinical signs up to 7950 and 8980 mg/kg/d for male and female rats, respectively. There were no gross findings of toxicity up to 50,000 ppm in feed.

Subchronic inhalation of silica at 53 mg/m^3 caused 44% mortality in rats from pulmonary vascular obstruction and emphysema. There was increased respiration rates and decreased weight gain during treatment. Necropsy findings included congestion of the lungs, lymph node enlargement, emphysema, vacuolated cells within alveolar spaces, and increased lung weights and collagen content. There were no mortalities at 31 mg/m^3. The LOAEL was 53 mg/m^3. The NOEL was 1.3 mg/m^3.

Montmorillonite

In a 90-day subchronic study of an organo-modified clay mineral derived from Montmorillonite, Wistar rats were exposed orally to 40 mg/kg/day to the clay.[31] No adverse effects were observed in the main organ tissues and no significant effects were observed in blood clinical biochemistry parameters, reduced/oxidized glutathione ratio, or interleukin-6 leakage in serum. The authors concluded that the modified Montomorillonite clay did not cause toxic effects in this oral study in rats.

In a 28-week study, male and female Sprague–Dawley rats were fed 0%, 0.25%, 0.5%, 1.0% or 2.0% (0, 2500, 5000, 10,000 or 20,000 ppm, respectively) Montmorillonite clay (calcium montmorillonite; 9.34% total Al).[32] This corresponded to a daily clay consumption of 75, 150, 300 and 600 mg/kg/day, respectively. There were no significant differences in either gender regarding feed consumption, body weight gain, feed efficiency or relative organ weights. There were no differences in gross lesions or histopathological changes in liver, kidney, lung, heart, brain, spleen, tibia, uteri or ovaries in any of the treated groups when compared to the control. There were no differences in hematologic parameters or in clinical chemistry parameters. Serum and hepatic vitamins A and E remained unaffected by clay ingestion. The authors concluded that concluded that feeding up to 2.0% (20,000 ppm or 600 mg/kg/day) Montmorillonite [equivalent to1860 ppm total Al as the hydrated aluminum silicate] to rats did not elicit signs of systemic toxicity.

Chronic Toxicity Studies

No lesions were found in rats dosed up to 1000 mg/kg Zeolite for 104 weeks.

Silica incorporated into the feed of rats at up to 10% for 6 months or more produced unremarkable necropsies.[7] Females had increased leukocytes and males had increased eosinophils at 10% in feed. Females had reduced liver weights at 12 and 24 months at 5%. Mice treated with Silica in their feed had similar results for up to 103 weeks.

In inhalation studies, mice bred to be susceptible to tumors exposed to aerosolized Silica at 0.5 g/d for a year had increased incidence of lung tumors with no obvious fibrosis of the lung tissue but fibrotic nodules in the tracheo-bronchial lymph nodes.[7] At 53 mg/m^3 for a year, treatment related deaths were 75% in rats from pulmonary vascular obstruction and emphysema starting in the 4th month. Guinea pigs exposed to Silica at 1.5 mg/ft^3 for up to 24 months had no deaths. A chronic reaction of the lung tissue was established at 4 months and emphysema after 4 to 8 months. Histologically, there [were] *periductal and peribronchiolar intra-alveolar accumulations of the giant cells. In the lymphoid tissue, medullary hyperplasia with the formation of slight amounts of reticulum was prominent during the second year of exposure. There were no macroscopically visible anomalies after 1 year of recovery.*

Rabbits chronically exposed to 0.2 and 5.0 mm aerosolized Silica had formation of nodular fibrotic or diffuse fibrotic changes in the lungs.[7] Rats exposed to aerosolized Silica at 15 mg/m^3 for 12 months had a few macrophages aggregated in the lungs. The LOAEL was 6 to 9 mg/m^3. At 126 mg/m^3 of Silica for up to 24 months, guinea pigs and rabbits had increased lung weights and particle phagocytosing macrophages accumulated in alveoli, bronchioles, and lymphoid tissue. There was complete reversibility of Silica retention and inflammatory responses in guinea pigs within 6 months of recovery. Silicotic processes were completely absent. Rabbits exposed to aerosolized silica at 1.5 mg/ft^3 for 12 months had progressive functional incapacitation and elevation of hematocrit levels observed in the majority of the rabbits, possibly due to the combined effect of pulmonary vascular obstruction and emphysema. During recovery, the cellular reactions

and emphysema regressed but minor focal alveolar mural collagen persisted. In rabbits exposed to 360 mg/m^3 for a year, emphysema, pulmonary emphysema, vascular stenosis, alveolar cell infiltration, sclerosis, and epithelization granulomatosis, macrophage catarrh were observed. Lesions were observed in the liver, spleen and kidney. The LOAEL was 28 mg/m^3.

Monkeys exposed to aerosolized silica at 15 mg/m^3 for 12 months had initial decreased activity and body weight gain.[7] There was emphysema at 3 months and considerable cellular infiltration of the alveoli and alveolar septa associated with distention of alveoli or accumulation of exudate and macrophages. After 12 months, the lesions were marked pulmonary emphysema, alveolar wall sclerosis, vascular occlusions, and cor pulmonale. The silica content remained low and decreased over time. At 50 and 100 mg/m3, there was interstitial fibrosis which did not resolve after 24 months. When monkeys were exposed to different types of Silica, the precipitated (hydrated) silica group had lower lung volumes. There were no changes in lung volume parameters, but in ventilatory performance and mechanical parameters, dynamic lung compliance, and forced expiratory flow when exposed to silica gel. The frequency and size of inflammatory cell aggregates varied with the type of Silica.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Calcium Silicate (250 to 1600 mg/kg) had no discernible effect on nidation or on maternal or fetal survival in rabbits.[1] Magnesium Aluminum Silicate (6000 mg/kg) had neither a teratogenic nor adverse effects on the mouse fetus. Female rats receiving 20% Kaolin diet exhibited maternal anemia but no significant reduction in birth weight of the pups was recorded. Type A Zeolite produced no adverse effects on the dam, embryo, or feuts in either rats or rabbits at any dose level (74 or 1600 mg/kg). Clinoptilolite had no effect on female rat reproductive performance.

Rats given Sodium Silicate (600 and 1200 ppm of added silica0 in the drinking water in reproductive studies produced a reduced number of offspring; to 67% of controls at 600 ppm and to 80% of controls at 1200 ppm.[2] Three adult rats injected intratesticularly and subcutaneously with 0.8 mM/kg of Sodium Silicate showed no morphological changes in the testes and no effect on the residual spermatozoa in the ductus deferens.

No reproductive or teratological effects were observed following the oral administration of Silica in rabbits at 1600 mg/kg/d, hamsters at 1600 mg/kg/d, mice 1340 mg/kg/d, and rats up to 1350 mg/kg/d.[7] An oral NOEL of 500 mg/kg/d was reported for rats; an oral NOAEL of 1350 mg/kg/d was also reported.

GENOTOXICITY STUDIES

No increase in mutation frequencies were seen in the Salmonella TA-1530 or G-46 assay and no significant increase in recombinant activity in the Saccharomyces D3 assay treated with Calcium Silicate.[1] A subacute dose of 150 mg/kg of Calcium Silicate produced 3% breaks in bone marrow cells arrested in c-metaphase. In a metaphase spread of bone marrow cells, Calcium Silicate produced no significant increase in the number of aberrations compared to controls and in a dominant lethal assay did not induce any dominant lethal mutations. In the S. typhimurium LT2 spot test (TA98, TA100, TA1535, TA1537, and TA1538) with or without metabolic activation, Magnesium Aluminum Silicate and Hectorite were found to be nonmutagenic. In primary hepatocyte cultures, the addition of Attapulgite at 10 µg/cm^2 caused significant increases in UDS in rat pleural mesothelial cells. Zeolite particles (< 10 µm) produced statistically significant increase in the percentage of aberrant metaphases, mostly chromatid breaks.

Sodium Metasilicate was nonmutagenic in a DNA damage and repair assay without metabolic activiation using B. subtilis.[2] Sodium Silicate was nonmutagenic in studies using E. coli strains B/Sd-4/1,3,4,5 and B/Sd-4/3,4.

Silica was not mutagenic using the Rec or Ames test up to 10 M.[7] Silica was not mutagenic in Ames test up to 1580 µg/plate. In a single-cell gel/Comet assay using Chinese hamster fibroblasts, there was an increase in DNA migration in a dose-dependent manner. A chromosomal aberration test was negative up to 300 µl/ml without and 1000 µl/ml with metabolic activation. A HGPRT was negative up to to 250 µm/ml without and 500 µm/ml with metabolic activation. An unscheduled DNA synthesis test was negative up to 1000 µm/ml. Silica was not mutagenic to CHO cells, hamster fibroblasts, rat hepatocytes, and human embryonic lung cells. Silica was not mutagenic to mice or rats. A positive sister chromatid exchange test of AFB_1 showed inhibition by 10^{-5} M Aluminum Calcium Sodium Silicate. Hydrated Aluminum Calcium Sodium Silicate at 0.5% in the feed of rats inhibited the effects of AF.

In Vitro

Genotoxicity data from recent literature searches are summarized in Table 7. Aluminum Silicate, Sodium Metasilicate, Sodium Silicate, and Zinc Silicate were not genotoxic in Ames tests, HPRT gene mutation assays, or chromosome aberration tests.[27,28,33,34] Potential genotoxicity was observed in Montmorillonite in an Ames test and a cytokinesis block micronucleus cytome assay.[35,36]

CARCINOGENICITY STUDIES

The Internaional Agency for Research on Cancer (IARC) has ruled Attapulgite fibers > 5µm as group 2B, possibly carcinogenic to humans, and fibers < 5µm as group3, not classified as to their carcinogenicity to humans.[1] The natural Zeolites (clinoptilolite, phillipsite, mordenite, and nonfibrous Japanese zeolite) and synthetic Zeolites cannot be classified as to their carcinogenicity to humans (group3) according to IARC.

Oral administration of silica to rats for 24 months was not carcinogenic up to 100 mg/kg/d.[7] In an inhalation study, Silica at 0.5 g/d administered to mice for a year increased the incidence of overgrowth or hyperplasia of the tracheobronchial lymph nodes from 14.3% to 29.5%.

OTHER RELEVANT STUDIES

Cytotoxicity

Silica is not cytotoxic to Chinese hamster V79 cells at up to 160 µg/l[7]. Pyrogenic silica and silica gel were cytotoxic to macrophages at 13.5 µg/cm^2; precipitated silica was less cytotoxic. Micronuclei were induced in Chinese hamster cells when incubated with 80 and 160 mg/ml. Micronuclei were induced with the presence of silica. There was ~85% lysis of sheep blood erythrocytes incubated with silica. Mesothelial cells incubated in silica were observed to accumulate silica in the cytoplasm, around the nucleus, and vacuoles. When incubated in pyrogenic silica, both macrophages and neutrophils were inhibited in their ability to phagocytose sheep red blood cells. Silica caused intracellular alteration in calcium homeostasis in renal cells. Alveolar macrophages exposed to silica had increased protein kinases, NO_x production, and cell death. Human primary fibroblasts exposed to silica produced COX-2 and PGE_2 in a dose dependent manner. COX-1 was not affected. Silica was not cytotoxic to human mesothelioma and rodent fibroblast cells. Sodium Potassium Aluminum Silicate, in the form of Mexicali dust, induced anaphasic alterations in Balb3T3 cells.

Montmorillonite

The cytotoxicity of 3 different organo-modified Montmorillonite clays was assessed using the human cell lines Caco-2 and HepG2.[37] The cells were exposed to the clay materials for 0, 24, or 48 h at concentrations dependent on the type of modifications to the clay material (maximum concentrations were 8µg/ml, 125 µg/ml, or 62.5 µg/ml, respectively). Only one clay material induced toxic effects in both cell lines. In calculating the mean effective concentration, it was determined that Caco-2 was more sensitive than HepG2. Mechanistic biomarkers were utilized to determine the toxicity mechanism of the clay that affected both cell lines; it was found that glutathione content decreased in HepG2, but interleukin leakages and generation of intracellular reactive oxygen species were not observed. DNA damage, as determined with a comet assay, was induced in both cell lines at the highest concentration tested. The authors concluded that toxicity of the modified clay materials was dependent on the type of clay modifications, the concentration, and the type of cell line tested.

In another cytotoxicity study by the same group of researchers, unmodified and organo-modified Montmorillonite clays were studied using human umbilical vein endothelial cells.[36] The unmodified clay was tested at up to 62.5 µg/ml and the modified clays were tested at up to 250 µg/ml. Two of the modified clays induced cytotoxic effects, while the third modified clay and the unmodified clay did not induce cytotoxicity.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal Irritation

Magnesium Aluminum Silicate (4%) was a weak primary skin irritant in rabbits and had no cumulative skin irritation in guinea pigs. No gross effects were reported in any of these studies. Sodium Magnesium Silicate (4%) had no primary skin irritation in rabbits and had no cumulative skin irritation in guinea pigs. Hectorite was nonirritating to the skin of rabbits in a Draize primary skin irritation study. Applications of 2 g of Magnesium Aluminum Silicate made to the skin of two humans daily for 1 week caused no effects.

Dermal irritation of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate ranged from negligible to severe, depending on the species tested and the molar ratio and concentration tested.[2] Sodium Metasilicate/carbonate detergent (37% Sodium Metasilicate) mixed 50/50 with water was considered a severe skin irritant when tested on intact and abraded human skin. Detergents containing 7%, 13%, and 6% Sodium Silicate mixed 50/50 with water, however, were negligible skin irritants to intact and abraded human skin. Sodium Silicate (10% of a 40% aqueous solution) was negative in a repeat-insult predictive patch test in humans. The same aqueous solution of Sodium Silicate was considered mild under normal use conditions in a study of cumulative irritant properties. Sodium Metasilicate and Sodium Silicate were studied in modified soap chamber tests. No burning or itching was observed and low erythema + edema scores were noted. Sodium Metasilicate and Sodium Silicate, tested in elbow crease studies and semioccluded patch tests, produced low grade and transient irritation.

Silica at 100% was nonirritating to intact and abraded rabbit skin.[7]

Dermal Sensitization

Sodium Metasilicate was negative in the local lymph node assay, but a delayed-type hypersensitivity response was observed in mice.[2]

A guinea pig sensitization study of 20% Hydrated Silica resulted in no reactions.[7] Hydrated Silica and Silica was non-sensitizing in humans at up to 21.7% and 45%, respectively.

In vitro and animal dermal irritation and animal sensitization data from recent literature searches are summarized in Table 8. Aluminum Silicate and Zinc Silicate were predicted to be not irritating in EpiDerm™ skin assays.[28,33] In rabbit studies, the irritation potential of Potassium Silicate (up to 36%) and Sodium Metasilicate (up to 97%) were dependent on concentration.[25,30,34] Aluminum Silicate (up to 25%) and Zinc Silicate (up to 50%) were not sensitizing in LLNA studies.[28,33] Potassium Silicate (30%) was not sensitizing in a Buehler sensitization test in guinea pigs.[25]

OCULAR IRRITATION STUDIES

A 4% solution of Magnesium Aluminum Silicate and a 4% solution of Sodium Magnesium Silicate caused minimal eye irritation in a Draize eye irritation test.[1] Bentonite caused severe iritis after injection into the anterior chamber of the eyes of rabbits. When injected intralamellarly, widespread corneal infiltrates and retrocorneal membrances were recorded. In a primary eye irritation study in rabbits, Hectorite was moderately irritating without washing and practically nonirritating to the eye with a washout. Rats tolerated a single dose of Zeolite A without any adverse reaction to the eye.

Potassium Silicate was nonirritating in two acute eye irritation studies in rabbits.[2] Sodium Metasilicate (42.4% H_2O) was corrosive to the rabbit eye. Sodium Silicate was a severe eye irritant in acute eye irritation studies. A skin freshener (10% of a 40% aqueous solution) containing Sodium Silicate was nonirritating. Sodium Silicate in another three Draize eye irritation studies was highly irritating, irritating, and nonirritating, respectively.

Silica was a non- to mild ocular irritant in rabbits up to 100 mg.[7]

In vitro and animal ocular irritation data from recent literature searches are summarized in Table 9. Aluminum Silicate (tested pure) was predicted to be not irritating using the hen's egg test chorioallantoic membrane (HET-CAM) method.[28] Sodium Metasilicate (concentration not reported) was predicted to be corrosive in an in vitro method using rabbit eyes, and Zinc Silicate (20%) was predicted to be irritating in a bovine corneal opacity and permeability (BCOP) test.[33,34] Potassium Silicate was not irritating to slightly irritating when tested at up to 35%.[25,30]

CLINICAL STUDIES

Clinical Assessment of Safety

Oral ingestion of Silica up to 1250 mg in humans resulted in a rapid increase of Silica blood levels and a rapid elimination in the urine over 8 to 24 h with no adverse effect reported.[7]

Montmorillonite

The safety of the oral use of Montmorillonite to protect against the adverse effects of the ingestion of aflatoxins was studied in 50 human subjects for 2 weeks.[38] The clinical study was randomized and double-blinded.

The 23 males and 27 females ranged in age from 20–45 years. The low-dose group received nine capsules containing 1.5 g/day processed Montmorillonite, and the high-dose group received nine capsules containing 3.0 g/day processed Montmorillonite. Blood and urine samples were collected before and after the study for analysis. All participants completed the trial and compliance was 99.1%. Mild gastrointestinal effects were reported, including abdominal pain (6%, 3/50), bloating (4%, 2/50), constipation (2%, 1/50), diarrhea (2%, 1/50), and flatulence (8%, 4/50). No statistical significance was found between the two groups for these adverse effects ($p > 0.25$). No significant differences were shown in hematology, liver and kidney function, electrolytes, vitamins A and E, and minerals in either group.

Case Reports

Colloidal Sodium Metasilicate was fatal to one man and neutralized Sodium Silicate produced vomiting, diarrhea, and gastrointestinal bleeding in another man in separate case reports.[2]

Sodium Metasilicate

Acute kidney injury was reported in a 52-year-old man who had ingested approximately 150 ml of a plate developer solution containing Sodium Metasilicate.[39] The patient also developed severe upper airway obstruction due to laryngeal edema, severe inflammation of the upper gastrointestinal tract with narrowing of the esophagus and pyloric region. The patient succumbed to his injuries a few months after the ingestion incident.

Reactive airway dysfunction syndrome was reported in 43-year-old man who had inhaled dishwasher detergent powder containing Sodium Metasilicate.[40] The patient was employed as an apprentice cook and accidentally inhaled the detergent while preparing to use an institutional dishwasher.

Occupational Exposure

Occupational exposure to mineral dusts has been studied extensively. Fibrosis and pneumoconiosis has been documented in workers involved in the mining and processing of Aluminum Silicate, Calcium Silicate, Zirconium Silicate, Fuller's Earth, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite.

Workers in environments with aerosolized silica had few signs of silicosis or pulmonary disease up to 100 mg/m^3.[7] *Smoking and exposure to silica synergize to induce small airway disease. Exposure to hydrated silica also had no evidence of silicosis or pulmonary disease. There were signs of dermal irritation due to the desiccative and defatting properties of silica.*

Bentonite

In a toxicological and epidemiological review of Bentonite, the authors concluded Bentonite is probably not more toxic than any other particulate. However, because some forms may contain variable amounts of respirable crystalline silica, prudent management and adherence to occupational exposure limits is appropriate.[41]

Zeolite

In a safety assessment of synthetic zeolites (zeolites A, P, X, and Y) used in detergents, the author concluded that these ingredients are safe for consumers under the conditions of recommended use.[42] The author further stated that due to irritant effects of undiluted zeolite material on mucous membranes and the respiratory tract, the exposure of workers should be controlled.

SUMMARY

The Panel previously reviewed the safety of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite in a report that was published in 2003 and concluded that these ingredients were safe as used in cosmetic products. In accordance with its procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued. Proposed ingredients to "add-on" to this report are the previously reviewed ingredients Potassium Silicate, Sodium Metasilicate, and Sodium Silicate that the Panel concluded were safe when formulated to avoid irritation, and the previously review ingredients Silica, Alumina Magnesium Metasilicate, Aluminum Calcium Sodium Silicate, Aluminum Iron Silicates, Hydrated Silica, and Sodium Potassium Aluminum Silicate that the Panel concluded were safe for use in cosmetic. Because of the similarity of these 9 ingredients to those of the original

2003 assessment, the Panel may be consider adding on these ingredients, plus 16 other related silicate ingredients that were not previously reviewed to this assessment.

According to 2018 VCRP data, Silica has the most reported uses in cosmetic products, with a total of 8024; the majority of the uses are in leave-on eye makeup preparations and makeup preparations. Kaolin has the second most reported uses in cosmetic products, with a total of 1794; the majority of the uses are also in leave-on eye makeup preparations and makeup preparations. The reported numbers of uses for the remaining ingredients in this report are much lower. The uses for both of these ingredients have greatly increased since the original safety assessments were finalized: in 2009, Silica was reported to have 3276 uses and in 1998, Kaolin was reported to have 509 uses. The results of the concentration of use survey conducted in 2018 by the Council indicate Kaolin has the highest reported maximum concentration of use; it is used at up to 53% in "other" manicuring products and up to 35% in rinse-off "other" skin care preparations. Zeolite is used at up to 37.8% in in paste masks and mud packs and up to 35.7% in hair tonics, dressings and other hair grooming aids. According to the original safety assessments, the maximum use concentration for Kaolin was 100% in leave-on "other" skin care preparations and the maximum use concentration for Hectorite was 100% in rinse-off skin cleansing preparations (the maximum leave-on concentration was 15% in makeup foundations). Silica was reported to be used at up to 44% in eye shadows.

Potassium Silicate (30%) had a dermal LD_{50} greater than 5 g/kg in rats. In oral rat studies, the LD_{50} for Aluminum Silicate (concentration not reported), Calcium Silicate (20%), Potassium Silicate (concentration not reported), Sodium Magnesium Aluminum Silicate (concentration not reported), and Sodium Silicate were > 2 g/kg, > 10g/kg, > 5 g/kg, > 2 g/kg, and up to 8.65 g/kg, respectively. An oral LD_{50} for Sodium Silicate in mice was 6.60 g/kg. In an inhalation study, the LC_{50} for 30% Potassium Silicate in rats was > 2.06 mg/l.

In oral subchronic rat studies up to 28 weeks, an organo-modified Montmorillonite clay (40 mg/kg /day) and an unmodified clay (up to 600 mg/kg/day) did not cause systemic toxicity.

Aluminum Silicate, Sodium Metasilicate, Sodium Silicate, and Zinc Silicate were not genotoxic in Ames tests, HPRT gene mutation assays, or chromosome aberration tests. Potential genotoxicity was observed in Montmorillonite in an Ames test and a cytokinesis block micronucleus cytome assay.

Aluminum Silicate and Zinc Silicate were predicted to be not irritating in EpiDerm™ skin assays. In rabbit studies, the irritation potential of Potassium Silicate (up to 36%) and Sodium Metasilicate (up to 97%) were dependent on concentration. Aluminum Silicate (up to 25%) and Zinc Silicate (up to 50%) were not sensitizing in LLNA studies. Potassium Silicate (30%) was not sensitizing in a Buehler sensitization test in guinea pigs.

Aluminum Silicate (tested pure) was predicted to be not irritating using the HET-CAM method. Sodium Metasilicate (concentration not reported) was predicted to be corrosive in an in vitro method using rabbit eyes, and Zinc Silicate (20%) was predicted to be irritating in a BCOP test. Potassium Silicate was not irritating to slightly irritating when tested at up to 35%.

A 2-week clinical oral study of Montmorillonite resulted in only mild gastrointestinal complaints in 50 subjects. Case reports of severe injury were reported from ingestion and inhalation of Sodium Metasilicate. Occupational exposures to Bentonite and Zeolite should be limited.

ORIGINAL REPORT DISCUSSIONS

2003 Silicates Report

The CIR Expert Panel determined that the data provided in this report are sufficient to assess the safety of the tested ingredients: Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite. The Panel did note a concern about inhalation of these ingredients due to reported cases of pneumoconiosis and fibrosis in humans and pulmonary lesions in animals. However, extensive pulmonary damage in humans was the result of direct occupational inhalation of the dusts and lesions seen in animals were affected by particle size, fiber length, and concentration. The Panel recognizes that most of the formulations are not respirable and of the preparations that are respirable, the concentration of the ingredient is very low. Even so, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation.

2005 Potassium Silicate, Sodium Metasilicate, and Sodium Silicate Report

The CIR Expert panel determined that the data provided in this report are sufficient to address the safety of the tested ingredients Potassium Silicate, Sodium Metasilicate, and Sodium Silicate. The Panel recognized the irritation potential of these ingredients, especially in leave-on products. However, because

these ingredients have limited dermal absorption and Sodium Metasilicate is a GRAS direct food substance, the Panel deemed the ingredients safe as currently used, when formulated to avoid irritation.

2009 Silica and Related Ingredients Report

The CIR Expert Panel emphasized that the Silica considered in this safety assessment is synthetic amorphous silica (gel, hydrated, and fumed/pyrogenic) and does not include any form of crystalline silica.

The Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

The Panel was concerned about the possibility of iron atoms reaching the lungs if Aluminum Iron Silicates were to be used in a spray. In the absence of inhalation toxicity data, the Panel determined that Aluminum Iron Silicates can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (10 μm). The Panel recognizes that most of the formulations are not respirable and of the preparations that are so, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation potential. Aluminum Iron Silicates is safe as a cosmetic ingredient because the particles for aggregates and agglomerates that are too large to be respirable.

The Panel determined that silicosis was not an issue since crystalline silica is not used in cosmetics.

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3]

Ingredient & CAS No.	Definition & Structure	Function(s)
Activated Clay	Activated Clay is the inorganic compound obtained by heating natural aluminum silicate with sulfuric acid.	Absorbents; Bulking Agents
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates	Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates is a ceramic powder consisting mainly of silicon dioxide, aluminum oxide, calcium oxide, magnesium oxide, potassium oxide, sodium oxide and zinc oxide.	Antimicrobial Agents
Aluminum Calcium Sodium Silicate 1344-01-0	Aluminum Calcium Sodium Silicate is a complex silicate refined from naturally occurring minerals.	Bulking Agents
Aluminum Iron Calcium Magnesium Germanium Silicates	Aluminum Iron Calcium Magnesium Germanium Silicates is a ceramic powder consisting mainly of silicon dioxide, aluminum oxide, ferric oxide, calcium oxide, magnesium oxide and germanium oxide.	Anticaries Agents; Antifungal Agents; Antimicrobial Agents; Antioxidants
Aluminum Iron Calcium Magnesium Zirconium Silicates	Aluminum Iron Calcium Magnesium Zirconium Silicates is a ceramic powder consisting mainly of silicon dioxide, aluminum oxide, ferric oxide, calcium oxide, magnesium oxide and zirconium oxide.	Bulking Agents
Aluminum Iron Silicates	Aluminum Iron Silicates is a ceramic powder consisting mainly of silicon dioxide, aluminum oxide, and ferric oxide.	Abrasives; Bulking Agents
Aluminum Silicate 1327-36-2	Aluminum Silicate is a complex inorganic salt that has a composition consisting generally of 1 mole of alumina and 1 to 3 moles of silica.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents: Opacifying Agents; Slip Modifiers
Ammonium Silver Zeolite	Ammonium Silver Zeolite is the ammonium salt of the product obtained by the reaction of silver nitrate and Zeolite.	Absorbents; Deodorant Agents; Preservatives
Ammonium Silver Zinc Aluminum Silicate	Ammonium Silver Zinc Aluminum Silicate is a complex silicate formed from the reaction of zinc nitrate, Ammonium Nitrate , and Silver Nitrate with Zeolite.	Absorbents; Deodorant Agents; Preservatives
Attapulgite 12174-11-7 1337-76-4	Attapulgite is a variety of Fuller's Earth found typically near Attapulgas, Georgia. It is characterized by having a chain structure rather than the usual sheet structure of other clay minerals.	Abrasives; Absorbents; Bulking Agents; Opacifying Agents; Viscosity Increasing Agents - Aqueous
Bentonite 1302-78-9	Bentonite is a native hydrated colloidal aluminum silicate clay.	Absorbents; Bulking Agents; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Opacifying Agents; Viscosity Increasing Agents - Aqueous
Calcium Magnesium Silicate 12765-06-9	Calcium Magnesium Silicate is a synthetic silicate clay consisting chiefly of calcium and magnesium silicates	Absorbents; Deodorant Agents
Calcium Silicate 1344-95-2	Calcium Silicate is a hydrous or anhydrous silicate with varying proportions of calcium oxide and silica.	Absorbents; Bulking Agents; Opacifying Agents
Fuller's Earth 8031-18-3	Fuller's Earth is a non-plastic variety of kaolin containing an aluminum magnesium silicate.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents
Gold Zeolite	Gold Zeolite is the product obtained by the reaction of gold chloride with Zeolite.	Absorbents; Cosmetic Astringents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Hectorite 12173-47-6 68084-71-9	Hectorite is one of the montmorillonite minerals that are the principal constituents of bentonite clay.	Absorbents; Bulking Agents; Dispersing Agents - Nonsurfactant; Opacifying Agents; Viscosity Increasing Agents - Aqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3]

Ingredient & CAS No.	Definition & Structure	Function(s)
Hydrated Silica 10279-57-9 112926-00-8 1343-98-2 (silicic acid) 63231-67-4 7631-86-9	Hydrated Silica is the inorganic oxide that conforms generally to the formula $SiO_2 \cdot xH_2O$.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Oral Care Agents; Skin-Conditioning Agents – Misc.; Viscosity Increasing Agents - Aqueous
Kaolin 1332-58-7	Kaolin is a native hydrated aluminum silicate with an approximate composition of $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Skin Protectants; Slip Modifiers
Lithium Magnesium Silicate 37220-90-9	Lithium Magnesium Silicate is a synthetic silicate clay consisting mainly of lithium and magnesium silicates.	Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Lithium Magnesium Sodium Silicate 53320-86-8	Lithium Magnesium Sodium Silicate is a synthetic silicate clay consisting mainly of lithium, magnesium and sodium silicates.	Bulking Agents; Viscosity Increasing Agents - Aqueous
Magnesium Aluminometasilicate 12408-47-8	Magnesium Aluminometasilicate is the inorganic compound consisting of varying amounts of magnesium oxide, aluminum oxide and silica.	Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Slip Modifiers; Viscosity Increasing Agents – Aqueous; Viscosity Increasing Agents – Nonaqueous
Magnesium Aluminum Silicate 12199-37-0 12511-31-8	Magnesium Aluminum Silicate is a complex silicate refined from naturally occurring minerals.	Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Slip Modifiers; Viscosity Increasing Agents - Aqueous
Magnesium Silicate 1343-88-0	Magnesium Silicate is an inorganic salt of variable composition which consists mainly of $MgO \cdot SiO_2 \cdot xH_2O$.	Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Slip Modifiers; Viscosity Increasing Agents - Aqueous
Magnesium Trisilicate 14987-04-3	Magnesium Trisilicate is the inorganic compound that conforms generally to the formula $2MgO \cdot 3SiO_2 \cdot xH_2O$.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents; Opacifying Agents; Slip Modifiers; Viscosity Increasing Agents - Aqueous
Montmorillonite 1318-93-0	Montmorillonite is a complex aluminum/magnesium silicate clay.	Abrasives; Absorbents; Bulking Agents; Emulsion Stabilizers; Opacifying Agents; Viscosity Increasing Agents - Aqueous
Potassium Silicate 1312-76-1	Potassium Silicate is a potassium salt of silicic acid.	Corrosion Inhibitors

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3]

Ingredient & CAS No.	Definition & Structure	Function(s)
Pyrophyllite 113349-10-3; 113349-11-4; 113349-12-5; 12269-78-2; 141040-73-5; 141040-74-6	Pyrophyllite is a naturally occurring mineral substance consisting predominantly of a hydrous aluminum silicate represented as $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$.	Absorbents; Colorants; Opacifying Agents
Silica 112945-52-5 60676-86-0 7631-86-9	Silica is the inorganic oxide that conforms to the formula SiO_2.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents; Dispersing Agents – Nonsurfactant; Opacifying Agents
Silver Copper Zeolite 130328-19-7 168042-42-0	Silver Copper Zeolite is the product obtained by the reaction of Zeolite with silver nitrate and cupric nitrate.	Absorbents; Deodorant Agents
Silver Zinc Zeolite	Definition under development.	Not reported
Sodium Magnesium Silicate	Sodium Magnesium Silicate is a synthetic silicate clay with a composition mainly of magnesium and sodium silicate.	Binders; Bulking Agents
Sodium Magnesium Aluminum Silicate 12040-43-6	Sodium Magnesium Aluminum Silicate is the complex silicate obtained by the reaction of Sodium Silicate and Sodium Aluminate in an aqueous solution of Magnesium Nitrate.	Absorbents
Sodium Metasilicate 6834-92-0	Sodium Metasilicate is the inorganic salt that conforms to the formula Na_2SiO_3.	Chelating Agents; Corrosion Inhibitors
Sodium Potassium Aluminum Silicate 12736-96-8 66402-68-4	Sodium Potassium Aluminum Silicate is a complex silicate refined from naturally occurring minerals, or derived synthetically.	Bulking Agents
Sodium Silicate 1344-09-8	Sodium Silicate is a sodium salt of silicic acid.	Buffering Agents; Corrosion Inhibitors; pH Adjusters
Sodium Silver Aluminum Silicate	Sodium Silver Aluminum Silicate is the complex silicate obtained by the reaction of sodium silicate with sodium aluminate in an aqueous solution of sodium nitrate, sodium hydroxide and silver nitrate.	Absorbents; Deodorant Agents
Titanium Zeolite	Titanium Zeolite is the product obtained by the reaction of Zeolite with titanium tetrachloride.	Absorbents; Light Stabilizers; Skin-Conditioning Agents – Misc.
Tromethamine Magnesium Aluminum Silicate	Tromethamine Magnesium Aluminum Silicate is a reaction product of Tromethamine (q.v.) and Magnesium Aluminum Silicate.	Viscosity Increasing Agents - Aqueous
Zeolite 1318-02-1	Zeolite is a hydrated alkali aluminum silicate.	Absorbents; Deodorant Agents
Zinc Silicate 13597-65-4	Zinc Silicate is an inorganic salt consisting of variable amounts of zinc oxide and silica.	Deodorant Agents
Zinc Zeolite	Zinc Zeolite is the product obtained by the reaction of Zeolite with zinc chloride.	Absorbents; Cosmetic Astringents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Zirconium Silicate 10101-52-7 1344-21-4	Zirconium Silicate is the inorganic compound that conforms to the formula $ZrSiO_4$.	Abrasives; Opacifying Agents

Table 2. Physical and chemical properties

Property	Value	Reference
Aluminum Silicate		
Physical Form	Light brown to brown, odorless beads	[28]
Molecular Weight (Da)	162.05 - 426.05	[1]
Density (g/cm^3 @ 20ºC)	3.156; 3.247	[1]
Attapulgite		
Physical Form	White, gray, or transparent, dull, elongated, lath-shaped crystals in bundles that comprise thin sheets of minute interlaced fibers; surface is protonated and hydrated	[1]
Density (g/cm^3)	2.2	[1]
Bentonite		
Physical Form	Crystalline, claylike material, available as an odorless, pale buff or cream to grayish-colored fine powder, which is free from grit; dioctahedral	[1]
Molecular Weight (Da)	359.16	[1]
pH	9.5-10.5 (2% aqueous solution)	[1]
Calcium Silicate		
Physical Form	White or slightly cream-colored free-flowing powder	[1]
Molecular Weight (Da)	116.16	[1]
Density (g/cm^3 @ 25ºC)	0.227	[29]
Melting Point (ºC)	1710	[29]
Water Solubility (mg/L @ 20ºC)	260	[29]
Fuller's Earth		
Physical Form	Nonplastic variety of Kaolin; sheet structure	[1]
Hectorite		
Physical Form	Translucent colorless mineral when mined and turns white when dried; tridecahedral	[1]
Specific Gravity (g/cm^3)	2.65	[1]
pH	8.5 (5% slurry)	[1]
Kaolin		
Physical Form	White or yellowish white, earthy mass or white powder; unctuous when moist	[1]
Molecular Weight (Da)	258.2	[1]
Magnesium Aluminum Silicate		
Physical Form	Off-white to creamy white small flakes or micronized powder	[1]
Molecular Weight (Da)	262.4	[1]
pH	9.0-10.0 (5% aqueous solution)	[1]
Magnesium Silicate		
Physical Form	Fine, white, odorless, tasteless powder, free from grittiness	[1]
Magnesium Trisilicate		
Physical Form	Fine, white, odorless, tasteless powder, free from grittiness	[1]
Potassium Silicate		
Physical Form	Yellowish to colorless, translucent to transparent, hygroscopic	[2]
Density (g/cm^3 @ 20ºC)	1.26-1.60	[25]
Vapor Pressure (mmHg @ 1175ºC)	0.00772	[25]
Melting Point (ºC)	905	[25]
Silica		
Physical Form	White fluffy powder (fumed hydrophobic or precipitated hydrophobic); white or white, milky (gel or colloidal)	[7]
Molecular Weight (Da)	60.1 (fumed hydrophobic)	[7]
Density (g/cm^3 @ 20ºC)	2.2 (fumed hydrophobic)	[7]
Specific Gravity (g/cm^3)	2.2-2.65 (fumed hydrophobic); 1.9-2.2 (precipitated hydrophobic); 1.8-2.2 (gel); 1.0-1.4 (colloidal.)	[7]
Vapor Pressure (mmHg)	0 (fumed hydrophobic)	[7]
Melting Point (ºC)	2230 (fumed hydrophobic)	[7]
Boiling Point (ºC)	1700-1710 (fumed hydrophobic)	[7]
Water Solubility (mg/L @ 20ºC)	15-68 (pH 5.5-6.6; fumed hydrophobic)	[7]
pH	3.7-4.5 (fumed hydrophobic); 5-9 (precipitated hydrophobic); 3-8 (gel); 3-5 or 8-11 (colloidal)	[7]
Sodium Magnesium Silicate		
pH	8.5-10.5 (2% aqueous dispersion)	[1]
Sodium Magnesium Aluminum Silicate		
Physical Form	White powder	[26]
Density (g/cm^3 @ 20ºC)	2.11	[26]
Melting Point (ºC)	> 400	[26]
Water Solubility (mg/L @ 20ºC)	2.24	[26]

Table 2. Physical and chemical properties

Property	Value	Reference
Sodium Metasilicate		
Physical Form	Nonahydrate, efflorescent platelets	[2]
Molecular Weight (Da)	122.08	[2]
Density (g/cm^3)	2.614	[2]
Vapor Pressure (mmHg @ 1175ºC)	0.00772	[34]
Melting Point (ºC)	1089	[2]
Water Solubility (g/L @ 20 ºC)	210	[34]
pH	12 (0.1% solution)	[2]
Sodium Silicate		
Physical Form	Colorless to white or grayish-white, crystal-like clumps or aqueous solutions	[2]
Density (g/cm^3)	1.26 - 1.71	[27]
Vapor Pressure (mmHg)	0.00120	[27]
Melting Point (ºC)	730 - 870	[27]
Water Solubility (mg/L @ 20 ºC)	115	[27]
Acidity/Alkalinity	Strongly alkaline	[2]
Zeolite		
Physical Form	Crystalline, hydrated alkali-aluminum silicates	[1]
Zinc Silicate		
Physical Form	White crystals or white powder	[22,24]
Molecular Weight (Da)	222.90	[24]
Density (g/cm^3)	4.103	[22]
Melting Point (ºC)	1509	[22]
Water Solubility (µg/L @ 20 ºC)	162.01	[33]
Zirconium Silicate		
Physical Form	Bipyramidal crystals, colorless unless has impurities and radioactive bombardment; red or various colored crystals	[1]
Molecular Weight (Da)	183.31	[1]
Density (g/cm^3)	4.56	[1]
pH	6-7.5 (10% aqueous slurry)	[1]

Table 3. Current (2018) and historical frequency and concentration according to duration and type of exposure for previously reviewed silicates[1,2,6,7]

	Aluminum Calcium Sodium Silicate				Aluminum Silicate			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**2009**	**2018**	**2008**	**2018**	**1998**	**2018**	**1999**
Totals*	**250**	**7**	**NS**	**0.4-6**	**68**	**10**	**NS**	**0.5-37**
Leave-On	250	7	NS	0.4-6	46	6	NS	0.5-3
Rinse-Off	NR	NR	NS	NR	22	4	NS	2-37
Diluted for (Bath) Use	NR	NR	NS	NR	NR	NR	NS	NR
Eye Area	65	NR	NS	0.5	1	2	NS	0.5
Incidental Ingestion	125	NR	NS	6	NR	NR	NS	37
Incidental Inhalation-Spray	13[a]; 3[b]	1[a]	NS	NR	6; 12[a]; 23[b]	1[a]	NS	NR
Incidental Inhalation-Powder	3; 3[b]	1	NS	NR	23[b]	NR	NS	NR
Dermal Contact	92	3	NS	0.4-6	58	8	NS	2-3
Deodorant (underarm)	NR	NR	NS	NR	NR	NR	NS	NR
Hair - Non-Coloring	1	NR	NS	NR	4	NR	NS	NR
Hair-Coloring	NR	NR	NS	NR	6	NR	NS	NR
Nail	32	4	NS	0.5	NR	NR	NS	NR
Mucous Membrane	125	NR	NS	6	4	NR	NS	37
Baby Products	NR	NR	NS	NR	NR	NR	NS	NR

	Attapulgite				Bentonite			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**1998**	**2018**	**1999**
Totals*	**4**	**10**	**NR**	**8**	**339**	**94**	**0.00002-29.7**	**0.5-80**
Leave-On	1	5	NR	8	157	37	0.00008-15	0.8-8
Rinse-Off	3	5	NR	8	180	57	0.00002-29.7	0.5-80
Diluted for (Bath) Use	NR	NR	NR	NR	2	NR	0.14	5
Eye Area	1	NR	NR	NR	38	8	0.00025-2	0.8-5
Incidental Ingestion	NR	NR	NR	NR	7	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	8[b]	1; 36[a]; 27[b]	5[a]; 7[b]	0.1	1-3[a]; 2-5[b]
Incidental Inhalation-Powder	NR	5	NR	8[b]	3; 27[b]; 1[c]	7[b]	2; 0.35-14.3[c]	2-5[b]
Dermal Contact	4	10	NR	8	276	88	0.00002-29.7	0.5-80
Deodorant (underarm)	NR	NR	NR	NR	5[a]	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	16	4	0.1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	17.3	NR
Nail	NR	NR	NR	NR	21	1	0.00008-0.88	1
Mucous Membrane	NR	NR	NR	NR	17	3	0.14-0.35	0.5-5
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

	Calcium Silicate				Fuller's Earth			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**1998**	**2018**	**1999**
Totals*	**101**	**132**	**0.00013-5**	**0.3-10**	**15**	**3**	**NR**	**NR**
Leave-On	91	115	0.00013-5	0.3-10	3	1	NR	NR
Rinse-Off	1	1	1.5	8	12	2	NR	NR
Diluted for (Bath) Use	9	16	0.86-1.3	NR	NR	NR	NR	NR
Eye Area	7	11	1	1-8	1	NR	NR	NR
Incidental Ingestion	NR	3	0.00013	0.5	1	NR	NR	NR
Incidental Inhalation-Spray	1[b]	NR	0.005	NR	1[b]	NR	NR	NR
Incidental Inhalation-Powder	61; 1[b]	75	0.25-5; 4.7-5[c]	0.3-10	1[b]	NR	NR	NR
Dermal Contact	100	128	0.25-5	0.3-10	14	3	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1.5	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	0.005	NR	NR	NR	NR	NR
Nail	1	1	NR	NR	NR	NR	NR	NR
Mucous Membrane	9	19	0.00013-1.3	0.5	2	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Current (2018) and historical frequency and concentration according to duration and type of exposure for previously reviewed silicates[1,2,6,7]

	Hectorite				**Hydrated Silica***			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**2009**	**2018**	**2008**
Totals*	**83**	**18**	**0.1-3.2**	**0.4-100**	**449**	**176**	**NS**	**0.001-34**
Leave-On	59	10	0.1-3.2	0.7-15	197	90	NS	0.001-4
Rinse-Off	24	8	0.5	0.4-100	244	78	NS	0.01-34
Diluted for (Bath) Use	NR	NR	NR	NR	8	8	NS	0.4-4
Eye Area	34	4	0.1-0.8	0.7	12	8	NS	0.06-2
Incidental Ingestion	NR	NR	NR	NR	83	25	NS	0.003-34
Incidental Inhalation-Spray	2[a]; 4[b]	1[a]	NR	8[b]	13[a]; 10[b]	10[a]; 12[b]	NS	0.04-2[a]; 0.06-2[b]
Incidental Inhalation-Powder	3; 4[b]	NR	0.8-1.1[c]	8[b]	31; 10[b]	33; 12[b]	NS	2-4; 0.06-2[b]
Dermal Contact	62	10	0.1-3.2	0.4-100	333	117	NS	0.001-17
Deodorant (underarm)	NR	1[a]	NR	0.7[a]	1[a]	NR	NS	2[a]
Hair - Non-Coloring	8	NR	NR	1	4	NR	NS	0.04-2
Hair-Coloring	1	5	NR	NR	9	20	NS	2
Nail	1	2	0.7	NR	16	13	NS	1-2
Mucous Membrane	NR	1	NR	NR	249	50	NS	0.003-34
Baby Products	NR	NR	NR	NR	NR	NR	NS	NR

	Kaolin				**Lithium Magnesium Silicate**			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018**	**1998**	**2018**	**1999**	**2018**	**1998**	**2018**	**1999**
Totals*	**1794**	**509**	**0.0001-53**	**0.01-100**	**2**	**NR**	**0.3-5**	**NR**
Leave-On	1171	501	0.0001-53	2-100	2	NR	0.3-5	NR
Rinse-Off	609	7	0.0005-35	0.01-84	NR	NR	NR	NR
Diluted for (Bath) Use	14	1	NR	NR	NR	NR	NR	NR
Eye Area	515	231	0.75-27.2	3-48	NR	NR	NR	NR
Incidental Ingestion	90	6	0.97-11.9	12-30	2	NR	NR	NR
Incidental Inhalation-Spray	69[a]; 84[b]	NR	0.0096; 0.15-25[a]; 4[b]	2-25[a]; 3[b]	NR	NR	0.4; 0.3[a]	NR
Incidental Inhalation-Powder	125; 84[b]; 3[c]	98	2-23.1; 4[b]; 1-25[c]	5-30; 3[b]	NR	NR	5[c]	NR
Dermal Contact	1566	466	0.0005-35	0.01-100	NR	NR	0.4-5	NR
Deodorant (underarm)	5[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	41	5	0.0096-25	4-15	NR	NR	0.3	NR
Hair-Coloring	25	1	0.4-31	NR	NR	NR	NR	NR
Nail	10	NR	0.0001-53	53-54	NR	NR	NR	NR
Mucous Membrane	147	8	0.05-11.9	3-30	2	NR	NR	NR
Baby Products	3	NR	NR	NR	NR	NR	NR	NR

	Lithium Magnesium Sodium Silicate				**Magnesium Aluminometasilicate**			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**2009**	**2018**	**2008**
Totals*	**56**	**NR**	**0.0005-6**	**NR**	**3**	**NR**	**NS**	**0.002-0.01**
Leave-On	35	NR	0.0005-6	NR	2	NR	NS	0.002-0.01
Rinse-Off	21	NR	0.4	NR	1	NR	NS	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NS	NR
Eye Area	5	NR	0.0005-4	NR	NR	NR	NS	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NS	NR
Incidental Inhalation-Spray	4[a]; 2[b]	NR	6	NR	1[b]	NR	NS	0.002-0.01[b]
Incidental Inhalation-Powder	2[b]	NR	3[c]	NR	1[b]	NR	NS	0.002-0.01[b]
Dermal Contact	31	NR	0.0005-4	NR	3	NR	NS	0.002-0.01
Deodorant (underarm)	NR	NR	0.5	NR	NR	NR	NS	NR
Hair - Non-Coloring	12	NR	6	NR	NR	NR	NS	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NS	NR
Nail	10	NR	NR	NR	NR	NR	NS	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NS	NR
Baby Products	NR	NR	NR	NR	NR	NR	NS	NR

Table 3. Current (2018) and historical frequency and concentration according to duration and type of exposure for previously reviewed silicates[1,2,6,7]

	Magnesium Aluminum Silicate				Magnesium Silicate			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**1998**	**2018**	**1999**
Totals*	**917**	**632**	**0.0004-11**	**0.1-5**	**70**	**NR**	**0.001-21.6**	**NR**
Leave-On	734	509	0.0008-11	0.1-5	68	NR	0.001-21.6	NR
Rinse-Off	183	122	0.0004-10	0.1-5	2	NR	NR	NR
Diluted for (Bath) Use	NR	1	NR	NR	NR	NR	NR	NR
Eye Area	207	76	0.0025-4.5	0.2-5	24	NR	3-21.6	NR
Incidental Ingestion	5	3	0.93	0.7	14	NR	10	NR
Incidental Inhalation-Spray	1; 144[a]; 148[b]	2; 106[a]; 75[b]	0.5-0.8[a]	0.3-5[a,b]	2[a]; 3[b]	NR	NR	NR
Incidental Inhalation-Powder	30; 148[b]; 8[c]	75[b]	1; 0.3-11[c]	0.3-5[b]	5; 3[b]	NR	1[c]	NR
Dermal Contact	862	583	0.0004-11	0.1-5	55	NR	0.001-21.6	NR
Deodorant (underarm)	8[a]	5[a]	0.5-0.7	0.5-1[a]	NR	NR	NR	NR
Hair - Non-Coloring	15	10	0.19-0.8	1-2	NR	NR	NR	NR
Hair-Coloring	6	1	NR	2	NR	NR	NR	NR
Nail	1	2	NR	NR	1	NR	NR	NR
Mucous Membrane	34	19	0.93	0.5-2	14	NR	10	NR
Baby Products	8	NR	NR	NR	NR	NR	NR	NR

	Magnesium Trisilicate				Montmorillonite			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**1998**	**2018**	**1999**	**2018**	**1998**	**2018**	**1999**
Totals*	**17**	**NR**	**NR**	**NR**	**177**	**NR**	**0.05-8.2**	**NR**
Leave-On	NR	NR	NR	NR	101	NR	0.05-6	NR
Rinse-Off	17	NR	NR	NR	75	NR	0.5-8.2	NR
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
Eye Area	NR	NR	NR	NR	39	NR	0.3-2.8	NR
Incidental Ingestion	NR	NR	NR	NR	13	NR	1.7	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	12[a]; 7[b]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	5; 7[b]; 1[c]	NR	2.5-6[c]	NR
Dermal Contact	16	NR	NR	NR	145	NR	0.05-6	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	9	NR	8.2	NR
Hair-Coloring	1	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	23	NR	0.5-1.7	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

	Potassium Silicate				Silica***			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2018	**2001**	**2018**	**1999/2000**	**2018**	**2009**	**2018**	**2008**
Totals*	**1**	**2**	**NR**	**NR**	**8024**	**3276**	**NS**	**0.0000003-44**
Leave-On	NR	1	NR	NR	7416	2937	NS	0.00004-44
Rinse-Off	1	1	NR	NR	558	316	NS	0.0000003-16
Diluted for (Bath) Use	NR	NR	NR	NR	50	23	NS	0.02-2
Eye Area	NR	NR	NR	NR	2403	867	NS	0.0004-44
Incidental Ingestion	NR	NR	NR	NR	1583	551	NS	0.01-21
Incidental Inhalation-Spray	NR	NR	NR	NR	131; 473[a]; 382[b]	19; 247[a]; 183[b]	NS	0.0005-6; 0.00004-8[a]; 0.02-10[b]
Incidental Inhalation-Powder	NR	NR	NR	NR	507; 382[b]; 3[c]	248; 183[b]; 1[c]	NS	1-26; 0.02-10[b]
Dermal Contact	1	1	NR	NR	5297	2298	NS	0.0000003-44
Deodorant (underarm)	NR	NR	NR	NR	31[a]	38[a]	NS	0.02-9[a]
Hair - Non-Coloring	NR	1	NR	NR	111	51	NS	0.0005-3
Hair-Coloring	NR	NR	NR	NR	187	149	NS	0.002-6
Nail	NR	NR	NR	NR	549	92	NS	0.3-9
Mucous Membrane	NR	NR	NR	NR	1792	624	NS	0.0000003-21
Baby Products	NR	NR	NR	NR	7	2	NS	0.003-10

Table 3. Current (2018) and historical frequency and concentration according to duration and type of exposure for previously reviewed silicates[1,2,6,7]

	Sodium Magnesium Silicate				Sodium Metasilicate			
	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2018	**1998**	**2018**	**1999**	**2018**	**2001**	**2018**	**1999/2000**
Totals*	**139**	**34**	**0.13-0.2**	**0.08-5**	**137**	**191**	**0.001-15**	**13-18**
Leave-On	84	33	0.13	0.08-5	1	NR	0.001	NR
Rinse-Off	54	1	0.2	0.3-5	136	191	1.2-15	13-18
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	0.1	NR
Eye Area	13	13	NR	0.08-0.4	NR	NR	NR	NR
Incidental Ingestion	9	1	NR	0.3-3	NR	NR	NR	NR
Incidental Inhalation-Spray	37[a]; 5[b]	2[a]; 5[b]	NR	1-5[a]; 0.1-5[b]	1[a]	NR	NR	NR
Incidental Inhalation-Powder	7; 5[b]	4; 5[b]	NR	0.4; 0.1-5[b]	NR	NR	NR	NR
Dermal Contact	127	31	0.13-0.2	0.08-5	NR	2	0.001-1.2	NR
Deodorant (underarm)	NR	NR	NR	0.5[a]	NR	NR	NR	NR
Hair - Non-Coloring	2	1	NR	NR	1	1	NR	NR
Hair-Coloring	NR	NR	NR	NR	136	188	5-15	13-18[d]
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	13	1	NR	0.3	NR	NR	0.1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Sodium Potassium Aluminum Silicate				Sodium Silicate			
	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2018	**2009**	**2018**	**2008**	**2018**	**2001**	**2018**	**1999/2000**
Totals*	**12**	**1**	**NS**	**0.001-4**	**91**	**22**	**0.017-35**	**0.06-55**
Leave-On	10	NR	NS	0.001-4	15	2	NR	0.6-1
Rinse-Off	2	1	NS	NR	76	20	0.017-35	0.06-55
Diluted for (Bath) Use	NR	NR	NS	NR	NR	NR	NR	NR
Eye Area	NR	NR	NS	NR	4	1	NR	NR
Incidental Ingestion	NR	NR	NS	NR	1	NR	0.44	0.6
Incidental Inhalation-Spray	5[a]	NR	NS	NR	1[a]; 6[b]	1[b]	NR	NR
Incidental Inhalation-Powder	NR	NR	NS	NR	6[b]	1[b]	NR	NR
Dermal Contact	12	1	NS	NR	35	14	0.017-1.5	0.06-10
Deodorant (underarm)	NR	NR	NS	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NS	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NS	NR	54	8	15-35	1-55[e]
Nail	NR	NR	NS	0.001-4	NR	NR	NR	NR
Mucous Membrane	1	NR	NS	NR	8	2	0.44-1.4	0.06-7
Baby Products	NR	NR	NS	NR	NR	NR	NR	0.6

	Zeolite			
	# of Uses		Max Conc of Use (%)	
	2018	**1998**	**2018**	**1999**
Totals*	**157**	**NR**	**0.0043-37.8**	**NR**
Leave-On	140	NR	0.03-35.7	NR
Rinse-Off	17	NR	0.0043-37.8	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Eye Area	25	NR	0.032-3.6	NR
Incidental Ingestion	3	NR	3	NR
Incidental Inhalation-Spray	3; 15[a]; 11[b]	NR	1; 35.7[a]	NR
Incidental Inhalation-Powder	45; 11[b]	NR	0.6-1.1; 0.5-1[c]	NR
Dermal Contact	146	NR	0.0043-37.8	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	8	NR	1-35.7	NR
Hair-Coloring	NR	NR	5	NR
Nail	NR	NR	NR	NR
Mucous Membrane	5	NR	3	NR
Baby Products	NR	NR	NR	NR

NR = Not reported. S = Survey in progress.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[d.] Hair bleaches were diluted from 13% to 18% to 7% to 14% before use.

[e.] Hair bleaches were diluted from 16%-55% to 1%-20% before use.

*Includes entries for Hydrated Silica and Silicic Acid from the VCRP database.

** Includes entries for Kaolinite from the VCRP database.

*** Includes entries for Silica; Silica, Amorphous; Silica, Fumed; and Silicon Dioxide, Colloidal from the VCRP database.

Table 4. 2018 frequency and concentration of use according to duration and type of exposure for potential Silicate add-on ingredients[6]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Ammonium Silver Zinc Aluminum Silicate		**Zinc Zeolite**	
Totals†	**17**	**0.001**	**1**	**NR**
Duration of Use				
Leave-On	16	NR	NR	NR
Rinse Off	1	0.001	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	13	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR
Incidental Inhalation-Powder	1	NR	NR	NR
Dermal Contact	17	0.001	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

NR = Not reported. S = Survey in progress.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

Table 5. Ingredients not reported to be in use.[6]

Activated Clay
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates
Aluminum Iron Calcium Magnesium Germanium Silicates
Aluminum Iron Calcium Magnesium Zirconium Silicates
Aluminum Iron Silicates*‡
Ammonium Silver Zeolite
Calcium Magnesium Silicate‡
Gold Zeolite
Pyrophyllite*
Silver Copper Zeolite‡
Silver Zinc Zeolite‡
Sodium Magnesium Aluminum Silicate
Sodium Silver Aluminum Silicate
Titanium Zeolite‡
Tromethamine Magnesium Aluminum Silicate
Zinc Silicate
Zirconium Silicate*

*Additionally, no uses were reported in original safety assessment.

‡ Not surveyed.

Table 6. Acute toxicity studies

Ingredient/Concentration/Vehicle	Dose/Study Protocol	Results	LD_{50} or LC_{50}	Reference
Dermal				
Bentonite (2/3 weight) and Zeolite (1/3 weight) in a hemostatic agent	~8 g applied on wounded skin to 12 male Sprague-Dawley rats, another 12 rats served as controls; wounds were circular, full-thickness and 2 cm in diameter; skin sampled excised and evaluated stereologically after scarification; 6 rats from test group and 6 rats from control group were killed on days 12 and 21	At day 12 termination, reduction in the length density of the blood vessels (31%) and diameter of the large and small vessels (38% and 16%, respectively) was observed in the rats that received the test material; at day 21 termination, volume density of both the dermis and collagen bundles was reduced by 25% in the treated rats when compared to the controls; authors concluded hemostatic agent containing Bentonite and Zeolite may cause vasoconstriction and inhibition of neoangiogenesis	Not measured	[43]
30% Potassium Silicate solution in water; molar ratio = 2.47	5000 mg/kg bw applied for 24 h to 5 male and 5 female Sprague-Dawley rats; test sites were occluded	Erythema and alopecia noted at application site of 4 females and 1 male between days 1 and 8; no other adverse effects during observation period or necropsy	> 5 g/kg	[25]
Oral				
Aluminum Silicate in water; concentration not reported	2000 mg/kg bw; 3 female Sprague-Dawley rats via gavage	No mortality occurred from dosing; no clinical signs of toxicity; no treatment-related effects at necropsy	> 2 g/kg bw	[28]
20% Calcium Silicate in feed	10 g/kg bw; 10 male and 10 female Wistar rats via diet	No mortality occurred from dosing; no significant clinical findings; no treatment-related effects at necropsy	> 10 g/kg bw	[29]
Potassium Silicate; concentration and vehicle not reported	3.30, 3.96, 4.75, 5.70, or 6.86 g/kg bw; 5 male and 5 female Cpb; Wu Wistar rats per dose; method of delivery not reported	Deaths per dose = 1/10 at 2.50 ml/kg, 2/10 at 3.00 ml/kg, 2/10 at 3.60 ml/kg, 3/10 at 4.32 ml/kg, and 10/10 at 5.20 ml/kg; sedation, signs of abdominal discomfort, sluggishness and unconsciousness were all reversible; no treatment-related effects at necropsy	5.70 g/kg bw	[30]
Potassium Silicate; undiluted; no further details reported	5.0 g/kg bw in 3 female Sprague-Dawley rats via gavage	No deaths occurred following treatment; no clinical or gross macroscopic signs of toxicity observed	> 5.0 g/kg bw	[25]
Sodium Magnesium Aluminum Silicate in water; no further details reported	2.0 g/kg bw in 6 female Sprague-Dawley rats via gavage	No deaths occurred following treatment; no clinical or gross macroscopic signs of toxicity observed	> 2.0 g/kg bw	[26]

Table 6. Acute toxicity studies

Ingredient/Concentration/Vehicle	Dose/Study Protocol	Results	LD_{50} or LC_{50}	Reference
Sodium Silicate; molar ratio 3.27; concentration and vehicle not reported	3.43, 4.11, 4.93, 5.89, 7.12, or 8.49 g/kg bw; 5 male and female Cpb:Wu Wistar rats per dose via gavage	Deaths per dose = 0/10 at 3.43 g/kg, 2/10 at 4.11 g/kg, 9/10 at 4.93, 5.89, and 7.12 g/kg, and 10/10 at 8.49 g/kg; sedation, signs of abdominal discomfort, sluggishness and unconsciousness; no treatment-related effects at necropsy	5.15 g/kg bw	[27]
Sodium Silicate in water; molar ratio = 3.38	Male Wistar rats; no additional details provided	Breathing difficulties, staggering gait, reduced motility; additional effects not reported	8.65 g/kg bw	[27]
Sodium Silicate; molar ratio = 3.3; no additional details provided	Rats; no additional details provided	No details provided	> 2.00 g/kg bw	[27]
Sodium Silicate; molar ratio = 3.35; no additional details provided	Male mice; no additional details provided	No details provided	6.60 g/kg bw	[27]
Inhalation				
30% Potassium Silicate solution in water; molar ratio 2.47	2.06 mg/l; whole body exposure for 4.4 h to 5 male and 5 female Sprague-Dawley rats; particle size distribution = 4% at 9 µm, 8.3% at 5.8 µm, 11.1% at 4.7 µm, 12% at 3.3 µm, 32% at 2.1 µm, 2.6% at 1.1 µm, 7.4% at 0.7 µm, and 2.6% at 0.4 µm	Animals had hunched posture and hypoactivity during exposure that reversed; no deaths or adverse effects during observation period or necropsy	> 2.06 mg/l	[25]

Table 7. Genotoxicity studies

Ingredient/Concentration/Dose	Species/Strain/Cell	Method	Results	Reference
		In Vitro		
Aluminum Silicate in water, up to 5017 µg/plate, with or without metabolic activation	*Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, and TA1535	Ames test	Not genotoxic	[28]
Aluminum Silicate in DMSO; up to 250 µg/ml without metabolic activation; up to 500 µg/ml with metabolic activation	Chinese hamster ovary	HPRT gene mutation assay	Not genotoxic	[28]
Montmorillonite in unmodified (1 type) and organo-modifed clay forms (3 types); unmodified tested at up to 125 µg/ml and the modified clays were tested at up to 250 µg/ml, with and without metabolic activation	*S. typhimurium* strains TA97a, TA98, TA100, TA102, TA104	Ames test	Two modified clays had significant increases in revertant colonies in strain TA98 with metabolic activation; no significant changes were observed in TA98 without metabolic activation or in the other strains; no mutagenic activity observed in the third modified clay or in the unmodified clay	[36]
Montmorillonite; 15.65, 31.25 or 62.5 µg/ml	Human hepatoma cell line (HepG2)	Cytokinesis block micronucleus cytome assay	Potentially genotoxic; an increased number of micro nuclei was observed but there were no effect observed in nucleoplasmic bridges or nuclear buds	[35]
Sodium Metasilicate; up to 5000 µg/plate, with or without metabolic activation	*S. typhimurium* strains TA98, TA100, TA 1535, TA 1537 and *Escherichia coli* WP2	Ames test	Not genotoxic	[34]
Sodium Metasilicate; up to 675 µg/ml without metabolic activation and up to 1800 µg/ml with metabolic activation	Chinese hamster V79 cells	HPRT gene mutation assay	Not genotoxic	[34]
36% Sodium Silicate; molar ratio = 3.3; up to 156.3 µg/ml with and without metabolic activation	Chinese hamster V79 cells	Chromosome aberration test	Not genotoxic	[27]
36% Sodium Silicate; molar ratio = 3.35; up to 675 µg/ml without metabolic activation and up to 1800 µg/ml with metabolic activation	Chinese hamster V79 cells	HPRT gene mutation assay	Not genotoxic	[27]
Zinc Silicate; 100, 316, 1000, 3160 or 5000 µg/plate with or without metabolic activation	*S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537	Ames test	Not genotoxic	[33]

Table 8. Dermal irritation and sensitization

Ingredient/Concentration/ Dose/Vehicle	Test System	Method	Results	Reference
		Irritation – In Vitro		
Aluminum Silicate; 25 mg in Dulbecco's phosphate buffered saline	EpiDerm tissue	EpiDerm human skin model; material applied for 30 min	Not irritating	[28]
Zinc Silicate; undiluted; 25 mg	EpiDerm tissue	EpiDerm reconstructed human epidermis model in accordance with OECD Test Guideline 439; test material applied to 0.63 cm^2 test tissue for 60 min	Not irritating	[33]
		Irritation - Animal		
36% (weight) Potassium Silicate; molar ratio = 2.0; 0.5ml in water	1 female New Zealand White rabbit	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed off with water; test site examined for up to 5 days	Slightly irritating; transient erythema observed cleared by day 5; primary dermal irritation index (PDII) = 1	[25,30]
33% (weight) Potassium Silicate; molar ratio = 3.0; 0.5ml in water	1 male New Zealand White rabbit	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed off with water; test site examined for up to 5 days	Moderately irritating; well-defined erythema and very slight edema persisted for at least 5 days; PDII =3	[25,30]
35% (weight) Potassium Silicate; molar ratio = 3.4; 0.5ml in deionized water	3 New Zealand White rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and occluded for 4 h before being rinsed; test site examined for up to 7 days	Not irritating; slight erythema after 1 h that cleared after 48 h; PDII = 0.17	[25,30]
25% dilution of 35% (weight) Potassium Silicate; molar ratio = 3.4; 0.5 ml in deionized water	3 New Zealand White rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and occluded for 4 h before being rinsed; test site examined for up to 7 days	Not irritating; very slight erythema 24 and 48 h after treatment; PDII = 0	[25,30]
25% dilution of 29% (weight) Potassium Silicate; molar ratio = 3.9; 0.5 ml in deionized water	5 New Zealand White rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and occluded for 4 h before being rinsed; test site examined for up to 7 days	Not irritating; PDII = 0	[25,30]
29% (weight) Potassium Silicate; molar ratio = 3.9; 0.5 ml in deionized water	5 New Zealand White rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and occluded for 4 h before being rinsed; test site examined for up to 7 days	Not irritating; slight erythema cleared by 24 h ;PDII = 0.25	[25,30]
Sodium Metasilicate (anhydrous); 0.5 g in water	1 male New Zealand White rabbits	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 5 days	Corrosive; necrosis observed; PDII = 8; no erythema or edema observed when applied as dry powder	[34]
Sodium Metasilicate (pentahydrate); 0.5 g in water	1 female New Zealand White rabbits	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 5 days	Corrosive; necrosis observed; PDII = 8; no erythema or edema observed when applied as dry powder	[34]
10% aq. Sodium Metasilicate; 0.5 ml in water	3 rabbits; strain and sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 72 h	Slightly irritating; severity of erythema reduced but persisted through day2; edema in 1 animal reversed by day 2; PDII = 1.22	[34]
50% aq. Sodium Metasilicate; 0.5 ml in water	3 rabbits; strain and sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 72 h	Irritating; PDII = 3.67	[34]

Table 8. Dermal irritation and sensitization

Ingredient/Concentration/ Dose/Vehicle	Test System	Method	Results	Reference
57.5% (weight) Sodium Metasilicate (pentahydrate); 0.5 g	3 white landrace rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 14 days	Corrosive; 2/3 animals had acute skin necrosis and the 3rd had pigmented necrosis; wounds persisted for more than 14 days; PDII = 7.8	[34]
97% (weight) Sodium Metasilicate (anhydrous); 0.5 g	3 white landrace rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 14 days	Corrosive; 2/3 animals had acute skin necrosis with well-defined edema; wounds persisted for more than 14 days; third animal had wounds that were observed at up to 72 h but had healed by day 14;PDII = 5.1	[34]
Sodium Metasilicate; concentration not reported; fine powder with pH of 12.4 tested undiluted; 0.5 g	3 New Zealand White rabbits; sex not reported	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 14 days	Not irritating; 1/3 animals had erythema and edema 1 h post-treatment that cleared by 72 h; PDII = 0.17	[34]
83% (w/w) Sodium Metasilicate as aqueous paste; pH 12.4; 0.5 g/0.10 purified water; 0.3 ml applied	3 male New Zealand hybrid rabbits	Dermal irritation study in accordance with OECD Test Guideline 404; test material applied to shaved test site and semi-occluded for 4 h before being rinsed; test site examined for up to 14 days	Corrosive; erythema persisted for at least 14 days; edema observed 1 h post-treatment but cleared by 72 h; necrosis persisted 7-14+ days;PDII = 4.67	[34]
Sensitization - Animal				
0%, 5%, 10%, or 25% (w/v) Aluminum Silicate in dimethyl sulfoxide; application volume = 25 µl	4 female CBA/CaOlaHsd mice/dose group	Local lymph node assay (LLNA)	Not sensitizing; stimulation indices (SI) below 3	[28]
30% Potassium Silicate solution; molar ratio = 2.47	20 male Hartley guinea pigs received test material; 10 animals served as control	Buehler sensitization test; animals were induced with undiluted test material and challenged at 75%	Not sensitizing	[25]
0%, 10%, 25%, or 50% Zinc Silicate in acetone/olive oil (4:1; v/v)	6 female NMRI mice/dose group	LLNA	Not sensitizing; SI below 1.4; irritant response noted	[33]

Table 9. Ocular irritation

Ingredient/Concentration/ Dose/Vehicle	Test System	Method	Results	Reference
		In Vitro		
Aluminum Silicate tested pure; no vehicle; 164.3 mg	Lohmann Leghorn chicken eggs	HET-CAM method; treatment duration = 5 min	Not irritating	[28]
Sodium Metasilicate; concentration not reported; undiluted; 50 mg	New Zealand White rabbit eyes	In vitro rabbit eye study; treatment duration = 0.17 min; eyes studied for opacity for up to 4 h post-treatment	Corrosive	[34]
Zinc Silicate; 20% suspension in 750 µl of physiological saline solution (0.9% NaCl)	Bovine corneas	Bovine corneal opacity and permeability test (BCOP); exposure was 4 h	Irritating; mean opacity score of 3 corneas was 6.31; mean fluorescein retentation/leakage score was < 0.01	[33]
		Animal		
29% (weight) Potassium Silicate; molar ratio = 3.9; 0.1 ml in water	6 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD Test Guideline 405; eyes not rinsed; observed for up to 7 days post-treatment	Not irritating	[25,30]
25% dilution of 29% (weight) Potassium Silicate; molar ratio = 3.9; 0.1 ml in deionized water	6 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD Test Guideline 405; eyes not rinsed; observed for up to 7 days post-treatment	Not irritating	[25,30]
35% (weight) Potassium Silicate; molar ratio = 3.4; 0.1 ml in water	3 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD Test Guideline 405; eyes not rinsed; observed for up to 7 days post-treatment	Slightly irritating; redness and chemosis of the conjunctivae (scores 1.0-1.3 and 1.3-1.5, respectively) observed up to 7 days post-treatment	[25,30]
25% dilution of 35% (weight) Potassium Silicate; molar ratio = 3.4; 0.1 ml in water	3 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD Test Guideline 405; eyes not rinsed; observed for up to 7 days post-treatment	Not irritating	[25,30]
~30% Potassium Silicate in water; molar ratio = 2.47; 0.1 ml	3 New Zealand White rabbits; sex not reported	Ocular irritation study; eyes not rinsed; observed for up to 7 days post-treatment	Slightly irritating	[25]

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Final Report on the Safety Assessment of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite[1]

This report reviews the safety of Aluminum, Calcium, Lithium Magnesium, Lithium Magnesium Sodium, Magnesium Aluminum, Magnesium, Sodium Magnesium, and Zirconium Silicates, Magnesium Trisilicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite as used in cosmetic formulations. The common aspect of all these claylike ingredients is that they contain silicon, oxygen, and one or more metals. Many silicates occur naturally and are mined; yet others are produced synthetically. Typical cosmetic uses of silicates include abrasive, opacifying agent, viscosity-increasing agent, anticaking agent, emulsion stabilizer, binder, and suspending agent. Clay silicates (silicates containing water in their structure) primarily function as adsorbents, opacifiers, and viscosity-increasing agents. Pyrophyllite is also used as a colorant. The International Agency for Research on Cancer has ruled Attapulgite fibers >5 μm as possibly carcinogenic to humans, but fibers <5 μm were not classified as to their carcinogenicity to humans. Likewise, Clinoptilolite, Phillipsite, Mordenite, Nonfibrous Japanese Zeolite, and synthetic Zeolites were not classified as to their carcinogenicity to humans. These ingredients are not significantly toxic in oral acute or short-term oral or parenteral toxicity studies in animals. Inhalation toxicity, however, is readily demonstrated in animals. Particle size, fibrogenicity, concentration, and mineral composition had the greatest effect on toxicity. Larger particle size and longer and wider fibers cause more adverse effects. Magnesium Aluminum Silicate was a weak primary skin irritant in rabbits and had no cumulative skin irritation in guinea pigs. No gross effects were reported in any of these studies. Sodium Magnesium Silicate had no primary skin irritation in rabbits and had no cumulative skin irritation in guinea pigs. Hectorite was nonirritating to the skin of rabbits in a Draize primary skin irritation study. Magnesium Aluminum Silicate and Sodium Magnesium Silicate caused minimal eye irritation in a Draize eye irritation test. Bentonite caused severe iritis after injection into the anterior chamber of the eyes of rabbits and when injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were recorded. In a primary eye irritation study in rabbits, Hectorite was moderately irritating without washing and practically nonirritating to the eye with a washout. Rats tolerated a single dose of Zeolite A without any adverse reaction in the eye. Calcium Silicate had no discernible effect on nidation or on maternal or fetal survival in rabbits. Magnesium Aluminum Silicate had neither a teratogenic nor adverse effects on the mouse fetus. Female rats receiving a 20% Kaolin diet exhibited maternal anemia but no significant reduction in birth weight of the pups was recorded. Type A Zeolite produced no adverse effects on the dam, embryo, or fetus in either rats or rabbits at any dose level. Clinoptilolite had no effect on female rat reproductive performance. These ingredients were not genotoxic in the Ames bacterial test system. In primary hepatocyte cultures, the addition of Attapulgite had no significant unscheduled DNA synthesis. Attapulgite did cause significant increases in unscheduled DNA synthesis in rat pleural mesothelial cells, but no significant increase in sister chromosome exchanges were seen. Zeolite particles (<10 μm) produced statistically significant increase in the percentage of aberrant metaphases in human peripheral blood lymphocytes and cells collected by peritoneal lavage from exposed mice. Topical application of Magnesium Aluminum Silicate to human skin daily for 1 week produced no adverse effects. Occupational exposure to mineral dusts has been studied extensively. Fibrosis and pneumoconiosis have been documented in workers involved in the mining and processing of Aluminum Silicate, Calcium Silicate, Zirconium Silicate, Fuller's Earth, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that the extensive pulmonary damage in humans was the result of direct occupational inhalation of the dusts and noted that lesions seen in animals were affected by particle size, fiber length, and concentration. The Panel considers that most of the formulations are not respirable and of the preparations that are respirable, the concentration of the ingredient is very low. Even so, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation. With this admonition to the cosmetics industry, the CIR Expert Panel concluded that these ingredients are safe as currently used in cosmetic formulations.

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The Panel did note that the cosmetic ingredient, Talc, is a hydrated magnesium silicate. Because it has a unique crystalline structure that differs from ingredients addressed in this safety assessment, *Talc is not included in this report.*

INTRODUCTION

Various silicates and silicate clays are used in cosmetics, largely for their adsorbent, anticaking, bulking, and other similar properties. They are created synthetically in some cases, e.g., Lithium Magnesium Silicate, or are refined from naturally occurring minerals, e.g., Magnesium Aluminum Silicate. In either case, variations in composition occur. Thus the Zeolite group of hydrated aluminosilicates has forms that are crystalline or fibrous, and contain interchangeable cations.

This report reviews the safety of these ingredients. Because the issues of safety are likely to be similar, many ingredients have been grouped. Although there are not data on each and every ingredient, it is expected that the data will be broadly applicable among the following ingredients: Aluminum Silicate (CAS no. 1327-36-2); Calcium Silicate (CAS no. 1344-95-2); Magnesium Aluminum Silicate (CAS no. 12199-37-0, 1327-43-1, 12511-31-8); Magnesium Silicate (CAS no. 1343-88-0); Magnesium Trisilicate (CAS no. 14987-04-3); Sodium Magnesium Silicate; Zirconium Silicate (CAS no. 14940-68-2); and the silicate clays/clay minerals: Attapulgite (CAS no. 1337-76-4, 12174-11-7); Bentonite (CAS no. 1302-78-9); Fuller's Earth (CAS No. 8031-18-3); Hectorite (CAS no. 12173-47-6); Kaolin (CAS no. 1332-58-7); Lithium Magnesium Silicate; Lithium Magnesium Sodium Silicate (CAS no. 53320-86-8); Montmorillonite (CAS no. 1318-93-0); Pyrophyllite (CAS no. 12269-78-2); and Zeolite (CAS no. 1318-02-1) used in cosmetics.

It is important to note that the cosmetic ingredient, Talc, is not included in this safety assessment. Talc is a hydrated magnesium silicate with the CAS no. 14807-96-6, but it should not be confused with any of the silicates in this report. Talc is differentiated by its definition, a hydrated magnesium silicate, and its unique crystalline form.

The safety of Quaternium-18 Hectorite and Quaternium-18 Bentonite have been previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel; the final conclusion indicated that "Quaternium-18 Hectorite and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration" (CIR 1980).

CHEMISTRY

Given the large number of ingredients, a tabular presentation of basic information concerning the chemical description has been provided (Table 1).

Zeolites

The Zeolite group is very diverse. Over 100 structural types of Zeolites, both natural and synthetic, have been reported, 40 of which are natural Zeolites (IARC 1997). Even though these Zeolites are considered to be a group, the formulas of the most common are listed in tabular form in Table 2 so the reader can understand the diversity in this category.

Physical and Chemical Properties

In alphabetical order according to the cosmetic ingredient name as specified in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger et al. 2000), Table 3 provides information on the various synonyms used to describe each cosmetic ingredient, lists the available information on physical properties, and, if available, provides the specifications for the cosmetic grade of the ingredient.

Clay Structure

According to Grim (1967), clays in general have atomic lattices consisting of two structural units. One unit consists of two sheets of closely packed oxygens or hydroxyls as shown in Figure 1. Aluminum, iron, or magnesium atoms are embedded within these sheets in octahedral coordination, so that they are equidistant from the oxygen or hydroxyl groups.

The second unit is composed of silica tetrahedrons as shown in Figure 2. Assuming there are no distortions in each tetrahedron, a silicon atom is equidistant from four oxygens or hydroxyls, if needed to balance the structure, arranged in the form of a tetrahedron with a silicon atom in the center. The silica tetrahedral groups are arranged in a hexagonal network, which is repeated infinitely to form a sheet of composition $Si_4O_6(OH)_4$. The tips of the tetrahedrons all point in the same direction and the bases are all in the same plane. Substantial distortion of these units occurs in order to fit into determined unit-cell dimensions of minerals (Grim 1967).

Attapulgite

The general attributes of structure and composition of the minerals are not very well known. The structurally important element is the amphibole double silica chain oriented with its long direction parallel to the *c* axis as shown in Figure 3. Attapulgite

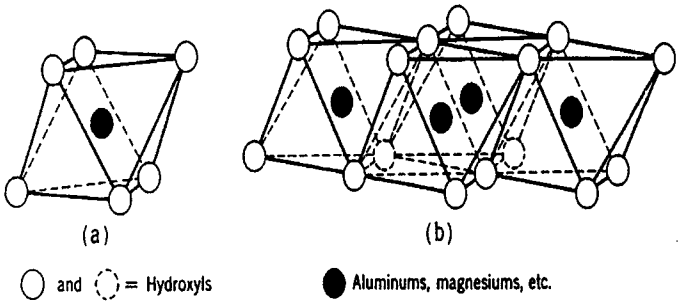

FIGURE 1
(*a*) Single octahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

TABLE 1
Chemical formulas and compositions of Silicates and Silicate Clays used in cosmetics

Ingredient	Description	Reference
Aluminum Silicate	$Al_2O_3 \cdot SiO_2$	Wenninger et al. 2000
	Complex inorganic salt that has a composition of consisting generally of 1 mole of alumina and 1 to 3 moles of silica	Wenninger et al. 2000
Calcium Silicate	Varying CaO and SiO_2	Wenninger et al. 2000
	Hydrous or anhydrous silicate with varying proportions of calcium oxide and silica	Wenninger et al. 2000
Magnesium Aluminum Silicate	$Al_2MgO_8Si_2$	Budavari 1989
	Complex silicate refined from naturally occurring minerals	Wenninger et al. 2000
Magnesium Silicate	$MgO \cdot SiO_2 \cdot xH_2O$	Wenninger et al. 2000
	Inorganic salt of variable composition	Wenninger et al. 2000
Magnesium Trisilicate	$2MgO_3 \cdot SiO_2 \cdot xH_2O$	Wenninger et al. 2000
	Inorganic compound	Wenninger et al. 2000
Zirconium Silicate	$ZrSiO_4$	Wenninger et al. 2000
	Inorganic compound	Wenninger et al. 2000
	Zircon sand or flour; specially sized grades of the mineral zircon—a naturally occuring zirconium silicate	American Minerals, Inc. 1998
Attapulgite	$[Mg(Al_{0.5-1}Fe_{0-0.5}]Si_4O_{10}(OH) \cdot 4H_2O$	IARC 1997
	Variety of Fuller's Earth (q.v.) found typically near Attapulgas, Georgia. It is characterized as having a chain structure rather than the usual sheet structure of other clays	Wenninger et al. 2000
	Hydrated magnesium aluminum silicate with magnesium partially replaced by aluminum, or to a lesser extent, iron	IARC 1997
	Purified native magnesium aluminum silicate	Barr and Arnista 1957
Bentonite	$Al_2O_3 \cdot 4SiO \cdot 2H_2O$[a] (empirical formula)	Informatics, Inc. 1974
	$Na_{0.33}[Al_{1.67}Mg_{0.33}]Si_4[OH]_2$	Rheox Inc. 1999
	Native hydrated colloidal aluminum silicate clay	Wenninger et al. 2000
	Commercial term for clays containing montmorillonite type minerals formed by the alteration of volcanic ash	Gamble 1986
Fuller's Earth	No specific formula	Wenninger et al. 2000
	Nonplastic variety of kaolin containing an aluminum magnesium silicate	Wenninger et al. 2000
	Porous colloidal aluminum silicate, a catch-all phrase for clay or other fine-grained earthy material suitable for use as an absorbent and bleach	Gamble 1986
Hectorite	$Na_{0.67}(Mg,Li)_6Si_8O_{20}(OH,F)_4$[a]	Budavari 1989
	$Na_{0.33}[Mg_{2.67}Li_{0.33}]Si_4O_{10}[OH]_2$	Rheox Inc. 1999
	Montmorillonite mineral that is the principle constituent of bentonite clays	Wenninger et al. 2000
	Fluorine-bearing magnesium rich montmorillonite	Grim 1972
	Almost a complete substitution of aluminum in the lattice structure of bentonite by magnesium in hectorite and the presence of lithium and flourine	United States Pharmacopeial Convention, Inc. 1994
Kaolin/Kaolinite	$Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$	Wenninger et al. 2000
	Native hydrated aluminum silicate	Wenninger et al. 2000
	Kaolinite is the mineral that characterizes most Kaolins	Ross and Kerr 1931
Lithium Magnesium Silicate	No specific formula	Wenninger et al. 2000
	Synthetic clay consisting of mainly lithium and magnesium silicates	Wenninger et al. 2000

(Continued on next page)

TABLE 1
Chemical formulas and compositions of Silicates and Silicate Clays used in cosmetics *(Continued)*

Ingredient	Description	Reference
Lithium Magnesium Sodium Silicate	No specific formula	Wenninger et al. 2000
	Synthetic clay consisting mainly of lithium, magnesium, and sodium silicates	Wenninger et al. 2000
Montmorillonite	$R^{+}_{0.33}(Al,Mg)_2Si_4O_{10}(OH)_2$, where $R^+ = Na^+$, K^+, Mg^{2+}, or Ca^{2+}	Budavari 1989
	Complex aluminum/magnesium silicate clay	Wenninger et al. 2000
	Term used to describe a group of minerals with an expanding lattice, except vermiculite and also a specific mineral with a high-alumina end member of the montmorillonite group with some slight replacement of Al^{3+} by Mg^{++} and substantially no replacement of Si^{4+} by Al^{3+}	Grim 1972
Pyrophyllite	$Al_2O_3 \cdot 4SiO \cdot 2H_2O$	Wenninger et al. 2000
	Naturally occurring mineral substance consisting predominantly of a hydrous aluminum silicate	Wenninger et al. 2000
Sodium Magnesium Silicate	No specific formula	Wenninger et al. 2000
	Synthetic silicate clay with a composition mainly of magnesium and sodium silicate	Wenninger et al. 2000
Zeolite	$M_{2/n}O \cdot Al_2O_3 \cdot ySiO_2 \cdot xH_2O$(M = a group IA or IIA element; n = cation valence; y = 2 or greater; x = the number of water molecules within the molecule)	IARC 1997
	Hydrated alkali aluminum silicate	Wenninger et al. 2000
	Group of hydrated, crystalline aluminosilicates containing exchangeable cations of group IA and IIA elements such as sodium, potassium, magnesium, and calcium	IARC 1997

TABLE 2
Zeolites (IARC 1997)

Zeolite	CAS no.	Chemical formula
Clinoptilolite	12173-10-3 (general)	Not given
	12271-42-0	$Na(AlSi_5O_{12} \cdot xH_2O)$
	67240-23-7	$AlNaH_{16}(SiO_4 \cdot 4H_2O)$
Mordenite	12173-98-7 (general)	Not given
	12445-20-4	$AlNaH_6(SiO_3)_5$
	66732-10-3	$Al_2CaH_{12}(SiO_3)_{10} \cdot H_2O$
	68652-75-5	$Na(AlSi_5O_{12})$
Phillipsite	12174-18-4 (general)	Not given
	61027-84-7	$CaK[Al_3O(SiO_3)_5] \cdot 6H_2O$
	66733-09-3	$AlNa(SiO_4) \cdot 6H_2O$
Zeolite A	68989-22-0	$Na_{12}[(AlO_2)_{12}(SiO_2)_{12}] \cdot 27H_2O$
Zeolite X	68989-23-1	$Na_{86}[(AlO_2)_{86}(SiO_2)_{106}] \cdot 264H_2O$
Zeolite Y	Not specified	$Na_{56}[(AlO_2)_{56}(SiO_2)_{136}] \cdot 250H_2O$
Zeolite L	Not specified	$K_9[(AlO_2)_9(SiO_2)_{27}] \cdot 22H_2O$
ZSM-5	79982-98-2	$(NaTPA)_3[(AlO_2)_3(SiO_2)_{93}] \cdot 16H_2O$*

*TPA = tetrapropylammonium.

consists of double silica chains situated parallel to the *c* axis with the chains linked together through oxygens at their longitudinal edges. Tetrahedral apexes in successive chains point in the opposite direction. The linked chains form a kind of double-ribbed sheet with two rows of tetrahedral apexes at alternate intervals in the top and bottom of the sheets. The ribbed sheets are arranged so that the apex oxygens of successive sheets point together and are held together by aluminum and/or magnesium in octahedral coordination between the apex oxygens of successive sheets. Chains of water molecules run parallel to the *c* axis and fill the interstices between the amphibole chains. Aluminum substitutions for silicon is considered probable (Grim 1967).

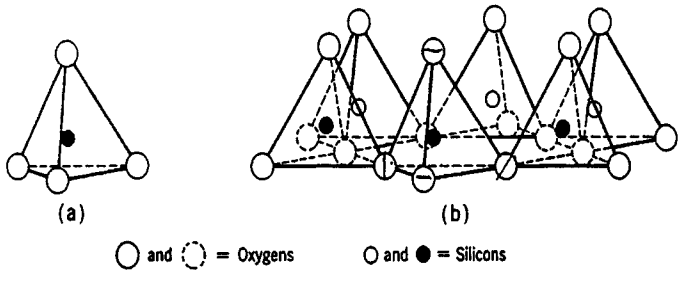

FIGURE 2
(*a*) Single tetrahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

TABLE 3

Synonyms for, physical properties of, and specifications for Silicates and Silicate Clays used in cosmetics

Item	Description	Reference
	Aluminum Silicate	
Synonyms	Anhydrous aluminum silicate, china clay, natural aluminum silicate, pyrophyllite, synthetic aluminum silicate, willinite	Wenninger et al. 2000
	Kaolin	Budavari 1989
	Aluminosilicate	Syracuse Research Corp. 1974
Form/description	Generally consisting of 1 mole of alumina and 1 to 3 moles of silica	Wenninger et al. 2000
	Four naturally occurring minerals (andalusite, cyanite, sillimainte, mullite); other associated minerals: anauxite, dickite, kaolinite, kochite, newtonite, pyrophyllite, takizolite, termierite, and ton	Budavari 1989
Molecular weight	Variable: ranging from 162.05 to 426.05 Da	Lide 1993
Density	Variable: 3.156, 3.247	Lide 1993
Solubility	Insoluble in water	Syracuse Research Corp. 1974
	Calcium Silicate	
Synonyms	Silicic acid, calcium salt	Wenninger et al. 2000
Form/description	Hydrous or anhydrous silicate with varying proportions of calcium oxide and silica	Wenninger et al. 2000
	White or slightly cream colored free-flowing powder	Budavari 1989
Molecular weight	116.16 Da	Lide 1993
Solubility	Insoluble in water	Budavari 1989
pH	8.0–10.0 (aqueous slurry)	Budavari 1989
	Magnesium Aluminum Silicate	
Synonyms	Aluminum magnesium silicate, magnesium aluminosilicate, complex colloidal, *Carrisorb*, Gelsorb, VEEGUM	Palmieri 1994
	Aluminosilicic acid, magnesium salt, aluminum magnesium silicate	Wenninger et al. 2000
Form/description	Complex silicate refined from naturally occurring minerals	Wenninger et al. 2000
	Off-white to creamy white small flakes or micronized powder	Palmieri 1994
Molecular weight	262.4 Da	Budavari 1989
Solubility	Insoluble in water, alcohol, and organic solvents	Palmieri 1994
pH	9.0–10.0 (5% aqueous solution)	Nikitakis and McEwen 1990b
Viscosity	225–2200 mPa	Palmieri 1994
CTFA specifications	Arsenic (as As), 3 ppm maximum	Nikitakis and McEwen 1990a
	Lead (as Pb), 10 ppm maximum	Nikitakis and McEwen 1990a
	Magnesium Silicate	
Synonyms	Silicic acid, magnesium salt (1:1)	Wenninger et al. 2000
Form/description	Fine, white, odorless, tasteless, powder, free from grittiness	United States Pharmacopeial Convention, Inc. 1994
Solubility	Insoluble in water and alcohol	United States Pharmacopeial Convention, Inc. 1994
CTFA specifications	Arsenic (as As), 3 ppm maximum	Nikitakis and McEwen 1990a
	Lead (as Pb), 20 ppm maximum	Nikitakis and McEwen 1990a
	Magnesium Trisilicate	
Synonyms	Silicic acid, magnesium salt (1:2)	Wenninger et al. 2000
Form/description	Fine, white, odorless, tasteless powder, free form grittiness	United States Pharmacopeial Convention, Inc. 1994
Solubility	Insoluble in water and alcohol	United States Pharmacopeial Convention, Inc. 1994
	Sodium Magnesium Silicate	
Synonyms	Synthetic sodium magnesium silicate	Wenninger et al. 2000
Form/description	Synthetic silicate clay with a composition mainly of magnesium and sodium silicate	Wenninger et al. 2000

(Continued on next page)

TABLE 3

Synonyms for, physical properties of, and specifications for Silicates and Silicate Clays used in cosmetics *(Continued)*

Item	Description	Reference
	Zirconium Silicate	
Synonyms	Silicic acid, zirconium salt (1:1)	Wenninger et al. 2000
	Zircon, zirconium orthosilicate	Budavari 1989
	Zirconium (IV) silicate (1:1)	Lewis 1993
Form/description	Bipyramidal crystals, colorless unless has impurities and radioactive bombardment	Budavari 1989
	Red or various colored crystals	Lewis 1993
Molecular weight	183.31 Da	Budavari 1989
Solubility	Insoluble in alcohol, aqueous solution, and alkali	Lide 1993
Density	4.56	Lide 1993
pH	6–7.5 (10% aqeous slurry)	American Minerals 1998
CTFA specifications	Arsenic (as As), 3 ppm maximum	Nikitakis and McEwen 1990a
	Lead (as Pb), 20 ppm maximum	Nikitakis and McEwen 1990a
	Attapulgite	
Synonyms	Activated attapulgite, Attaclay, Attagel, Attasorb, Min-u-gel, palygorskit, Permagel, Zeogel	Registry of Toxic Effects of Chemical Substances (RTECS) 1999
	Palygorskite	IARC 1997
Form/description	Variety of Fuller's Earth; characterized by a chain structure rather than the sheet structure of other clay minerals	Wenninger et al. 2000
	White, gray, or transparent, dull, elongated, lath-shaped crystals in bundles that comprise thin sheets of minute interlaced fibers; surface is protonated and hydrated	IARC 1997
Density	2.2	IARC 1997
Solubility	Insoluble in water	United States Pharmacopeial Convention, Inc. 1994
	Bentonite	
Synonyms	CI 77004, soap clay	Wenninger et al. 2000
	Albagel Premium USP 4444, Bentonite magma, Hi-gel, Imvite I.G.B.A., Magbond, montmorillonite, Tixoton, Volclay, Wilkinite	RTECS 1999
	BentoPharm, E558, mineral soap, soap clay, taylorite, Veegum HS, wilkinite	Belmonte 1994
Form/description	Native hydrated colloidal aluminum silicate clay	Wenninger et al. 2000
	Crystalline, claylike material, available as an odorless, palebuff or cream to grayish-colored fine powder, which is free from grit	Belmonte 1994
	Dioctahedral	Rheox Inc. 1999
Molecular weight	359.16 Da	Belmonte 1994
Solubility	Practically insoluble in ethanol, fixed oils, glycerin, propan-2-ol and water	Belmonte 1994
pH	9.5–10.5 for a 2% aqueous solution	Belmonte 1994
Particle size	Mainly 50–150 μm along with 1–2 μm particles	Belmonte 1994
	0.8 × 0.8 × 0.01 μ	Rheox Inc. 1999
Color	Grey to green	Rheox Inc. 1999
Swelling ability	15×	Rheox Inc. 1999
Iron	2.3%	Rheox Inc. 1999
	Fuller's Earth	
Synonyms	English Fuller's earth	Wenninger et al. 2000
Form/description	Nonplastic variety of kaolin	Wenninger et al. 2000
	Sheet structure	Gamble 1986

(Continued on next page)

TABLE 3
Synonyms for, physical properties of, and specifications for Silicates and Silicate Clays used in cosmetics *(Continued)*

Item	Description	Reference
	Hectorite	
Synonyms	Macaloid, Ben-A-Gel	Barr 1963
	Bentone and Bentone Gel	Rheox Inc. 1999
Form/description	Translucent colorless mineral when mined and turns white when dried	Barr 1963
	Tridecahedral	Rheox Inc. 1999
Particle size	$0.8 \times 0.08 \times 0.01\ \mu$	Rheox Inc. 1999
pH	8.5 (5% slurry)	Rheox Inc. 1999
Iron	0.2% (typical)	Rheox Inc. 1999
Color	Light pink to tan; off-white	Rheox Inc. 1999
Swelling ability	35×	Rheox Inc. 1999
Odor	None	Rheox Inc. 1999
Specific gravity	2.65	Rheox Inc. 1999
	Kaolin	
Synonyms	Bolbus Alba, China Clay, CI 77004, Kolite, Pigment White 19	Wenninger et al. 2000
	Altowhites, Argilla, Bentone, China Clay, Emathlite, Fitrol, Glomax, Hydrite, Kaopaous, Langford, Mcnamee, Parclay, Porcelin Clay, Snow tex	RTECS 1999
	Bolbus alba, China clay, white bole, argilla, terra alba, porcelin clay	Informatics, Inc. 1974
	White or yellowish white, earthy mass or white powder; unctous when moist	Budavari 1989
Form/description	Native hydrated aluminum silicate	Wenninger et al. 2000
Molecular weight	258.2 Da	Budavari 1989
Solubility	Insoluble in water, cold acids, or in alkali hydroxides	Budavari 1989
Cation exchange capacity	3–15 mEq/100 g	Carrol 1959
CTFA specifications	Arsenic (as As), 3 ppm maximum	Nikitakis and McEwen 1990a
	Lead (as Pb), 20 ppm maximum	Nikitakis and McEwen 1990a
	Lithium Magnesium Silicate	
Synonyms	Silicic acid, lithium magesium salt	Wenninger et al. 2000
Form/description	Synthetic silicate clay consisting mainly of lithium and magnesium silicates	Wenninger et al. 2000
	Lithium Magnesium Sodium Silicate	
Synonyms	Magnesium lithium sodium silicate; silicic acid, lithium, magnesium, and sodium salt	Wenninger et al. 2000
Form/description	Synthetic silicate clay consisting mainly of lithium, magnesium and sodium silicates	Wenninger et al. 2000
	Montmorillonite	
Synonyms	Smectite	Grim 1972
Form/description	Complex aluminum/magnesium silicate clay	Wenninger et al. 2000
Cation exchange capacity	80–150 mEq/100 g	Carrol 1959
	Pyrophyllite	
Synonyms	Pyrophyllite clay	Wenninger et al. 2000
Form/description	Naturally occurring mineral—predominantly hydrous aluminum silicate	Wenninger et al. 2000
	Sodium Magnesium Silicate	
Synonyms	Synthetic sodium magnesium silicate	Wenninger et al. 2000
Form/description	Synthetic silicate clay with a composition mainly of sodium and magnesium silicate	Wenninger et al. 2000
pH	8.5–10.5 of 2% aqueous dispersion	Nikitakis and McEwen 1990b
Solubility	Insoluble in organic solvents and disperses in water	Nikitakis and McEwen 1990b

(Continued on next page)

TABLE 3

Synonyms for, physical properties of, and specifications for Silicates and Silicate Clays used in cosmetics *(Continued)*

Item	Description	Reference
	Zeolite	
Synonyms	Aluminosilicates, Bacterkiller, CS100, Sitton, Zeokar, Zeolith, Zeolum, Zeostar	Wenninger et al. 2000
	Clinoptilotile, Mordenite, Phillipsite, Zeolite A, Zeolite X, ZSM-5, Non-fibrous Japanese Zeolite	IARC 1997
Form/description	Crystalline, hydrated alkali-aluminum silicates	Budavari 1989; Wenninger et al. 2000

Kaolin

Kaolin's structure is composed of a single silica tetrahedral sheet and a single alumina octahedral sheet combined in a unit so that the tips of the silica tetrahedrons and one of the layers of the octahedral sheet form a common layer as shown in Figure 4. All the tips of the silica tetrahedrons point in the same direction and toward the center of the unit made by the silica and octahedral sheets. Composite octahedral-tetrahedral layers are formed due to the similarity between the sheets *a* and *b* dimensions. The common layer between the octahedral and tetrahedral groups consists of two thirds of shared atoms between silicon and aluminum that become O instead of OH. Analyses of Kaolin have shown there is little substitution within the lattice. In a small percentage of cases, iron and/or titanium has replaced aluminum. This has only been seen in the relatively poor crystalline varieties of Kaolin (Grim 1967).

Smectites (Montmorillonites, Hectorite, and Bentonite)

Smectite units comprise of two silica tetrahedral sheets with a central alumina octahedral sheet as shown in Figure 5. All tetrahedral tips point in the same direction and toward the center of the unit. The tips of the tetrahedrons of each silica sheet and one of the hydroxyl layers of the octahedral sheet form a common layer. As in Kaolin, the atoms common to both the tetrahedral and octahedral layer become O instead of OH. These layers are continuous in the *a* and *b* directions and are stacked one above the other in the *c* direction. As a consequence, O layers in the units become adjacent and a very weak bond is created with the possibility of cleavage. The preeminent feature of smectites is the ability of water and other organic molecules to enter between unit layers and expand in the *c* direction. Expansion properties are reversible; however, the structure is completely collapsed by removal of interlayer polar molecules. Most smectites have substitutions within their lattices: aluminum or phosphorous for

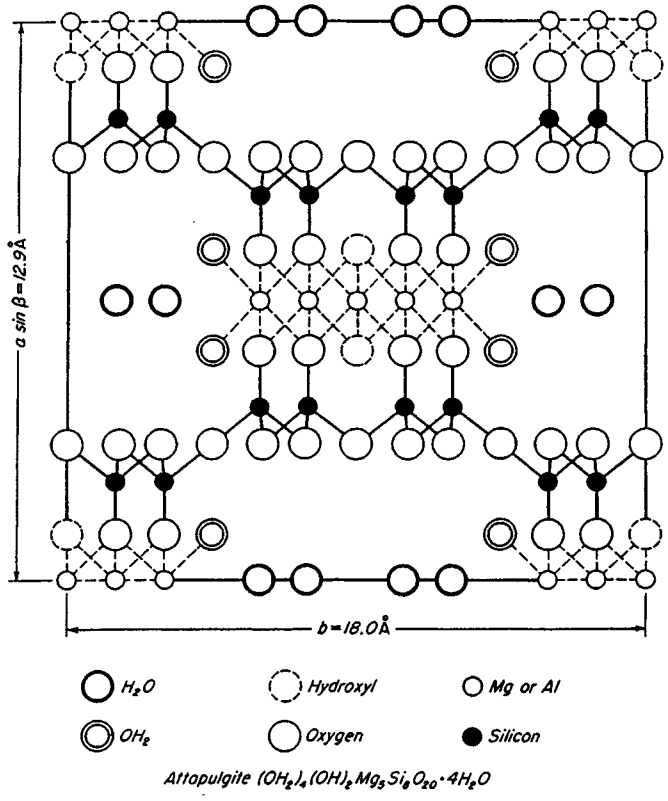

FIGURE 3
Attapulgite structure (taken from Grim 1967 with permission).

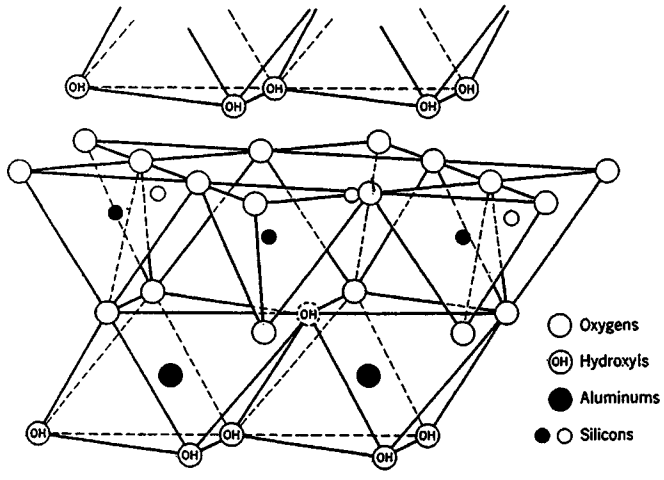

FIGURE 4
Kaolin layer (taken from Grim 1967 with permission).

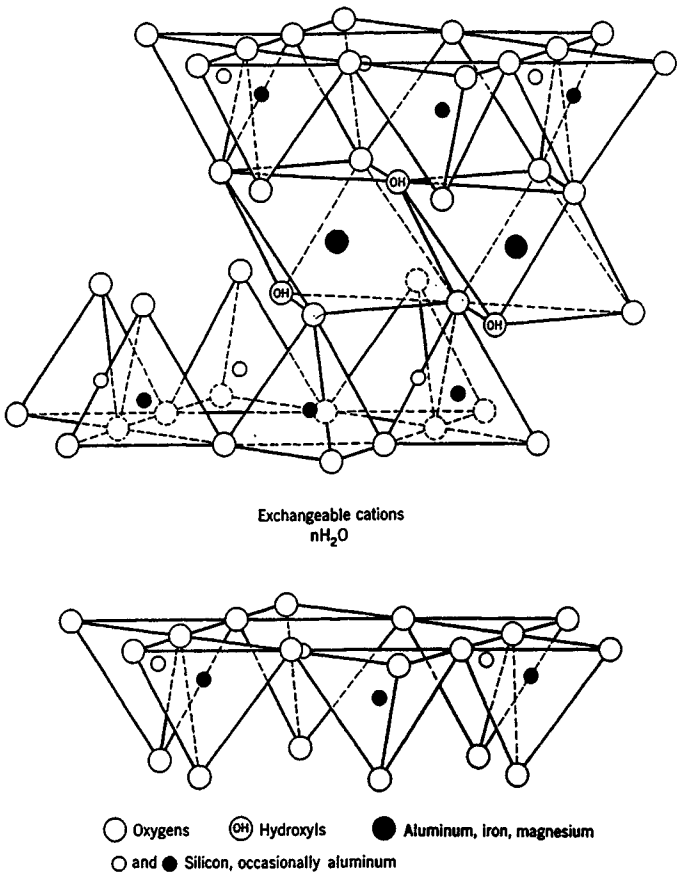

FIGURE 5
Smectite structure (taken from Grim 1967 with permission).

silicon in the tetrahedral coordination and/or magnesium, iron, zinc, nickel, lithium, etc. for aluminum in the octahedral sheet (Grim 1967).

Natural Occurrence of Clays

Aluminum Silicate

Natural Aluminum Silicates are reportedly being mined in India, California, North Carolina, and Georgia (Gamble 1986).

Attapulgite

Attapulgite is mined in 10 countries: Australia, China, France, India, Russia, Senegal, South Africa, Spain, Turkey, and the United States (Informatics, Inc. 1974).

Bentonite

Large deposits of Bentonite have been discovered in Canada, China, France, Germany, Great Britain, Greece, Hungary, Italy, Japan, Mexico, New Zealand, North Africa, Poland, South Africa, the former Soviet Union, and the United States (Informatics, Inc. 1974).

Kaolin

Deposits of Kaolin have been found in England, the United States, France, Czechoslovakia, Germany, and Japan (Informatics, Inc. 1974).

Pyrophyllite

Gamble (1986) reported Pyrophyllite being mined primarily in North Carolina.

Zeolite

Natural Zeolites are mined in Japan, the United States, Hungary, Bulgaria, Cuba, Italy, and South Africa (Roskill Informations Services Ltd. 1988).

Method of Manufacture

Aluminum Silicate

Aluminum Silicate is a naturally occurring mineral as well as artificially produced. The naturally occurring Aluminum Silicate minerals are know as andalusite, sillimanite, and cyanite. Natural Aluminum Silicate is mined from an ore and synthetic Aluminum Silicate is formed by heating compositions of controlled proportions of silica, alumina, and alkalis under conditions to promote the specific structure (Syracuse Research Corp. 1981).

Attapulgite

Hevilin and Murray (1994) describe the mining process of Attapulgite as an opencast technique, stripping layers with heavy machines such as bulldozers, backhoes, and excavators. The clay is then transported to a processing plant where crushing, drying, classification, and pulverizing takes place. High-heat drying to remove water may occur to enhance absorbent qualities.

Bentonite

The mined ore of Bentonite is processed to remove grit and nonswelling materials (Belmonte 1994).

Kaolin

In a process described by Wells, Bhatt, and Flanagan (1985), Kaolin is extracted from kaolinized granite by washing it out with powerful and remote water hoses. The clay stream is then pumped to the separation plant where sand and mica are removed. The purified clay is filtered when wet and then dried. The very fine powder is formed by milling.

Magnesium Aluminum Silicate

Magnesium Aluminum Silicate is obtained from silicate ores of the montmorillonite group. The ores are blended with water to produce a slurry, which is then processed to remove impurities and separate out the colloidal fractions. Refined colloidal fractions are dried to form a small flake and then is microatomized to form various powder grades (Palmieiri 1994).

Zeolite

Roskill Informations Services Ltd. (1988) reported natural Zeolites being recovered from deposits by selective opencast or strip mining processes. The raw material is then processed by crushing, drying, powdering, and screening. Synthetic Zeolite synthesis requires the following conditions: reactive starting materials; a high pH; a low-temperature hydrothermal state with concurrent low autogenous pressure at saturated water pressure; and a high degree of supersaturation of a large number of crystals.

Analytical Methods

Montmorillonite has been detected using far infrared spectra (Angino 1964). Bentonite and Kaolin are described by Angino (1964) using far infrared spectra and by Sadik (1971) using x-ray diffraction. Attapulgite has been detected with the use of transmission or scanning electron microscope (Zumwalde 1976), and by means of x-ray powder diffraction analysis (Keller 1979). The characterization of Hectorite was achieved through x-ray diffraction, infrared spectroscopy, and chemical analysis (Browne et al. 1980). Zeolites have been examined using scanning electron microscopy (Wright and Moatamed 1983; van Hoof and Roelofsen 1991) and x-ray diffraction (van Hoof et al. 1991). Magnetic angle spinning nuclear magnetic resonance (NMR) has confirmed the structural breakdown of Fuller's Earth (Drachman, Roch, and Smith, 1997).

IMPURITIES/COMPOSITION

Aluminum Silicate

Other minerals associated with natural Aluminum Silicates are anauxite, dickite, kaolinite, kochite, mullite, newtonite, pyrophyllite, takizolite, terierite, and ton (Budavari 1989).

Attapulgite

Attapulgite commonly is found with smectites, amorphous silica, chert, and other minerals (Bish and Guthrie 1993).

A typical composition is shown in Table 4 (Keller 1979).

Bentonite

The principle constituent is Montmorillonite. However, other minerals such as illite, kaolinite, and nonargillaceous detrital minerals can be present. Most Bentonites appear relatively pure and other mineral contributions rarely exceed 10%. Cristobalite is often present. Montmorillonite compositions frequently vary either in its lattice structure or in the exchangeable ions present (Informatics, Inc. 1974).

A typical composition is shown in Table 4 (Belmonte 1994).

Fuller's Earth

Principle deposits of Fuller's Earth include Montmorillonite, Bentonite, Attapulgite, and sepiolite (Gamble 1986).

TABLE 4

Mineral composition of individual samples of Magnesium Aluminum Silicate, Attapulgite, Bentonite, Hectorite, Kaolinite, and Montmorrillonite (Barr 1963)

	Silicate clays analyzed					
Mineral	Magnesium Aluminum Silicate (%)	Attaplugite (%)	Bentonite (%)	Hectorite (%)	Kaolinite (%)	Montmorillonite (%)
SiO_2	61.1	55.03	59.92	55.86	45.44	51.14
Al_2O_3	9.3	10.24	19.78	0.13	38.52	19.76
Fe_2O_3	—	3.53	—	0.03	0.80	0.83
FeO	0.9	—	2.96	—	—	—
MgO	13.7	10.49	1.53	25.03	0.08	3.22
CaO	2.7	—	0.64	Trace	0.08	1.62
K_2O	0.3	0.47	0.57	0.10	0.14	0.11
Na_2O	2.9	—	20.6	2.68	0.66	0.04
TiO_2	0.1	—	—	—	0.16	—
CO_2	1.8	—	—	—	—	—
LiO_2	—	—	—	1.05	—	—
F	—	—	—	5.96	—	—
MnO	—	—	—	—	—	Trace
ZnO	—	—	—	—	—	0.10
H_2O	7.2	19.86	Not reported	12.14	14.20	22.80
Reference	Palmieri 1994	Keller 1979	Belmonte 1994	Keller 1979	Keller 1979	Keller 1979

Hectorite

Principle impurities include calcite, dolomite, silica crystals, and grit (Barr 1963). A typical composition is shown in Table 4 (Keller 1979).

Kaolin

Quartz, mica, and feldspar are often found associated with the crude mineral and is often removed through screening and elutriation (Informatics, Inc. 1974).

Ferreira and Freitas (1976) surveyed Kaolin for any potentially pathogenic organisms and a mean viable count. *Pseudomonas aeruginosa*, *Salmonella typhosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Clostridium tetani* were absent. The mean viable count was $74 \times 10^3/6$ M. The bacteria present were mostly gram-positive aerobic spore-formers.

A typical composition is shown in Table 4 (Keller 1979).

Magnesium Aluminum Silicate

One trade-name group of products contain 1% to 6% by volume weight crystalline silica in the form of cristabalite; they also comment that a few grades may contain quartz as well (Kelse 1997).

A typical composition is shown in Table 4 (Palmeiri 1994).

Montmorillonite

A typical composition of Montmorillonite is shown in Table 4 (Keller 1979).

Zeolite

Valatina, Pylev, and Lemjasev (1994) analyzed the chemical compositions of five samples of Zeolite dusts taken from mines in Russia (Table 5). The benzo[a]pyrene content in the dusts of natural Zeolite tuffs (rock deposits) ranged from 0.0 to 3.6 μg/kg.

TABLE 5
Zeolite mine dust chemical analysis (Valatina, Pylev, and Lemjasev 1994)

Dust sample	1	2	3	4	5
Molar ratio of SiO_2/Al_2O_3	9.0	8.3	9.8	7.4	9.4
Zeolite (%)	83	50.6	73	63	56
Silicon dioxide (%)	66.84	0	70.92	62.64	68.6
Aluminum oxide (%)	12.36	12.62	12.11	14.17	12.16
Iron (III) oxide (%)	0.92	4	1.03	2.65	0.2
Magnesium oxide (%)	1.53	1.34	0.53	1.19	0.93
Calcium oxide (%)	2.36	4.15	2.56	2.01	1.93
Sodium oxide (%)	2.65	0.15	0.62	1.75	2
Benzo[a]pyrene	2.5	3.6	0.1	1.3	0

USE

Cosmetic

According to the European Cosmetic Directive (EU reference no. 391 Annex II), Zirconium and its compounds are listed under substances that must not form part of the composition of cosmetic products, with the exception of complexes in Annex III, Part I. These complexes are aluminum zirconium chloride hydroxide complexes and the aluminum zirconium chloride hydroxide glycine products used in antiperspirants; and the zirconium lakes, salts, and pigments of coloring agents listed in reference 3 in Annex IV, Part I (Cosmetics Directive of the European Union 1995).

Aluminum Silicate, anhydrous, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Bentonite, Hectorite, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite are listed in the *Japanese Comprehensive Licensing Standards by Category* (CLS) (Rempe and Santucci 1998). Aluminum Silicate, anhydrous has no concentrations limits and is listed in all categories except eyeliner preparations and lip preparations. Calcium Silicate, is listed in all categories. Magnesium Aluminum Silicate, which is listed under Aluminum Magnesium Silicate, is listed in all categories. Magnesium Silicate is listed in all categories. Hectorite is listed in all categories except eyeliner preparations, lip preparations, and oral preparations. Montmorillonite is excluded from only eyeliner preparations. Pyrophyllite is listed in all groups except eyeliner, lip, oral, and bath preparations. Bentonite, Kaolin, and Zeolite are listed in all categories.

Information on use of ingredients in cosmetic formulations is available from the Food and Drug Administration (FDA) as part of a voluntary industry reporting program (FDA 1998). These data are presented in the first two columns of Table 6.

In addition, the Cosmetic, Toiletry, and Fragrance Association (CTFA) provides information from the industry directly to CIR on the current concentration of use (CTFA 1999a). In some cases a current concentration of use is provided even when there is no current use reported to FDA. It is presumed that an industry report of a current concentration of use means the ingredient is in use. These data are included in the third column of Table 6.

In those cases where there is a use reported to FDA, but there is no current concentration of use data available, the last column in Table 6 includes historical data from 1984 when FDA collected information on concentration as part of the voluntary reporting program described earlier (FDA 1984). If no historical data are available, no concentration is listed.

Aluminum Silicate

Aluminum Silicate functions as an abrasive, anticaking agent, bulking agent, and opacifying agent in cosmetics (Wenninger et al. 2000). In 1998 it was reported as an ingredient in 10 formulations in seven different categories (FDA 1998).

TABLE 6
Frequency of use and concentration of use as a function of product category

Product category (Number of formulations reported to FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999a) (%)	Historical concentration of use (FDA 1984) (%)
	Aluminum Silicate		
Mascara (167)	2	0.5	
Blushers (all types) (238)	1	—	—
Dentifrices (38)	—	37	
Shaving cream (139)	1	—	—
Cleansing (653)	2	2	
Paste masks (mud packs) (255)	1	—	1–5
Skin fresheners (184)	1	—	0.1–1
Other skin preparations (692)	2	3	
1998 total uses of Aluminum Silicate	10		
	Calcium Silicate		
Bath oils, tablets, and salts (124)	12	—	0.1–5
Bubble baths (200)	2	—	0.1–25
Other bath preparations (159)	2	—	0.1–25
Eye shadow (506)	11	1–8	
Powders (247)	35	2	
Blushers (all types) (238)	17	5–8	
Face powders (250)	40	0.3–10	
Foundations (287)	5	2–8	
Lipstick (790)	3	0.5	
Makeup bases (132)	1	0.5	
Rouges (12)	1	—	1–5
Other makeup preparations (135)	1	—	1–5
Other manicuring preparations (61)	1	—	1–5
Skin cleansing preparations (653)	1	8	
Men/s talcum (8)	—	8	
1998 total for Calcium Silicate	132		
	Magnesium Aluminum Silicate		
Other bath preparations (159)	1	—	—
Eye makeup remover (84)	20	—	0.1–25
Eye shadow (506)	4	1	
Eye lotion (18)	1	1	
Eye makeup remover (84)	2	—	0.1–25
Mascara (167)	33	0.4–5	
Eyeliner (514)	—	0.2–0.5	
Eyebrow pencil (91)	—	0.5	
Other eye makeup preparations (120)	16	1–5	
Cologne and toilet waters (656)	1	—	—
Other fragrance preparations (148)	1	—	>0–1
Hair conditioners (636)	1	—	0.1–1
Hair straighteners (63)	3	—	0.1–1
Hair dyes and colors (1572)	—	2	
Shampoos (noncoloring) (860)	3	1–2	
Other hair preparations (276)	3	—	—
Hair rinses (coloring) (33)	1	—	—
Foundations (287)	130	0.4–5	
Lipstick (790)	3	—	0.1–1
Makeup bases (132)	60	1–2	

(Continued on next page)

TABLE 6
Frequency of use and concentration of use as a function of product category *(Continued)*

Product category (Number of formulations reported to FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999a) (%)	Historical concentration of use (FDA 1984) (%)
Makeup fixatives (11)	3	2	
Other makeup preparations (135)	24	0.8	
Cuticle softeners (19)	1	—	—
Nail creams and lotions (17)	1	—	0.1–5
Dentifrices	—	0.7	
Bath soaps and detergents (385)	1	0.5–1	
Deodorants (underarm) (250)	5	0.5–1	
Other personal cleanliness products (291)	14	2	
Aftershave lotion (216)	9	—	1–>50
Other shaving preparations (60)	2	—	0.1–5
Skin cleansing preparations (653)	41	0.1–5	
Face and neck skin care preparations (263)	16	0.6–3	
Body and hand skin care preparations (796)	56	0.3–5	
Foot powders and sprays (35)	3	—	—
Moisturizers (769)	70	0.3–4	
Night creams, lotions, powders, and sprays (188)	11	0.3–2	
Paste masks (mud packs) (255)	34	3–5	
Other skin care preparations (692)	33	0.1	
Suntan gels, creams, and liquids (136)	6	2–5	
Indoor tanning preparations (62)	19	0.5–2	
1998 total for Magnesium Aluminum Silicate	632		
	Attapulgite		
Powders (fragrance) (247)	5	—	—
Body and hand skin care preparations (796)	—	8	
Paste masks (mud packs) (255)	5	8	
1998 total for Attapulgite	10		
	Bentonite		
Bath, oils, tablets, and salts (124)	—	5	
Eyeliner (514)	6	5	
Mascara (167)	1	0.8	
Other eye makeup preparations (120)	1	—	—
Hair conditioners (636)	1	—	—
Hair straighteners (63)	3	—	0.1–1
Foundations (287)	5	2–8	
Makeup bases (132)	3	1	
Cuticle softeners (19)	1	1	
Bath soaps and detergents (385)	1	0.5	
Other personal cleanliness products (291)	2	—	0.1–10
Skin cleansing preparations (653)	6	—	>0–10
Face and neck skin care preparations (excluding shaving) (263)	1	2–5	
Body and hand skin care preparations (excluding shaving) (796)	6	2–5	
Moisturizers (769)	2	3	
Night creams, lotions, powders, and sprays (188)	1	—	—
Paste masks (mud packs) (255)	44	12–80	
Skin fresheners (184)	1	—	—

(Continued on next page)

TABLE 6
Frequency of use and concentration of use as a function of product category *(Continued)*

Product category (Number of formulations reported to FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999a) (%)	Historical concentration of use (FDA 1984) (%)
Other skin preparations (692)	8	—	—
Suntan gels, creams, and liquids (136)	1	—	—
Other suntan preparations (38)	—	1	
1998 total for Bentonite	73		
	Fuller's Earth		
Paste masks (mud packs) (255)	2	—	—
Other skin preparations (692)	1	—	25–50
1998 total for Fuller's Earth	3		
	Hectorite		
Eyeliner (514)	3	—	—
Mascara (167)	1	0.7	
Shampoos (noncoloring) (860)	—	1	
Hair bleaches (113)	5	—	—
Foundations	—	15	
Other makeup preparations (135)	1	—	1–5
Basecoats and undercoats (manicuring) (48)	1	—	—
Nail polish and enamel (80)	1	—	—
Deodorants (underarm) (250)	1	0.7	
Other personal cleanliness products (291)	1	—	—
Paste masks (mud packs) (255)	2	0.4	
Skin cleansing preparations (653)	—	100	
Body and hand creams, lotions, powders, and sprays (796)	—	8	
Other skin preparations (692)	1	—	—
Paste masks (mud packs) (255)	—	8	
Other suntan preparations (38)	1	—	
1998 total for Hectorite	18		
	Sodium Magnesium Silicate		
Eyeliner	—	0.08	
Eye shadow (506)	11	0.08	
Mascara (167)	1	0.4	
Other eye makeup preparations (120)	1	—	—
Powders (fragrance) (247)	1	—	—
Tonics, dressings, and other hair-grooming aids (549)	1	—	—
Blushers (all types) (238)	2	—	—
Face powders (250)	3	0.4	
Foundations (287)	4	0.4	
Lipstick (790)	1	3	
Makeup bases (132)	—	0.1	
Other makeup preparations (135)	1	—	—
Dentifrices (38)	—	0.3	
Deodorants (underarm) (250)	—	0.5	
Skin cleansing preparations (653)	—	0.5	
Face and neck skin care preparations (excluding shaving) (263)	3	0.8–5	
Body and hand skin care preparations (excluding shaving) (796)	2	0.1	
Moisturizers (769)	1	1	

(Continued on next page)

TABLE 6
Frequency of use and concentration of use as a function of product category *(Continued)*

Product category (Number of formulations reported to FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999a) (%)	Historical concentration of use (FDA 1984) (%)
Paste masks (mud packs) (255)	1	5	
Skin fresheners (184)	—	5	
Other skin preparations (692)	1	—	1–5
1998 total for Sodium Magnesium Silicate	34		
	Kaolin		
Other bath preparations (159)	1		1–10
Eyebrow pencil (91)	5	15–17	
Eyeliner (514)	9	25–48	
Eye shadow (506)	171	3–29	
Mascara (167)	31	8–18	
Other eye makeup preparations (120)	15	20	
Powders (247)	40	5	
Hair conditioners (636)	5	4	
Tonics, dressings, and other hair-grooming aids (549)	—	15	
Other hair-coloring preparations (59)	1	5	
Blushers (all types) (238)	72	14–20	
Face powders (250)	58	30	
Foundations (287)	45	6–36	
Lipstick (790)	6	12–30	
Makeup bases (132)	24	7–25	
Rouges (12)	2	—	>0–50
Makeup fixatives (11)	3	—	1–5
Paste masks (mud packs) (255)	—	12–84	
Other makeup preparations (135)	20	10–24	
Bath soaps and detergents (385)	1	3	
Other manicuring preparations (61)	—	53–54	
Skin cleansing preparations (653)	—	0.01	
Face and neck skin care preparations (263)	—	3	
Moisturizers (769)	—	25	
Skin fresheners (184)	—	2	
Other skin care preparations (692)	—	3–100	
Suntan gels, creams, liquids (136)	—	25	
1998 total for Kaolin	509		

Attapulgite

Attapulgite functions as an abrasive, bulking agent, opacifying agent, and viscosity-increasing agent (Wenninger et al. 2000). The FDA reported in 1998 Attapulgite being used in 10 formulations (FDA 1998).

Bentonite

Bentonite functions as an absorbent, bulking agent, emulsion stabilizer, opacifying agent, suspending agent—nonsurfactant, and viscosity-increasing agent—aqueous in cosmetic formulations (Wenninger et al. 2000). In 1998, 94 formulations were reported (FDA 1998). Of the 94 formulations, 47% were reported within paste masks (mud packs) (FDA 1998).

Calcium Silicate

Calcium Silicate functions as an absorbent, bulking agent, and an opacifying agent in cosmetic formulations (Wenninger et al. 2000). The FDA reported 132 formulations containing Calcium Silicate in 1998, of which 30% of the formulations were face powders (FDA 1998).

Fuller's Earth

Fuller's Earth functions as an absorbent, anticaking agent, bulking agent, and opacifying agent (Wenninger et al. 2000). Fuller's Earth was reported in three formulations in 1998 (FDA 1998).

Hectorite

Hectorite functions as an absorbent, bulking agent, opacifying agent, suspending agent—nonsurfactant, and viscosity-increasing agent—aqueous (Wenninger et al. 2000). In 1998, Hectorite was reported in 18 formulations (FDA 1998). Rheox Inc. (1999a) reported Hectorite as being used in antiperspirants, suntan products, eye products, hair products, creams and lotions, lip products, facial masks, and nail products.

Kaolin

Kaolin functions as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent in cosmetic formulations (Wenninger et al. 2000). Of the 509 formulations reported by FDA in 1998, 34% were eye shadows (FDA 1998).

Lithium Magnesium Silicate

Lithium Magnesium Silicate functions as a binder, bulking agent, and viscosity-increasing agent—aqueous in cosmetic formulations (Wenninger et al. 2000). There were no current uses reported to FDA.

Lithium Magnesium Sodium Silicate

Lithium Magnesium Sodium Silicate functions as a bulking agent and viscosity-increasing agent—aqueous (Wenninger et al. 2000). There were no current uses reported to FDA.

Magnesium Aluminum Silicate

Magnesium Aluminum Silicate functions as an absorbent, anticaking agent, opacifying agent, and viscosity-increasing agent—aqueous in cosmetics (Wenninger et al. 2000). It was reported that Magnesium Aluminum Silicate was used in 629 formulations in 1998 (FDA 1998). Of those 629 formulations, 21% were used in foundations.

Magnesium Aluminum Silicate (VEEGUM) was reported by Carlson (1977) to typically be used at a concentration of 1% to 2%, consistent with the data in Table 6. Another source reported Magnesium Aluminum Silicate used at concentrations of 10% to 50% for adsorbents, 0.5% to 2.5% for stabilizing agents, 1% to 10% for suspending agents, 2% to 10% for tablet and capsule disintegrants, 2% to 10% tablet binders, and 2% to 10% viscosity-increasing agents, again consistent with data in Table 6 (Palmieri 1994).

Additional historical data on concentration of use of this ingredient are available from a Toilet Good Association survey. Table 7 is a summary of that information (Toilet Goods Association 1969).

Magnesium Silicate

Magnesium Silicate functions as an absorbent, anticaking agent, bulking agent, opacifying agent, and viscosity-increasing agent—aqueous in cosmetic formulations (Wenninger et al. 2000). There were no current uses reported to FDA.

Magnesium Trisilicate

Magnesium Trisilicate functions as an abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, and viscosity-increasing agent—aqueous in cosmetics (Wenninger et al. 2000).

TABLE 7

Magnesium Aluminum Silicate in cosmetic preparations (Toilet Goods Association 1969).

Product category	Use in product	Concentration (%)
Face cream/lotion (cleansing, hormone, night, acne, astringent)	Thickener, binder, emulsion stabilizer	2.1
Hand cream/lotion	Thickener, binder, emulsion stabilizer	1.3
Body cream/lotion (moisturizer, suntan preparations)	Thickener, binder, emulsion stabilizer, slip agent	1.6
Makeup (lotion, cream, medicated, matte, highlight)	Thickener, binder, emulsion stabilizer, pigment suspender	1.8
Rouge (cream, liquid, blusher, toner)	Thickener, binder, pigment suspender	1.8
Face mask	Thickener, binder	8.9
Powder aerosol	Anticaking	8.0
Powder compact/pressed	Oil absorption	1.0
Leg makeup	Thickener	3.9
Deodorant/antiperspirant	Thickener, emulsion stabilizer	1.8
Eye makeup (eyeshadow, mascara, eyeliner)	Thickener, emulsion stabilizer, pigment suspender	2.0
Depilatory	Thickener	2.0
Shave preparations	Thickener	0.5
Shampoo	Thickener	3.5
Cream sachet	Thickener, emuslion stabilizer	0.8

Montmorillonite

Montmorillonite functions as an abrasive, absorbent, emulsion stabilizer, opacifying agent, and viscosity-increasing agent—aqueous in cosmetics (Wenninger et al. 2000). There were no current uses reported to FDA.

Pyrophyllite

Pyrophyllite functions as an absorbent, colorant, and opacifying agent (Wenninger et al. 2000). There were no current uses reported to FDA.

Sodium Magnesium Silicate

Sodium Magnesium Silicate functions as binder and bulking agent (Wenninger et al. 2000). In 1998, Sodium Magnesium Silicate was reported in 34 formulations (FDA 1998).

Zeolite

Zeolite functions as an absorbent and deodorant agent in cosmetic formulations (Wenninger et al. 2000). There were no current uses reported to FDA.

Zirconium Silicate

Zirconium Silicate functions as an abrasive and opacifying agent in cosmetic formulations (Wenninger et al. 2000). There were no current uses reported to FDA.

Noncosmetic

Aluminum Silicate

Aluminum Silicate is approved, under the heading of indirect food additives, as a substance used as basic components of single or repeated use of the food contact surfaces cellophane (21 Code of Federal Regulations [CFR] 177.1200) and rubber (21 CFR 177.2600).

Attapulgite

Attapulgite is listed in the OTC Active Ingredient Status Report as proposed category I, as an antidiarrheal ingredient (FDA 1994). Attapulgite is listed by Gamble (1986) as being primarily used in absorbents, pesticides, oil and petroleum treatment, and as a filler in many products.

Bentonite

Bentonite is considered by FDA to be generally recognized as safe (GRAS) as a direct food additive (21 CFR 184.1155).

Bentonite is listed by Gamble (1986) as being used in foundry sand bonding, bleaching clay in oil refining and decolorizers, filtering agents, water impedance, animal feed, pharmaceuticals, paint, plasticity increasers, and iron-ore pelletizing. Another source reported Bentonite as being used as an adsorbent, emulsion stabilizer, and suspending agent (Belmonte 1994). Bentonite is categorized by the *National Formulary* as a suspending and/or viscosity-increasing agent (United States Pharmacopeial Convention, Inc. 1994).

Calcium Silicate

Calcium Silicate is listed in the OTC Active Ingredient Status Report as an external analgesic and skin protectant (FDA 1994). The *National Formulary* category is as a glident and/or anticaking agent (United States Pharmacopeial Convention, Inc. 1994).

The American Conference of Governmental Industrial Hygienists (ACGIH) TLV-TWA (threshold limit value–time weighted average) is 10 mg/m^3 for inhalable dust (ACGIH 1997).

Hectorite

Hectorite has two listings of category IISE in the OTC Active Ingredient Status Report (FDA 1994). It is listed as being used as an external analgesic and skin protectant. Barr (1957) stated that the Federal Drug Administration (sic) has given approval for the use of Hectorite in internally and externally applied products, as well as dentifrices, cosmetics, and externally approved pharmaceuticals.

Kaolin

According to FDA, Kaolin is considered GRAS as an indirect food additive (21 CFR 186.1256). Kaolin is listed as being used in antacids, anorectals (external and interrectal), antidiarrheals, skin protectants, and digestive aids (colloidal Kaolin) in the OTC Active Ingredient Status Report. The final rulings are as follows: antacids: category IIE; anorectals (both): category I; and digestive aid: category IISE. Proposed rulings are as follows: antidiarrheal: category IIIE; skin protectant diaper rash: category I; skin protectant poison ivy: category I; and skin protectant: category I. Category III is designated as the conditions for which the available data are insufficient to permit final classification at this time.

Gamble (1986) reports Kaolin's main use in the paper industry to fill and coat the surface of paper. Kaolin is also reported being used as a filler in rubber, paint extender, filler in plastics, ceramics manufacture, ink, adhesives, insecticides, medicines, food additives, bleaching, adsorbents, cement, fertilizers, crayons, pencils, detergents, porcelain enamels, paste, foundries, linoleum, floor tiles, and textiles.

The *National Formulary* classifies Kaolin as a tablet and/or capsule diluent (United States Pharmacopeial Convention, Inc. 1994).

The *Food Chemicals Codex* specifies limits of impurities for clay (Kaolin) as: acid-soluble substances <2%; Arsenic (as As) <3 ppm; Heavy Metals (as Pb) <40 ppm; Lead <10 ppm (National Academy of Science 1996).

Magnesium Aluminum Silicate

Magnesium Aluminum Silicate (MAS) is listed as being used in acne treatments and in antacids in the OTC Active Ingredient Status Report (FDA 1994). As an antacid, MAS is a category I listing, meaning it is generally recognized as safe and effective and is not misbranded. However, MAS is a category IISE listing as used for acne. MAS was listed as category IISE due to safety and/or effectiveness.

Other uses for Magnesium Aluminum Silicate have been reported as: adsorbent, suspending agents, tablet and capsule disintegrant, tablet binder, and viscosity-increasing agent (Palmieri 1994).

The *National Formulary* classifies Magnesium Aluminum Silicate as a suspending and/or viscosity-increasing agent (United States Pharmacopeial Convention, Inc. 1994).

VEEGUM, a tradename for Magnesium Aluminum Silicate, has been designated by the FDA as a raw material with the following number: FD-CRMCS no. R0010045 and has an individual Chemical Abstract Registry (CAS) number 12199-37-0.

Magnesium Silicate

Magnesium Silicate is classified as a glidant or anticaking agent by the *National Formulary* (United States Pharmacopeial Convention, Inc. 1994).

Magnesium Trisilicate

Magnesium Trisilicate is listed in the OTC Active Ingredient Status Report as being used as antacids, digestive aids, and overindulgence remedy (FDA 1994). In antacids, FDA has listed Magnesium Trisilicate as category I (generally recognized as safe and effective). FDA concluded that Magnesium Trisilicate use in digestive aids is category IISE (not generally recognized as safe and effective). FDA has proposed that Magnesium Trisilicate use in overindulgence remedies is category I.

Pyrophyllite

Pyrophyllite is listed under Code of Federal Regulations (21 CFR 73.1400) as a naturally occurring color additive and must conform to the following specifications: lead (as Pb) not more than 20 ppm; and arsenic (as As) not more than 3 ppm. Also Pyrophyllite may be used safely for coloring externally applied cosmetics, in amounts consistent with good manufacturing practice (21 CFR 73.2400).

Pyrophyllite is listed by Gamble (1986) as being used in refractories, rubber, ceramics, insecticides, plastics, paint, roofing, bleaching powder, textiles, cordage, and wall board.

Zeolite

Zeolites are reported by Gamble (1986) as being used in CO_2 recovery from natural gas, aromatic separates dimension stones, filler in paper, isolation of radioactive wastes, water aeration, dietary supplements for animals, neutralization of acidic soils, carriers for pesticides and fungicides, sorbents for oil spills, polishing agent in toothpastes, and petroleum solvents. International Agency for Research on Cancer (IARC) (1997) lists the three main uses of synthetic Zeolite as: detergents, catalysts, and adsorbents or desiccants.

Zirconium Silicate

Zirconium Silicate is reported by Kleber and Putt (1986) as being used in chewing gum and in a dental prophylaxis paste.

GENERAL BIOLOGY

Adsorption

The large volume of general data available on the adsorption of various chemicals, cells, etc., to these silicate clays is presented in Table 8. In addition, to this general information, specific reactions are described using specific silicate clays—these data are described below.

Hectorite

Bujdak and Rode (1996) reported that Hectorite-catalyzed glycine and diglycine oligomerizations were performed as drying/wetting cycles. Approximately 7% of glycine was converted to diglycine and diketopiperazine on Hectorite after 7 days. It may be noted that the Hectorite sample was altered by substituting Li(I) for Mg(II), which caused a greater effect on oligomerizations.

Porter et al. (1998) reported condensation reactions of the amino acid glycine on the surface of Cu(II)-exchanged Hectorite. Polymerization of gylcine oligomers was seen primarily at the edges or topmost layer. These reactions were facilitated by the availability of intergallery metal cations at the step edges or pores in the surface region.

Kaolin

Adenosine monophosphate molecules were adsorbed onto Kaolinite, modified with Mg^{2+} and irradiated with ultraviolet (UV) light. These synthesis products were tested for their bond types by enzymatic hydrolysis and analyzed by ion-exchange chromatography. Considerable portions of the products were phosphodiesterase hydrolyzed, which implies a 3′–5′, 2′–5′, or both, nature of the bonds (Strigunkova, Lavrentiev, and Ostroshchenko 1986).

Montmorillonite

Dougherty et al. (1985) incubated Montmorillonite saturated with magnesium chloride (10 mg) with 5×10^6 human neutrophils. Effects were determined by phase contrast microscopic examination and by the measurement of lactate dehydrogenase. Both untreated and clay treated with human albumin were used to stimulate neutrophil chemiluminescence. Montmorillonite was also incubated with human erythrocytes and the free hemoglobin was measured at 430 nm and the effect of clay on zymosan-activated serum was also investigated. Rapid neutrophil lysis was observed in cells exposed to untreated clay. After lysis, lactate dehydrogenase rapidly adsorbed to the surface of the clay. Clay pretreatment with human albumin blocked the enzyme surface adsorption and cell lysis. Neutrophil chemiluminescence was stimulated by untreated clay but not by clay pretreated with 5% albumin. Clay lysis of erythrocytes was incomplete as compared to neutrophil lysis. Zymosan-activated serum samples exposed to clay; complement activity as measured by neutrophil chemotaxis was suppressed in a dose-dependent manner.

TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays

Compound adsorbed	Experimental design	Results	Reference
		Magnesium Aluminum Silicate	
Dicumarol	The drug dicumarol was given to dogs with 50% colloidal Magnesium Aluminum Silicate (MAS); the plasma level of dicumarol in dogs was measured	Significantly lower plasma levels and delayed appearance of dicumarol resulted from administration with 50% MAS; drug concentration at peak level was 16.7% (25.8% in controls) and peak plasma levels were seen at 12–24 h (8–12 h in controls)	Akers, Lach, and Fischer 1973
Streptomycin sulphate and neomycin sulphate	Adsorption studies were carried out in vitro in McIlvaine's Buffer and water	MAS had the greatest affinity for streptomycin sulphate in water (adsorption coefficient of $111 \cdot 10^{-3}$ for water and $33 \cdot 10^{-3}$) whereas the adsorption coefficient for MAS in water to neomycin sulphate was $34 \cdot 10^{-3}$	Ghazy, Kassem, and Shalaby 1984
Bromohexine HCL	MAS was mixed with bromohexine HCL to make tablets and were stored in polyethylene film for various times; the amount of bromohexine remaining in the tablet was determined	Bromohexine remaining in the tablets increased with increasing concentrations of MAS, indicating that MAS prevented the adsorption of bromohexine to polyethylene film; no bromohexine degradation was reported	Kukita et al. 1992
Tetracycline	In vitro and in vivo adsorption of tetracycline by VEEGUM was studied	The maximum serum concentration of tetracycline was decreased by 21%; the maximum adsorption in vitro occurred at pH 1.2, where the % adsorbed ranged from 91.5% to 97.2%	Healy et al. 1997
Trimethoprim	The concentration of trimethoprim in the blood was determined at 0, 15, and 30 min and 1, 2, 4, and 6 h	The mean decrease in the maximum blood concentration of trimethoprim was 49.94%	Babhair and Tariq 1983
Aminosidine sulphate, chloramphenicol, erythromycin, neomysin B sulphate, novobiocin sulphate, penicillin V, streptomycin sulphate, and tetracycline hydrochloride	Each antibiotic was added to 250 mg of magnesium trisilicate; the antibiotic activity was determined by cup-plate method using *Staphylococcus aureus*	Magnesium Trisilicate reduced the activity of all antibiotics except chloramphenicol	El-Nakeeb and Youssef 1968
Ampicillin and amoxycillin	In vitro adsorption and desorption studies were carried out at different pHs	Hydrated silica gel formed from decomposition of the antacid at pH 2.1 and Magnesium Trisilicate had no adsorptive effect on either antibiotic	Khali, Mortada, and El- Khawas 1984a
		Attapulgite	
Strychnine, quinine, and atropine	Adsorption isotherms for each of the drugs and the clay was determined using spectrophotometric or colorimetric methods	Attapulgite adsorbed strychnine better than atropine than quinine; an increase in the hydrogen ion concentration was found to have a slight decreasing effect on the adsorptive ability for strychnine	Evcim and Barr 1955

(Continued on next page)

TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
Strychnine and atropine	Activated attapulgite was added to both compounds and adsorption isotherms were calculated	Both compounds were adsorbed by Attapulgite; optimum adsorbent properties were calculated at pH 6.8 and 7.2	Barr and Arnista 1957
Agrobacterium radiobacter	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Attapulgite contained excess basic cations, which accounted for the initial high pH and the reduction on respiration elicited by the addition of buffer	Stotzky 1966
Vibrio cholerae and *Escherichia coli* enterotoxins	The toxins and Attapulgite were injected into the intestinal loop of rabbits	Attapulgite prevented the toxic effects caused by enterotoxins in the intestinal loop by adsorption; Attapulgite was effective when injected simultaneously with the toxin and before the toxin is injected	Drucker et al. 1977
Ampicillin and amoxycillin	In vitro adsorption and desorption studies were carried out at different pHs	Both drugs were adsorbed at pH 2.1; desorption experiments at pH values of 2.0 and 6.5 showed only partial release of the adsorbed antibiotics	Khali, Mortada, and El-Khawas 1984a
		Bentonite	
Escherichia coli, *Serratia marcescens*, and *Bacillus* species	Each organism was cultivated in broth portions with 3% and 10% Bentonite	All organisms were absorbed by Bentonite at each concentration; *Bacillus* species was almost completely absorbed at each concentration	Novakova 1977
Escherichia coli 0111 endotoxins (ETU 144, 150, and 153)	In vitro and in vivo endotoxin binding was studied	In vitro, Bentonite was an effective endotoxin binder and binding was pH dependent (lower pHs yielded better results); 75 mg completely eliminated endotoxemia. At pH 3.0, the ED_{50} was 20 mg	Ditter, Urbaschek, and Urbascek 1985
Zearalenone and nivalenol	20 or 50 g/kg of Bentonite was added to the feed of pigs contaminated with zearalenone and nivalenol and was ingested for 29 days	Bentonite was unsuccessful at overcoming the estrogenic or depressed performance effects caused by the mycotoxins	Williams, Blaney, and Peters 1994
Aflatoxins B_1, B_2, G_1, G_2, M_1	Various methods	2% Bentonite adsorbed 400 μg of B_1; 2% adsorbed 89% of M_1; 2.5% adsorbed 5 ppm of B_1 and G_1 and 0.5 to 5 ppm of B_2 and G_2; 10% adsorbed 70% B_1	Ramos, Fink-Gremmels, and Hernandez 1996
		Kaolin	
Strychnine and atropine	Kaolin was added to both compounds and adsorption isotherms were calculated	Both compounds were adsorbed by Kaolin	Barr and Arnista 1957

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TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
Aminosidine sulphate, chloramphenicol, erythromycin, neomysin B sulphate, novobiocin sulphate, penicillin V, streptomycin sulphate, and tetracycline hydrochloride	Each antibiotic was added to 250 mg of Kaolin; the antibiotic activity was determined by cup-plate method using *Staphylococcus aureus*	Kaolin adsorbed significant amounts of aminosidine, neomysin, streptomycin, and tetracycline; Kaolin had no effect on antibiotic activity	El-Nakeeb and Youssef 1968
Agrobacterium radiobacter	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Kaolin did not maintain the pH therefore the bacteria could not maintain respiration even with an optimal pH for growth	Stotzky 1966
Bacillus subtilis, *Bacillus megaterium*, *Aerobacter aerogenes*, *Escherichia intermedia*, *Pseudomonas aeruginosa* and *P. aeroginosa* C-II, *Flavobacterium* species, *Proteus vulgaris*	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Kaolin in unadjusted pH systems reduced respiration of the bacteria below that of cultures without clay; but in adjusted systems some stimulation of respiration with the addition of Kaolin was apparent	Stotzky and Rem 1966
Mycelial homogenates of 27 species of fungi	Fungal mycelium and Kaolinite were cultured together and the O_2 uptake and pH were recorded	Kaolinite concentrations <4% generally did not effect respiration; respiration was only markedly inhibited at concentrations >40%	Stozky and Rem 1967
Crystal violet	2 g of Kaolin was added to 100 ml of a crystal violet solution	Adsorption was examined over a pH range of 2.5–9.5; adsorption increased with increasing pH	Armstrong and Clarke 1971
Staphylococcus aureus	Suspension of the organism, Kaolinite, and NaCl were studied	Increasing electrolyte concentration was accompanied by increased edge-to-face Kaolinite flocculation and organism-Kaolin aggregates	Steel and Anderson 1972
Escherichia coli	*E. coli* was cultivated in broth portions with 3% and 10% Kaolinite	*E. coli* was absorbed by Kaolin at both concentrations; the greatest adsorption occurred at 10% Kaolin at all phases of bacterial growth	Novakova 1977
^{125}I-labeled *Pseudomonas aeruginosa* toxin	The in vitro adsorption of the toxin by Kaolin was investigated over a range of pHs	The maximum adsorption occurred at pHs below 4.1; minimal values occurred at pH 4.1, 7.4, and 8	Said, Shibal, and Abdullah 1980
Acetohexamide, tolazamide, and tolbutamide	In vitro (pH 7.4) and in vivo (rats) adsorption studies were carried out	All 3 drugs bound and acetohexamide had the greatest binding; the hypoglycemic activity of the 3 drugs were suppressed and blood glucose concentrations were increased; desorption of the drugs from Kaolin ranged from 1.8% to 24.5%	Said and Al-Shora 1980

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TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
Coliphages T1 and T7 of *Escherichia coli*	1 ml suspensions of the coliphages were added to various concentrations of Kaolin	Adsorption of both coliphages by Kaolin were approximately the same 99%	Schiffenbauer and Stotzky 1982
Trimethoprim	The concentration of trimethoprim in the blood was determined at 0, 15, and 30 min and 1, 2, 4, and 6 h in the presence of Kaolin-Pectin	The mean decrease in the maximum blood concentration of trimethoprim was 29.42%	Babhair and Tariq 1983
Cationic surfactants: distearyl dimethyl ammonium chloride (74%); lauryl dimethylbenzyl ammonium chloride (50%)	A Kaolinite solution with added copper ions was added to surfactants and the metal ion uptake was recorded	Cationic surfactant result: the equilibrium between the metal ions and the organic cations was not effected	Beveridge and Pickering 1983
Anionic surfactants: sodium alkylbenzene aulphonate (80%); Monoethanolamine lauryl sulphate (34%); lauryl alcohol polyethylene condensate (28%)		Anionic surfactants: increased metal uptake by the clay was observed	
Nonionic surfactants: alcohol ethoylates; tridecaml ethoxylate (90%); cetystearyl alcohol ethoxylates; stearic acid ethoxylate; cocnut monoethanolamide ethoxylate; octadecylamine ethoxylate; castor oil ethoxylate; nonyl phenol ethoxylates; dinonyl pheno ethoxylate; polypropylene glycol ethoxylates		Nonionic surfactants: many surfactants had no effect and some caused enhanced loss of the metal ions from solution	
Escherichia coli 0111 endotoxins (ETU 144, 150, and 153)	In vitro and in vivo endotoxin binding to Kaolin	In vitro Kaolin was an effective endotoxin binder and binding was pH dependent (lower pHs yielded better results); 300 mg of Kaolin eliminated endotoxemia, at pH 7.4, the ED_{50} was 900 mg	Ditter, Urbaschek, and Urbascek 1983
Reovirus type 3	Chymotrypsin, ovalbumin, and lysozyme were added to Kaolinite and reovirus type 3	Chymotrypsin and ovalbumin reduced the adsorption of reovirus but lysozyme did not	Lipson and Stotzky 1984
Ampicillin and amoxycillin	4 g of Kaolin was ingested and 2 h later, 500 mg of the drugs were administered. This protocol was repeated 2 h later and urine (human) samples were collected	All volunteers showed reduced drug bioavailability following treatment; after 8 h, the reduced bioavailability for ampicillin ranged from 51.2 to 76.3 and 63.6 to 80.6 for amoxycillin	Khali, Mortada, and El-Khawas 1984b

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TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
Ampicillin and amoxycillin	In vitro adsorption and desorption studies to Kaolin (light, natural, and fine) were carried out at different pHs	The 3 types of Kaolin adsorbed only ampicillin and adsorption decreased as the pH increased; only partial release of the antibiotics was seen at pH 2.0 and 6.5	Khali, Mortada, and El-Khawas 1984a
Reovirus type 3 and coliphage T1	Competitive adsorption studies were carried out with Kaolin in estuarine water and distilled water	Reovirus type 3 and coliphage T1 did not share common adsorption sites on Kaolin and the coliphage did not interfere with the reovirus adsorption in estuarine water; the reovirus had no apparent effect on the adsorption of the phage in estuarine water	Lipson and Stotzky 1985
LT toxins of *Vibrio cholerae* and *Escherichia coli*, the ST toxin of ETEC, and the verotoxin of EHEC	Not specified	Kaolin inactivated the LT toxin and adsorption was a result of hydrogen bonding; it was ineffective against the verotoxin when the pH was alkaline; Kaolin was only slightly effective against the ST toxin	Brouillard and Rateau 1989
		Montmorillonite	
Agrobacterium radiobacter	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Montmorillonite spurred bacterial respiration by maintaining the initial pH; when the pH was adjusted to 7.0 respiration was its highest and similar to the buffered systems	Stotzky 1966
Bacillus subtilis, *Bacillus megaterium*, *Aerobacter aerogenes*, *Escherichia intermedia*, *Pseudomonas aeruginosa* and *P. aeroginosa* C-II, *Flavobacterium* species, *Proteus vulgaris*	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Montmorillonite increased the respiration of all species regardless of pH and characteristics of the bacteria primarily by maintaining the pH of the systems favorable for growth	Stotzky and Rem 1966
Mycelial homogenates of 27 species of fungi	Fungal mycelium and Montmorillonite were cultured together and the O_2 uptake and pH were recorded	Montmorillonite concentrations <4% generally did not effect respiration; respiration was markedly inhibited at concentrations of 4% and above	Stozky and Rem 1967
Cationic drugs: chlorpheniramine maleate, amphetamine sulfate, and propoxyphene hydrochloride; Anionic drugs: not specified Nonionic drugs: xanthines, theophylline, and caffeine	Dissolution and dialysis were carried out in vitro	All the cationic drugs and certain nonionic drugs bound tenaciously; the anionic drugs and nonionic drugs that exist as nonionics bound very weakly and rapidly pass into solution	McGinity and Lach 1976

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TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
Carbon tetrachloride, ethylene dibromide, trichlorethylene	10–1000 ppb/water of the three compounds were exposed to aluminum-saturated Montmorillonite and calcium-saturated Montmorillonite	Aluminum-saturated Montmorillonite absorbed 17% of trichloroethylene and 6% of the other cmpds; calcium-saturated Montmorillonite did not absorb carbon tetrachloride or trichloroethylene	Rogers and MacFarlane 1981
Coliphages T1 and T7 of *Escherichia coli*	1 ml suspensions of the coliphages were added to various concentrations of Montmorillonite	Adsorption of T1 coliphages by Montmorillonite was 84% and T7 was 96%	Schiffenbauer and Stotzky 1982
Cationic surfactants: distearyl dimethyl ammonium chloride (74%); lauryl dimethylbenzyl ammonium chloride (50%)	A Montmorillonite solution with added copper ions was added to surfactants and the metal ion uptake was recorded	Cationic surfactant result: metal ion uptake was reduced by competing surface sites	Beveridge and Pickering 1983
Anionic surfactants: sodium alkylbenzene aulphonate (80%); monoethanolamine lauryl sulphate (34%); lauryl alcohol polyethylene condensate (28%);		Anionic surfactants: increased metal uptake by the clay was observed	
Nonionic surfactants: alcohol ethoylates; tridecaml ethoxylate (90%); cetystearyl alcohol ethoxylates; stearic acid ethoxylate; coconut monoethanolamide ethoxylate; octadecylamine ethoxylate; castor oil ethoxylate; nonyl phenol ethoxylates; dinonyl pheno ethoxylate; polypropylene glycol ethoxylates		Nonionic surfactants: surfactants reduced the amount of metal ion adsorbed by the clay	
Reovirus type 3	Chymotrypsin, ovalbumin, and lyso-zyme were added to Montmorillonite and reovirus type 3	Chymotrypsin, ovalbumin, and lysozyme reduced the adsorption of reovirus	Lipson and Stotzky 1984
Poliovirus-1 (Lsc 2ab strain)	500, 15, 3 mg/L of Sodium Montmorillonite and the virus were suspended in seawater and the adsorption, desorption, and virus survival were studied	99.9% of the virus was absorbed in less than 30 min; 500 mg/L of Na-Montmorillonite significantly increased the survival duration of of the virus and desorption tests showed elution of 76%	Gantzer, Quignon, and Schwartzbrod 1994
Reovirus type 3 and coliphage T1	Competitive adsorption studies were carried out with Montmorillonite in estuarine water and distilled water	Reovirus type 3 and coliphage T1 did not share common adsorption sites on Kaolin and the coliphage did not interfere with the reovirus adsorption in estuarine water or distilled water; the reovirus suppressed the adsorption of the coliphage in estuarine water	Lipson and Stotzky 1985

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TABLE 8
Adsorption of various chemicals, cells, etc., to Silicate clays *(Continued)*

Compound adsorbed	Experimental design	Results	Reference
		Pyrophyllite	
Agrobacterium radiobacter	The measurement of O_2 uptake by calculating the respiration quotients (Q_{O_2}) was performed on all species of bacteria in the presence of 2% Kaolin with either adjusted (7.0) or unadjusted pHs	Pyrophyllite did not maintain a favorable pH for sustained respiration in either buffered or nonbuffered systems	Stotzky 1966
		Zeolite	
Zearalenone	5% of a synthetic anion-exchange zeolite and a cation-exchange zeolite and 250 μg/g of zearalenone were added to the feed of rats	The anion-exchange zeolite was completely effective and the cation-exchange zeolite was not	Smith 1980
Aflatoxin B1	Two samples of natural Zeolites in different liquids were incubated with B_1	The average aflatoxin retention rate was 605; effectiveness was lower in media containing nitrogen compounds	Dvora'k 1989

Bujdak and Rode (1996) reported peptide formation on the surface of three Montmorillonite samples. The Montmorillonite-catalyzed reaction produced diglycine and diketopiperazine from glycine.

Ferris et al. (1996) studied the catalytic properties of Na^+-Montmorillonite by adding daily ImpA to a decanucleotide ([^{32}P]-dA(pdA)$_8$pA, where Im = imidazole; pA = adenosine-5′-phosphate; pdA = 3′-deoxyadenosine-5′-phosphate; ^{32}P = radioactively labeled phosphate group). Polyadenylates were formed after two additions of ImpA, with the main products being monomers ranging from 11 to 14. Polynucleotides, with more than 50 monomers, were formed after 14 additions. The principle oligomeric products contained 20 to 40 monomers.

Ertem and Ferris (1998) reported Montmorillonite-catalyzed ImpA and ImpA-A5′ reactions. Oligomer yields decreased significantly when the addition of alkylammonium or aluminum poly oxo cations blocked the interlayer surfaces of the Montmorillonite particles.

Absorption, Distribution, Metabolism, and Excretion

Magnesium Trisilicate

Page, Heffner, and Frey (1941) measured the urinary excretion of silica in five men given 5 g of synthetic Magnesium Trisilicate orally for 4 consecutive days. Urine samples were collected for 24 h on the second day after the end of administration and analyzed for silica content. The mean 24-h excretion of all subjects was 16.2 mg of SiO_2. On the second, third, and fourth days after administration, the mean excretion rose to 172, 178, and 162 mg SiO_2. A total of 20 mg of Magnesium Trisilicate was taken and contained 9.2 g of SiO_2. An approximation of 5.2% SiO_2 excretion was estimated.

Benke and Osborn (1979) conducted a study in which groups of four to six male Sprague-Dawley Cox rats were fasted for 17 to 18 h and then were administered Magnesium Trisilicate orally in doses of 40, 200, or 1000 mg/kg of their body weight. Control animals received 10 ml of quartz-distilled water. All suspensions contained <0.5 ppm of silicon and aluminum. Urine samples were collected over an 8-h period, and the remaining urine in the bladder was collected afterwards. The concentrations of silicon was measured by induction-coupled radiofrequency (RF) plasma optical emission spectrometry. Silicon excretion was most rapid in the first 24 h after dosing. The control values were subtracted from the final values and the following number resulted. The urinary silicon excretion at 40, 200, and 1000 mg/kg Magnesium Trisilicate was 16.8%, 5.1%, and 1.5%, respectively.

Dobbie and Smith (1982) reported a 24-h urinary excretion study in which Si was determined by atomic absorption spectroscopy in one male and one female participant. A normal diet was given to the participants and four urine collections were made. A single dose of Magnesium Trisilicate was ingested at the beginning of the second 24-h collection. Magnesium Trisilicate doses given were as follows: 2, 5, and 10 g to the male subject and 2.5, 5, and 7.5, and 10 g in the female subject. The amount of Si excreted at the 5-g dose was greater than any other dose in the male subject and was greater than the 2.5- and 7.5-g doses in the female subject. The value of Si excretion for the male and female subjects were 3.63 and 3.31 mmol/day, respectively. Maximum excretion occurred in the first 24 h after ingestion.

The oral bioavailability of silicon and aluminum in Magnesium Trisilicate was studied by Cefali et al. (1995). Twelve female beagle dogs were administered a single 20-mg/kg dose of Magnesium Trisilicate and their blood was sampled at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing. The plasma

samples were assayed for silicon and aluminum by graphite furnace atomic adsorption. No dogs displayed emesis, but four had soft stool. The area under the curve (AUC, mg · h/L), concentration maximum (C_{max}, mg/L), and time maximum (T_{max}, h) for silicon absorption was 8.8, 0.75, and 6.9, respectively. The AUC (mg · h/L), C_{max} (mg/L), and T_{max} (h) for aluminum absorption was 315, 24, and 5.7, respectively. There was no statistically significant absorption of aluminum from the aluminum containing compounds.

Montmorillonite

Retention of monodisperse and polydisperse Montmorillonite particles inhaled by dogs, rats, and mice was studied by Snipes, Boecker, and McClellan (1983a). Cations normally present in Montmorillonite were exchanged with ^{134}Cs. Polydisperse and monodisperse ^{134}Cs-labeled Montmorillonite suspensions were administered to groups of 40 rats and mice and to 120 beagle dogs by a multiport nose-only inhalation exposure system. Aerosol concentrations ranged from 10^{-3} to 10^{-1} mg of fused Montmorillonite per liter of air. Equal numbers of male and female rats and mice and 74 male and 46 female dogs were utilized. Exposure times for rats and mice ranged from 25 to 45 min and for dogs 15 to 50 min. All animals were whole-body counted for the labeled particles. Rats and mice were counted on exposure days 2, 4, 8, 16, 32, 64, 128, 256, 365, 512, 730, and 850 and the dogs were also counted on the same schedule, but also at 4, 5, 7, and 9 years after inhalation exposure. Excreta collections were made for animals from each exposure group. Five rats and five mice from each group were killed 4 h after exposure. The remaining rats and mice were killed at various times after exposure. Two dogs were scheduled for termination at times ranging from 4 h to 9 years. All animals were necropsied and tissues from lungs, lung-associated lymph nodes (LALNs), gastrointestinal tract, spleen, kidneys, abdominal lymph nodes, blood, skeleton, muscle, and skin were prepared for analysis of ^{134}Cs exposure. Results of the counts were converted into disintegrations per minute.

The mass of material deposited into the lungs of rats and mice was ~0.01 to 0.1 mg and for dogs was ~1 to 10 mg. The mass of Montmorillonite for all three species was <0.1 mg per gram of lung. Clearance of the initial ^{134}Cs occurred by dissolution and mechanical clearance. Mechanical clearance from the nasopharynx was rapid, and the clearance rate was decreased to a negligible value for all three species within a few days. Most initial deposit cleared via the gastrointestinal tract. Long-term mechanical clearance from the pulmonary region occurred at a constant rate for all species. Solubilization was the primary factor in long-term lung clearance for most particles inhaled by dogs and mechanical clearance was dominant in rats and mice. Most of the long-term clearance of deposited particles went to LALNs in dogs and occurred at a slower rate as compared to rats and mice. Rats and mice had a rapid clearance from the pulmonary region, where most of the mechanical clearance occurred via the gastrointestinal tract. Long-term clearance of the particles in dogs occurred at 3500-day half-time in the lymph nodes and 6900-day half-time clearance in the gastrointestinal tract. The transport rate of the particles in the dog was 0.0002 day^{-1} of the lung burden. The long-term biological clearance half-term day was 690 days for rats and 490 days for mice. The lymph node accumulation process was modeled by a short-term process that became negligible after a few days (Snipes, Boecker, and McClellan 1983a).

Snipes, Muggenburg, and Bice (1983b) instilled radio-labeled (^{134}Cs) fused Montmorillonite particles into specific lung lobes or injected intraperitoneally into 32 beagle dogs. Necropsy was performed at 34, 182, and 365 days later. Specific sites of instillation included right apical lobe, right cardiac lobe, right diaphragmatic lobe, right intermediate lobe, left apical lobe, left diaphragmatic lobe, and intraperitoneal. Initial burdens in the peritoneal cavity or the lungs ranged from 0.50 to 14 μCi of ^{134}Cs for 29 dogs and from 42 to 64 μCi of ^{134}Cs for lung burdens for the other three dogs. Effective translocation half-time of lung instillations was 390 days. The accumulation rate of ^{134}Cs-labeled particles in the lymph nodes was 0.03% per day. Individual lung lobes cleared particles to one or two lymph nodes, and specific lymph nodes accumulated particles from one to three lung lobes. Lymph nodes that collected particles from the lung included the left mediastinal node, left tracheobronchial lymph node (TBLN), right TBLN, left middle TBLN, and right middle TBLN. The destination for translocated particles were primarily the nodes proximate to the tracheal bifurcation. Particles injected into the peritoneal cavity were translocated mainly to mesenteric lymph nodes and left sternal and right sternal lymph nodes. A small percentage of particles went to the left TBLN.

Zeolite

The oral bioavailability of silicon and aluminum in Zeolite A was studied by Cefali et al. (1995). Twelve female beagle dogs were administered a single 20-mg/kg dose of Zeolite A and blood was sampled at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing. The plasma samples were assayed for silicon and aluminum by graphite furnace atomic adsorption. No dogs displayed emesis but four had soft stool. The AUC (mg · h/L), C_{max} (mg/L), and T_{max} (h) for silicon absorption was 9.5, 1.07, 7.9, respectively. The AUC (mg · h/L), C_{max} (mg/L), and T_{max} (h) for aluminum absorption was 342, 29, and 3.5, respectively. The AUC and C_{max} values were elevated after the addition of the silicon containing compounds compared to the baseline and the AUC was significantly elevated. There was no statistically significant absorption of aluminum from the other aluminum-containing compounds.

In a study by Cefali et al. (1996), the bioavailability of silicon and aluminum in Zeolite A administered in either a capsule, an oral suspension, or an oral solution relative to an intravenous bolus infusion administered over a 1- to 1.5-min period was investigated. Twelve beagle dogs were given single doses of Zeolite A and their plasma samples, drawn at 0 and 36 h, were analyzed for silicon and aluminum concentrations by graphite furnace

atomic absorption. The plasma aluminum AUC values from the oral capsule and suspension were not statistically different from those during the control period. However, the aluminum AUC of the oral solution was statistically greater than the AUC of the corresponding control period. The extent of absorption of aluminum form the oral dosage forms was less than 0.1% relative to the intravenous infusion.

In Vitro Assays

Aluminum Silicate

Nadeau et al. (1987) tested Fiberfrax, an aluminum silicate, in several in vitro assays for red blood cell (RBC) hemolysis, lactate dehydrogenase activity (LDH), β-galactosidase (β-GAL) activity, lactic acid production, cellular ATP activity, and the cellular DNA contents. The mean length and diameter of this sample were determined to be 8.3 μm and 0.2 μm, respectively. Approximately 60% of this Fiberfrax sample was nonfibrous.

For the hemolysis assay, RBCs from rats were isolated and exposed to 100, 250, 500, 750, or 1000 μg/ml of fibers for 1 h. The percentage of release of hemoglobin was compared with that of a fully lysed sample. The target cells for the other experiments were obtained by bronchoalveolar lavage from black hooded rats. Each of the experiments tested both fresh cell monolayers and 1-day-old monolayers. Fiber samples were added to the cultures at two doses, 33.3 μg/ml and 166.7 μg/ml. LDH activity was based on the formation rate of NADH at 340 nm. The β-GAL activity was based on the measurement of *p*-nitrophenyl release. The amount of metabolite released from PAMs (pulmonary alveolar macrophages) into the medium was the measurement of lactic acid production. PAMs were treated with 1 ml of dimethyl sulfoxide to release the nucleotides and the ATP was measured later by a bioluminesence assay.

Fiberfrax particles produced no hemolytic activity at any concentration except 1000 μg/ml. Even at 1000 μg/ml, the particles had very weak hemolytic properties with only 2.0% hemolysis. In fresh PAM monolayers, Fiberfrax was very cytotoxic at 166.7 μg/ml. The extracellular releases of LDH and β-GAL were approximately 60% to 70% and 40% to 50%, respectively. A low cell viability was confirmed by an 80% decrease in ATP cell contents. Even at the lower dose, 33.3 μg/ml, a significant cytotoxic effect resulted, as judged by enzyme releases and ATP cell contents. Again in the day-old cultures, Fiberfrax was highly cytotoxic to PAM. LDH and β-GAL activities were as great and ATP cell contents were significantly decreased. At the lower dose, a moderate cytotoxic effect was observed. Decreases in lactic acid production were more pronounced at 166.7 μg/ml. No significant effect on total DNA cell content was noted in either the fresh or day-old cultures (Nadeau et al. 1987).

Attapulgite

Colony formation of human embryo intestinal cells (I-470) was examined by Reiss, Millette, and Williams (1980). At a dose of 0.001 to 1 mg/ml of Attapulgite with fibers <2 μm, colony formation was not modified. Colony formation was inhibited by 35% and 43% at doses of 2.5 and 5.0 mg/ml, respectively.

Oscarson, Van Scoyoc, and Ahlrichs (1981) added Attapulgite to a culture of bovine RBCs to study the extent of hemolysis. Saline was added to cultures as a control and in a separate experiment, the polymer poly-2-vinylpyridine-*N*-oxide was also added to study its inhibiting effects. No other details were given. The concentration of Attapulgite that caused 50% hemolysis in 1 ml of a 3% solution of RBCs was determined as 0.06 mg Attapulgite/ml of silicate-erythrocyte-buffer suspension. A concentration of 0.2 and 1.0 μm/ml of polymer caused 20% and 3% hemolysis, respectively. This was somewhat less hemolysis than without the polymer.

Chamberlain et al. (1982) tested two samples, one with short fibers and one with long fibers, of Attapulgite for their cytotoxicity in three cell lines: mouse peritoneal macrophages, human type II alveolar tumor (A549) cells, and Chinese hamster V79-4 lung cells. Attapulgite samples of 50, 100, and 150 $\mu g/ml^{-1}$ were added to mouse peritoneal macrophages for 18 h. The medium and cell lysates were assayed for LDH activity. The control received no dust sample. In the second experiment Attapulgite, 100 $\mu g/ml^{-1}$ and 200 $\mu g/ml^{-1}$, were added to A549 cultures and incubated for 5 days. The diameters of the cells were assessed for giant cell formation. The control treatment received no dust. In the last experiment, the survival of V79-4 cells in the presence of a series of concentrations of each dust was determined. Specific concentrations were not given. The cells and dust samples were incubated for 6 days and counted after the incubation. The controls received no dust.

The mouse macrophages released 57.7% LDH from interaction with 150 $\mu g/ml^{-1}$ of short fiber Attapulgite and was considered cytotoxic. However, the short fiber sample was considered inert to the A549 cells and V79-4 cells. The long fiber Attapulgite was cytotoxic to all three cell types. It was noted by investigators that mouse peritoneal macrophages are sensitive to both fibrogenic and carcinogenic dusts; whereas nonmacrophage cell lines such as V79-4 and A549 cells are insensitive to fibrogenic dusts but sensitive to the fiber morphology of carcinogenic dusts (Chamberlain et al. 1982).

Gormley and Addison (1983) investigated the cytotoxic effect of Attapulgite with a particle size of 2.6 μm. Clay suspensions, 20 and 80 μg/ml, were added to P388D1, a macrophage-type cell line for 48 h. Three sets of controls were included: a positive control, 20 μg of quartz DQ_{12}/ml; and two negative controls, 80 μg of TiO_2/ml, and an undusted set of cultures. The following assessments were made: cell viability; the activity of LDH; the activity of *p*-nitrophenyl-*N*-acetyl-β-D-glucosamide; L-(+)-Lactic acid production; and total cellular protein concentrations. Cellular viability was expressed as a percentage of the titanium dioxide control (100.0%) $\pm$ the standard deviation. The 20-μg/ml dose of Attapulgite produced a 65.8% $\pm$ 9.2% viability and the 80 μg/ml dose produced a 30.9% $\pm$ 17.4% viability. Cellular LDH activities fell with decreasing cell viability, whereas the percentage of LDH in the medium increased.

Similar results were seen with glucosamidase. Also, the amount of lactate produced decreased as cell viability decreased. However, little change in the total cellular protein was recorded.

The induction of squamous metaplasia in tracheal organ cultures was investigated by Woodworth, Mossman, and Craighead (1983). Suspensions of Attapulgite at concentrations of 1, 4, and 16 mg/ml were added to the mucosal surface of the tracheal explants for 1 h. After experimental treatments, extracts were transplanted to another surface more suitable for cell attachment. Mucocillary differentiation was maintained for 4 weeks and the explants were examined at 2, 4, and 6 weeks after exposure to Attapulgite. The extent of squamous metaplasia was evaluated by SEM (scanning electron microscope). The explants were labeled with [^{3}H]-thymidine and the labeling index was scored. Four weeks after exposure to Attapulgite, the explants underwent both proliferative and metaplastic alteration. Attapulgite induced an increase in metaplasia at low doses (1.0 and 4.0 mg/ml), but the increase was not statistically significant. The labeling index was also increased slightly but statistically significant. SEM was used to determine the association of fibers with metaplastic lesions. Most fibers aggregated at the margins of the explant, although small numbers of individual fibers were distributed along the mucosal surface. These fibers either rested on nonciliated cells or protruded into the mucosal surface. They were often encompassed by accumulations of epithelial cells. Metaplastic foci tended to be small. Many foci associated with the lesions but some were located at sites where no lesions could be seen.

The binding capacity, in vitro cytotoxicity, and percentage of hemolysis were investigated in a study by Harvey, Page, and Dumas (1984). Binding assays were carried out using the known carcinogens benzo(α)pyrene (B(α)P), nitrosonornicotine (NNN), and *N*-acetyl-2-aminoflurene (NAAF) and 2 mg/ml of Attapulgite. A 2% suspension of sheep erythrocytes were added to 30 mg of Attapulgite and incubated for 50 min. Cytotoxicity was measured using 1000 μg of Attapulgite and macrophage-like P399D1 cells and using the Trypan blue dye exclusion method. Hemolysis was calculated by measuring the optical density at 540 nm. All experiments included the positive control UICC chrysotile A and the negative control titanium dioxide. Chrysotile binds significantly more to all three carcinogens than the other fibers ($p < .005$) except Attapulgite. Attapulgite and chrysotile had very comparable binding capacities. Again Attapulgite and chrysotile had the greatest hemolysis and cytotoxicity compared to the negative control. On a scale of 1 to 5, 5 being the greatest, Attapulgite scored a 3.72 and 4.26 in hemolysis and cytotoxicity, respectively.

The cellular interactions between Attapulgite and rat hepatocytes were examined in a study by Denizeau et al. (1985a). Primary cultures of rat hepatocytes were exposed to 10 μg/ml of Attapulgite fibers for 20 h. Ultrastructural analysis was performed by transmission electron microscopy. Fiber length was not indicated in this study. Fibers are phagocytized by the cells and numerous phagolysosomes are distributed throughout the cytoplasm. The phagolysosomes also appear in the vicinity of charged vacuoles. Invaginations of the plasma membrane engulfing fibers and formation of vacuoles are identifiable. Deeper in the cytoplasm vacuoles with various shapes show the presence of fibers.

Beck and Bignon (1985) incubated leukemic mouse cells with two samples of 10, 50, or 100 μg/ml of Attapulgite. Viable cell counts were taken at 0, 24, 48, and 72 h. A positive control consisting of UICC amosite and untreated negative controls were also used in this experiment. The majority of fibers in the Attapulgite samples were <1.0 μm. No evidence of cytotoxicity was measured over the 72-h period. The results from the Attapulgite samples were indistinguishable from the untreated controls.

The cytotoxic effects of Attapulgite on rabbit alveolar macrophages and rat pleural mesothelial cells were investigated by Jaurand et al. (1987). Attapulgite samples with a mean fiber length of 0.77 μm were added at concentrations 4 and 8 μg/cm^2 to rabbit alveolar macrophage cultures for 4 and 20 h; control cultures received medium with no fibers. Enzyme release, activity of cytoplasmic LDH and lysosomal β-GAL was tested. The presence of LDH activity in cultures was the gauge of cytotoxicity and the presence of β-GAL was the gauge of cell stimulation. Attapulgite at both concentrations was cytotoxic at 20 h. β-GAL release percentages for Attapulgite and quartz after 20 h were almost identical.

Again Attapulgite was added at concentrations of 1, 2, 4, and 10 μg/cm^2 to rat pleural mesothelial cells. The cell number was determined daily with the use of a Nachet NS 1002 image analyzer. Attapulgite was not cytotoxic except at 10 μg/cm^2. At the lower doses, cell number increases were comparable to that of the controls (Jaurand et al. 1987).

Nadeau et al. (1987) tested Attapulgite for its effects on cells in several in vitro assays for RBC hemolysis, LDH activity, β-GAL activity, lactic acid production, cellular ATP activity, and the cellular DNA contents. The mean length and diameter of this sample were determined to be 0.8 μm and 0.1 μm, respectively. The same study was conducted on Aluminum Silicate and all protocol and procedures are explained under that section. Attapulgite particles produced no hemolysis except at 1000 μg/ml. Even at 1000 μg/ml, the particles showed very weak hemolytic properties with only 2.0% hemolysis. Analysis with the fresh PAM monolayers revealed Attapulgite to be very cytotoxic at 166.7 μg/ml. The extracellular releases of LDH and β-GAL were approximately 60% to 70% and 40% to 50%, respectively. A low cell viability was confirmed by an 80% decrease in ATP cell contents. Even at the lower dose, 33.3 μg/ml, a significant cytotoxic effect resulted, as judged by enzyme releases and ATP cell contents. Again in the day old cultures, Attapulgite was highly cytotoxic to PAM. LDH and β-GAL activities were very large and ATP cell contents were significantly decreased. At the lower dose, a moderate cytotoxic effect was observed. Decreases in lactic acid production were more pronounced at 166.7 μg/ml. No significant effect on total DNA cell content was noted in either the fresh or day-old cultures.

Garcia, Dodson, and Callahan (1989) investigated the effects of Attapulgite on cultures of human umbilical vein and bovine artery endothelial cell monolayers. Chrysotile asbestos was also studied as a positive control. Rapid phagocytosis of Attapulgite and chrysotile particulates was evident in endothelial cell monolayers. Attapulgite was markedly toxic according to a gradient of time-dependent and concentration-dependent endothelial cell injury measured by specific ^{51}Cr release. Chrysotile was much less toxic. Responses of bovine pulmonary artery and human vein endothelial cells to fiber phagocytosis and fiber-induced injury were similar. Fiber-mediated stimulation in human umbilical cell monolayers of the arachidonate metabolite prostacyclin paralleled endothelial injury. Attapulgite was stimulatory in this experiment, whereas chrysotile was only weakly cytotoxic. Superoxide dismutase and catalase produced significant protection against fiber-mediated endothelial cell injury. Chelation by deferoxamine of elemental Fe in the fiber preparations was also protective.

Perderiset et al. (1989) reported the hemolytic activity of Attapulgite on human red blood cells at five concentrations (0.05, 0.1, 0.2, 0.4, and 0.5 mg/ml). Additional studies tested the hemolytic activity of dipalmitoyl phosphatidylcholine (DPPC) and bovine serum albumin (BSA)-treated Attapulgite (2 mg/ml). The mean fiber length was <2 μm. The percentage of hemolysis was determined by measuring the absorbance of the supernatant at 540 nm. At 0.5 mg/ml, Attapulgite caused 82% hemolysis. The maximum amount of BSA adsorbed was 70 ± 10 μg/mg of Attapulgite, and the maximum occurred at an initial concentration of 200 μg/ml. For DPPC, the maximum amount of BSA adsorbed was 210 ± 14 μg/mg of Attapulgite, and the maximum occurred at an initial concentration of 250 to 300 μg/ml. Both compounds reduced the hemolytic effect of Attapulgite due to adsorption on the particle's surface.

Nolen, Langer, and Herson (1991) tested nine different samples of Attapulgite for their membrane-lysing activity using human RBCs. The HC_{50} (concentration of particulate in μg/ml required to lyse 50% of the erythrocytes in a suspension containing 1.8×10^8 cells/ml) was determined quantitatively. Three samples of Chrysolite were used as positive controls. No other details of the experiment were given. The fiber characteristics were determined by light microscopy and x-ray diffraction and the HC_{50} values are presented in Table 9.

Attapulgite's cytotoxicity was investigated in rat pleural mesothelial cells (RPMCs) by Yegles et al. (1995). A suspension of 0.5 mg/ml of Attapulgite was added to RPMCs, and a 3,(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) viability test and anaphase/telophase abnormalities test were performed. The clay sample had no fibers measuring greater than 4 μm. Cytotoxicity was expressed as the concentration that provides 75% of cell viability compared to untreated controls (IC_{75}). Attapulgite was only poorly toxic with an IC_{75} of >100 $\mu g/cm^3$. Untreated controls averaged about 3.4% of abnormal anaphases; no significant anaphase abnormalities were seen with Attapulgite as well.

Bentonite

The hemolysis of human erythrocytes and methylene blue adsorption by two Bentonite samples were investigated by M'anyai et al. (1969). A white Bentonite sample consisted of 50% illite, 25% quartz, and 25% Montmorillonite; the yellow Bentonite sample consisted of predominately Montmorillonite. The data in Table 10 show that the hemolytic effect varied as a function of both of the amount of clay (mg) and the surface area (m^2).

TABLE 9
Fiber characteristics of nine Attapulgite samples tested for their membranolytic activity using human red blood cells (Nolen, Langer, and Herson 1991)

		Fiber length (μm)				
Sample	Fiber character	<1.0	1.1–5.0	5.1–10.0	>10.0	HC_{50}* (μg/ml)
1	Fibrous	71.5	26.3	1.7	0.5	400
2	Fibrous	92.7	7.1	—	—	Inactive
3	Nonfibrous	90.2	9.3	0.3	0.3	746
4	Fibrous	78.0	21.3	0.7	0.2	211
5	Fibrous	75.1	22.4	2.0	0.6	369
6	Nonfibrous	91.1	8.7	0.1	0.1	76
7	Nonfibrous	83.4	16.6	—	—	83
8	Nonfibrous	83.1	16.8	—	—	109
9	Fibrous	59.4	37.5	2.6	0.6	51
Chrysolite 1	Fibrous	77.2	20.5	1.8	0.5	41
Chrysolite 2	Fibrous	84.9	13.6	0.6	0.4	82
Chrysolite 3	Fibrous	88.8	10.6	0.4	0.2	59

*The HC_{50} is the concentration of silicate clay (in μg/ml) required to lyse 50% of the erythrocytes in a 1.8×10^8cells/ml suspension.

TABLE 10
Hemolysis and methylene blue adsorption results (M'anyai et al. 1969)

Mineral	Sample description	50% hemolysis in 1 ml of a 2% erythrocyte suspension as function of: Amount of clay (mg)	Surface area of clay (m^2)	Amount of methylene blue adsorbed by 1 m^2 clay surface (mg)
Bentonite	White	1.66	0.039	3.59
Bentonite	Yellow	1.0	0.135	2.13
Montmorillonite	Ca-substituted	5.0	0.50	1.46
Montmorillonite	+Quartz	0.8	0.02	—
Kaolin		2.0	0.06	1.09
Kaolin	Fat	1.5	0.07	1.60
Kaolin	White	4.0	0.06	0.12
Kaolin	Pink	5.0	0.115	0.19

Beck and Bignon (1985) dosed peritoneal macrophages with two samples of Bentonite and the triphenyltetrazolium chloride (TTC) reduction, LDH activity, and methylene blue adsorption were used to assess cytotoxicity. One sample of Bentonite contained 3% SiO_2 and the other 34%. Bentonite inhibited TTC reduction similar to the fibrogenic dusts such as quartz. However, the extracellular LDH activity was not increased and methylene blue adsorption was very high.

Hatch et al. (1985) examined the cytotoxicity of Bentonite to rabbit alveolar macrophages. The alveolar macrophages were incubated with 1.0 mg/ml of Kaolin for 20 h at 37°C. Control cultures received 1.0 mg/ml of TiO_2. The viability percentage of the macrophages and the ATP content of the cells as index of cytotoxicity were determined. Bentonite caused a large reduction in both the viability and ATP levels. The viability index and ATP levels were presented as percentage reductions and were 64.7% and 92.0%, respectively. Controls figures were 18.3% and 0.7%, respectively.

TTC reduction, LDH activity, and methylene blue adsorption were measured as an index of cytotoxicity in a study by Adamis et al. (1986). Bentonite was added to peritoneal macrophages obtained from rats. No specific dose of Bentonite or other details were stated. TTC reduction was much greater and proved Bentonite to be cytotoxic. Extracellular LDH was almost half for Bentonite compared to control values. Methylene blue adsorption was significantly higher for Bentonite.

Murphy, Roberts, and Horrocks (1993a) investigated the cytotoxicity of Bentonite to human umbilical vein endothelial (HUVE) cells, undifferentiated N1E-115 neuroblastoma cells, and ROC-1 oligodendrogial cells. Indices of cytotoxicity used in this study were morphological examination, LDH activity, and fatty acid release. A suspension of Bentonite (1 to 2 μm in fiber length) was added to the cultures at concentrations of 0.1, 0.03, and 0.01 mg/ml and incubated for 1, 6, and 24 h. Following incubations, the cells were examined morphologically. The medium and cells were extracted for free fatty acid quantitation. LDH activities were assayed after 24 h of incubation at a Bentonite concentration of 0.10 mg/ml.

Bentonite did not lyse ROC-1 oligodendrogial and the neuroblastoma cells and did not cause a dose-dependent increase in fatty acids at 24 h. No significant increases in LDH activity were detected utilizing any of these cell lines. However, Bentonite caused a dose-dependent increase in fatty acid concentrations only after 24 h of incubation. A 4.5-fold increase in fatty acid concentrations over control values was calculated. Increases over control activities of LDH were 141% with Bentonite. Within 1 h, Bentonite associated with the plasma membrane of HUVE cells and the morphology was drastically changed after treatment (no details given). Cell lysis was also apparent with treatment. After trypan blue staining, 94% of HUVE cells were nonviable with Bentonite treatment (Murphy, Roberts, and Horrocks 1993a).

In a separate study by Murphy et al. (1993b), the cytotoxicity of Bentonite was examined in two cell lines: primary murine spinal cord neurons and differentiated N1E-115 neuroblastoma cells. A clay suspension with a concentration of 0.1 mg/ml was added to the cultures. The neuronal cells were incubated for 1 h with Bentonite. Photomicrographs were taken at 5, 15, and 60 min following treatment. For the N1E-115 cells, incubation lasted 18 h and photomicrographs were taken at 5 and 15 min and 3, 6, and 18 h after the treatment. Morphological changes were observed using a phase contrast microscope. Within 5 min, clay particles were observed on the neuronal cell bodies. Cell bodies appeared granular within 15 min. The cells were completely lysed after 60 min and there was no evidence of any remaining cell bodies or processes. Cell membrane contact was apparent after 5 min in N1E-115 cultures. No morphological changes were apparent at this point. At 18 h, the cells were covered with

clay but cellular processes remained intact. N1E-115 cell lysis did not occur and no cytotoxicity was recorded as a result of Bentonite treatment.

Calcium Silicate

Hunt, Pooley, and Richards (1981) tested three samples of Calcium Silicate (A, B, and C) for biological reactivity in three in vitro test systems. Table 11 presents the differences in SiO_2 and Al_2O_3 percentages between the three samples.

In the first test system, 50, 100, 150, and 200 mg of the three samples of Calcium Silicate, UICC chrysotile (positive control), and titanium dioxide (negative control) were added to rabbit erythrocytes. The cultures were incubated for 50 min. The percentage of hemolysis was calculated. Rabbit erythrocytes were also incubated with 10, 30, and 50 mg heated, crushed samples of Calcium Silicate to calculate the percentage of hemoglobin binding. In the second study, rabbit alveolar macrophages were incubated with 5 mg of the Calcium Silicate samples for time intervals up to 60 min. The results were expressed as total viable cells. In the third study, sonicated Calcium Silicate samples (100 to 2000 μg) were added to rabbit lung fibroblasts. On days 7, 10, 17, and 24 after treatment, the cultures were analyzed for cellular DNA, protein, other cellular material, and hydroxyproline. Cytological studies on the same cells were carried out using dust concentrations of 50 to 400 μg and staining the cultures to visualize reticulin fibers.

In order to obtain 20% hemolysis, 0.4 mg of chrysotile, 2.8 mg of A, 25.0 mg of B, and 15.0 mg of C are required. Titanium dioxide did not produce 20% hemolysis at any concentration. Sonication of all samples enhanced hemolysis and a "respirable" preparation of A had the same hemolytic activity as chrysotile. Sample B binds more hemoglobin than A or C but not more than chrysotile. Samples B and C had enhanced hemolytic activity when heated above 300°C. Heating had no effect on sample A. All samples produced similar macrophage mortality and at concentrations of 5 mg, only 60% of the cells were surviving at 60 min. Chrysotile at 5 mg resulted in a 20% viability. Samples A and B produced greater DNA and protein concentrations at day 7. However, sample A induced greater protein concentrations at day 24 with normal hydroxyproline levels. Sample B at day 24 had decreased concentrations of protein and hydroxyproline with an increase in mineral concentration. Sample A produced few changes in fibroblast morphology and reticulin deposits.

TABLE 11
Aluminum and Silicon content in Calcium Silicate samples used in biological reactivity study (Hunt, Pooley, and Richards 1981)

Calcium Silicate sample	SiO_2 %	Al_2O_3 %
A	57.3	2.6
B	52.3	4.4
C	53.7	1.0

TABLE 12
Sample characterisitcs of five Calcium Silicates tested for hemolytic activity in vitro (Skaug and Gyseth 1983)

Sample	Chemical formula	SiO_2 %	Fibrous character
CaSi A, natural wollastonite	$CaSiO_3$	—	+++
CaSi B, natural wollastonite	$CaSiO_3$	2	+
CaSi C, synthetic wollastonite	$CaSiO_3$	9	–
CaSi D, synthetic tobermorite	$Ca_5Si_6O_{17} \cdot 2.5\ H_2O$	10	–
CaSi E, synthetic tobermorite	$Ca_5Si_6O_{17} \cdot 2.5\ H_2O$ $Ca_6Si_6O_{17}(OH)_2$	2	+

Sample B produced sparse and irregular deposition of reticulin (Hunt, Pooley, and Richards 1981).

Skaug, Davies, and Glyseth (1984) tested five Calcium Silicate dust samples for hemolytic activity in vitro. Electron microscopy and x-ray diffractions techniques were used to characterize the Calcium Silicates and the results are presented in Table 12. The Calcium Silicate samples A to E, chrysotile B (positive control), and titanium dioxide were added to RBCs at concentrations of 0, 5, and 10 mg/ml. The effect of sonication of the dust samples and the addition of 30 mM $CaCl_2$, EDTA, and EGTA were also investigated. Sample E produced the greatest hemolysis at nearly 40%. The hemolytic activity of the synthetic Calcium Silicate samples were greater. In all experiments, greater dust concentrations increased hemolysis. Sonication increased the hemolytic activity of the synthetic samples but had no effect on the natural samples. The 30 mM $CaCl_2$ increased the hemolysis of samples D and E, but not C. EDTA did not decrease hemolysis for samples D and C, and EGTA did not inhibit hemolysis of samples B, C, D, and E.

Five samples of Calcium Silicate also were used to test cytotoxic effects on mouse peritoneal macrophages in vitro. Calcium Silicate concentrations of 0, 20, 40, and 60 $\mu g/cm^3$ were added to mouse peritoneal macrophages for 18 h. The medium and cell lysates were assayed for LDH and β-glucuronidase (β-GLUC). The positive-control dust utilized was DQ12 quartz standard and the negative-control dust was magnetite. Characterization of the five samples were carried out by means of x-ray diffraction and scanning electron microscopy. The results of the mineral characterization are presented in Table 13. The samples A, B, C, and D had little effect on LDH release but sample E, the fibrous tobermorite, was clearly cytotoxic. Samples A and B caused release of large levels of β-GLUC. Sample E also caused the release of significant amounts of β-GLUC due to its cytotoxicity. Samples C and D caused the release of amounts comparable to the negative controls (Skaug, Davies, and Glyseth 1984).

TABLE 13

Mineral characterization of five samples of Calcium Silicate used to test cytotoxic effects on mouse peritoneal macrophages in vitro (Skaug, Davies, and Glyseth 1984)

Sample	Description	Chemical formula	% SiO_2 added	Presence of fibers
A	US wollastonite	$CaSiO_3$	—	+
B	Natural wollastonite	$CaSiO_3$	2	+
C	Synthetic wollastonite	$CaSiO_3$	9	−
D	Synthetic tobermorite	$Ca_5Si_6O_{17} \cdot 2.5\ H_2O$	10	−
E	Synthetic tobermorite and xonotlite	$Ca_5Si_6O_{17} \cdot 2.5\ H_2O$ $Ca_6Si_6O_{17}(OH)_2$	2	+

Hectorite

In a study by Gormley and Addison (1983) mentioned earlier, the cytotoxic effects of Hectorite were investigated. The Hectorite sample had a particle size of 2.8 μm. The procedures are detailed in the study under the Attapulgite heading. Cellular viability was expressed as a percentage of the titanium dioxide control (100.0%) ± the standard deviation. The 20-μg/ml dose of Hectorite produced an 83.4% ± 10.9% viability and the 80 μg/ml dose produced a 56.4% ± 13.3% viability. Cellular LDH activities decreased with decreasing cell viability while the activity of LDH in the medium increased. Similar results were seen with glucosaminidase. Also, the amount of lactate produced decreased as cell viability decreased. However, little change in the total cellular protein was recorded.

Banin and Meiri (1990) reported that they added Hectorite to murine neuroblastoma cells at a concentration range of 70 to 1000 μg/ml, although details were not provided. They concluded that clear morphological signs of cell deterioration were evident and, at the concentrations listed, an acute toxic effect was seen.

Kaolin

Results from a study by M'anyai et al. (1969) on the hemolysis and methylene blue adsorption by Kaolin are presented in Table 10.

Kaolin was heated to temperatures of 290°C, 350°C, 500°C, 650°C, 800°C, and 950°C and changes in the internal structure and surface properties were investigated and compared to alterations in hemolytic activity in vitro. The measurement of methylene blue adsorption and investigation of the crystal structure by x-ray diffraction were made. In addition, Kaolin was added to human erythrocytes and the amount of lysed hemoglobin release was determined following an 1-h incubation. Complete dehydration of Kaolin resulted in the formation of metakaolinite between the temperatures 500°C to 650°C. The formation of metakaolinite resulted in complete loss of hemolytic activity. Heating to higher temperatures, 800°C and 950°C, resulted in the formation of γ-Al_2O_3 (mullite) or SiO_2 (cristobalite), which led to greater intensification of hemolytic activity. The extent of hemolysis depended on the crystal structure and hydration of the surface (M'anyai et al. 1970).

Oscarson et al. (1981) added Kaolin to a culture of bovine RBCs to study the extent of hemolysis. Saline was added to cultures as a control and in a separate experiment, the polymer poly-2-vinylpyridine-*N*-oxide was also added to study its inhibiting effects. No other details were given. The concentration of Kaolin that caused 50% hemolysis in 1 ml of a 3% solution of RBCs was determined as 0.6 mg Kaolin/ml of silicate-erythrocyte-buffer suspension. A concentration of 0.2 and 1.0 μM/ml of polymer caused 50% and 20% hemolysis, respectively. This was somewhat less hemolysis than without the polymer.

Mossman and Craighead (1982) adsorbed 3-Methylcholanthrene (3MC) onto heat-sterilized preparations of Kaolin (4, 8, and 16 mg dust/ml medium). The tracheas of female golden Syrian hamsters were excised, and prepared for organ cultures and exposed to 3MC/Kaolin preparations. After 4 weeks in vitro, the organ cultures were examined morphologically or implanted subcutaneously into syngeneic weanling female hamsters. The hamsters were palpated for tumors at 3-week intervals and any masses >5 mm in diameter were excised. Animals with no tumors were killed at 105 to 110 weeks of age and the tracheal implants were removed. The tracheal organ cultures and tumors were fixed for microscopic examination. Explants exposed to Kaolin had differentiated mucociliary epithelium for periods of several weeks. In vitro the columnar mucosal cells acquired a cuboidal configuration and the foci of the epithelial hyperplasia appeared at sites where microscopically evident accumulations of particles were deposited on the tracheal epithelium. No keratinizing squamous metaplasia was evident. Neoplasms developed in the tracheal implants exposed to 3MC-coated Kaolin. Tumor development was dosage dependent. No sarcomas developed only carcinomas. In the highest Kaolin/3MC-treated group, 28% of the animals developed tumors. Tumors failed to develop in tissues treated with Kaolin alone.

The comparative effects of Kaolinite (Kaolinite is the raw mineral that comprises Kaolin) on cellular and artificial membranes were examined using three test systems: tracheal epithelial cells, sheep erythrocytes (RBCs), and preparations of phospholipid-cholesterol vesicles in a study by Woodworth, Mossman, and Craighead (1982). Kaolinite doses of 0.003, 0.01, 0.03, and 0.1 mg/ml were added to tracheal epithelial cells for 24 h. Control cultures received no particulate. The ^{51}Cr release

was determined by liquid scintillation. Spontaneous release was determined from the control cultures. The second experiment, a hemolytic assay, combined RBC and Kaolinite doses of 0.1, 0.5, 1.0, 5.0, and 20.0 mg/ml were added at 37°C for 1 h. The optical density was determined at 540 nm. One milliliter of the preparation of liposomes (11.5 μg lipids) was added to 1 ml of a Kaolinite suspension. After 1 h, the optical density of the mixture was measured at 380 nm. The percentage of CrO_4^{2-} release was calculated. Control cultures received no particulate.

Kaolinite induced release of ^{51}Cr by tracheal epithelium was almost 50% at the highest dose. The cells phagocytized the particles, as demonstrated by SEM and phase-contrast microscopy. This process was most evident after 24 h. Cells containing intracellular particles demonstrated retraction of lamellopoidal extensions, surface blebbing, and a change in morphology from flattened to round.

A dose-dependent relationship between mineral concentration and hemolysis was demonstrated. Hemolysis was rapid. Approximately 50% of the RBCs were hemolyzed within 10 min. SEM revealed remnants of RBCs in cultures with complete hemolysis.

CrO_4^{2-} release at 10 mg/ml of Kaolinite was ~35% after 1 h. A dose-dependent relationship between particle concentration and CrO_4^{2-} release was again demonstrated (Woodworth, Mossman, and Craighead 1982).

In a study by Gormley and Addison (1983) described earlier, the cytotoxic effects of two Kaolins (K-1 and K-2) were investigated. K-1 had a particle size of 3.2 μm, and K-2 had a particle size of 3.9 μm. The procedures are detailed in the study Gormley and Addison (1983) under the Attapulgite heading.

Cellular viability was expressed as a percentage of the titanium dioxide control (100.0%) ± the standard deviation. The 20-μg/ml dose of Kaolin (K-1) resulted in a 101.4% ± 6.7% viability and the 80-μg/ml dose produced a 69.5% ± 6.5% viability. With a 20-μg/ml dose of Kaolin (K-2), viability was 93.6% ± 4.5%, with the 80 μg/ml dose, it was 60.0% ± 4.1%. It may be noted that K-1 has a finer particle size but a smaller surface area as compared to K-2. Cellular LDH activities decreased with decreasing cell viability, whereas the percentage of LDH in the medium increased. Similar results were seen with glucosaminidase. Also the amount of lactate produced decreased as cell viability decreased. However, little change in the total cellular protein was recorded (Gormely and Addison 1983).

The cytotoxicity of Kaolinite toward mouse peritoneal macrophages was examined in a study by Davies et al. (1984). This three-part study investigated whether or not respirable china clay (Kaolinite) was cytotoxic toward macrophages in vitro, the components responsible for the toxicity, and the factors responsible for the components toxicity. The assessment of toxicity was indicated by the activity of LDH assayed from the medium and cell lysates.

China clay dusts (60 μg/culture) from 12 separate drying plants were added to mouse peritoneal macrophage cultures and incubated for 18 h. The medium and cell lysates were collected and assayed for LDH activity. All 12 cultures had changes that indicated dust cytotoxicity. Between 19.5% and 60.0% LDH was released from the cultures. Four other dust samples, three of quartz (5,10,15, 20 μg/culture) and one of magnetite, were also assayed. The cytotoxicity of quartz indicated a dose-dependent relationship and was quite toxic. The magnetite dust had little effect on LDH release.

Mineral composition of the dusts was determined using x-ray diffraction analysis. A summary of the dust samples' composition was as follows: Kaolinite (84% to 96%), mica (3% to 6%), quartz (1%), and feldspar (0% to 7%). Due to the possibility of other dust cytotoxicity, the biological effects of the ancillary minerals and Kaolin was studied. Two high-purity Kaolins were tested in the same method as above and were clearly cytotoxic toward the macrophages. By x-ray diffraction, these two Kaolins were both 98% pure Kaolin. The feldspar sample had lower activity than titanium dioxide, a material considered nonfibrogenic and is used as a control dust in cell studies. The mica dust samples were cytotoxic but much lower than that of the Kaolin. By mineral analysis, it was found that mica dusts had 34% Kaolinite. Quartz was ruled out as the cytotoxic agent due to the very low concentrations (1%) in the initial experiment.

In a separate experiment, Kaolin pretreated with poly-2-vinyl pyridine-*N*-oxide (PVPNO) (0.45 μg/mg), was added to mouse peritoneal macrophages. (Note: PVPNO has been demonstrated to reduce the cytotoxicity of Kaolin [Davies and Preece 1983]). Electron micrographs were taken of the macrophages with and without the pretreated Kaolin for analysis of the factors causing the toxicity. The ultrastructural alterations and number of particles within the cells appeared to be similar in both the treated and nontreated cultures. It was concluded that PVPNO has no effect on the inhibition of the uptake of Kaolin. Dust particles were found adjacent to cell surfaces and in membrane-bound intracytoplasmic vesicles. However, no particles penetrated or were seen penetrating the nucleus and no lysed cells were seen.

In the last set of experiments, the physical structure of Kaolin and how it relates to dust toxicity was studied. Four components of Kaolin's structure were examined: gibbsite or mica-like surfaces, positively charged edges, negative charged particles, and an amorphous 'gel' coating on kaolinite. Transmission electron micrographs of gibbsite or mica-like surfaces indicated low toxicity and were ruled out as a possible marked toxic factor. A colloidal gold decoration technique was to study the positively charged edges of Kaolinite. Gold binds to the positively charged particles of Kaolinite and treatment of polyacrylic acid abolishes the gold decoration. In this study, mouse peritoneal macrophages were incubated with polyacrylic treated Kaolin (120 μg/culture). Only a small drop in the cytotoxicity of Kaolin was observed. The electrophoretic mobility of negatively charged Kaolin particles was also studied. Increased amounts of ammonium chloride produced a significant decrease in electrophoretic mobility. It is important to note that the greater concentrations did not produce negatively charged Kaolin particles. These same aluminum-treated Kaolins were added to mouse

peritoneal macrophages (120 μg/culture) and the cytotoxicity changed very little based on the amount of LDH activity released. The last experiment examined the effect of the amorphous 'gel' coating of Kaolin and its cytotoxicity. Plasma-ashing and the same LDH assay were performed on the samples. The first group, Kaolin (40 mg/cm^3), was plasma-ashed after 24 h and no effect was observed. Plasma-ashing after 72 h did reduce cytotoxicity. The second group of Kaolin dusts were mixed with formalin-fixed lung tissue and then immediately plasma-ashed. The cytotoxicity was not reduced. The last groups included Kaolin recovered from air-dried lungs of Fischer rats exposed to china clay dust (10 mg/m^3) for 40 h/week for 1 year, left for 1 year, then ashed to a constant weight. Inhalation of these dusts was significantly less toxic. Reductions in cytotoxicity was probably due to alterations in the surface coating of Kaolin (Davies et al. 1984).

Beck and Bignon (1985) dosed peritoneal macrophages with a sample of Kaolin and the TTC reduction, LDH activity, and methylene blue adsorption were used to assess cytotoxicity. The sample contained 30% SiO_2. The results from this study classified Kaolin as an inert dust and nontoxic. Methylene blue adsorption was slight.

Gormley, Kowolik, and Cullen (1985) used luminol-dependent chemiluminescence (CL) to assess the in vitro production of reactive oxygen species by human neutrophils and monocytes after exposure to Kaolinite. Either opsonized or nonopsonized Kaolinite dust was added to either neutrophil or monocyte suspensions and luminol. The suspensions were assayed for CL and measured in millivolt. Concentrations of dust ranged from the maximum of 3 mg/ml downwards. A control suspension of zymosan (2 mg/ml) was also assayed for CL production. Neutrophils challenged with opsonized dust had relatively low dose-dependent CL production compared to controls. However, when neutrophils challenged with nonopsonized dust, CL production peaked at 67%. Again dose-dependent responses were obtained when monocytes were tested. However, monocytes had a greater CL response in the presence of opsonized dust. These results were the reverse of the earlier neutrophil responses as a very low monocyte CL production was obtained with nonopsonized dust.

In a study by Wallace et al. (1985), the cytotoxicity of native and surface-modified Kaolin and the effect of pulmonary surfactant were studied. Cell membrane damage and cytotoxicity were measured by the release of alveolar macrophage cytoplasmic enzyme LDH, the lysosomal enzymes β-n-acetylglucosaminidase (β-NAG) and β-GLUC, and sheep blood cell hemolysis. Dipalmitoyl lecithin (DPL) emulsions made from synthetic L-α-lecithin β,γ-dipalmitoyl were added to Kaolin to produce a concentration of 7.5 mg dust/ml. Controls of saline and Kaolin without DPL were also utilized. For the hemolysis assays, the mixtures were resuspended in phosphate-buffered saline (PBS) at a concentration of 2.0 mg dust/ml PBS.

Fresh sheep blood erythrocytes were mixed with dust suspensions in concentrations of 0.1 to 1.0 mg/ml. Untreated Kaolin and DPL-treated Kaolin erythrocytes were incubated for 1 h at 37°C. Negative controls were made with erythrocytes in PBS and positive controls were made by lysing erythrocytes. All samples were read at 540 nm using a spectrophotometer and the percentage of lysis was calculated. The lecithin treated Kaolin suppressed erythrocyte activity to near "background levels." The hemolysis value for the maximum nontreated Kaolin concentration (1 mg/ml) was 42%, whereas the hemolysis value for the lecithin-treated Kaolin at the same concentration was 2%. Adsorption isotherm data estimated that 0.1 mg Lecithin/mg Kaolin would provide full surface coverage and suppress the hemolytic capacity to 97% lower than the native Kaolin.

In the second experiment of the same study, alveolar macrophage enzyme release studies were carried out using macrophages from Sprague-Dawley rats. Untreated Kaolin and DPL-Kaolin samples at a concentration of 1 mg/ml were mixed with macrophages and incubated for 2 h at 37°C. The results were similar as in the above experiment. The nontreated Kaolin caused release of enzymes: 570% LDH, 600% β-GLUC, and 570% β-NAG of the control values. The treated Kaolin did not cause the release of these enzymes. These results imply that Kaolin damages erythrocytes and macrophages through cell membrane–dust surface interactions and that pulmonary surfactants can absorb the mineral surfaces for a short time (Wallace et al. 1985).

Mossman and Be'gin (1989) conducted a study in which Kaolin samples were coated with the enzymes L-alpha-dipalmitoyl glycerophosphorylcholine (DGPL) and phospholipase A_2 (PLA_2) and the hemolytic potential of both coated and noncoated samples were studied in vitro. The samples were incubated with sheep erythrocytes and the optical density of the supernatant at 540 nm was determined to measure hemoglobin release. With increasing amounts of DGPL, neutralization of the hemolytic potential occurred at 75 to 85 mg DGPL/g of Kaolin. The residual adsorbed value was 83.0 mg DGPL/g Kaolin. The digestive removal of DGPL by Kaolin was measured at the applied specific activity of 0.96 units PLA_2 per molecule DGPL on Kaolin. Most of the produced lysolecithin remains adsorbed at 2 h.

Banin and Meiri (1990) added Kaolinite to murine neuroblastoma cells at concentrations of 100 to 1000 μg/ml. Within minutes, the Kaolinite increased the increasing permeability of the membranes, depolarized resting potential, and the maintaining action potentials in response to stimulation were lost. Within 30 min, the cells had alterations of morphological deterioration. Microvilli retracted, the surface assumed an unruffled, smooth appearance, and large holes developed in the plasma membrane.

Murphy, Roberts, and Horrocks (1993a) investigated the cytotoxicity of Kaolinite using three cell lines: HUVE cells, undifferentiated N1E-115 neuroblastoma cells, and ROC-1 oligodendrogial cells. Indices of cytotoxicity used in this study were morphological examination, LDH activity, and fatty acid release. Exact experimental details are provided in the Bentonite section under the same heading.

Kaolinite did not lyse ROC-1 oligodendroglia and the neuroblastoma cells and did not cause a dose-dependent increase in fatty acids at 24 h. No significant increases in LDH activity were detected utilizing either of these cell lines. However, Kaolinite increased fatty acid concentrations after 24 h of incubation in a dose-dependent fashion. A 1.7-fold increase in fatty acid concentrations over control values was calculated. Increases over control activities of LDH were 146% with Kaolinite. Within 1 h, Kaolinite associated with the plasma membrane of HUVE cells and the morphology was drastically changed after treatment (no details given). Cell lysis was also apparent. After trypan blue staining, 90% of HUVE cells were nonviable with Kaolinite treatment (Murphy, Roberts, and Horrocks 1993a).

Kaolinite dust was tested for potential human leukocyte elastase (HLE)-inhibiting effects (Oberson et al. 1996). HLE inhibition was evaluated by incubating 15 nM HLE for 1 h in the presence of 5 μg of Kaolinite. Suc(Ala)$_3$pNA was then added for 30 min. Activity was measured at 410 nM. The 5 μg Kaolinite abolished (90% inhibition) the activity of 0.45 μg HLE.

Montmorillonite

Results from a study by M'anyai et al. (1969) on the hemolysis and methylene blue adsorption by Montmorillonite are presented in Table 10.

Oscarson, Van Scoyoc, and Ahlrichs (1981) added Montmorillonite to a culture of bovine RBCs to study the extent of hemolysis. Saline was added to cultures as a control and in a separate experiment, the polymer, poly-2-vinylpyridine-*N*-oxide, was also added to study its inhibiting effects. No other details were given. The concentration of Montmorillonite that caused 50% hemolysis in 1 ml of a 3% solution of RBCs was determined as 0.006 mg Montmorillonite/ml of silicate-erythrocyte-buffer suspension. A concentration of 0.2 and 1.0 μM/ml of polymer reduced hemolysis to 23% and 0%, respectively.

The comparative effects of Montmorillonite on cellular and artificial membranes were examined using three test systems—tracheal epithelial cells, sheep erythrocytes (RBCs), and preparations of phospholipid-cholesterol vesicles—in a study by Woodworth, Mossman, and Craighead (1982). Montmorillonite doses of 0.003, 0.01, 0.03, and 0.1 mg/ml were added to tracheal epithelial cells for 24 h. Control cultures received no particulate. The ^{51}Cr release was determined by liquid scintillation. Spontaneous release was determined from the control cultures. A second experiment, a hemolytic assay, combined RBC and Montmorillonite doses of 0.1, 0.5, 1.0, 5.0, and 20.0 mg/ml at 37°C for 1 h. The optical density was determined at 540 nm. Control cultures received no particulate. One milliliter of the preparation of liposomes (11.5 μg lipids) was added to 1 ml of a Montmorillonite suspension. After 1 h, the optical density of the mixture was measured at 380 nm. The percentage of CrO_4^{2-} release was calculated. Control cultures received no particulate.

Montmorillonite induced release of ^{51}Cr by tracheal epithelium was almost 60% at the highest dose. The cells phagocytized the particles, as demonstrated by SEM and phase-contrast microscopy. This process was most evident at after 24 h. Cells containing intracellular particles demonstrated retraction of lamellopoidal extensions, surface blebbing, and a changed morphology from flattened to round.

A dose-dependent relationship between mineral concentration and hemolysis was demonstrated. Hemolysis was rapid. Approximately 50% of the RBCs were hemolyzed within 10 min. SEM revealed remnants of RBCs in cultures exhibiting complete hemolysis.

CrO_4^{2-} release at 10 mg/ml of Montmorillonite was ~40% after 1 h. A dose-dependent relationship between particle concentration and CrO_4^{2-} release was again demonstrated (Woodworth, Mossman, and Craighead 1982).

In the Gormley and Addison study (1983) described earlier, the cytotoxic effects of three samples of Montmorillonite (CaM-1, CaM-2, and NaM) were investigated. CaM-1 and -2 have calcium substitutions in their lattices whereas NaM has sodium substitutions. Particle sizes ranged from 2.0 to 3.1 μm. The procedures are detailed under the Attapulgite heading. Cellular viability was expressed as a percentage of the titanium dioxide control (100.0%) ± the standard deviation. The 20-μg/ml dose of CaM-1 with particle size of 3.1 μm produced a 79.1% ± 19.2% viability and the 80-μg/ml dose produced a 51.9% ± 15.6% viability; CaM-2 with a particle size of 2.5 μm produced viabilities of 21.2% ± 3.5% (20 μg/ml) and 13.1% ± 2.2% (80 μg/ml); and NaM with a particle size of 2.0 μm produced viabilites of 47.3% ± 7.4% (20 μg/ml) and 37.2% ± 4.6% (80 μg/ml). The sample CaM-1 had the largest surface area, whereas sample NaM, had the smallest. Sample CaM-2 had the lowest viability percentage despite the median particle size and surface area. Investigators attributed the marked toxicity of sample CaM-2 due to the presence of ~1% of quartz and 10% cristobalite in the sample. Sample NaM, which also exhibited a greater toxicity, contained ~5% quartz and ~2% calcite. Cellular LDH levels fell with decreasing cell viability whereas the percentage of LDH in the medium increased. Similar results were seen with glucosaminidase. Also, the amount of lactate produced decreased as cell viability decreased. However, little change in the total cellular protein was recorded.

Gormley, Kowolik, and Cullen (1985) used luminol-dependent CL to assess the in vitro production of reactive oxygen species by human neutrophils and monocytes on exposure to Montmorillonite. Either opsonized or nonopsonized Montmorillonite (containing a calcium as its exchange ion) dust was added to either neutrophil or monocyte suspensions and luminol. The suspensions were assayed for CL and measured in millivolt. Concentrations of dust ranged from the maximum of 3 mg/ml downwards. A control suspension of zymosan (2 mg/ml) was also assayed for CL production. Neutrophils challenged with opsonized dust resulted in relatively low dose-dependent CL production compared to controls. However, when neutrophils were challenged with nonopsonized dust, a marked response of CL peak production at 114% was elicited. Again dose-dependent responses were obtained when monocytes were tested. However,

monocytes elicited a slightly higher response in the presence of opsonized dust. These results proved to be the reversal of the earlier neutrophil responses. A very low monocyte CL production was obtained with nonopsonized dust.

Banin and Meiri (1990) reported a study in which Montmorillonite was added to murine neuroblastoma cells at a concentration range of 100 to 1000 μg/ml, but no details were given. The authors concluded that clear morphological signs of cell deterioration were evident and, at the concentrations listed, an acute toxic effect was seen.

Murphy, Roberts, and Horrocks (1993a) investigated the cytotoxicity of Montmorillonite to three cell lines: HUVE cells, undifferentiated N1E-115 neuroblastoma cells, and ROC-1 oligodendrogial cells. Indices of cytotoxicity used in this study were morphological examination, LDH activity, and fatty acid release. Exact experimental details are provided in the Bentonite section under the same heading.

Montmorillonite did not lyse ROC-1 oligodendroglia and the neuroblastoma cells and did not cause a dose-dependent increase in fatty acids at 24 h. No significant increases in LDH activity were detected utilizing either of these cell lines. However, Montmorillonite caused a dose-dependent increase in fatty acid levels only after 24 h of incubation. A 10-fold increase in FA levels over control values was calculated. Increases over control activities of LDH were 154%. Within 1 h, Montmorillonite associated with the plasma membrane of HUVE cells and the morphology was drastically changed after treatment (no details given). Cell lysis was also apparent with treatment. After trypan blue staining, 99% of HUVE cells were nonviable with Montmorillonite treatment (Murphy, Roberts, and Horrocks 1993a).

In a study by Murphy et al. (1993b), the cytotoxicity of Montmorillonite was examined in two cell lines: primary murine spinal cord neurons and differentiated N1E-115 neuroblastoma cells. A clay suspension with a concentration of 0.1 mg/ml was added to the cultures. The neuronal cells were incubated for 1 h with Montmorillonite. Photomicrographs were taken at 5, 15, and 60 min following treatment. For the N1E-115 cells, incubation lasted 18 h and photomicrographs were taken at 5 and 15 min and 3, 6, and 18 h after the treatment. Morphological changes were observed using a phase-contrast microscope. Within 5 min, clay particles were observed on the neuronal cell bodies. Cell bodies appeared granular within 15 min. The cells were completely lysed after 60 min and there was no evidence of any remaining cell bodies or processes. Cell membrane contact was apparent after 5 min in N1E-115 cultures. No morphological changes were apparent at this point. At 18 h, the cells were covered with clay but cellular processes remained intact. N1E-115 cell lysis did not occur and no cytotoxicity was recorded.

Montmorillonite dust was tested for potential HLE-inhibiting effects (Oberson et al. 1996). HLE inhibition was evaluated by incubating 15 nM HLE for 1 h in the presence of 5 μg of Montmorillonite. Suc(Ala)$_3$pNA was then added for 30 min. Activity was measured at 410 nM. The 5 μg Montmorillonite (98% inhibition) abolished the activity of 0.45 μg HLE.

Pyrophyllite

The cytotoxicity of Pyrophyllite dust on rat alveolar macrophages was investigated in a study by Zhang, Zhang, and Song (1997). Cytotoxicity was measured by the potassium content of the macrophages and the levels of LDH. Alveolar macrophages were isolated from bronchi alveolar lavages of male Wistar rats. These animals were divided into six groups based on the dust concentrations. The groups were as follows: quartz (75.72 μg/ml) dust group; Pyrophyllite mine (PM) dust group A, 200 μg/ml (75.72 μg/ml SiO_2 and 30.42 μg/ml Al_2O_3); PM dust group B, 200 μg/ml (75.72 μg/ml SiO_2 and 30.42 μg/ml Al_2O_3); Pyrophyllite carving mills (PCM) dust group A, 200 μg/ml (31.68 μg/ml SiO_2 and 40.58 μg/ml Al_2O_3); PCM dust group B, 200 μg/ml (31.68 μg/ml SiO_2 and 40.58 μg/ml Al_2O_3); normal control of saline. Both PM group B and PCM group B were imitated groups of the natural dusts from the mines used to study the toxicity of SiO_2 and Al_2O_3. They did not include the metals Fe, Cu, Ni, and Zn as did both samples A. The cell cultures were incubated at 37°C for 16 and 22 h.

The LDH activity of quartz was greater than all other groups except PM group A incubated at 22 h. When compared to the saline controls, all exposed groups had significantly lower increases in LDH activity. Both the LDH activities of the PM dust groups were greater than those of the PCM dust groups ($p < .5$). However, no differences between the PM groups A and B or between the PCM groups A and B were detected. The K^+ content of the saline controls was greater than all exposed groups. The quartz group had the lowest concentrations of K^+ followed by the PM dust groups and then the PCM dust groups. Again, no differences between either A or B groups was observed. It was concluded that Pyrophyllite dust exposure is cytotoxic to alveolar macrophages and people working in a PM have greater risk of respiratory problems than people working on PCMs.

Mineralogical analysis of the dust samples taken from the mines was performed using an atomic absorption spectrophotometer. The SiO_2 content was 37.9% higher in the PM group than in the PCM group 15.8%. Al_2O_3 concentrations were lower in the PM dust groups (15.2%) than in the PCM dust groups (20.3%). Toxicity due to metals in the samples A was ruled out. The samples B did not include the metals and had similar LDH activity as the samples A (Zhang, Zhang, and Song 1997).

Zeolite (Zeolite A)

Zeolite A at concentrations of 0.1 to 100 μg/ml was incubated for 48 h with normal human osteoblast-like cells. An induction of a dose-dependent increase in DNA synthesis and the proportion of cells in mitosis occurred. This mitogenic action was dependent on cell seeding density. Alkaline phosphatase activity and osteocalcin release were also increased but no significant effect on collagen production per cell occurred. Zeolite treatment increased the steady-state mRNA levels of transforming growth factor β (Keeting et al. 1992).

Zeolite (Clinoptilolite)

Total degradation of rat peritoneal macrophages incubated with Clinoptilolite dust particles occurred during 15- and 30-min time periods at concentrations of 1.0 and 0.5 mg/ml, respectively. Dust particles measured <5 μm. Thirty-eight percent of macrophages and 57.5% of RBCs were killed within 30 min at a Zeolite concentration of 0.25 mg/ml. Dose-dependent CL was observed in the first 10 to 20 s when luminol was added to the cultures. Catalase (30% to 50%) decreased the cytotoxic effects of Zeolite, whereas ethanol, sodium azide, and mannitol had no effect (Korkina et al. 1984).

Zeolite (Mordenite)

Syrian hamster and rat alveolar macrophages were exposed to nontoxic concentrations of Mordenite and the reduction of cytochrome *c* in the presence and absence of superoxide dismutase, and the amount of O_2 released were indicators of cytotoxicity. Other fibrous particles were used as positive controls. Mordenite as compared to the positive controls was less active at comparable concentrations (Hansen and Mossman 1987).

Zeolite (Nonfibrous Japanese Zeolite)

Japanese Nonfibrous Zeolite was incubated with two cell lines, Chinese hamster V79-4 and A579 at concentrations ranging from 5 to 100 μg/ml. Two samples of erionite and a sample of UICC crocidolite, a positive control, were also tested. Concentrations that inhibited plating were estimated using the LD_{50}. Compared to the positive control and the erionite samples, the Zeolite had a much greater LD_{50} value and was nontoxic in the A549 assay (Brown et al. 1980).

ANIMAL TOXICOLOGY

Acute Oral

Calcium Silicate

Calcium Silicate FDA compound 71-41 was suspended in 0.85% saline and administered to 10 male rats by intubation. Each animal that received a dose of 5000 mg/kg died within 24 h. Doses of 100, 500, 1000, 2000, 3000, and 4000 mg/kg were selected to determine the acute LD_{50} using the Litchfield-Wilcoxson method. Groups of 5 male rats were administered the doses and were killed for necropsy. The LD_{50} was determined as 3400 mg/kg; at the highest dose, necropsy findings included bloody gastric mucosa with distension, hydrothorax, and congested lungs. In a second LD_{50} assessment, Calcium Silicate was prepared as 24.1% (w/v) suspension and administered orally to a group of 10 male rats at a single dose of 5000 mg/kg. No signs of toxicity or abnormal behavior were observed within a 7-day period. No deaths occurred. All animals were killed and on necropsy no gross findings were observed. The acute oral LD_{50} was considered to be greater than 5000 mg/kg (Litton Bionetics, Inc. 1974).

Hectorite

Five male and five female Sprague-Dawley rats were administered a single dose of 5 g/kg of the test article by gavage. The animals were observed the day of dosing and 15 days after for gross and visible toxic or pharmacological effect. No such effects were seen and none of the animals died. All animals were killed for necropsy. No findings were reported. The acute oral LD_{50} was >5.0 g/kg of body weight (FDRL Inc. 1980b).

Kaolin

A report by the Federation of American Societies for Experimental Biology (1977) included an acute oral study in which 120 rats were fed doses of Kaolin ranging from 100 to 210 g/kg. Fourteen rats were controls. Kaolin was inert and nonstatic except for the danger of bowel obstruction resulting in perforation. The clinical signs were listlessness, anorexia, oliguria, hypothermia, and dyspnea. These were a pathological reaction from overdistension of the alimentary canal by an inert solid. The number of fatalities and the incidence and advance of bowel obstruction along the small intestine were dose related. The dose that killed 50% of the rats by bowel obstruction was 149 g/kg.

McClurg, Beck, and Powers (1980) fed a group of 10 male Sprague-Dawley rats a control diet plus 0.5 ml Kaolin 20%–pectin 1%. The control diet was then fed for 48 h and 72 h later stool samples were collected. The samples were analyzed for volume, sodium, potassium, and fat content. The results were 103% increase in sodium; 184% increase in potassium; fat excretion remained at baseline.

Magnesium Aluminum Silicate

Suspensions of 1 ml of Magnesium Aluminum Silicate at doses of 100–2000, 5000,10000, 20000, and 50000 mg/kg were administered to a series of 37 mice. At the greatest dose, the mortality rate was 33%. The LD_{50} was considered to be >50,000 mg/kg (Munch 1944).

Zirconium Silicate

In a study conducted by Stookey et al. (1967), the LD_{50} of Zirconium Silicate was determined. Oral intubations of a 60% aqueous slurry of Zirconium Silicate containing 1% carboxymethylcellulose to prevent settling was given to 80 albino mice. Doses ranged from 70 to 200 gm/kg body weight. A dosage of 200 g of Zirconium Silicate per kilogram body weight was not sufficient to create a 50% mortality rate in mice. Dosages greater than 200 g were not tested due to the limitations of the mouse gastrointestinal tract. A 37.5% mortality rate was recorded for the dosage of 200 g/kg of body weight.

Short-Term Oral

Bentonite

Carson and Smith (1982) fed Bentonite at concentrations 0%, 2.5%, 7.5%, or 10% to male weanling rats to determine the most effective level to overcome the effects of T-2 toxicosis.

Increasing the concentration of Bentonite resulted in significant increases in body weight and feed consumption. The most effective concentration tested was 10%. Bentonite had no effect on the activity of nonspecific hepatic esterase.

The role of Bentonite in the prevention of T-2 toxicosis in rats was further investigated by Carson and Smith (1983). Groups of 10 male Wistar rats were fed diets containing 5% Bentonite for 2 weeks and the feed consumption and growth were recorded. Each diet was administered with or without 3 μg T-2 toxin/g of feed for 2 weeks. Bentonite reduced the decreases in final body weight and feed consumption as compared to controls. The livers from this test group were excised and assayed for nonspecific esterase (E.C.3.1.1.1). Five percent Bentonite had no significant effect on the activity of this enzyme. In a second experiment, Bentonite was supplemented in the control diet at 2.5%, 5.0%, 7.5%, and 10%. Bentonite at 2.5% greatly increased feed consumption and final body weights and feeding. Ten percent Bentonite overcame the toxicosis completely. In a third study, rats were fed 0%, 5%, 7.5%, or 10% Bentonite for 2 weeks and then dosed with [^{3}H] T-2 toxin. The urine and feces were collected at 21 h and tissues were excised for determination of residual ^{3}H. Feeding Bentonite had little effect on the fraction of the dose excreted in the urine. Feeding 5%, 7.5%, and 10% Bentonite resulted in significant increases in the fecal excretion of ^{3}H when compared to controls. Bentonite had no effect on residual ^{3}H in the liver or kidneys but all concentrations reduced residual ^{3}H in muscle. Rats fed 5% Bentonite had more ^{3}H in the digesta in the small intestine and in the wall of the intestinal tissue when compared to controls. Intestinal transit time was reduced as well.

Bartko et al. (1983) fed a group of five sheep a diet containing 0.15 g/kg body weight of Zeolite for 3 months. Other sheep received no additions to their normal diet. At the end of the study, no difference in health effects was found between the two groups. The health effects included general behavior, total and acute acidity, content of volatile fatty acids in rumen contents, hematological values, content of microelements, transaminase activity, and acid-base homeostasis in the blood.

Magnesium Aluminum Silicate

Munch (1945) gave groups of 10 mice daily doses of either 5 or 10 g/kg of body weight orally for 10 days. Two days separated the first five doses from the second five doses. No signs were observed in any mouse at any time when administered 5 g/kg. The animals were killed and no pathological changes were seen at necropsy. No tissue was taken for further examination. One mouse died after five doses of 10 g/kg and one mouse died after nine doses of 10 g/kg. Neither mouse had lesions at postmortem examination.

This same author administered VEEGUM orally to 10 rabbits for a total of 10 doses. The first four animals were given 5 g/kg of body weight; the fifth animal was a control. The second four animals were given 10 g/kg of body weight; the fifth was also a control. No changes in body weight, no signs at toxicity, and no deaths were recorded. All animals were killed and at necropsy no lesions were seen in the stomach, liver, kidneys, or other viscera. No tissue was taken for microscopic examination (Munch 1945).

Zeolite (Clinoptilolite)

In a 148-day feed-lot experiment reported by McCollum and Galyean (1983), 48 cross-bred steers were fed a 70% sorghum diet with Clinoptilolite substituted at 0%, 1.25%, and 2.5% of the diet dry matter. No differences were found among treatments in average daily weight gain, feed intake or feed efficiency.

Pond, Yen, and Crouse (1989) fed 32 castrated male pigs various diets of calcium, iron, and Clinoptilolite to study tissue storage of major and trace elements with the addition of Clinoptilolite. At day 84, all pigs were killed and analyzed. Dietary concentrations of calcium, iron, and Clinoptilolite had no effect on daily weight gain, daily feed intake, or the ratio of weight gain:feed intake of growing pigs.

Zeolite (Clinoptilolite and Sodium Zeolite A)

Weanling Landrace × Yorkshire pigs were fed diets containing 3% Clinoptilolite with or without 150 ppm cadmium chloride or 3% Sodium Zeolite A with or without 150 ppm cadmium chloride for 31 days. Pigs fed cadmium and Zeolites did not have decreased hematocrit and hemoglobin values similar to those of pigs fed diets without the Zeolites. Hepatic cadmium concentration was significantly reduced in animals fed with Clinoptilolite. Hepatic iron was not affected significantly by either Zeolite; hepatic iron and zinc were decreased by dietary cadmium. Hepatic zinc was increased by Sodium Zeolite A (Pond and Yen 1983b).

Zeolite A

Various diets containing no Zeolite, 0.3% Zeolite A, or 0.5% Clinoptilolite were fed to cross-bred pigs for 6 weeks. The average daily weight gain, average daily feed intake, and feed:weight gain ratio were unaffected by supplementation of either Zeolite. Energy utilization was improved by feeding diets containing either Zeolite (Shurson et al. 1984).

Subchronic Oral

Magnesium Aluminum Silicate

The Food and Drug Research Laboratories (FDRL 1958a) carried out a 90-day feeding study using 220 weanling albino rats divided into five groups. The largest dose group consisted of 10 male and 10 female rats; control animals totaled 25 rats of each sex. A commercial ration was supplemented with 2%, 5%, 10%, and 20% VEEGUM. Control diets were unmodified. Body weight and feed intake were recorded daily and the efficiency of feed utilization (EFU; gram gained per 100 g) was calculated. Hematological examinations were made at 6 and 12 weeks on half of the test group. Blood sugar and nonprotein nitrogen determinations and urine analyses were also completed. Four rats in the 20% group, four rats in the 10% group, and control group

were placed on a modified program to estimate the balance between the intake of dietary ash and the ash excreted. Rats fed the 20% diet were examined at 8 weeks and rats fed the 10% diet at 12 weeks. All animals were killed at the end of the 90-day period. Liver, kidneys, spleen, heart, and adrenal glands weights were determined. Microscopic examination of the liver, kidneys, spleen, and portions of the gastrointestinal tract of four rats of each sex and control, 10%, and 20% groups were carried out.

The average body weights and net gains were not adversely affected by the ingestion of VEEGUM up to 10% in the diet. Growth was diminished slightly but with statistical significance ($p = .05$) when 20% VEEGUM was fed to both sexes. With EFU corrections, only the 20% dose significantly lowered the observed EFU value. One male rat of the 2% group died and one of each sex of the 10% group died. These rats had fibrinous exudates in the thorax, hemorrhagic lungs, and evidence of respiratory infection at necropsy. Gross findings for the rest of the animals revealed no significant abnormalities other than in the lungs. The incidences of pulmonary lesions did not differ among controls and test animals. Organ weights fell within normal limits. Hematological observations were within normal limits, including the rats of the 20% group. Blood sugar and nonprotein nitrogen values were also within normal limits. Females of the 20% group had slightly increased values compared to controls but still were in the normal range. Silicon content of the spleens of control animals were about the same as in the 2% group. However, in the 5% and 10% groups, the silicon content was slightly increased. Microscopic examination disclosed no abnormalities in the liver, kidneys, and gastrointestinal tract. Ash data indicated that 81% of VEEGUM of the 20% group was excreted and 73% of the 10% group was excreted (FDRL 1958a).

FDRL (1958b) fed two groups of four mongrel dogs, two female and two male for each group, a basal diet and a diet supplemented with 10% VEEGUM for 90 days. At 6 and 12 weeks, complete blood counts were made and blood sugar and nonprotein nitrogen were determined. Urine specimens were examined at 12 weeks for acidity, sugar, albumin, and microscopic elements in the sediment. At the end of 90 days, all dogs were killed for necropsy. Silicon content of the spleen was also determined. Body weight did not change despite a depression of appetite with the addition of VEEGUM. No abnormalities were seen upon hematological examination at the 6- or 12-week periods. Two of the test animals had slightly increased blood sugar at the end of the testing period. All other values for sugar and nonprotein nitrogen levels were normal. No difference in organ weight was seen. Silicon concentration of the spleens of the test animals were slightly elevated compared to controls (143 versus 103 mg/spleen). No microscopic lesions were compound induced.

CTFA (1999b) reported that in feeding tests with dogs and rats ingesting large amounts of VEEGUM (10% of ration) for 90 days, all responses were negative and VEEGUM was considered nontoxic.

Magnesium Trisilicate

Page, Heffner, and Frey (1941) gave six white rats daily doses of 0.6 g of Magnesium Trisilicate for 6 months. A litter was born and divided into two groups, a control and a treated group. The treated group received Magnesium Trisilicate doses from the time of weaning that corresponded to a daily dose of 3 or 4 pounds for a healthy human. This litter was also mated. Tissues from the animals of the first and second generation were examined microscopically. No evidence of tissue changes were recorded.

Dobbie and Smith (1982) gave six male guinea pigs a suspension in tap water of 250 mg/L Magnesium Trisilicate over a 4-month period for 5 days each week. Atomic absorption spectroscopy established that the soluble Si in the suspension was 267 μmol/L. Normal tap water was given to six control animals 7 days a week and 2 days a week to the test guinea pigs. At 4 months, all animals were killed for necropsy. The kidneys were processed for microscopic examination. All six animals had renal lesions that involved the distal nephron. Lesions of the distal tubule were dilation or cystic change. Some tubules were plugged with proteinaceous material. The interstitium of the kidneys was expanded by chronic inflammatory cells and excess collagen fibers. No lesions were seen in control animals.

Chronic Oral

Zeolite (Synthetic Zeolite A)

Groups of 50 male and female Wistar rats were fed 1, 10, 100, or 1000 mg/kg of Synthetic Zeolite A in their diets for up to 104 weeks. Clinical signs, mortality, and gross and microscopic lesions were recorded. No differences in body weight gain or clinical parameters were observed between control and treated animals. Based on feed intake, the Zeolite intake of the 10-, 100-, and 1000-mg/kg groups was 0.62, 6.1, and 58.5 mg/kg body weight/day for males and 0.65, 6.53, and 62.2 mg/kg body weight/day for females, respectively. No significant treatment-related lesions were observed in any of the organs examined and there was no effect on the types or incidence of any neoplastic changes seen (Gloxhuber et al. 1983).

Acute Parenteral

Aluminum Silicate

Musk et al. (1988) exposed Syrian golden hamsters to saline suspensions of Aluminum Silicate at 3.75 and 0.75 mg/100 g body weight by intratracheal instillation and sacrificed the animals at day 1. Their lungs were lavaged and the lavage fluid was characterized using cellular and biochemical indicators (lactic dehydrogenase, albumin, macrophages, polymorphs, and RBCs) of pulmonary damage. Either dose did not alter the biological parameters tested in comparison to those animals only exposed to saline.

Lemaire et al. (1989) gave Fiberfrax, an aluminum silicate, by intratracheal instillation at doses of 1, 5, and 10 mg to groups of

five rats. The details of this experiment are explained by Lemaire et al. (1989) under the Attapulgite heading in this section. The average length of Fiberfrax fibers were 8.3 μm and <50% were under 5 μm. The significant inflammatory response was mainly numerous lymphocytes and epithelioid giant cells. The lesions were located predominantly around the terminal bronchioles. Areas of early fibrosis were seen in the lesions. Every test animal developed type C lesions, described above. A dose-dependent reaction was suggested due to more extensive lesions seen in animals dosed with 10 mg. The bronchoalveolar lavage fluid had macrophages as the predominant cells followed by neutrophils and then by lymphocytes.

Pigott and Ishmael (1992) studied the effects of intrapleural injections of Aluminum Silicate in rats. A single intrapleural injection of 20 mg of four Aluminum Silicate samples (Saffil, aged Saffil, aluminosilicates A and B) and chrysotile A asbestos was administered to dose and control groups consisting of 24 rats of each sex. The control group received only a saline injection. The predominant length of the fibers in each sample were Saffil, 10 to 20 μm; aged Saffil, 20 to 40 μm; aluminosilicate A, 20 to 40 μm; and aluminosilicate B, 0 to 10 μm. Each rat was allowed to live out its lifespan or until it appeared distressed until 85% mortality was reached. All animals, were then killed and organs were taken for microscopic examination. Reactions to both forms of Saffil were very similar. In almost all animals, a minimal focal chronic pleurisy/fibrosis was minimal with adhesion formation. Pericardial adhesions and mesothelial proliferation with some Saffil fibers were seen. The reactions to both aluminosilicate samples were very similar. Minimal to moderate focal chronic pleurisy/fibrosis was often associated with mesothelial proliferation. Aluminosilicate B caused three malignant mesotheliomas, one pleural and two peritoneal. A benign testicular mesothelioma was seen in one rat dosed with Saffil, two dosed with aged Saffil, and four dosed with aluminosilicate A. Incidences of tumors are presented in Table 14.

Attapulgite

Pott et al. (1987) injected three samples of 25 mg of Attapulgite dust intraperitoneally into 40 Wistar rats. Electron microscopy of the sample revealed 37.5% of fibers <2 μm long and 70.0% <5 μm. All animals were observed until they died either spontaneously or were killed. Saline was injected into 80 control animals. The time required to produce the first tumor in the rats was 257 days and the tumor incidence rate was 65%.

Stanton et al. (1981) reported that two groups of 30 to 50 female Osbourne-Mendel rats received a single direct application to the left pleural surface by open thoracotomy of 40 mg of one of two Attapulgite samples. The samples were 90% pure with quartz being the other component. One dose consisted of fibers >4 μm and the other contained no fibers >4 μm. The rats were killed at the end of 2 years. Pleural sarcomas were seen in 2/29 rats. The incidences of pleural sarcomas in the untreated groups were 3/491 and 17/615 of the rats receiving the pleural implants of Attapulgite. Of rats receiving UICC crocidolite, 14/29 developed pleural mesotheliomas.

Be'gin et al. (1987) delivered Attapulgite with a mean fiber length of 0.8 μm and diameter of 0.02 μm to the lungs of sheep by bronchioscopic cannulation. The tracheal lobe of 16 sheep was subjected to a single exposure of 100 mg of Attapulgite in 100 ml of saline. A bronchoalveolar lavage (BAL) was conducted at 2, 12, 24, 40, and 60 days, and necropsy was conducted on day 60. Total BAL cells, macrophages, and neutrophils, fibronectin content, and LDH and β-GLUC activity were examined. Nine samples of the tracheal lobe of the lung were obtained each time for microscopic examination. The controls were saline-exposed sheep and had no changes in BAL or pulmonary morphology. The total BAL cells/ml and subpopulations increased significantly above control numbers at days 12, 24, and 40 but returned to control levels by day 60. Albumin and procollagen III did not differ from controls, whereas fibronectin, LDH, and β-GLUC activities were significantly above the controls. Microscopic examination revealed infiltrates that were predominantly alveolar and peribronchial lesions. Macrophagic alveolitis with minimal airway distortion was seen. Three sheep had lesions of peribronchiolar alveolitis.

Jaurand et al. (1987) injected samples (20 mg/ml of 0.9% NaCl) of Attapulgite fibers with the median length of 0.77 μm into the pleural cavities of 36 2-month-old Sprague-Dawley rats. Two control groups, untreated and saline-injected, were utilized. Necropsy was performed after the rats died or killed when moribund. No mesothelial neoplasms were found in either controls or in rats treated with Attapulgite. Survival times between the Attapulgite-treated group and the controls were not statistically different.

Wagner, Griffiths, and Munday (1987) injected 20 male and 20 female, SPF Fischer rats intrapleurally with single injections of Attapulgite. Three samples of Attapulgite named after the location of their discovery (Lebrija, Torrejon, and Leichester) were utilized in this study. No concentrations were provided.

TABLE 14

Tumors in rats treated with intrapleural injections of four Aluminum Silicate samples (Pigott and Ishmael 1992)

Tumor	Control	Chry. Asbestos	Saffil	Saffil aged	Alumosil. A	Alumosil. B
Total no. of animals	62	81	71	68	57	67
No. of benign	44	55	57	56	46	49
No. of malignant	17	26	16	14	10	19
Malignant mesothelioma	0	7	0	0	0	3

TABLE 15
Toxic reactions to intrapleural injections of Attapulgite (Wagner, Griffiths, and Munday 1987)

Dust	Mesothelioma	Nonmesothelioma
Lebrija Attapulgite	2	38
Torrejon Attapulgite	14	26
Leichester Attapulgite	30	2
Crocidolite	34	6
Kaolin	0	40
Saline	1	39

However, fiber length information was provided. Lebija Attapulgite had fiber lengths of ≤ 2 μm. Torrejon Attapulgite contained at the most 0.54% of fibers ≥ 6 μm. Leichester Attapulgite contained about 19% of fibers ≥ 6 μm. The animals were allowed to live their life span but were killed if they appeared distressed. Upon death, necropsy and microscopic examination of tissue were performed. Dust extraction was obtained from granulomas removed from the diaphragm or mediastinal tissue. Two controls were used in this experiment; Kaolin and saline. One positive-control crocidolite was also used. The results from this experiment are summarized in Table 15.

Lebrija Attapulgite dust extracted from the lung had fibers ≤ 2 μm. Material examined from Torrejon Attapulgite was fibrous and have fiber length up to 8 μm. Leichester Attapulgite fibers from extracted lungs were up to 25 μm. The investigators considered these fibers to be tumorigenic. Kaolin was a nonfibrous dust and crocidolite was fibrous. The authors concluded that exposure to Torrejon, and Leichester Attapulgite should be avoided (Wagner, Griffiths, and Munday 1987).

Lemaire et al. (1989) reported a study in which groups of five rats received single intratracheal instillations of Attapulgite at 1, 5, and 10 mg. One month after treatment, BAL and microscopic examination of the lungs were performed. The average length of the fibers were 0.8 μm and 100% of the fibers were less than 3 μm. Every test animal had type A lesions. Type A lesions are characterized by an accumulation of inflammatory cells mostly macrophages, and epithelioid cells around fiber deposits. These inflammatory cells form a compact cellular infiltrate at the periphery of the deposits and some are focally dispersed throughout the alveolar region. The BAL had mostly macrophages and a small number of neutrophils at 5- and 10-mg doses. At the 5-mg dose, 3.6% of the cells were lymphocytes.

In a study by Renier et al. (1989), intrapleural injections of 20 mg of different Attapulgite fiber samples in 1 ml of saline were given to 2-month-old Sprague-Dawley rats. The control group received only a saline injection. All rats were allowed to live full life span. The mean length of Attapulgite fibers in this experiment was 0.77 μm. The number of groups were not reported; however, 36 rats were reported to comprise each group. Pulmonary and thoracic neoplasms were fixed and processed for histopathological examination. The survival time of the treated groups (788 ± 155 days) was very similar to that of the control groups (809 ± 110 days). The incidence of mesothelioma was 0% for control groups and treated groups. Attapulgite in the present experiment was not carcinogenic (Renier et al. 1989).

Lemaire (1991) reported a study in which groups of five animals received doses of 1, 5, or 10 mg of Attapulgite by transtracheal injection to examine alveolar macrophage (AM) production of interleukin-1 (IL-1) and macrophages-derived growth factor (MDGF) from fibroblasts. Saline and UICC chrysotile B asbestos were used as controls. At 1 month, Attapulgite produced granulomas and the UICC chrysotile B produced fibrosis. At 8 months, the granulomatous reactions had either resolved or were greatly diminished, whereas the fibrosis persisted. Cells obtained by BAL included multinucleated giant macrophages in animals treated with Attapulgite, but not in those treated with UICC chrysotile B. Enhanced production of IL-1 was seen in all treated groups. MDGF production was only seen in animals with lung fibrosis.

Coffin, Cook, and Creason (1992) injected a single dose of 0.5, 2, 4, 8, 16, or 32 mg of Attapulgite intrapleurally into six groups of 25 Fischer 344 rats. Nearly all the fibers were <1 μm in length. Mesotheliomas were present in 2/140 treated rats compared to 1/79 incidences in control groups. The median life span was 839 days for Attapulgite-treated animals and 729 days for nontreated animals.

Bentonite

Sykes et al. (1982) investigated the effects of Bentonite dust administered by intratracheal instillation in rats. A 0.5-mg dose of Bentonite with a mean size of 0.3 μm was instilled intratracheally. Control animals were injected with sterile saline and TiO_2 (a nontoxic dust). Animals were killed at 1, 2, 6, 24, and 48 h; and 4 and 7 days after instillation. Bronchopulmonary lavage (BPL) was carried out and AMs and polymorphonuclear (PMN) leukocytes were recovered. The activity of LDH and protein content of the lavage fluid were also determined. In a second experiment, after instillation of 5 mg of Bentonite, the animals were killed at 1, 7, 49, and 100 days. In addition to the above, peroxidase and lysozyme activity were measured.

In the first experiment, a rapid influx of PMN leukocytes was detected at 6 h. PMN leukocyte response peaked at $\sim 19 \times 10^6$ cells after instillation and started declining more slowly up to 4 days. At 7 days, the PMN leukocyte numbers were 2.5×10^6. The greatest increase in the numbers of AMs recovered occurred at 4 and 7 days. The mean diameter of macrophages increased from 11.0 to 12.5 μm over the first 48 h after instillation. The mean diameter decreased at 4 and 7 days. LDH activity at 24 h was maintained at 40 mU cm^{-3} and then increased (73 mU cm^{-3}) with the influx of PMN leukocytes into the lungs after 48 h. Protein concentration was calculated at 500 μg cm^{-3} for the first 24 h and was maintained for 48 h.

In the second experiment, large number of PMN leukocytes were recovered at day 1. However the severity of the response did not differ significantly from the 0.5 mg dose. By 7 days,

the numbers had decreased and was similar to control values. A significant decrease in the number of AMs compared to controls was observed at 24 h after instillation. This decrease was followed by a sharp increase that exceeded control values by 7 days. Total number estimates were similar to those of the first experiment. LDH activity and protein concentration from Bentonite and TiO_2 were very similar. The initial rise at day 1 following administration was short-lived. Peroxidase activity was minimal. Lysozyme activity rose sharply between 1 and 7 days, but returned to control values at 49 and 100 days (Sykes et al. 1982).

Marek and Blaha (1985) gave subplantar injections of 0.05 ml of a 5% solution of Bentonite to male Wistar rats. The rats either received both hind paw injections at an interval of 24 h or their left paw was injected with Bentonite and their right paw injected with 0.05 ml of a 10% solution of Kaolin. The injection was of Kaolin. Subcutaneous Bentonite granulomas were produced on the left side, both dorsally and ventrally. Simultaneously Kaolin granulomas were produced on the right side analogous to the Bentonite injection. Sodium salicylate and prednisone suppressed the Bentonite edema during the first 24 h. The presence of mononuclear cells was confirmed.

Tatrai et al. (1983) administered a single dose of 40 mg of Bentonite suspended in 1 ml of physiological saline containing 40,000 IU of crystalline penicillin intratracheally to male CFY rats. The Bentonite's composition consisted of 73% Montmorillonite, 18% cristobalite, 3% quartz, 3% feldspar, and 3% other minerals. Particle sizes were <2 μm. The control group received 1 ml of physiological saline containing 40,000 IU of crystalline penicillin. Animals were killed 12, 24, 48, or 72 h or 90 days after exposure. Body and lung weight of the rats were measured. The right lung was fixed and sectioned for microscopic examination. The lipids and phospholipids were analyzed in the left lung.

The body weights of the rats were moderately decreased and the lung weight increased 72 h after Bentonite exposure. After 90 days, the lung weight was only slightly greater than that of the control animals. Upon microscopic examination at 12 h, Bentonite exposure had resulted in a nonspecific inflammation of mostly neutrophils with perivascular edema, alveolitis, and incipient bronchopneumonia. A small number of macrophages and lymphocytes were detected. Dust particles were observed in the leukocytes and macrophages or extracellularly in the alveoli. After the 24th h, bronchopneumonia was present after coalescence of the inflammatory foci; the pneumonia then became necrotizing and desquamative. Necrotic neutrophilic leukocytes and eosinophil leukocytes were observed. The reticular network collapsed between the 48th and 72nd h. Exposure after 90 days, included dust storage foci filled with large foamy cells with pale cytoplasm. Closely packed cells with dark cytoplasm and nuclei were located at the periphery.

After 12 and 24 h, the amount of lipids and phospholipids in the lungs was not altered. However, between 48 and 72 h, the lipid and phospholipid content increase but distribution remained the same. After 90 days, the value was the same as seen at 72 h. (Tatrai et al. 1983).

Hatch et al. (1985) assessed the ability of Bentonite to increase susceptibility to bacterial pneumonia. Bentonite was injected intratracheally into mice at concentrations of 1, 10, and 100 μg. In vivo bacterial-infectivity screening assays were conducted by exposing the animals to aerosolized Group C *Streptococcus* species. The severity of infection was calculated by recording the deaths of the mice over a 15-day period. Control animals were exposed to TiO_2, a nontoxic dust. At the 100-μg dose, Bentonite increased the infectivity of the bacteria. Mortality was 85%. Even at 10 μg, Bentonite caused increased animal mortality (43.3%). Control dusts at 100 μg produced only a 5% mortality (Hatch et al. 1985).

In a study by Tatrai et al. (1985), male CFY rats were given a single dose of 60 mg of Bentonite, in 1 ml of physiological saline containing 40,000 IU crystalline penicillin, by the intratracheal route. Bentonite particle size was less than 5 μm. Control groups received 1 ml physiological saline containing 40,000 IU penicillin. Animals were killed at the end of 72 h, the 2nd and 4th week, and the 3rd, 6th, and 12th month. The acid phosphatase activity and the progression of fibrosis was determined. The lungs were processed for microscopic examination and fibrosis determined by Belt and King's classification. The results from this experiment are presented in Table 16. Acid phosphatase activity was increased at 72 h and had returned to normal by the first month.

Bentonite dust was administered intratracheally as a single 60-mg dose to Sprague-Dawley rats in a study by Adamis et al. (1986). The animals were killed 3, 6, and 12 months after exposure. The right lung was studied microscopically and the lipids, phospholipids, and hydroxyproline were determined. Significantly greater phospholipid values compared to controls were observed. Among the phospholipid fractions, the greatest quantitative increase was seen in phosphatidylcholine (more than twice the control) and the smallest increase was seen in phosphatidylethanolamine (less than 1.6 times). After 6 and 12 months, the values were similar. Lung lipids had a greater range of values than did the phospholipids (no details given). The wet weight of the lung in grams increased in 5% to 10% Bentonite-treated rats compared to controls at month 3. No

TABLE 16
Toxic effect of intratracheal instillation of Bentonite (Tatrai et al. 1985)

	Time after instillation		
End point	72 hours	1st month	12th month
Acid phosphatase activity	72	—	—
Fibrosis	N/A	Loose reticulin fibrils, no collagen	Loose reticulin fibrils, no collagen

difference was detected at 6 and 12 months. Hydroxyproline content of treated rats (mg/g lung wet weight) was very similar to controls at 3, 6, and 12 months (Adamis et al. 1986).

Calcium Silicate

Bolton et al. (1986) injected three Calcium Silicate samples into the peritoneal cavity of three groups of 36 rats. Each rat was given a single injection of 25 mg of dust and allowed to live out their life span. At necropsy, little dust or dust-related fibrosis was visible in the peritoneal cavity. No mesotheliomas developed in any of the animals.

Richards, Tetley, and Hunt (1981) compared the biological reactivity of three samples of Calcium Silicate (A, B, and C) in vivo to that of chrysotile and titanium dioxide. Titanium dioxide and saline were considered negative controls, while chrysotile was considered a positive control. Groups of 32 female, MRC hooded rats were instilled intratracheally with 0.25, 0.50, 1.0, or 5.0 mg of Calcium Silicate. At weeks 1 and 4 after instillation, the control and treated rats were killed. The lungs were lavaged and the reactivity of the minerals to free cell populations, lavaged lung tissue, and pulmonary surfactant was conducted. All mineral doses of 5 mg induced an increase in the number of free cells at week 1. Only sample B increased in cell numbers at lower doses. At the end of 1 week, sample B was considered more reactive than either sample A or C, but chrysotile was considered more reactive than sample B. At 4 weeks, the effects seen from samples A and B are almost completely reversed and were comparable to that of titanium dioxide. Sample B at 4 weeks produced a greater or a comparable activity to chrysotile. No mineralogical analysis of the Calcium Silicate samples was provided.

Kaolin

Zaidi et al. (1981) investigated the effect of *Candida albicans* in modifying the fibrogenisis caused by Kaolin. Five groups of guinea pigs were injected intratracheally with *C. albicans* (500 μg); Talc dust (75 mg); Talc and *C. albicans*; Kaolin (75 mg); or Kaolin and *C. albicans*. Two animals from each group were killed at 1, 7, 15, 30, 60, 90, 120, and 180 days after injection. The lungs were collected for bacteriological and microscopic examination. The combined effect of Kaolin and the organism incited an acute inflammatory reaction similar to Kaolin dust alone at day 1. However, Kaolin and the organism produced thick reticulin and collagenous fibrosis, unlike Kaolin alone. Talc produced only a thin reticulin fibrosis not enhanced by the presence of the organism. The enhanced fibrogenicity was attributed to the adjuvant activity of Kaolin with the polysaccharide glucan component of *C. albicans*.

Edwards et al. (1984) gave 12 fetal lambs and six fetal monkeys subarachnoid injections of Kaolin. A sterile suspension of 2% Kaolin in saline was injected into the cisterna magna. Fetal lambs received 1 to 3 ml of Kaolin and fetal rhesus monkeys received 0.5 to 1.0 ml. After injection the fetuses were replaced into the uterus. Prenatal ultrasound monitoring was used to document the progression of fetal ventriculomegaly. Cesarean sections were scheduled for 140 to 145 days for the sheep and 160 to 165 days for monkeys. Newborn animals with gross head enlargement were killed 2 h after birth and necropsy was performed. Brains were sectioned for gross and microscopic examination. Five lambs and one monkey underwent ventriculoamniotic shunting at 120 days after gestation.

Ventricular dilatation was apparent at 1 week following Kaolin injections. The cerebral mantle was markedly thinned, with relative preservation of the cortex and severe attenuation of the white matter. The average cortical thickness of the cingulate gyrus in the Kaolin-injected sheep was 716 μ compared to 1225 μ in control animals. The corpus callosum was an average of 125 μ in thickness in the sheep compared to 475 μ in control animals. Microscopic examination of the cortical neurons were well preserved and contained the complexity and density of neural processes. A mild-to-moderate fibrotic reaction and inflammatory cell response along the basal meninges was apparent. A large number of macrophages containing Kaolin infiltrated the subarachnoid space. In five fetuses, Kaolin was injected mistakenly into either the epidural tissues superficial to the cisterna magna or into the cervical musculature. None of these fetuses had hydrocephalus at birth (Edwards et al. 1984).

Hatch et al. (1985) assessed the ability of Kaolin to increase susceptibility to bacterial pneumonia. Kaolin was injected intratracheally into mice at a dose of 100 μg. In vivo bacterial-infectivity screening assays were conducted by exposing the animals to aerosolized Group C *Streptococcus* species. The severity of infection was calculated by recording the deaths of the mice over a 15-day period. Control animals were exposed to TiO_2, a nontoxic dust. A 100-μg dose of Kaolin caused statistically significant but modest (<50%) increased death due to infection by a large dose. Mortality was calculated at 38.9%. Control dusts at 100 μg produced only a 5% increase in mortality.

Wagner, Griffiths, and Munday (1987) used Kaolin as a negative control in a previous intrapleural injection study. The protocol and results are cited under Attapulgite in this section.

Fugiyoshi, Hayashi, and Oh-ishi (1989) reported a study in which Kaolin, a known activator of factor XII, was injected intraperitoneally into mice at 2.5 mg/mouse to study the Kaolin-induced writhing response. The writhing responses were observed in the 10 min after treatment and the mean number of responses was 9.2. Sixty minutes after the Kaolin injection, captopril (20 μg/mouse) was injected and the writhing response was observed again for 10 min after injection. Captopril is an antihypertensive and vasodilator. A second study was conducted by administering bromelain (10 mg/kg intravenously) followed by the injection of Kaolin 30 min later. Bromelain is a standardized complex of proteases from the pineapple plant purported to have primarily antiedema, antiinflammatory, and coagulation-inhibiting effects. The response was not reproduced.

Montmorillonite

Heat-treated Montmorillonite in doses of 5, 15, and 45 mg was given to groups of four Sprague-Dawley rats by intratracheal

instillation. Following a 3-month postexposure period, the animals were killed and tissues were subjected to microscopic examination. The Montmorillonite particles were mainly restricted to alveoli within and adjacent to alveolar ducts regardless of dose. Most particles were contained within small to moderate numbers of pulmonary AMs. However, some particles were free in alveoli. Adjacent alveoli septae were mildly thickened. Interstitial fibrosis was present in all groups. At the 5- and 15-mg doses, fibrosis was mild to moderate, multifocal, and loose, meaning less collagen. The 45-mg dose produced dense fibrosis. Macrophages contained clay particles and lymphocytes were present in the lesions. Occasionally giant multinucleate cells were seen (Schreider, Culbertson, and Raabe 1985).

Zeolite

A single intratracheal administration of 50 mg of Zeolite dust was given to male rats and observations were made at 1 and 3 days, and 1 and 3 months after injection. Time-dependent increases in phagocytosis were observed. Morphological changes in the lungs was described as exogenous fibrous alveolitis (Kruglikov, Velichkovsky, and Garmash 1990).

Zeolite (Clinoptilolite)

Kruglikov et al. (1992) reported a study in which a single intratracheal instillation of 50 mg of Clinoptilolite was made to male rats. On days 1, 3 to 5, and 18 after injection, lung tissues were examined histopathologically. On the first day, the smallest Zeolite particles were phagocytized by neutrophils, whereas larger particles were phagocytized by macrophages. About a fourth of macrophages had phagocytized more than six dust particles per cell and <2% of macrophages were degenerated. At 3 to 5 days, no more particles were seen in neutrophils and their numbers had decreased. However, the percentage of macrophages containing more than six dust particles in the cytoplasm increased to 90%. Only 7% of macrophages degenerated. On day 18, the pattern of phagocytosis was similar to that at days 3 to 5, but 4% of macrophages were degenerated.

Tatrai and Ungv'ary (1993) instilled single intratracheal doses of 30 and 60 mg of Clinoptilolite particles to groups of 50 male and female (equal numbers) Wistar rats. The particles were <5 μm and were suspended in 40,000 IU crystalline penicillin. Controls received only saline instillations. All survivors were killed at the end of the study. Examination for gross and microscopic lesions were conducted. None of the treated groups had a significant increase in the incidence of any specific neoplasms compared to the controls. No positive trend was noted in the occurrence of neoplasms. Neoplasms seen within both control and treated animals were similar in the anatomical sites in which they were found and their histological feature.

Zeolite (Mordenite)

Suzuki (1982) gave two groups, one of 18 and one of 5 male Swiss albino mice, a single injection of 10 or 30 mg Zeolite intraperitoneally. The control animals were untreated. Ten months after exposure, no neoplastic changes were observed in the treated animals. Nearly all (98%) of the sample particles were <5 μm.

Suzuki and Kohyama (1984) administered a single injection of 10 mg of Mordenite to a group of 50 male BALB/c mice. The control animals received saline injections. The Mordenite sample was comprised of 94% of particles <3 μm. No peritoneal tumors were observed in any of the control animals. Mild peritoneal fibrosis was seen in treated mice, but no peritoneal or any other organ neoplasms were observed between 7 to 23 months.

Tatrai, Wojn'arovits, and Ungv'ary (1991) made intratracheal instillations of 60 mg of Mordenite to groups of 10 rats. The animals were killed at 1 week, and 1, 3, 6, and 12 months after exposure. Lesions in the lungs were observed. Nonspecific confluent bronchopneumonia was observed at 1 week after exposure and sequestration of macrophages at 1 month after exposure. Mild fibrosis was observed at later times. After 12 months, the aluminum:silicon ratio in macrophages was similar to the ratio in natural Zeolites.

Tatrai et al. (1992) reported the changes in cervical and hilar lymph nodes in the test animals treated in the above study as seen by electron microscopy and light microscopy. By the end of the first year, dust storing macrophage foci developed in the lymph nodes with minimal fibrosis. Also 3/10 of the rats had atypical hyperplasia. Electron microscopy showed the dust stored in macrophages without structural changes. However, dispersive x-ray microanalysis of the intracellularly stored dust revealed the ratio of the two main elements, aluminum and silicon, changed with respect to aluminum as compared to the original Zeolite sample.

Zeolite (Nonfibrous Japanese Zeolite)

A single intrapleural injection of 20 mg of Nonfibrous Japanese Zeolite was administered to two groups of 20 male and 20 female Fischer 344 rats. Control rats received saline injections alone. Mean survival time for control animals was 720 days and 715 days for treated animals. One pleural mesothelioma was found in the control group and one pleural and one peritoneal mesothelioma was found in the treated group (Wagner et al. 1985).

Zeolite (Synthetic Zeolite 4A)

A single intraperitoneal injection of 10 mg of Synthetic Zeolite 4A was given to groups of 50 male BALB/c mice. The average particle length of the sample was 2.24 μm. Treated animals were observed for 7 to 23 months after exposure and no mesothelioma were observed (Suzuki and Kohyama 1984).

Zeolite (Synthetic Zeolite MS4A and MS5A)

Maltoni and Minardi (1988) reported a study in which groups of 20 male and 20 female Sprague-Dawley rats received a single intraperitoneal injection of 25 mg of Zeolite MS4A (sodium aluminum silicate) or MS5A (calcium aluminum silicate) or water

only (control). Observations were made for the animal's entire life span and microscopic examination was performed. One peritoneal mesothelioma in an Zeolite MS4A-exposed rat was found at 141 weeks after treatment.

These same authors administered single intrapleural injections and single subcutaneous injections of 25 mg of Zeolite MS4A and MS5A or water to separate groups of 20 male and 20 female Sprague-Dawley rats. No difference in incidences of tumors was found among control and treated animals (Maltoni and Minardi 1988).

Zirconium Silicate

In a study by Harding (1948), a 3-ml dose of a 10% suspension of Zircon in milk and saline was injected intraperitoneally into three cavies (guinea piglike rodent). The animals were killed nearly a year later. At microscopic examination, a dry opaque material was embedded in the peritoneum of the abdominal wall over the small intestine, and in the omentum. Growth was not affected.

The accumulation of Zirconium Silicate in tissue was reported by Stookey et al. (1967). In one study, six young adult male rats were anesthetized and were given subcutaneous injections into their back. Half of the rats were injected with saline to serve as controls and the other half were injected with 0.3 ml of an aqueous 50% slurry of Zirconium Silicate. Three weeks after the injections, the animals were killed. Tissue surrounding the injection site was excised and prepared for microscopic examination. Zirconium Silicate deposits were observed as discrete nodules with a narrow surrounding connective tissue wall in the deep connective tissues of the back. Saline controls had no lesions and in some cases, healing was complete.

In another study in this report, eight young adult female rats were divided into four equal groups according to body weight and their tissues were subjected to microscopic examination following saline and Zirconium Silicate or sodium zirconium lactate injections. Group 1, the control group, was given a single injection of 0.05 ml of isotonic saline in four different areas: subcutaneous injections in the right buccal mandibular mucosa; periosteal injections in the left buccal mandibular periosteum; intramuscular injections on the ventral side of the left thigh; subcutaneous injections in a shaved area on the back located about 1 inch behind the shoulders of the midline. Group 2 was similarly injected with 0.05 ml of a 20% slurry of Zirconium Silicate. Groups 3 and 4 were injected with 0.05 ml of a 20% solution of sodium zirconium lactate and a 20% slurry of flour of pumice. All animals were killed 1 week after the injections and tissue samples for histological sections were taken at each injection site. An identical study with the same experimental procedures as the above study used adult male guinea pigs. In each species, saline injections produced no effect, Zirconium Silicate caused minimal toxicity, and sodium zirconium lactate plus pumice was toxic. The results from these two studies are listed in Table 17.

The results pertain to both the rat and guinea pig studies. Zirconium Silicate deposits were described as well circumscribed masses of particulate material surrounded by a narrow zone of new connective tissue. Nonspecific muscle damage, without necrosis due to the presence of the particulate matter and the volume of injected material, was localized to the immediate vicinity of the injection site. Macrophages along a border of a mass of Zirconium Silicate had reflective material within their cytoplasm. Dispersed particles were phagocytized by macrophages, with little or no associated inflammatory response. No evidence of bone resorption was found adjacent to periosteal deposits.

In another study by these authors, skin and muscle tissue samples were taken for microscopic examination. Eight adult rats were anesthetized and a deep incision was made on the ventral side of the left rear leg. The incision was made in the quadratus femoris muscle. The animals were exposed to 50 mg of pumice flour, silica dioxide, and Zirconium Silicate, respectively. Insertion of the appropriate substance was made into the muscle

TABLE 17
Toxic reactions to injected Zirconium Silicate (Stookey et al. 1967)

Animal species	Agent injected	Concentration (%)	Degree* of tissue reaction			
			Oral mucosa	Subcutaneous tissues	Periosteal tissue	Intramuscular tissue
Rat	Saline		0	0	0	0
Rat	Zirconium Silicate	20	+	+	0	+
Rat	Sodium zirconium lactate and pumice	45 and 20	+++	+++	+++	+++
Guinea pig	Saline		0	0	0	0
Guinea pig	Zirconium Silicate	20	+	+	+	+
Guinea pig	Sodium zirconium lactate and pumice	45 and 20	+++	+++	+++	+++

*0 = reaction absent.
+ = mild inflammatory reaction of little consequence.
++ = mild reaction with granulomatous response.
+++ = destructive granulomatous reaction.

TABLE 18
Toxic reactions to implantation of Zirconium Silicate in muscle tissue (Stookey et al. 1967)

Agent embedded in muscle	Amount (mg)	Degree of tissue reaction*	
		Subcutaneous tissue	Intramuscular tissue
Pumice	50.0	+	+
Silica dioxide	50.0	++	+++
Zirconium Silicate	50.0	+	+
Control		0	0

*0 = reaction absent.
+ = mild inflammatory reaction of little consequence.
++ = mild reaction with granulomatous response.
+++ = destructive granulomatous reaction.

incision and into the skin 1 cm lateral to the muscle incision. Control animals had the same muscle incision, but no foreign material was inserted. One animal from each group was sacrificed 10 days following surgery. The remaining animals were sacrificed 30 days from the incision. All tissue was fixed and prepared for microscopic examination. Table 18 presents the data from this experiment.

Adjacent tissues were free of inflammation or evidence of injury at 10 and 30 days. Deposits of Zirconium Silicate were identified and were surrounded by a narrow zone of new connective tissue. No necrosis was identified (Stookey et al. 1967).

Short-Term Parenteral

Attapulgite

Pott et al. (1987) conducted a study in which three samples of Attapulgite labeled Georgia, Lebrija, and Morimoiron were injected intraperitoneally to study their carcinogenic effects in rats. Each sample was injected one time each week for 9 weeks at 60 mg per injection. The number of female Wistar rats for each of the samples (Georgia, Lebrija, and Morimoiron) was 112, 115, and 114, respectively. Fiber analysis was made of each of the samples Morimoiron, Georgia, and Lebrija. The <50% fiber length was 0.7, 0.5, and 0.8 μm, respectively, and a <50% fiber diameter of 0.07, 0.07, and 0.04 μm, respectively. Some rats died spontaneously or others in poor health were killed. Surviving animals were killed 2.5 years after treatment for necropsy. At necropsy, neoplasms or organs with suspected neoplasm tissue were fixed for microscopic examination. These three samples were noncarcinogenic. The results are presented in Table 19.

In another experiment by the same investigators, a fourth sample of Attapulgite from Caceres was tested. Intraperitoneal injections of 2, 4, and 4 mg were administered consecutively for 3 weeks. The fiber length and diameter of this sample were <50% 1.3 and 0.07 μm, respectively. Animals in poor health were killed. Surviving animals were killed 2.5 years after treatment for necropsy. At postmortem examination, parts of neoplasms or organs with suspected neoplasm tissue were fixed for microscopic examination. The results were considered moderate in relation to the dose. The Caceres Attapulgite sample results are also presented in Table 19 (Pott et al. 1987).

Kaolin

Toxicity of some of the minerals present in coal-mine dust was examined by Martin, Daniel, and Le Bouffant (1975). Five hundred female SPF Sprague-Dawley rats were divided into groups each with 10 animals. The rats were exposed over a period of 3 months to 50-mg/rat intratracheal instillations of Kaolin. The following assessments were made: weight of the fresh lungs; macroscopic and microscopic lesions in the lungs; amount of collagen and dust present in the lungs; and calculation of the toxicity index from the amount of collagen formed per mg of dust. The weight of fresh lungs subjected to Kaolin was 1.76 g. Collagen formed per lung was 23.9 mg. The dust per lung was 30.2 mg and the collagen/dust ratio was 0.79. Microscopic examinations of the lungs showed no alveolar proteinosis but Kaolin was detected in the bronchiolovascular lymphoid sheaths. No information regarding nonexposed lungs was presented. The opinion of the investigators was that exposure to

TABLE 19
Carcinogenic effect of intraperitoneal injection of Attapulgite from four sources (Pott et al. 1987)

Attapulgite sample source	No. of rats	% of rats with tumors	Lifespan (weeks) after treatment of					
			All rats				Rat with tumors	
			Time to death for <20% of all rats	Time to death for <50% of all rats	Time to death for <80% of all rats	All rats dead by this time	Time to death of first rat with tumor	Average time to death of rats with tumors
Mormoiron	114	3.5	92	116	138	164	47	92
Lebrija	115	3.5	95	116	134	164	98	114
Georgia	112	3.6	89	108	129	163	75	100
Caceres	30	40.0	94	109	132	142	74	116

Kaolin results in "pulmonary toxicity" and possesses "fibrogenic capacity" (Martin, Daniel, and Le Bouffant 1975).

Magnesium Silicate

An emulsion of Magnesium Silicate, 500 mg in 1 ml of saline, was injected subcutaneously into groups of 10 female Wistar rats once daily at 2, 4, 6, 13, or 20 days. As controls, 12 nontreatment rats were killed on the first experimental day and 12 rats were injected with 1 ml of saline once daily for 20 days. The trabecular bone, sinusoids, and hematopoietic cells were processed for microscopic examination. No significant change in the volume percentage of hematopoietic cells, sinusoids, or trabecular bone was present in the day-2 treatment group. After 4 days of treatment, the volume percentage of hematopoietic cells increased rapidly, sinusoids decreased rapidly, and trabecular bone decreased gradually. The volume percentage of hematopoietic cells was about 2.6 times normal, and that of sinusoids and trabecular bone was about 30% and 60% of normal, respectively, after 20 days of treatment. The tibia metaphyses had the following changes after 4, 6, 13, and 20 days of treatment; sinusoids were compressed by the markedly proliferated myelocytic element and severely narrowed the distance between the sinusoidal wall and the surface of trabecular bone was markedly increased. Atrophy of the thin trabecular bone was seen but no significant changes in osteocytes, osteoblasts, or osteoclasts were seen (Shibayama, Nishioto, and Nakata 1993).

Zeolite (Clinoptilolite)

Three intrapleural injections of 20 mg of Clinoptilolite were given in monthly increments to a group of 44 male and 49 female rats. Control animals received only saline injections. The Zeolite sample was described as having the formula: $(Na,K)\ Ca[Al_6Si_{30}O_{72}] \cdot 20H_2O$, with Cu, Pb, Zn, Ni, Co, Mo, Mn, Ti, Sr, Ba, and Hg contamination. Particle size measurements were recorded as follows: $<3\ \mu m$, 6.5%; $5\ \mu m$, 5.9%; $10\ \mu m$, 5.9%; 10–30 μm, 20.6%; 30–100 μm, 35.1%; 100–500 μm, 26.1%. Pulmonary lymphosarcomas, pleural and abdominal lymphosarcomas, and lymphatic leukemias were observed in 47/93 treated animals and 5/45 saline-treated animals. No mesothelioma or pulmonary neoplasms were observed in the controls. Mesothelioma and bronchial carcinoma were detected in 2/93 and 1/93 treated animals, respectively (Pylev et al. 1986).

Zeolite (Phillipsite)

Three intrapleural injections of 20 mg of Phillipsite given in monthly increments were administered to a group of 44 male and 49 female rats. Control animals received only saline injections. The Zeolite sample was described as having the formula: $(Na_{1.38}K_{0.53}Ca_{0.87}Mg_{0.25})(Si_{11.93}Al_{4.03}O_{32}) \cdot 9H_2O$. Particle size measurements were recorded as follows: $<5\ \mu m$, 14.5%; 10–30 μm, 32.8%; 50–70 μm, 16%; $\geq 100\ \mu m$, 36.7%. Neoplasms were found in 41/101 Zeolite-treated rats (50 tumors). Tumor types included 1 pleural mesothelioma, 2 pulmonary adenocarcinoma, 29 hemoblastosis, 7 mammary gland neoplasms, and 11 neoplasms found at other sites. In control animals, 16 neoplasms (pulmonary, pleural, and abdominal lymphosarcomas, lymphocytic leukemias, and mammary gland neoplasms) were identified in 14/52 rats (Pylev et al. 1986).

Zirconium Silicate

Harding (1948) reported results when an adult rabbit received intravenously four doses over 1 week of a 5-ml suspension of a 10% solution of Zircon. The animal was killed 33 weeks later. At microscopic examination revealed small clumps of crystals were close to the portal tracts of the liver. The clumps were in the Kupfer cells. Fibrosis was detected. Small clumps of crystals were also observed in the spleen and alveolar walls and spaces of the lungs.

In another study in this report, six young rats were injected intratracheally with 1 ml of a 10% solution of Zircon. Three rats were killed after 7 and 9 months. The lungs were radiographed and sectioned for microscopic examination. Much of the material was found free within the alveoli and lymph vessels of the lungs. A small amount was found within phagocytic cells. Swollen histiocytes were seen in a few alveoli. Fibrosis was not evident (Harding 1948).

Inhalation

Attapulgite

Wagner, Griffiths, and Munday (1987) exposed 40 (20 male and 20 female) SPF Fischer rats to Attapulgite dust in an inhalation chamber. The rats were exposed to two samples of Attapulgite (named by the region in which they were mined, Lebrija and Leichester) at a concentration of 10 mg/m^3 for 6 h/day for 5 day/week until they were killed. At 3, 6, and 12 months, four animals were killed. All remaining rats were allowed to live their life span. All animals were subject to necropsy; the lungs, liver, spleen, kidneys, and other relevant organs were examined microscopically. Mineralogical analysis, examination of ashed lung sections and examination of macerated lung tissue, were also performed. Kaolin, the negative-control dust, and Chrocidolite UICC, the positive-control dust, were also administered at a dose of 10 mg/m^3.

At microscopic examination, one peritoneal mesothelioma, one adenocarcinoma, and three bronchoalveolar hyperplasia were found in rats treated with Lebrija Attapulgite. Thirty-five rats had no proliferative changes. In rats treated with Leichester Attapulgite, proliferative lesions observed included two mesothelioma, one peritoneal mesothelioma, one malignant alveolar neoplasm, two benign alveolar neoplasms, and eight bronchoalveolar hyperplasias. Twenty-seven rats had no proliferative lesions. Rats exposed to the negative-control Kaolin had two bronchoalveolar tumors. Rats in the positive-control Crocidolite group had one adenocarcinoma and three bronchoalveolar tumors. The mean fibrosis grades of each treatment group are presented in Table 20.

TABLE 20
Toxicity of inhaled Attapulgite dust (Wagner, Griffiths, and Munday 1987)

Dust source	Total no. of rats	Mean fibrosis grade as function of time after exposure			
		3 months	6 months	12 months	24 months
Lebrija Attapulgite	40	3.1	2.6	3.2	3.2
Leichester Attapulgite	40	3.0	3.1	4.0	—
Kaolin	40	2.8	2.75	2.4	2.1
Crocidolite UICC	40	4.1	3.3	3.1	3.8

The classification of proliferative lesions and neoplasms corresponding to the mean fibrosis grades are as follows: (1) bronchoalveolar hyperplasia—no malignant proliferation of the epithelia; (2) benign alveolar neoplasm; (3) malignant alveolar neoplasm; (4) adenocarcinoma; (5) squamous carcinoma; (6) adenosquamous carcinoma; and (7) mesothelioma.

The Lebrija Attapulgite dust extracted from the animal lungs did not have short fibers and the presence of granular material and long fibers. The Leichester Attapulgite dust also had the presence of long fibers. Kaolin is a nonfibrous dust. UICC Crocidolite is a fibrous dust but lengths were not published in this study (Wagner, Griffiths, and Munday 1987).

Calcium Silicate

Bolton et al. (1986) exposed white male Wistar rats to clouds of Calcium Silicate dust at a concentration of 10 mg/m^3 for 7 h/day, 5 days/week, for a total of 224 days over an elapsed period of 12 calendar months. A total of four inhalation chambers were used with 48 animals/chamber. One chamber was reserved for control animals receiving only filtered air. The remaining three chambers were used to test three samples (A, B, and C) of Calcium Silicate. Twelve rats were killed from each of the chambers at the end of the dusting period. The final surviving animals were killed at the end of 19 months after exposure. At necropsy, tissue samples and one lung were taken from all major organs for microscopic examination. The other lung was taken for lung-dust analysis. The lung was dried and prepared for infrared analysis. Blood samples were taken 5 days prior to the start of the exposure and 3 days after the exposure.

All Calcium Silicate–treated groups had dust-containing macrophages scattered throughout the alveolar regions of the lung at the end of the exposure period. Occasional fibers were seen in animals with exposure to the Calcium Silicate 3. The frequency of dust-containing macrophages declined at the end of the dust exposure. Fewer dust-containing cells were in animals exposed to samples C than A or B. The number of animals with interstitial fibrosis for samples A, B, C, and controls were three, five, five, and five, respectively. In all cases, the alveolar septa were thickened with abnormal deposits of reticulin and in old animals with collagen. Although most cells were relatively flat in some areas, some cells were cuboidal and had the appearance of adenomatosis. Peribronchiolar fibrotic areas were close to the respiratory bronchioles and small granulomatous nodules with macrophages and fibroblasts were seen in rats exposed to sample A. Mediastinal lymph nodes from all treated animals showed no particulate material at the end of exposure. Small primary neoplastic lesions were found in two animals exposed to sample B. One lesion was described as a small squamous cell carcinoma and the other as an adenoma. No pathological changes were observed in all other organs. All examined blood parameters were within normal ranges for both animals studied before and after exposure (Bolton et al. 1986).

Kaolin

Kaolin was used as a negative control in a previous inhalation study. The protocol and results are cited under Attapulgite in this section (Wagner, Griffiths, and Munday 1987).

Zeolite (Synthetic Zeolite A)

A group of 15 male and 15 female Wistar rats were exposed to 20 mg/m^3 of Synthetic Zeolite A for 5 h/day, three times a week for 22 months. The Zeolite was characterized by $(Na_{12}(Al)_2)(SiO_2)_{12}\cdot 27H_2O$ and consisted of particles ranging from 0.5 to 10 μm. Thirty untreated males were the control group. Histopathological examinations of the trachea and the lung were completed. Moderate to extensive respiratory disease was seen in treated and control groups. No neoplasms were observed in any group (Gloxhuber et al. 1983).

In another study by Gloxhuber et al. (1983), a chronic inhalation study of Zeolite A batch F 325 dust was conducted. Groups of 15 male and 15 female hamsters and 15 male and 15 female rats were exposed for 5-h periods three times a week for 12 months for hamsters and 22 months for rats. Control animals were exposed to untreated air. The trachea and lungs of the animals were examined microscopically. Microscopic examination was limited to the trachea and lungs of 10 treated hamsters and 8 controls and to 10 treated rats and 5 controls due to deaths caused by a specific infection. Both species had moderate signs of respiratory disease in the treated and controls. In Zeolite-exposed hamsters, macrophages with accumulations of foreign material were found, mainly in alveoli. No other lesions of inflammation or connective tissue reactions were seen. Rat lungs had grey-white deposits in macrophages of the alveoli and the peribronchiolar lymph nodes near the hilus. Isolated

clay deposits were found in the mediastinal lymph nodes but no reactions were seen about the deposits.

Zeolite (Synthetic Nonfibrous Zeolite)

Groups of 20 male and 20 female Fischer 344 rats were exposed in inhalation chambers to a mean respirable dust concentration of 0 or 10 mg/m^3 of a Synthetic Nonfibrous Zeolite. Exposures were for 7 h/day, five days/week for 12 months. All animals were observed for their life span. Three males and three females per group were killed at 3, 6, 12, and 24 months after exposure. Erionite and UICC crocidolite were used as positive controls. The mean survival time for animals exposed to the Zeolite was 797 days, 504 days for animals exposed to erionite, 718 days for animals exposed to UICC crocidolite, and 738 days for untreated animals. One pleural mesothelioma and one pulmonary adenocarcinoma were seen in Zeolite-exposed rats. No neoplasms were found in controls; 27 mesotheliomas were found in erionite-treated rats and 1 squamous-cell carcinoma of the lungs was found in UICC crocidolite-treated rats (Wagner et al. 1985).

Dermal Irritation

Hectorite

A primary irritation study patterned after the Draize method was conducted using six white rabbits. Either a 0.5-ml or a 0.5-g sample of Hectorite was applied to two sites, one on abraded skin, and the other on intact skin of the backs of the rabbits. The test sites were occluded for 24 h. At the end of the 24 h, the binders were removed and the sites were gently wiped clean. One-half hour later, the sites were examined and scored for erythema and edema. The sites were examined again at 72 h. The average score was 0.0 and the test subject was nonirritating to the skin of rabbits (FDRL Inc. 1980a).

Magnesium Aluminum Silicate

VEEGUM (2 g) was applied daily to the external ears of four rabbits for 10 days. These applications were made to both abraded and intact skin. The abraded skin healed completely within 4 to 6 days after application. No gross effects were noted in any of the animals. No tissue was taken for microscopic examination (Munch 1944).

VEEGUM was applied to the closely clipped intact and abraded abdominal skin of two groups of four rabbits each. A nonabsorbent paper binder was place onto the treated area. The dose was 3.4 g/kg of body weight. After 24 h, the binder was removed and any residual test material was removed by washing. Dermal irritation was recorded at 24 h and once daily after application for 7 days. All the animals were killed and necropsy was performed. No deaths and no systemic toxicity occurred from percutaneous absorption. The acute dermal LD_{50} was >3.5 g/kg of body weight. Dermal irritation generally consisted of moderate erythema and slight edema. The edema completely subsided within an additional 24 h, and erythema completely subsided in all animals between days 2 and 4. No major necropsy findings were reported (Hazelton Laboratories, Inc. 1968).

Eight male white rabbits were used in a primary skin irritation test with a solution of 4% MAS; 0.3 ml of the test substance was applied to the intact and abraded skin of the backs of four rabbits. The test substance was applied under occlusive patches for 24 h. The plaster was removed 24 h after application and the skin reactions were evaluated at 24 and 72 h. The primary irritation index was 0.1, suggesting that Magnesium Aluminum Silicate is a weak primary skin irritant (CTFA 1970a).

Three male guinea pigs were used in a cumulative skin irritation test with a solution of 4% MAS (in deionized water). The test substance (0.05) was applied to the flank of the animals once daily for 3 consecutive days. Skin reactions were evaluated at 24 h after each application. The cumulative irritation index was 0.0 and MAS had no cumulative skin irritation under the test conditions (CTFA 1970a).

Sodium Magnesium Silicate

CTFA (1970b) reported a study in which eight male, white rabbits were used in a primary skin irritation test with a solution of 4% Sodium Magnesium Silicate (in deionized water). The test substance (0.3 ml) was applied to the intact and the abraded skin on the backs of four rabbits. The test substance was applied under occlusive patches for 24 h. The plaster was removed 24 h after application and the skin reactions were evaluated at 24 and 72 h. The primary irritation index was 0.0, suggesting that Sodium Magnesium Silicate has no primary skin irritation under these test conditions.

CTFA (1970b) reported that three male guinea pigs were used in a cumulative skin irritation test with a solution of 4% Sodium Magnesium Silicate (in deionized water). The test substance (0.05 ml) was applied the flank of the animals once daily for 3 consecutive days. Skin reactions were evaluated at 24 h after each application. The cumulative irritation index was 0.0 and Sodium Magnesium Silicate had no cumulative skin irritation under the test conditions.

Ocular and Mucosal Irritation

Bentonite

Preparations of Prophypaste, Bentonite, tragacanth, trypsin, and sterile water were injected either intralamellarly or directly into the anterior chamber of six adult New Zealand rabbits at concentrations ranging from 1 to 5 mg/ml. No significant reactions were recorded with sterile water, Prophypaste, tragacanth, or combinations of tragacanth and Bentonite. Bentonite caused severe iritis after injection into the anterior chamber, but no corneal or retrocorneal reaction was noted grossly or microscopically. In five of the eyes where Bentonite was injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were observed within 2 to 5 days. The sixth eye had no reaction, only 0.1 ml of 0.25 mg/ml was injected. Anterior chamber taps of the eyes showed viscous mucopurulent material. Microscopic sections showed pseodoeosinophils, retrocorneal membranes,

and fibrovascular membranes in the anterior segment. Polarized light revealed highly birefringent particles were found at the injections sites, but not in the retrocorneal masses (Austin and Doughman 1980).

Hectorite

A primary eye irritation study using nine New Zealand white rabbits was carried out according to the Wolcott Procedure. A 0.1-ml liquid or semisolid (100 mg of the solid) sample was instilled into the one eye of each rabbit. Six of the nine animals' eyes were not rinsed and the eyes of three of the animals were rinsed approximately 4 s. All untreated eyes served as controls. The eyes were then examined with sodium fluorescein and an ultraviolet lamp at 24, 48, and 72 h and at 7 days. The mean score at 24 h was 2.0. All subsequent scores were 0.0. The test sample was considered moderately irritating to rabbit eyes without rinsing and practically nonirritating to the eyes with rinsing 4 s after instillation (FDRL Inc. 1981).

Magnesium Aluminum Silicate

Hazelton Laboratories, Inc. (1968) made a single application of 100 mg of VEEGUM or 0.1 ml of a 50% weight/volume to rabbit eyes. An aqueous suspension was made into the conjunctival sac of the left eye of each of six (undiluted) and three (50% suspension) rabbits. Three eyes (undiluted) were washed for 4 s after application and the remaining six eyes were not irrigated but held closed for 1 s. Control rabbits were not treated. Observations were made at 1, 4, 24, 48, and 72 h and at 4 and 7 days following application. Irritation was graded according to the Draize system. On day 7, the eyes were treated with 2% sodium fluorescein strain to provide evidence of corneal damage. Irritation generally consisted of moderate conjunctival hyperemia in all eyes and slight iritis in five of the eyes (one in the nonirrigated, undiluted group and two in each of the other groups). In the nonirrigated eye treated with the dry material, the iritis persisted until 72 h, whereas it was only present at the 1- and 4-h observations in the other eyes. The irritation gradually subsided completely in all within 2 to 4 days. The sodium fluorescein test was negative for corneal damage.

CTFA (1970a) reported that three male, white rabbits were used in an eye irritation test using a 4% solution of MAS. The test substance (0.01 ml) was instilled into the conjunctival sac of one eye of the animals without irrigation. Acute reactions were evaluated at 1 and 4 h, and 1, 2, 3, 6, and 7 days after application according to the Draize scoring system. The average irritation score at the time of maximum score (1 h) for the cornea, iris, and conjunctivae was 0, 0, and 6.7, respectively. The average total score was 6.7 suggesting that MAS produced minimal eye irritation under these test conditions.

Sodium Magnesium Silicate

Three male, white rabbits were used in an eye irritation test using a 4% solution of Sodium Magnesium Silicate (in deionized water). The test substance, 0.1 ml, was instilled into one eye of the animals without irrigation. Eye reactions were evaluated at 1 and 4 h, and 1, 2, 3, 6, and 7 days after application according to the Draize scoring system. The average irritation score at the time of maximum score (1 h) for the cornea, iris, and conjunctivae was 0, 0, and 6.0, respectively. The average total score was 6.0, suggesting that Sodium Magnesium Silicate had minimal eye irritation under these test conditions (CTFA 1970b).

Zeolite (Zeolite A)

In an acute ocular study, rats tolerated a single dose of 10 g of Zeolite A without any adverse reaction (Gloxhuber et al. 1983).

Zirconium Silicate

Gingival tissue was histologically examined in a study conducted by Stookey et al. (1967). Six weanling albino rats were given an oral prophylaxis using a paste containing 75% Zirconium Silicate and 25% distilled water. The animals were anesthetized and given a routine prophylaxis for 30 s per mandibular hemijaw. Three of the animals were killed 1 h following treatment. The other three animals were killed 24 h following treatment. Gingival tissue of the buccal surface of the mandibular molar areas were removed for microscopic examination.

No unusual tissue response was observed in either group. At 1 h, scattered particles of Zirconium Silicate were noted on the surface of the gingiva. Occasional particles could be identified in the superficial epithelium. Only an occasional mild local inflammatory response was noted in the subepithelial tissue. It was presumed to be secondary to the prophylaxis procedure (Stookey et al. 1967).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Calcium Silicate

FDRL Inc. (1973) conducted a study in which adult, Dutch-belted female rabbits were artificially inseminated and received oral intubations of Calcium Silicate at doses of 250, 500, 750, 1000, 1250, 1500, and 1600 mg/kg on days 6 through 18 after insemination. On day 29, cesarean section was performed and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of live pups were recorded. The urogenital tracts of the animals were examined in detail. All fetuses underwent detailed gross examination. Calcium Silicate administered at 1600 mg/kg to pregnant rabbits for 13 consecutive days had no clear discernible effect on nidation or on maternal or fetal survival. Skeletal or soft tissue abnormalities did not differ from the number occurring in control groups.

Kaolin

Groups of 12 Sprague-Dawley female rats were fed three diets: control diet, 20% Kaolin diet, or iron-supplemented 20% Kaolin diet. The diets were fed for 37 to 86 days, 69 to 85 days, and 96 to 117 days prior to fertilization. These same diets were fed for the duration of the gestation period. The animals fed

the 20% Kaolin diet had significant reductions in hemoglobin, hematocrit, and RBC numbers, indicating maternal anemia. Significant reduction in the birth weight of the pups was observed. Animals fed the iron-supplemented diet maintained their hematocrit, hemoglobin, and RBC levels (Patterson and Staszak 1977).

Magnesium Aluminum Silicate

According to Sakai and Moriguchi (1975), "MAS has neither teratogenic nor had adverse effects on the mouse fetus." MAS was administered at doses of 600, 3000, and 6000 mg/kg/day orally to pregnant mice (ICR-JCL) for 6 days on the 7th to 12th day of gestation. No significant differences between MAS-administered and control groups were observed in body weight gain, gross lesions, implantations, resorbed or dead fetuses, or growth inhibition of live fetuses. Incidences of skeletal anomalies were significantly greater in MAS-exposed fetuses, but none resulted in skeletal malformation. Development, external differentiation, body weight gain, and behavior were normal in all offspring.

Zeolite (Type A)

Type A Zeolite containing 15.8% sodium 19.0% silicon, and 20.1% aluminum was tested for its teratogenic potential by Nolen and Dickerman (1983). Sprague-Dawley rats and New Zealand rabbits were utilized under the standard FDA Segment II protocol. Zeolite A in distilled water was given to rats by gavage at concentrations of 74 or 1600 mg/kg of body weight on days 6 to 15. Rabbits were given doses of 74, 345, and 1600 mg/kg of Zeolite A by oral gavage on days 6 to 18. Vehicle controls were included but no details were provided. Type A Zeolite produced no adverse effects on the dam, embryo, or fetus in either the rats or rabbits at any dose.

Zeolite (Clinoptilolite)

Pond and Yen (1983a) investigated whether Clinoptilolite offers protection against the toxic effect of long-term cadmium ingestion by examining the effects of long-term ingestion of Clinoptilolite on reproduction and on the postnatal development of the progeny. Four groups of female Sprague-Dawley rats were fed the following diets: control; control and Clinoptilolite; control plus cadmium; and control plus cadmium and Clinoptilolite. At 13 weeks, male rats were placed with the females for mating. The female reproductive performance was unaffected by any of the various diets. The supplemental level of Clinoptilolite resulted in reduced body weight during gestation; body weight at parturition and postpartum was similar for rats of all diet groups.

GENOTOXICITY

Attapulgite

DNA damage caused by Attapulgite was evaluated through the measurement of unscheduled DNA synthesis (UDS) in a study conducted by Denizeau et al. (1985b). Hepatocytes taken from male Sprague-Dawley rats were prepared according to the collagenase perfusion technique. Attapulgite fibers were added at concentrations of 1 and 10 μg/ml to the primary cultures 2 h after the cells were seeded. 2-Acetylaminofluorene (AAF), a known UDS-inducing agent of rat hepatocytes, was added to the cultures at 0.05 and 0.25 μg/ml for each concentration of Attapulgite. Therefore, Attapulgite was used alone in this UDS assay system or in combination with AAF. The cultures were incubated for 20 h. Labeled thymidine was added to final concentration of 4 μCi/ml. The amount of thymidine in the DNA was evaluated by liquid-scintillation counting. Cytotoxicity was also measured in this study by measuring LDH activity using a spectrophotometer.

A significant increase in [^{3}H]-thymidine incorporation took place with the addition of AAF (0.05 and 0.25 μg/ml). However, at both Attapulgite concentrations, no significant increase in DNA-specific activity was observed. No alteration occurred in the UDS (induced by AAF) by secondary agents when both the fibers and AAF were applied. No statistically significant fiber effect of AAF-fiber interaction was recorded. Extracellular LDH activity was observed after 20-h incubations of Attapulgite at 1 and 10 μg/ml applied to the cells. No significant differences were found between the LDH activity in the treated samples versus the controls (Denizeau et al. 1985b).

Beck and Bignon (1985) tested Attapulgite and UICC chrysotile asbestos B for UDS in primary hepatocyte cultures. Attapulgite fibers (96%) averaged 0.8 μm in length. Cells were also exposed to AAF alone and mixed with fibers. Within 20 h, both types of fibers were found in various cell structures, i.e., plasma membrane invaginations, cytoplasmic vacuoles, and phagolysosome-like components. Chrysotile B and Attapulgite did not induce a significant UDS response or modulate the response to AAF.

The UDS and cellular growth was studied utilizing rat pleural mesothelial cells (RPMCs) in a study conducted by Renier et al. (1989). RPMCs were cultured to confluence on glass coverslips in multiwell plates. Concentrations 2, 4, and 10 μg/cm^2 of Attapulgite and [^{3}H]-thymidine were added to cultures for 20 h. UDS was not modified at concentrations of 2 and 4 μg/cm^2 of Attapulgite. However, in one experiment, 10 μg/cm^2 produced a significant increase in UDS. Cellular growth was measured by counting in situ with an inverted phase-contrast microscope after 24 h of treatment of 1, 2, 4, and 10 μg/cm^2 of Attapulgite. Results were similar to that of the UDS. Attapulgite was considered noncytotoxic at concentrations of 1, 2, and 4 μg/cm^2. However, at 10 μg/cm^2, cell growth was inhibited. No specific details were given.

Adachi et al. (1992) studied the effect of asbestos fibers on DNA by measuring the yield of 8-hydroxy-2′-deoxyguanosine (8-OH-dGuo). 8-OH-dGuo is an OH adduct at the 8-position of a guanine base thought to induce an AT-to-GC transversion in DNA which may lead to a point mutation. For comparison purposes, Attapulgite was also studied. Results for

Attapulgite were not different from controls (Adachi et al. 1992).

Calcium Silicate

Litton Bionetics, Inc. (1974) conducted a study in which FDA compound 71-41, hydrated Calcium Silicate, was suspended in 0.85% saline at concentrations of 1000, 500, 200, 100, and 10 μg/ml and applied to WI-38 cells in a logarithmic phase of growth. The cells were observed for cytopathic effects (CPEs) and the presence of mitosis at 24 and 48 h. Inhibition of mitosis was observed at all concentrations except 100 and 10 μg/ml. A closer range of concentrations, 200, 150, 100, 75, and 50 μg/ml, were employed and tested for the same findings. Mitosis was stopped only in the cells dosed at 200 μg/ml.

FDA compound 71-41, hydrated Calcium Silicate, was also tested for mutagenic properties in a host-mediated assay using the microorganisms *Salmonella* TA-1530 and G-46 and *Saccharomyces* D3. These experiments were carried out in mice orally administered (acute and subacute) 15, 150, and 1500 mg/kg of Calcium Silicate. No increased mutation frequencies were seen in *Salmonella* TA-1530 or G-46. *Saccharomyces* D3 had no significant increase in recombinant activity. In fact, a reduction in recombinant activity was produced by the compound. In a second host-mediated assay, Calcium Silicate was administered at 5000 mg/kg to mice against *Salmonella* TA-1530 and G46 and *Saccharomyces* D3. All tests were negative.

Cytogenetic studies in vivo examined bone marrow cells arrested in C-metaphase from rats exposed to FDA compound 71-41, Calcium Silicate. Rats were administered 15, 150, and 1500 mg/kg doses. The positive-control was triethylene melamine (TEM) and the negative-control was saline. The chromosomal abnormalities observed in the positive-control animals were significantly greater than those of either the negative control or the compound. The maximum effect of the positive control was observed at 48 h after administration. Calcium Silicate produced breaks in the range of 1% to 3% in all three acute dosage levels. However, these were not significantly higher than the negative controls. The subacute dose of 150 mg/kg produced breaks at 3%. The negative-control breaks were consistent with those of other experiments.

These same cytogenetic tests were observed in vitro. Cells (not specified) were observed in anaphase for chromosomal aberrations such as bridges, psuedochiasmata, multipolar cells, acentric fragments, etc. Doses of Calcium Silicate were as follows: 1.0, 10.0, and 100.0 μg/ml. Controls, both positive and negative, were the same as reported above. The positive control produced significantly greater percentages of chromosomal aberrations than the negative control or test compound. There were no aberrations observed due to Calcium Silicate.

In a third cytogenetic test, Calcium Silicate was administered to male rats in one dose and in five doses of 5000 mg/kg. A positive-control, TEM, and a negative-control, saline, were also tested. Metaphase spreads were prepared from the bone marrow cells of these animals and scored for chromosomal aberrations. Neither the variety nor the number of the aberrations differed significantly from the negative controls. Calcium Silicate was nonmutagenic.

Dominant lethal assays were carried out in male rats administered FDA compound 71-41, hydrated Calcium Silicate, at doses of 15, 150, and 1500 mg/kg, both as one dose and as five doses. Also tested were the negative saline control and a positive TEM control. This assay measures the amount and type of fetal wastage that may occur following administration of a potential mutagen. Each treated male rat was mated with two virgin female rats each week for eight (acute) or seven (subacute) doses. Two weeks after mating, the female rats were sacrificed and the fertility index, preimplantation loss, and lethal effects were determined and compared with the same parameters calculated from the negative and positive controls. No significant findings were observed in the fertility index or preimplantation loss. The test compound was also administered at a dose of 5000 mg/kg. The protocol was the same as listed above. All parameter values did not differ significantly from that of the negative control. Comparing the data of both experiments indicates that hydrated Calcium Silicate does not induce dominant lethal mutations (Litton Bionetics, Inc., 1974).

Hectorite

Hectorite suspended in dimethylsulfoxide (DMSO) at concentrations of 10 to 3000 μg/plate was subjected to spot test using five mutant strains of *Salmonella typhimurium* LT2, hisTA98, hisTA100, hisTA1535, hisTA1537, and hisTA1538, with and without metabolic activation. Positive controls were carried out utilizing Aroclor 1254. Hectorite was nonmutagenic in all five test strains (Inveresk Research International 1995).

Magnesium Aluminum Silicate

MAS was subjected to spot test using five mutant strains of *S. typhimurium* LT2, hisTA98, hisTA100, hisTA1535, hisTA1537, and hisTA1538. Positive and negative controls were carried out utilizing S9 mitochondrial preparations from the livers of Sprague-Dawley rats and 2-aminoanthracene. MAS was found to be nonmutagenic in all five test strains (Blevins and Taylor 1982).

Zeolite

Durnev et al. (1993) tested the clastogenic potential of Zeolite particles <10 μm in length in peripheral human blood lymphocytes. Chrysotile fibers were used as a positive control. Both fibers produced statistically significant increases in the percentage of aberrant metaphases, mostly from chromatid breaks. Superoxide dismutase (50 μg/ml) protected against the induction of aberrant metaphases by chrysotile asbestos, but not by Zeolite. However, catalase (20 μg/ml) protected against induction of aberrant metaphases by Zeolite, but not by chrysotile asbestos.

Chromosomal aberrations in cells of C57BL/6 mice were also investigated. The cells were collected by peritoneal lavage and

from the bone marrow of mice and were sampled at 1, 2, 7, and 28 days after the intraperitoneal injection of 100 μg/mouse natural Zeolite particles. Chrysotile asbestos was used as a positive control. The lavage sample contained 20% lymphocytes, 20% to 30% macrophages, and 50% to 60% PMN leukocytes. The injection of the Zeolite induced a statistically significant increase in aberrant metaphases after 7 and 28 days in the peritoneal lavage cells. Chrysotile induced the aberrant metaphases at all times in both the peritoneal lavage and bone marrow cells (Durnev et al. 1993).

Valatina, Pylev, and Lemjasev (1994), tested the clastogenic effect on bone marrow cells of five dust samples from Zeolite tuffs. Presterilized dusts were administered intraperitoneally to BALB/C mice. The known clastogen mitomycin C was used as a positive control and 0.5 ml of saline as a negative control. The animals were killed 24 h after administration and mice bone marrow samples were taken. Polychromatophilic erythrocytes (PCEs), which contain micronuclei that are formed during mitosis on acentric fragments of the chromosomes as a result of clastogenic actions, were counted. Many of the dust samples were as potent a clastogenic agent as mitomycin C. A summary of the results is listed in Table 21.

CARCINOGENICITY

The IARC (1997) has placed Attapulgite fibers >5 μm in Group 2B, *possibly carcinogenic to humans*. Fibers <5 μm *cannot be classified as to their carcinogenicity to humans* and were classified in group 3. The Utrecht University's Institute for Earth Sciences and Vening Meinesz Institute for Geodynamic Research (Englehard 1998) analyzed Engelhard's Attapulgite clay by transmission electron microscopy to determine the fiber length. The transmission electron microscopic analytical results was <5 μm.

TABLE 21
Micronuclei induced by Zeolite tuffs (Valatina, Pylev, and Lemjasev 1994)

Administered substance	Dose (mg/g)	Amount of PCEs with micronuclei (per 1000 PCEs)
Dust 1	2.0	8.33 ± 0.5
	0.8	5.83 ± 0.5
Dust 2	1.4	2.83 ± 0.3
	2.1	3.83 ± 0.6
Dust 3	3.15	0.5 ± 0.8
	1.26	3.8 ± 0.5
Dust 4	2.15	6.7 ± 0.5
	.86	5.2 ± 0.5
Dust 5	3.25	4.83 ± 0
	1.3	3.66 ± 0.5
Mitomycin C	0.16 mg/kg	7.70 ± 0.3
Saline control	0.5 ml	2.70 ± 0.03

Clinoptilolite, Phillipsite, Mordenite, Nonfibrous Japanese Zeolite, and synthetic Zeolites *cannot be evaluated as to their carcinogenicity to humans* (group 3) according to the IARC (1997).

Table 22 is a summary of carcinogenicity data, which were detailed earlier in the section *Animal Toxicology*.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Magnesium Aluminum Silicate

Applications of 2 g of VEEGUM were made to the skin of two human subjects in an 1-inch area daily for 1 week. No effects were noted and no other details were given (Munch 1944).

Inhalation

Aluminum Silicate

Musk et al. (1980) surveyed 17 workers exposed to the Aluminum Silicate dust, alunite. Respiratory questionnaires and occupational history, pulmonary function testing, and posterioanterior chest radiographs were obtained. The alunite chemical analysis was that 48.5% of it was Al_2O_3 and 35.0% was SiO_2. The average age of the subjects was 29.1 years. The mean transfer factor for carbon monoxide (T_L) predicted for the whole group was 85.8% and the mean ratio of T_L to effective alveolar volume (V_A) was 83.8%. The actual group T_L and T_L/V_A was less than predicted. Overall, the group had comparable predicted levels of forced expiratory volume (FEV) in 1 second, vital capacity (VC), and total lung capacity (TLC). Two subjects had small irregular opacities on chest films. Neither of these subjects had previous exposure.

Attapulgite

Churg (1983) surveyed the total pulmonary nonasbestos mineral content in 20 patients who had no occupational dust exposure. The lungs were autopsied and 3- to 5-g pieces were dissolved in bleach and the treated sediment was transferred to a electron microscope grid. Mineral fibers were identified using electron diffraction and energy dispersive x-ray spectroscopy. No correlations were between numbers or types of fibers and age, sex, or smoking. Attapulgite was identified in 12/20 patients and approximately 8400/106000 fibers (7.9%) were Attapulgite. Further mineralogical analysis revealed 100% of the Attapulgite fibers were 1 to 4.9 μm in length.

Kaolin

Churg (1983) surveyed the total pulmonary nonasbestos mineral content in 20 patients who had no occupational dust exposure. The lungs were autopsied and 3- to 5-g pieces were dissolved in bleach and the treated sediment was transferred to an electron microscope grid. Mineral fibers were identified using electron diffraction and energy dispersive x-ray spectroscopy. No correlations were between numbers or types of fibers and

TABLE 22
Summary of carcinogenicity data

Procedure	Dose/concentration	Result	Reference
	Aluminum Silicate		
Single intrapleural injections of four samples into rats (lived life span)	20 mg (0–40 μm)	3 malignant mesotheliomas (1 pleural and 2 peritoneal)	Pigott and Ishmael 1992
	Calcium Silicate		
Single intraperitoneal injections into rats (lived life span)	25 mg	Little dust or dust-related fibrosis was visible; no mesotheliomas	Bolton et al. 1986
Chronic inhalation exposure for 1 year in rats	10 mg/m^3	Interstitial fibrosis, 1 small squamous cell carcinoma, 1 adenoma in lungs	Bolton et al. 1986
	Attapulgite		
Single intraperitoneal injections into rats	25 mg	Tumor incidence rate was 67%	Pott, Huth, and Friedrichs 1974
Single direct pleural application to left pleural surface of rats (killed 2 years later)	40 mg	17/615 of treated rats developed pleural sarcomas	Stanton et al. 1981
Single intrapleural injections into rats (lived life span)	20 mg/ml of 0.9% NaCl (0.77 μm)	No mesothelial neoplasms in either control or treated rats	Jaurand et al. 1987
Single intraperitoneal injections into rats (lived life span)	No concentrations given (fiber lengths ranged from 0 to 25 μm)	46 mesotheliomas	Wagner, Griffiths, and Munday 1987
Single intrapleural injections into rats (lived life span)	20 mg (0.77 μm)	No mesotheliomas	Renier et al. 1989
Single intrapleural injections into rats (lived life span)	0.5, 2, 4, 8, 16, or 32 mg (<1 μm)	2/140 had mesotheliomas	Coffin, Cook, and Creason 1992
3 samples were injected one time each week for 9 weeks into rats (surviving animals were killed at 2.5 years)	60 mg (0.04 to 0.8 μm)	Noncarcinogenic results for all three samples	Pott et al. 1987
Single intraperitoneal injections were administered for 3 weeks in rats (killed at 2.5 years)	2, 4, and 4 mg (1.3 and 0.07 μm)	40% of 30 rats had neoplasms	Pott et al. 1987
Inhalation chamber exposure to rats for 6 h/day for 5 day/week (killed at 3, 6, and 12 months)	10 mg/m^3	2 mesotheliomas, 2 peritoneal mesotheliomas, 1 malignant alveolar neoplasm, 2 benign alveolar neoplasms, 11 bronchoalveolar hyperplasias	Wagner, Griffiths, and Munday 1987
	Zeolite		
Oral administration for 104 weeks in rats	1, 10, 100, or 1000 mg/kg	No incidence of neoplastic changes	Gloxhuber et al. 1983
Single intratracheal instillations into rats (killed at end of study)	30 and 60 mg (< 5 μm)	No significant increase in the incidence of any specific neoplasm	Tatrai and Ungv'ary 1983
Single intraperitoneally injections into mice (10 month study)	10 or 30 mg (< 5 μm)	No neoplastic changes were observed	Suzuki 1982
Single intraperitoneal injection into mice	10 mg (<3 μm)	Mild peritoneal fibrosis but no neoplasms	Suzuki and Kohyama 1984

(Continued on next page)

TABLE 22
Summary of carcinogenicity data *(Continued)*

Procedure	Dose/concentration	Result	Reference
Single intraperitoneal injections into mice (7–23-month exposure)	10 mg (2.24 μm)	No mesotheliomas observed	Suzuki and Kohyama 1984
Single intrapleural injection into rats (chronic study)	20 mg	1 pleural and 1 peritoneal mesothelioma	Wagner et al. 1985
Single intraperitoneal injections into rats (141 weeks)	25 mg	1 peritoneal mesothelioma	Maltoni and Minardi 1988
Single intrapleural injections in rats	25 μm	No difference in tumor incidence between control and treated groups	Maltoni and Minardi 1988
Single subcutaneous injections	25 μm	No difference in tumor incidence between control and treated groups	Maltoni and Minardi 1988
3 intrapleural injections were given in monthly increments to rats	20 mg (3 to 500 μm)	2 mesotheliomas and 1 bronchial carcinoma/93 treated animals	Pyev et al. 1986
3 intrapleural injections were given in monthly increments to rats	20 mg (5 to 100 μm)	Neoplasms were found in 41/101 animals	Pyev et al. 1986
Inhalation exposure to rats for 7 h/day, 5 days/week for 1 year (lived life span)	10 mg/m^3	1 mesothelioma and 1 pulmonary adenocarcinoma	Wagner et al. 1985

age, sex, or smoking. Kaolin was identified in 12/20 patients and approximately 3500/106000 (3.3%) fibers were Kaolin. Further mineralogical analysis revealed 94% of the Kaolin fibers were 1 to 4.9 μm in length.

Morgan et al. (1988) surveyed and studied the prevalence of ventilatory impairment, chest symptoms, and radiographic abnormalities in over 2000 Kaolin workers representing over 95% of the current employees in the industry. Of the participants, 19% admitted having a cough. Of those participants with a cough, 17% had an abnormal FEV and 14% had an abnormal VC. Of those without a cough, 5.5% had an abnormal FEV and 7% had an abnormal VC. Also, 18% of the participants admitted to chronic sputum production. Of those with sputum production, 16% had abnormal FEV, and 12.5% had abnormal VC. Of those without the production, 6% had an abnormal FEV, and 7.5% had an abnormal VC. About 30% of the participants complained of shortness of breath, 3.1% was classified as severe. Wheezing was reported by 29% of the subjects. Satisfactory chest films for 2069 of the subjects were available for examination. Radiographic findings of 90 subjects revealed simple pneumoconiosis. Of these cases, 3.16% had category 2 pneumoconiosis, 1.0% had category 5, and 0.25% had category 3. Eighteen subjects (0.89%) had complicated pneumoconiosis. Of these cases, five had stage A, eight had stage B, and five had stage C. Of men with either case of pneumoconiosis, 51.1% were dry processors, compared to 6.3% of the men who worked in wet processing. Of the nonsmoking participants (549), 542 and 537 men had a satisfactory FEV and forced vital capacity (FVC), respectively, in addition to an acceptable chest radiograph. Of these nonsmoking workers, 516 were studied for dust exposure and pulmonary function. Among the nonsmokers with no pneumoconiosis, those persons working in calcined clay had a greater prevalence of lung function abnormalities. This group had a significant increase in the risk of having an abnormal FEV but tended to have less incidences of pneumoconiosis. In short, ventilatory impairment was related to the presence of complicated pneumoconiosis, employment in clay calcining, and cigarette smoking. Also work in dry processing was associated with a greater risk of developing pneumoconiosis (Morgan et al. 1988).

Waxweiler et al. (1988) evaluated the possible health effects of occupational exposure to Attapulgite. A cohort study of 2302 men employed for at least 1 month at an Attapulgite mining and milling facility was followed through 1975. A significant deficit of mortality from nonmalignant respiratory disease (NMRD) was observed based on age, calendar year, and rates was observed. A marked deficit of NMRD was seen regardless of presumed dust exposure level, induction-latency period, or duration of employment. A statistically significant excess of mortality from lung cancer was observed among whites, but a deficit occurred among nonwhites. Lung-cancer risk in either race was not altered substantially with presumed dust exposure level, induction-latency period, or duration employed, with one exception—those employed for at least 5 years in high-exposure-level jobs. An increased mortality was observed for gastric cancer (six observed) and a deficit due to nonmalignant respiratory disease was observed (nine observed).

The lungs of 62 recently deceased men between the years of 1968 to 1981 were taken for an assessment of the severity

of lung disease (Wagner et al. 1996). Fifty-four of the 62 men worked with china clay or china stone. All the test subjects were employed in the mining industry. Test subjects were divided into groups according to their contact with the minerals: dusty china clay; wet, nondusty china clay; china stone; other dusty environments. The authors of this publication define china clay as "consisting mainly of the mineral kaolinite and in most other countries it is referred to as Kaolin." China stone "consists essentially of a mixture of quartz, feldspars, micas, and amorphous silicon dioxide." Chest radiographs were available for 39 of the 62 cases. Sections of lung tissue were examined microscopically for nodular and interstitial fibrosis and an overall grade ranging from 0 (none) to 3 (severe). Samples from 42 cases were analyzed for mineral content by x-ray diffraction and lung-dust concentrations.

Radiographic lesions included 13 cases of progressive massive fibrosis and 22 cases of simple pneumoconiosis. Only four cases had no evidence of any disease. Nodular opacities tended to reflect a high quartz content, whereas high-Kaolin lung content had interstitial changes and irregular radiological changes.

Mineralological analysis of the 42 cases revealed two separate groups of mineral composition and one miscellaneous group. The china clay group was composed of ≥90% Kaolinite in its samples consisted of 16 cases. The other distinct group, the clay and stone group, was composed of <90%; Kaolinite and greater contents of subsidiary components including quartz comprised 16 cases. The other group had a large variation of mineral composition. Lung-dust concentrations were greatest in the china clay group as shown in Table 23.

The grades of nodular fibrosis ranged in the china clay group from 0 (none) to 2 (moderate—up to 7 nodules/section or nodules of 3 to 6 mm in diameter). In china stone/clay group half, 8 of 16, were grade 3 (severe—more than 7 nodules/section or 6 to 10 mm in diameter). An increasing quartz concentration appears to be related to nodular fibrosis. Interstitial fibrosis in group ranged from 1 (slight—fibrosis located around respiratory bronchioles, which may extend into alveolar ducts and adjacent alveoli, but with areas remaining free of fibrosis between adjacent respiratory bronchioles) to 3 (severe—widespread diffuse fibrosis with few recognizable alveoli; honeycomb may or may not be present). No correlation was found between Kaolinite concentration and interstitial fibrosis grades; however, the china clay group had little exposure to anything but china clay. The degree of interstitial fibrosis appears to be more related to dust lung concentrations, although these results failed to reach statistical significance (Wagner et al. 1996).

TABLE 23
Dust concentrations in lung tissue of deceased men who worked in the mining industry (Wagner et al. 1996)

	Lung dust concentrations (mg/g)		
Mineral group	Minimum	Maximum	Median
China Clay (a)	7.6	289.3	40.0
China Stone/Clay (b)	4.1	44.8	15.0
Miscellaneous (c)	1.6	28.7	6.5

The ACGIH does not classify Kaolin as a human carcinogen and gives a TLV-TWA of 2 mg/m^3 for respirable dust and total dust (ACGIH 1997).

Zhang, Zhang, and Song (1997) reported the results of environmental monitoring and health surveillance performed on 781 Pyrophyllite miners and Pyrophyllite dust carvers from the years of 1954 to 1986. Routine radiographs of the workers lungs were studied for lesions of pneumoconiosis. The PM workers were divided into three groups, manual drillers (A), mechanical dry drillers (B), and mechanical wet drillers (C). The PCM workers were divided in two groups, carvers in factories (A) and carvers working at home (B).

PM workers, group B, had a greater incidence (43.5%) of pneumoconiosis than all other groups. In order to exclude the effect of the duration of exposure (DE), the DE-adjusted prevalence rate was calculated. The DE-adjusted rates are as follows, PM groups, 36.6% and PCM groups, 14.4% of pneumoconiosis (Zhang, Zhang, and Song 1997).

Case Reports

Aluminum Silicate

Sherwin (1979) found abnormal numbers of birefringent particles in the lungs of seven patients: five vineyard workers, one farmer, and one rural resident. A spectrum of early-to-late interstitial inflammation and fibrosis were seen. Nodular granulomas seen in silicosis were absent. Mineralogical analysis revealed mostly silicates, i.e., aluminum and potassium silicate.

Musk, Greville, and Tribe (1980) reported a case of a 42-year-old woman who had no history of previous exposure to Aluminum Silicate dust until she started working at an alunite-residue bagging mill. Chemical analysis of the alunite-residue showed 48.5% of constituents to be Al_2O_3 and 35.0% to be SiO_2. Eight months after working, she noticed the onset of dry cough and shortness of breath. Within 3 months these signs lasted throughout the day. She remained working for 18 months and after leaving work, the cough completely subsided within 3 months. She also complained of pain and morning stiffness in joints, wrists, elbows, and right knee. Corticosteroid treatment was started after a lung biopsy. A chest film taken 3 months after the onset of symptoms had lesions of diffuse small irregular opacities throughout both lungs. Subsequently, pulmonary function tests revealed a decrease in transfer factor for carbon monoxide (TL) and effective alveolar volume (TL/VA) and abnormal transpulmonary pressure–lung volume relationships. Pulmonary lesions included examination interstitial infiltration with small round cells, variable fibrosis, and scattered granulomas. Alveoli were distorted and the granulomas were moderately well formed with multinucleate giant cells and epithelioid histiocytes. After corticosteroid treatment, no increase in severity of the lung lesions was seen.

Calcium Silicate

A 23-year-old man was involved in the bagging process of a food additive. The food additive produced a white thin layer of powder that continuously covered the work floor. An antibiotic, carboxymethylcellulose, and Calcium Silicate comprised the food additive. On the third day of working, the patient experienced an itchy eruption on his face, neck, and forearms. The rash was erythematopapular with no vesicles. The redness was not diffuse and patches of erythema and papules were confluent on the neck and forearms. All signs faded the following morning. The rash occurred again when the patient returned to work. Patch tests were performed using the food additive, an antibiotic, carboxymethylcellulose, and Calcium Silicate. All tests were negative and there were no clinical signs of irritation at the test sites. No late reaction was recorded either. A sample of the food additive was examined under the microscope. Analysis revealed sharp-edged particles corresponding to Calcium Silicate. It was determined that the Calcium Silicate dust caused an "airborne irritant contact reaction." The problem was eliminated by increasing the humidity in the workplace and aspirating the air (Lachapelle 1984).

Bentonite

Phibbs, Sundin, and Mitchell (1971) reported many case studies involving Bentonite workers. Some milling plants had dangerous concentrations of silica that ranged from 2 to 10 times the safe maximal concentration according to the U.S. Bureau of Mines. Silicotuberculosis developed in four patients studied.

Austin and Doughman (1980) reported a 20-year-old dental assistant who noted a foreign body in her right eye after using a drill to polish a patient's teeth with Prophypaste. Immediately she noticed decreased vision and photophobia. Several opaque deposits superficially embedded in her right cornea were removed within 2 h. There was no evidence of corneal perforation or iritis. A residual superficial corneal infiltrate was noted paracentrally. An anterior uveitis developed and was treated. One month after the injury, the cornea was edematous with a superficial, peripheral ringlike stromal infiltrate and a deep inferior stromal infiltrate. A retrocorneal abscess was present. There was no eyelid edema present. Culture results were negative. Anterior segment inflammation, progression of the corneal edema, and an enlarged ring abscess in the corneal stroma continued. There was complete loss of red reflex and iris detail. The diagnosis was infectious endophthalmitis and anterior chamber and vitreous aspirations were performed. No organisms were seen but a few PMN leukocytes were present in the aspirations. These authors undertook the toxicity studies in rabbits presented in the ocular animal toxicity section under Bentonite. They concluded that the similarity of the findings in animals after injection of Bentonite with the findings in this case report suggested that Bentonite was the responsible agent in the dental assistant's symptoms.

Fuller's Earth

Tonning (1949) reported a man having worked in a Fuller's Earth plant as a young man. The length of employment was estimated at no more than 15 years. He was diagnosed with terminal aspiration pneumonia, pneumoconiosis due to Fuller's Earth exposure, bilateral emphysema, and fibrous pleural adhesions. Lesions differed from typical silicotic lesions of the lungs; no formations of the whorled, acellular collagen typical of silicotic nodules were observed. Isolated cavities in the apices were filled with black sludge and surrounded by vascular and cellular collagen. The dust in the lymph nodes had only stimulated the formation of reticulin fibers. No subpleural nodules were present. At mineralogical analysis, the Fuller's Earth deposits were constituted mainly of Montmorillonite (85.2% to 90%).

Sakula (1961) reported two cases of pneumoconiosis due to Fuller's Earth (Table 24). Mineralogical analysis of the Fuller's Earth established Montmorillonite as the major component.

Kaolin

Lynch, Harrison, and Nagelschmidt (1954) investigated two case studies of men who worked in a Kaolin-processing plant for many years. The lungs of the two persons and chest x-ray films were evaluated. The first case was a 36-year-old man who worked on the plant for 17 years. Chest films were taken at the end of his career and detected lesions of extensive confluent consolidation and nodule formation of advanced pneumoconiosis with infection. Autopsy and microscopic findings included alveolar spaces uniformly expanded, three areas of whorled fibrous tissue, scattered areas of cystic spaces, hilar nodes heavily pigmented, deposits of brownish black particulate matter, a large vessel with recent thrombus, hemorrhage, and necrosis, marked fibrous thickening of the pleura, and dense fibrous scarring of the lymph nodes. The final diagnosis was pneumoconiosis (kaolinosis) with pulmonary thrombosis and infarction of the lungs. The second case study was a 35-year-old man who worked in a Kaolin-processing plant for 21 years. Within his last 3 years, he had dyspnea and a slight cough with small

TABLE 24
Pneumoconiosis cases reportedly linked to exposure to Fuller's Earth (Sakula 1961)

Patient	Symptoms
Male who worked in a Fuller's Earth processing plant for 42 years	Fine to medium miliary mottling of both lungs; sputum examinations were negative for *M. tuberculosis*; slowly deteriorating pulmonary function; recurrent bronchitis
Male who worked for 28 years in milling	Chronic cough and sputum; fine miliary mottling throughout both lungs; increasing dyspnea

TABLE 25
Pneumoconiosis cases reportedly linked to exposure to Kaolin (Hale et al. 1956)

Patient	Symptoms	Diagnosis
44-year-old man; worked in a Kaolin mill for 28-years	Cough with thick white sputum; easily dysponeic on slight exertion; well-marked nodulation of silicotic type with coalesence of the nodules in several areas and emphysema	Pneumoconiosis
67-year-old man; worked in china clay bagging for nearly his entire life	Several years of a productive cough; emphysema; massive fibrosis on both sides; no evidence of neoplasm	Pneumoconiosis
44-year-old man; worked in china clay bagging for nearly his entire life	Diffuse nodular mottling with considerable attenuation of the bronchovascular markings	Pneumoconiosis
39-year-old man; worked 14 years with clay	Fine miliary mottling in both lungs; well-marked calcification at the left hilum	Pneumoconiosis
73-year-old man; worked 12 years in open limestone quarries	Small discrete nodular mottling with an increase in the root shadows and the lung markings	Pneumoconiosis
64-year-old man; 43 years loading china clay	Cough and shortness of breath; emphysema; definite nodular mottling	Pneumoconiosis

amounts of dark colored sputum. The sputum was negative for bacteria. Chest films revealed advanced pneumoconiosis with infection, confluent consolidation, nodular infiltration, cavitation, and emphysema. Autopsy and microscopic findings included nodules in the right and middle lobes, pleural spaces were thickened and shaggy, large bulbous emphysematous blebs, a pulmonary artery with organizing thrombus, heavily pigmented hilar lymph nodes, whorled fibrous collagenous tissue, and spaces and walls with macrophages. The final diagnosis was pneumoconiosis (kaolinosis).

Hale et al. (1956) reported six cases of pneumoconiosis due to Kaolin. These are given in Table 25 and not further discussed here.

Butz (1970) reported that a 47-year-old man who was a chronic intravenous drug user died from tetanus. The man had been injecting paregoric, a camphorated opium tincture containing 35 to 46 mg of morphine per 100 ml. Paregoric can be found in proprietary preparations that do not require prescriptions; intravenous drug users often attempt to separate the paregoric from the Kaolin. Often the injection of Kaolin, either through shunts in the lung of an intravenous drug user with obliterative pulmonary arteritis and angiomatoid formations or by extrusion from the arterial lumen and transfer to the pulmonary veins, allows the Kaolin crystals to go into the peripheral circulation. In this patient, numerous skin abcesses were noted on the neck, shoulders, upper extremities, chest, thighs, and lower extremities. In skin sections, the lesions were multiple foreign body granulomata and large birefringent crystals. Adhesions over the pleural surface of the lungs were also noticed. At microscopic examination the lungs had foreign body granulomata within the pulmonary arterioles. Extensive pulmonary edema and masses of pigmented histiocytes filled the alveolar spaces. Extensive periportal fibrosis was seen in the liver. The central nervous system lesions were extremely fine, double refractile particles in nerve bundles entering the anterior roots in the central region.

Herman, Olscamp, and Weisbord (1982), reported a patient with multiple pulmonary Kaolin granulomas. The man had a history of bilateral recurrent pneumothorax. Both pleural spaces were destroyed with a suspension of liquid Kaolin. Recurrent right-sided pneumothorax devolved and reobliteration was again performed. In a follow-up chest radiograph, multiple well-defined peripheral nodules were in both lungs and pathological analysis revealed a bland acellular material surrounded by chronic inflammatory cells. By light microscopy, the particles were consistent with Kaolin. It was presumed that Kaolin entered the lungs through pleuroalveolar or pleurobronchial openings.

Lapenas and Gale (1983) reported that a 35-year-old man who worked at a Kaolin-processing plant for 17 years complained of chest pain and was hospitalized. For the previous 2 years before admittance, the man had packaged dried, processed Kaolin. Chest films revealed diffuse reticulonodular pulmonary infiltrates and a well-defined, noncalcified mass in the upper right lobe. A thoracotomy was performed and an 8 × 12 × 10-cm conglomerate pneumoconiotic lesion containing large amounts of Kaolin was found. X-ray diffraction material from the lesion had peaks corresponding to Kaolinite. The presence of silica was not confirmed by x-ray diffraction.

Lapenas et al. (1984) obtained pulmonary tissue from five Kaolin workers with advanced pneumoconiosis. Chest radiographs detected small irregular shadows and large opacities typical of Kaolin pneumoconiosis. At autopsy, firm, grey-brown nodules and masses were in the parenchyma and in the hilar lymph nodes. Microscopic lesions were extensive pulmonary Kaolinite deposition associated with the formation of peribronchiolar nodules. The nodules were comprised of Kaolinite aggregates transversed by bands of fibrous tissue rather than dense whorled collagen. Kaolin was detected in the lungs. Silica was not detected by either analytical scanning electron microscopy or x-ray diffractometry.

Levin et al. (1996) investigated the death of a 62-year-old man who worked in a cotton textile mill for 43 years. The patient complained of progressive dyspnea and a productive cough. After being admitted to the hospital, a bronchoscopy was performed and no endobronchial lesions were found. A lung biopsy had lesions of severe interstitial fibrosis with bronchioalveolar structures extensively involved in the fibrotic process. Pathological alterations such as bronchiolectasis, interstitial fibrosis with thickening of alveolar septa, mobilization of macrophages, and multinucleated giant cells were identified. Neither ferruginous bodies nor pleural hyaline plaque was identified. Kaolin particles were present with a mean size of 0.88 μm. Chrysotile asbestos was also detected, but the majority of particles were Kaolin. The man died as a consequence of respiratory failure despite an aggressive therapy of antibiotics and tuberculosis therapy.

Magnesium Trisilicate

Lee et al. (1993) reported a case of a 30-year-old female with a long-term history of ingesting trisilicate-containing antacids. The patient had repeated attacks of renal colic but the presence of calculi could not be determined by intravenous pyelography nor ureteroscopy. X-ray diffraction did detect a silicate stone. The patient stopped taking trisilicate containing products. The frequency of stone passage decreased and the renal colic was relieved.

Montmorillonite

A 73-year-old Montmorillonite worker developed signs of pneumoconiosis. A chest radiograph was taken 2 years before his death and a bilateral fine reticulonodular shadowing was observed. The man died of acute gastrointestinal hemorrhage from a benign gastric ulcer. A few weeks before his death another chest radiograph indicated a slight increase in the reticulonodular opacities and a mass at the left hilum and apex. At autopsy, numerous soft stellate grey-black dust lesions 4 to 5 mm in diameter that occupied most of the lungs were found. No lesions of progressive massive fibrosis were identified. Also present were lesions of severe emphysema and a 4-cm diameter neoplasm arising from the bronchus of the left upper lobe. At microscopic examination, numerous interstitial collections of dust-laden macrophages were situated around the respiratory bronchioles and along the adjacent alveolar septa. There was a slight degree of fibrosis associated with the dust lesions and the neoplasm was a poorly differentiated adenocarcinoma containing giant cell areas. Mineralogical analysis showed a large amount of calcium Montmorillonite (Gibbs and Pooley 1994).

Zeolite

Casey et al. (1985) reported a patient living in the Nevada desert who developed extensive pleural thickening and interstitial fibrous associated with the pulmonary deposition of Zeolite. An open biopsy of the right lung and pleura was performed on the 52-year-old man. Mycobacterial and fungal cultures were negative. Histopathological evaluation established lesions of chronic inflammation and fibrosis and presence of many fibrous and nonfibrous particles. The particles were analyzed by SEM and were identified as aluminum silicates. The analytic pattern was characteristic of Zeolites. No asbestos fibers were found and exposure to these fibers was unlikely.

Zirconium Silicate

A nonsmoking 25-year-old woman developed a worsening dry cough and dyspnea after 3.5 years as a tile sorter and glazer. The woman had a history of atopic dermatitis and at age 13 developed pneumonia. An open lung biopsy specimen had lesions of a severe granulomatous interstitial pneumonia with mild fibrosis and numerous very small birefringent crystals around the terminal airways and occasionally in the granulomas. Pulmonary particle analysis established a dust burden almost 100 times the normal. The particles consisted mainly of clay minerals and Zirconium Silicate (Lippo et al. 1993).

SUMMARY

This report provides a review of the safety of Aluminum, Calcium, Lithium Magnesium, Lithium Magnesium Sodium, Magnesium Aluminum, Magnesium, Sodium Magnesium, and Zirconium Silicates, Magnesium Trisilicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite. These ingredients are termed silicates because they contain silicon, oxygen, and one or more metals. Many silicates occur naturally and are mined; yet others are made synthetically.

Typical cosmetic uses of silicates include abrasive, opacifying agent, viscosity-increasing agent, anticaking agent, emulsion stabilizer, binder, and suspending agent. Clay silicates (silicates containing water in their structure) primarily function as adsorbents, opacifiers, and viscosity-increasing agents. Pyrophyllite is also used as a colorant. Current concentrations of use range from as low as 0.01% for Zeolite to a high of 84% for Kaolin. Some ingredients with no uses reported to FDA in 1998 have current concentrations of use reported by the industry, so it is assumed they are in use.

Aluminum Silicate is approved as an indirect food additive in the Code of Federal Regulations (21 CFR 177.2600 and 21 CFR 177.1200). VEEGUM, a tradename for Magnesium Aluminum Silicate, has been designated by the FDA as a raw material with the following number: FD CRMCS no. R0010045 and has an individual Chemical Abstract Registry number, 12199-37-0. According to the European Cosmetic Directive (EU reference no. 391 Annex II), zirconium and its compounds are listed under substances that must not form part of the composition of cosmetic products, with the exception of complexes in Annex III, Part I. IARC has ruled Attapulgite fibers >5 μm as group 2B, *possibly carcinogenic to humans*, and fibers <5 μm as group 3, *not classified as to their carcinogenicity to humans* (IARC 1997). Bentonite is considered GRAS as a direct food additive (21 CFR 184.1155). Kaolin is considered GRAS as an indirect

food additive (21 CFR 186.1256). Pyrophyllite is listed as a naturally occurring color additive in the Code of Federal Regulations (21 CFR 73.1400). The natural Zeolites (Clinoptilolite, Phillipsite, Mordenite, Nonfibrous Japanese Zeolite) and synthetic Zeolites *cannot be classified as to their carcinogenicity to humans* (group 3) according to IARC (1997). Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Trisilicate, Attapulgite, Hectorite, and Kaolin are all used in over-the-counter products.

Hectorite and Montmorillonite catalyzed glycine and diglycine oligomerization reactions; oligomers were formed by self-condensation of both purines and pyrimidines in the presence of Montmorillonite treated with Na^+. Under UV light, adenosine monophosphate molecules were absorbed onto Kaolin and the products were hydrolyzed by phosphodiesterase.

All silicates have the great ability to absorb, especially the clays. Reports describe drugs, bacteria, viruses, and toxins absorbed to clays due to the physical structure of clays and their cationic nature.

No statistically significant absorption of aluminum and elevated levels of silicon were recorded in assayed plasma samples of dogs given Magnesium Trisilicate and Zeolite orally. The urinary excretion of silica was 5.2% in males given 20 g of Magnesium Trisilicate. Ten percent Bentonite in the diets of rats overcame T-2 toxicosis completely. Various Zeolites were added to the diets of pigs. No adverse effects were noted by the supplementation.

A sample of Aluminum Silicate was toxic to pulmonary alveolar macrophages and LDH activity and β-GAL release were increased. Aluminum Silicate had relatively no effect on the hemolysis of rat RBCs. Synthetic Calcium Silicate samples and higher concentrations of Calcium Silicate caused increased hemolysis of human RBCs; a greater fibrous character of Calcium Silicate samples caused increased LDH and β-GAL release. Many clays (Attapulgite, Bentonite, Hectorite, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite) demonstrated cytotoxicity to several macrophage type cell lines and have hemolytic activity towards several species' RBCs. Particle size, fibrogenicity, concentration, and mineral composition had the greatest effect on toxicity. Larger particle size and longer and wider fibers cause more adverse effects. In most of the studies, a dose-dependent effect on cytotoxicity or lysis was observed. Most mineral samples were not 100% pure and many samples already contained toxic dusts or minerals like quartz or cristobalite.

The following are a list of acute oral LD_{50} determinations: Calcium Silicate, 3400 mg/kg in rats; Magnesium Aluminum Silicate, 50000 mg/kg in mice; Zirconium Silicate, >200 g/kg in mice; Hectorite, >5 g/kg in rats; Kaolin, 149 g/kg in rats (death due to bowel obstruction); 15 natural Zeolites, 10 g/kg in rats. In short-term oral toxicity studies, no adverse effects were seen in mice or rabbits dosed up to 5 g/kg Magnesium Aluminum Silicate; beagle dogs and rats fed Aluminum Silicate had no renal lesions. Dogs and rats fed Magnesium Trisilicate for 4 weeks had polydypsia and polyuria, and all dogs had renal cortical lesions. Guinea pigs had renal lesions after 4 months of drinking Magnesium Trisilicate in their tap water. Rats fed 10% Magnesium Aluminum Silicate had slightly elevated silicon levels of the spleen and dogs and rats fed 10% VEEGUM had no negative responses in 90-day feeding studies. No lesions were found in rats dosed up to 1000 mg/kg for 104 weeks.

The following results are from acute parenteral injection studies. Intratracheal injections of Aluminum Silicate caused lesions in a dose-dependent manner and the intrapleural injections of four different Aluminum Silicate samples all resulted in lesions. One aluminosilicate injection caused three malignant mesotheliomas, one pleural and two peritoneal. No mesotheliomas developed in rats injected intraperitoneally with 25 mg of Calcium Silicate dust. Subcutaneous injection into the oral mucosa and into the back, periosteal injections into periosteal tissue, and intramuscular injections into the thigh of rats and guinea pigs with Zirconium Silicate resulted in mild inflammatory reactions. Attapulgite was injected intraperitoneally, intrapleurally, and intratracheally in various studies. Most studies reported that lesions and mesotheliomas were dependent on fiber length. Samples with a longer length caused greater numbers of mesotheliomas. Subplantar injections of Bentonite caused granulomas. Intratracheal injections of Bentonite and group C *Streptococcus* species caused an 85% mortality compared to a 5% control mortality in mice; another intratracheal injection caused loose reticulin fibrils with no collagen. Kaolin injected with the *Streptococcus* species caused statistically significant but modest mortality in mice. In a series of intrapleural injections, Kaolin was used as a negative control. Heat treated Montmorillonite dosed to rats by means of intratracheal instillation was restricted to alveoli within and adjacent to alveolar ducts. Minor inflammatory reactions, but no lesions, were found in rats given intratracheal injections of Clinoptilolite, and intraperitoneal injections of Mordenite, Synthetic Zeolite 4A, and synthetic Zeolite MS5A (one mesothelioma was seen in rats given MS4A). An intrapleural injection of Nonfibrous Japanese Zeolite caused two mesotheliomas in rats.

Small primary neoplastic lesions were found in two rats exposed to a Calcium Silicate sample in an inhalation chamber. The mass of silicate measured in the lungs ranged from 0.1 to 0.8 mg. Lebrija and Leichester Attapulgite samples caused one peritoneal mesothelioma, one adenocarcinoma, and three bronchoalveolar hyperplasia and two mesotheliomas, one peritoneal mesothelioma, one malignant alveolar tumor and eight bronchoalveolar hyperplasia (inhalation route) in rats, respectively. Both samples contained long fibers. Moderate to extensive respiratory disease was noted in rats chronically exposed to Synthetic Zeolite A by inhalation methods.

The acute dermal LD_{50} was >3.5 g/kg for rabbits exposed to VEEGUM. Magnesium Aluminum Silicate (4%) was a weak primary skin irritant in rabbits and had no cumulative skin irritation in guinea pigs. No gross effects were reported in any of these studies. Sodium Magnesium Silicate (4%) had no primary skin irritation in rabbits and had no cumulative skin irritation in

guinea pigs. Hectorite was nonirritating to the skin of rabbits in a Draize primary skin irritation study.

A 4% solution of Magnesium Aluminum Silicate and a 4% solution of Sodium Magnesium Silicate caused minimal eye irritation in a Draize eye irritation test. Bentonite caused severe iritis after injection into the anterior chamber of the eyes of rabbits. When injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were recorded. In a primary eye irritation study in rabbits, Hectorite was moderately irritating without washing and practically nonirritating to the eye with a washout. Rats tolerated a single dose of Zeolite A without any adverse reaction in the eye.

Calcium Silicate (250 to 1600 mg/kg) had no discernible effect on nidation or on maternal or fetal survival in rabbits. Magnesium Aluminum Silicate (6000 mg/kg) had neither a teratogenic nor adverse effects on the mouse fetus. Female rats receiving a 20% Kaolin diet exhibited maternal anemia but no significant reduction in birth weight of the pups was recorded. Type A Zeolite produced no adverse effects on the dam, embryo, or fetus in either rats or rabbits at any dose level (74 or 1600 mg/kg). Clinoptilolite had no effect on female rat reproductive performance.

No increase mutation frequencies were seen in the *Salmonella* TA-1530 or G-46 assay and no significant increase in recombinant activity in the *Saccharomyces* D3 assay treated with Calcium Silicate. A subacute dose of 150 mg/kg of Calcium Silicate produced 3% breaks in bone marrow cells arrested in c-metaphase. In a metaphase spread of bone marrow cells, Calcium Silicate produced no significant increase in the number of aberrations compared to controls and in a dominant lethal assay did not induce any dominant lethal mutations. In the *S. typhimurium* LT2 spot test (TA98, TA100, TA1535, TA1537, and TA1538) with or without metabolic activation, Magnesium Aluminum Silicate and Hectorite were found nonmutagenic. In primary hepatocyte cultures, the addition of Attapulgite had no significant unscheduled DNA synthesis (UDS) response or modulated response to AAF (a positive control); Attapulgite at 10 $\mu g/cm^2$ caused significant increases in UDS in rat pleural mesothelial cells. Zeolite particles (<10 μm) produced statistically significant increase in the percentage of aberrant metaphases, mostly chromatid breaks.

Applications of 2 g of VEEGUM made to the skin of two humans daily for 1 week caused no effects.

Occupational exposure to mineral dusts has been studied extensively. Fibrosis and pneumoconiosis has been documented in workers involved in the mining and processing of Aluminum Silicate, Calcium Silicate, Zirconium Silicate, Fuller's Earth, Kaolin, Montmorillonite, Pyrophyllite, and Zeolite.

DISCUSSION

The CIR Expert Panel determined that the data provided in this report are sufficient to assess the safety of the tested ingredients: Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite. The Panel did note a concern about inhalation of these ingredients due to reported cases of pneumoconiosis and fibrosis in humans and pulmonary lesions in animals. However, extensive pulmonary damage in humans was the result of direct occupational inhalation of the dusts and lesions seen in animals were affected by particle size, fiber length, and concentration. The Panel recognizes that most of the formulations are not respirable and of the preparations that are respirable, the concentration of the ingredient is very low. Even so, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation.

Note: The cosmetic ingredient, *Talc*, is a hydrated magnesium silicate with the chemical composition of $Mg_3Si_4O_{10}(OH)_2$. Talc occurs in various forms and has a unique crystalline structure which differs from ingredients addressed in this safety assessment. Talc is not included in this report.

CONCLUSION

The CIR Expert Panel concludes that Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite are safe as used in cosmetic products.

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Final Report on the Safety Assessment of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate[1]

Potassium Silicate, Sodium Metasilicate, and Sodium Silicate combine metal cations with silica to form inorganic salts used as corrosion inhibitors in cosmetics. Sodium Metasilicate also functions as a chelating agent and Sodium Silicate as a buffering and pH adjuster. Sodium Metasilicate is currently used in 168 formulations at concentrations ranging from 13% to 18%. Sodium Silicate is currently used in 24 formulations at concentrations ranging from 0.3% to 55%. Potassium Silicate and Sodium Silicate have been reported as being used in industrial cleaners and detergents. Sodium Metasilicate is a GRAS (generally regarded as safe) food ingredient. Aqueous solutions of Sodium Silicate species are a part of a chemical continuum of silicates based on an equilibrium of alkali, water, and silica. pH determines the solubility of silica and, together with concentration, determines the degree of polymerization. Sodium Silicate administered orally is readily absorbed from the alimentary canal and excreted in the urine. The toxicity of these silicates has been related to the molar ratio of SiO_2/Na_2O and the concentration being used. The Sodium Metasilicate acute oral LD_{50} ranged from 847 mg/kg in male rats to 1349.3 mg/kg in female rats and from 770 mg/kg in female mice to 820 mg/kg in male mice. Gross lesions of variable severity were found in the oral cavity, pharynx, esophagus, stomach, larynx, lungs, and kidneys of dogs receiving 0.25 g/kg or more of a commercial detergent containing Sodium Metasilicate; similar lesions were also seen in pigs administered the same detergent and dose. Male rats orally administered 464 mg/kg of a 20% solution containing either 2.0 or 2.4 to 1.0 ratio of sodium oxide showed no signs of toxicity, whereas doses of 1000 and 2150 mg/kg produced gasping, dypsnea, and acute depression. Dogs fed 2.4 g/kg/day of Sodium Silicate for 4 weeks had gross renal lesions but no impairment of renal function. Dermal irritation of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate ranged from negligible to severe, depending on the species tested and the molar ratio and concentration tested. Sodium Metasilicate was negative in the local lymph node assay (LLNA), but a delayed-type hypersensitivity response was observed in mice. Potassium Silicate was nonirritating in two acute eye irritation studies in rabbits. Sodium Metasilicate (42.4% H_2O) was corrosive to the rabbit eye. Sodium Silicate was a severe eye irritant in some eye irritation studies, but was irritating or nonirritating in others. A skin freshener containing Sodium Silicate was nonirritating. Sodium Metasilicate was nonmutagenic in bacterial cells. Rats given Sodium Silicate (600 and 1200 ppm of added silica) in the drinking water in reproductive studies produced a reduced number of offspring: to 67% of controls at 600 ppm and to 80% of controls at 1200 ppm. Three adult rats injected intratesticularly and subcutaneously with 0.8 mM/kg of Sodium Silicate showed no morphological changes in the testes and no effect on the residual spermatozoa in the ductus deferens. Sodium Metasilicate (37% in a detergent) mixed with water was a severe skin irritant when tested on intact and abraded human skin, but 6%, 7%, and 13% Sodium Silicate were negligible skin irritants to intact and abraded human skin. Sodium Silicate (10% of a 40% aqueous solution) was negative in a repeat-insult predictive patch test in humans. The same aqueous solution of Sodium Silicate was considered a mild irritant under normal use conditions in a study of cumulative irritant properties. The Cosmetic Ingredient Review (CIR) Expert Panel recognized the irritation potential of these ingredients, especially in leave-on products. However, because these ingredients have limited dermal absorption and Sodium Metasilicate is a GRAS direct food substance, the Panel deemed the ingredients safe for use in cosmetic products in the practices of use and concentration described in this safety assessment, when formulated to avoid irritation.

INTRODUCTION

This report reviews the safety of silicate salts as used in cosmetic formulations. Because they are considered to have similar safety profiles, the following silicate salts are reviewed in this assessment: Potassium Silicate (CAS no. 1312-76-1), Sodium Metasilicate (CAS no. 6834-92-0), and Sodium Silicate (CAS no. 1344-09-8).

CHEMISTRY

These ingredients combine metal cations (potassium or sodium) with silica to form inorganic salts. A tabular presentation of chemical descriptions is provided in Table 1.

Physical and Chemical Properties

The properties, synonyms, and specifications are listed in tabular form in Table 2.

According to O'Conner (1961), pH determines the solubility of silica and, together with concentration, determines its degree of polymerization. At about pH 7, silica is only slightly soluble in water. At around pH 12, in a Sodium Metasilicate solution (0.1%), silica is very soluble and exists in monomeric form. At an intermediate pH, Sodium Metasilicate is partially neutralized; that is, it changes ratio and becomes a Sodium Silicate of $1Na_2O{:}XSiO_2$, where X is greater than unity. Conversely, a Sodium Silicate of the ratio $1Na_2O{:}XSiO_2$ could be converted to Metasilicate by the addition of alkali.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Amy R. Elmore, former CIR Scientific Analyst and Writer. Address correspondence to F. Alan Andersen, Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

TABLE 1
Ingredient descriptions

Ingredient	Description	Reference
Potassium Silicate	SiO_2:K_2O ratio varies	Budavari (1989)
	Potassium salt of silicic acid	Gottschalck and McEwen (2004)
Sodium Metasilicate	Na_2SiO_3	Gottschalck and McEwen (2004)
	Inorganic salt	Gottschalck and McEwen (2004)
Sodium Silicate	$Na_2O{\cdot}xSiO_2$	Lide (1993)
	Sodium salt of silicic acid	Gottschalck and McEwen (2004)

Method of Manufacture

Soluble silicates (Sodium Silicate and Sodium Metasilicate) are manufactured by the reaction of silica sand and sodium carbonate (soda ash) at ~1400°C. Typically, a no. 1 grade of glass sand containing no more than 300 ppm iron and a medium density soda ash are used. Potassium Silicates are manufactured in a similar manner by the reaction of K_2CO_3 and sand (Kirk-Othmer 1982).

Sodium Silicates are either made by the high temperature fusion of silica sand (SiO_2) and soda (Na_2CO_3) at about 1300°C or by a hydrothermal process using silica sand and sodium hydroxide as starting materials. Solutions, termed "waterglass," are prepared by the solubilization of lumps of silicate salts in water at elevated temperatures and pressure. The water content of "waterglass" is between 45% and 80%. Powders are prepared by spray- or drum-drying of "waterglass" solutions. The residual water content can be between 0% and 25% (EUCLID 2000).

Impurities

Kirk-Othmer (1982) provided a range of trace elements in a typical Sodium Silicate solution as shown in Table 3. Impurity limits for Arsenic and Lead are shown in Table 2.

TABLE 2
Properties, synonyms, and specifications

	Potassium Silicate	
Synonyms	Silicic acid, potassium salt	Gottschalck and McEwen (2004)
Form/description	Yellowish to colorless, translucent to transparent, hygroscopic	Budavari (1989)
Solubility	Insoluble in alcohol, slightly soluble in water	Budavari (1989)
	Sodium Metasilicate	
Synonyms	Silicic acid, disodium salt	Gottschalck and McEwen (2004)
	Crystamet, disodium metasilicate, disodium monosilicate, Metso, water glass, sodium metasilicate anhydrous	RTECS (1999)
Form/description	Nonahydrate, efflorescent platelets	Budavari (1989)
Molecular weight	122.08	Budavari (1989)
pH	12 (0.1% solution)	O'Conner (1961)
Density	2.614	Budavari (1989)
Solubility	Insoluble in alcohol, acids, and salt solns.	Budavari (1989)
Melting point	1089°C	CTFA (2000a)
Forms	Anhydrous, pentahydrate, and nonahydrate	21 CFR 184.1769a
Impurity limits	Arsenic (as As) 3 ppm maximum	Nikitakis and McEwen (1990)
	Lead (as Pb) 20 ppm maximum	Nikitakis and McEwen (1990)
	Sodium Silicate	
Synonyms	Silicic acid, sodium salt	Gottschalck and McEwen (2004)
	Sodium waterglass, waterglass, soluble glass, sodium silicate glass	EUCLID (2000)
Form/description	Colorless to white or grayish-white, crystal-like clumps or aqueous solutions	Budavari (1989)
pH	Strongly alkaline	Budavari (1989)
Impurity limits	Arsenic (as As) 3 ppm maximum	Nikitakis and McEwen (1990)
(40% solution)	Lead (as Pb) 20 ppm maximum	Nikitakis and McEwen (1990)

TABLE 3
Trace elements in Sodium Silicate (Kirk-Othmer 1982)

	Measured Values			Measured Values	
Impurity	Low	High	Impurity	Low	High
F	6.7 ppm	9.5 ppm	V	Below 0.3 ppm detection limit	0.8 ppm
Cl	130 ppm	1900 ppm	Cr	Below 0.3 ppm detection limit	1.0 ppm
SO_4	Below 160 ppm detection limit	1700 ppm	Ni	Below 0.3 ppm detection limit	0.3 ppm
N	0.1 ppm	44 ppm	Co	Below 0.3 ppm detection limit	<0.3 ppm
As	Below 1 ppm detection limit	<1 ppm	Zn	Below 0.6 ppm detection limit	2.8 ppm
Hg	Below 0.26 ppb detection limit	2.5 ppb	Cu	Below 0.6 ppm detection limit	1.1 ppm
Pb	0.17 ppm	0.60 ppm	Bi	Below 25 ppm detection limit	<25 ppm
Cd	Below 10 ppb detection limit	21 ppb	Sr	Below 0.2 ppm detection limit	1.5 ppm
Fe	36 ppm	120 ppm	Ba	Below 0.2 ppm detection limit	2.8 ppm
Mg	4 ppm	26 ppm	Mn	0.1 ppm	1.8 ppm
Ca	Below 1 ppm detection limit	76 ppm	Sn	Below 60 ppm detection limit	<60 ppm
Al	50 ppm	220 ppm	Sb	Below 15 ppm detection limit	< 15 ppm
P	Below 18 ppm detection limit	<18 ppm	Se	Below 20 ppm detection limit	<20 ppm

USE

Cosmetic

Potassium Silicate functions as a corrosion inhibitor in cosmetics (Gottschalck and McEwen 2004). Voluntary reports by industry to the Food and Drug Administration (FDA) on product use included use of Potassium Silicate in two formulations as shown in Table 4 (FDA 2001). Industry did not report any concentration of use information for Potassium Silicate.

Sodium Metasilicate functions as a chelating agent and corrosion inhibitor in cosmetic formulations (Gottschalck and McEwen 2004). Of the 191 formulations reported to the FDA, over 80% were used in hair dyes and colors (FDA 2001). Table 4 shows the types of cosmetic formulations in which Sodium Metasilicate is reported to be used and gives current concentrations of use as provided by industry.

In those cases where a current concentration of use is provided, but there are no reports to FDA of use, it should be assumed that the ingredient may be in current use.

Sodium Silicate functions as a buffering agent, corrosion inhibitor, and a pH adjuster (Gottschalck and McEwen 2004). Sodium Silicate was reported to be used in 22 formulations (FDA 2001). Table 4 shows the types of cosmetic formulations in which Sodium Silicate is reported to be used and gives current concentrations of use as provided by industry.

There are no restrictions for the use of these silicate salts in cosmetics in Japan according to the Ministry of Health, Labor, and Welfare (2000) nor in Europe according to the European Economic Community (1999).

Noncosmetic

The principle uses of soluble silicates are in the manufacturing of soaps and detergents. They provide a constant pH value in the detergent system and aid in the saponification of oils and fats by means of their alkaline nature and buffering ability. Soluble Silicates are also used in water treatment, as an adhesive and fireproof coating additive, as a paper de-inking agent, as an egg preservative, and as a inhibitor of metal corrosion (Kirk-Othmer 1982).

FDA affirmed Sodium Metasilicate as a GRAS (generally regarded as safe) direct food substance (Code of Federal Regulations, 21CFR184.1769a) with no limitation other than current good manufacturing practice. Sodium Metasilicate's uses in foods include processing aid; washing and lye peeling of fruits, vegetables, and nuts; denuding agent in tripe; hog scald agent in removing hair; and a corrosion preventative in canned and bottled water. The Select Committee of the Federation of American Societies for Experimental Biology (FASEB) (1981) concluded: "There is no evidence in the available information on Sodium Metasilicate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used as a food ingredient in a manner now practiced at levels that are now current or might reasonably be expected in the future."

Rhone-Poulenc (1971a) reported Sodium Silicate being used in industrial cleaners and detergents.

Potassium Silicate was reported by Reynolds et al. (1998) as an alternative to sulfur for controlling powdery mildew. Rhone-Poulenc (1971b) reported Potassium Silicate being used in industrial cleaners and detergents.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Two groups of four male Sprague-Dawley Cox rats were fasted for 17 to 18 h and then administered Sodium Silicate orally in doses of 40 or 1000 mg/kg body weight (bw). Four control

TABLE 4
Product formulation data

Product category (number of formulations in each category) (FDA 2001)	Formulations containing ingredient (FDA 2001)	Reported range of use concentrations (CTFA 1999, 2000b)
	Potassium Silicate	
Noncoloring hair preparations		
Other hair preparations (276)	1	—
Skin care preparations		
Paste masks (mud packs) (269)	1	—
Totals/ranges for Potassium Silicate	2	
	Sodium Metasilicate	
Noncoloring hair preparations		
Hair straighteners (63)	1	—
Hair coloring preparations		
Hair dyes and colors (1588)	158	—
Hair lighteners with color (5)	2	14%
Hair bleaches (115)	24	13%–18% (diluted to 7%–14% before use)
Other hair coloring preparations (59)	4	—
Shaving preparations		
Shaving cream (133)	2	—
Totals/ranges for Sodium Metasilicate	191	
	Sodium Silicate	
Baby products		
Other baby products (29)	—	0.6%
Eye makeup preparations		
Other eye makeup preparations (151)	1	—
Hair-coloring preparations		
Hair bleaches (115)	7	16%–55% (diluted to 1%–20% before use)
Hair dyes and colors (1572)	—	1%
Other hair coloring preparations (59)	1	35%
Bath preparations		
Bath soap and detergents (405)	2	0.06%–7%
Oral hygiene products		
Dentrifrices (aerosol, liquid, pastes, and powders) (38)	—	0.6%
Shaving preparations		
Shaving cream (133)	6	0.3%–5%
Shaving soap (<4)	—	0.4%
Skin care preparations		
Skin cleansing creams, lotions, liquid, and pads (653)	—	10%
Depilatories (28)	4	2%
Face and neck skin care preparations (304)	1	—
Other skin preparations (692)	—	1%
2001 Totals/ranges for Sodium Silicate	22	0.06%–35%

animals received 10 ml of quartz-distilled water. All suspensions contained <0.5 ppm of silicon and aluminum. Urine samples were collected over an 8-h period and afterwards the remaining urine in the bladder was collected. The concentrations of silicon were measured by induction-coupled RF plasma optical emission spectrometry. Silicon excretion was most rapid during the first 24 h after dosing. After subtracting the control values, the urinary silicon excretion at 40 and 1000 mg Sodium Silicate/kg was 18.9% and 2.8%, respectively (Benke and Osborn 1979).

In Vitro Assays

Sodium Metasilicate

Neutralized Sodium Metasilicate, at concentrations of up to 0.025 M, inhibited urease and invertase in vitro, but had

little effect on many other enzymes such as pepsin, trypsin, lipase, catalase, or cholinesterase (Kind et al. 1954; Alexander 1968).

Skin^2 ZK 1350 cultures were used to evaluate skin corrosion and develop a classification of 50 chemicals in a study by Liebsch et al. (1995). Skin^2 cultures are a three-dimensional human skin model with a stratum corneum grown from neonatal human skin cells. The epidermal side of the cultures was placed onto 15 μl of Sodium Metasilicate on glass coverslips for 10 s. Phosphate-buffered saline was used to wash the test material residue. Cell viability was assessed using the tetrazolium derivative reduction cytotoxicity assay. The controls were treated with distilled water. In this assay, a corrosive chemical will have a <80% viability rate. A noncorrosive classification corresponds to a >80% viability rate. Sodium Metasilicate had a mean viability (±SD) of 65.8 ± 10.4. The authors classified Sodium Metasilicate as corrosive.

Sodium Silicate

Sodium Silicate was also tested by Liebsch et al. (1995) in the same study as the previous experiment. Two different chemical names were tested, Sodium Silicate A140 and Sodium Silicate H100. Sodium Silicate A140 is classified as group II and Sodium Silicate H100 is classified as non-corrosive according to in vivo UN packing guidelines. The ZK 1350 percent viability mean ± *SD* for Sodium Silicate A140 and Sodium Silicate H100 were 82.3 ± 12.0 and 91.5 ± 10.9, respectively. The corrosivity classification for Sodium Silicate A140 was determined to be non-corrosive, but was noted to be a false negative. Sodium Silicate H100 was classified as non-corrosive. Both chemicals were predicted by the ZK 1350 assay to be non-corrosive according to United Nations (UN) packing guidelines.

ANIMAL TOXICOLOGY

Acute Oral

Sodium Metasilicate

Rhone-Poulenc (1971b) conducted a study in which male Sprague-Dawley rats were administered a 20% solution of Sodium Metasilicate by gastric intubation. Five animals per dose of 464, 1000, 2150, and 4640 mg/kg were used. The animals were observed for 14 days for mortality and signs of toxicity.

All rats given the largest dose died and necropsy was performed on these animals. No apparent signs of toxicity were produced at 464 mg/kg. Animals treated with either ratio at doses of 1000 and 2150 mg/kg had gasping, dyspnea, and acute depression. Signs in groups given 4640 mg /kg included acute depression, nasal discharge, dyspnea, and gasping. All dead rats had gross gastrointestinal hemorrhages with congestion of the kidneys, adrenal glands, liver, lungs, and heart. The acute oral LD_{50} was 847 mg/kg (Rhone-Poulenc 1971b).

Muggenberg et al. (1974) gave groups of three beagle dogs single doses of 0.1, 0.25, 0.5, 1.0, and 2.5 g/kg of a commercially available detergent containing Sodium Metasilicate. No details about the percentage of Sodium Metasilicate in the detergent were given.

All dogs that received the highest dose died within 54 h. Gross lesions of variable severity were found in the oral cavity, pharynx, esophagus, stomach, larynx, lungs, and kidneys of all dogs receiving 0.25 g/kg or more. No lesions were found in dogs that received 0.1 g/kg. Microscopic lesions included acute necrosis of the epithelial lining of the digestive tract, necrosis, ulceration and edema of the larynx, edematous lungs, and necrosis of the proximal renal tubules.

In a second experiment, three pigs were given a single dose of 0.25 g/kg of the same detergent used in the dog study. One pig died 95 h after ingestion. Lesions in the pigs were similar to those found in the dogs (Muggenberg et al. 1974).

The Federation of American Societies for Experimental Biology (1981) listed the following LD_{50} values for Sodium Metasilicate: rat (oral) 1.28 g/kg; rat (oral) 3 g/kg; and mouse (oral) 3 g/kg, and stated that "accidental exposure to strongly alkaline, concentrated solutions of Sodium Metasilicate such as those used in certain common detergent preparations, can produce caustic, irritating effects on contact with the eye, skin, and mucous membranes of the alimentary tract and respiratory system."

Ito et al. (1986) reported the LD_{50} of Sodium Metasilicate as 1152.8 mg/kg in male rats, 1349.3 mg/kg in female rats, 820 mg/kg in male mice, and 770 mg/kg in female mice. Changes in the animals that survived after peroral administration of large doses in acute studies were mainly bleeding in the stomach and duodenum, and erosion of the small intestine.

Sodium Silicate

A summary of information on Sodium Silicate provided by European companies (EUCLID 2000) included acute oral toxicity data shown in Table 5.

In a study by Rhone-Poulenc (1971b), male Sprague Dawley rats were administered a 20% solution of a 2.0 and 2.4 ratio of Sodium Silicate to 1.0 ratio of sodium oxide by gastric intubation. The 2.0 and 2.4 ratios were corrected for moisture content and tested on an equivalent anhydrous basis. Five animals per dose group at 464, 1000, 2150, and 4640 mg/kg were used. The animals were observed for 14 days for mortality and other signs of toxicity. Necropsy was performed on animals of the largest doses.

In the higest dose group, 4/5 rats of the 2.0 ratio material and 5/5 rats of the 2.4 ratio material died. No apparent signs of toxicity were produced at 464 mg/kg. Animals treated with either ratio at doses of 1000 and 2150 mg/kg had gasping, dyspnea, and acute depression. The highest dose group animals had acute depression, nasal discharge, dyspnea, and gasping. Dead animals had gastrointestinal hemorrhages and congestion of the kidneys, adrenal glands, liver, lungs, and heart. The acute oral LD_{50} was reported to be 1960 mg/kg in groups receiving the 2.0 ratio material of Sodium Silicate and 2710 mg/kg

TABLE 5
Sodium Silicate oral LD_{50} values in the rat (EUCLID 2000)

LD_{50}	Molar ratio/concentration	Remarks
2000–2500 mg/kg	Molar ratio of 1.6 and a concentration of 51%	The acute oral toxicity of alkaline sodium silicates is dependent on the SiO_2/Na_2O molar ratio, and to a lesser extent on the concentration of dissolved dry matter (due to pH dependence); autopsy results showing acute gastroenteritis, vascular congestion, and mottled livers are consistent with nonspecific causes of death.
1600–8600 mg/kg	Molar ratio of 3.0 and various concentrations	
1500–2200 mg/kg	Molar ratio of 2.0 and concentration of 81%	
1300–2100 mg/kg	Molar ratio of 2.0 and various concentrations	
1600 mg/kg	Molar ratio of 2.0 and concentration of 81%	
7150–10500 mg/kg	Molar ratio of 3.4	Ten male rats of different species were used and the observed range in LD_{50} values was due to intraspecies susceptibility.
>2000 mg/kg	Molar ratio of 3.45 and concentration of 35%	All symptoms of intoxication were reversible and no signs of histopathologic abnormalities were observed 14 days after application of the substance.

in groups receiving the 2.4 ratio material (Rhone-Poulenc 1971b).

Short-Term Oral

Sodium Metasilicate

Albino mice (210) and rabbits (20) dosed daily with 200 to 300 mg/kg Sodium Metasilicate for 1 month showed "a cellular proliferation in the internal organs." No details of number of animals by dose, sex, age, strain, or mortality were reported (Shakhbazyan and Karapetyan 1963).

Schwarz and Milne (1972) found that Sodium Metasilicate ($Na_2SiO_3 \cdot 9H_2O$) added to silicon-depleted, chemically defined diets of weanling Fisher 344 rats resulted in 25% to 34% increases in growth rates compared with control animals on silicon-depleted diets. The estimated dose of silicon was about 100 mg/kg/day. Growth retardation and a disturbance in bone formation were reported to be signs of silicon deficiency, presumably as a result of faulty bone matrix formation and inadequate cross-linkage of acid mucopolysaccharides and other connective tissue components.

Sodium Silicate

In a study by Kayongo-Male and Jia (1999), 36 male Sprague-Dawley albino rats were randomly allotted into a two-dietary-treatment experiment. The dietary treatments included a control basal diet consisting of dextrose–egg album in that contained <5.0 ppm Si and a diet supplemented with 500 ppm Si obtained by the addition of Sodium Silicate.

The addition of dietary Si affected rat body-weight changes. Rats on the supplemented diet had slower growth rates than control rats. At the end of 8 weeks, rats on the treated diet weighed 257 g on average compared to 273 g for control rats. Hemoglobin levels were lower ($p < .05$) in treated rats. Plasma Ca content was also lower in treated rats ($p < .05$). Plasma Mg levels were higher ($p < .05$) in control rats. Plasma Cu and P were not affected. The source of Si did not affect ($p < .05$) organ weights or their mineral concentrations except liver Zn concentrations, which were higher in the control group (Kayongo-Male and Jia 1999).

Subchronic Oral

Sodium Metasilicate

In a subchronic study with Sodium Metasilicate in the drinking water of Wistar rats, no specific changes in the high-dose animals were observed. Slight degenerative changes in the epithelium of renal tubules were observed in higher doses. Maximum safety concentrations were 1500 ppm/L/day (792 mg/kg/day) (Ito et al. 1986).

Sodium Silicate

Newberne and Wilson (1970) fed eight female and eight male beagle dog 2.4 g/kg/day of Sodium Silicate in their diets for 4 weeks to study renal damage. Six animals of each sex were used as controls, receiving the same diet without Sodium Silicate. In addition, 15 rats (Charles River CD strain) of each sex were fed the same diet with Sodium Silicate and 15 rats of each sex received the control diet. Animals were killed at the end of 4 weeks and necropsied. Tissues were preserved in formaldehyde for histopathologic examination.

Body weight, feed intake, and urinary specific gravity and blood (protein and glucose) measurements were the same for both test and control dogs and rats. Polydipsia and polyuria were

observed in both the dogs and rats. Gross renal cortical lesions were seen in 8/8 male and 7/8 female dogs. The authors stated that the appearance of the cut surface suggested cortical infarcts. Despite extensive renal damage, impairment of renal function was not detected. No treatment-related lesions were found in the rats (Newberne and Wilson 1970).

Smith et al. (1973) added a Sodium Silicate solution to the drinking water containing 600 and 1200 ppm of added silica and given to groups of six weanling male and six female Sprague-Dawley rats. Growth, nitrogen and phosphorous retention, and reproductive effects were investigated (discussed later in this report). Control groups received no Sodium Silicate in their drinking water. At 4 months of age, the rats of treatment groups were mated. The treated water, 600 ppm, combined with a normal, commercial diet for rats increased body weight gains of the male rats by ~6% over controls but decreased gains of the female rats by ~5% compared to controls. Retention of nitrogen and phosphorous were significantly affected. No apparent effect of the treatment in the drinking water was found on the longevity in rats having started treatment after weaning.

Acute Parenteral

Intraperitoneal injections of a neutralized 2% solution of Sodium Metasilicate (~1200 mg/kg on day 1 and 800 mg/kg on days 2 and 3) into white rats resulted in a 60% decrease in spleen weight and relative enlargement of the kidneys when the animals were examined on the third day. There were microscopic lesions of the lymphatic tissues and cellular damage in parts of the intestinal mucosa (Nanetti 1973).

Dermal Irritation

Potassium Silicate

Potassium Silicate was tested for primary skin irritation according to the Draize Dermal procedure after a 24-h exposure in six rabbits (three male and three female). No dose was indicated. The primary irritation index was 1.83 and the compound was classified as a mild irritant (Rhone-Poulenc 1971a).

A summary of information on Potassium Silicate put together by European companies (EUCLID 2000) included the skin irritation data shown in Table 6.

Sodium Metasilicate

Sodium Metasilicate (42.4% H_2O) was tested for skin irritation according to the Draize Dermal procedure in six rabbits (three male and three female). The results were scored at 8.0 and was classified as a corrosive. The authors stated that the result was expected because the pH of the solution was 12.4 (Rhone-Poulenc 1971b).

A commercial product containing 5% Sodium Metasilicate was tested in acute dermal toxicity studies using male and female white New Zealand rabbits. The dermal LD_{50} was >200 mg/kg. Necrosis and edema were observed at the treatment site (Rhone-Poulenc 1976).

A Sodium Metasilicate/carbonate granular detergent was applied to intact and abraded skin of rabbits and guinea pigs for 4 h. Skin responses were graded at 4, 24, and 48 h after the patch applications. The detergent contained 37% Sodium Metasilicate. Rabbit skin and guinea pig skin reacted differently as shown in Table 7 (Nixon, Tyson, and Wertz 1975).

Sodium Silicate

Sodium Silicate was tested for primary skin irritation according to the Draize Dermal procedure after 4 and 24 h exposures in rabbits. Both primary irritation indexes for 4 and 24 h were 8.0 and the compound was classified as corrosive (Rhone-Poulenc 1971a).

A 2.0 ratio and 2.4 ratio of Sodium Silicate to 1.0 sodium oxide with 19.5% water was tested for skin irritation according to the Draize Dermal procedure in rabbits. The 2.0 ratio material was scored a 5.9 and was classified as a severe irritant; the 2.4 ratio material was scored a 4.12 and was classified as a moderate irritant. An acute dermal toxicity study utilizing New Zealand white rabbits was also conducted. Both ratio materials of Sodium Silicate were applied to the closely clipped intact abdominal skin and the skin was exposed for 24 h. After the 24 h, the binders were removed and any residual chemical was removed by washing. The animals were observed for 14 days for toxicity. No signs of toxicity were apparent in any of the animals. The 2.0 ratio material produced severe, irreversible erythema and edema at the test site; while the 2.4 ratio material caused more moderate, reversible irritation at the test site. The acute rabbit dermal LD_{50} was >4640 mg/kg (Rhone-Poulenc 1971b).

TABLE 6

Potassium Silicate: acute dermal irritation in rabbits (EUCLID 2000)

Method	Result	Remarks
OECD Guideline 404 "Acute Dermal Irritation/Corrosion"	Nonirritating	Diluted Potassium Silicate solution Molar ratio = 3.4 Concentration = 8.5–9%
OECD Guideline 404 "Acute Dermal Irritation/Corrosion"	Nonirritating	Diluted Potassium Silicate solution Molar ratio = 3.9 Concentration = 7–7.5%

TABLE 7
Sodium Metasilicate: dermal irritancy (Nixon, Tyson, and Wertz 1975)

Concentration of detergent (*w/v* aqueous)	Animal species	Mean scores			Tissue destruction		Irritancy judgement
		Intact	Abraded	PII	Intact	Abraded	
50%	Rabbit	>6.8	>8.0	>7.4	5/5	5/5	Corrosive
50%	Guinea pig	0.0	0.6	0.3	0/6	0/6	Negligible

Three detergents containing Sodium Silicate (7% in a high-carbonate detergent, 13% in a low-12 carbonate detergent, and 6% in a phosphate detergent) were applied to intact and abraded skin of rabbits and guinea pigs for four hours. Skin responses were graded at 4, 24, and 48 h after the patch applications. The results from this study are presented in Table 8 (Nixon, Tyson, and Wertz 1975).

In a single insult occlusive patch test, nine rabbits were treated with a skin freshener that contained 10% of a 40% aqueous solution of Sodium Silicate. The compound had a typical weight ratio of SiO_2/Na_2O of 3.25. The skin irritation potential of the test material was nonirritating (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1979a).

Patch tests were performed using three female Hartley guinea pigs. Occlusive patches containing 20% Sodium Silicate were applied to the shaved backs of the three animals. Erythema was detected 48 h later but did not progress to ulceration. Pathological findings at the occlusive patch test site included dyskeratotic cells in the epidermis and polymorphonuclear leukocytic infiltration around the blood vessels (Tanka, Miyachi, and Horio 1982).

A summary of information on Sodium Silicate put together by European companies (EUCLID 2000) included the skin irritation data shown in Table 9.

Immunomodulation

The National Toxicology Program (NTP) (2001) evaluated Sodium Metasilicate as an immunomodulatory agent when applied to female BALB/c mice in a mouse ear swelling test and local lymph node assay (LLNA) to measure contact hypersensitivity. Concentrations used in the contact hypersensitivity assays were determined by irritancy testing. The minimal irritating concentration was found to be 6% and the maximal nonirritating concentration was 4%. The. Sodium Metasilicate concentrations were 0.4%, 2%, and 4% for the sensitization phase, and 6% for the challenge phase. In the LLNA, mice were sensitized to 2%, 4%, and 6% Sodium Metasilicate. 1-Fluoro-2,4-dinitrobenzene (DNFB) was used as a positive control at a concentration of 0.15% for the irritancy test and LLNA, and 0.20% for the swelling test. An evaluation of lymph node subpopulations, cytokine mRNA, and serum immunoglobulin E (IgE) levels was also conducted.

Dermal exposure to (2% to 6%) Sodium Metasilicate did not produce cell proliferation in the draining lymph nodes as measured by the LLNA. However, a delayed-type hypersensitivity (DTH) response was observed when mice were sensitized on the back with 4% Sodium Metasilicate, then challenged on the ear with 6% Sodium Metasilicate. The positive control, DNFB, induced cell proliferation in the draining lymph nodes, and elicited a DTH response. Lymph node subpopulations were also altered by treatment with Sodium Metasilicate. Only B220+Ig+ lymph nodes were shown to increase when the data were presented as a percentage of the total lymph node count. The response was observed at concentrations as low as 4%. An evaluation of the cytokine mRNA revealed an increase in the expression of interferon (IFN)-γ, tumor necrosis factor (TNF)-β, and migration inhibitory factor (MIF) mRNAs. No change in total serum IgE levels was detected (NTP 2001).

TABLE 8
Sodium Silicate: dermal irritancy (Nixon, Tyson, and Wertz 1975)

Detergent type (Sodium Silicate concentration)	Concentration of detergent (*w/v* aqueous)	Animal species	Mean scores			Tissue destruction		Irritancy judgement
			Intact	Abraded	PII	Intact	Abraded	
High carbonate (7%)	50%	Rabbit	0.9	2.6	1.7	0/6	0/6	Negligible
	50%	Guinea pig	0.0	0.4	0.2	0/6	0/6	Slight
Low carbonate (13%)	50%	Rabbit	0.7	0.8	0.8	0/6	0/6	Slight
	50%	Guinea pig	0.1	1.0	0.5	0/6	0/6	Slight
Phosphate (6%)	50%	Rabbit	1.2	>5.6	>3.4	0/5	2/5	Moderate
	50%	Guinea pig	0.2	1.0	0.6	0/6	0/6	Slight

TABLE 9
Sodium Silicate acute dermal results in rabbits (EUCLID 2000)

Method	Result
Undiluted substance (0.5 ml) applied for 4 h; molar ratio of 3.45; concentration of 35%	Nonirritating
0.5 g substance moistened with physiological saline applied to intact abraded skin for 24 h; molar ratios of 2.9 and 3.2; concentrations of 43%, 36%, and 80%	Irritating; the PII was 3, 3, 0 respectively for 43%, 36%, and 80%
Same application, but molar ratios of 2.4 and 3.2, and concentrations of 44% and 38%	Irritating
Same application, but pH 13.6 material; molar ratio of 1.6; concentration of 52%	Corrosive
0.5 ml solution of pH 12 with a molar ratio of <2	Corrosive
A powder product—2:1 dilution with water; molar ratio was 2; concentration was 66.6%	Nonirritating
Undiluted substance (0.5 ml) applied for 4 h; molar ratio was 3.91; concentration was 28%	Nonirritating
Same application, but molar ratio was 2.83 and concentration was 45%	Slightly irritating
Same application, but molar ratio was 2.09 and concentration was 55%	Moderately irritating
Same application, but molar ratio was 3.3 and concentration was 38%	Slightly irritating
Same application, but molar ratio was 2.09 and concentration was 55%	Slightly Irritating
Same application, but molar ratio was 2.4 and concentration was 40%	Irritating
Same application, but molar ratio was 2 and concentration was 41%	Irritating
The powder was applied dry. The molar ratio was 2	Nonirritating
Molar ratio of 1.6 and concentration of 53.5%	Corrosive
Molar ratio of 3.4 and concentration of 34.5%	Slightly irritating

Ocular Irritation

Potassium Silicate

A summary of information on Potassium Silicate put together by European companies (EUCLID 2000) included the ocular irritation data shown in Table 10.

Sodium Metasilicate

Sodium Metasilicate (42.4% H_2O) was tested in acute ocular irritation studies that were in accordance with the procedure outlined in the Code of Federal Regulations (21CFR191.12.1). Six New Zealand rabbits were exposed to 0.1 ml in one eye; the other eye served as a control. The sample was corrosive to the eye; total destruction of the eye of all the test animals was observed (Rhone-Poulenc, 1971b).

Sodium Silicate

Sodium Silicate ratios (2.0: 1.0 and 2.4:1.0 Na_2O with 19.5% H_2O) were tested in acute ocular irritation studies that were in accordance with the procedure outlined in the Code of Federal Regulations (21CFR191.12.1). Six New Zealand rabbits were exposed to 0.1 ml in the conjunctival sac of one eye; the other eye served as a control. The 2.0 ratio material produced corneal opacity with scar tissue formation in four of the six rabbits. The remaining two had severe iritis and conjunctivitis. The 2.0 ratio material was classified as corrosive. The 2.4 ratio material produced conjunctivitis, moderate iritis, and two of six test rabbits had slight corneal opacity. Sodium Silicate was classified as a severe occular irritant (Rhone-Poulenc 1971b).

A skin freshener (10% of a 40% aqueous solution of Sodium Silicate) was tested in a Draize eye irritation study in six rabbits. The compound had a typical weight ratio of SiO_2/Na_2O of 3.25. No eye irritation potential as judged by the Draize classification of eye irritation was demonstrated in this study (CTFA 1979b).

A summary of information on Sodium Silicate put together by European companies (EUCLID 2000) included the ocular irritation data shown in Table 11.

TABLE 10
Potassium Silicate: ocular irritation in rabbits (EUCLID 2000)

Method	Result
Diluted solution; molar ratio = 3.9; concentration = 7%–7.5%	Nonirritating
Diluted solution; molar ratio = 3.4; concentration = 8.5%–9%	Nonirritating

GENOTOXICITY

Sodium Metasilicate

DNA damage and repair assays without metabolic activation were conducted on *Bacillus subtilis* recombination-repair-deficient and wild-type strains. Sodium Metasilicate at concentrations of 0.005–0.5 M was not genotoxic (Kada, Brun, and Marcovich 1960).

Sodium Silicate

Strains B/Sd-4/1,3,4,5 and B/Sd-4/3,4 of *Escheria coli* were used to study the mutagenic action of Sodium Silicate (Demerec, Bertani, and Flint 1951). The streptomycin-dependent bacteria

TABLE 11
Sodium Silicate: Draize ocular irritation in rabbits (EUCLID 2000)

Method	Result	Remark
Molar ratios of 1 and 2; concentrations of 10% and 8%	Irritating	Sodium Silicate solutions of less than 10% are irritating but not highly irritating.
Molar ratios of 2 and 2.9; concentrations of 44% and 43%	Highly irritating	Concentrated solutions of molar ratios >2.9 are severely irritating.
Molar ratio of 3.2; concentration of 36%	Nonirritating	

(Sd-4) were treated with 0.025%, 0.01%, 0.05%, 0.1%, 0.15%, or 0.3% Sodium Silicate for three hours at 37°C. The control suspension was distilled water instead of streptomycin. At the end of treatment, both treated and control suspensions were assayed on streptomycin-agar plates. Samples from the suspensions (0.1 ml) were also plated on streptomycin-free plates, incubated for 6 days, and the frequency of mutants was calculated. Sodium Silicate was nonmutagenic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Groups of three adult albino rats were injected intratesticularly and subcutaneously with doses of 0.08 mM/kg Sodium Silicate. By the testicular route, the left testis was treated and the right testis served as the control. The rats were killed 2, 7, and 30 days after injection. The testis and the spermatozoa were prepared for microscopic examination. No morphological changes were seen in the testis at anytime after either of the Sodium Silicate injections. No effect on the residual spermatozoa in the ductus deferens was apparent either (Kamboj and Amiya 1964).

As described earlier, Smith et al. (1973) added a Sodium Silicate solution to the drinking water containing 600 and 1200 ppm of added silica and given to groups of six weanling male and six female Sprague-Dawley rats. Control groups received no Sodium Silicate in their drinking water. At 4 months of age, the rats of treatment groups were mated. At 600 ppm and 1200 ppm, the treated water decreased the numbers of offspring born to 67% and 80% of controls, respectively. Also these treatments decreased the numbers of surviving offspring until weaning (3 weeks) to 46% and 24% of the control values.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Sodium Metasilicate

A Sodium Metasilicate/carbonate granular detergent was applied to intact and abraded skin of humans for four hours. Each subject afforded eight test sites aligned four on each side of the back about 5 cm from the midline. Sites were vertically spaced 3 cm apart in the area between the scapula and the waist. Erythema and edema were graded 4, 24, and 48 h after the patch applications. Primary irritation indices (PIIs) were calculated by averaging the scores for all test sites. The detergent contained 37% Sodium Metasilicate and was applied at a concentration of 50% (w/v aqueous). The results from this study are presented in Table 12. The PII was >3.6 and the material was judged to be a severe irritant (Nixon, Tyson, and Wertz 1975).

Clairol (2000a) studied the irritancy of Sodium Metasilicate in a modified soap chamber test. Two hair color kits including a developer, activator, and lightener were tested. Sodium Metasilicate was a component of the activator at a concentration (*w/w*) of 13.5% in both kits; on-head concentrations were 1.34% (kit 1) and 1.43% (kit 2). The two test patches, a positive-control patch dosed with 2% sodium lauryl sulfate (SLS), and a negative-control patch dosed with deionized water were applied to the lower back of nineteen subjects for approximately 4 h. The test sites were graded for erythema, edema, burning, stinging, and itching approximately 4 h after application (20 min after removal) and approximately 28 h after application (24 h after removal). A separate 24-h 0.75% SLS reactivity patch was applied to the upper back and graded at the 28-h time point only.

No fissuring or scaling was observed over the course of the study. The kit 1 mean erythema + edema grade at 4 h was 1.00 and for 28 h was 0.50. For kit 2, the mean erythema + edema scores at 4 h was 0.95 and for 28 h was 0.53. The positive control had a 28-h erythema + edema grade of 2.92. No adverse events occurred during the course of the study (Clairol 2000a).

In a second modified soap chamber test, Clairol (2000b) tested Sodium Metasilicate to determine the incidence and severity of irritation. Procedures stated in the above study were followed. Twenty-one subjects completed this study. Sodium Metasilicate was a part of the activator in the hair coloring system and concentrations (*w/w*) were 13.5% in the activator and 2.58% on the head.

No burning or itching was recorded. The mean 6-h and 24-h erythema + edema scores were 1.36 and 0.56, respectively.

TABLE 12
Sodium Metasilicate: human dermal irritancy (Nixon, Tyson, and Wertz 1975)

End point	Intact	Abraded
Mean irritation scores	>3.0	>4.2
Tissue destruction	0/8	1/8

The reactivity control containing 0.75% SLS had a 28-h mean erythema + edema score of 0.89 (Clairol 2000b).

L'Oreal (2000a) assessed 15 bleach formulations in the elbow crease test. Experimental groups comprised 20 to 40 healthy adults. Approximately 0.7 ml of mixed product (developer + activator or developer + base + activator) was applied in the elbow creases on 40 cm^2 for 50 min without occlusion. The test sites were evaluated for erythema, edema, and vesicles by a trained grader using a 4-point visual scoring system for each parameter. Time points for evaluation were 5 min, 4 h, and 24 h following the removal of the products by rinsing. The Sodium Metasilicate concentrations in the activators and in the product mixtures ranged from 3.4% to 14% and 1% to 7%, respectively.

Under the study conditions, all products induced low grade irritation: almost exclusively mild erythema and only occasionally moderate erythema at 5 min. Observable changes subsided quickly after product removal, leaving slight erythema at 1 h in only a few volunteers. No correlation could be observed between Sodium Metasilicate concentrations and the irritation potential of the product (L'Oreal, 2000a).

L'Oreal (2000b) tested 32 hair bleaches in semioccluded patch tests. Sodium Metasilicate concentrations ranged from 3.4% to 14% in the activators and from 0.75% to 6.8% in mixed products; 0.2 ml of the mixed product were applied under patch tests for 1 h and 15 min on the back. Experimental groups were comprised of 25 healthy adults. Test sites were evaluated for erythema, edema, and vesicles using a 7-point visual scoring system encompassing all the parameters at 30 min and 24 h following the removal of the products by rinsing. Mean irritation scores were calculated for each time point.

Under the study conditions, Sodium Metasilicate produced only mild and transient irritation under exaggerated conditions of application. Irritation scores appeared to be independent of silicate concentration (L'Oreal 2000b).

Sodium Silicate

Nixon, Tyson, and Wertz (1975) applied three detergents containing Sodium Silicate to intact and abraded skin of humans for four hours. One sample contained 7% Sodium Silicate in a high-carbonate detergent, the second contained 13% in a low-carbonate detergent, and the third contained 6% in a phosphate detergent. Eight subjects were tested for each detergent. Each subject afforded eight test sites aligned four on each side of the back about 5 cm from the midline. Sites were vertically spaced 3 cm apart in the area between the scapula and the waist. Erythema and edema were graded 4, 24, and 48 h after the patch applications. PIIs were calculated by averaging the scores for all test sites.

The authors concluded that each sample had negligible irritancy. The results from this study are presented in Table 13 (Nixon, Tyson, and Wertz 1975).

Hill Top Research, Inc. (1979) conducted a study of cumulative irritant properties of a series of test materials with 10% of a 40% aqueous solution of Sodium Silicate on 12 male and female panelists. The test material was applied to the backs of the panelists in randomized manner. Each sample was reapplied to the same test site on each panelist for the remainder of the study (21 consecutive days) or until the max irritation score was reached. If the max score was reached, the patch was omitted and the patch area was scored for residual irritation for the next three scoring dates.

The test patches were removed by the panelists 23 h after application. The panelists were instructed to take a bath or shower immediately following removal of the patches and to keep the patch areas dry at other times. Approximately 0.3 ml of each sample was applied to each patch. Reactions to the test samples were scored 24 h after application (1 h after patch removal). Scores were classified as following: 0–49 (mild material, no irritation); 50–199 (probably mild in normal use); 200–449 (possibly mild in normal use); 450–580 (experimental cumulative irritant); 581–630 (experimental primary irritant).

The total score calculated for the panelists was 155, classifying the test compound as probably a mild irritant in normal use (Hill Top Research, Inc. 1979).

A skin freshener (10% of a 40% aqueous solution of Sodium Silicate) was evaluated via a 4-day minicumulative irritancy assay. A currently marketed product was used as a mildness frame of reference. Both materials were tested full strength under occlusive patch conditions in 20 humans. The PII for the test product was 0.5 and was 0.88 for the currently marketed product. The test product exhibited acceptable irritancy results and was significantly milder than the reference control (CTFA 1989).

Clairol (2000c) studied the irritancy of Sodium Silicate in a modified soap chamber test. Two hair color kits including a developer, activator, and lightener were tested. Sodium Silicate

TABLE 13

Sodium Silicate: human dermal irritancy (Nixon, Tyson, and Wertz 1975)

Detergent type (Sodium Silicate concentration)	Concentration of detergent (*w/v* aqueous)	Mean scores			Tissue destruction		Irritancy judgement
		Intact	Abraded	PII	Intact	Abraded	
High carbonate (7%)	50%	0.0	0.0	0.0	0/8	0/8	Negligible
Low carbonate (13%)	50%	0.0	0.2	0.1	0/8	0/8	Negligible
Phosphate (6%)	50%	0.0	0.4	0.3	0/8	0/8	Negligible

was a component of the activator at 35.75% (*w/w*) with on the head concentrations of 4.26% (kit 1) and 7.61% (kit 2). The two patches listed before, along with a positive-control patch dosed with 2% SLS and a negative-control patch dosed with deionized water, were applied to the lower back of 19 subjects for approximately 4 h. The test sites were graded for erythema, edema, burning, stinging, and itching approximately 4 h after application (20 min after removal) and approximately 28 h after application (24 h after removal). A separate 24-h 0.75% SLS reactivity patch was applied to the upper back and graded at the 28-h time point only.

No fissuring or scaling was observed over the course of the study. The mean erythema + edema scores at 4 and 28 h were 1.24 and 0.45, respectively, for kit 1; the mean erythema + edema scores at 4 and 28 h were 1.26 and 0.53, respectively, for kit 2. The positive control containing 0.75% SLS had a mean 28-h erythema + edema score of 2.92. No adverse events occurred during the course of the study (Clairol 2000c).

In a second modified soap chamber test, Sodium Silicate was tested to determine the incidence and severity of irritation. Procedures stated in the Clairol 2000 study were followed. Twenty-one subjects completed this study. Sodium Silicate was a part of the activator in the hair coloring system and concentrations (%, *w/w*) in the activator and on the head were 35.75 and 2.13, respectively. No burning or itching was recorded. The mean 6-h and 24-h erythema + edema scores were 0.58 and 0.19, respectively. The reactivity control containing 0.75% SLS had a 28-h mean erythema + edema score of 0.89 (Clairol 2000d).

Sodium Silicate was evaluated in an elbow crease test previously described in the clinical dermal irritation section under Sodium Metasilicate (L'Oreal 2000). Sodium Silicate was present in only two activators at concentrations of 10.6% and 29.6% (2.1% and 8.5% respectively, in the product mixture). Under the study conditions, all products induced low-grade irritation: almost exclusively mild erythema and only occasionally moderate erythema at 5 min. Observable changes subsided quickly after product removal, leaving slight erythema at 1 h in only a few volunteers (L'Oreal, 2000c).

Sodium Silicate was evaluated in semiocclusive patch tests previously described in the clinical dermal irritation section under Sodium Metasilicate (L'Oreal 2000b). Sodium Silicate concentrations ranged form 10.6% to 29.6% in the activators and 1.2% to 6.5% in the mixed products. Under the conditions of this study, all products induce only mild and transient irritation under exaggerated conditions of application. Irritation scores appeared to be independent of silicate concentration (L'Oreal 2000d).

Skin Sensitization

To determine its capacity to induce skin irritation and allergic sensitization, 10% of a 40% aqueous solution of Sodium Silicate was used in a repeat-insult predictive patch test. Ten patches were applied to the upper backs of 94 panelists. Five were placed on the right side and five were placed on the left side. The sample was applied to all panelists for 24 h every Monday, Wednesday, and Friday for 3 consecutive weeks. The samples were applied to the same site each time. The challenge was conducted in week 6 of the study. A single patch was applied to a previously unpatched site. These patches were removed 24 h following application. Reactions were scored 24 and 48 h after removal. Subjects exhibiting challenge patch reactions indicative of possible induced sensitization participated in follow-up testing after 1 week. Within the limits imposed by the sample size and the test procedure itself, the test material did not exhibit any potential for inducing allergic sensitization (CTFA 1979c).

Case Reports

Sodium Metasilicate

Colloidal Sodium Metasilicate, 0.5 L, was orally ingested and led to the patient's death within 1 to 1.5 h. At autopsy, alkali burns were present in the gastric mucosa; and the stomach contained a small amount of liquid with a pH of 11.5. The liquid was chemically analyzed and was found to be condensed "waterglass." At microscopic examination of the lungs, numerous bronchioles and alveoli were filled with amorphous Sodium Metasilicate. Due to the obstruction of the airways, inhibition of alveolar gas diffusion could have been the cause of death. Liquid Sodium Metasilicate solidification occurred in the lungs by means of carbonic acid of expired air. This occurred due to the fact that Sodium Metasilicate starts to solidify at pH 11.3. Gas tric secretions had lowered the pH of the Sodium Metasilicate from 12.5 to 11.5 (Sigrist and Flury 1985).

Sodium Silicate

A man who drank 200 ml of a neutralized Sodium Silicate solution (estimated to contain about 100 g of solid Sodium Silicate or more than 1 g/kg) demonstrated prompt vomiting, diarrhea, and gastrointestinal bleeding, and later had albumin, acetone, "sugar," and blood in the urine. The patient recovered even at this dose. The authors noted that such a neutral silicate would be expected to be less corrosive than unneutralized, strongly alkaline Sodium Metasilicate (Eichhorst 1921).

Tanka, Miyachi, and Horio (1982) reported a case involving a 57-year-old man exposed to Sodium Silicate. At first examination, the eruption consisted of lichenified lesions with hyperpigmentation and four ulcers on the dorsum of the left hand. The lesions appeared oval to round and punched out with irregular and elevated margins. Urticarial wheals were not present and axillary lymph nodes were not palpable. A patch test was performed on the flexor surface of the skin using 20% aqueous solution of Sodium Silicate. Within 24 h, macular erythema and papules with itching were noted. A wheal appeared at the application site immediately after the patch was removed at 24 h. The wheal was not seen after a 15-min patch test. Itchy erythema progressed into ulcer formation after 1 week. A scratch test was also performed and resulted in wheal formation after

15 min. A skin biopsy of a lichenified site near an ulcer revealed spongiosis and exocytosis with individual cell keratinization in the upper epidermis. Patchy perivascular cell infiltration of polymorphonuclear leukocytes also was noted. The patch test biopsy specimen had similar lesions.

To further investigate these findings, these authors performed patch tests with 20% Sodium Silicate on the flexor surface of 30 people. After 48 h, positive reactions were noted in 22 of the volunteers. Erythema similar to that of the case study was seen. No ulcers formed. Scratch tests were also performed on the same volunteers with 20% Sodium Silicate. No wheal formation was observed (Tanka, Miyachi, and Horio, 1982).

SUMMARY

This report provides a review of the safety of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate. These ingredients combine metal cations (potassium or sodium) with silica to form inorganic salts.

Aqueous solutions of Sodium Silicate species are a part of a chemical continuum of silicates based on an equilibrium of alkali, water, and silica. pH determines the solubility of silica and, together with concentration, the degree of polymerization.

These ingredients function as corrosion inhibitors in cosmetics; Sodium Metasilicate also functions as a chelating agent and Sodium Silicate as a buffering and pH adjuster. Sodium Metasilicate is currently used in 168 formulations at concentrations ranging from 13% to 18%. Sodium Silicate is currently used in 24 formulations at concentrations ranging from 0.3% to 55%.

Potassium Silicate and Sodium Silicate were reported as being used in industrial cleaners and detergents. Sodium Metasilicate is a GRAS food ingredient.

Sodium Silicate administered orally acts as a mild alkali and was readily absorbed from the alimentary canal and excreted in the urine. Urinary excretion of Sodium Silicate given orally to rats at 40 and 1000 mg/kg was 18.9% and 2.8%, respectively.

The toxicity of these silicates has been related to the molar ratio of SiO_2/Na_2O and the concentration. The acute oral LD_{50} of Sodium Metasilicate ranged from 847 mg/kg in male rats to 1349.3 mg/kg in female rats, and from 770 mg/kg in female mice to 820 mg/kg in male mice. Gross lesions of variable severity were found in the oral cavity, pharynx, esophagus, stomach, larynx, lungs, and kidneys of dogs receiving 0.25 g/kg or more of a commercial detergent containing Sodium Metasilicate. Similar lesions were seen in pigs given the same detergent and dose as in the previous study. Male Sprague-Dawley rats orally administered 464 mg/kg of a 20% solution containing either 2.0 or 2.4 ratio to 1.0 ratio of sodium oxide showed no signs of toxicity, whereas doses of 1000 and 2150 mg/kg produced gasping, dypsnea, and acute depression.

Beagle dogs fed 2.4 g/kg/day of Sodium Silicate for 4 weeks had gross renal lesions but no impairment of renal function. In a oral subchronic study (drinking water containing 600 and 1200 ppm of added silica), there were body weight gains in male rats, but decreases in female rats. No apparent effect of the treatment in the drinking water was found on the longevity in rats having started treatment after weaning.

Intraperitoneal injections of a neutralized 2% solution of Sodium Metasilicate in white rats resulted in a decrease in spleen weight and relative enlargement of the kidneys.

Dermal irritation of Potassium Silicate, Sodium Metasilicate, and Sodium Silicate ranged from negligible to severe, depending on the species tested and the molar ratio and concentration tested.

Sodium Metasilicate was negative in the local lymph node assay, but a delayed-type hypersensitivity response was observed in mice.

Potassium Silicate was nonirritating in two acute eye irritation studies in rabbits. Sodium Metasilicate (42.4% H_2O) was corrosive to the rabbit eye. Sodium Silicate was a severe eye irritant in acute eye irritation studies. A skin freshener (10% of a 40% aqueous solution) containing Sodium Silicate was nonirritating. Sodium Silicate in another three Draize eye irritation studies was highly irritating, irritating, and nonirritating, respectively.

Sodium Metasilicate was nonmutagenic in a DNA damage and repair assay without metabolic activation using *B. subtilis*. Sodium Silicate was nonmutagenic in studies using *E. coli* stains B/Sd-4/1,3,4,5 and B/Sd-4/3,4.

Rats given Sodium Silicate (600 and 1200 ppm of added silica) in the drinking water in reproductive studies produced a reduced number of offspring; to 67% of controls at 600 ppm and to 80% of controls at 1200 ppm. Three adult rats injected intratesticularly and subcutaneously with 0.8 mM/kg of Sodium Silicate showed no morphological changes in the testes and no effect on the residual spermatozoa in the ductus deferens.

Sodium Metasilicate/carbonate detergent (37% Sodium Metasilicate) mixed 50/50 with water was considered a severe skin irritant when tested on the intact and abraded human skin. Detergents containing 7%, 13%, and 6% Sodium Silicate mixed 50/50 with water, however, were negligible skin irritants to intact and abraded human skin. A 10% of a 40% aqueous solution of Sodium Silicate was negative in a repeat-insult predictive patch test in humans. The same aqueous solution of Sodium Silicate was considered mild under normal use conditions in a study of cumulative irritant properties. Sodium Metasilicate and Sodium Silicate were studied in modified soap chamber tests. No burning or itching was observed and low erythema + edema scores were noted. Sodium Metasilicate and Sodium Silicate, tested in elbow crease studies and semioccluded patch tests, produced low grade and transient irritation.

Colloidal Sodium Metasilicate was fatal to one man and neutralized Sodium Silicate produced vomiting, diarrhea, and gastrointestinal bleeding in another man in separate case reports.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel determined that the data provided in this report are sufficient to

address the safety of the tested ingredient Potassium Silicate, Sodium Metasilicate, and Sodium Silicate. The Panel recognized the irritation potential of these ingredients, especially in leave-on products. However, because these ingredients have limited dermal absorption and Sodium Metasilicate is a GRAS direct food substance, the Panel deemed the ingredients safe as currently used, when formulated to avoid irritation.

CONCLUSION

Based on the available data contained within this report, the CIR Expert Panel concluded that Potassium Silicate, Sodium Metasilicate, and Sodium Silicate are safe for use in cosmetic products in the practices of use and concentration described in this safety assessment, when formulated to avoid irritation.

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Final Report of the Cosmetic Ingredient Review Expert Panel

Safety Assessment of Silica and Related Cosmetic Ingredients

September 25, 2009

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ABSTRACT

This is a safety assessment of silica and the related cosmetic ingredients: alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate. These ingredients are synthetic amorphous silicas and silicates; crystalline silica is not a cosmetic ingredient and is not used in cosmetics. These ingredients are used as bulking agents and for various other functions. The human and animal safety data relevant to the cosmetic use of these ingredients were assessed by the Cosmetic Ingredient Review (CIR) Expert Panel. The Panel concluded that these ingredients are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment when formulated to be non-respirable.

INTRODUCTION

There are 2 categories of silica, crystalline and amorphous. Only the amorphous forms of silica, and more specifically, synthetic amorphous silica and silicates, are used in cosmetics. Accordingly, this safety assessment addresses silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate.

Crystalline silica is not used in cosmetics.

Synthetic amorphous silica is created by 2 methods, wet and thermal. The wet process creates silica gel and hydrated silica (also known as precipitated silica). The thermal process creates fumed silica, which is also referred to as pyrogenic silica in recent publications. These are the only forms of silica addressed in this safety assessment. The fumed silica is not to be confused with silica fume, which is a crystalline form of silica, not used in cosmetics, and is not considered in this safety assessment. Figure 1 demonstrates the different polymorphs of silica.

In each summary of data, the term for the form of silica used by the author is used. When the type of silica is not made clear the term silica is used.

An earlier safety assessment by the Cosmetic Ingredient Review (CIR) Expert Panel addressed the safety of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, potassium silcate, pryrophyllite, sodium metasilicate, sodium silicate, and zeolite. The CIR Expert Panel concluded that these ingredients were "...safe as used in cosmetic products...". The Panel also reviewed potassium silicate, sodium metasilicate, and sodium silicate and concluded that they were "...safe for use in cosmetic products in the practices of use and concentration described in this safety assessment, when formulated to avoid irritation..." (Andersen 2003, 2005).

CHEMISTRY

Definition and Structure

Silica

The CAS No. 7631-86-9 is the general CAS No. which includes all forms of Silicas including amorphous, crystalline, synthetic, and natural forms (United Nations Environmental Programme Chemicals Unit [UNEP] 2004). This safety assessment is limited to amorphous forms of silica.

According to the *International Cosmetic Ingredient Dictionary and Handbook*, silica (CAS Nos. 7631-86-9 [colloidal], 60676-86-0, 112945-52-5 [fumed]) is the inorganic oxide that conforms to the formula SiO_2. Silica functions as an abrasive, absorbent, anti-caking agent, bulking agent, opacifying agent, and suspending agent - nonsurfactant. Other technical names for Silica are:

- amorphous silica;
- amorphous silcon oxide hydrate;
- silica, amorphous;
- silicon, anhydride;
- silicon dioxide; and
- silicon dioxide, fumed (Gottschalck and Bailey 2008).

The current terminology for “silicon dioxide, fumed” is “pyrogenic silica.”

Alumina Magnesium Metasilicate

Alumina magnesium metasilicate (no CAS No.) is the inorganic compound that conforms generally to the formula:

$MgSiO_3 \cdot Al_2O_3$.

Alumina Magnesium metasilicate functions as an absorbent, bulking agent, and a viscosity increasing agent - nonaqueous. Another technical name is magnesium metasilicate/aluminate (Gottschalck and Bailey 2008).

Aluminum Calcium Sodium Silicate

Aluminum Calcium sodium silicate (CAS No. 1344-01-0) is a complex silicate refined from naturally occurring minerals. Aluminum calcium sodium silicate functions as a bulking agent (Gottschalck and Bailey 2008). Other technical names include:

- aluminosilicic acid (unspecified), calcium sodium salt, hydrate;
- aluminosilicic acid, calcium sodium salt;
- calcium sodium aluminosilicate;
- sodium calcium aluminosilicate;
- sodium calcium aluminosilicate, hydrated;
- sodium calcium silicoaluminate; and
- sodium calcium silicoaluminate hydrate (ChemIDplus Lite 2009).

Aluminum Iron Silicates

Aluminum iron silicates (no CAS No.) is a ceramic powder consisting mainly of silicon dioxide, aluminum oxide, and

ferric oxide. Aluminum iron silicates function as abrasives and bulking agents. Another technical name is silica aluminum silicate ceramics (Gottschalck and Bailey 2008).

Hydrated Silica

Hydrated silica (CAS Nos. 1343-98-2 [Silicic Acid]; 10279-57-9; 63231-67-4; 112926-00-8) is the inorganic oxide that conforms generally to the formula

$SiO_2 \cdot xH_2O$

where x varies with the method of production and extent of drying performed on the material. Hydrated silica functions as an abrasive, absorbent, anti-caking agent, bulking agent, opacifying agent, oral care agent, skin-conditioning agent - miscellaneous, and viscosity increasing agent - aqueous. It is also referred to as:

- silicic acid;
- hydrosilicic acid;
- precipitated silica;
- silica gel;
- silica hydrate;
- silicic acid hydrate; and
- silicon dioxide hydrate (Gottschalck and Bailey 2008)
- colloidal silica (Arts et al. 2007).

Sodium Potassium Aluminum Silicate

Sodium Potassium aluminum silicate (CAS No. 12736-96-8 and 66402-68-4) is a complex silicate refined from naturally occurring minerals, or derived synthetically. It functions as a bulking agent (Gottschalck and Bailey 2008).

Amorphous Vs. Crystalline Silica

Silica is a silicon-oxygen tetrahedral unit where a silicon atom is central within 4 oxygen atoms that are shared with adjacent silicon atoms. Various physical forms of silica are caused by differences in the spatial relationships of the tetrahedral that determine physical characteristics. Amorphous silica has an irregular tetrahedral pattern. Crystalline silica is polymorphic where each variety has a characteristic regular 3-dimensional arrangement of the tetrahedral (Heppleston 1969). As would be predicted from these descriptions, crystalline silica has a well-defined x-ray diffraction pattern; whereas amorphous forms of silica do not (Villota and Hawkes 1986).

There are 3 classifications of amorphous silica. Vitreous silica, or fused crystalline silica, is formed by the supercooling of molten silica. It has a low coefficient of thermal expansion, high thermal shock resistance and high ultraviolet transparency. Microamorphous silica is a dense thermally unstable amorphous silica which converts to quartz at high temperatures. Microamorphous silica includes solutions, gels, powders, and porous glasses. This group has the subclasses amorphous silica fibers; microscopic fibers; and microparticulate silica, which includes precipitated and fumed silicas (Villota and Hawkes 1986). Kaewamatawong et al. (2005) divides the microamorphous forms of amorphous silica

into fumed, colloidal, precipitated, diatomaceous earth, gel, and hydrous. The colloidal form ranges in size from 10 micrometers to <10 nanometers.

The different polymorphs of silica are shown in Figure 1. Again, only synthetic amorphous silica forms are used in cosmetics. Crystalline silica forms are not used in cosmetics.

Physical and Chemical Properties

Properties

Silica

The acidity of synthetic amorphous silica is related to the number and reactivity of the silanol groups present on the solid silica surface. Surface silanols (pKa = 7.1) are more acidic than monosilicic acid (pKa = 9.8). The acidity increases with the degree of polymerisation (Yates and Healy 1976).

Villota and Hawkes (1986) stated that the surface of silica may be made up of free silanol groups (isolated hydroxyls), hydrogen-bonded silanol groups (hydroxyl groups on adjacent surface silicon atoms) and siloxane groups.

Amorphous silica is capable of rehydroxylating in aqueous systems to form a high ratio of silanol to siloxane groups. Depending on the hydrophobic properties of the solvent, it may form a network-like structure through hydrogen bonding. This gives amorphous silica gelling and thickening abilities in various solvent systems.

Oxygen electron donors of compounds such as ethers, alcohols, and ketones or the nitrogens of amides and amines may interact through hydrogen bonding due to the acid dissociation constant of the silanol groups on the silica surface. Esterification has been reported with an Si-O-C-R structure. A totally dehydrated silica or a fully hydrated silica has little or no adsorption of hydrophobic organocompounds (Villota and Hawkes 1986).

The *Food Chemicals Codex* states that silica is a white, fluffy nongritty powder of extremely fine particle size that is hygroscopic. Silica absorbs moisture from the air in varying amounts (Food and Nutrition Board [FNB] 1996).

Cabot Corporatation (2004) stated that silica has thixotropic properties. The particles form a 3-dimensional network in a liquid system which increases viscosity. When shear forces are applied (i.e., stirring), the material flows as a liquid. When the forces cease, the material gels again.

The saturation concentrations for a set of analyzed Silicas ranged from 1.91 to 2.51 mmol/l (European Centre for Ecotoxicology and Toxicology of Chemicals [ECETOC] 2006). Saturation concentration increased with specific surface area. Surface treated, hydrophobic silica had a low solubility compared to hydrophilic silica. This was due to reduced wetting of the surface in aqueous systems. Wetting was increased by alcohol which decreased solubility.

Additional chemical and physical properties of silica are listed in Table 1. Physical properties by Brunauer, Emmett, and Teller (B.E.T.; a rule for the physical adsorption of gas molecules on a solid surface that serves as the basis for the

measurement of the specific surface area of a material) surface areas of 200, 325, or 380 m^2/g are shown in Table 2. Note that the properties are the same regardless of B.E.T. in this range.

Particle Size and Form

Silica

Amorphous Silicas are composed of very fine particles (average of 20 µm) which tend to aggregate loosely in the air (Byers and Gage 1961).

Primary particles, or single particles, do not exist in isolation in fumed (pyrogenic) and precipitated silica; only in silica sol (colloidal). Aggregates assemble in chains (fumed) or clusters (precipitated and gel). Agglomerates are assemblies of aggregates, held together by strong physical adhesion forces and not in a dispersible nano size (< 100 nm) (ECETOC 2006; Gray and Muranko 2006).

Methods of Manufacture

All of the cosmetic ingredients in this assessment have mineral sources, but may be synthetically manufactured. Sodium Potassium Aluminum Silicate is refined from naturally occurring minerals or derived synthetically. Aluminum Calcium Sodium Silicate is refined from naturally occurring minerals (Gottschalck and Bailey 2008).

Silica

Amorphous silicas used in cosmetics (silica gel, precipitated silica, and pyrogenic silica in Figure 1) are synthetically produced. A manufacturing process for amorphous pyrogenic silica is shown in Figure 2 (Villota and Hawkes 1986).

Lewinson et al. (1994) stated that silica may be produced by a vapor-phase process producing fumed (pyrogenic) silica or by a wet process producing precipitated silica (silica gel or precipitated silica in Figure 1). Fumed silica is produced in a relatively anhydrous state, whereas precipitated silica contains a larger amount of bound water.

Mean particle size, particle size distribution, and degree of aggregation and/or agglomeration can be determined by adjusting the process parameters (Hurd and Flower 1988).

ECETOC (2006) reports that the thermal synthesis process without liquid water results in the presence of fewer silanol groups on pyrogenic silica (Figure 1).

Silicas manufactured by the wet process (silica gel and precipitated silica) contain between 2% and 10% physically bonded water which can be removed by drying.

Amorphous pyrogenic silica (Figure 1) is manufactued by the hydrolysis of volatile silanes, usually silicon tetrachloride, in the flame of an oxygen-hydrogen burner. The silicon tetrachloride is continuously vaporized, mixed with dry air then hydrogen, and then hydrolysed. The silica is then grown (nucleation, condensation, coagulation) and aggregated.

Precipitated silica and silica gels (Figure 1) are produced from an alkali metal silicate dissolved in water (i.e., water

glass) and an acid, usually sulphuric acid. After the reaction of water glass with the acid, silica is precipitated. The properties of the silica can be influenced by the type of reactor and process parameters. The silica is filtered out and the resulting cake is 15% to 25% silica by weight. The cake is then dried and then milled.

Silica gels (Figure 1) are produced by the neutralization of an aqueous solution of alkali metal silicate with sulfphuric acid (gelation). Mixing continues until solidification begins; the gelation conditions dictate particle size in the hydrogel. The gel is then washed of excess salts; this procedure determines specific surface area. The silica gel is now a continuous structure with pores filled with water. The silica may be used as is, or dried. Xerogels are dried until water is still evaporating but the gel no longer shrinks. Aerogels are dried with negligible loss of pore volume.

Silica sols (colloidal silica; Figure 1) are dispersions of silica particles in a liquid, usually water, at 15% to 50%. These are sub-micron particles of silica and the sols flow like water. Silica sols are also produced by hydrolysis of monomeric $SiCl_4$ in aqueous solution followed by condensation of the original particles. Large particles are produced by hydrolysis of tetraethoxysilane in an alkaline solution of water and alcohol. Silica sols are also produced by redisperion of existing silicas (gels, precipitated or, occasionally pyrogenic). For any process, the dispersed silica particles are stabilized by the addition of KOH, NaOH, NH_3, or HCl (ECETOC 2006).

There was no information found on the manufacturing processes for the salts of silica in this report.

Analytical Methods

Silica

Surface silanols of silica may be analyzed by Fischer titration; chlorination with thionylchloride ($SOCl_2$); Zerewitinoff determination with methyl magnesium iodide (CH_3MgI) or methyl lithium (CH_3Li); infrared-spectroscopy; ^{29}Si cross-polarization magic-angle-spinning (CP-MAS) nuclear magnetic resonance (NMR) spectroscopy; titration with caustic soda (NaOH); and thermo-gravimetric analysis (loss on ignition) (ECETOC 2006).

Gas adsorption may be used to determine specific surface area and porosity of pyrogenic silica (ECETOC 2006). Infrared (IR) spectroscopy was used to analyze silanol groups, alkyl groups, and silonol groups. NMR spectroscopy was used to determine relative amounts of mono-, di-, and trialkylsilane groups, cross-linking of alkylsilanes, side chains, ethoxy and methoxy groups, extractable organic compounds, and Si-O-Si bond distribution. Electron spectroscopy was used to analyze composition and chemical state of the surface and concentration gradients and diffusion profiles of silica. Mass spectroscopy was used for trace analysis of the surface of silica. Atomic force microscopy (AFM) was used to analyze morphology and porosity. Gravimetry and titration was used to analyze silanol groups.

Particle size analysis may be done by sieving, cascade impactor, time-of-flight, dynamic light scattering, static light scattering, Fraunhofer diffraction with air disperison, and Fraunhofer diffraction with liquid disperison (ECETOC 2006).

Sayes et al. (2007) stated that the surface area of silica particles may be measured by the B.E.T. method; and size, size distribution, and surface charge by dynamic light-scattering (DLS) spectroscopy.

Impurities

Silica

Cabot Corporation (2004) states that its silica products are >99.8% pure. The moisture content of untreated silica is < 1 wt%. Treated silicas are susceptible to adsorbing chemical vapors.

Pyrogenic silica was reported to be >99.8% pure with Al_2O_3 (< 0.05%), Fe_2O_3 (0.003%), TiO_2 (< 0.03%), Na_2O (<0.0009%), and chlorides as Cl (<0.025%). Precipitated silica and silica gel were reported to be ≥ 95% pure with Na_2O (0.2% to 2.4%), sulphates as SO_3 (0.2% to 3.0%), Fe_2O_3 (<0.05%), and trace oxides (<0.07%) (Roempp 2001).

The composition of colloidal silica was reported to be: SiO_2 (≥30%), Na_2O (0.1% to 0.4%), sulfates as $NaSO_4$ (0.01% to 0.03%), and aluminum oxide as a stabilizer (0.2%) (W.R. Grace & Co. 2003).

UNEP (2004) reported silica to be >95% pure. Possible impurities include: Na_2O (0.2% to 2.1% wt.), sulfates as SO_3 (0.2% to 3.0% wt.), Fe_2O_3 (< 0.05% wt.), and trace oxides (<0.07% wt.). Heavy metal impurities include: antimony (<5 ppm), barium (<50 ppm), chromium (<10 ppm), arsenic (<3 ppm), lead (<10 ppm), mercury (<1 ppm), cadmium (<1ppm), and selenium (<1 ppm).

USE

Cosmetic

According to information supplied to the Food and Drug Administration (FDA 2009) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), silica was used in a total of 3,276 cosmetic products. Use concentrations ranged from 0.0000003 - 44% according to a survey of current use concentrations conducted by the Personal Care Products Council (Council 2008). Hydrated silica is reported to be used in 176 products in the VCRP, at use concentrations of 0.001 - 34% based on the Council survey. Alumina magnesium metasilicate was not reported to be used in any products in the VCRP, but use concentrations between 0.001 and 0.02% were reported in the Council survey. Aluminum calcium sodium silicate was reported to be used in 7 cosmetic products in the VCRP, at use concentrations of 0.4 - 6% in the Council survey. Sodium potassium aluminum silicate was reported to be used in 1 product in the VCRP, with a use concentration of 0.001 - 4% in the Council survey. There were no reported uses in the VCRP or concentration of use reported in the Council survey for Aluminum iron silicates. Available data for the number of uses and use concentrations as a function of cosmetic product type are given in Table 3.

Silica is used in hair color sprays/aerosols. Jensen and O'Brien (1993) reviewed the potential adverse effects of

inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

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

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

Non-Cosmetic

Silica

Silica is used as a filler in rubber formulations (Byers and Gage 1961).

Silica is used in food preparations as an anticaking agent in dry powders, dispersion agent for dry powders in liquids, antisettling or suspending agent, stabilizer in oil/water emulsions, thickening or thixotropic agent, gelling agent, flavor carrier, extrusion aid, clarification and separation aid, and support matrix for immobilization of enzymes. It is also a general excipient for pharmaceuticals (Villota and Hawkes 1986). It is also used as a defoaming agent, conditioning agent, a chillproofing agent in malt beverages, and a filter aid in foods (FNB 1996). UNEP (2004) states that silica is used in pharmaceuticals as a thickener in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products. It is also used in foods. Silica can function as a carrier for fragrances or flavors. It is used in beer and wine clarification. Silica is used in animal feed as carriers and anticaking agents in vitamins and mineral premixes. Silica is used as reinforcing fillers for many non-staining and colored rubber and silicone products. It is used in "green tires". Silica is also used in paints, lacquers, plastics, and paper. Silica is used as an insecticide by it sorption of the cuticular lipid layer causing dehydration.

The colloidal form of silica is used in fiber, sizing, diazo paper manufacture, cellophane film, ceramics, grass fiber, paints, batteries, foods, and polishing (Kaewamatawong et al. 2005).

Javadzadeh et al. (2007) investigated the use of silica in a drug delivery system.

Aluminum Calcium Sodium Silicate

Aluminum calcium sodium silicate (sodium calcium aluminosilicate, hydrated) is generally recognized as safe (GRAS) in food for use at a level not exceeding 2% in accordance with good manufacturing processes as an anticaking agent (FDA

2007).

Hydrated aluminum calcium sodium silicate is used for countering the effects of aflatoxin (AF) in animal feed (Colvin et al 1989; Kubena et al. 1991; Chestnut et al. 1992; Harvey et al 1994; Smith et al. 1994; Abo-Norag et al 1995; Sarr et al. 1995; Edrington et al 1996; Abdel-Wahhab et al. 1998; Kubena et al. 1998; Ledoux et al. 1998; Mayura et al 1998; Bingham et al. 2004; Sehu et al 2007).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

Oral

Silica and Hydrated Silica

Sauer et al. (1959a,b) orally administered silica (80 mg/dose) in the form of sodium metasilicate, hydrated silica, and silica solution (30%) to guinea pigs (n = 5) in a single dose or in 4 repeated doses every 48 h. Urine and feces were collected in 48-h increments after each dose and analyzed for silica content.

The urinary output of silica, in the form of sodium metasilicate, when orally administered peaked within 48 h and gradually returned to normal after 8 days. When administered 4 times, 48 hours apart, the peak was maintained, but not increased. Forty-eight h after the last dose the concentration of silica in the urine began to return to normal.

The urinary output of silica, in the form of silica solution and precipitated silicic acid, when orally administered peaked within 48 h and gradually returned to normal after 8 days. These peaks were much lower than those of sodium metasilicate. When administered 4 times, 48 hours apart, the silica concentrations behaved similarly to the orally administered silica with a lower peak. When orally administered, 63% of the silica was recovered. The authors suggested that all of the silica in the urine was in the soluble or molybdate reactive form and that the silica particles underwent depolymerization prior to excretion (Sauer et al. 1959a,b).

UNEP (2004) reported an unpublished oral study of silica (1500 mg/kg/d) using female rats (strain and n not specified). Silica was orally administered daily for 30 days. The rats were then killed and necropsied. The silica content in the livers was 1.5 µg, in the kidneys was 6.4 µg, and in the spleen was 5.3 µg. The control values were 1.8, 7.2, and 7.8 µg silica, respectively.

In another unpublished study, female Sprague-Dawley (n not specified) rats were orally administered silica (100 mg/rat; ~500 mg/kg; aqueous suspension) 20 times over 1 month. No clinical signs were observed. The silica content in the liver was 4.2 µg (control value = 1.8 µg), in the spleen was 5.5 µg (7.2 µg), and in the kidneys was 14.2 µg (7.8 µg) (UNEP 2004).

Parenteral

Silica and Hydrated Silica

Sauer et al. (1959a) also administered silica solution or precipitated silica by intraperitoneal (i.p.) injection to guinea pigs (n = 5; see ORAL section above for details). Urinary silica increased above normal for 16 days. The levels of silica as silicic acid increased above normal for 28 days. Recovery of silica was 48%. The authors suggest that conditions in the peritoneal cavity favor the depolymerization and subsequent excretion of silica.

Intratraceal

Silica and Hydrated Silica

Byers and Gage (1961) intratracheally injected 3 types of silica (25 mg; 2.5% in 1 ml suspension) into adult albino Wistar rats (n = 100; 50 male, 50 female). Type A1 had a particle size of 19 µm; type A2 had a particle size of 20 µm but after storage became 60 µm; and type B had a particle size of 25 µm. Types A1 and A2 were from the same manufacturer. Rats were killed and necropsied at 12, 24, and 52 weeks. The amounts of silica in the tissues are given in Table 4.

The 3 types of silica elicited the same type of response in the lungs between types and sexes. Distribution of silica particles in the lungs was not uniform but aggregated in small areas throughout 1 or both lungs with the occasional large deposit. Silica particles were contained within macrophages, aggregated into foci around terminal and respiratory bronchioles. Some lymphocytes and fibroblasts surrounded these foci and intermingled within the macrophages with reticulin fibers woven through and around the lesion. Where dust deposits were heavy, the structure of the lung segments was completely obliterated by the lesions consisting of a group of macrophages with a few fibroblasts and lymphocytes that were contiguous and distinguished by the peripheral zone of fibroblasts and lymphocytes. These lesions were maximal at 12 weeks and gradually reduced with some contraction resulting in varying degrees of deformity of the lung. The lesions decreased in size and number over time and as function of the amount of silica present in the lungs.

Type B was the most quickly eliminated from the lungs; type A2, the largest particles, were the slowest. Type A2 also had larger lesions and induced a greater amount of fibroblastic proliferation. Lesions in the type B group were initially similar to A1 but the regression of the former was more rapid and final sections showed either a complete resolution or small scattered dust foci with few reticulin fibers. There also remained a few areas of confluent lesions which were small and irregular with a light reticulin network and little retraction. Evidence of infection (mild emphysema, few large abscesses, foci of bronchiectasis, pneumonia and bronchopneumonia) was infrequent and similar to controls.

The authors concluded that the dust from these 3 samples of precipitated silica do not aggregate sufficiently to be entirely retained by the upper respiratory passages and is still detectable in the lungs after 12 months. The lesions are different from those reported to be from quartz. The greater severity of the lesions from types A2 can be attributed to those

surface properties which resulted in its greater tendency to aggregate (Byers and Gage 1961).

Inhalation

Silica and Hydrated Silica

Klosterkötter and Bünemann (1961, 1962) exposed female rats (strain and n not provided) to aerosolized pyrogenic or precipitated silica (concentration and particle size not provided) for up to 6 days. After 3 months of recovery, 73.8% of the inhaled silica had been eliminated from the lungs. Only small amounts of silica were observed in the mediastinal lymph nodes.

In a second similar study, female rats were exposed to aerosolized pyrogenic or precipitated silica (particle size not provided) to study elimination from the lungs. Elimination was only slightly influenced by particle size. The lymphnodes were moderately enlarged with a silica content of < 2% eliminated. Most of the silica was eliminated within 1 to 2 months. Small amounts were detected in the lymph nodes. The precipitated silica, which was less soluble, was more slowly eliminated than the more soluble pyrogenic types (Klosterkötter and Bünemann 1961,1962).

UNEP (2004) reported several unpublished studies. In an unpublished inhalation study of silica (0.050 to 0.055 mg/l; particle size not provided) using female Sprague-Dawley rats (n not provided) the rats were exposed to aerosolized silica for 5 h/d for 5 d/weeks for 1 year. The rats had occurrences of bronchitis, putrid, lung inflammation, and pronounced cell reactions so exposure was reduced to 2 or 3 d/week; the exact time of the change was not provided. Rats in each group were killed and necropsied periodically during treatment and after treatment.

After 6 weeks of treatment, silica was observed in the lungs (0.5 mg) and the mediastinal lymph node (0.02 mg); after 18 weeks these values were 1.2 mg and 0.11 mg; and after 12 months, 1.37 mg and 0.13 mg, respectively. Corresponding to the respiration volume, 1% of the inhaled silica was retained in the lungs. After a recovery period of 5 months, there was 0.160 mg and 0.047 mg silica observed in the lungs and mediastinal lymph node, respectively, a reduction of 88% in the lung and > 50% in the lymph nodes. The increase in lung deposition was rapid at the initial exposure; levels of deposited silica were low from 18 weeks to 12 months of exposure.

In another unpublished inhalation study, female inbred albino rats (strain not specified; n not provided) were exposed to aerosolized silica (dose and particle size not provided) for 40 days. The amount was then increased to 40 to 50 mg/m^3 until day 120. A few of the rats were killed and necropsied periodically.

The average 1-day retention value was 28 µg/lung at the lower unspecified concentration. During the first 10 days, a steep linear increase was seen with ~28 µg/day as theoretically expected. Increments then became smaller. The author suggested that elimination increased and that an equilibrium between retention and elimination was established. After 40 exposures, the average 1-day retention value was 59 µg/lung at the high concentration. After 120 exposures, the total deposit

(lung and medistinal lymph nodes) was 435 µg/lung, equivalent to 7.4 % of the theoretically deposited material (5840 µg/lung, based on the measured 1-day retention); more than 92% of the deposited silica in the alveoli was eliminated during the exposure period. At that time, the mean retention of the lungs was only 300 µg/lung (~ 69% of the total). The deposition rate in the mediastinal lymph nodes was negligible during the first 40 days, but increased gradually. After 120 exposures, the retention was substantial amounting to 135 µg (~ 31% of the total deposit). A test for the determination of free alveolar cells showed a decrease immediately after a single exposure and 24 hours later an increase of 100% was observed.

In another unpublished inhalation study, aerosolized silica (0.05 mg/l; particle size not provided) was administered for 5 h per day for 3 days to female Sprague-Dawley rats (n not specified). They were observed for up to 3 months. Twenty h after the last exposure, 0.25 mg silica was found in the lungs. After 3 months, the silica content was 0.018 mg. In the lymph node, 0.018 mg silica was found after 1 month and 0.008 mg silica after 3 months.

In an unpublished inhalation study of precipitated and pyrogenic silica (55 mg/m^3; particle size not provided), rats (strain and n not specified) were exposed for 5 h to precipitated silica. For the precipitated silica, the mean retention value at 20 h was 0.138 mg/lung. For the pyrogenic silica, the mean retention value was 0.130 mg/lung. For the precipitated silica, the mean silica-content of the lungs after 4 months recovery was 1.022 mg, and 3.113 mg after 12 months. The corresponding values for the mediastinal lymphatic nodes were 0.033 mg and 0.069 mg, respectively. Five months after exposure, the average value for the lungs was only 0.457 mg (87% elimination rate) and 0.052 mg for the mediastinal lymphatic nodes (UNEP 2004).

ECETOC (2006) reported an unpublished study in which rats (strain and n not provided) were exposed to aerosolized hydrophobic silica (50 mg/m^3; particle size not provided) for 1 or 3 days. The rats were killed and necropsied after 20 h, 1 month, or 3 months. At 1 month recovery, elimination of silica was 78% (1 day exposure) and 75% (3 days exposure). After 3 months recovery, elimination was 87% and 92%, respectively. There was little silica in the mediastinal lymph nodes.

In another unpublished study, rats (strain and n not provided) were exposed to aerosolized hydrophobic silica (200 mg/m^3; particle size not provided) for 5 h/d for 3 days. After 3 months recovery, 81% of the silica was eliminated. Elimination by the lymph nodes was marginal (ECETOC 2006).

Subcutaneous

Pyrogenic Silica

UNEP (2004) reported an unpublished subcutaneous (s.c.) study of a single dose of silica (10 mg) using female Sprague-Dawley rats (n not provided). After 24 hours, 6.89 mg silica was found in the tissue at the application site. After 1 month the amount was decreased to 0.646 mg; after 2 months 0.298 mg was found.

ECETOC (2006) reported an unpublished report where pyrogenic silica (10 mg in water) was subcutaneously injected

in rats (strain and n not specified). It was quickly removed from the injection site. Mean recovery was 6.90 mg at 24 h, 0.65 mg after 1 month, and 0.30 mg after 2 months.

In another study, pyrogenic silica (30, 40, or 50 mg in water) injected subcutaneously in rats was 95% to 97% recovered after 6 weeks (ECETOC 2006).

Cytotoxicity

Pyrogenic and Hydrated Silica

Mammalian Cells

FDA (no date) reported the results of a cytotoxicity test using Chinese hamster V79 cells. There were no effects after 144 h of exposure to silica.

Davies (1981) incubated pyrogenic or hydrated (precipitated) silica or silica gel (13.5, 25 or 50 µg/cm^3) with mouse macrophages for 18 h. Pyrogenic silica and silica gel were cytotoxic to mouse macrophages similarly to crystalline silica (also tested); precipitated silica was less cytotoxic. The author concluded that all 3 silica types were cytotoxic at 13.5 µg/cm^3.

Zimmerman et al. (1986) exposed macrophages and neutrophils from C57BL/6 x DBA/2)F_1 (DBF_1) mice to pyrogenic silica (0, 100, 300, or 500 µg) for 1 to 3 h. Incubation with mid or high concentrations killed 80% to 100% of both types of phagocytes. An additional experiment showed that macrophages and neutrophils incubated with 10 or 30 µg silica were 88% to 99% viable after 1 to 3 h. When incubated in silica, both macrophages and neutrophils were inhibited in their ability to phagocytize sheep red blood cells, less so on neutrophils. The ability of these cells to phagocytize *Listeria monocytogenes* was completely inhibited at 300 µg and above; the inhibition was concentration dependent between 10 and 100 µg. Pre-incubation with silica (100 to 500 µg) also inhibited bactericidal activity of the macrophages and neutrophils; there was no effect on bacterial growth. There was a concentration dependent inhibition of bactericidal activity when the phagocytes were pre-incubated in silica at 10 to 300 µg.

Nyberg et al. (1996) incubated macrophages from male Sprague-Dawley rats with silica particles (3.2 ± 0.4 µm) for 30 min. The number of ingested yeasts were higher than the control silica particles. Silica treated macrophages were similar to resting macrophages.

Pandurangi et al. (1990) incubated sheep blood erythrocytes (1%) with pyrogenic silica (0.02 to 1.0 mg/ml) for 30 min. There was ~85% lysis for all concentrations tested. The authors concluded that the hemolytic activity may be connected to surface free OH group concentration.

Liu et al. (1996) exposed Chinese hamster lung fibroblasts (V79 cells) to silica (0, 20, 40, 80, or 160 µg/ml) for 24 h. Silica was cytotoxic at 80 µg/ml and no effects were observed at 40 µg/ml.

Mollo et al. (1997) incubated rat pleural mesothelial cells in fluorescein isothiocyanate-labeled silica (17, 33, and 66

µg/ml) for 6 and 24 h. The silica was present in the cytoplasm and concentrated around the nucleus, suggesting particle uptake, at both observation times. There was evidence of silica particles present in internalization vacuoles. The authors suggested that exposure to silica elicited an immediate defense response from cells through release of oxidizing and/or radical annealing agents.

Cha et al. (1999) incubated 2 renal cell lines (S_1 and IMCT) from transgenic mice harboring the SV40 large T antigen gene with various concentrations of silica (particle size 0.5 to 10 µm), or saline (control) for 1 h. The effect of silica (0.6 to 600 µg/ml) on cell injury was examined using trypan blue exclusion. After 1 h, silica-induced injury increased in a concentration-dependent manner in both cell lines. Cell injury increased at 60 µg/ml for S_1 cells and at 6 µg/ml for IMCT cells. At 600 µg/ml, cell injury was 28.0 ± 1.5% and 47.0 ± 2.2%, respectively. Cell injury was reduced with the addition of the chelator as well as a calcium channel blocker. Cells incubated for 1 h in silica had reduced $[ATP]_i$ in a concentration-dependent manner in both cell lines, but increased $[Ca^{2+}]$. The authors suggested that alteration of intracellular calcium homeostasis by silica is closely related with renal cell injury.

Kim et al. (2002) exposed alveolar macrophages collected from the lungs of Sprague-Dawley rats to silica (0.5 - 10 µm particle size). When macrophages were exposed to silica, cell death occurred in a concentration dependent manner with ~60% viability in cells exposed to 100 to 200 µg/ml which was attenuated by ambroxol. The authors concluded that ambroxol had a depressant effect on the silica-stimulated responses and cell death, which may be due to the inhibiton of activation processes, protein kinases, and calcium transport.

Human Cell Lines

O'Reilly et al. (2005) exposed normal human primary fibroblasts to silica (10 to 100 µg/ml) for 24 h to explore the sources of pulmonary inflammation from silica inhalation. Silica exposure induced cyclooxygenase (COX)-2 in a dose dependent manner starting at 10 µg/ml (10-fold more than crystalline silica). COX-1 expression was not affected by silica. Silica was nontoxic to the fibroblasts up to 100 µg/ml. COX-1 mRNA was unchanged by silica exposure. When exposure time was increased to 6 h, expression of COX-1 was induced at all concentrations. Prostaglandin (PG)E_2 was increased in a dose and time dependent manner, ~7 times more potent than crystalline silica. There was no increase in interleukin (IL)-1β expression. Silica exposure increased mPGES expression and was persistent up to 72 h. Silica exposure stimulated production of $PGF_{2\alpha}$ in a dose dependent manner and was 10-fold lower than PGE_2. Silica did not induce IL-6, monocyte chemoattractant protein (MCP)-1, or transforming growth factor (TGF)-β production but did strongly induce IL-8 production. The authors suggest that increased production of PGE_2 prevents the lung's transient inflammatory response from developing into fibrosis.

Brunner et al. (2006) tested the cytotoxicity of silica. Human mesothelioma MSTO-211H and rodent 3T3 fibroblast

cells were cultured with silica (0 to 15 ppm and 0 to 30 ppm) for 6 and 3 days, respectively. By measuring both the 3-(4,5-dimethylthiazol-2-yI)-2,5-diphenyltetrazolium bromide (MTT)-conversion and DNA content, there were no effects on the cells by silica.

Sayes et al. (2007) incubated immortalized rat L2 lung epithelial cells, rat lung alveolar macrophages, or both of these cells combined with silica. In L2 cells, silica produced increases in LDH levels at 520 µg/cm^2 of cell culture at 4 h. At 24 and 48 h, LDH levels increased over controls at 5.2, 52, and 520 µg/cm^2 in L2 cells. In alveolar macrophages, silica produced no increase in LDH levels up to 48 h and 5200 µg/cm^2. The 2 cell types were cultured together; silica produced no increase in LDH except for 520 µg/cm^2 at 24 and 48 h.

Silica produced decreases in cellular MTT levels at doses of 5.3 and 52 µg/cm^2 at 4 and 24 h in alveolar macrophages and no effect in L2 cells. In the combined cultures, there were no changes in MTT values due to silica at 4 h but a decrease in MTT levels at 5.2 and 52 µg/cm^2. MIP-2 production did not increase due to L2 cells exposed to silica but did in alveolar macrophages after 24 h. There was no increase in tumor necrosis factor (TNF)-α for either cell type when exposed to silica but levels were increased at 0.52 and 5.2 µg/cm^2 after 24 h. Interleukin (IL)-6 levels were not increased for either type of cell at 24 h, however, when the cells were combined, IL-6 levels were increased at 0.52, 5.2, 52, and 520 µg/cm^2. The authors concluded that there was little correlation between in vivo (see Intratracheal section below) and in vitro results (Sayes et al. 2007).

Bacterial Cells

Several strains of bacteria (0.15 ml bacterial suspension) were exposed to pressed and unpressed high purity silica (0.2 g). Rod-shaped gram-negative strains (*Escherichia coli*, *Bacterium proteus*, *Pseudomonas aeruginosa*, and *Aerobacter aerogenes*) died between 6 h and 3 days in contact with unpressed silica. Gram-positive strains (*Proteus* sp., *Micrococcus pyrogenes aureus*, *Streptococus faecalis*, *Streptococcus pyrogenes humanus*, *Corynebacterium diphtheriae*, *Candida albicans*, and *Bacillus subtilis*) were somewhat more resistant. Survival of bacteria exposed to unpressed silica was shorter than pressed silica (Keinholz 1970).

Various bacteria were incubated in silica (0.2 g; dilution 1:50,000 for *A. Aerogenes*, *Proteus* sp., *P. aeruginosa*, *E. coli*, and *S. aureus*, and 1:100,000 for *C. albicans* and *B. subtilis*) at 22°C or 37°C. The time until complete mortality was recorded up to 28 days (EC_{100}). ED_{100} ranged from 6 h to 22 days (UNEP 2004).

Sodium Potassium Aluminum Silicate

Alfaro Moreno et al. (1997) incubated thawed Balb 3T3 cells with Mexicali dust (sodium potassium aluminum silicate present as potassium aluminum silicates [98%] and sodium dioxide [2%]; 20, 40, or 80 µg/ml), chrysotile asbestos (40 µg/ml; positive control), or nothing (negative control) for 12 h. The medium was then changed and the cells allowed to incubate for

7 h. The cells were fixed. Between 220 and 280 anaphases for each concentrations were examined blind. Abnormal anaphases were observed in 27.42% of the cases in the low dose group, 29.60% in the mid dose group, and 37.10% in the high dose group. The asbestos induced abnormal anaphases in 34.78% of the cases and 11.62% in the control. The most frequent alterations were multipolar anaphases. An increase in anaphases with retarded chromosomes was observed in the test groups and the positive control. The frequency of anaphase bridges was lower in the treated groups than in the positive control group ($p < .05$). When comparing the mid dose group to the positive control group, there were more lagging chromosomes (23.95% vs 18.20%), fewer anaphase bridges (10.40% vs. 78.80%), and more anaphase bridges (10.40% vs. 1.51%). No changes were observed in the mitotic index of cells exposed to Mexicali dust. The authors concluded that Mexicali dust is capable of inducing anaphasic alterations.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Silica

Hazelton Laboratories (1958a) administered a single oral dose of pyrogenic silica (1.00, 2.15, or 3.16 g/kg) to male albino rats (n = 5). There were no gross signs of systemic toxicity observed and no mortalities. The LD_{50} was reported to be >3.16 g/kg.

W.R. Grace & Co. (1981) reported that the LD_{50} of pyrogenic silica was > 5.62 g/kg for male rats (n = 30). There were no toxic signs or deaths over the 2 weeks observation.

Lewinson et al (1994) orally administered pyrogenic silica (5040, 6350, or 7900 mg/kg in olive oil or 2500 or 5000 mg/kg in peanut oil) to Sprague-Dawley rats (n = 10) after fasting. The rats were monitored for 4 weeks, then killed and necropsied. There was no mortality. There were no toxicological signs and the necropsies were unremarkable. The authors concluded that acute dosing with silica is virtually nontoxic by the oral route.

UNEP (2004) and ECETOC (2006) reported several unpublished studies of acute oral toxicity of silica. The results of these studies are summarized in Table 5. ECETOC (2006) reported that there were no signs of toxicity. There were no macroscopic findings at necropsy. Animals died at doses of 10,000 and 20,000 mg/kg. At doses of 5,620 mg/kg and higher, the feces in some animals were white.

Aluminum Calcium Sodium Silicate

Abbés et al. (2006a) orally administered a single dose of hydrated aluminum calcium sodium silicate (400, 600, or 800 mg/kg) to female Balb/c mice (n = 6) with or without Zearalenone (ZEN; a mycotoxin produced by fusarium genera; 40

mg/kg). After 48 h, blood samples were collected and the mice killed and examined. ZEN caused reduced total cholesterol, high denisty lipoprotien (HDL), low density lipoprotein (LDL), triglycerides, total protein, albumin, white blood cell count, immunoglobulin profile (Ig A and Ig G) and T-cell subtypes. ZEN increased uric acid and urea and induced degenerative changes in the spleen tissues. The low dose of hydrated aluminum calcium sodium silicate alone had levels similar to control. The mid and high dose groups had increased cholesterol levels. Hydrated aluminum calcium sodium silicate mitigated the effects of ZEN at all dose levels. No adverse effects were reported for hydrated aluminum calcium sodium silicate alone at any dose.

Abbés et al. (2006b) orally administered a single dose of hydrated aluminum calcium sodium silicate (40 mg/kg or 500 mg/kg) to female Balb/c mice (n = 6) with or without ZEN (40 or 500 mg/kg). The high dose of ZEN is the reported LD_{50}. After 48 h, blood samples were collected and the mice were killed and the kidneys and livers dissected. ZEN increased hematocrit, hemaglobin, white blood cells, lymphocytes, eosinophils, neutrophils, monocytes, and most of the biochemical serum parameters. ZEN reduced platelets and induced degenerative changes in the hepatic and renal tissues. Hydrated aluminum calcium sodium silicate alone had no effect on these parameters.

Parenteral

Silica

Policard and Collet (1954) i.p. injected silica (30, 50, or 100 mg/kg in saline) to Wistar rats and rabbits. At 100 mg/kg, 20% to 30% of the animals died quickly. At 50 mg/kg, all the animals survived.

At necropsy, in the peritoneal cavity, vacuoles were observed in the cytoplasm and the nuclei were fragmented or destroyed; there were areas of damaged cells with normal or slightly altered histocytes at the periphery. Edema was observed that diminished with time. The lymph nodes were enlarged and contained large histocytes in various stages of degeneration. Lymphocytes were less numerous; the medullary sinuses were packed with clear cells. The thymus was atrophied. The spleen was hypertropied and altered; the malpighian corpuscles were almost gone; the zones of blood sinusoids were disorganized. The liver was enlarged with many fat cells and clusters of cells, mainly histocytes. The adrenals were enlarged (50% to 97%); the lipids in the cortex had a change in distribution; there was a general increase of lipid cells throughout the cortex.

Surviving animals were killed after 8, 20, 30, and 60 days. Peritoneal edema diminished then disappeared over time. Small spherical nodules (1.5 to 2 mm) were observed on the omentum. Mesenteric and tracheobroncheal lymph nodes were 2- to 4-fold larger than controls. Microscopic examination revealed granuloma in the peritoneal lesions. The center was degenerating and there were dead cells and histocytes; the outer edge was made up of histocytes. Connective tissue showed a fibrous reaction. At 20 and 30 days, the center of the granuloma had a few cells and irregular thickened collagen fibers; the

periphery was packed with reticular fibers filling the intercellular spaces and surrounding the cells. The fibrosis gradually increased; after 30 and 60 days there were extensive fibrous areas that were almost acellular; the lymph nodes were similar (Poicard and Collet 1954).

Schepers et al. (1957d) injected silica (10% in saline; 2 ml) into the peritoneal cavity of 2 guinea pigs. Both animals died on day 2 of generalized acute peritoneal inflammatory reaction. The lungs were slightly congested and the spleen was swollen. There was a small amount of fluid and adhesions of the intestines and fibrin deposits on the liver. The remains of the silica were near these reactions.

Kang et al. (1992) intraperitoneally injected female Wistar rats (n = 5) with a single dose of pyrogenic silica (0.02, 0.1, and 0.5 g). After 5 days, the rats were killed and necropsied. The control group was injected with saline. No adhesions, ascites, or other intra-abdominal pathology was observed in the control group. The rats in the low, mid, and high dose groups treated with silica had 5 mild, 4 severe, and 4 severe adhesions, respectively. There were no, 4, and 5 occurrences of ascites and deposits of powder adherent to viscera and 5, 4, and 5 rats with ascites in the low, mid, and high dose groups, respectively.

UNEP (2004) reported an unpublished study that concluded that single i.p. injections of ≥50 mg silica caused death in rats.

Intravenous

Silica

Swensson et al. (1956) injected amorphous silica (0.01 to 0.1 μm diameter particles), in the form of commercial silica, or ground fused crystalline silica (0.15 to 0.45 μm), 0.05 mg at a time up to 0.1 ml in saline or all at once, into the tail vein of mice until the animals died or were in an unrecoverable condition. The mice survived larger quantities of silica if delivered in smaller doses. The toxicity decreased with increasing particle size. Toxicity of amorphous silica was lower than crystalline silica. The lethal dose of commercial silica ranged from 0.2 ± 0.01 to 0.5 ± 0.02 mg/30 g body weight depending on particle size. The lethal dose of fused silica ranged from 2.1 ± 0.06 to 4.5 ± 0.39 mg/30 g .

In a study described previously, Byers and Gage (1961) injected various amounts of 3 types of silica into rats (strain and n not provided). Most deaths occurred within 2 h. Rats that survived for 24 h recovered fully. The LD_{50} for types A1, A2, and B were 35.2 (confidence interval [CI] 23 to 39), 41.2 (CI 34.5 to 42), and 44.4 (CI 40.5 to 49) mg/kg.

UNEP (2004) reported an unpublished acute i.v. toxicity study of pyrogenic silica using rats. The LD_{50} was 15 mg/kg.

Intratracheal

Pyrogenic and Hydrated Silica

Yuen et al. (1996) intratracheally instilled male Crl:CD BR rats (n = 3; 7 to 9 weeks old) with silica particles (10

mg/kg; particle size range 2 to 3.5 µm). The mice were killed and examined 0.5, 2, and 5 h, and 2 and 10 days after exposure. Neutrophilic inflammation was induced as early as 5 h after exposure. Maximal infiltration of neutrophils into the lungs occurred at 5 to 6 h. The inflammatory response for silica was transient, diminishing at 2 days and back to control levels at 10 days. Within 2 h, chemotactic activity for neutrophils was detected directly in BAL fluids with the influx and appearance of neutrophils into alveolar regions of the lungs. The mRNA expression of 2 known neutrophil chemotactic cytokines in BAL cells, macrophage inflammatory protein-2 (MIP-2) and keratinocyte-derived chemokine (KC), correlated with chemotactic activity and acute pulmonary inflammatory responses. MIP-2 mRNA was expressed prior to detection of chemotactic activity in BAL fluids and was no longer detectable after 2 days. The authors stated that silica produced a potent but trantient pulmonary inflammatory response.

Jones et al. (2002) explored the kinetics of lung macrophages by instilling silica (50 mg; 5 µm particle size) into the right upper lobe of the lungs of New Zealand white rabbits (n = 12). At intervals, the rabbits were re-anesthetized and injected with [^{11}C]R-PK11195 and scanned using positron emission tomography. The rabbits were killed at different times and the lungs examined. All of the rabbits remained healthy throughout the study. Three and 6 days following instillation, the [^{11}C]R-PK11195 was localized to the challenged lung and observed caudally on the contralateral side. On day 1 post-instillation, there were many macrophages containing particles in airspace. On day 5, some particle-bearing macrophages had migrated into the interstitium. There were few neutrophils present. At week 2, most of the particle-bearing macrophages were found in the interstitium and the perivascular lymph vessels. The macrophages did not appear to be highly activated. The silica was removed from the lungs in a highly organized manner and no fibrosis developed.

Kaewamatawong et al. (2005) compared the effects of particle size of colloidal (hydrated) silica on female ICR mice. Ultrafine (14 nm particle size) colloidal silica (120 mg/ml in water) or fine (213 nm) colloidal silica (239 mg/ml in water) were intratracheally administered to the mice (n = 3; 5 control groups, 10 exposure groups). The mice were killed and necropsied at 30 min and 2, 6, 12, and 24 h.

Both types of silica produced bronchiolar degeneration and necrosis, neutrophilic inflammation in alveoli with alveolar type II cell swelling, and particle-laden alveolar macrophage accumulation. Ultrafine silica induced more alveolar hemorrhage, compared to fine silica, from 30 min. There was also more severe broncholar epithelial cell necrosis and neutrophil influx in alveoli in the ultrafine-treated mice than in the fine silica-treated mice at 12 and 24 h. Immunolabelling of Laminin in basement membranes of bronchioles and alveoli in the ultrafine silica-treated groups was weaker than the fine silica-treated groups at all time periods. Electron microscopy revealed both types of silica on bronchiolar and alveolar wall surfaces as well as in the cytoplasm of alveolar epithelial cells, alveolar macrophages, and neutrophils. Type I alveolar epithelial cell erosion with basement membrane damage was greater in the ultrafine silica groups than in the fine silica

groups. Bronchiolar epithelial cells in the ultrafine silica groups had more intense vacuolation and necrosis than in the fine silica groups. The authors suggested that ultrafine silica had greater ability to induce lung inflammation and tissue damage than fine silica (Kaewamatawong et al. 2005).

Kaewamatawong et al. (2006) instilled ultrafine colloidal (hydrated) silica (0, 0.3, 3, 10, 30, or 100 µg; 120 mg/ml in water; 14 nm particle size) into the tracheas of male ICR mice (n = 10). After 3 days, the mice were killed and the lungs examined. The total cell counts in broncho alveolar lavage fluid (BALF) were increased for 10, 30 and 100 µg groups. Cell differential analysis of BALF of the 2 highest groups showed increases in numbers of neutrophils and lymphocytes. All exposure groups had increased total protein values in BALF.

In a followup experiment, mice (n = 8) were instilled with 50 µl of 30 µg of ultrafine silica of the same particle size. The groups were killed at 1, 3, 7, 15, and 30 days and the lungs examined. There was a transient increase in the total numbers of cells, macrophages, neutrophils, and lymphoctyes in BALF. Total numbers of lung cells increased and persisted to day 15 and resolved by day 30. Alveolar macrophages were elevated at day 1 to day 7. Lymphocytes increased until day 7 then returned to control levels by day 30. Total protein in BALF was greater than control at day 1 and returned to control levels by day 15.

On day 1 there were moderate increases of neutrophils sharply demarcated from normal alveoli. There were nodular aggregates of neutrophils and particle-laden alveolar macrophages in some alveolar regions adjacent to the bronchioles. Nodular lesions consisted of neutrophils, active alveolar macrophages, particle-laden alveolar macrophages, and cell debris. At day 3, moderate focal alveolitis was observed at the terminal abronchiolar and alveolar duct regions. Alveolar septal walls were thickened. At day 7, changes were only in the appearance of the aggregated foci consisting of particle-laden alvoelar macrophages, lymphocytes, and fibroblasts with occasional collagen fibers. Lesions were located around blood vessels adjacent to terminal bronchioles and alveolar ducts. At day 15, inflammatory signs were decreased and almost or completely resolved. Terminal deoxynucleotidyl transferase mediated dUTP nick end labeling (TUNEL) analyses showed an increase of the apoptotic index in lung parenchyma at all time points. 8-Hydroxy-2'-deoxyguanosine (8-OhdG) was detected in lung epithelial cells and activated macrophages and corrolated with lung lesions. The authors suggested that small doses of ultrafine colloidal silica caused transient, acute moderate lung inflammation and tissue damage. Oxidative stress and apoptosis may underlie the tissue injury induction (Kaewamatawong et al. 2006).

Sayes et al. (2007) instilled precipitated (hydrated) silica (1 or 5 mg/kg; 1000 to 3000 nm), as well as other particles, intratracheally to male Crl:CD (SK)IGS BR rats (n = 20). Controls were administered phosphate-buffered saline (PBS). At 24 h, 1 week, and 1 and 3 months, the BALF of 5 rats/group was analyzed. The number of cells at 24 h was higher than at other time points. Exposure to both doses produced transient and reversible neutrophilic lung inflammation responses at 24 h

which was diminished at 1 week.

Inhalation

Pyrogenic and Hydrated Silica

Lewinson et al. (1994) placed Wistar rats (n = 10; 5 males, 5 females) into an exposure chamber circulating pyrogenic silica (mean exposure 477 mg/m^3; lowest reading 342 mg/m^3) for 4 h. Approximately 56% of the particles were < 5 µm. The rats were observed for 2 h after exposure then daily for 14 days and periodically weighed. The rats were then killed and necropsied. The rats were restless and had drooping eyelids during exposure. There was no mortality during exposure or during the observation period. Body weights decreased during the first 2 days after exposure then the rats gained weight normally. Necropsies were unremarkable.

Warheit et al (1995) exposed male CD rats (n = 24) to aerosolized precipitated (hydrated) silica (10 and 100 mg/m^3) 6 h/d for 3 days followed by recovery periods of 1, 8, 30, and 90 days. The low dose produced a transient inflammatory response which was present 24 h post-exposure and subsided within 8 days. Recovery in the high dose group was similar to low dose group. The author concluded that low concentrations of silica induces a transient inflammatory tissue reaction.

UNEP (2004) reported an unpublished inhalation study (nose only exposure) of precipitated silica (< 5 µm particle size) in Wistar rats (n = 10; 5 male, 5 female). The LC_{50} was > 0.691 mg/l for 4 h. Clinical signs were restlessness and eye closing. There was no body weight gain in females the first 3 days after exposure and then weight gain was normal. There were no remarkable findings at necropsy after a 14-day observation period.

An unpublished inhalation study of precipitated (hydrated) silica (< 5 µm particle size) used Sprague-Dawley rats (n =10; 5). The LC_{50} was > 2.2 mg/l for 1 h. Clinical signs were irritation and dyspnea in most of the rats. One rat died during the 14-day observation period. The editors of the UNEP report considered this study invalid due to methodological deficiences and short length of exposure.

An unpublished inhalation study (full body exposure) of pyrogenic silica used Sprague-Dawley rats (n = 10). Approximately 84% of the particles were ≤ 3 µm. The LC_{50} was > 2.08 mg/l for 4 h. Clinical signs were nasal discharge during exposure and crusty eyes and nose, and alopecia during the 14 day observation period. There was no body weight gain in females the first 3 days after exposure and then weight gain was normal. One rat had discolored lungs at necropsy (UNEP 2004).

Unpublished studies of the acute inhalation toxicity of hydrophilic and hydrophobic silica are summarized in Table 6 (ECETOC 2006).

Intramuscular

Silica

W.R. Grace & Co. (1981) reported a study where silica (200 mg) was implanted into the paravertebral musculature of the lumbar region of rabbits (n = 6). The rabbits were killed and necropsied at 6, 12, and 24 weeks. There were local inflammatory reactions at 6 weeks. There was granulomatous scarring with necrotic muscle fibers and fatty degeneration of local macrophages at the site of implantation.

Dermal

Pyrogenic and Hydrated Silica

UNEP (2004) reported an unpublished acute dermal toxicity test of precipitated (hydrated) silica using rabbits (n and strain not provided). Silica was applied to intact and abraded skin for 48 h with no effect. The no observed effect level (NOEL) was > 2 g/kg.

In another unpublished study, a single application of 4 different precipitated (hydrated) silica products (in an aqueous paste) was applied to the intact and abraded skin of New Zealand white rabbits (n = 16) under an occlusive patch (length of time not specified). The rabbits were observed for 14 days. There was very slight erythema that disappeared after 2, 4 or 5 days for 3 silica products and no effects by the fourth product (UNEP 2004).

ECETOC (2006) reported several unpublished studies on the acute dermal toxicity of silica to rabbits. Only slight erythema with intact skin and slight erythema and edema with abraded skin were observed. Precipitated silica had an LD_{50} of > 5 g/kg in 4 studies. Silica gel had an LD_{50} of > 2 g/kg in 1 study.

Short-Term Toxicity

Oral

Silica

FDA (no date) reported the results of a dog feeding study of 28 days. There were no effects and the highest no effect level (HNEL) for silica was 800 mg/kg/d. In another study using rats, the oral HNEL was 1 g/kg/d. For doses >2 g/kg/d, the rats had dirty fur, shyness, decreased motor activity, and hemorrhage of the mucous membrane of the eyes and nose. There was a decrease in body weights, feed consumption, hemorrhaging, and cellular atrophy in the liver epithelium.

Silica (8 g/kg/d) was incorporated into the feed of Beagle dogs and CD rats (n not provided) for 4 weeks. The animals were then killed and necropsied. There were no indications of any treatment-related effects observed in either species (Newberne and Wilson 1970).

Silica (0.2%, 1.0%, or 2.5%) was incorporated into the feed of male rats (n = 10) for 28 days. There were no adverse effects or mortality reported. Gross necropsy findings were unremarkable (W.R. Grace & Co. 1981).

Lewinson et al. (1994) administered pyrogenic silica (0, 500, 1000, 2000 mg/kg/d) in the diet of Wistar rats (n = 20; 10 males, 10 females) for 8 weeks. Since the high dose was well tolerated, the dose was increased to 4 g/kg/d after 14 days, to 8 g/kg/d after another 14 days, and finally to 16 g/kg/d. The rats were observed for clinical signs, weighed, and blood sampled before and at the end of the experiment. The rats were killed and necropsied.

Only the 16 g/kg/d dose (~25% of daily feed intake) caused any clinical signs, shyness, dirty fur, reduced activity, cachexia, and hemorrhage in the mucous membranes of the eyes and nose. Two males and 2 females died with severe cachexia in week 8 (days 9 and 13 of the highest dose). This group had pronounced reduction in body weight and decreased feed intake. No changes were observed in hematological parameters. Microscopic evaluation revealed severe atrophy in the epithelium of the liver in the 1 and 16 g/kg dose groups; condensation of the cytoplasm, loss of basophilic structure, and hyperchromatic and contracted nuclei occurred in the liver cells. These findings were observed to a lesser extent in 2 females in the 1 g/kg dose group. There were no effects to the kidneys. There were no treatment-related effects observed in the 500 mg/kg dose group. The authors concluded that lowest observed effect level (LOEL) was 1 g/kg/d and the NOEL was 500 mg/kg/d (Lewinson et al. 1994).

UNEP (2004) and ECETOC (2006) reported unpublished short-term oral toxicity studies of silica. The studies are summarized in Table 7.

Dermal

Silica

ECETOC (2006) reported an unpublished dermal toxicity study of pyrogenic silica (0, 5, and 10 g/kg/d) using albino rabbits (n = 4; 2 male, 2 female). The silica was applied for 18 h/d, 5 d/week for 3 weeks to intact and abraded skin. There were no signs of systemic toxicity. There were no gross or microscopic pathological findings. The silica content of blood, urine, spleen, liver and kidney was similar among groups.

Inhalation

Pyrogenic and Hydrated Silica

Low et al. (1985) and Hemenway et al. (1986) exposed male Fischer 344 rats (n = 45) to aerosolized precipitated (hydrated) silica (30 mg/m^3; particle size not provided) for 6 h/d for 8 days. The recovery period was up to 112 days. During exposure, there was an early and transient influx of cells into the lung tissue which returned to normal by day 12. At 5 days post-exposure, the number and differential counts of alveolar lavage-derived cells were similar to controls. The BAL protein, lipid phosphorus, and saturated dipalmitoyl phosphatidyl-choline levels increased immediately after exposure and were normal by day 5 post exposure. There were no differences between controls and treated lungs as to weight, DNA-, protein-, or hydroxyproline-content. The authors concluded that inhaled silica caused an early, transient alveolar inflammatory

response, without producing fibrosis. There was only a mild inflammatory response with no evidence of connective tissue response.

Hemenway et al. (1986) exposed Fischer 344 rats (n = 15) to aerosolized silica (concentration unclear; particle size not provided) for 8 days. Three of the rats were killed and necropsied at days 0, 5, 12, 60, and 120 after exposure. There was initial inflammation, predominantly alveolar, which subsided before day 12.

Warheit et al. (1990, 1991) exposed male CD BR rats (n not provided) to aerosolized colloidal (hydrated) silica (10.1, 50.5, and 154 mg/m^3; diluted 4:1 with deionized, distilled water; particle size not provided) for 6 h/d, 5 d/week, for 4 weeks followed by a 10 and 94 day recovery period. The controls were unexposed. Lesions were only observed in lungs and associated draining lymph nodes. There was a dose-dependent increase in mean lung weight and lung to body weight ratio after 4 weeks of exposure in the mid and high dose groups. The mean lung to body weight ratio continued to increase in the high dose group 10 days into recovery, but was similar to controls after 3 months. There were dust laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia observed in the alveolar duct region of the lungs. Pulmonary lesions progressively decreased in rats examined after the 10 day and 3 month recovery period.

At 3 months post-exposure, most dust laden alveolar macrophages were cleared from the lungs, but small numbers of minute silicotic nodule-like lesions were present in the alveolar ducts and perivascular regions where dust laden alveolar macrophages had aggregated. There was minimal collagen deposition observed in the silicotic nodule-like lesions; the lesions did not increase in size or number over time. The lung clearance half-life was ~50 days for the mid and high dose groups. In the high dose group, there was an increase in mean neutrophil count and globulin concentration and a decrease in mean lymphocyte count at the end of the treatment. The increase in mean neutrophil count and decrease in mean lymphocyte count were still present after 3 months of recovery. The tracheal and mediastinal lymph nodes were enlarged with nodular aggregates of dust-laden alveolar machophages and hyperplastic reticulo-epithelial (RE) cells. The NOAEL was 10.1 mg/m^3 (Warheit et al. 1990,1991).

Reuzel et al. (1991) exposed Wistar rats (n = 80; 40 male, 40 female) to pyrogenic silica (17, 44, 164 mg/m^3; particle size not provided) in a whole body exposure chamber for 6 h/d, 5 d/week for a total of 14 days. The control was 6 male and 6 female unexposed rats. There was respiratory distress in all groups. One female in the high dose group died. There was decreased body weights and feed consumption in the males in the mid and high dose groups. Hematological measurements were unremarkable. There was increased lung weights in both sexes (47%, 65%, and 86% for the low, mid, and high dose groups) compared to controls. The absolute and relative liver weights were decreased in males, but not females. There were dose-dependent changes in the lungs (i.e., pale, spotted and/or spongy, occasionally irregular surface, alveolar interstitial pneumonia, early granulomata). The mediastinal lymph nodes were enlarged.

The above study was repeated with silica (46, 180, and 668 mg/m^3) on Wistar rats (n = 60; 30 males, 30 females). There was respiratory distress in all groups. One male died in the high dose group. There was decreased body weights and feed consumption in the mid and high dose groups. There were increased lung weights in both sexes compared to controls (males 25%, 39%, and 68%; females 34%, 50%, and 86% in the low, mid, and high dose groups, respectively). There were decreased liver weights in all dose groups of the males and the high dose group of the females. The lungs were spotted, swollen, and had irregular surfaces in the high dose groups as well as interstitial pneumonia and early granulomata. There was silica in the mediastinal lymph nodes in the mid and high dose groups and 1 rat in the low dose group. There was accumulation of alveolar macrophages and particulate material in the lungs of males in the mid and high dose group (Reuzel et al 1991).

Lee and Kelly (1993) exposed male Crl:CD(SD)BR rats (n = 25) to aerosolized colloidal (hydrated) silica (0, 10, 50, 150 mg/m^3; particle size not provided) for 6 h/day, 5 days/week for 4 weeks. Some of the rats were killed at the end of the exposure period, at 10 days, or 3 months. There were dose dependent lesions observed in the mid and high dose groups but not in the low dose group. Particles were mostly phagocytized by alveolar macrophages in the alveolar duct region and a few free particles were observed in Type I pneumonocytes in the alveoli. Particle-laden alveolar macrophages directly penetrated into the brochiolar interstitium from alveoli and accumulated in bronchus-associate lymphoid tissue, peribronchial, or perivascular interstitium and accumulated in the tracheo-bronchial lymph nodes. Some particle-laden alveolar macrohages in the bronchus-associated lymphoid tissue transmigrated directly into bronchial lumen through the epithelium. The transmigrated particle-laden alveolar macrophages in the tracheo-bronchial lymph nodes were similar to those in the alveoli. They were characterized by slender cytoplasmic processes, phagosomes, myelin figures, cholesterol clefts, and lipid droplets. Migrated particle-laden alveoli macrophages were observed to be necrotic and have released particles in the tracheo-bronchial lymph nodes.

At 3 months, the lungs of the low dose group were normal. The lungs of the mid dose group were normal in appearance, but a small number of tiny nodular aggregates of dust-laden alveoli macrophages and epithelioid cells were observed. One rat had a few silicotic nodules in perivascular regions adjacent to the bronchioles. The high dose group had decreased numbers of particle-laden alveoli macrophages that were sharply circumscribed in the alveoli. Some aggregates of particle-laden alveoli macrophages and epitheliod cells were closely apposed with alveolar walls and transformed into nodular aggregates without any collagen fiber deposition. Three of 10 rats had silicotic nodules in the perivascular region of the bronchioles (Lee and Kelly et al 1993).

UNEP (2004) reported an unpublished short-term inhalation toxicity study using female Wistar rats (n not clear) exposed to aerosolized silica (8 and 40 mg/m^3; particle size not provided) for 1 h/d, 5 d/week for up to 3 months. The rats

were killed and necropsied at 7 d and 3 weeks after treatment. There were no macroscopic changes. Histopathologically, there was an occurrence of dust cells in the lungs which decreased during post-exposure. There was no fibrosis of the reticulo-cellular type and normal parenchma of the lungs. There was no emphysema. A decrease of silica content in the lungs was observed 7 and 48 days after treatment termination. After 3 months, there was almost no silica in the lungs.

ECETOC (2006) reported several unpublished short-term inhalations studies of silica. These studies are summarized in Table 8.

Arts et al. (2007) exposed young adult Wistar (Crl:WI)WU BR) rats (n = 20; 10 male and 10 female) to 3 types of aerosolized silica (1, 5, or 25 mg/m^3; particle sizes not provided): precipitated (hydrated) silica, silica gel, and pyrogenic silica for 6 h/d for 5 consecutive days followed by a 3-month recovery period. The rats were killed and necropsied. There were no clinical signs during exposure. The effects were limited to 1 day post exposure. Silica levels in the tracheobronchial lymph nodes were below detection limits in all 3 groups. Silica was found in the lungs at day 1 but had cleared by 3 months. All 3 types of silica induced biomarkers of cytotoxicity in BAL fluid, increases in lung and tracheobronchial lymph node weights, and histopathological lung changes in the high dose groups at day 1 post exposure. The mid dose only induced histopathological changes and changes in BAL fluid. The effects of all 3 types of silica, with the exception of slight histopathological lung changes at the higher exposure levels, were reversed during the recovery period. The low dose caused no adverse effects.

Intratracheal

Silica

Schepers et al. (1957d) intratracheally injected rats (n = 10) with silica (5%; 0.25 ml) once per week for 3 weeks. Two rats died after the first injection, 3 died before the third injection. Three rats survived the observation period (length not stated). Pleural effusion was observed in 4 rats, 2 responses were delayed, 1 supervened and the rat survived 220 days. Pulmonary congestion was observed in 3 rats until the ninth month. Tracheobronchial lymph nodes were moderately to markedly enlarged and firm for 5 months. There was abscess formation associated with pneumonitis; accompanying cells were macrophages. Focal granulomatous inflammation was observed in both lungs in rats that survived more than 2 days. Hyperemia of the alveolar walls later resolved. Infiltration of the alveolar walls was mostly by macrophages. Early collagen became profuse in the alveolar walls in relation to focal granulomatous inflammation and cell necrosis.

This experiment was repeated with guinea pigs at double the dose of silica. At 2 weeks, 2 guinea pigs died; the rest survived to be killed and necropsied at intervals. Most of the effects were confined to the lungs; a few consolidated areas were palpable in a few animals. There were multiple foci of atelectasis in the lungs. Tracheobronchial lymph nodes were moderately to markedly enlarged. Cellular phenomena predominated early and resolved with residual fibrotic change.

Granulomatous inflammation was observed in the first month. There was a tendency toward cellular invasion. Slight to moderate atrophic vesicular emphysema was detectable during the second half of the year of observation (Schepers et al. 1957d).

Intravenous

Silica

Schepers et al. (1957d) intravenously injected silica (1% in saline; 5 ml) into rabbits (n = 5) 20 times biweekly. One rabbit died after the second injection and another after half the injections. One died on the 70th day and the last 2 were killed on the 120th and 300th days. There was slight to moderate pleural effusion with pleuritits. The longest surviving rabbits had mediastinal abscesses. The lungs had moderate to marked congestion, which was most severe in the rabbits that died first. There were no foci consolidation but small areas of atelectasis. The lymph nodes were not markedly enlarged. The right ventricles were dilated and hypertrophic, most obviously in the rabbit that died first. The livers were moderately to markedly enlarged, turning pale and firm over time. However, the liver had returned to normal in the rabbit killed on the 300th day. There was some splenomegaly in the 2 rabbits that died during treatment. Atrophy of the spleen increased over time. The size of the kidneys increased over time, to almost double normal size. Histological changes included hyperemia with associated exudate into alveolar spaces, ischemia, dust-filled macrophages in alveolar spaces, distension of the proximal convoluted tubules with fibrosis, and small granulomata that diminished over time. The epithelial cells were well preserved. There was minimal collagenosis. The alveolar walls thickened then became thin.

Subchronic Toxicity

Oral

Pyrogenic and Hydrated Silica

FDA (no date) reported the results of a 90-day rat feeding study of silica. There were no effects and the HNEL was 5 g/kg/d. In another study using rats for 180 days with a 3-week recovery period, the lowest effect level (LEL) was 500 mg/kg/d. There was an increase in adrenal weight in the males. Adrenal weight also increased in the females but only during the recovery period. Histopathology showed an increase in lipid content in the adrenal glands; this resolved during the recovery period.

Hazelton Laboratories (1958c) incorporated pyrogenic silica (1.0%, 3.0%, or 5.0%: 10,000, 30,000, or 50,000 ppm) into the feed of male and female albino weanling rats (n = 30; 15 male, 15 female) for 90 days. Controls were fed the basal diet or 3.0% #1625 Cosmetic Talc. The rats were killed and necropsied at 45 and 90 days. There were no gross signs of toxicity. Growth rates, feed consumption, and survival were similar to controls. The silica content of the liver, kidneys, spleen, blood, and urine was similar to controls. There were no gross, microscopic, nor pathological changes associated with

silica consumption at any dose level.

Silica (50 mg/d) was fed to male and female rats (n = 30) by stomach tube for 3 months. No adverse effects on body weight gain or mortality were observed. The results of pathological examination were similar to controls (W. R. Grace & Co. 1981).

In another experiment, silica (0, 1.0%, 3.0% 5.0%) was incorporated into the feed of male and female rats (n = 30) for 90 days. The positive control group was fed cosmetic talc. There was no systemic toxicity by silica in terms of survival, weight gain, and feed consumption observed. There was no increase in deposition of silica observed in the kidney, livers, spleen, blood, or urine (W. R. Grace & Co. 1981).

Lewinson et al. (1994) orally administered pyrogenic silica (500 mg/kg/day) in the feed of Wistar rats (n = 40; 20 males, 20 females) for 6 months. The animals were then killed and necropsied except for the animals of both sexes which were kept on normal feed for an additional 3 weeks. The animals were observed daily; blood was sampled and the rats weighed periodically.

There were no clinical signs during the treatment period. One male in the treatment group died; a lung infection was observed. Two rats in the control group died with enteritis and cachexia. There were no differences in weights or feed consumption. There were no differences in hematological parameters. Macroscopic evaluation at necropsy was unremarkable. Histopathological examination revealed increased lipid content in the fasciculata and zone fasciculata of the adrenal glands; this condition resolved after the recovery period. No other differences between treated and control animals were observed. The authors concluded that the NOEL was 500 mg/kg/day (Lewinson et al. 1994).

UNEP (2004) reported an unpublished feeding study of precipitated (hydrated) silica (0.5%, 2%, and 6.7%; 300 to 330, 1200 to 1400, and 4000 to 4500 mg/kg/d) using Wistar rats (n = 20; 10 male, 10 female) for 13 weeks. There were no clinical signs; hematological, blood chemistry, and urinary parameters were normal. Feed intake was slightly increased in the high dose females after 4 weeks. Gross and microscopic examinations were unremarkable.

In another unpublished feeding study, precipitated (hydrated) silica gel (3.2% and 10%) was fed to CD-1 rats (n = 24; 12 males, 12 females) for 6 months. Calculated doses were 2170 and 7950 mg/kg/d for the males and 2420 and 8980 mg/kg/d for females. At 6, 13, and 26 weeks, 4 rats of each sex in each group were killed and necropsied and the bone marrow analyzed. There were no treatment-related findings. Behavior was normal. Body weights were not affected. There were no histopathological changes in the kidneys. The NOAEL was 8980 mg/kg/d.

Another unpublished study in which Wistar rats (n = 40; 20 male, 20 female) were fed silica (495 to 497 mg/kg/d) for 6 months resulted in an NOAEL of 497 mg/kg. No further information was provided (UNEP 2004).

ECETOC (2006) reported 2 sub-chronic oral toxicity studies where hydrophobic pyrogenic silica (500 mg/kg/d) was

administered by gavage to Wistar rats (n = 40; 20 male, 20 female) 5 d/week for 6 months. There were no clinical signs nor macroscopic findings at necropsy (ECETOC 2006).

Inhalation

Pyrogenic and Hydrated Silica

Schepers et al. (1957a) placed male and female Wistar rats (n = 25) in inhalation chambers to expose them to pyrogenic silica (average 1.5 mg/ft^3 [53 mg/m^3]; most measurements ranged from 0.7 to 2.4 mg/ft^3 [25 to 85 mg/m^3]; particle size not provided). The rats were exposed to aerated silica for 8 h/d then had passive exposure (dust settling) for the remaining 16 h. The exposure was for 5 d/week for 6 months followed by 6 months of recovery. Rats were periodically killed and necropsied. The control group (n = 42) was in normal air and killed and necropsied at 6 and 12 months.

In the test group, 11/25 (44%) died, mostly during the silica exposure. The death rate decreased during the recovery period. The majority of the rats died from pulmonary vascular obstruction and emphysema beginning at the 4th month. Focal pigmentation was conspicuous after 3 months of exposure with profusely scattered small, dark-pink discrete but irregular subpleural foci of reaction. Congestion of the lungs was dominant after 3 months. There was lymph node enlargement after 3 months. There was an incipient tendency toward pulmonary emphysema after 4 months of exposure with lung distension and superficial alveoli dilation. Atelectasis was noted in some rats after 4 to 5 months.

Histological examination revealed invasion of the lymphatic system of the lung by mononuclear macrophages forming clusters of plasma cells and lymphocytes. There was infiltration of large vacuolated cells within the alveolar spaces; the cytoplasm had a foamy appearance with macrophages fused to giant cells. There were large vacuolated cells within the alveolar spaces, with the cytoplasm having foamy appearance, macrophages apparently fused to giant cells. There was progressive nodule formation in the lung parenchyma and peri- and paravascular, in some cases parabronchiolar distribution and accumulation, consisting of central macrophages and surrounding plasma cells, some nodules enveloped by an epithelial layer of cells. Some necrosis was noted in the central zone of the nodules; there was progressive tendency toward fibrosis in the nodules and evidence of progressive emphysematous processes around the nodules.

Average silica load in the lung increased to 1.5 mg/lung after 3 months and remained at that level through exposure. At the end of recovery, the level reduced to 0.3 mg/lung. The authors concluded that the lowest observed adverse effects level (LOAEL) was 53 mg/m^3 (Schepers et al. 1957a).

Rats (strain and n not provided) were exposed to aerosolized hydrophilic silica (40 to 50 mg/m^3; particle size not provided) for 4 h/d, 5 d/week for 2 to 12 weeks (Klosterkötter 1963). The overall elimination of silica was high without accumulation in the lungs. Equilibrium between retention and elimination was reached quickly. Only 5% to 6% of theoretical deposit of silica was observed after 120 days exposure. There was transfer of silica to the mediastinal lymph

nodes, ~31% of total deposited (1.5% to 2% theoretical deposition). The authors stated that involvement of the lymphatic elimination appeared not to be relevant up to 8 weeks of exposure. The silica particles were able to bypass the lymph nodes and were removed quickly.

Reuzel et al. (1991) reported an unpublished inhalation study of silica (1.3, 5.9, 31 mg/m^3; particle size not provided) using Wistar rats (n = 100; 50 male, 50 female). The rats were subjected to full body exposure for 6 h/d, 5 d/week, for 13 weeks. Ten rats of each sex were killed and necropsied at weeks 13, 26, 39, and 52.

There were no mortalities during treatment or recovery. Clinical signs were increased respiration rates in a dose dependent manner and body weight gains were depressed. Red blood cell (RBC) count was increased in males in the high-dose group. In the mid- and high-dose groups, white blood cells (WBC) were elevated in both males and females; the concentration-response relationship was poor. Blood cell counts returned to normal by week 39. Necropsy at 13 weeks revealed swollen and spotted lungs and enlarged mediatinal lymph nodes; the severity was dose dependent. All groups had increased lung weights and collagen content, less so in the low-dose group. All these effects reduced to control levels by the end of the study except for collagen content in males in the mid- and high-dose groups.

After treatment, silica could be detected in the lungs of all the rats in relatively small amounts. In the high-dose group, the average silica amount in the lungs was 0.2 mg. Silica was detected in 1 male in this group in the regional lymph node. At the end of the study, no silica above control levels could be detected in any rat. Microscopic evaluation after treatment revealed accumulation of alveolar macrophages and granular material, cellular debris, polymorphonuclear leukocytes, increased septal cellularity, alveolar bronchialization, focal interstitial fibrosis, cholesterol clefts, and granuloma-like lesions in the lung. The lesions in the lung did not have fibroblastic activity or hyalinization and regressed during recovery. All types of pulmonary lesions were more marked in males than in females. Accumulation of macrophages was observed in the mediastinal lymph node at 13 and 26 weeks. Treatment-related, microscopic changes in the nasal region were occasionally found at week 13 such as focal necrosis and slight atrophy of the olfactory epithelium. Interstitial fibrosis was not noted directly after the exposure period, but was observed for the first time after 13 weeks postexposure, with increasing incidence especially in the high-dose group, and a few in the mid-dose group. There was decreased severity and frequency of the effects until the end of the study. The authors concluded that the NOEL was 1.3 mg/m^3.

In a second study, male and female Wistar rats were placed in a whole body inhalation chamber 6 h/d, 5 d/week, for 13 weeks to be exposed to precipitated silica at 35 mg/m^3 (particle and agglomerate/aggregage size 1 to ~120 µm). The rats were periodically killed and necropsied over the 52-week recovery period.

Slightly decreased body weight and increased lung and thymus weights were observed. Necropsy revealed swollen and spotted lungs and enlarged mediastinal lymph nodes. Microscopic examination of the lungs revealed accumulation of

alveolar macrophages, intra-alveolar leukocytes, and increased septal cellularity. There was also accumulation of macrophages in the lymph nodes. The collagen content in the lungs was slightly increased. During the recovery period, the effects of silica exposure were mostly gone within 26 weeks. Accumulation of silica and macrophages in the mediastinal lymph nodes were still present at the end of the recovery period (Reuzel et al. 1991).

Johnston et al. (2000) exposed male Fischer 344 rats (n = 4) to aerosolized pyrogenic silica (50.4 ± 19 mg/m^3; mean diameter 0.81 µm) for 6 h/d, 5d/week, for 13 weeks. The control group was not treated. The silica burden was determined after 6.5 and 13 weeks of exposure and after 3 and 8 months of recovery. The silica load increased quickly during the first 6.5 weeks of exposure (0.76 mg/lung) but less so after 13 weeks (0.88 mg/lung). During recovery, the silica burden disappeared rapidly from lung tissue (15% after 12 weeks; 6% after 32 weeks). BAL showed mean cell numbers in the lavage increased 5- to 15-fold compared to control. The cells comprised > 50% polymorphonuclear leukocytes (PMN) and some 2% lymphocytes whereas the control lavages only contained < 1% of either cell type. Protein content and enzyme activities (LDH and glucuronidase) were markedly higher than under control conditions. All BAL markers approached normal levels after 13 weeks recovery in most rats, however, a few had minimal increases.

There was invasion of neutrophils and macrophages into the alveoli after 6.5 weeks but this effect tended to decrease during recovery. Fibrosis was observed in alveolar septa which subsided during recovery. After 13 weeks of exposure, intensely stained TUNEL-positive cells were detected throughout the terminal bronchiolar epithelium and through the parenchyma of the lungs. The authors concluded that aerosolized silica produced transient pulmonary inflammatory response and most biochemical markers return to control levels post exposure (Johnston et al. 2000).

ECETOC (2006) reported an unpublished study where Wistar rats (n = 20; 10 males, 10 females) were exposed to hydrophobic pyrogenic silica (0, 0.51, 2.05, and 10.01 mg/m^3; particle size not provided) for 6 h/d, 5 d/week for 13 weeks. A group of rats was allowed to recover for 13 weeks before being killed and necropsied. Silica was observed in the lungs in a concentration dependent manner at the end of exposure. Silica was observed in the tracheobronchial lymph nodes in 3 of 5 animals in the high dose group. After recovery, the amount of silica in the lungs was below detection limits in the low dose group and only a small amount was detected in the high dose group.

ECETOC (2006) reported an unpublished study in which Wistar rats (n = 20; 10 male, 10 female) were exposed to aerosolized hydrophobic pyrogenic silica (0, 0.51, 2.05, or 10.01 mg/m^3; particle size not provided) for 6 h/d, 5d/week for 13 weeks followed by a 13 week recovery. Most effects were in the high-dose group. There was an increase in asparate-amino-transferase level and alkaline phospatase activities in males. There was an increase in absolute and relative lung and tracheobronchial lymph node weights. The lungs had a red appearance with white spots. There was an accumulation of alveolar macrophges with few PMN cells accompanied by bronchiolar-alveolar epithelial hyperplasia and interstitial

inflammatory cell infiltrates in lungs. The lung draining mediastinal lymph nodes showed increased histiocytosis and macrophage aggregates in paracortex and/or germinal centers.

Chronic Toxicity

Oral

Pyrogenic and Hydrated Silica

Silica (3.2% or 10%) was incorporated into the feed of rats (n = 24; 12 male, 12 female) for 6 months (W.R. Grace & Co 1981). There were no mortalities. The only clinical sign was discolored stools. Growth and development was normal and feed consumption similar to controls. Necropsy was unremarkable; organ weights, absolute and relative, were similar to controls. Histology and hemotology was unremarkable. There were no changes in clinical chemistry.

In another feeding study, rats (n = 24; 12 males, 12 females) were fed silica for 6 months. The low dose males and females consumed an average of 0.78 and 0.55 g silica/week, respectively. The high dose males and females consumed and average of 3.00 and 2.11 g silica/week, respectively. There was no effect with regards to body weight gain, feed consumption, blood chemistry, or urinalysis. There was an increase in the number of leukocytes in the female high dose group and eosinophils in the male high dose group. There was a decrease in glucose concentration and AP activity in the male rats in a dose dependent manner. There was decreased serum calcium concentration in the female rats in a dose dependent manner. There were reduced absolute and reduced liver and prostate weights (W. R. Grace & Co. 1981).

Takizawa et al. (1988) fed precipitated (hydrated) silica gel (1.25, 2.5, or 5% incorporated into feed) to male and female Fischer 344 rats (n = 80; 40 males, 40 females) for 103 weeks. The mean cumulative intake of silica was 143.46, 179.55, and 581.18 g/male rat and 107.25, 205.02, and 435.33 g/female rat for the low, mid and high dose groups, respectively. Survival for all treatment groups was similar to controls. There were no differences between treatment groups and controls with regards to body weight, feed intake, behavior, or in hematological or chemistry parameters. Liver weights in the females in the mid and high dose groups were lower at 12 to 24 months. There were no significant findings at the histopathological examinations.

The above experiment was repeated feeding B6C3F1 mice (n = 80; 40 male, 40 female) for 93 weeks. The mean cumulative intake of silica was 38.45, 79.78, and 160 g/male mouse and 37.02, 72.46, and 157.59 g/female mouse for the low, mid, and high dose groups, respectively. There were no differences in survival between treatment groups and controls. Feed consumption was increased in the mid and high dose groups whereas there was reduced weight increase in the males during weeks 15 through 50 ($p < .01$) and weeks 30 through 50 for the females ($p < .05$). There were no remarkable findings with regards to hematology or organ weights. There was no increase in the incidence of tumors (Takizawa et al. 1988).

Inhalation

Pyrogenic and Hydrated Silica

Jötten and Klosterkötter (1951) reported that when rabbits were exposed to aerosolized silica (0.2 to 5.0 µm particle size) there was formation of nodular fibrotic or diffuse fibrotic changes in the lungs. The authors concluded that the concentration of the dissolved silica, the surface forces of the colloidal particles, mechanical and physiochemical condidtions were factors in the observed changes.

Schepers et al. (1957a) performed a parallel study (see SUBCHRONIC above for more details) where the Wistar rats (n = 35) were exposed to aerosolized precipitated silica (average 1.5 mg/ft^3 [53 mg/m^3]; most measurements ranged 0.7 to 2.4 mg/ft^3 [25 to 85 mg/m^3]; particle size not provided) for 8 h/d, 5 d/week for 12 months. Treatment related deaths were 26/35 (75%). After 6 months of exposure, aggregations of focal pigmentation visible as reddish-tan foci of dust were observed. There was also moderate, well-established generalized emphysema and lymph nodes that were greatly enlarged and firm. The majority of the rats died from pulmonary vascular obstruction and emphysema from the 4th to the 9th month. The authors concluded that high subchronic/chronic exposure to amorphous silica causes severe progressive pulmonary inflammation associated with increased mortality of the animals, primarily through partial obstruction of the pulmonary vasculature combined with pulmonary insufficiency due to emphysema.

Schepers et al. (1957b) exposed male and female albino guinea pigs to aerosolized pyrogenic silica (average concentration 1.5 mg/ft^3; ranging 0.7 to 2.4 mg/ft^3; 85% between 1 to 10 µm) in 3 experiments. The whole body exposure was for 8 h/d with the remaining 16 h as passive exposure (dust settling). In experiment 1, the guinea pigs (n = 40) were exposed to the silica up to 24 months, with a few killed and necropsied every 2 months. In experiment 2, the guinea pigs were exposed for 12 (n = 15) or 24 (n = 18) months with variable recovery periods up to 12 months. In experiment 3, the guinea pigs (n = 17) were exposed for 12 months, followed by a 1 month recovery period, then re-exposure for 8 to 24 h. A control group of 80 guinea pigs were sampled and necropsied from 1 to 36 months.

Two guinea pigs died from non-experimental causes. Overall, the chronic reaction of the lung tissue was established by 4 months of exposure. There was focal pigmentation after 1 month. Lymph nodes were enlarged by 1 month and did not increase over time, including hepatic lymph nodes. There was a tendency for lung emphysema after 4 to 8 months of exposure. Atelectasis was observed histologically.

Histologically, the dominant response was bronchial and peribronchiolar intra-alveolar accumulations of giant cells. At 8 to 12 months there was incipient atrophy of infiltrated alveoli which apparently led to compensatory expansion of adjacent alveoli. There was a combined effect of atelectasis and consolidation around bronchioli, but at the expense of bronchioli distortion. Incipient fibrosis around bronchioli and shrunken alveoli was noted at this stage. There was a marked

tendency toward cuboidal epithelization of atelectactic alveoli by the end of the second year of exposure.

In the lymphoid tissue, medullary hyperplasia with the formation of slight amounts of reticulum was prominent during the second year of exposure. No inflammation, sinus catarrh, nor fibrosis were noted in the lymph nodes.

In the recovery phase after 12 months of exposure, there was progressive recovery beginning almost immediately. There were no macroscopically visible anomalies after 1 year of recovery. Residual sequelae of the tissue reactions were emphysema, mural fibrosis, and bronchiolar and bronchial ectasia stenosis. The authors concluded that chronic exposure to amorphous silica was non-lethal to guinea pigs, but caused significant inflammatory reactions and pulmonary lesions, however, without apparent disability of the animals (Schepers et al. 1957b).

Schepers et al. (1957c) exposed New Zealand white rabbits (n = 10) to aerosolized pyrogenic silica (1.5 mg/ft^3, 53 mg/m^3; ranging from 0.7 to 2.4 mg/ft^3, 25 to 85 mg/m^3; 1 to 10 µm) for 8 h/d for 12 months. There was a 6 and 12 month recovery period. There was progressive functional incapacitation and increased hematocrits observed in the majority of the rabbits, possibly due to the combined effect of pulmonary vascular obstruction and emphysema. Blood pressure changes (both increases and decreases) were observed in the majority of the animals which partially recovered with discontinuation of treatment. Essential pulmonary changes included peribronchiolar cellular catarrh, mural cellular infiltration along with deposition of reticulum and some collagen, the formation of peri-vascular cellular nodules, ductal stenosis, and emphysema. During recovery, the cellular reactions and emphysema regressed but minor focal alveolar mural collagen persisted.

Schepers (1959) exposed New Zealand white rabbits (n not clear, ~16) to aerosolized precipitate silica (0, 28, 134, and 360 mg/m^3; particle size not provided) for 8 h/d, 5 d/week. The mid and high dose groups were exposed for 9 months, the low dose and the control groups were exposed for 27 months. The rabbits in the mid and high dose became distressed during exposure. Clinical signs were fewer, commenced later, and receded more quickly in the lower concentrations. There was increased body weight gain which corrected when exposure was terminated. The author suggested that this was due to edema. The body weights then decreased. The rabbits had dyspnea and shortness of breath accompanied by cyanosis. Elevated right and left ventriclar pressures were concentration and time related.

In the high dose group, emphysema was observed which decreased after termination of treatment. Pulmonary emphysema, vascular stenosis, alveolar cell infiltration, sclerosis, and epithelization granulomatosis, macrophage catarrh were observed. Lesions were observed in the liver, spleen and kidney.

After 6 months of exposure, the cardiac pressure of the low dose group increased steadily. At 24 months, the elevation was 64% over pre-exposure pressure. This effect was partially reversed with termination of treatment (34% after 12 months). The author reported concomitant radiographic changes, electrocardagraphic deviations, modification of lung functions, hematolytic changes, anatomical cor pulmonale, congestive cardiac failure, emphysema, and chemical pneumonitis. The

LOAEL was 28 mg/m^3 (Schepers 1959).

Schepers (1962) exposed monkeys (*Macacus mulatta*; n = 5) to aerosolized synthetic silica (15 mg/m^3; particle size not provided) for up to 12 months. A monkey was killed and necropsied at 3 and 6 months. The remaining monkeys were killed and necropsied after 12 months of exposure. There were 15 untreated control monkeys. Body weight gains decreased and activity decreased during the initial exposures. At 3 months, emphysema was detectable. There was considerable cellular infiltration of the alveoli and alveolar septa was associated with distention of alveoli or accumulation of exudate and macrophages.

After 12 months, the lesions were marked pulmonary emphysema, alveolar wall sclerosis, vascular occlusions, and cor pulmonale. Cor pulmonale was attributed to the emphysema and alveolar wall destruction. Tracheobrochial lymph nodes were slightly enlarged but not fibrotic. The silica content remained low and decreased over time (Schepers 1962).

Klosterkötter (1965) exposed female albino rats (n = 120) to aerosolized pyrogenic silica (~45 mg/m^3; particle size not provided) for 4 h/d for up to 1 year followed by a 3 to 8 month recovery period. Some of the rats were killed and necropsied periodically. There were 41/120 deaths. At necropsy, there were small white foci under the pleura, enlarged and discolored lymph nodes with formation of collagen and local necrosis, perivascular and peribronchiolar dust cell granuloma with reticulin and collagen fibers, necrotic cells, desquamative catarrh and thickened alveolar septa.

After the recovery periods, the dust cell granulomas were fewer and reduced in size with only a few dust cells and fibers. The alveolar septa had not completely disappeared. After 3 months, the lymph nodes were enlarged; after 8 months, the size of lymph nodes and the extent of recovery were reduced. The mean silica content of the lungs was 0.32 mg/lung or lymph node (0.6 mg maximum). At the end of exposure, 0.132 mg was found in the mediastinal lymph node (Klosterkötter 1965).

With continued exposure, the cellular reaction decreased and was replaced by degenerative processes (loss of septa with confluence of alveoli), followed by destructive emphysema. Circulatory continuity was extensively impaired by extensive rupture of alveolar septa. Collagen appeared in the alveolar septa.

Groth et al. (1981) exposed male Sprague Dawley rats (n = 80) to aerosolized pyrogenic silica, precipitated silica, or silica gel (15 mg/m^3; 6 to 9 mg/m^3 respirable $\leq$4.7 µm). Exposure was for 5.5 to 6 h/day, 5 d/week for up to 12 months. At maximum exposure, a few macrophage aggregates were found in the lungs. Interstitial fibrosis associated with dense collections of mast cells appeared in some of the rats of the control and treatment groups, although there was a trend of a more frequent incidence in those exposed to pyrogenic silica, but was a few were observed in some control animals. The authors concluded that the LOAEL was 6 to 9 mg/m^3. Macrophage aggregation was less pronounced in rats than in monkeys under these test conditions (see below). Fibrosis was of minor importance as test and control groups were similar.

Another experiment was conducted using male monkeys (*Macaca fascicularis*; n = 10) with exposure to the 3 types of silica for 6 h/d, 5 d/week, 13 or 18 months. The decrease in lung respiratory volume and ventilatory mechanics in the monkeys was more marked in the pyrogenic silica group. Dynamic pulmonary compliance, forced vital capacity, inspiratory capacity, total lung capacity, and forced expiratory flow were decreased. Average flow resistance and closing volume were increased. In the precipitated silica group, lower lung volumes were observed. There were no changes in lung volume parameters, but there were reductions in ventilatory performance and mechanical parameters, dynamic lung compliance, and forced expiratory flow when exposed to silica gel.

Cytoplasmic changes (increases in number of vacuoles) in macrophages in the lungs and tracheal lymph nodes were observed. Large numbers of macrophages and mononuclear cell aggregates (bronchioles, alveolar spaces venules, arterioles) were observed in the lungs. The frequency and size of the cell aggregates varied with the type of silica (precipitated > pyrogenic > gel). Reticulin fibers were present in the aggregates in all 3 groups. In 6/9 monkeys exposed to pyrogenic silica, collagen in varying quantities was found in 5 to 50% of the aggregates, with signs of early nodular fibrosis. In 3/9 monkeys no or little collagen was present. No collagen fibers were observed in aggregates in the lung of monkeys exposed to silica gel and only very few after exposure to precipitated silica. The authors concluded that early nodular fibrosis indicated that pyrogenic silica is more detrimental than precipitated silica or silica gel. The smaller particle size of pyrogenic silica may be a contributing factor. UNEP (2004) reviewed this study and noted that the monkeys were transported in bags that had contained asbestos and that suspect particles in the lungs were identified as mica and kaolin. Quartz or asbestos fibers could not be ruled out.

In a third study, the authors exposed male Hartley guinea pigs (n = 20) to the 3 types of silica for 5.5 to 6 h/d, 5 d/week for 12 months. A few macrophages containing particles of silica were observed in the lungs and lymph nodes, similar to the findings in rats (see above) (Groth et al. 1981).

Schepers (1981) exposed rabbits (n = 50), rats (n = 84), and guinea pigs (n = 82) to aerosolized precipitated (hydrated) silica (average of 126 mg/m^3 (3.57 mg/ft^3; particle size not provided) for 8 h/d, 5 d/week, for 12, 15, and 24 months, respectively, followed by a recovery period of up to 12 months. Control groups were not treated. There were no treatment-related differences in mortality between treated and control groups. For the rats, most of the deaths were due to intercurrent infection.

Lung weights increased during exposure but returned to normal during recovery. Particle-phagocytosing macrophages accumulated in alveoli, bronchioles, and lymphoid tissue in all species. Hilar lymph nodes were enlarged, mildly in rats and more evidently in the guinea pigs and rabbits; this disappeared with the termination of treatment. Epithelial proliferation was minimal. Mild deposition of reticulin fibers occurred in alveoli with no evidence of collagen formation. Bronchial and

tracheal epithelia remained intact. No epithelization or pleural changes were observed; no neoplasia occurred.

The emphysema was equally distributed between treated and control groups. It was dominated by the diffuse hypertrophic vesicular distention but apparently did not result from destructive effects on the mucosa or terminal bronchioles and disruption of the continuity of alveolar walls. The author stated that the emphysematous effect in the rats could possibly be due to aging and recurrent epizootic pneumontitis. There was complete reversibility of silica retention and inflammatory responses in guinea pigs within 6 months of recovery. Silicotic processes were completely absent in all species (Schepers 1981).

UNEP (2004) reported several unpublished chronic inhalation toxicity studies of silica. The studies are summarized in Table 9.

ECETOC (2006) reported a series of unpublished studies. Rats (strain and n not provided) were exposed to aerosolized hydrophilic silica (50 to 55 mg/m^3; 30 mg/m^3 respirable [sic]) for 12 months. Rats were killed and necropsied periodically and after 5 months recovery. At 3 days, there was 0.25 mg silica in the lung and 0.5 mg at 6 weeks. At 12 months, ~1% of the total administered respirable silica was observed in the lungs. Initial accumulation was rapid and dropped off between week 18 and 12 months (0.5 mg at 6 weeks; 1.2 mg at 18 weeks; 1.37 mg at 12 months). At 6 weeks, the mediastinal lymph nodes contained ~ 0.02 mg silica and 0.13 at 12 months. After 5 months of recovery, the silica in the lungs decreased to 0.16 mg/lung (88% reduction) and 0.047 mg/lymph node (> 50% reduction).

Rats (strain and n not provided) were exposed to aerosolized hydrophobic silica (50 mg/m^3; particle size not provided) for 5 h/d, 2 d/week for 8 and 12 months. The lungs retained 1.448 mg silica (1.3% of exposure) and 1.759 mg (1.1%), respectively. The lymph nodes retained 0.05 and 0.113 mg, respectively. After 12 month exposure and 1 month recovery, the lungs contained 1.1 mg silica (37.5% elimination) and the lymph nodes contained 0.16 mg. After 3 months recovery, the lungs contained 0.43 mg and the lymph nodes 0.12 mg. After 5 months recovery, the lungs contained 0.41 mg (76.7% elimination) and the lymph nodes 0.13 mg.

Rats (strain and n not provided) were exposed to aerosolized hydrophobic silica (100 mg/m^3; particle size not provided) for up to 1 year. Silica content of the lungs and the lymph nodes was 4.33 and 0.132 mg at 3 months, 6.71 and 0.214 mg at 5 months, and 11.46 and 0.378 mg, respectively. After 6 months of recovery, 55.5% of the silica was eliminated from the lungs. Lymph node elimination could not be observed.

Male rats (strain and n not provided) were exposed to aerosolized hydrophobic pyrogenic silica (0, 10, 50, or 150 mg/m^3; particle size not provided) for 6 h/d, 5 d/week for 12 months. The low dose had no effect. The mid- and high-dose groups had white foci on the lung surfaces and collections of foamy macrophages within the alveoli. The peribronchial lymph nodes were enlarged.

Male Cynomolgus monkeys (*Macaca fascicularis*; n not provided) were exposed to aerosolized hydrophobic pyrogenic silica (0, 10, 50, or 100 mg/m^3; particle size not provided) for 6 h/d, 5 d/week for 12 months. Recovery was 2 or 24 months. The low dose had no effect. The mid- and high-dose groups had interstitial fibrosis, which did not resolve or progress during recovery. Peribronchial lymph nodes were enlarged (ECETOC 2006).

Intratracheal

Silica

Ernst et al. (2002) used female Wistar WU rats (Crl:WI(WU)BR) to test the carcinogenicity of silica after intratracheal instillation in several experiments. The authors also tested the preventive effects of poly-2-vinylpyridine-N-oxide (PVNO) against silica carcinogenicty. Starting at 8 weeks of age, the rats were anesthetized and treated by intratracheal instillation of a particle suspension of silica. In the first experiment, the rats (n = 4) were treated 20 times at 2-week intervals with silica (0.5 mg). A second set was treated 30 times. Two weeks after the last instillation, the rats were killed and the lungs examined. Rats treated with silica had moderate, but transient dyspnea that resolved in 1 to 4 h.

The experiment was repeated with various doses and with the addition of PVNO measuring various parameters, comparing the results to the control saline solution. Silica administered twice at 0.3 mg at 7-day intervals increased lung weights compared to controls. At 1 and 3 mg, there were increased leukocytes, PMNs, lymphocytes, and lung weights. Similar results were observed when administered 3 times. When administered 4 times, there was also an increase in leukocytes and PMNs at 0.3 mg/dose. Rats administered 0.2 mg once had increased leukocytes and PMNs; at 2 mg, there was increased leukocytes, PMNs, and lung weight. PVNO administered with 2 mg of silica reduced the number of leukocytes, PMNs, lymphocytes, and lung weight compared to silica alone.

Using the data from the above experiments, the authors designed experiments lasting 3 and 9 months. The rats treated with silica had decreased body weights of ~5% after 9 months.

The particle-laden alveolar macrophages in the lungs of the silica-treated groups appeared to be generally intact. In the 4-week experiment there was multifocal moderate to severe granulomatous alveolitis characterized by abundant macrophages, fewer fibroblasts, and T-lymphocytes and only a few granulocytes. Over time after instillation of silica, the majority of these inflammatory foci had progressed to “scar-like” interstitial fibrotic granulomas. This process was markedly augmented by additional treatment with PVNO. The authors stated that fibrotic lesions were considered to represent chronic stages of alveolitis induced by silica.

Cells lavaged from the lungs of the rats treated for 9 months had increased reactive nitrogen intermediates, reactive oxygen intermediates and TNF-α than controls when exposed to lipopolysaccharides or Zymosan. The authors concluded that amorphous silica is more toxic than quartz (also tested in this study) but recruitment of leukocytes and PMN

concentration in the lavage seems to be lower and may decrease faster than for quartz. This may be due to amorphous silica's rapid elimination from the lungs. Silica induced inflammation persisted as long as there were repeated instillations.

Lesions in the lungs were characterized by a lack of alveolar lipoproteinosis and relatively low numbers of intra-alveolar macrophages. Most of the macrophages were foamy but not necrotizing. Silica also produced a pronounced but localized interstitial fibrosis (interstitial fibrotic granulomas). The authors suggested that these developed from acute alveolitis observed after a single administration of silica. The authors also suggested that the lesions resulted from acute epithelial damage at the sites of particle deposition with subsequent (granulomatous) inflammation and production of granulation tissue. Silica is not carcinogenic under these test conditions (Ernst et al. 2002).

Ocular Irritation

Precipitated and Hydrated Silica

Hazelton Laboratories (1958a) instilled a single dose of an aqueous solution of pyrogenic silica (3 mg) to the eyes of albino rabbits (n = 3). The eyes were observed at 1, 4, and 24 h. There was mild eye irritation in the form of erythema and vascularization of the lower sclera and nictating membrane, which resolved within 48 h.

W. R. Grace & Co. (1981) reported a Draize test of silica (9 mg) using rabbits (n not provided). The dry material was a mild irritant (score of 2.4) in the unrinsed eyes. The authors suggested that was due to the strongly hydrophilic silica. There was no irritation when the eyes were rinsed or treated with an aqueous suspension.

In another study, silica (10 mg) was instilled into the eye of rabbits and not rinsed or rinsed after 2 or 4 sec. There was faint irritation of the mucous tissues in the eyes not rinsed which resolved after 1 day. There was no irritation in the eyes that were rinsed. When the test was repeated with the same amount of silica in aqueous solution there was no irritation.

Lewinson et al. (1994) instilled pyrogenic or precipitated (hydrated) silica (0.1 g in olive oil) into the eyes of male New Zealand white rabbits (n = 8). After 5 min, the eyes of 5 rabbits in each group were rinsed. After 24 h, the rest of the rabbits' eyes were rinsed. The eyes were examined with a split lamp at 1, 24, 48 and 72 h (24-h exposure only).

The rabbits treated with precipitated silica had slight redness of the conjuctiva at 1 and 24 h in the group rinsed after 5 min and at 1, 24, and 48 h in the group rinsed after 24 h. There were no signs of irritation in the rabbits treated with pyrogenic silica. There were no clinical signs. The authors concluded that precipitated silica was slighly irritating to the eyes of rabbits and pyrogenic silica was not irritating. It is not clear whether the greater water solubility of precipitated silica or the incomplete removal of olive oil caused the difference (Lewinson et al. 1994).

UNEP (2004) reported several unpublished ocular studies. One irritation study of pyrogenic silica (100 mg) used rabbits (n = 3). The silica was instilled without rinsing. There were no signs of irritation up to 96 h after application.

In another ocular irritation study of pyrogenic silica (100 mg) using rabbits (n = 3), the silica was instilled without

rinsing. There were weak irritating effects in the conjuctivae with a redness score of 2/4 in all rabbits at 1 and 2 h, 1 rabbit at 24 h, and non at 72 h. Chemosis and discharge were slight after 1 h. The authors concluded that pyrogenic silica was non-irritating.

In another unpublished study of precipitated (hydrated) silica using rabbits, silica was found to be nonirritating.

In another unpublished study of precipitated silica gel (hydrated; suspended in water), the eyes were unrinsed or rinsed after 2 or 4 sec. The authors concluded that precipitated silica was nonirritating.

In another unpublished study, 4 products of precipitated (hydrated) silica (100 mg) were instilled in the eyes of rabbits. All types had isolated cases of very slight and transient irritating effects on the conjunctiva with a redness score of 1/4. The authors concluded the precipitated silica products were nonirritating.

In another unpublished ocular irritation study, precipitated (hydrated) silica (50% w/v in an aqueous slurry) was nonirritating to rabbits (UNEP 2004).

Unpublished ocular irritation studies are summarized in Table 10 (ECETOC 2006).

Dermal Irritation

Pyrogenic and Hydrated Silica

Hazelton Laboratories (1958b) applied pyrogenic silica (5 or 10 g as a paste in water) to the intact and abraded skin of albino rabbits (n = 4) daily, 5 d/week, for 15 applications. Mild dermal irritation consisting of erythema, atonia, and desquamation was observed for both doses. The abraded skin healed completely.

W. R. Grace & Co. (1981) reported a study where a US Department of Transportation test for skin irritation of silica (assumed at 100%) was performed on rabbits (n = 8) on intact and abraded skin. One rabbit showed very mild reddening of the abraded skin. Silica was determined to be virtually non-irritating.

Lewinson et al. (1994) used a gauze patch to apply pyrogenic silica (0.5 g in olive oil) or precipitated silica (0.5 g in aqueous methylhdroxyethyl cellulose gel 300 P [1%]) to the intact and abraded skin of New Zealand white rabbits (n = 6; 3 male, 3 female) for 24 h. The patch site was scored after removal and 48 h later. The rabbits were observed for clinical signs during exposure and for 14 d after exposure. No irritation was observed for either type of silica on either intact or abraded skin. No effects were observed.

UNEP (2004) reported an unpublished dermal irritation study of pyrogenic silica (0.5 g; 12% suspension/gel in 1% methylhydroxyethyl cellulose in water) using rabbits. The silica was applied under occlusion to the intact (n = 6) and scarified (n = 6) skin of the rabbits for 24 h. There were no signs of irritation under either skin condition. The authors concluded that pyrogenic silica was non-irritating.

In another unpublished dermal irritation study, precipitated (hydrated) silica (0.5 g; 23% suspension/gel in 1%

methylhydroxyethyl cellulose in water) using rabbits, silica was applied under occlusion to the intact (n = 6) and scarified (n = 6) skin of rabbits for 24 h. There were no signs of irritation under either skin condition. The authors concluded that pyrogenic silica was non-irritating.

Another unpublished study reported a dermal irritation study of precipitated (hydrated) silica (0.5 g in 0.5 ml water) on rabbits (n = 3). The test substance was applied to the skin under occlusion for 4 h. There were no irritating effects.

Another unpublished study reported a dermal irritation study of precipitated silica (0.5 g) on rabbits (n = 12). The test substance was applied to the skin under occlusion for 24 h. There were no irritating effects.

Another unpublished study reported a dermal irritation study of precipitated (hydrated) silica (20 mg) on rabbits (n = 8). The test substance was applied to the skin under occlusion for 24 h. There were no irritating effects.

Another unpublished study reported that a patch test of silica was non-irritating to rabbits. No further details were provided.

Another unpublished study reported a dermal irritation study of precipitated (hydrated) silica (190 mg; 17% w/w; ~0.38 g/ml) on rabbits (n = 6). The test substance was applied to the skin under occlusion for 24 h. There was slight erythemas in 4/6 rabbits 0.5 h after removal. There were no irritating effects at 72 h. The authors concluded that precipitated silica was non-irritating.

Another unpublished study reported a dermal irritation study of precipitated (hydrated) silica (33 mg) on rabbits (n = 6). The test substance was applied to the skin under occlusion for 24 h. There was slight erythema at 24 h after removal. The authors concluded that precipitated silica was non-irritating (UNEP 2004).

ECETOC (2004) reported an unpublished dermal toxicity study of pyrogenic silica (0, 5,000, 10,000 mg/kg/d) using albino rabbits (n = 4; 2 male, 2 female). The silica was applied for 18 h/d, 5 d/week for 3 weeks to intact and abraded skin. There were no signs of systemic toxicity. There was no difference in dermal irritation between treated and control (cosmetic talc) groups as both produced mild dermal irritation consisting of erythema, atonia, and desquamation.

Unpublished studies of skin irritation of hydrophilic and hydrophobic silica on rabbits are summarized in Table 11 (ECETOC 2006).

Dermal Sensitization

Hydrated Silica

A guinea pig (n =10) sensitization study of hydrated silica (20% in distilled water) was conducted. No reactions were observed in either the test group or the control group (distilled water; n = 5) (Council 1984).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Pyrogenic Silica

W. R. Grace & Co. (1981) reported a study in which silica (500 mg/d) was fed to male and female rats (n = 40) for 6 months. After 4.5 months, 5 females were mated. There were no adverse effects observed for mortality, body weight gain, hematology, and reproductive performance. Histology of the stomach, intestines, pancreas, liver, and kidneys were similar to controls. Litter size, birth weight, morphology, and development of the offspring were similar to controls.

In another study, pregnant female mice were fed up to 1340 mg/kg silica for 10 days (specific gestation days not provided). There were no effects on nidation or on maternal or fetal survival. Fetal abnormalities were similar to controls.

The same results were reported for rats (up to 1350 mg/kg for 10 days), hamsters (up to 1600 mg/kg for 5 days) and rabbits (up to 1600 mg/kg for 13 days) (W. R. Grace & Co. 1981).

Lewinson et al. (1994) administered pyrogenic silica (500 mg/kg/day) to female Wistar rats (n not provided) in their feed. The female rats were mated with male rats consuming 500 mg/kg/day from the subchronic study (above) at weeks 8 and 17. The rats were weighed periodically, blood sampled monthly (except during pregnancy), and observed daily. The progeny from both matings were examined for abnormalities. At 6 months, the rats were killed and necropsied except for 5 rats which had a 3 week treatment-free period prior to being killed and necropsied.

There were no clinical signs during treatment. Body weights and feed consumption were similar between treatment and control groups. Hematological parameters and organ weights were unremarkable. Reproductive performance was similar between groups. Pathological examination revealed no differences between the groups.

At the first mating, 6 control and 9 treatment dams became pregnant; 7 from each group became pregnant at the second mating. There were no treatment-related effects in litter size, birth weight, physical parameters, or behavior. Development of progeny during lactation was without adverse effects; weight gains were normal. No treatment related effects were found during gross pathology. The authors conclude that the oral NOEL was >500 mg/kg for developmental and reproductive toxicity (Lewinson et al. 1994).

GENOTOXICITY

Mammalian Mutagenicity

Pyrogenic and Hydrated Silica

Liu et al. (1996) performed an in vitro micronucleus test using Chinese hamster lung fibroblasts on silica (20, 40, 80, and 160 $\mu g/cm^3$; 0.12, 0.23, 0.46, and 0.93 mg/ml). There was weak, but significant, dose dependent induction of micronuclei at cytotoxic concentrations with the results of the 2 highest dose groups (13.33 ± 1.77, $p < .05$; 18.00 ± 2.08, $p <$

.01) being greater than controls (7.67 ± 2.33; correlation coefficient 0.96). No clastogenicity was observed in concentrations lower than cytotoxic levels.

Zhong et al. (1997) performed a single-cell gel/Comet assay using Chinese hamster fibroblasts (V79) and human embryonic lung fibroblasts (HEL 299) on silica (68.9 and 137.9 µg/cm^2). There was a dose dependent increase in DNA migration in the gel in both cell types in a similar manner.

UNEP (2004) and ECETOC (2006) reported several unpublished in vitro mutagenicity studies of silica in mammalian cells. Silica was not mutagenic. The studies are summarized in Table 12.

ECETOC (2006) reported several unpublished in vivo mutagenicity studies of silica gel. Silica gel was not mutagenic The studies are summarized in Table 13.

Microbial Mutagenicity

Silica

Kanematsu et al. (1980) performed a Rec assay and an Ames assay (using *Escherichia coli* TA98, TA100, TA1535, TA1538) on silica. Both assays were negative at 0.001 to 10 M.

Prival et al. (1991) performed an Ames test on synthetic silica (0.033 to 10 mg/plate in dimethylsulfoxide [DMSO]) using *Salmonella typhimuriun* (TA98, TA100, TA1535, TA1537, TA1538) and *E. coli* (WP 2) with and without metabolic activation. All results were negative.

Lewinson et al. (1994) exposed *S. typhimurium* (strains TA98, TA100, and TA1535) and *E. coli* (WP2uvrA) to a toluene extract of pyrogenic silica (5 to 1580 µg/plate) with and without metabolic activation. The toluene extract of pyrogenic silica was not mutagenic at any concentration with or without activation. In an additional test, the extract was not mutagenic to *S. typhimurium* TA98 where the epoxide hydrolase inhibitor and glutathione depletor 1,1,1-trichloropropene-2,3-oxide was added to the activation mix to increase sensitivity of the test toward compounds that are activated to mutagenic epoxides.

UNEP (2004) and ECETOC (2006) reported several unpublished mutagenicity studies of silica. There was no evidence of mutagenic activity. The studies are summarized in Table 14.

Mutagenic Inhibition

Hydrated Aluminum Calcium Sodium Silicate

Abdel-Wahhab et al. (1998) incorporated aflatoxin (AF; 2.5 mg/kg feed) with or without hydrated aluminum calcium sodium silicate (0.5%) into the feed of Sprague-Dawley rats (n = 10) for 15 days. The rats were killed and bone marrow samples were collected for chromosomal analysis. AF caused structural and numerical aberrations of chromosomes, mainly chromatid breaks and chromatid gaps. Hydrated aluminum calcium sodium silicate decreased these effects for every category

of aberration except polyploidy. Hydrated aluminum calcium sodium silicate alone did not cause an increase in aberrations.

Şişman (2006) incorporated AF B_1 (0, 0.2, 0.5, or 0.8 ppm) with and without hydrated aluminum calcium sodium silicate (5.0 or 10.0 ppm) into the agar feed of adult Oregon-R wild type *Drosophilia melanogaster* flies. The flies were then paired and mated and the offspring observed. The low, mid, and high dose of AF caused the retardation of development of the F_1 adults by 1, 2, and 3 days, respectively. Both doses of hydrated aluminum calcium sodium silicate prevented the delayed development. Malformations in the AF treated groups increased from 0.38% (control) to 7.35%, 9.10% and 11.11%, respectively. The low and high dose of hydrated aluminum calcium sodium silicate reduced malformations but not to the levels of the controls. The AF reduced the number of offspring ($p < .05, .01$). Hydrated aluminum calcium sodium silicate mitigated this effect but not to control levels. No ill effects were reported due to hydrated aluminum calcium sodium silicate, only protective effects.

CARCINOGENICITY

Oral

Pyrogenic and Hydrated Silica

In an experiment described earlier by Takizawa et al. (1988), the female mice were fed precipitated (hydrated) silica in feed, the frequency of adenocarcinomas in the lungs was 1/16 (6.25%) for the control and 1/19 (5.3%), 0/20 (0%), and 1/20 (5%) for the low, mid, and high dose groups. In the males, the frequency of adenocarcinomas in the lungs was 1/16 (6.25%) for the control and 2/17 (11.8%), 3/14 (21.4%), and 3/16 (18.8%) for the low, mid, and high dose groups. There was low correlation of hyperplastic nodules/hepatocellular carcinoma/hemangioma/fibrosarcoma in the treatment groups compared to controls. The authors concluded that the non-neoplastic lesions were of no toxicological significance.

Lewinson et al. (1994) orally administered pyrogenic silica to Wistar rats (n = 40; 20 males, 20 females) in their feed (100 mg/kg) for 24 months. The rats were weighed before and after treatment. The rats were killed and necropsied. There were no clinical signs observed during the treatment period. The rates of tumors observed in the treated rats were comparable to historical controls. The authors concluded that there were no carcinogenic effects due to pyrogenic silica exposure.

Intratracheal

Pyrogenic Silica

Pott and Roller (2005) intratracheally instilled pyrogenic silica (3 mg in 0.9% PBS; 0.01 to 0.03 µm) into female SPF Wistar rats (HsdCpb:WU) (n = 40; 8 to 9 weeks old) 5 times weekly. The rats were then followed until death or the 30th month when they were killed and necropsied. A second group had silica at the same dose instilled 10 times weekly. Controls (n = 48) were untreated. In the first group, 37 rats survived the entire experiment, 35 in the second group, and 46/48 in the

control group. The period of time after the first treatment in which 50% of the rats died was 113 and 112 weeks in the first and second groups and 113 weeks in the control group. The percentage of rats with macroscopic lung tumor(s) was 13.5% in the first group, 2.9% in the second group, and 6.5% in the control group. The percentage of rats with macroscopic lung tumor(s) which are probably not a metastasis of other tumors located elsewhere was 8.1% in the first group, none in the second group, and none in the control group. The percentage of rats with benign tumors in the second group was 5.7% and there were none in the control group; this was not analyzed in the first experiment. Neither group had malignant tumors. The percentage of rats with tumors that were metatases of other tumors was 14.3% in the treatment groups 13.0% in the control group.

Inhalation

Hydrated Silica

Campbell (1940) exposed 3 month old mice susceptible to tumors (n = 75) to aerosolized precipitated (hydrated) silica (0.5 g/d; ≤ 5 µg particle size) once/h, 6h/d, 5 d/week for a year. The mice were allowed to live out their natural life span up to 917 days from the start of the experiment. Incidence of primary lung tumors was 7.9% in the control group and 21.3% in the treated group in mice living 10 months or longer. There was no obvious fibrosis in the lung tissue; there was fibrotic nodules in the tracheo-bronchial lymph nodes in > 50% of the mice. The author suggested that most of the silica dust was removed by cilia action through the trachea and also through the lymphatics. Half of the treated mice had overgrowth of the mediastinal connective tissue covering the tracheo-bronchial nodes which occurred in only 10% of the controls. In the treated group, 29.5% had an increase in incidence of overgrowth or hyperplasia of the tracheo-bronchial lymph nodes compared to 14.3% of the controls.

CLINICAL ASSESSMENT OF SAFETY

Oral

Pyrogenic and Hydrated Silica

Worth and Campen (1951) assessed the silica level in the blood of volunteers (n = 264) before and after the oral administration of colloidal silica protein or silica acid, tetrayglycol ester (amount not provided). There was a rapid increase of silica blood levels and a rapid elimination in the urine over 8 to 24 h. There was no influence of sex, age, employment, lung disease (dust lung), or other disease.

UNEP (2004) reported an unpublished study of orally administered silica (1250 mg in apple juice) in the form of pyrogenic (n = 6; 5 males, 1 female) and precipitated (hydrated; n = 6; 5 males, 1 female) silica, to volunteers. The solutions were consumed in 2 doses, morning and midday on the same day. The total urine was collected daily and analyzed. During

the 4 days post-treatment, changes of renal silica secretion were not observed. Daily silica increments in urine after ingestion ranged between 7 and 23 mg. For the pyrogenic silica, the individual baseline values of the pre-test phase were very variable and individually different; mean excretion rates ranged from 25 to 87 mg/day. In the post-treatment phase, individual mean excretion rates ranged from 32 to 61 mg/day. For the precipitated silica, the individual baseline values of the pre-test phase were very variable and individually different; mean excretion rates ranged from 16 to 71 mg/day. In the post-treatment phase, individual mean excretion rates ranged from 20 to 81 mg/day. Overall, increases in excretion were not unequivocally detectable. The authors noted that the small apparent increases were in marked contrast to the high dose of 2500 mg silica applied.

In an unpublished study on the effectiveness of silica gel in the treatment of type II hyperlipoproteinemia, 6 adults (3 men, 3 women; 20 to 51 years old) were admitted to a metabolic unit for 3 weeks. Silica was administered with the morning and evening meals starting with an oral dose of 1.0 g/d which increased by 1.0 g/d until 16 g/d was reached. There were no increases in the serum or urinary levels of silica. The number of white and red blood cells and platelets were unaffected. Two subjects had a decrease in serum iron levels, 1 had a decrease in hemoglobin concentration, 2 had a decrease in carotene, 1 had a decrease in serum folate, and 1 had a decrease in vitamin A. Clinical side effects included constipation in half the subjects and an unusual aftertaste in all subjects. One subject had gastritis. The authors concluded that there were no adverse effects of the silica on hepatic or renal function. Silica gel was not absorbed significantly from the intestine (UNEP 2004).

Dermal Irritation and Sensitization

Hydrated Silica

W. R. Grace & Co. (1981) reported a dermal study of a dusting powder that included micronized silica gel (amount not provided) on patients (n = 300). The authors concluded that the powder was non-irritating and non-toxic and could be safely applied to babies, children, and adults; and, from the allergic tests performed, there were little or no sensitizing properties of the powder.

Aqueous sodium lauryl sulfate (25%; ~0.05 ml) was applied to the upper outer arm, volar forearm, or the back of volunteers (n = 27; 18 males, 9 females) under occlusion for 24 h. This was followed by the application of a facial mask containing hydrated silica (0.05 ml; 17%) for 48 h (or 72 h over weekends), under occlusion. This was repeated for 5 inductions. After a 10-day rest, a challenge application was applied on a naive site (upper outer arm, volar forearm, or the back) for 48 h. There was no sensitization observed. The authors concluded that the test material was not likely to cause contact sensitivity under normal use (KGL, Inc. 2003).

Aqueous sodium lauryl sulfate (25%; ~0.05 ml) was applied to the upper outer arm, volar forearm, or the back of volunteers (n = 27; 18 males, 9 females) under occlusion for 24 h. This was followed by the application of a facial powder

containing hydrated silica (21.7436%) made into a 30% aqueous solution for 48 h (or 72 h over weekends), under occlusion. This was repeated for 5 inductions. After a 10-day rest, a challenge application was applied on a naive site (upper outer arm, volar forearm, or the back) for 48 h. There was no sensitization observed. The authors concluded that the test material was not likely to cause contact sensitivity under normal use (KGL, Inc. 2004).

UNEP (2004) reported an unpublished sensitization study of colloidal silica (45%). Patches were applied to volunteers (n = 20; 10 men, 10 women) for 6 days. After 2 weeks, challenge patches were applied for 48 h. Skin under the patches was examined at 1, 2, 3, and 6 days after the first application and on removal of the challenge patch. No skin reactions were observed (UNEP 2004).

Immune Response

Hydrated Silica

Epstein et al. (1963) injected colloidal (hydrated) silica (1 to 4 mg in saline; ~15 µm particle size) subcutaneously 2 to 8 times in volunteers (n = 28). Biopsies were taken from day 1 to 6 months. Granulomatous inflammation was observed within 7 days and persisted for months. The authors suggested that this was a particular type of foreign body response to a fibrogenic agent and not typical epithelioid cell nodules.

Occupational Exposure

Pyrogenic and Hydrated Silica

Volk (1960) studied workers (n = 215) with exposure to silica between 1947 and 1959 using chest x-rays. Exposure ranged from 15 to 100 mg/m^3, 2 to 6 mg/m^3, and 3 to 7 mg/m^3 , depending on workstation. Hairline actuation of the interlobar fissures, suggesting slight interlobar pleuritis, was the only remarkable sign. There were no signs of silicosis.

Plunkett and DeWitt (1962) examined 78 workers (aged 21 to 67 years; average 34.23 years) who had been occupationally exposed to precipitated silica from 1941 to 1959. Dust concentrations ranged from 0.35 to 204 mg/m^3. There was no evidence of silicosis or other pulmonary disease.

Wilson et al. (1979,1981) examined workers (n = 165) exposed to precipitated silica a mean of 8.6 years (44 workers had been exposed a mean of 18 years [10-35 years]). Dust levels varied from <1 to 10 mg/m^3 with some higher intermittent levels. Examination included spirograms, respiratory questionnaires, and chest radiographs. Cough and dyspnea correlated with level/time of smoking and not silica exposure. There were no correlations between yearly change of pulmonary function and dose or time of exposure. The workers with the mean exposure time of 18 years had pulmonary function similar to the rest of the group. There was radiographic evidence of minimal pneumoconiosis that was biased due to prior exposure to limestone. None of the 143 workers with exposure only to silica showed radiographic evidence of pneumoconiosis.

Choudat et al. (1990) examined workers (n = 41) exposed to precipitated silica and compared them to a control group.

The examination included blood gas analysis and chest radiographs. There was a reduction in forced expiratory flow in the exposed group. There was no correlation between the exposure index and pulmonary function. The authors concluded that smoking and exposure to silica synergise to induce small airway disease.

UNEP (2004) reported several unpublished studies of silica exposure. Workers (n = 200) with intensive and regular contact with silica from 1972 to 2000 were evaluated. There was no evidence of skin allergy caused by the silica. There were signs of irritation attributed to the desicative and defatting properties of silica which resulted in skin dryness which could be controlled by regular use of skin-protection ointment.

In another unpublished study, an occupational study of workers (n = 143) exposed to silica from 1959 to 1985 was performed. Exposure ranged from 1 to 34 years. There were complaints of some disorder or exhibition of abnormalities in lung function or histology in 54/143 (36%) of the workers. Dry cough, expectoration or dyspnea was reported in 34/54 of these workers. A total of 42/54 (78%) of these workers had some possible confounding factor (i.e., smoking). Radiological examination did not show any signs of fibrotic disease. Spirometric examination showed obstructive and/or restrictive ventilation disturbances in 24 workers. Most of the adverse findings were associated with confounding factors such as smoking.

In an unpublished occupational exposure study, x-rays were take of 99 workers who had manufactured silica for various amounts of time. The x-rays revealed no evidence of any occupational disease, including silicosis.

In an unpublished occupational study of workers in precipitated silica factories (1952 to 1981), there was no silicosis in workers employed for 1 to >20 years (mean 13.2 years). There were negative results in hematology, urine analysis, lung functions, and chest x-rays.

In an unpublished study of workers (n = 78) in a factory that manufactured hydrated silica pigment between 1941 and 1959, dust concentrations ranged from 0.35 to 205 mg/m^3. No evidence of silicosis or other pulmonary disease was observed. The incidence of illness and injuries were similar to other workers in this plant (UNEP 2004).

ECETOC (2006) reported an unpublished study of workers exposed to pyrogenic (3 factories) or precipitated (2 factories) silica. There were 510 current workers with at least 1 month exposure studied. Complete data sets were collected from 397 workers. Data were also collected from 178 men who were no longer working in the factories. Unexposed workers totaled 210. Chronic bronchitis rates were within expected ranges for all group but somewhat higher in exposed subjects. Differences between factories were absent. The percentage of subjects with obstruction or restriction in breathing were similar between plants. Bronchial hyperresponsiveness was within expected levels. Chest radiographs showed no increased risk of pneumoconiosis in exposed subjects compared to controls. Relevant pleural thickening was not observed. The authors concluded that occupational exposure to silica was not a health risk.

In an unpublished study, 150 workers in a precipitated silica factory were examined by pulmonary function test and X-ray. The workers were exposed for ≥ 6 h/d for at least 5 continuous or discontinuous years. The mean duration was 12.2 years. The control group had been exposed for a maximum of 3 continuous or discontinuous months. The mean ages for the experimental and control groups were 43.1 and 44.3 years, respectively. There were no differences in the distributions and types of dysfunctional measurements observed between exposed and non-exposed groups. There were no differences in the mean percentage of predicted pulmonary function values between exposed and non-exposed groups. None of the X-rays showed signs of pneumoconiosis or fibrosis.

In an unpublished study, 29 workers in a silicone products manufacturing plant were surveyed. Silica exposure ranged from 0.15 to 10 mg/m^3 with a mean of 1.7 mg/m^3. Ten of 15 workers in the room temperature vulcanizing rubber area complained of upper respiratory tract irritation. In the heat curable rubber compounding area, the potential exposure to silica was greater, some of the workers complained about eye irritation, nausea, headaches, or rashes, none reported upper or lower respiratory problems (ECETOC 2006).

OTHER EVALUATION

The International Agency for Research on Cancer (IARC; 1996) concluded that amorphous silica is not classifiable as to its carcinogenicity to humans based on inadequate evidence in humans and inadequate evidence of increased tumors in animals.

OCCUPATIONAL EXPOSURE LIMITS

OSHA (2004) standard for exposure to amorphous silica is 80 mg/mm^3 or 20 mppcf air averaged over an 8-h work shift. NIOSH (2005) recommended that exposure to respirable silica be limited to 6 mg/m^3.

SUMMARY

This is a safety assessment of silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate. Silica is a silicon-oxygen tetrahedra where a silicon atom is central within 4 oxygen atoms that are shared with adjacent silicon atoms. There are many forms of silica. Only the safety of pyrogenic and hydrated amorphous silica and their salts are evaluated in this assessment; crystalline silicas are not included in this assessment.

Free silanol groups on the surface of silica particles influence the adsorption behavior. Silica has thixotropic properties. Amorphous silica does not exist as primary particles, except in solution-based forms, but as aggregates and agglomerates.

Amorphous pyrogenic silica (Figure 1) is manufactued by the hydrolysis of volatile silanes, usually silicon tetrachloride, in the flame of an oxygen-hydrogen burner. Precipitated silica and silica gels are produced from an alkali metal silicate dissolved in water (i.e., water glass) and an acid. Silica sols (colloidal silica) are dispersions of silica particles in a liquid, usually water. Impurities include calcium, sodium, potassium, antimony, barium, chromium, arsenic, lead, mercury, cadmium and selenium.

Analytical methods include colorimetric technique, electron microscopy, ICP-AES, CT-MAS, NMR, IR, BET, DLS, and AFM.

Silica was used in a total of 3,276 cosmetic products. Use concentrations ranged from 0.0000003% to 40%. Hydrated silica was reported to be used in 176 cosmetic products at 0.001% to 34%; aluminum calcium sodium silicate in 7 cosmetic products at 0.4% to 6%; and Sodium potassium aluminum silicate in 1 cosmetic product at 0.001% to 4%. Alumina magnesium metasilicate was not reported to be used by a voluntary FDA survey but was reported to be used at 0.002% to 0.001% in an industry survey. There were no reported uses or concentration of use reported for aluminum iron silicates.

Silica is used in food preparation as an anticaking agent, dispersion agent, suspending agent, and thickening agent. It is a defoaming and conditioning agent in malt beverages. Silica is a thickener in pastes and ointments.

Orally administered silica was mostly excreted through the urine in guinea pigs. Some studies showed accumulation of silica from oral exposure whereas others did not. Silica intraperitoneally injected into guinea pigs was mostly excreted through the urine.

When silica is inhaled by rats, it accumulates in the lungs and lymph nodes initially. The accumulated amount remains at a steady state with continued treatment. When treatment ceases, the silica decreases. When subcutaneously injected into rats, silica is absorbed over a few months.

When silica is inhaled or intratracheally instilled into rats, mice, and rabbits, there is a transient inflammatory response that resolves in days. Incubated macrophages ingested fewer silica particles than *C. albicans* or *S. cerevisiae*. Ultra-fine silica (14 nm) did more damage to the lungs during the inflammation than did fine silica (213 nm).

Silica is not cytotoxic to Chinese hamster V79 cells up to 160 μg/l. Pyrogenic silica and silica gel were cytotoxic to macrophages at 13.5 $\mu g/cm^2$; precipitated silica was less cytotoxic. Micronuclei were induced in Chinese hamster cells when incubated with 80 and 160 mg/ml. Micronuclei were induced with the presence of silica. There was ~85% lysis of sheep blood erythrocytes incubated with silica. Mesothelial cells incubated in silica were observed to accumulate silica in the

cytoplasm, around the nucleus, and vacuoles. When incubated in pyrogenic silica, both macrophages and neutrophils were inhibited in their ability to phagocytose sheep red blood cells. Silica caused intracelluar alteration in calcium homeostasis in renal cells.

Alveolar macrophages exposed to silica had increased protein kinases, NO_x production, and cell death. Human primary fibroblasts exposed to silica produced COX-2 and PGE_2 in a dose dependent manner. COX-1 was not affected. Silica was not cytotoxic to human mesothelioma and rodent fibroblast cells.

Sodium potassium aluminum silicate, in the form of Mexicali dust, induced anaphasic alterations in Balb3T3 cells.

Hydrated aluminum calcium sodium silicate countered the effects of aflatoxin in animal feed.

Silica was reported to have an oral LD_{50} up to > 40,000 mg/kg in rats and > 8,000 mg/kg in mice.

Orally administered aluminum calcium sodium silicate had no adverse effects up to 800 mg/kg in mice.

The acute dermal NOEL for silica is > 2,000 mg/kg for rabbits. When applied as an aqueous paste, there were no adverse effects. LD_{50} was > 5,000 mg/kg for precipitated (hydrated) Silcia and > 2,000 mg/kg for silica gel on intact and abraded rabbit skin with mild erythma.

Intraperitoneally injected silica was lethal to 20% to 30% of rats and rabbits at 100 mg/kg; all survived at 50 mg/kg. Peritoneal edema diminished and fibrosis increased over time. Silica injected i.p. was fatal to guinea pigs at 10%. Rats survived 5 days after an i.p. injection of 0.5 g silica, whereas another study reported 50 mg silica to be lethal in rats.

Silica injected in the veins of mice was better tolerated in small doses than in 1 large dose. The lethal dose ranged from 0.2 to 0.5 mg/30 g body weight, depending on particle size. The intravenous LD_{50} of silica was 15 to 44.4 mg/kg in rats, depending on type and source.

The minimum lethal dose of acute intratracheal administration of silica was 1.8 mg/cm^3 in rats. In rats, silica at 30 and 50 mg/kg was fatal to 80% to 90% immediately or within a few hours; these doses were nearly always fatal for rabbits. Silica particles (10 mg/kg; particle size range 2 to 3.5 µm) produced potent but transient pulmonary inflammation. Ultrafine silica induced more alveolar hemorrhage, compared to fine silica.

The acute inhalation of silica at 477 mg/m^3 by rats resulted in restlessness, droopy eyelids, lethargy, and dyspnea during treatment. Clinical signs resolved quickly after treatment and necropsies were unremarkable.

Silica at 200 µg instilled into the musculature induced local inflammation for up to 6 month with granulomatous scarring with necrotic muscle fibers and fatty degeneration of local macrophages.

Short-term oral doses of silica at 8,000 mg/kg/d produced no clinical effects in dogs. Short-term oral doses of silica produced no clinical effects for rats; HNELs were up to 1000 mg/kg/d. At 16,000 mg/kg clinical signs were observed: shyness, dirty fur, reduced activity, cachexia, hemorrhages of mucous membranes of the eyes and nose.

Short-term dermal application of silica to intact and abraded skin resulted in no dermal toxicity in rabbits.

Short-term inhalation of silica up to 668 mg/m^3 resulted in respiratory distress during treatment and a short-term inflammation response in the lungs, which resolved quickly when treatment ceased in rats. The lung clearance half-life was ~50 day for 50.5 and 154 mg/m^3. The NOAEL was 10.1 mg/m^3 in one study. In other studies, the NOEL was 1 and 46 mg/m^3.

Intratracheal injections of 5% silica resulted in the death of 3 of 10 rats and 2 of 10 guinea pigs at 10%.

Intravenous injections of 1% silica biweekly for 20 weeks into 5 rabbits resulted in 2 deaths. One more died during recovery. There was pleural effusion with pleuritis, mediastinal abscess formation, and marked congestion of the lungs. Right ventricles were dilated, the livers enlarged, and the spleen atrophied.

The oral subchronic HNEL was 5000 mg/kg/d, the NOEL was 500 mg/kg/d and the lowest effect level was 500 mg/kg/d for rats. There were no clinical signs up to 7950 and 8980 mg/kg/d for male and female rats, respectively. There were no gross findings of toxicity up to 50,000 ppm in feed.

Subchronic inhalation of silica at 53 mg/m^3 caused 44% mortality in rats from pulmonary vascular obstruction and emphysema. There was increased respiration rates and decreased weight gain during treatment. Necropsy findings included congestion of the lungs, lymph node enlargement, emphysema, vacuolated cells within alveolar spaces, and increased lung weights and collagen content. There were no mortalities at 31 mg/m^3. The LOAEL was 53 mg/m^3. The NOEL was 1.3 mg/m^3.

Silica incorporated into the feed of rats at up to 10% for 6 months or more produced discolored stool and unremarkable necropsies. Females had increased leukocytes and males had increased eosinophils at 10% in feed. Females had reduced liver weights at 12 and 24 months at 5%. Mice treated with silica in their feed had similar results for up to 103 weeks.

Rabbits chronically exposed to 0.2 and 5.0 μm aerosolized silica had formation of nodular fibrotic or diffuse fibrotic changes in the lungs. Mice bred to be susceptible to tumors exposed to aerosolized silica at 0.5 g/d for a year had increased incidence of lung tumors with no obvious fibrosis of the lung tissue but fibrotic nodules in the tracheo-bronchial lymph nodes. At 53 mg/m^3 for a year, treatment related deaths were 75% in rats from pulmonary vascular obstruction and emphysema starting in the 4th month.

Guinea pigs exposed to silica at 1.5 mg/ft^3 for up to 24 months had no deaths. A chronic reaction of the lung tissue was established at 4 months and emphysema after 4 to 8 months. Histologically, there was periductal and peribronchiolar intra-alveolar accumulations of the giant cells. In the lymphoid tissue, medullary hyperplasia with the formation of slight

amounts of reticulum was prominent during the second year of exposure. There were no macroscopically visible anomalies after 1 year of recovery.

At 126 mg/m^3 of silica for up to 24 months, guinea pigs and rabbits had increased lung weights and particle-phagocytosing macrophages accumulated in alveoli, bronchioles, and lymphoid tissue. There was complete reversibility of silica retention and inflammatory responses in guinea pigs within 6 months of recovery. Silicotic processes were completely absent.

Rabbits exposed to aerosolized silica at 1.5 mg/ft^3 for 12 months had progressive functional incapacitation and elevation of hematocrit levels observed in the majority of the rabbits, possibly due to the combined effect of pulmonary vascular obstruction and emphysema. During recovery, the cellular reactions and emphysema regressed but minor focal alveolar mural collagen persisted. In rabbits exposed to 360 mg/m^3 for a year, emphysema, pulmonary emphysema, vascular stenosis, alveolar cell infiltration, sclerosis, and epithelization granulomatosis, macrophage catarrh were observed. Lesions were observed in the liver, spleen and kidney. The LOAEL was 28 mg/m^3.

Monkeys exposed to aerosolized silica at 15 mg/m^3 for 12 months had initial decreased activity and body weight gain. There was emphysema at 3 months and considerable cellular infiltration of the alveoli and alveolar septa associated with distention of alveoli or accumulation of exudate and macrophages. After 12 months, the lesions were marked pulmonary emphysema, alveolar wall sclerosis, vacular occlusions, and cor pulmonale. The silica content remained low and decreased over time. At 50 and 100 mg/m^3, there was interstitial fibrosis which did not resolve after 24 months.

When monkeys were exposed to different types of silica, the precipitated (hydrated) silica group had lower lung volumes. There were no changes in lung volume parameters, but in ventilatory performance and mechanical parameters, dynamic lung compliance, and forced expiratory flow when exposed to silica gel. The frequency and size of inflammatory cell aggregates varied with the type of silica.

Rats exposed to aerosolized silica at ~45 mg/m^3 for 1 year had 41/120 deaths. There were small white foci under the pleura, enlarged and discolored lymph nodes with formation of collagen and local necrosis, perivascular and peribronchiolar dust cell granuloma with reticulin and collagen fibers, necrotic cells, desquamative catarrh and thickened alveolar septa. After 3 to 8 months recovery, the dust cell granuloma were fewer and reduced in size with only a few dust cells and fibers. The alveolar septa had not completely disappeared and lymph nodes were enlarged.

Rats exposed to aerosolized silica at 15 mg/m^3 for 12 months had a few macrophages aggregated in the lungs. The LOAEL was 6 to 9 mg/m^3. Rats exposed to aerosolized silica at 50 mg/m^3 for 12 months had 1.759 mg silica in the lungs, which decreased to 1.1, 0.43, and 0.41 mg after 1, 3, and 5 months recovery, respectively.

Intratracheal instillation of silica at 0.5 mg in rats every other week for 20 and 30 times resulted in 0.44 mg

silica/lung and associated lymph node.

Silica was a non- to mild ocular irritant in rabbits up to 100 mg.

Silica at 100% was nonirritating to the intact and abraded skin of rabbits.

A guinea pig sensitization study of 20% hydrated silica resulted in no reactions .

No reproductive or teratological effects were observed following the oral administration of silica in rabbits at 1600 mg/kg/d, hamsters at 1600 mg/kg/d, mice 1340 mg/kg/d, and rats up to 1350 mg/kg/d. An oral NOEL of 500 mg/kg/d was reported for rats; an oral NOAEL of 1350 mg/kg/d was also reported.

Silica was not mutagenic using the Rec or Ames test up to 10 M. Silica was not mutagenic in Ames test up to 1580 µg/plate. In a single-cell gel/Comet assay using Chinese hamster fibroblasts, there was an increase in DNA migration in a dose dependent manner. A chromosomal aberration test was negative up to 300 µl/ml without and 1000 µl/ml with metabolic activation. A HGPRT was negative up to to 250 µm/ml without and 500 µm/ml with metabolic activation. An unscheduled DNA synthesis test was negative up to 1000 µm/ml.

Silica was not mutagenic to CHO cells, hamster fibroblasts, rat hepatocytes, and human embryonic lung cells. Silica was not mutagenic to mice or rats.

A positive sister chromatid exchange test of AFB_1 showed inhibition by 10^{-5} M aluminum calcium sodium silicate. Hydrated aluminum calcium sodium silicate at 0.5% in the feed of rats inhibited the effects of AF.

Oral administration of silica to rats for 24 months was not carcinogenic up to 100 mg/kg/d.

A single intratracheal instillation of of 3 mg silica was not carcinogenic. Intratracheal instillation of silica at 0.5 mg twice per week for 30 weeks to rats was not carcinogenic. Silica at 3 mg was not carcinogenic in rats intracheally instilled 5 times weekly for 30 months.

Silica at 0.5 g/d instilled into mice for a year increased the incidence of overgrowth or hyperplasia of the tracheo-bronchial lymph nodes from 14.3% ot 29.5%.

The oral lethal dose of pyrogenic silica in humans is 15 g/kg.

Oral ingestion of silica up to 1250 mg resulted in a rapid increase of silica blood levels and a rapid elimination in the urine over 8 to 24 h with no adverse effect reported.

Silica subcutaneously instilled in humans caused granulomatous inflammation within 7 days that persisted for months.

Silica was non-sensitizing at 45%. A powder containing silica up to 45% was non-irritating and non-sensitizing in humans.

Workers in environments with aerosolized silica had few signs of silicosis or pulmonary disease up to 100 mg/m^3.

Smoking and exposure to silica synergise to induce small airway disease. Exposure to hydrated silica also had no evidence of silicosis or pulmonary disease. There were signs of dermal irritation due to the desicative and defatting properties of silica.

DISCUSSION

The CIR Expert Panel emphasized that the silica considered in this safety assessment is synthetic amorphous silica (gel, hydrated, and fumed/pyrogenic) and does not include any form of crystalline silica.

The Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

The Panel was concerned about the possibility of iron atoms reaching the lungs if aluminum iron silicates were to be used in a spray. In the absence of inhalation toxicity data, the Panel determined that aluminum iron silicates can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (10 μm). The Panel recognizes that most of the formulations are not respirable and of the preparations that are so, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation potential. Aluminum iron silicates is safe as a cosmetic ingredient because the particles for aggregates and agglomerates that are too large to be respirable.

The Panel determined that silicosis was not an issue since crystalline silica is not used in cosmetics.

CONCLUSION

Silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.[1]

[1]Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

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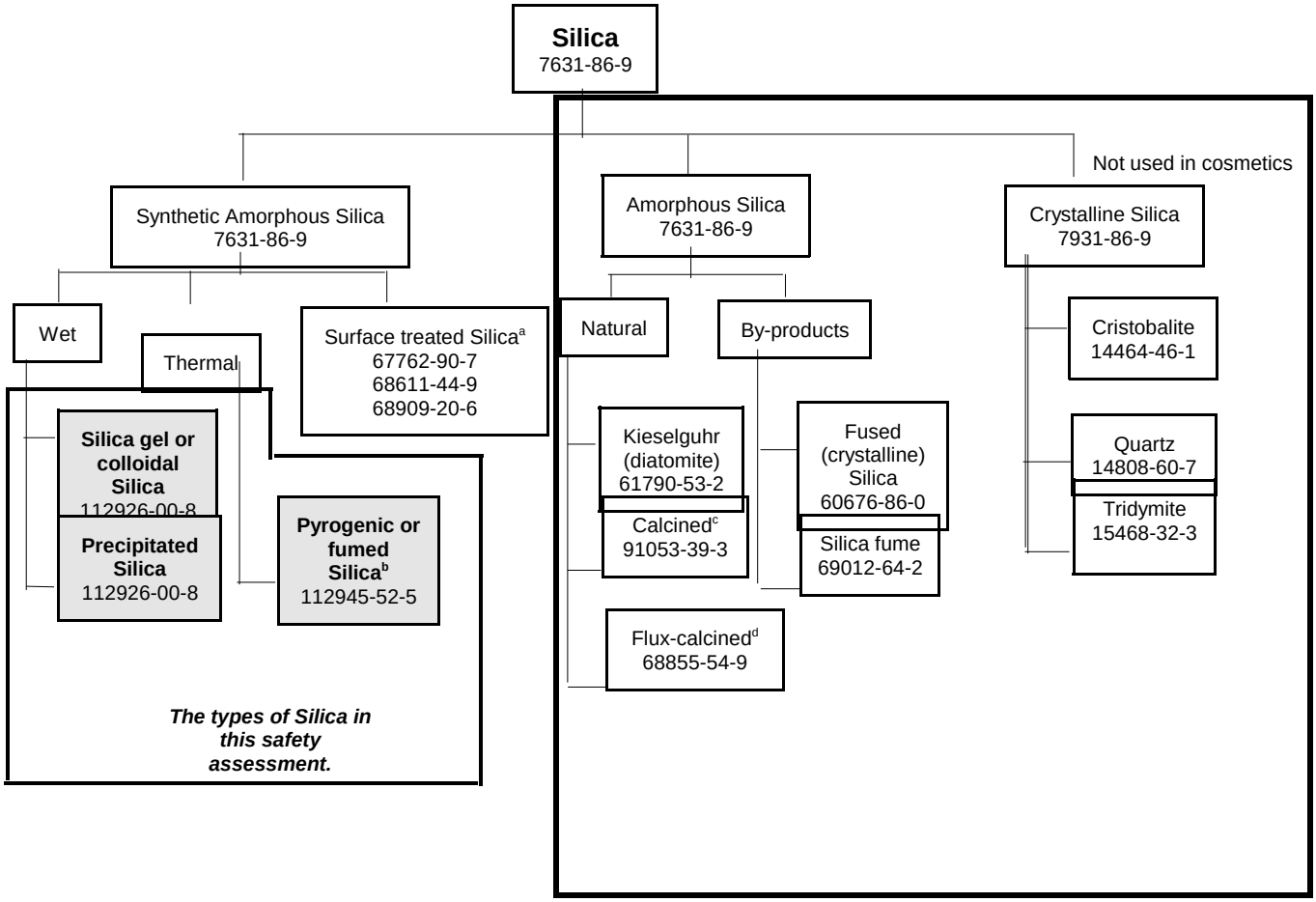

Figure 1. Different polymorphs of silica with CAS Numbers. Shaded boxes represent the types of silica covered in this report. a) All forms of synthetic amorphous silicas can be surface modified either physically or chemically; most common treating agents are organosilicon compounds. b) Pyrogenic silica is also known as fumed silica in English speaking countries and is not to be confused with silica fume, which is crystalline. Pyrogenic is used in recent publications. c) By-product from electrical furnace. d) Partial transformation into cristobalite (after Arts et al. 2007).

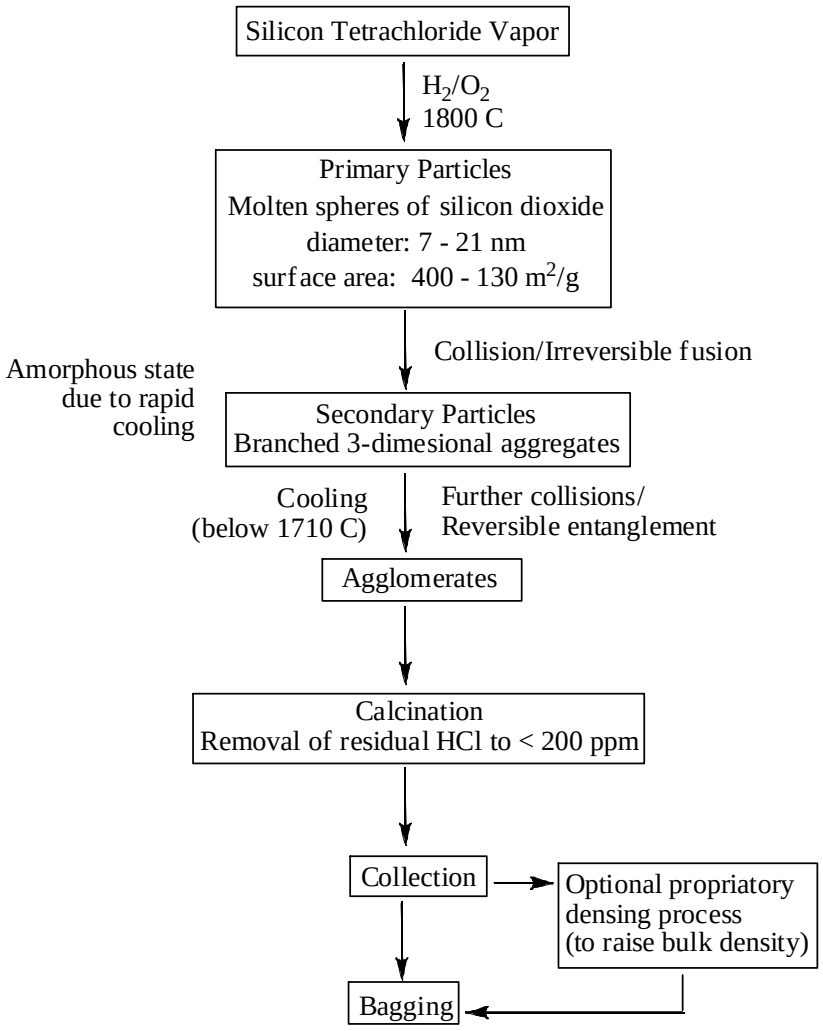

Figure 2. Process for the manufacture of pyrogenic silica (Villota and Hawkes 1986).

Table 1. Physical properties of fumed hydrophobic silica, precipitated hydrophobic silica, silica gel, and silica sol.

Property	Fumed hydrophobic silica	Precipitated hydrophobic silica	Gel[a]	Sol	Reference
Appearance	Fluffy powder	Fluffy powder			Lewinson et al. 1994
	White	White	White	White, milky	Ferch 1976
Molecular weight	60.1				NIOSH 2005
Particle size	1-350 µm				UNEP 2004
pH[b]	3.6-4.5	5-9	3-8	3-5; 8-11	Ferch 1976
	4-9				UNEP 2004
	~3.7 (4% aqueous slurry)				UNEP 2004
Boiling point	4046°F (2230°C)				NIOSH 2005
Melting point	3110°F (1710°C)				NIOSH 2005
	~1700 °C				UNEP 2004; OSHA 2004
BET surface area (m^2/g)	110-250	100			Lewinson et al. 1994
	50-400	30-500	250-1,000[c]	50-400	Ferch 1976
Tapped (bulk) density (g/l)	30-250	30-500	500-1,000	n/a[d]	Ferch 1976
	50-320 g/l				UNEP 2004
	40-60 g/l				American International Chemical, Inc. (no date)
Density	~2.2 at 20°C				UNEP 2004
Specific gravity (g/cm^3)	2.2	1.9-2.2	1.8-2.2	1.0-1.4	Ferch 1976
	2.65				OSHA 2004
Solubility	Insoluble				NIOSH 2005
Water solubility (saturation)	~15-68 mg/l at 20°C (pH 5.5-6.6)				UNEP 2004
	Insoluble				FNB 1996
Saturation	2.0 mmol/l(120 mg/l)				ECETOC 2006
Moisture (%)	<0.5	3			Lewinson et al. 1994
Stability in water	Stable; ion exchange processes possible				UNEP 2004
Loss on Ignition	1.0% max (2 hr @ 1,000°C)				UNEP 2004
Loss on drying (% by weight)	< 2.5	5-7	2-6	50-85	Ferch 1976
Loss on heating	1.0% max				American International Chemical, Inc. (no date)
Vapor pressure	~0 mm HG				NIOSH 2005; OSHA 2004
	None				UNEP 2004
Ignition loss (%)	<2	7			Lewinson et al. 1994
	<2	3-14	2-15	50-90	Ferch 1976
Temperature at ignition (°C)	400	400			Lewinson et al. 1994
Decomposition temperature of methyl groups (°C)	300	300			Lewinson et al. 1994
Purity of SiO_2 (%)	>99.8	>99.5			Lewinson et al. 1994
	> 99.8	> 95	> 95[e]	15-50	Ferch 1976
Carbon, bound	1	2			Lewinson et al. 1994
Al_2O_3 (%)	<0.05	0.1			Lewinson et al. 1994

Table 1. Physical properties of fumed hydrophobic silica, precipitated hydrophobic silica, silica gel, and silica sol.*(continued)*

Property	Fumed hydrophobic silica	Precipitated hydrophobic silica	Gel[a]	Sol	Reference
Fe_2O_3 (%)	<0.01	0.03			Lewinson et al. 1994
TiO_2 (%)	<0.03	0.03			Lewinson et al. 1994
HCl (%)	<0.025	<0.025			Lewinson et al. 1994
Dimethyldichlorosilane (%)	<0.1	<0.1			Lewinson et al. 1994
Primary particle size (µm)	0.005-0.05[f]	0.005-0.1[f]	0.001-0.01	0.005-0.02	Ferch 1976
Aggregate size (µm)	0.1-1	0.1-1	1-20	n/a	Ferch 1976
Agglomerate size (µm)	1-250	1-250	n/a	n/a	Ferch 1976
Mean pore size (µm)	None	> 0.03	0.0001-1	n/a	Ferch 1976
Pore size distribution	None	Very wide	Narrow	Wide	Ferch 1976
Structure, DBP[g] absorption (ml/100 g)	250-350	80-320	80-350	n/a	Ferch 1976

[a] After drying according to DIN 66131 or direct by titration with NaOH solution (Sears 1956).
[b] Hydrophilic grades.
[c] Porous surface.
[d] Not applicable.
[e] Dry product, no hydrogel.
[f] Primary particles do not normally exist as individual units.
[g] Dibutyl phthalate.

Table 2. Physical properties of silica with B.E.T. surface areas of 200, 325, or 380 m^2/g (Cabot Corporation 2006a,b,c).

	Value
pH (4% aqueous slurry)	3.7-4.3
325 Mesh residue (44 microns)	0.02% max
Tamped density	50 g/l
Loss on heating	< 1.5%
Specific Gravity Wt./gallon	2.2 g/cm^3 18.3 lbs
Refractive index	1.46
X-ray form	Amorphous
Assay (% SiO_2)	>99.8
Oil adsorption	~350 g/100 g oil
Average particle (aggregate) length	0.2-0.3 microns

B.E.T. - a rule for the physical adsorption of gas molecules on a solid surface that serves as the basis for the measurement of the specific surface area of a material

Table 3. Cosmetic product uses and concentrations for silica, hydrated silica, alumina magnesium metasilcate, aluminum calcium sodium silicate, and sodium potassium aluminum silicate.

Product Category (Total products in category - FDA 2008)	2008 uses (FDA 2009)	2008 concentrations (%) (Council 2008)
Silica[a]		
Baby products		
Shampoos (55)	-	0.003
Lotions, oils, powders, etc. (132)	1	-
Other (138)	1	10[b]
Bath products		
Soaps and detergents (1329)	22	0.02-10
Oils, tablets, and salts (257)	18	0.9-2
Capsules (4)	2	-
Other (239)	3	0.02
Eye products		
Eyebrow pencil (147)	42	0.01-6
Eyeliner (684)	89	0.3-19
Shadow (1196)	472	0.001-44
Lotion (177)	46	0.02-4
Makeup remover (131)	4	0.0004
Mascara (463)	135	0.2-10
Other (288)	79	0.04-3
Fragrance products		
Colognes and toilet waters (1288)	-	0.1
Perfumes (569)	6	1
Powders (278)	49	1-10
Sachets (28)	-	-
Other (399)	8	6-18[c]
Noncoloring hair care products		
Conditioners (1249)	12	0.002
Sprays/aerosol fixatives (371)	-	0.0005
Straighteners (144)	2	3[d]
Permanent waves (141)	1	-
Rinses (47)	-	0.003
Shampoos (1403)	7	0.02
Tonics, dressings, etc. (1097)	13	0.02-3
Other (716)	16	-
Hair coloring products		
Dyes and colors (2481)	80	0.002-0.3
Tints (58)	1	2
Color sprays/aerosol (8)	5	0.4
Hair lighteners with color (22)	3	-
Bleaches (152)	46	6[e]
Other (166)	14	1
Makeup		
Blushers (539)	122	2-20
Face powders (613)	198	1-26
Foundations (635)	268	0.01-40
Leg and body paints (29)	2	-
Lipstick (1912)	536	0.01-21
Makeup bases (164)	40	0.5-20
Rouges (99)	35	0.09-3

Table 3. Cosmetic product uses and concentrations for silica, hydrated silica, alumina magnesium metasilcate, aluminum calcium sodium silicate, and sodium potassium aluminum silicate. *(Continued)*

Product Category (Total products in category - FDA 2008)	2008 uses (FDA 2009)	2008 concentrations (%) (Council 2008)
Silica (continued)		
Fixatives (38)	16	0.3-3
Other (406)	107	2-4[f]
Nail care products		
Basecoats and undercoats (62)	5	5
Creams and lotions (17)	1	2-3
Polish and enamel (419)	70	0.3-9
Other (124)	16	5
Oral hygiene products		
Dentifrices (59)	12	3-16
Other (48)	3	-
Personal hygiene products		
Underarm deodorants (540)	38	0.02-9
Feminine deodorants (21)	1	
Other (514)	27	0.0000003-0.06[g]
Shaving products		
Aftershave lotions (395)	6	0.2-0.9
Men's talcum (7)	1	-
Preshave lotions (27)	-	5
Shaving cream (162)	1	-
Other (107)	9	0.003
Skin care products		
Cleansing creams, lotions, liquids, and pads (1368)	47	0.002-5
Depilatories (62)	3	1
Face and neck creams, lotions, etc. (1195)	125	0.03-10
Body and hand creams, lotions, etc. (1513)	50	0.02-5[h]
Foot powders and sprays (48)	7	0.8
Moisturizers (2039)	163	0.008-8
Night creams, lotions, powder and sprays (343)	32	0.01-3
Paste masks/mud packs (418)	22	0.02-6
Fresheners (285)	5	0.00004-3
Other (1244)	97	0.04-11[i]
Suntan products		
Suntan gels, creams, liquids and sprays (156)	8	0.03-2
Indoor tanning preparations (200)	19	-
Other (62)	7	0.6
Total uses/ranges for Silica	**3276**	**0.0000003-44**
Hydrated Silica[j]		
Bath products		
Soaps and detergents (1329)	**13**	**0.05-4**
Oils, tablets, and salts (257)	**7**	**0.4-2**
Other (239)	**1**	**4**
Eye products		
Eyeliner (684)	**1**	-
Shadow 1196)	**2**	-
Lotion (177)	**1**	**0.06-1**
Mascara (463)	**1**	-
Other (288)	**3**	**2**

Table 3. Cosmetic product uses and concentrations for silica, hydrated silica, alumina magnesium metasilcate, aluminum calcium sodium silicate, and sodium potassium aluminum silicate. *(Continued)*

Product Category (Total products in category - FDA 2008)	2008 uses (FDA 2009)	2008 concentrations (%) (Council 2008)
Hydrated Silica (continued)		
Fragrance products		
Powders (278)	**10**	**2**
Noncoloring hair care products		
Conditioners (1249)	-	**0.04**
Shampoos (1403)	-	**0.05**
Tonics, dressings, etc. (1097)	-	**2**
Hair coloring products		
Bleaches (152)	**18**	**2**[l]
Other (166)	**2**	-
Makeup		
Blushers (539)	-	-
Face powders (613)	**23**	**4**
Foundations (635)	**4**	**3**
Makeup bases (164)	**1**	-
Lipstick (1912)	-	**0.003**
Other (406)	**3**	-
Nail care products		
Basecoats and undercoats (62)	**6**	-
Cuticle softeners (18)	**1**	-
Creams and lotions (17)	**1**	-
Polish and enamel (419)	**2**	**1-2**
Other (124)	**3**	-
Oral hygiene products		
Dentifrices (59)	**23**	**7-34**
Mouthwashes and breath fresheners (85)	-	-
Other (48)	**2**	**0.2**
Personal hygiene products		
Underarm deodorants (540)	-	**2**
Douches (12)	-	**0.03**
Feminine deodorants (21)	**1**	-
Other (514)	**3**	**6**
Skin care products		
Cleansing creams, lotions, liquids, and pads (1368)	**5**	**3-17**
Depilatories (62)	**10**	-
Face and neck creams, lotions, etc. (1195)	**6**	**0.09**
Body and hand creams, lotions, etc. (1513)	**4**	**0.06-2**
Foot powders and sprays (48)	**1**	-
Moisturizers (2039)	**3**	**1-2**
Night creams, lotions, powder and sprays (343)	**1**	**0.04**
Paste masks/mud packs (418)	**2**	**0.01-10**
Fresheners (285)	**4**	-
Other (1244)	**6**	**0.001-0.004**
Suntan products		
Suntan gels, creams, liquids and sprays (156)	**1**	**0.2-2**
Other (62)	**1**	-
Total uses/ranges for Hydrated Silica	**176**	**0.001-34**

Table 3. Cosmetic product uses and concentrations for silica, hydrated silica, alumina magnesium metasilcate, aluminum calcium sodium silicate, and sodium potassium aluminum silicate. *(Continued)*

Product Category (Total products in category - FDA 2008)	2008 uses (FDA 2009)	2008 concentrations (%) (Council 2008)
Alumina Magnesium Metasilicate		
Skin care products		
Face and neck creams, lotions, etc. (1195)	-	**0.01**
Body and hand creams, lotions, etc. (1513)	-	**0.002**
Total uses/ranges for Magnesium Aluminum Metacilicate	-	**0.002-0.01**
Aluminum Calcium Sodium Silicate		
Eye products		
Mascara (463)	-	**0.5**
Makeup		
Blushers (539)	**1**	-
Face powders (613)	**1**	-
Foundations (635)	-	**0.4-6**
Lipstick (1912)	-	**6**
Nail care products		
Polish and enamel (419)	**4**	**0.5**
Skin care products		
Moisturizers (2039)	**1**	-
Total uses/ranges for Aluminum Calcium Sodium Silicate	**7**	**0.4-6**
Sodium Potassium Aluminum Silicate		
Nail care products		
Basecoats and undercoats (62)	-	**4**
Polish and enamel (419)	-	**0.001**
Skin care products		
Paste masks/mud packs (418)	**1**	-
Total uses/ranges for Sodium Potassium Aluminum Silicate	**1**	**0.001-4**

[a] Silica; silica, amorphous; silica, fumed; and silicon dioxide, colloidal were listed by the FDA. These data were combined.
[b] 10% in a diaper liner.
[c] 10% and 18% in a solid perfume
[d] 1.5% after dilution.
[e] 3% after dilution.
[f] 2% in a concealer.
[g] 0.006% in a shower gel.
[h] 2% in body and hand sprays.
[i] 0.6% in a lip moisture cream/ 10% in a foot exfoliant.
[j] 1% after dilution.
[k] Hydrated silica and silicic acid were listed by the FDA. These data were combined.
[l] 6% in a body scrub.

Table 4. Retention of silica (25 mg/rat) in rat tissues after intratracheal injection (Byers and Gage 1961).

Sample (particle size)	Time after injection (weeks)	Lungs (µg/rat)	Liver (µg/rat)	Kidneys (µg/rat)	Spleen (µg/rat)
A1(19 µm)	12	1570	177	33	0
	24	755	20	12.4	1.4
	52	210	61	9.7	0
A2 (20 µm, 60 µm after storage)	12	5150	249	138	0
	24	1550	153	44	19
	52	720	153	56	0
B (25 µm)	12	656	234	34	5.8
	24	324	43	8.9	1.4
	52	108	38	12	0
Average found in normal rat tissue		28	37	11	5

Table 5. Unpublished acute oral toxicity studies of silica reported by UNEP (2004) and ECETOC (2006).

Species (n)	Test substance	Notes	LD_{50}
Sprague-Dawley rats (20; 10 males, 10 females)	Fumed silica in aqueous solution	There were no clinical signs or pathological observations at necropsy	> 3300 mg/kg
Wistar rats (10)	Precipitated silica	None	> 5110 mg/kg
Sprague-Dawley rats (20; 10 male, 10 female)	Precipitated silica	None	> 5000 mg/kg
Male rats (strain and n unspecified)	Precipitated silica (10 to 5000 mg/kg)	Followed by a 10-day observation period. >100 mg/kg, distended stomachs with bloody patches at the pyloric end were observed at necropsy. At the highest dose, a vascular stomach and reddened intestinal lining were observed. The editors concluded that the test was questionable due to the non-lethality of silica in other studies at similar doses.	470 mg/kg
Male rats (strain and n unspecified)	Precipitated silica in saline	No clinical signs in a 10 day observation period	> 5000 mg/kg
Rats (strain not specified; 10; 5 male, 5 female)	Precipitated silica	No clinical signs	> 5000 mg/kg
Wistar rats (10)	Silica incorporated into a stock diet at a ratio of 1:4 (w/w) for 24 h	Most rats consumed the diet quantitatively. There were no clinical signs or remarkable findings at necropsy. Stool change color to grey with normal consistency but larger than normal pellets.	> 10,000 mg/kg
Male rats (strain and n unspecified)	Precipitated silica in saline	No clinical signs in a 10 day observation period	> 5000 mg/kg
Male Sprague-Dawley rats (30)	Precipitated silica in water	No clinical signs in a 14-day observation period. The stool turned white for 2 days.	> 5620 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Precipitated silica in water	No clinical signs in a 14 day observation period. The stool turned white for 2 days.	> 20,000 mg/kg
Rats (strain and n not specified)	Aqueous colloidal silica (30%)	None	10,000 mg/kg
Rats (strain and n not specified)	Silica	None	40,000 mg/kg
Boltzman rats (5 male)	Hydrophilic fumed silica in 0.5% methylcellulose	None provided.	> 3,160 mg/kg
Sprague-Dawley (10; 5 male, 5 female)	Hydrophilic fumed silica in water	None provided.	> 5,000 mg/kg
Sprague-Dawley (10; 5 male 5 female)	Hydrophilic fumed silica in deionized water	None provided.	> 5,000 mg/kg

Table 5. Unpublished acute oral toxicity studies of Silica reported by UNEP (2004) and ECETOC (2006). *(continued)*

Species (n)	Test substance	Notes	LD_{50}
Swiss Mice (10 males)	Hydrophilic fumed silica in corn oil	None provided.	> 3,160 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in 1% aqueous gum arabic solution	None provided.	>31,800 mg/kg
Sprague-Dawley rats (20; 10 male, 10 female)	Hydrophilic precipitated silica in Aqueous carboxymethylcellulose	None provided.	5,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in olive oil	None provided.	6,350 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in 10% aqueous arabic gum	None provided.	> 5,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in water	None provided.	> 20,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in water	None provided.	> 10,000 mg/kg
Sprague-Dawley (10; 5 male, 5 female)	Hydrophilic precipitated silica in water	None provided.	> 20,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophilic precipitated silica in water	None provided.	> 20,000 mg/kg
Male Sprague-Dawley rats (n not provided)	Hydrophilic silica gel in saline	None provided.	> 5,000 mg/kg
Male Sprague-Dawley rats (30)	Hydrophilic silica gel in distilled water	None provided.	> 5,620 mg/kg
Sprague-Dawle Rats (10; 5 male, 5 female)	Hydrophilic silica gel in water	24 h observation.	> 31,600 mg/kg
Male rats (strain and n not provided)	Hydrophilic silica sol in aqueous solution (colloidal)	None provided.	> 10,000 mg/kg
Male Sprague-Dawley rats (10)	Hydrophilic silica sol in aqueous solution (colloidal)	None provided.	> 40,000 mg/kg
Sprague-Dawley rats (20; 10 male, 10 female)	Hydrophobic fumed silica in peanut oil	None provided.	> 5,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic fumed silica in corn oil	None provided.	> 5,000 mg/kg
Male Sprague-Dawley (10)	Hydrophobic fumed silica in corn oil	None provided.	> 3,160 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic fumed silica in distilled water	None provided.	Males - 9,200 mg/kg Females - > 10,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic fumed silica in corn oil	None provided.	> 5,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic fumed silica in corn oil	None provided.	> 5,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic fumed silica in corn oil	None provided.	> 5,000 mg/kg
Wistar rats (10; 5 males, 5 females)	Hydrophobic fumed silica in polyethylene glycol 400	None provided.	> 2,000 mg/kg
Sprague-Dawley rats (10; 5 male, 5 female)	Hydrophobic precipitated silica in olive oil	None provided.	> 7,900 mg/kg

Table 6. Acute inhalation toxicity studies of hydrophilic and hydrophobic silica (ECETOC 2006).

Species (n)	Test substance (surface area [m^2/g])	Notes	LC_{50} (mg/m^3)
		Hydrophilic	
Wistar rats (10; 5 male, 5 female)	Pyrogenic silica (200)	Exposure 4h, nose only. Particle size not provided, 56% of particles < 5 µm. No clinical signs observed and no organ abnormalities at necropsy.	> 139
Male albino rats (strain not specified; 10)	Pyrogenic silica (380)	Exposure for 1 h, nose only. No data on particle size. Vigorous cleansing, hypoactivity, abdominal respiration, gasping nasal exudation, closed eyes. Crust-like material around nose and mouth, fur chalky to touch for 2 days post exposure. Resolved quickly.	>207,000
Albino rats (strain, sex, and n not provided)	Pyrogenic silica (200)	Exposure for 1 h, nose only. No data on particle size.	> 191,300
Sprague-Dawley rats (10; 5 male, 5 female)	Pyrogenic silica (200)	Exposure for 4 h, nose only. Particle size 0.76 5 µm	> 2,080
Wistar rats (10; 5 male, 5 female)	Precipitated silica (190)	Exposure for 4 h, whole body. Particle size not provided, 45% of particles < 5 µm. Some decreased body weight in the females 2 days after exposure which resolved.	> 691
Male Sprague-Dawley rats (10)	Silica gel (not specified)	Exposure for 1 h, nose only. Particle size not provided. 1/10 rats died 2 h after exposure.	> 2,200
Male rats (strain not specified; 2)	Silica sol "solid" (not specified)	Exposure for 4 h, nose only. Particle size not provided.	> 3,100
Male rats (strain not specified; 2)	Silica sol (not specified)	Exposure for 2.5 and 6 h, mist, nose only, at 560 and 520 mg/m^3. Particle size not provided.	No deaths
Male albino rats (not provided)	Silica sol (not specified)	Exposure for 3.25 h, mist, whole body at 760 mg/m^3. Particle size not provided.	No deaths
Male albino rats (not provided)	Silica sol (not specified)	Exposure for 4.2 h, mist, whole body at 2,240 and 2500 mg/m3. Particle size not provided.	No deaths
Male albino rats (not provided)	Silica sol (not specified)	Exposure for 1.5 h, mist, whole body, at 3,300 mg/m^3. Particle size not provided.	No deaths
		Hydrophobic	
Wistar rats (10; 5 male, 5 female)	Fumed silica (80)	Exposure for 4 h, whole body. Particle size 1.4 - 1.8 µm.	2,863 - 3,730
Rats, strain not specified (10; 5 male, 5 females)	Fumed silica (130)	Exposure for 1 h, whole body. Particle size 0.15 µm.	> 2,280
Wistar rats (10; 5 male, 5 female)	Fumed silica (200)	Exposure for 4 h, whole body with 14 days recovery. Particle size 56% < 5 µm, ≥7.7 µm. Clinical signs transient body weight loss for 2 days. No abnormalities at necropsy.	> 477
SD rats (10; 5 male, 5 female)	Fumed silica (200)	Exposure for 4 h, whole body. Particle size 0.36 µm.	< 4,900
SD rats (10; 5 male, 5 female)	Fumed silica (200)	Exposure for 4 h, whole body. Particle size 0.54 µm. All died at 2,190 mg/m^3.	< 2,190

Table 6. Acute inhalation toxicity studies of hydrophilic and hydrophobic silica (ECETOC 2006).*(continued)*

Species (n)	Test substance (surface area [m^2/g])	Notes	LC_{50} (mg/m^3)
SD rats (10; 5 male, 5 female)	Fumed silica (200)	Exposure for 1 h, whole body. Particle size 0.48 µm.	1,260 - 2,830
Male Wistar rats (10); male Swiss mice (10); male English short hair guinea pigs (10)	Fumed silica (not specified)	Exposure for 6 h, whole body. Particle size not specified. All species preened. Rats hunched. Rats and mice had occasional prostration. No clinical signs in guinea pigs. Consolidation observed in 2/9 guinea pigs. Necropsies unremarkable.	> 250 for all species
Male albino rats (strain not specified; 10)	Fumed silica (not specified)	Exposure for 1 h, whole body. Particle size not specified.	> 3,150
Wistar rats (10; 5 male, 5 female)	Fumed silica (130)	Exposure for 4 h, whole body. Particle size 1.175-1.275 µm with 14 days recovery. At 2,100 mg/m^3, all rats died within 2.5 h. Clinical signs were few feces; closed eyes; wet, red staining on mouth/nose; labored breathing; respiratory distress; hunched position. Necropsy showed opaqued eyes, enlarged darkened lungs with red areas, white material in nasal turbinates, red areas in intestines. At 540 mg/m^3, 7/10 died. Clinical signs were closed eyes, red staining of mouth/nose, fur coated with silica, labored breathing, respiratory distress, hunched back. During recover, lethargy, ploerection, dyspnea, ptosis, few feces, eye crusting/lachrymation, unkempt appearance, anogenital wetness. Necropsy of survivors showed darkened lungs with red and white areas. At 210 mg/m^3, all rats survived. Clinical signs were closed eyes, labored breathing. Licking inside of mouth, laying on back. During recovery, sporadic instances of few feces, anorexia, chromodacryorrhea, labored breathin, wetness of nose/mout, diarhea. Transient decreases in body weight. After 14 days recovery, lungs darkened with white and red areas.	450
Wistar rats (10; 5 male, 5 female)	Fumed silica (300)	Exposure for 4 h, whole body. Particle size 0.95-2.15 µm. Results similar to above.	90 - 840 [sic]
SD rats (10; 5 male, 5 female)	Fumed silica (130)	Exposure for 4 h, whole body. Particle size < 0.2 µm. All rats died at 2,530 and 5,300 mg/m^3. Severe red discoloration of the lungs of rats that died.	1,650
SD rats (10; 5 male, 5 female)	Fumed silica (130)	Exposed for 4 h, nose only. Particle size 7.2-7.7 µm. 4/10 died at 2,200 mg/m^3. Severe discoloration of the lung in rats that died. Surviving rats had normal lungs except 1 male and 2 females with trace discoloration.	> 2,200
SD rats (10; 5 male, 5 female)	Fumed silica (300)	Exposure for 4 h, whole body. Particle size < 0.1 µm.	90
SD rats (10; 5 male, 5 female)	Fumed silica (300)	Exposure for 4, nose only. Particle size 7-7.1 µm.	500
SD rats (10; 5 male, 5 female)	Fumed silica (300)	Exposure for 4 h; whole body. Particle size < 0.4 µm.	800

Species (n)	Test substance (surface area [m^2/g])	Notes	LC_{50} (mg/m^3)
SD rats (10; 5 male, 5 female)	Fumed silica (300)	Exposure for 4 h, nose only. Particle size 6.3-7.7 µm. Author concluded that number of particles (surface area) may be responsible for observed effects.	600
SD rats (6; 3 male, 3 female)	Fumed silica (300)	Exposure for 4 h, whole body. Particle size 83% 1-5 µm, 17% 5-100.	660

Table 7. Short-term oral toxicity studies of silica reported by UNEP (2004) and ECETOC (2006).

Species (n)	Test substance; dose	Notes and results
Sprague-Dawley rats (5)	Precipitated silica gel; 16.5 mg/kg/d (10% w/w in feed), 5.8 g/kg/d for days 1-10 then 24.2 mg/kg/d for days 11-14 (20% in feed)	No observed adverse effects level (NOAEL) ≥24.2 mg/kg. No clinical signs observed.
Female inbred rat (not provided)	Precipitated silica; 1500 mg/kg/d in aqueous solution by gavage daily for 1 month	No clinical signs. Silica content in liver, 1.5 µg; kidney, 6.4 µg; spleen 5.3 µg; 1.8, 7.2, and 7.8 µg in controls, respectively.
Charles river rats (30; 15 male 15 female)	Hydrophilic fumed silica;0, 1%, 3%, 5% (0, 1,000, 3,000, 5,000 mg/kg) in diet for 13 weeks	No gross signs of systemic toxicity. No effect on growth rate, feed consumption, or survival. No increase in silica content of the liver, kidney, spleen blood, or urine after 45 and 90 days. No gross or microscopic pathological changes.
Female rats (strain and not specified)	Hydrophilic precipitated silica; 0 or 1500 mg/kg by gavage for 4 weeks	No effects to body weight gain, feed consumption, and behavior.
Wistar rats (20; 10 male, 10 female)	Hydrophilic precipitated silica; 0, 0.5%, 2%, or 8% (0, 250, 1,000, 4,000 mg/kg) in diet for 13 weeks	Increased feed intake associated with decreased feed efficiency in the high-dose group; mean absolute and relative weight of the cecum increased in the high-dose group. General condition, behavior, survival, body weights, water intake, and hematological and urinary parameters were not adversely affected. No gross or microscopic pathological abnormalities observed. NOEL = 4,000 mg/kg.
SD rats (10; 5 male, 5 female)	Hydrophilic silica gel; 0 or 10% (0, 16,500 mg/kg) for 2 weeks or 5% (5,800 mg/kg) for days 1-10 then 20% (24,200 mg/kg) for days 11 -14	No gross signs of systemic toxicity. No effect on growth rate, feed consumption, or survival. No gross or microscopic pathological changes.
Male rats (strain not specified; 6)	Hydrophilic silica sol; 7,500 mg/kg in diet, 5 d/week for 2 weeks	All animals lost weight during treatment but gained over the weekend and during recovery period. No effects on organs.
CD rats (n not specified; male and female)	Hydrophilic silica sol; 0 or 800 mg/kg in diet for 4 weeks	No treatment effects in clinical symptoms, urine and blood parameters, necropsy or histopathology.
Beagle dogs (17; 9 male, 8 female)	Hydrophilic silica sol; 0 or 800 mg/kg in diet for 4 weeks	No treatment effects in clinical symptoms, urine and blood parameters, necropsy or histopathology.

Table 7. Short-term oral toxicity studies of silica reported by UNEP (2004) and ECETOC (2006).

Species (n)	Test substance; dose	Notes and results
Wistar rats (10; 5 male, 5 female)	Hydrophobic fumed silica; 0, 500, or 1,000 mg/kg in diet for 5 week or 2,000 mg/kg increased stepwise every 2 weeks to 16,000 mg/kg (25% of daily feed intake) for 8 weeks.	At 2,000 mg/kg, pronounced reduction of body weight associated with reduced feed intake. No changes in biological parameters or macroscopic findings. As the rats reached the highest dose the last 2 weeks, clinical signs were observed: shyness, dirty fur, reduced activity, cachexia, hemorrhages of mucous membranes of the eyes and nose. 2 males and 2 females died in week 8. Microscopic evaluation of the liver showed severe atrophy in the epithelium. NOEL assumed to be 1,000 mg/kg.
Charles River rats (20; 10 male, 10 female)	Fumed silane-treated silica;1, 2%, 2%, 4% (0, 1,000, 2,000, 4,000 mg/kg) in diet for 13 weeks	No effect on appearance, behavior, growth, survival, clinical studies, or gross pathology. No cytopathological changes. Minimal change in thyroid gland morphology (smaller follicles lined by slightly taller epithelial cells) in males in mid- and high-dose groups.

Table 8. Unpublished short-term inhalation toxicity studies of silica (ECETOC 2006).

Species (n)	Test substance; dose	Notes and results
Male Wistar rats (10)	Hydrophilic fumed silica (0, 1.39, 5.41, 25.3 mg/m^3) for 6 h/d for 5 days. Recovery for 1 or 3 months.	There were no effects in the low-dose group. Mid- and high-dose groups had incidences of pulmonary inflammation after exposure. Effects diminished or disappeared during recovery.
Wistar rats (20; 10 male, 10 female)	Hydrophilic fumed silica (0, 17, 44, 164 mg/m^3) for 6 h/d, 5 d/week for 2 weeks.	Respiratory distress observed in all treatment groups. Reduced body weight gain and feed consumption in the mid- and high-dose groups. Hematological parameters were unremarkable. Increased absolute and relative lung weight in a dose-dependent manner. Lungs of several rats in each test group discolored, spotted, spongy, or irregular on the surface. Lungs increased septal cellularity, alveolar interstitial pneumonia, and early granulomata. Mediastinal lymph nodes of several rats were enlarged. Early granulomata observed in mediastinal lymph nosed in mid- and high-dose groups.
Wistar rats (20; 10 male, 10 female)	Hydrophilic precipitated silica (0, 1.16, 5.39, or 25. mg/^{3}) for 6 h/d, 5 d/week. Recovery for 1 and 3 months.	No deaths. No adverse effects in low-dose group. There was a slight decrease in breathing. Incidence of pulmonary inflammation increased in mid- and high-dose groups. Effects lessened or resolved during recovery. NOEL = 1 mg/m^3.
Wistar rats (20; 10 male, 10 female)	Hydrophilic precipitated silica (0, 46, 180, 668 mg/m^3) 6 h/d, 5 d/week for 2 weeks.	Signs of respiratory distress in all treatment groups. Males in mid- and high-dose groups had reduced body weight and feed consumption. Dose dependent increase in absolute and relative lung weights. In high-dose groups, several rats had spotted and swollen lungs with irregular surface. Males in mid- and high-dose groups had increased septal cellularity, alveolar macrophages and and particulates. Some of these changes were present in some mediastinal lymph nodes. Early granulomata in lungs in the high-dose group and mediatinal lymph nodes in the mid- and high-dose groups. NOEL < 46 mg/m^3.
Male Wistar rats (10)	Hydrophilic silica gel (0, 0.94, 5.13, 25.1 mg/m^3) 6 h/d for 5 days. Recovery for 1 and 3 months.	No effects in low-dose group. Pulmonary inflammation increased in the mid- and high-dose groups. Changes disappeared or lessened during recovery.
CD rat (80; 40 male, 40 female)	Hydrophobic fumed silica (0 or 60 mg/m^3 on day 1 then 30 mg/m^3 thereafter) 6 h/d, 5 d/week for 4 weeks. Recovery for 1, 2, 4, 6, and 12 weeks.	9 male rats died after first day due to acute pulmonary hemorrhage with bronchiolar plugs with emphysema. Active interstitial/alveolar inflammation that changed from diffuse to localized consolidation. After recovery, active inflammation was less prominent but some fibrosis and collagen apparent in the interstitium.
Wistar rats (20; 10 male, 10 female)	Hydrophobic fumed silica (0, 31, 87, or 209 mg/m^3) for 6 h/d, 5 d/week for 2 weeks.	Signs of respiratory distress in all test groups. Body weight and feed consumption reduced in mid- and high-dose groups. Hematological parameters were unremarkable. Increases in absolute and relative lung weights were dose-dependent. Lungs of several rats in all groups were pale, spotted, swollen and spongy. Lungs in all treatment groups had increased cellularity, accumulation of alveolar macrophages, alveolar edema, and early granulomata. NOAEL < 31 mg/m^3.

Table 9. Chronic inhalation studies of silica reported by UNEP (2004).

Species (n)	Test substance; dose	Notes and results
Female, inbred white rats (n = 10)	Precipitated synthetic silica; 55 mg/m^3 for 5 h/d, 5 d/week/ 3, 6, and 12 months. Post exposure 5 months.	At necropsy, some white-grey foci were observed subpleurally. Desquamation of alveolar cells with fine granula after 4 months. After 12 months, peribronchial and intra-alveolar small dust cell foci with few reticulin fibres were found. Small increased cell numbers and fibers were observed. The mediastinal lymph nodes were enlarged and contained dust cells with fine granules. Neither a diffuse nor nodular fibrosis was observed in lungs or lymph nodes. At recovery, effects regressed. Lung weights were normal with a few foci left. There was no significant desquamation. Lymph nodes were slightly enlarged with some dust cells. One day retention value of silica was 0.138 mg/lung. Average silica content was 1.022 mg/lung after 4 months and 3.443 mg after 12 months. Conclusion: The lymphatic system appears to play a minor role in the elimination of silica from the lung. Therefore, there is no evidence for a silicosis or a lymphatic-type pneumoconiosis to develop from exposure to synthetic silica.
Female Sprague-Dawley Rats (n = 150)	Fumed silica; 50 - 55 mg/m^3, ~30 mg/m^3 respirable for 5 h/d, 5x/week then 2 - 3x/week partway through the experiment for 12 months. Post exposure up to 5 months.	Frequency of exposure was reduced due to fatal cases caused by massive substance-related purulent bronchitis, focal pneumontitis, and massive cellular reactions. After 12 months, ~1% of respirable dust was still retained in the lung. The increase in lung deposition was low from 18 weeks (1.2 mg) to 12 months (1.37 mg) of exposure. Mediastinal lymph nodes contained ~0.13 mg silica after 12 months. After 5 months post exposure, mean silica load was 0.16 mg/lung and 0.047 mg/lymph node, a reduction of 88% in the lung and > 50% in the lymph nodes. Microscopically visible dust foci under pulmonary pleura, mediastinal lymph nodes were moderately enlarged. Interior of alveoli: numerous macrophages accumulated, partially destroyed, associated with deposition of cell debris. Perivascular and peribronchiolar small dust foci of macrophages, associated with mild and moderate formation of connective tissue. Increased collagen formation in alveolar septa. Foci and clusters of phagocytes (partially normal, partially showing decay) and some collagenic fibrosis was observed in the mediastinal lymph nodes. Conclusion: In some cases, silica, at sites of highly concentrated deposits, caused a marked collagenic fibrosis, but without signs of typical silicosis.
Female albino rats (not provided)	Fumed silica; 0.112 mg/l; 5 h/d, 5 d/week for 1 year followed by 4 month recovery.	At 4 months, 1.578 mg were in the lungs and 0.151 in the lymph nodes; at 12 months, 1.820 and 0.430 mg, respectively. At necropsy, white foci in the plasma were observed, the mediastinal lymph node was enlarged. Histological examination revealed desquamative catarrh, sporadic dust modules, and foci with minimal to moderate fibrosis, increased collagen, and sporadic diffuse fibrosis of the alveolar septae and perifocal emphysema. Silicatic nodules were not observed. Lymph nodes: increase of dusted cells and slight to moderate fibrosis, sporadic collagen fibrosis. After recovery, silica content of lungs, 0.92 mg and lymph nodes, 0.814 mg. Necropsy revealed subpleural dust foci and enlarged lymph nodes. Lung weight increased. Microscopically cell desquamation gone whereas there was no improvement in other parameters.
Rabbits (not provided)	Silica; dose not provided; 4-5 h/d, 5 d/week for ~ 3 years followed by 30 to 150 days recovery	No clinical signs during inhalation. Mortality relationship to treatment not clear. Macroscopic examination: emphysema of the lungs. Microscopic evaluation: bronchial and alveolar dequamative catarrh, lymphocityes and leukocytes increased in the alveolas, edema, accumulation of macrophages in the lymph nodes and in the interstitium (perivascular, peribronchial, alveolar septea), granuloma of macrophages, dust cells, some thickening of the alveolar septas. Formation of connective tissue was minimal.

Table 10. Ocular irritation studies of hydrophilic and hydrophobic silica on rabbits (ECETOC 2006).

Type of silica	N	Description	Results
		Hydrophilic	
Fumed	8	Instilled 100 mg. Not rinsed (5) or rinsed after 5 min (3)	No signs of irritation.
Fumed	3	Instilled 3 mg	Slight to mild erythema; resolved at 48 h.
Fumed	6	Instilled 3.5 mg	Slight conjuctival erythema or chemosis in some animals at 24, 48, and 72 h. Mean score 0.6 and 0.1, respectively [sic]. Transient opacity in 2 animals at 4 h.
Fumed	9	Instilled 100 mg; not rinsed (6), rinsed (3)	No signs of irritation in washed eyes at 24, 48, and 72 h. Mean score 0.15; very slight conjuctival erythema up to 48 h.
Precipitated	3	Instilled 40 or 100 mg	No signs of irritation at 40 mg. At 100 mg, slight redness at 24, 48, and 72 h; mean score 0.7. Resolved by day 4.
Precipitated	8	Instilled 100 mg; not rinsed (5), rinsed (3)	No signs of irritation.
Precipitated	8	Instilled 0.1 ml of 50% dilution in olive oil; eyes not rinsed (5), rinsed in 5 min (3)	No signs of irritation in rinsed eyes. Very slight erythema (score 1) up to 24 h.
Precipitated	9	Instilled 100 mg; eyes not rinsed (6), rinsed at 4 s (3)	No signs of irritation.
Precipitated	6	Instilled 100 mg, 0.2 ml of 50% slurry	No signs of irritation.
Precipitated	9	Instilled 100 mg; eyes not rinsed (6), rinsed at 4 s (3)	No signs of irritation.
Precipitated	9	Instilled 100 mg; eyes not rinsed (6), rinsed at 4 s (3)	No signs of irritation.
Precipitated	9	Instilled 100 mg; eyes not rinsed (6), rinsed at 4 s (3)	No signs of irritation.
Silica gel	9	Instilled 9 mg; eyes not rinsed (3), rinsed at 2 s (3) or 4 s (3)	No signs of irritation.
		Hydrophobic	
Fumed	8	Instilled 100 mg; eyes not rinsed (5), rinsed after 5 min (3)	No signs of irritation.
Fumed	9	Instilled 25 mg; eyes not rinsed (6), rinsed after 30 s (3)	No signs of irritation in washed eyes. 2 unwashed eyes had slight erythema for 24 h. Mean score 0.1 at 24, 48, and 72 h.
Fumed	9	Instilled 3 mg; eyes not rinsed (3), rinsed after 2 s (3) or 4 s (3)	Transient slight to moderate conjunctival erythema at 1 and 4 h. Resolved at 24 h.
Fumed	9	Installed 10 mg; eyes not rinsed (6), rinsed after 30 s (3)	No signs of irritation.
Fumed	9	Instilled 10 mg; eyes not rinsed (6), rinsed after 30 s	No signs of irritation.
Fumed	9	Installed ~10-20 mg; eyes not rinsed (6), rinsed after 30 s	No sign of irritation in washed eyes; 2 unwashed eyes had slight erythema for 24 h (mean score 1 at 24, 48, and 72 h).
Fumed	9	Installed 6 mg: eyes not rinsed (3), rinsed after 2 s (3) or 4 s (3)	No signs of irritation.
Fumed	3	Installed 100 mg; eyes not rinsed (6), rinsed at 4 s (3)	No signs of irritation.

Table 11. Rabbit skin irritation studies of hydrophilic and hydrophobic silica (ECETOC 2006).

Type of silica	N	Description	Results
		Hydrophilic	
Fumed silica	6	Occlusive patch of 500 mg in 3 ml saline to intact and abraded skin for 24 h.	No signs of irritation to intact skin. Slight erythema on 3 abraded sites
Fumed silica	6	Occlusive patch of 500 mg moistened with saline to intact and abraded skin for 24 h.	Very slight erythema on 1 intact site at 24 h; very slight to well-defined erythema on abraded sites. No sign of erythema at 72 h.
Precipitated silica	3	Occlusive patch of 500 mg to intact skin for 4 h.	No signs of irritation.
Precipitated silica	12	Occlusive patch of 500 mg in methylelthyl cellulose to intact and abraded skin for 24 h.	No signs of irritation.
Precipitated silica	6	Occlusive patch of 23 mg to intact and abraded skin for 24 h.	Very slight erythema on 3 abraded sites and 5 intact sites at 24 h.
Precipitated silica	6	Occlusive patch of 190 mg to intact and abraded skin for 24 h.	Very slight erythema on 3 abraded and 4 intact sites at 24 h.
Precipitated silica	12	Occlusive patch of 500 mg in olive oil to intact and abraded skin for 24 h.	No signs of irritation
Precipitated silica	12	Occlusive patch of 500 mg to intact and abraded skin for 24 h.	No signs of irritation.
Precipitated silica	6	Occlusive patch of 500 mg to intact skin for 24 h.	No signs of irritation.
Silica gel	8	Occlusive patch of 20 mg to intact and abraded skin for 24 h.	No signs of irritation.
		Hydrophobic	
Fumed silica	12	Occlusive patch of 500 mg in methylethyl cellulose to intact and abraded skin for 24 h.	No signs of irritation.
Fumed silica	6	Occlusive patch of 500 mg moistened with PEG to intact and abraded skin for 24 h.	No signs of irritation.
Fumed silica silane treated	6	Occlusive patch of 500 mg moistened with corn oil to intact and abraded skin for 24 h.	No signs of irritation.
Fumed silica	6	Occlusive patch of 500 mg in 2 ml water to intact and abraded skin for 24 h.	No signs of irritation.
Fumed silica	6	Semi-occlusive application of 500 mg to intact skin for 4 h.	No signs of irritation.
Fumed silica	6	Semi-occlusive application of 500 mg to intact skin for 4 h.	No signs of irritation.
Fumed silica	6	Semi-occlusive application of 500 mg to intact skin for 4 h.	No signs of irritation.
Fumed silica	6	Semi-occlusive application of 500 mg to intact skin for 4 h.	No signs of irritation.
Precipitated silica	12	Occlusive patch of 500 mg in olive oil to intact and abraded skin for 24 h.	No signs of irritation.

Table 12. Unpublished in vitro mutagenicity and chromosomal aberration tests of cultured mammalian cells (UNEP 2004; ECETOC 2006).

Test	Test system	Silica type (concentration)	Results
Chromosomal aberration test, with and without metabolic activation	Chinese hamster ovary (CHO) cells	Fumed silica (19-300 µl/ml without S9, 250-1000 µl/ml with S9)	Negative
Hypoxanthine-guanine phosphoribosyl transferase test (HGPRT)	CHO cells	Fumed silica (10-250 µg/ml without S9, 100-500 µg/ml with S9).	Negative
Unscheduled DNA synthesis	Primary rat hepatocytes	Fumed silica (0.3-1000 µg/ml)	Negative; cytotoxic at 260 - 500 µg/ml
6-Thioguanine resistance	CHO cells	Hydrophilic fumed silica(10-250 µg/ml without S9, 100-500 µg/ml with S9)	No significant mutagenic activity
Chromosome aberration	CHO cells	Hydrophilic fumed silica (38-1,000 µg/ml without S9, 250-1,000 µg/ml with S9)	No clastogenic activity
Unscheduled DNA synthesis	Primary rat hepatocytes	Hydrophilic fumed silica (0.3-1,000 µg/ml with and without S9)	No genotoxic activity
Chromosome aberration	Human embryonic lung cells (Wi-38)	Hydrophilic silica gel (1-1,000 µg/ml without S9)	Clastogenic activity not significant
Clastogenic activity	CHO Cells	Hydrophobic fumed silica (63-500 µg/ml with and without S9)	No clastogenic activity
Clastogenic activity	CHO Cells	Hydrophobic fumed silica (63-500 µg/ml with and without S9)	No clastogenic activity
Clastogenic activity	CHO Cells	Hydrophobic fumed silica (63-500 µg/ml with and without S9)	No clastogenic activity
Clastogenic activity	CHO Cells	Hydrophobic fumed silica (42-333 µg/ml with and without S9)	No clastogenic activity
Chromosomal aberration test, with and without metabolic activation	CHO cells	Fumed silica (19 - 300 µl/ml without S9, 250 - 1000 µl/ml with S9)	Negative
Hypoxanthine-guanine phosphoribosyl transferase test (HGPRT)	CHO cells	Fumed silica (10 - 250 µg/ml without S9, 100 - 500 µg/ml with S9).	Negative

Table 13. Unpublished in vivo mutagenicity studies of silica gel (ECETOC 2006).

Test	Test system	Protocol (dose)	Results
Gene mutation (host mediated)	Mice + *S. typhimurium* TA1530, G-46 (indicator)	i.p. injection of *S. typhimurium* cells collected 3 h after last administration (1 or 5 x 1.4-5,000 mg/kg)	No mutagenic activity
Mitotic recombination (host mediated)	Mice (host) + *S. cerevisiae* D3 (indicator)	i.p. injection of *S. cerevisiae* cells collected 3 h after last administration (1 or 5 x 1.4-5,000 mg/kg)	No genotoxic activity
Chromosome aberration	Male Sprague-Dawley rat bone marrow	Killed at 6, 24, and 48 h (1 x 1.4-5,000)	Negative
Chromosome aberration	Male Sprague-Dawley rat bone marrow	Killed 6 h after last administration (5 x 1.4-5,000 mg/kg)	Negative
Dominant lethal mutation	Female Sprague-Dawley rat	8 mated, killed 14 days after mating for uterus examination (1 x 1.4-5,000 mg/kg)	Negative
Dominant lethal mutation	Female Sprague-Dawley rat	8 mated, killed 14 days after mating for uterus examination (5 x 1.4-5,000 mg/kg)	Negative

Table 14. Unpublished in vitro mutagenicity studies of silica reported by UNEP (2004) and ECETOC (2006).

Test	Test systems	Silica type (concentration)	Results
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Fumed silica (667 - 10,000 µg/plate)	Negative
Unscheduled DNA synthesis	Primary rat hepatocytes	Fumed silica (0.3 - 1000 µg/ml)	Negative; cytotoxic at 260 - 500 µg/ml
Ames, with metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophilic fumed silica (≤ 10,000 µg/plate)	Negative; not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophilic fumed silica (≤ 5,000 µg/plate	Negative; not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophilic silica gel (≤ 10,000 µg/plate)	Negative; not cytotoxic
Tryptophan reversion, with and without metabolic activation	*Escherichia coli* WP2	Hydrophilic silica gel (≤ 10,000 µg/plate)	Negative; not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA1530, G-46)	Hydrophilic silica gel (not provided)	Negative
Forward mutation, without metabolic activation	*Saccharomyces cerevisiae* (D3)	Hydrophilic silica gel (not provided)	Negative
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1537, TA98)	Hydrophobic fumed silica (1,580 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Tryptophan reversion, with and without metabolic activation	*E. coli* (WP2)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Ames, with and without metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, TA1537)	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic
Triptophan reversion, with and without metabolic activation	*E. coli* (WP2)August 17, 2009	Hydrophobic fumed silica (5,000 µg/plate)	Negative, not cytotoxic

2018 FDA Raw Data

03B - Eyeliner	ALUMINUM SILICATE	1
05E - Rinses (non-coloring)	ALUMINUM SILICATE	1
05F - Shampoos (non-coloring)	ALUMINUM SILICATE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	ALUMINUM SILICATE	2
06E - Hair Color Sprays (aerosol)	ALUMINUM SILICATE	6
07A - Blushers (all types)	ALUMINUM SILICATE	1
10A - Bath Soaps and Detergents	ALUMINUM SILICATE	2
10E - Other Personal Cleanliness Products	ALUMINUM SILICATE	2
12A - Cleansing	ALUMINUM SILICATE	9
12C - Face and Neck (exc shave)	ALUMINUM SILICATE	22
12D - Body and Hand (exc shave)	ALUMINUM SILICATE	1
12F - Moisturizing	ALUMINUM SILICATE	9
12H - Paste Masks (mud packs)	ALUMINUM SILICATE	7
12I - Skin Fresheners	ALUMINUM SILICATE	1
12J - Other Skin Care Preps	ALUMINUM SILICATE	3
03B - Eyeliner	ATTAPULGITE	1
12H - Paste Masks (mud packs)	ATTAPULGITE	3
01B - Baby Lotions, Oils, Powders, and Creams	BENTONITE	1
02A - Bath Oils, Tablets, and Salts	BENTONITE	1
02D - Other Bath Preparations	BENTONITE	1
03A - Eyebrow Pencil	BENTONITE	1
03B - Eyeliner	BENTONITE	8
03C - Eye Shadow	BENTONITE	3
03D - Eye Lotion	BENTONITE	2
03F - Mascara	BENTONITE	19
03G - Other Eye Makeup Preparations	BENTONITE	5
04C - Powders (dusting and talcum, excluding aftershave talc)	BENTONITE	1
05A - Hair Conditioner	BENTONITE	2
05B - Hair Spray (aerosol fixatives)	BENTONITE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	BENTONITE	11
05I - Other Hair Preparations	BENTONITE	2
07B - Face Powders	BENTONITE	2
07C - Foundations	BENTONITE	10
07F - Makeup Bases	BENTONITE	2
08E - Nail Polish and Enamel	BENTONITE	20
08F - Nail Polish and Enamel Removers	BENTONITE	1
09A - Dentifrices	BENTONITE	3

09C - Other Oral Hygiene Products	BENTONITE	4
10A - Bath Soaps and Detergents	BENTONITE	6
10B - Deodorants (underarm)	BENTONITE	5
10E - Other Personal Cleanliness Products	BENTONITE	2
11E - Shaving Cream	BENTONITE	1
11F - Shaving Soap	BENTONITE	2
11G - Other Shaving Preparation Products	BENTONITE	1
12A - Cleansing	BENTONITE	23
12C - Face and Neck (exc shave)	BENTONITE	23
12D - Body and Hand (exc shave)	BENTONITE	4
12F - Moisturizing	BENTONITE	20
12G - Night	BENTONITE	2
12H - Paste Masks (mud packs)	BENTONITE	135
12I - Skin Fresheners	BENTONITE	1
12J - Other Skin Care Preps	BENTONITE	12
13A - Suntan Gels, Creams, and Liquids	BENTONITE	1
13C - Other Suntan Preparations	BENTONITE	1
02A - Bath Oils, Tablets, and Salts	CALCIUM SILICATE	6
02C - Bath Capsules	CALCIUM SILICATE	1
02D - Other Bath Preparations	CALCIUM SILICATE	2
03C - Eye Shadow	CALCIUM SILICATE	7
04C - Powders (dusting and talcum, excluding aftershave talc)	CALCIUM SILICATE	44
07A - Blushers (all types)	CALCIUM SILICATE	16
07B - Face Powders	CALCIUM SILICATE	17
07C - Foundations	CALCIUM SILICATE	3
07F - Makeup Bases	CALCIUM SILICATE	1
07I - Other Makeup Preparations	CALCIUM SILICATE	1
08G - Other Manicuring Preparations	CALCIUM SILICATE	1
12A - Cleansing	CALCIUM SILICATE	1
12C - Face and Neck (exc shave)	CALCIUM SILICATE	1
03G - Other Eye Makeup Preparations	FULLER'S EARTH	1
07E - Lipstick	FULLER'S EARTH	1
10A - Bath Soaps and Detergents	FULLER'S EARTH	1
12A - Cleansing	FULLER'S EARTH	3
12C - Face and Neck (exc shave)	FULLER'S EARTH	1
12H - Paste Masks (mud packs)	FULLER'S EARTH	8
03A - Eyebrow Pencil	HECTORITE	2
03B - Eyeliner	HECTORITE	20

03F - Mascara	HECTORITE	11
03G - Other Eye Makeup Preparations	HECTORITE	1
05A - Hair Conditioner	HECTORITE	3
05E - Rinses (non-coloring)	HECTORITE	1
05F - Shampoos (non-coloring)	HECTORITE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	HECTORITE	1
05I - Other Hair Preparations	HECTORITE	1
06D - Hair Shampoos (coloring)	HECTORITE	1
07A - Blushers (all types)	HECTORITE	3
07B - Face Powders	HECTORITE	3
07C - Foundations	HECTORITE	7
07D - Leg and Body Paints	HECTORITE	1
07I - Other Makeup Preparations	HECTORITE	2
08G - Other Manicuring Preparations	HECTORITE	1
12A - Cleansing	HECTORITE	8
12C - Face and Neck (exc shave)	HECTORITE	3
12D - Body and Hand (exc shave)	HECTORITE	1
12G - Night	HECTORITE	1
12H - Paste Masks (mud packs)	HECTORITE	9
12J - Other Skin Care Preps	HECTORITE	1
01B - Baby Lotions, Oils, Powders, and Creams	KAOLIN	3
02A - Bath Oils, Tablets, and Salts	KAOLIN	9
02D - Other Bath Preparations	KAOLIN	2
03A - Eyebrow Pencil	KAOLIN	20
03B - Eyeliner	KAOLIN	26
03C - Eye Shadow	KAOLIN	356
03D - Eye Lotion	KAOLIN	6
03E - Eye Makeup Remover	KAOLIN	1
03F - Mascara	KAOLIN	62
03G - Other Eye Makeup Preparations	KAOLIN	28
04C - Powders (dusting and talcum, excluding aftershave talc)	KAOLIN	18
05A - Hair Conditioner	KAOLIN	5
05F - Shampoos (non-coloring)	KAOLIN	8
05G - Tonics, Dressings, and Other Hair Grooming Aids	KAOLIN	21
05I - Other Hair Preparations	KAOLIN	6
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	KAOLIN	1
06F - Hair Lighteners with Color	KAOLIN	4
06G - Hair Bleaches	KAOLIN	15

06H - Other Hair Coloring Preparation	KAOLIN	5
07A - Blushers (all types)	KAOLIN	66
07B - Face Powders	KAOLIN	106
07C - Foundations	KAOLIN	62
07D - Leg and Body Paints	KAOLIN	10
07E - Lipstick	KAOLIN	88
07F - Makeup Bases	KAOLIN	9
07G - Rouges	KAOLIN	8
07H - Makeup Fixatives	KAOLIN	6
07I - Other Makeup Preparations	KAOLIN	40
08A - Basecoats and Undercoats	KAOLIN	1
08E - Nail Polish and Enamel	KAOLIN	6
08G - Other Manicuring Preparations	KAOLIN	3
09A - Dentifrices	KAOLIN	1
09B - Mouthwashes and Breath Fresheners	KAOLIN	1
10A - Bath Soaps and Detergents	KAOLIN	22
10B - Deodorants (underarm)	KAOLIN	5
10E - Other Personal Cleanliness Products	KAOLIN	16
11C - Mens Talcum	KAOLIN	1
11E - Shaving Cream	KAOLIN	1
11F - Shaving Soap	KAOLIN	2
11G - Other Shaving Preparation Products	KAOLIN	2
12A - Cleansing	KAOLIN	83
12C - Face and Neck (exc shave)	KAOLIN	67
12D - Body and Hand (exc shave)	KAOLIN	16
12F - Moisturizing	KAOLIN	34
12G - Night	KAOLIN	6
12H - Paste Masks (mud packs)	KAOLIN	432
12I - Skin Fresheners	KAOLIN	4
12J - Other Skin Care Preps	KAOLIN	50
13A - Suntan Gels, Creams, and Liquids	KAOLIN	1
13B - Indoor Tanning Preparations	KAOLIN	1
02A - Bath Oils, Tablets, and Salts	KAOLINITE	1
02C - Bath Capsules	KAOLINITE	2
03C - Eye Shadow	KAOLINITE	16
05F - Shampoos (non-coloring)	KAOLINITE	1
07C - Foundations	KAOLINITE	17
10A - Bath Soaps and Detergents	KAOLINITE	5
12C - Face and Neck (exc shave)	KAOLINITE	1
12F - Moisturizing	KAOLINITE	1

12H - Paste Masks (mud packs)	KAOLINITE	4
07E - Lipstick	LITHIUM MAGNESIUM SILICATE	2
03F - Mascara	LITHIUM MAGNESIUM SODIUM SILICATE	3
03G - Other Eye Makeup Preparations	LITHIUM MAGNESIUM SODIUM SILICATE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	LITHIUM MAGNESIUM SODIUM SILICATE	3
05I - Other Hair Preparations	LITHIUM MAGNESIUM SODIUM SILICATE	9
07C - Foundations	LITHIUM MAGNESIUM SODIUM SILICATE	3
07D - Leg and Body Paints	LITHIUM MAGNESIUM SODIUM SILICATE	1
07I - Other Makeup Preparations	LITHIUM MAGNESIUM SODIUM SILICATE	1
08E - Nail Polish and Enamel	LITHIUM MAGNESIUM SODIUM SILICATE	10
12A - Cleansing	LITHIUM MAGNESIUM SODIUM SILICATE	1
12B - Depilatories	LITHIUM MAGNESIUM SODIUM SILICATE	17
12C - Face and Neck (exc shave)	LITHIUM MAGNESIUM SODIUM SILICATE	2
12F - Moisturizing	LITHIUM MAGNESIUM SODIUM SILICATE	1
12H - Paste Masks (mud packs)	LITHIUM MAGNESIUM SODIUM SILICATE	3
01B - Baby Lotions, Oils, Powders, and Creams	MAGNESIUM ALUMINUM SILICATE	8
03A - Eyebrow Pencil	MAGNESIUM ALUMINUM SILICATE	20
03B - Eyeliner	MAGNESIUM ALUMINUM SILICATE	49
03C - Eye Shadow	MAGNESIUM ALUMINUM SILICATE	83
03D - Eye Lotion	MAGNESIUM ALUMINUM SILICATE	12
03F - Mascara	MAGNESIUM ALUMINUM SILICATE	28
03G - Other Eye Makeup Preparations	MAGNESIUM ALUMINUM SILICATE	15
04C - Powders (dusting and talcum, excluding aftershave talc)	MAGNESIUM ALUMINUM SILICATE	3
05A - Hair Conditioner	MAGNESIUM ALUMINUM SILICATE	2
05B - Hair Spray (aerosol fixatives)	MAGNESIUM ALUMINUM SILICATE	1
05F - Shampoos (non-coloring)	MAGNESIUM ALUMINUM	3

	SILICATE	
05G - Tonics, Dressings, and Other Hair Grooming Aids	MAGNESIUM ALUMINUM SILICATE	8
05I - Other Hair Preparations	MAGNESIUM ALUMINUM SILICATE	1
06B - Hair Tints	MAGNESIUM ALUMINUM SILICATE	1
06H - Other Hair Coloring Preparation	MAGNESIUM ALUMINUM SILICATE	5
07A - Blushers (all types)	MAGNESIUM ALUMINUM SILICATE	34
07B - Face Powders	MAGNESIUM ALUMINUM SILICATE	27
07C - Foundations	MAGNESIUM ALUMINUM SILICATE	64
07D - Leg and Body Paints	MAGNESIUM ALUMINUM SILICATE	3
07E - Lipstick	MAGNESIUM ALUMINUM SILICATE	3
07F - Makeup Bases	MAGNESIUM ALUMINUM SILICATE	11
07G - Rouges	MAGNESIUM ALUMINUM SILICATE	1
07H - Makeup Fixatives	MAGNESIUM ALUMINUM SILICATE	1
07I - Other Makeup Preparations	MAGNESIUM ALUMINUM SILICATE	23
08E - Nail Polish and Enamel	MAGNESIUM ALUMINUM SILICATE	1
09A - Dentifrices	MAGNESIUM ALUMINUM SILICATE	2
10A - Bath Soaps and Detergents	MAGNESIUM ALUMINUM SILICATE	3
10B - Deodorants (underarm)	MAGNESIUM ALUMINUM SILICATE	8
10E - Other Personal Cleanliness Products	MAGNESIUM ALUMINUM SILICATE	26
11A - Aftershave Lotion	MAGNESIUM ALUMINUM SILICATE	6
11E - Shaving Cream	MAGNESIUM ALUMINUM SILICATE	1
11G - Other Shaving Preparation Products	MAGNESIUM ALUMINUM SILICATE	1
12A - Cleansing	MAGNESIUM ALUMINUM SILICATE	73
12C - Face and Neck (exc shave)	MAGNESIUM ALUMINUM SILICATE	67
12D - Body and Hand (exc shave)	MAGNESIUM ALUMINUM SILICATE	80
12E - Foot Powders and Sprays	MAGNESIUM ALUMINUM SILICATE	1
12F - Moisturizing	MAGNESIUM ALUMINUM SILICATE	100
12G - Night	MAGNESIUM ALUMINUM	16

	SILICATE	
12H - Paste Masks (mud packs)	MAGNESIUM ALUMINUM SILICATE	66
12I - Skin Fresheners	MAGNESIUM ALUMINUM SILICATE	2
12J - Other Skin Care Preps	MAGNESIUM ALUMINUM SILICATE	40
13A - Suntan Gels, Creams, and Liquids	MAGNESIUM ALUMINUM SILICATE	3
13B - Indoor Tanning Preparations	MAGNESIUM ALUMINUM SILICATE	15
03B - Eyeliner	MAGNESIUM SILICATE	8
03C - Eye Shadow	MAGNESIUM SILICATE	14
03G - Other Eye Makeup Preparations	MAGNESIUM SILICATE	2
07A - Blushers (all types)	MAGNESIUM SILICATE	1
07B - Face Powders	MAGNESIUM SILICATE	5
07C - Foundations	MAGNESIUM SILICATE	2
07E - Lipstick	MAGNESIUM SILICATE	14
07I - Other Makeup Preparations	MAGNESIUM SILICATE	16
08E - Nail Polish and Enamel	MAGNESIUM SILICATE	1
12C - Face and Neck (exc shave)	MAGNESIUM SILICATE	2
12D - Body and Hand (exc shave)	MAGNESIUM SILICATE	1
12F - Moisturizing	MAGNESIUM SILICATE	2
12H - Paste Masks (mud packs)	MAGNESIUM SILICATE	2
06G - Hair Bleaches	MAGNESIUM TRISILICATE	1
12B - Depilatories	MAGNESIUM TRISILICATE	16
01B - Baby Lotions, Oils, Powders, and Creams	MONTMORILLONITE	1
02A - Bath Oils, Tablets, and Salts	MONTMORILLONITE	1
03A - Eyebrow Pencil	MONTMORILLONITE	2
03B - Eyeliner	MONTMORILLONITE	3
03C - Eye Shadow	MONTMORILLONITE	18
03E - Eye Makeup Remover	MONTMORILLONITE	3
03F - Mascara	MONTMORILLONITE	10
03G - Other Eye Makeup Preparations	MONTMORILLONITE	3
04C - Powders (dusting and talcum, excluding aftershave talc)	MONTMORILLONITE	1
05F - Shampoos (non-coloring)	MONTMORILLONITE	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	MONTMORILLONITE	1
05I - Other Hair Preparations	MONTMORILLONITE	2
07A - Blushers (all types)	MONTMORILLONITE	6
07B - Face Powders	MONTMORILLONITE	4

07C - Foundations	MONTMORILLONITE	11
07E - Lipstick	MONTMORILLONITE	11
07F - Makeup Bases	MONTMORILLONITE	4
07I - Other Makeup Preparations	MONTMORILLONITE	1
09A - Dentifrices	MONTMORILLONITE	1
09C - Other Oral Hygiene Products	MONTMORILLONITE	1
10A - Bath Soaps and Detergents	MONTMORILLONITE	8
10E - Other Personal Cleanliness Products	MONTMORILLONITE	1
12A - Cleansing	MONTMORILLONITE	20
12C - Face and Neck (exc shave)	MONTMORILLONITE	4
12D - Body and Hand (exc shave)	MONTMORILLONITE	2
12E - Foot Powders and Sprays	MONTMORILLONITE	1
12F - Moisturizing	MONTMORILLONITE	11
12H - Paste Masks (mud packs)	MONTMORILLONITE	35
12J - Other Skin Care Preps	MONTMORILLONITE	5
02C - Bath Capsules	SODIUM MAGNESIUM SILICATE	1
03A - Eyebrow Pencil	SODIUM MAGNESIUM SILICATE	1
03B - Eyeliner	SODIUM MAGNESIUM SILICATE	2
03C - Eye Shadow	SODIUM MAGNESIUM SILICATE	7
03F - Mascara	SODIUM MAGNESIUM SILICATE	1
03G - Other Eye Makeup Preparations	SODIUM MAGNESIUM SILICATE	2
05A - Hair Conditioner	SODIUM MAGNESIUM SILICATE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	SODIUM MAGNESIUM SILICATE	1
07A - Blushers (all types)	SODIUM MAGNESIUM SILICATE	5
07B - Face Powders	SODIUM MAGNESIUM SILICATE	7
07C - Foundations	SODIUM MAGNESIUM SILICATE	1
07D - Leg and Body Paints	SODIUM MAGNESIUM SILICATE	1
07E - Lipstick	SODIUM MAGNESIUM SILICATE	7
07G - Rouges	SODIUM MAGNESIUM SILICATE	2
07H - Makeup Fixatives	SODIUM MAGNESIUM SILICATE	1
07I - Other Makeup Preparations	SODIUM MAGNESIUM SILICATE	4
09A - Dentifrices	SODIUM MAGNESIUM SILICATE	1

09C - Other Oral Hygiene Products	SODIUM MAGNESIUM SILICATE	1
10A - Bath Soaps and Detergents	SODIUM MAGNESIUM SILICATE	1
10E - Other Personal Cleanliness Products	SODIUM MAGNESIUM SILICATE	2
12A - Cleansing	SODIUM MAGNESIUM SILICATE	5
12B - Depilatories	SODIUM MAGNESIUM SILICATE	8
12C - Face and Neck (exc shave)	SODIUM MAGNESIUM SILICATE	5
12F - Moisturizing	SODIUM MAGNESIUM SILICATE	36
12H - Paste Masks (mud packs)	SODIUM MAGNESIUM SILICATE	35
12J - Other Skin Care Preps	SODIUM MAGNESIUM SILICATE	1
03A - Eyebrow Pencil	ZEOLITE	2
03B - Eyeliner	ZEOLITE	3
03C - Eye Shadow	ZEOLITE	20
05B - Hair Spray (aerosol fixatives)	ZEOLITE	3
05E - Rinses (non-coloring)	ZEOLITE	1
05F - Shampoos (non-coloring)	ZEOLITE	3
05I - Other Hair Preparations	ZEOLITE	1
07A - Blushers (all types)	ZEOLITE	32
07B - Face Powders	ZEOLITE	45
07C - Foundations	ZEOLITE	1
07E - Lipstick	ZEOLITE	3
07I - Other Makeup Preparations	ZEOLITE	4
10A - Bath Soaps and Detergents	ZEOLITE	2
12A - Cleansing	ZEOLITE	7
12C - Face and Neck (exc shave)	ZEOLITE	9
12D - Body and Hand (exc shave)	ZEOLITE	2
12F - Moisturizing	ZEOLITE	14
12H - Paste Masks (mud packs)	ZEOLITE	4
12I - Skin Fresheners	ZEOLITE	1
12H - Paste Masks (mud packs)	POTASSIUM SILICATE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	SODIUM METASILICATE	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SODIUM METASILICATE	88
06F - Hair Lighteners with Color	SODIUM METASILICATE	6
06G - Hair Bleaches	SODIUM METASILICATE	41

06H - Other Hair Coloring Preparation	SODIUM METASILICATE	1
03G - Other Eye Makeup Preparations	SODIUM SILICATE	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	SODIUM SILICATE	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SODIUM SILICATE	12
06F - Hair Lighteners with Color	SODIUM SILICATE	7
06G - Hair Bleaches	SODIUM SILICATE	33
06H - Other Hair Coloring Preparation	SODIUM SILICATE	2
09A - Dentifrices	SODIUM SILICATE	1
10A - Bath Soaps and Detergents	SODIUM SILICATE	5
10E - Other Personal Cleanliness Products	SODIUM SILICATE	2
11E - Shaving Cream	SODIUM SILICATE	1
12B - Depilatories	SODIUM SILICATE	13
12C - Face and Neck (exc shave)	SODIUM SILICATE	6
12J - Other Skin Care Preps	SODIUM SILICATE	4
03C - Eye Shadow	AMMONIUM SILVER ZINC ALUMINUM SILICATE	13
07A - Blushers (all types)	AMMONIUM SILVER ZINC ALUMINUM SILICATE	2
07B - Face Powders	AMMONIUM SILVER ZINC ALUMINUM SILICATE	1
12H - Paste Masks (mud packs)	AMMONIUM SILVER ZINC ALUMINUM SILICATE	1
05F - Shampoos (non-coloring)	ZINC ZEOLITE	1
03C - Eye Shadow	ALUMINUM CALCIUM SODIUM SILICATE	65
04C - Powders (dusting and talcum, excluding aftershave talc)	ALUMINUM CALCIUM SODIUM SILICATE	2
05I - Other Hair Preparations	ALUMINUM CALCIUM SODIUM SILICATE	1
07A - Blushers (all types)	ALUMINUM CALCIUM SODIUM SILICATE	5
07B - Face Powders	ALUMINUM CALCIUM SODIUM SILICATE	1
07E - Lipstick	ALUMINUM CALCIUM SODIUM SILICATE	125

07I - Other Makeup Preparations	ALUMINUM CALCIUM SODIUM SILICATE	3
08E - Nail Polish and Enamel	ALUMINUM CALCIUM SODIUM SILICATE	31
08G - Other Manicuring Preparations	ALUMINUM CALCIUM SODIUM SILICATE	1
12D - Body and Hand (exc shave)	ALUMINUM CALCIUM SODIUM SILICATE	3
12F - Moisturizing	ALUMINUM CALCIUM SODIUM SILICATE	13
07G - Rouges	ALUMINA MAGNESIUM METASILICATE	1
12C - Face and Neck (exc shave)	ALUMINA MAGNESIUM METASILICATE	1
12H - Paste Masks (mud packs)	ALUMINA MAGNESIUM METASILICATE	1
02A - Bath Oils, Tablets, and Salts	HYDRATED SILICA	7
02D - Other Bath Preparations	HYDRATED SILICA	1
03C - Eye Shadow	HYDRATED SILICA	7
03F - Mascara	HYDRATED SILICA	4
03G - Other Eye Makeup Preparations	HYDRATED SILICA	1
04C - Powders (dusting and talcum, excluding aftershave talc)	HYDRATED SILICA	3
05A - Hair Conditioner	HYDRATED SILICA	1
05F - Shampoos (non-coloring)	HYDRATED SILICA	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDRATED SILICA	1
06F - Hair Lighteners with Color	HYDRATED SILICA	1
06G - Hair Bleaches	HYDRATED SILICA	8

07A - Blushers (all types)	HYDRATED SILICA	2
07B - Face Powders	HYDRATED SILICA	28
07C - Foundations	HYDRATED SILICA	36
07E - Lipstick	HYDRATED SILICA	42
07F - Makeup Bases	HYDRATED SILICA	4
07G - Rouges	HYDRATED SILICA	1
07I - Other Makeup Preparations	HYDRATED SILICA	6
08A - Basecoats and Undercoats	HYDRATED SILICA	2
08E - Nail Polish and Enamel	HYDRATED SILICA	12
08G - Other Manicuring Preparations	HYDRATED SILICA	1
09A - Dentifrices	HYDRATED SILICA	36
09C - Other Oral Hygiene Products	HYDRATED SILICA	4
10A - Bath Soaps and Detergents	HYDRATED SILICA	34
10B - Deodorants (underarm)	HYDRATED SILICA	1
10E - Other Personal Cleanliness Products	HYDRATED SILICA	113
12A - Cleansing	HYDRATED SILICA	15
12B - Depilatories	HYDRATED SILICA	14
12C - Face and Neck (exc shave)	HYDRATED SILICA	5
12D - Body and Hand (exc shave)	HYDRATED SILICA	4
12E - Foot Powders and Sprays	HYDRATED SILICA	1
12F - Moisturizing	HYDRATED SILICA	4
12G - Night	HYDRATED SILICA	2
12H - Paste Masks (mud packs)	HYDRATED SILICA	3
12I - Skin Fresheners	HYDRATED SILICA	3
12J - Other Skin Care Preps	HYDRATED SILICA	22
13A - Suntan Gels, Creams, and Liquids	HYDRATED SILICA	3

01B - Baby Lotions, Oils, Powders, and Creams	SILICA	3
01C - Other Baby Products	SILICA	1
02A - Bath Oils, Tablets, and Salts	SILICA	44
02C - Bath Capsules	SILICA	1
02D - Other Bath Preparations	SILICA	5
03A - Eyebrow Pencil	SILICA	46
03B - Eyeliner	SILICA	217
03C - Eye Shadow	SILICA	1568
03D - Eye Lotion	SILICA	77
03E - Eye Makeup Remover	SILICA	6
03F - Mascara	SILICA	296
03G - Other Eye Makeup Preparations	SILICA	189
04A - Cologne and Toilet waters	SILICA	23
04B - Perfumes	SILICA	10
04C - Powders (dusting and talcum, excluding aftershave talc)	SILICA	65
04E - Other Fragrance Preparation	SILICA	64
05A - Hair Conditioner	SILICA	9
05B - Hair Spray (aerosol fixatives)	SILICA	3
05C - Hair Straighteners	SILICA	3
05F - Shampoos (non-coloring)	SILICA	47
05G - Tonics, Dressings, and Other Hair Grooming Aids	SILICA	31
05I - Other Hair Preparations	SILICA	16
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SILICA	81
06B - Hair Tints	SILICA	12
06C - Hair Rinses (coloring)	SILICA	1

06E - Hair Color Sprays (aerosol)	SILICA	31
06F - Hair Lighteners with Color	SILICA	8
06G - Hair Bleaches	SILICA	25
06H - Other Hair Coloring Preparation	SILICA	29
07A - Blushers (all types)	SILICA	295
07B - Face Powders	SILICA	437
07C - Foundations	SILICA	436
07D - Leg and Body Paints	SILICA	4
07E - Lipstick	SILICA	1527
07F - Makeup Bases	SILICA	84
07G - Rouges	SILICA	58
07H - Makeup Fixatives	SILICA	9
07I - Other Makeup Preparations	SILICA	336
08A - Basecoats and Undercoats	SILICA	7
08B - Cuticle Softeners	SILICA	2
08C - Nail Creams and Lotions	SILICA	5
08D - Nail Extenders	SILICA	3
08E - Nail Polish and Enamel	SILICA	480
08F - Nail Polish and Enamel Removers	SILICA	1
08G - Other Manicuring Preparations	SILICA	27
09A - Dentifrices	SILICA	28
09C - Other Oral Hygiene Products	SILICA	4
10A - Bath Soaps and Detergents	SILICA	84
10B - Deodorants (underarm)	SILICA	31
10E - Other Personal Cleanliness Products	SILICA	75
11A - Aftershave Lotion	SILICA	21
11E - Shaving Cream	SILICA	11

11G - Other Shaving Preparation Products	SILICA	5
12A - Cleansing	SILICA	78
12B - Depilatories	SILICA	4
12C - Face and Neck (exc shave)	SILICA	278
12D - Body and Hand (exc shave)	SILICA	99
12E - Foot Powders and Sprays	SILICA	3
12F - Moisturizing	SILICA	341
12G - Night	SILICA	54
12H - Paste Masks (mud packs)	SILICA	41
12I - Skin Fresheners	SILICA	8
12J - Other Skin Care Preps	SILICA	130
13A - Suntan Gels, Creams, and Liquids	SILICA	8
13B - Indoor Tanning Preparations	SILICA	26
13C - Other Suntan Preparations	SILICA	4
07C - Foundations	SODIUM POTASSIUM ALUMINUM SILICATE	1
07G - Rouges	SODIUM POTASSIUM ALUMINUM SILICATE	3
07I - Other Makeup Preparations	SODIUM POTASSIUM ALUMINUM SILICATE	1
10E - Other Personal Cleanliness Products	SODIUM POTASSIUM ALUMINUM SILICATE	1
12F - Moisturizing	SODIUM POTASSIUM ALUMINUM SILICATE	5
12H - Paste Masks (mud packs)	SODIUM POTASSIUM ALUMINUM SILICATE	1
03C - Eye Shadow	SILICA, AMORPHOUS	1

03F - Mascara	SILICA, AMORPHOUS	1
07C - Foundations	SILICA, AMORPHOUS	1
09A - Dentifrices	SILICA, AMORPHOUS	1
12C - Face and Neck (exc shave)	SILICA, AMORPHOUS	1
05I - Other Hair Preparations	SILICA, FUMED	2
08E - Nail Polish and Enamel	SILICA, FUMED	11
12D - Body and Hand (exc shave)	SILICA, FUMED	1
01C - Other Baby Products	SILICON DIOXIDE, COLLOIDAL	3
03C - Eye Shadow	SILICON DIOXIDE, COLLOIDAL	2
07B - Face Powders	SILICON DIOXIDE, COLLOIDAL	5
07C - Foundations	SILICON DIOXIDE, COLLOIDAL	1
07E - Lipstick	SILICON DIOXIDE, COLLOIDAL	18
07H - Makeup Fixatives	SILICON DIOXIDE, COLLOIDAL	1
07I - Other Makeup Preparations	SILICON DIOXIDE, COLLOIDAL	1
08D - Nail Extenders	SILICON DIOXIDE, COLLOIDAL	1
08E - Nail Polish and Enamel	SILICON DIOXIDE, COLLOIDAL	12
09A - Dentifrices	SILICON DIOXIDE, COLLOIDAL	5
12F - Moisturizing	SILICON DIOXIDE, COLLOIDAL	1
08G - Other Manicuring Preparations	SILICIC ACID	1
09A - Dentifrices	SILICIC ACID	1
10A - Bath Soaps and Detergents	SILICIC ACID	11
12B - Depilatories	SILICIC ACID	1
12J - Other Skin Care Preps	SILICIC ACID	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 21, 2018

SUBJECT: Concentration of Use by FDA Product Category: Silicates

Concentration of use by FDA Product Category – Silicates*

Attapulgite
Bentonite
Calcium Silicate
Fuller's Earth
Hectorite
Kaolin
Lithium Magnesium Silicate
Lithium Magnesium Sodium Silicate
Magnesium Aluminum Silicate
Magnesium Silicate
Magnesium Trisilicate
Montmorillonite
Pyrophyllite
Sodium Magnesium Silicate
Zeolite
Zirconium Silicate
Sodium Silver Aluminum Silicate
Tromethamine Magnesium Aluminum Silicate
Activated Clay
Ammonium Silver Zinc Aluminum Silicate
Aluminum Calcium Magnesium Potassium Sodium Zinc Silicates
Aluminum Iron Calcium Magnesium Germanium Silicates
Aluminum Iron Calcium Magnesium Zirconium Silicates
Sodium Silicate
Sodium Metasilicate
Potassium Silicate
Sodium Magnesium Aluminum Silicate
Zinc Silicate
Ammonium Silver Silicate
Gold Zeolite
Zinc Zeolite

Ingredient	**Product Category**	**Maximum Concentration of Use**
Bentonite	Bath oils, tablets and salts	0.14%
Bentonite	Eyebrow pencils	0.25%
Bentonite	Eyeliners	0.25%
Bentonite	Eye lotions	1.5%
Bentonite	Mascaras	2%
Bentonite	Other eye makeup preparations	0.00025%
Bentonite	Hair sprays Pump spray	 0.1%
Bentonite	Other hair coloring preparations	17.3%
Bentonite	Face powders	2-2.6%
Bentonite	Makeup bases	0.5%
Bentonite	Nail polish and enamel	0.00008-0.88%
Bentonite	Bath soaps and detergents	0.35%
Bentonite	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00002-3%
Bentonite	Face and neck products Not spray	 0.35-13.7%
Bentonite	Body and hand products Not spray	 0.35-14.3%
Bentonite	Paste masks and mud packs	4-29.7%
Bentonite	Other skin care preparations Rinse-off	 7-15%
Calcium Silicate	Bath oils, tablets and salts	0.86-1.3%

Calcium Silicate	Eye shadows	1%
Calcium Silicate	Powders (dusting and talcum)	3%
Calcium Silicate	Shampoos (noncoloring)	1.5%
Calcium Silicate	Hair color sprays	0.005%
Calcium Silicate	Blushers	3-5%
Calcium Silicate	Face powders	0.25-5%
Calcium Silicate	Foundations	1.3%
Calcium Silicate	Lipstick	0.00013%
Calcium Silicate	Face and neck products Not spray	 4.7-5%
Hectorite	Eyebrow pencils	0.3%
Hectorite	Eyeliners	0.1-0.4%
Hectorite	Eye shadows	0.27%
Hectorite	Mascaras	0.5-0.8%
Hectorite	Blushers	3.2%
Hectorite	Nail polish and enamel	0.7%
Hectorite	Skin cleansing (cold cream, cleansing lotions, liquids and pads)	0.5%
Hectorite	Face and neck products Not spray	 0.8%
Hectorite	Body and hand products Not spray	 1.1%
Hectorite	Paste masks and mud packs	0.5%
Kaolin	Eyebrow pencils	0.78-27.2%
Kaolin	Eyeliners	2-16%
Kaolin	Eye shadows	2-15%
Kaolin	Eye lotions	1-3%
Kaolin	Mascaras	7-21.5%
Kaolin	Other eye makeup preparations	0.75%
Kaolin	Hair conditioners	2.5-5%
Kaolin	Shampoos (noncoloring) Aerosol	0.058% 0.0096%
Kaolin	Tonics, dressings and other hair grooming aids	0.15-25%
Kaolin	Other hair preparations (noncoloring)	4.6%
Kaolin	Hair lighteners with color	31%
Kaolin	Hair bleaches	0.5%
Kaolin	Other hair coloring preparations	0.4%
Kaolin	Blushers	1.5-5%
Kaolin	Face powders	2-23.1%
Kaolin	Foundations	0.8-17.4%
Kaolin	Lipstick	0.97-11.9%
Kaolin	Makeup fixatives	13.3%
Kaolin	Other makeup preparations	1%
Kaolin	Basecoats and undercoats (manicuring preparations)	0.0001%

Kaolin	Nail polish and enamel	0.17%
Kaolin	Other manicuring preparations	35.7-53%
Kaolin	Bath soaps and detergents	0.05%
Kaolin	Shaving soap	1.5%
Kaolin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-20.2%
Kaolin	Depilatories	0.25%
Kaolin	Face and neck products Not spray	 1-25%
Kaolin	Body and hand products Not spray	 3.5-23%
Kaolin	Foot powders and sprays	4%
Kaolin	Paste masks and mud packs	2-33%
Kaolin	Other skin care preparations Rinse-off	 35%
Lithium Magnesium Silicate	Tonics, dressings and other hair grooming aids	0.3%
Lithium Magnesium Silicate	Face and neck products Not spray Spray	 5% 0.4%
Lithium Magnesium Sodium Silicate	Eyeliners	3%
Lithium Magnesium Sodium Silicate	Eye shadows	4%
Lithium Magnesium Sodium Silicate	Mascaras	1.4%
Lithium Magnesium Sodium Silicate	Other eye makeup preparations	0.0005%
Lithium Magnesium Sodium Silicate	Tonics, dressings and other hair grooming aids	6%
Lithium Magnesium Sodium Silicate	Deodorants Not spray	 0.5%
Lithium Magnesium Sodium Silicate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.4%
Lithium Magnesium Sodium Silicate	Body and hand products Not spray	 3%
Magnesium Aluminum Silicate	Eyebrow pencils	1.7-2%
Magnesium Aluminum Silicate	Eyeliners	0.25-0.4%
Magnesium Aluminum Silicate	Eye shadows	0.25-4.5%
Magnesium Aluminum Silicate	Eye lotions	0.5-1%
Magnesium Aluminum Silicate	Mascaras	0.15-0.5%
Magnesium Aluminum Silicate	Other eye makeup preparations	0.0025-4%
Magnesium Aluminum Silicate	Shampoos (noncoloring)	0.19%
Magnesium Aluminum Silicate	Tonics, dressings and other hair grooming aids	0.5-0.8%
Magnesium Aluminum Silicate	Blushers	0.96-2%
Magnesium Aluminum Silicate	Face powders	1%
Magnesium Aluminum Silicate	Foundations	0.15-2.8%
Magnesium Aluminum Silicate	Makeup bases	2.5%
Magnesium Aluminum Silicate	Makeup fixatives	0.75%

Magnesium Aluminum Silicate	Other makeup preparations	0.0008%
Magnesium Aluminum Silicate	Dentifrices	0.93%
Magnesium Aluminum Silicate	Deodorants Not spray	 0.5-0.7%
Magnesium Aluminum Silicate	Aftershave lotions	0.5%
Magnesium Aluminum Silicate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0004-10%
Magnesium Aluminum Silicate	Face and neck products Not spray	 0.4-11%
Magnesium Aluminum Silicate	Body and hand products Not spray	 0.3-1.6%
Magnesium Aluminum Silicate	Moisturizing products Not spray	 0.9%
Magnesium Aluminum Silicate	Night products Not spray	 0.6%
Magnesium Aluminum Silicate	Paste masks and mud packs	0.0008-6%
Magnesium Aluminum Silicate	Other skin care preparations Leave-on Rinse-off	 1.1% 4.5%
Magnesium Aluminum Silicate	Suntan products Not spray	 0.3-0.6%
Magnesium Silicate	Eyebrow pencils	12-14.1%
Magnesium Silicate	Eyeliners	4.5-20%
Magnesium Silicate	Eye shadows	3-21.6%
Magnesium Silicate	Foundations	0.001-4.5%
Magnesium Silicate	Lipstick	10%
Magnesium Silicate	Makeup fixatives	2.3%
Magnesium Silicate	Other makeup preparations	19%
Magnesium Silicate	Body and hand products Not spray	 1%
Montmorillonite	Eyeliners	2.8%
Montmorillonite	Eye shadows	0.3%
Montmorillonite	Shampoos (noncoloring)	8.2%
Montmorillonite	Blushers (all types)	1%
Montmorillonite	Foundations	0.31%
Montmorillonite	Lipstick	1.7%
Montmorillonite	Bath soaps and detergents	0.5%
Montmorillonite	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2.5%
Montmorillonite	Face and neck products Not spray	 2.5%
Montmorillonite	Body and hand products Not spray	 6%
Montmorillonite	Paste masks and mud packs	5%
Montmorillonite	Other skin care preparations	0.05%
Sodium Magnesium Silicate	Paste masks and mud packs	0.2%

Sodium Magnesium Silicate	Other skin care preparations	0.13%
Zeolite	Eyebrow pencils	3.6%
Zeolite	Eyeliners	0.6%
Zeolite	Eye shadows	0.6-1.1%
Zeolite	Eye lotions	0.032%
Zeolite	Hair sprays Aerosol	 1%
Zeolite	Tonics, dressings and other hair grooming aids	35.7%
Zeolite	Hair bleaches	5%
Zeolite	Blushers	0.6%
Zeolite	Face powders	0.6-1.1%
Zeolite	Foundations	0.25%
Zeolite	Lipstick	3%
Zeolite	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0043%
Zeolite	Face and neck products Not spray	 0.5-1%
Zeolite	Paste masks and mud packs	28-37.8%
Zeolite	Other skin care preparations	0.03-0.5%
Zeolite	Suntan products Not spray	 0.25%
Ammonium Silver Zinc Aluminum Silicate	Other skin care preparations Rinse-off	 0.001%
Sodium Silicate	Hair dyes and colors	17.2%
Sodium Silicate	Hair lighteners with color	15%
Sodium Silicate	Hair bleaches	35%
Sodium Silicate	Dentifrices	0.44%
Sodium Silicate	Bath soaps and detergents	1.4%
Sodium Silicate	Shaving cream	0.017-1.5%
Sodium Silicate	Depilatories	1.2%
Sodium Metasilicate	Bath oils, tablets and salts	0.1%
Sodium Metasilicate	Hair dyes and colors	5%
Sodium Metasilicate	Hair tints	15%
Sodium Metasilicate	Hair bleaches	5-13%
Sodium Metasilicate	Depilatories	1.2%
Sodium Metasilicate	Other skin care preparations Leave-on	 0.001%

*Ingredients included in the title of the table but not found in the title of the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2018
Table prepared May 21, 2018