Amended Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	February 10, 2023
Panel Meeting Date:	March 6-7, 2023

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Ronald C. Shank, Ph.D. and Daniel C. Liebler, PhD. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR.

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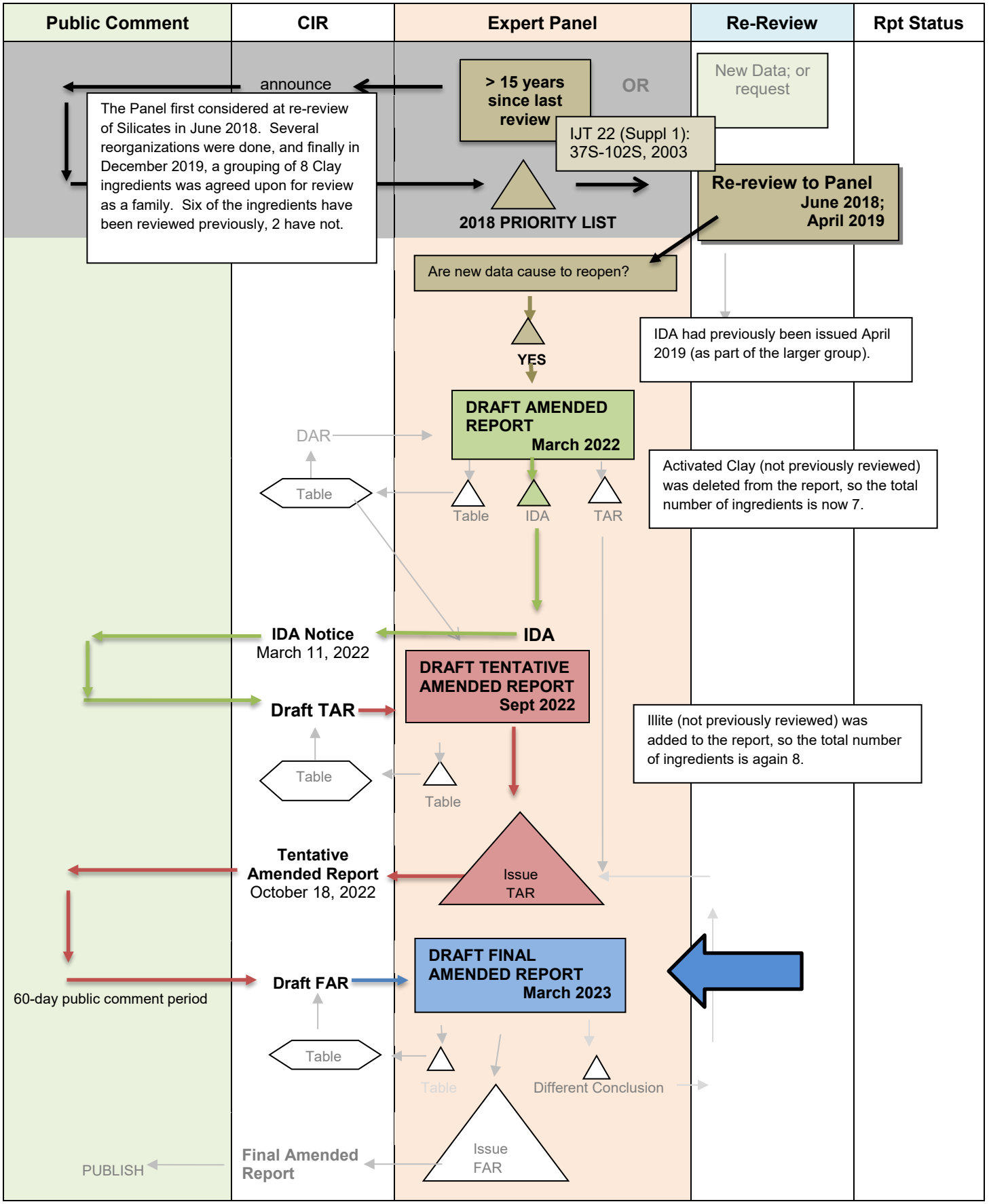
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Clays

MEETING March 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR
Date: February 10, 2023
Subject: Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics

Enclosed is the Draft Final Amended Report of the Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics. (It is identified as *report_Clays_032023* in the pdf document.) At the September 2022 meeting, the Panel issued a Tentative Amended Report with the conclusion that Kaolin is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the remaining 7 naturally-sourced clay ingredients are safe in cosmetics in the present practices of use and concentration, with the exception that the available data are insufficient to make a determination that these ingredients are safe in products that may be incidentally inhaled.

Since the September meeting, CIR has received no new unpublished data. Data that CIR staff discovered in a literature search for Illite have been incorporated into the report and highlighted to aid the Panel's review. The attached Council comments on the Tentative Amended Report have been addressed (*PCPCcomments_Clays_032023*), as noted in the check sheet immediately following the comments (*response-PCPCcomments_Clays_032023*).

As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category.

The previously published report that included clay ingredients is 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) [*originalreport_Clays_032023*]

Transcripts from all past meetings at which any of the clay ingredients named in this amended report were originally discussed, as well as transcripts from discussions of the current report, are included with this submission:

- June 2018 through September 2022 – Minutes for the Panel's deliberations since June 2018 when the re-review commenced [*transcripts_Clays_032023*]
- 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 [*originalminutes_Clays_032023*]

Additional supporting documents for this report package include a flow chart (*flow_Clays_032023*), report history (*history_Clays_032023*), a search strategy (*search_Clays_032023*), and a data profile (*dataprofile_Clays_032023*).

The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: October 28, 2022

SUBJECT: Tentative Amended Report: Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics (release date: October 18, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative amended report, Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics.

Key Issues

Please add some information about the structure, chemical properties, and composition of Illite to this report. For example, the chapter "Basics of Clay Minerals and Their Characteristic Properties" at https://www.intechopen.com/chapters/76780 appears to include some useful information.

Discussion – It is not correct to state that "there are no inhalation data for the remaining 7 naturally-sourced clays". There are some inhalation data, especially on Attapulgite that led to the IARC conclusion based on fiber length.

Table 2 – Information on Illite should be added to Table 2.

Additional Considerations

Cosmetic Use – Please indicate the FDA cosmetic product category in which Bentonite was reported at 8%.

Non-Cosmetic Use – Please correct: "safety of effectiveness" to "safety and effectiveness"

Summary – Rather than saying "phagocytized alveolar macrophages", it would be clearer to state "alveolar macrophages containing Kaolin".

Discussion – In the paragraph regarding heavy metals, it would be helpful to mention the dermal penetration study that found that heavy metals associated with clays did not penetrate the skin. Even if there are metals associated with clay, they were not found to be bioavailable.

Naturally-Sourced Clays - March 2023 – Christina Burnett	
Comment Submitter: Alexandra Kowcz, PCPC **Date of Submission:** October 28, 2022	
Comment	**Response/Action**
Key Issue: Please add some information about the structure, chemical properties, and composition of Illite to this report. For example, the chapter "Basics of Clay Minerals and Their Characteristic Properties" at https://www.intechopen.com/chapters/76780 appears to include some useful information.	Data has been added to the report and highlighted for the Panel's convenience.
Key Issue: Discussion – It is not correct to state that "there are no inhalation data for the remaining 7 naturally-sourced clays". There are some inhalation data, especially on Attapulgite that led to the IARC conclusion based on fiber length.	Sentence rewritten.
Key Issue: Table 2 – Information on Illite should be added to Table 2.	Data has been added.
Cosmetic Use – Please indicate the FDA cosmetic product category in which Bentonite was reported at 8%.	Added "face and neck skin care preparations".
Non-Cosmetic Use – Please correct: "safety of effectiveness" to "safety and effectiveness"	Corrected.
Summary – Rather than saying "phagocytized alveolar macrophages", it would be clearer to state "alveolar macrophages containing Kaolin".	Suggestion accepted.
Discussion – In the paragraph regarding heavy metals, it would be helpful to mention the dermal penetration study that found that heavy metals associated with clays did not penetrate the skin. Even if there are metals associated with clay, they were not found to be bioavailable.	Currently written in accord with CIR SOPs.

Clays 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.

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

June 2018 - The Panel decided to re-open the 2003 Silicates report and add an additional 23 ingredients, which include 1 zeolite ingredient that was previously reviewed by the Panel and 5 zeolite ingredients that have not been reviewed by the Panel.

Concentration of use survey on Activated Clay, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, and Montmorillonite received.

December 2018 - The Panel issued an IDA for the 40 ingredients in the safety assessment. The additional data needed for the safety assessment of these cosmetic ingredients are:

- The range of particle sizes for all silica and silicate ingredients that are used in spray and powder formulations
- Chemical characterization, composition, and impurities data for all ingredients, except Silica
- Method of manufacturing and/or source data for all ingredients, except Silica and Hydrated Silica.

January 2019 – Unpublished data on Bentonite received.

April 2019 - The Panel tabled discussion on 40 ingredients for administrative reorganization. CIR staff will reorganize these ingredients into 2 separate reports with the first report to be reviewed to include Silica, Hydrated Silica, and silicate ingredients, with a focus on ingredients that are synthetically derived. The second report will be comprised of the ingredients that are determined to be naturally sourced (i.e. mined), including clay materials, zeolites, and any other ingredients in the above list that are mined.

The data on all these ingredients are still considered insufficient to determine the conclusion on safety. The additional data needed for the two safety assessments of these cosmetic ingredients comprise:

- The mean and range of particle sizes for all silica and silicate ingredients (and corresponding sizes of final formulation particles) that are used in spray and powder formulations
- Chemical characterization, composition, and impurities data for all ingredients, except Silica
- Method of manufacturing and/or source data for all ingredients, except Silica and Hydrated Silica.

December 2019 - The Panel considered the proposed groupings of the 38 ingredients that had been previously removed from the Amended Safety Assessment on Silica and Hydrated Silica and a larger re-review package of silicate ingredients. The Panel accepted the groupings proposed by CIR Staff, which will be presented in 3 separate reports at future Panel meetings. The Panel also accepted the proposed addition of the ingredient, Clay, to the reviews. The groups are as follows:

Clays

Activated Clay
Attapulgite
Bentonite
Clay
Fuller's Earth
Hectorite
Kaolin
Montmorillonite

Zeolites

Ammonium Silver Zeolite
Gold Zeolite
Silver Copper Zeolite
Titanium Zeolite
Zeolite
Zinc Zeolite

Silicates

Aluminum Silicate
Aluminum Calcium Sodium Silicate
Aluminum Iron Silicates
Aluminum Iron Calcium Magnesium Germanium Silicates
Aluminum Iron Calcium Magnesium Zirconium Silicates

Ammonium Silver Zinc Aluminum Silicate
Calcium Silicate
Calcium Magnesium Silicate
Lithium Magnesium Silicate
Magnesium Aluminometasilicate
Magnesium Aluminum Silicate
Magnesium Silicate
Magnesium Trisilicate
Potassium Silicate
Pyrophyllite
Sodium Magnesium Silicate
Sodium Metasilicate
Sodium Magnesium Aluminum Silicate
Sodium Potassium Aluminum Silicate
Sodium Silver Aluminum Silicate
Sodium Silicate
Tromethamine Magnesium Aluminum Silicate
Zinc Silicate
Zirconium Silicate

April 2020 – Concentration of use survey on the ingredient Clay received.

March 2022 - The Panel issued an IDA for the 7 clay ingredients. The additional data needed to determine safety for these cosmetic ingredients are:

- Particle size distribution (mean and range) on all ingredients, except Bentonite
- Chronic inhalation data on all ingredients, except Attapulgite and Kaolin
- Human dermal irritation and sensitization data at maximum use concentrations

March-July 2022 – Unpublished data received on Bentonite, Hectorite, Kaolin, and Montmorillonite.

September 2022 – The Panel issued a Tentative Amended Report with the conclusion that Kaolin is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the remaining 7 naturally-sourced clay ingredients are safe in cosmetics in the present practices of use and concentration, with the exception that the available data are insufficient to make a determination that these ingredients are safe in products that may be incidentally inhaled.

The ingredient, Illite, was added to the report, as it was reported by industry to be a large component of the ingredient, Clay.

Post- September 2022 – Literature search performed on Illite. Relevant data incorporated into the report.

Clays Data Profile – March 2023, Christina Burnett

	Use				Toxico-kinetic		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci			Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	**Old Rpt**	**Method of Mfg**	**Composition/ Impurities**	**Dermal Pen.**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**Dermal**	**Oral**	**Inhalation**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**	**Phototoxicity**	**In Vitro**	**Animal**	**Retrospective/ Multicenter**	**Case Reports**
Attapulgite	X	O	O	O											O				O											
Bentonite	X	O	XO	XO											X							X			X	X				O
Clay*	X																													
Fuller's Earth	X	O		O																										O
Hectorite	X	O		O				O							O						O			X				O		
Illite	X		X	X					X																					
Kaolin	X	O	XO	XO		X O	X	X O	X					O	X				O		X	X		X	X			X		O
Montmorillonite	X		X	XO		X O	X	X	X		X				X	X				X		X		X	X			X		O

*Not previously reviewed

"X" indicates that new data were available in this category for the ingredient; "O" indicates that data from the original assessment were available

Clays

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Attapulgite	12174-11-7 1337-76-4	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bentonite	1302-78-9	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Clay	53801-44-8	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Fuller's Earth	8031-18-3	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Hectorite	12173-47-6 68084-71-9	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Illite	12173-60-3	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Kaolin	1332-58-7	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Montmorillonite	1318-93-0	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy (from 1999 for re-review)

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

PubMed

Activated Clay (no time frame limits) – 383 hits (0 relevant)
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 relevant), limited with sensitization = 0 hits, limited with dermal = 7 hits (1 relevant)
Clay (no time frame limits) – 19,404 hits ***overly broad term***
Fuller's Earth – 50 hits (12 relevant)
Hectorite – 89 hits (0 relevant)
Illite (no time frame limits) – 636 hits, limited with toxicity = 43 hits (11 relevant), limited with irritation = 1 hit (0 relevant), limited with sensitization = 1 hit (0 relevant), limited with dermal = 1 hit (1 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)
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)

Typical Search Terms (this is informational – not for inclusion for search strategy that goes to the Panel)

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

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

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;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- 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
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- 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) - https://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- 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
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.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 - https://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

JUNE 2018 PANEL MEETING – RE-REVIEW
Belsito's Team Meeting – June 4, 2018

DR. BELSITO: Silicates. This was also part of Wave 2. And this is a re-review with a question of add-ons, correct?

MS. BURNETT: Correct. And I handed out at the table this morning to help clarify what add-ons are where, hopefully to help your discussion.

DR. BELSITO: Yes, I didn't see that. I said combined them all, add in the new ones. We need to take a look regardless. Usage has increased astronomically for many, and we need a sense of concentration of use, regardless of what we decide to do. That was my analysis.

DR. LIEBLER: Yeah, I said reopen to add all the new ingredients. This is a chemically heterogeneous group, so the new ingredients easily belong. That's the benefit of the dog's breakfast, by the way.

However, their properties aren't significantly different, and existing data covers the entire group. No need for new data, we can affirm the previous conclusion.

DR. BELSITO: I don't know that we can confirm it until we get a sense of concentration of use.

DR. LIEBLER: Fine.

DR. EISENMANN: And the report is not correct. The concentration of use survey has not been started on silica and hydrated silica. Those weren't included in the list they gave me. And I don't expect that to be -- if I get it started -- those are high use ingredients, so it's going to take at least --

DR. BELSITO: That's fine.

DR. EISENMANN: So, don't expect to see this until December.

DR. BELSITO: Oh, I wanted to see it in September.

DR. EISENMANN: Well --

DR. BELSITO: I'm teasing you Carol.

DR. EISENMANN: -- I doubt we'll get to those that quick.

DR. BELSITO: No, I mean, that's fine. I just thought that we could open, merge them all, add in the new ones. But the use has increased astronomically, which is part of the reason to look at it again anyway.

DR. EISENMANN: I was a little concerned about -- see I think this isn't chemistry that drives the toxicity of these ingredients, it's more structure. And it wasn't really addressed at all in this report. There is a discussion that's in the silica report about amorphous versus crystalline. I don't know, that's part of my concern about combining this, that that might get lost.

DR. BELSITO: Okay, so, run that by me again. Your concern here is not the chemistry it's the structure.

DR. EISENMANN: It's the physical structure of these compounds.

DR. BELSITO: Dan, you need to address that because that's above my head.

DR. EISENMANN: Right, and I'm not an expert in it either. I just know that was a big issue in the report, and the report hasn't been published, so I'm a little concerned about --

MS. BURNETT: Because that report hasn't been published, pretty much the entirety -- it will be reorganized into current format. But the bulk of the data will still be there. It's not going to be like the published paper re-review, where we italicize it, and then it doesn't get published. This will go directly into this paper; and so, it will be like a, you know, silica 2.0 version for the panel to review.

DR. BELSITO: Right. How come that report wasn't published?

MS. FIUME: I don't know. It may have been internal. It may have been journal, I'm not sure. But it did need some reorganization. So, it'll be incorporated in here and all of the information will get published.

DR. BERGFELD: With the mention of the structural differences, is it possible to reorganize according to the structure?

DR. BELSITO: Anything is possible.

DR. LIEBLER: To the extent that they're all structurally characterized. I suppose. The structure issue, as opposed to the chemical substance issue, Don, is like these crystalline silica versus amorphous silica. Chemically, in a chemical composition sense, they're about the same. In the way that the structure is, they're very different. And because the structure is different, they interact with biological components differently.

MS. BURNETT: I'm still reading and trying to understand the original report. But as I have read the physical properties and method of manufacture section, we have clearly stated that the cosmetic silica is amorphous not crystalline.

So as far as I understand, the data that is in this report is only on the amorphous silica. And there are like different names within the amorphous silica, but we go by the INCI names. So, if the amorphous silica is the silica, that's what the report is on.

DR. LIEBLER: I use that as an example of a structure difference for Don to explain, I think, what Carol was pointing out. I don't know how these partition into crystalline or amorphous. If the data you have so far says these are all amorphous silicates, then that's what they are. And I guess we're going to need more data to make decisions about grouping them.

MS. BURNETT: Okay.

DR. LIEBLER: Are you going to think about subgrouping them? I don't know if we are. I don't know if we need to.

DR. KLAASSEN: Here we do have, in contrast to one of the chemicals we were talking about this morning, you know, It is well known -- and as you know -- that some silica compounds can cause silicosis, which is a real lung disease. And so, we need to make sure that we know which ones might cause silicosis and which ones don't cause silicosis.

DR. BELSITO: But isn't that the point Christina was making with the amorphous versus crystalline? Because it's the crystalline ones that cause silicosis.

DR. KLAASSEN: But that's what I'm saying; we need to make sure that all of these that we have here -- or what is known about it to make -- we need to make sure that these are all the amorphous. And how strong is the data, first of all, that it has to be an amorphous compared to a crystalline, et cetera; which I don't know offhand.

MS. FIUME: I do know, looking at the minutes, PDF Page 54, maybe that's the 2009 review; where the Panel determined that silicosis is not an issue since crystalline silica is not an ingredient used in cosmetics. So, that's what was discussed at that time, that it's not crystalline.

DR. BELSITO: So, as you go through the add-ons, et cetera, just make sure that what we're talking about is amorphous. Anything else?

Marks' Team Meeting – June 4, 2018

DR. MARKS: I know. Silicates. Let's see, I have silicates are the next.

DR. SHANK: That's what I have.

DR. MARKS: And this is silicate related ingredients re-review.

MS. BURNETT: This morning, to help in the discussion -- I apologize, when I wrote this report, I didn't put in a table summarizing which ingredients were the existing ingredients, which were the previously reviewed ingredients, and which were the brand new potential add-ons.

It was clear to me because I had my table, but I didn't include it in the report. I handed that out this morning to help you see which was which; so that when you're talking you know which ingredients --

DR. SHANK: Thank you. Thank you.

DR. ANSELL: Do you have an extra copy of that by any chance?

MS. BURNETT: I don't have any extra copies.

DR. SHANK: Here, I'll give you mine.

DR. ANSELL: Can you part with it?

DR. SHANK: Sure. Who needs it?

MS. BURNETT: Oh, she has electronic.

DR. SHANK: You want it?

MS. BURNETT: No. I'm good, I have mine. I have it on my computer, so I can view it.

DR. SHANK: Okay.

DR. MARKS: Thank you, Christina. I know when I went through this I was going back to the original reports, which the last one I have is on page 226 of the PDF, which was the conclusion on the silicate aluminum magnesium, et cetera. Okay.

As Christina documents in her memo on May 23rd, this is a re-review. And basically, we have a conglomeration of stuff. There are ingredients -- there is the suggestion to consolidate ingredients from three reports previously. And they are on page 89, 155 and 226, for those who want to refer to that. And then 16 add-ons.

And then, in terms of the reports themselves, in 2003, there are 17 silicates that were safe. Then in the next paragraph, Christina talks about the 16 possible add-ons. And then, let me see, in the 2005 and 2009 reports with -- I have to look at the conclusions. Did I put -- are they all safe? Or one them was irritation, wasn't there?

MS. BURNETT: 2005 the potassium sodium, metasilicate and sodium silicate have a formulated to be nonirritating.

DR. MARKS: Nonirritating, yes.

MS. BURNETT: They were part of the original group, that were reviewed, and the panel decided to split them off.

Then during the discussion in 2009, for the silica report, it was mentioned that when these were re-reviewed, that they would all be grouped together. I don't know if you saw that; but I had a good laugh when I read that. Saying, we will let the folks in 2018 deal with it. Well, guess what? You guys are all still here.

DR. HILL: Here we are. I saw that. I chuckled.

MS. BURNETT: And you have to deal with it.

DR. HILL: It's 2018 already.

MS. BURNETT: And just to remind the panel, the final report of the 2009 silica report was never published.

DR. MARKS: Yes. Thank you.

MS. BURNETT: It's kind of hanging in limbo right now.

DR. MARKS: Yeah. Okay. Yeah, the irritation and sensitization were okay, except the silicates were irritating. That's page 83.

I think the first question, is do we want to open this? Obviously this 2003 report. And that can either be for changing the conclusion, or it can be for add-ons and consolidation. Do we want to reopen or not?

DR. SHANK: I don't think it's useful to reopen.

DR. SLAGA: I've been with reopening this; I like combining all of these together.

DR. MARKS: Hmm, interesting.

DR. SLAGA: I don't remember who pushed to have it separated a long time ago. I know the panel did, but I --

MS. BURNETT: I don't remember.

DR. SLAGA: The other group, way over there?

MS. BURNETT: The team minutes were not really published back then, so I can't really tell.

DR. MARKS: Oh, is that right?

MS. BURNETT: It's summarized.

DR. HILL: They're summary versions.

MS. BURNETT: Yeah. They're summary versions.

DR. SHANK: I don't see how it's useful, what that accomplishes. And I think you may have trouble publishing that if most of the report is already -- if you put it all together, you're going to have to justify it, to some journal, that it's already been published, now we're putting it together. I don't see -- it's not worth the effort.

DR. SLAGA: Well, what about the 16 though? The 16 possible.

DR. MARKS: Yeah. That's the question I would add, is the new 16 add-on ingredients that have never been reviewed before.

DR. SHANK: Okay. There's very little data on those 16, and only two of them are used. So that could be handled in the re-review summary without reopening. I certainly would not combine --

DR. SLAGA: Published data.

DR. SHANK: -- all of these into one report.

DR. ANSELL: That's really our comment for recommending not reopening; is that we would like to hear a much more substantive discussion as to why these three reports form a relevant family.

DR. HILL: Here's what I wrote. I think in general, maybe we should bring everything together and get a global view of properties; and then respectively separate into either different reports, or at least different subsections very carefully constructed so any read across that is or isn't used is very clear.

Sodium metasilicate is very different from synthetic amorphous silica or zeolite. And I'm also not prepared to read across from sodium silicate to something like sodium aluminum silver silicate, or silver copper zeolite, where there are different metals with different redox properties, blah, blah, blah, blah, blah. Anyway, so I guess I'm at a level agreeing with Dr. Shank.

DR. SLAGA: But how do we deal -- there's two of them that are being used.

DR. HILL: Which two are they?

DR. SLANK: Zinc zeolite and --

DR. SLAGA: Would that be worthwhile to add those two? I mean, being consistent with earlier, where we didn't want to add them because they were not in use. But two of them are in use out the 16.

MS. BURNETT: Ammonium silver and zinc.

DR. HILL: Ammonium silver --

DR. SLAGA: I know doesn't seem much to add but --

MS. BURNETT: Ammonium silver zinc.

DR. SLAGA: -- some consistency here.

DR. ANSELL: Well, then we would just open up that report. We don't have to open all three of them to merge them. If we feel that --

DR. SLAGA: No, no. Eliminate the others that have been published already. I'm talking 2 out of 16.

DR. HILL: Well then actually, the six that haven't been published from 2009.

MS. FIUME: Right. So, it would be 22 that have not been published yet.

DR. SLAGA: Oh, okay.

DR. HILL: And are they across all three families?

MS. FIUME: The 2009 ingredients, that report has not been published. So, it wouldn't be republishing existing information.

DR. SLAGA: Which one?

MS. FIUME: The 2009 report. The silica and silicate ingredients. I mean, if there's commonality to create a family out of all of these -- or any of these; because we do need to consider, number one, the re-review. But once you reopen the re-review, you don't have to read across. You can make a split conclusion if the family fits together, but you don't have enough information to decide on all of them.

You can do a split conclusion. It doesn't have to be read across. Once you decide to reopen, you know, if you're combining -- because there are different conclusions among the ingredients you would be combining. Then you can start a whole new review.

DR. ANSELL: I think we would have an issue with reopening to add an ingredient, and then determine that the existing data is insufficient to support that new ingredient.

DR. SHANK: That's not a no-brainer then.

DR. ANSELL: Yeah. It would need its own report, which you guys could always do.

DR. SHANK: Why were the six ingredients in 2009 never published?

MS. FIUME: I believe the journal may have liked to see some additional information, or it may have needed a little bit of --

MS. BURNETT: Reorganization.

MS. FIUME: -- reorganization for publication.

DR. SHANK: So, it was sent to a journal and the peer review said change it?

MS. FIUME: I'm not sure if it's an internal decision or if it was a journal decision. I'm not sure, at that point, if it was done or not.

DR. SHANK: Okay.

MS. BURNETT: It's been almost ten years, so.

MS. FIUME: Yeah.

DR. ANSELL: Yeah. And I think that's our core point. I mean, safety is one thing. We just don't understand why we would reopen for purposes of merging these without --

MS. FIUME: Well, we have done it in the past, where we've reopened and based on the ingredients themselves, the conclusion it may not have been worthwhile to go forward. But we have created bigger families and looked at it as a full report, not simply -- once the decision was made to reopen because some of them were no brainers, those were brought in, because we were initiating a full report.

So, we've done it both ways in the past. But again, it's the panel's purview as to how they'd like to go forward, with this group, based on the similarity -- the information that's already included.

DR. HILL: For me, the 2003 grouping is a strange looking family. I mean, I would have put the clays together and that's it. You know, and then some of these other silicates together and that's it.

And then some of the new ones and some of these ones in the other report fit with that, but not that. You know, so that's when I say -- I mean, you published in 2003, you reached conclusions, but it's a strange grouping.

DR. MARKS: We're still at the point -- initially, we said we did not want to reopen. We don't want to consolidate the ingredients from the previous reports -- the previous three reports. Two out of the three reports were published.

And then we didn't like all the add-ons, but two of them are being used. Do we reopen to address the two add-ons that are being used?

And then obviously, the comments you made, Ron Hill, about the lack of consistency of the grouping of the ingredients raises some issue. Although that 2003, all them were safe. Even though maybe the grouping isn't to your liking.

So, where should we go team? Do you want to not reopen, or do you want to -- and which of the two of the new add-ons are being used?

DR. ANSELL: Ammonium silver zinc --

DR. HILL: Aluminum silicate. It's the fifth one down in her table. And zinc zeolites, all the way at the --

DR. MARKS: Zinc zeolite. That's one use. And then what was the other? The ammonium silver zinc aluminum silicate, is that the one?

DR. HILL: Yes.

DR. MARKS: And how many ingredients is that? Or how many products?

DR. ANSELL: Seventeen.

MS. BURNETT: It's in 17 and has a use concentration.

DR. MARKS: Yeah, 17 is a lot.

DR. HILL: So, one way to fly on this, or at least for discussion to think about, is pull ingredients out of that 2009 group that never got published, that go with this one or that one. I don't see any zeolites, but there are silicates that would fit.

So, you pull the silicates that go with the ammonium silver zinc aluminum silicate and see what data you got. And then we had that sassy publication in the interim. I think that was actually my second meeting here in 2009, if I'm not mistaken.

And we have the whole transcript covered, which I captured, which I read. And I thought that was -- it reminded me of things I heard -- it's hard to say, nine years ago, but nine years ago.

DR. MARKS: So, what you're suggesting is -- and that would be reopening, but not reopening the '03 report, reopening the '09 report. Because it is a report even though it wasn't published.

DR. HILL: Well, it never was published.

DR. MARKS: Well, that doesn't matter. From a CIR point of view, it's a report.

DR. SHANK: Right.

DR. MARKS: Am I not correct?

DR. SHANK: Yes.

DR. HILL: I got you. Okay, well -- okay then maybe --

DR. SLAGA: But that could be decided some other time.

DR. MARKS: We could talk about that today and perhaps -- so we don't want to reopen the 2003 report? We're pretty solid about that.

And then should we mention, tomorrow, to consider -- because it'll be very interesting to see, obviously, what the Belsito team, their approach. Our approach would be to reopen the 2009 report and add, where appropriate, the new add-ons which is --

DR. HILL: It's really the one that has 17 uses, I think, I heard.

DR. MARKS: Seventeen uses. The zeolite is chemically significant, different from the silicate ingredients in the 2009; you would include that, since that has one use?

DR. HILL: Yeah. I mean, if you're going -- a re-review summary is going to be written for the 2003; so, if you don't want to reopen, I guess then that zinc zeolite stays in orphan. Is there any downsize to having it stay in orphan other than just one we have in the dictionary that's not been reviewed?

DR. MARKS: Right. And the other is if we suggest the 2009 report, 15 years, that's 2000 -- let me see, 2024 right? We put it off for another eight years or so.

DR. SHANK: Beyond my time.

DR. MARKS: So, second, not reopen the 2003 report. We're solid on that one, team? And then we could consider reopening the -- our suggestion would be if there is -- it doesn't sound like there's any urgency to these new add-ons. I mean, is the aluminum silver -- there are no alerts or concerns about these two that are in use.

MS. FIUME: Not that I'm aware of. But I can I just -- for a procedural question. I know there's been a lot of discussion this morning about whether they're in use or not in use. As part of the reopen decision, which is a new turn as I'm sure Dr. Bergfeld will point out tomorrow. But a lot of these silicates that are just a combination of aluminum, or calcium, or magnesium, which were in the 2003 report, you don't feel they can be no-brainers; and added to that report and be reopened for add-ons as no-brainers?

DR. SLAGA: I mean, that's what I originally thought.

MS. FIUME: That would be our typical --

DR. ANSELL: Ammonium, silver, zinc and zinc zeolite add to the '03.

MS. FIUME: But there is aluminum calcium magnesium potassium sodium zinc silicate. And you know, we've done aluminum silicate. And, you know, we've done aluminum silicate, we've done calcium silicate, we've done magnesium silicate. So, there is a calcium magnesium silicate as a proposed add-on.

If you don't want the entire list of 16 -- regardless of in use or not in use -- are there some that can be brought in as no-brainers, and brought into the 2003 report? And would you consider, at least, taking that step?

DR. HILL: For me, as soon as you have silver in there then that's not necessarily, chemically a no-brainer without some additional information. Because there's nothing with silver in it, on it, or around it, in the original 2003.

DR. MARKS: Okay.

DR. HILL: And that has redox properties that aren't present in these other metals from the 2003 one.

MS. FIUME: But there is a calcium magnesium silicate.

DR. SLAGA: Right.

DR. HILL: Silver is nothing --

MS. FIUME: There's a sodium magnesium aluminum silicate, as ingredients that have not yet been reviewed.

MS. BURNETT: So, possibly eliminate the silver ones.

MS. FIUME: So, could they be brought in reopened to add these no-brainers?

DR. MARKS: And then we can list the specific ones. But I see what you're saying, that of the potential add-ons, limit that 16 to ones which are chemically very similar to the 2003 report no-brainers, and reopen and add those. Don't consolidate.

Tom, you seem to be indicating that sounds okay. Ron Shank, do you have a problem with that? And we can list which ones. We mentioned the calcium magnesium silicate, and there are several others -- or a couple others. What is your sense, Ron Shank?

DR. SHANK: You're taking the no-brainers from the new add-ons?

DR. MARKS: Yes.

DR. SHANK: And adding them to the 2003?

DR. MARKS: So, like calcium magnesium silicate would be one of the no-brainers. Not silver, based on Ron Hill's concern.

DR. SHANK: Okay. So, out of those 16, the only --

DR. MARKS: Yes. So, let's go there.

DR. SHANK: -- one that is used is zinc zeolite.

DR. HILL: And ammonium silver --

DR. SHANK: Or the silver. And Dr. Hill says count in -- that's not a no-brainer. So, you're reopening to add zinc zeolite, which has one use.

DR. SLAGA: No, no. Add even the ones that are not being used --

DR. MARKS: Calcium magnesium silicate.

DR. SLAGA: -- to this because they've never been reviewed.

MS. FIUME: I mean, they're in the dictionary.

DR. SLAGA: We eliminated -- re-reviewed based on it wasn't a no-brainer. That was the final earlier today. These are --

DR. ANSELL: So, you dropped silver. You'd keep germanium?

DR. HILL: There's still quite a few that you could keep though.

DR. SHANK: What about iron?

DR. HILL: Yeah. I think so.

DR. MARKS: So, let's go from the top. Obviously not activated clay. How about the second one, the aluminum calcium magnesium potassium sodium zinc silicate?

DR. HILL: So why not activated clay, because you've already got -- in the 2003 -- you've got attapulgite, bentonite, Fullers Earth, hectorite and kaolin.

DR. MARKS: So, you would add that?

DR. HILL: I think activated clay would be fine.

DR. MARKS: Okay.

DR. HILL: The next one would be fine. The next one would be fine. The next one would be fine. The next one would be fine. Then we've got two silvers, but I think the calcium magnesium silicate would be fine.

DR. ANSELL: Calcium magnesium germanium would be okay?

DR. HILL: Where's that?

DR. MARKS: Well, no.

DR. ANSELL: That's number three.

MS. BURNETT: The third one down.

DR. HILL: I don't know about germanium. That's iffy. I'd have to think about that. I'm sorry I didn't yet. Remember, my take was put them all together and then split them back out. But, I'm in a different mode now. I think germanium would be okay.

DR. MARKS: Okay. So, you don't like the silvers. Now we're down to the gold zeolite. Zeolite was safe in the '03 report. Adding gold to it, does that change it? And then we're into silver copper zeolite.

DR. HILL: So, I'd have to see what the definition of the gold one -- it really isn't very clear if I remember right.

MS. BURNETT: Yeah.

DR. HILL: What form the gold is in.

MS. BURNETT: Gold zeolite is a product obtained by the reaction of gold chloride with zeolite.

DR. MARKS: Yeah. So, it's gold plus zeolite.

DR. HILL: I have to think about that one and the germanium. But anyway, skipping that for the moment and the two silvers, then you still -- you have sodium magnesium, aluminum, here's another silver. I think titanium's okay. Tromethamine is new. So I flagged that at least.

But then the last of them is probably fine, based on what's in that grouping in 2003. I know it seems like I'm cherry picking, but I'm just looking at chemistry that I know.

DR. MARKS: So, you would have two, four, six, eight, nine ingredients if I count --

DR. HILL: Six, seven, eight, nine, maybe ten if we do zinc silicate. Did you catch that one?

DR. MARKS: Yup.

DR. HILL: Let's see, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 I count.

MS. BURNETT: I have nine.

DR. MARKS: Oh, I didn't include the gold since you were hesitating.

DR. HILL: No, I didn't. but I did include the last four -- all of the last four.

DR. MARKS: Okay. The last four.

DR. HILL: But that's just --

MS. BURNETT: Eliminating all the ones with silver.

DR. HILL: And I'm not sure about gold; I have to think about that.

DR. MARKS: And you've eliminated the zinc, the one that has 17 uses, the ammonium silver zinc aluminum silicate. So, we're adding on virtually everything with no use; although that hasn't been a -- these are no-brainers.

DR. HILL: And now the interesting question is, would you group all the ones that had silver and possibly with the gold in there, and then make another group and another report. But the only ingredient that's in use -- and I don't know about data --

MS. BURNETT: None of those are in use.

DR. HILL: -- would be the ammonium silver zinc aluminum silicate. What do we have in the way of data?

DR. MARKS: So, now we're at reopen the 2000 report and add approximately -- I'll say approximately -- somewhere around ten ingredients, which are no-brainers from that new add-on list. What's your sense, Ron Hill? You don't have a problem with that?

DR. HILL: I don't have a problem with that; or I don't have a problem with do not reopen, since most of those are not in use.

DR. MARKS: Ron Shank, which way do you lean? Still not reopen.

DR. SHANK: Yes. Not reopen.

DR. SLAGA: Reopen.

DR. MARKS: So, we have a split here. I mean the question is, is it really worth it for a bunch of ingredients that have no uses. But that shouldn't be --

DR. SLAGA: Well, zinc zeolite a product, right?

DR. MARKS: Yeah. One use for that one.

MS. BURNETT: I have data on that one.

DR. MARKS: But again, that's the criteria. Do we use that criteria for reopening? Some things I don't think we have. It's just as a no brainer.

MS. FIUME: I would like to state CIR has been trying to create, through the past couple of years, complete families, even if ingredients had been reviewed in the past.

DR. MARKS: Right.

MS. FIUME: Regardless of the number of uses. Because then I was going to channel Bart, a little bit, and say thank you for potentially adding the add-ons to the report. But then can we look at the 2005 and 2009 reports, because again, there are similar ingredients. So that our family is complete, in one place, could you consider bringing those into the report as well.

And they do have conclusion, but again, there is sodium potassium aluminum silicate in the 2009 report. So, it's sort of out there.

I guess one of our goals has been recently, as we prepare these bigger families, is that it makes sense to have a family of ingredients in one place. And that's, you know, what we've been striving to do. So, is it possible to make, even albeit large, a family of ingredients out of these combined four categories, if it was going to be redundant.

DR. ANSELL: Right.

DR. MARKS: And that's -- Ron Shank, right from the beginning, you didn't like the idea of combining all into one report?

DR. SHANK: I didn't see the need. Had that been done at the beginning, okay. But to go back and put them all together, half of them have already been published. So, now what you're saying is taking the 16 add-ons, and the 2009, and putting them all into a reopened 2003.

DR. MARKS: No. Actually --

DR. SHANK: And leaving the three irritating ones --

DR. MARKS: No. I wasn't that far along, Ron Shank.

DR. SLAGA: Ten out of 16 for the --

DR. MARKS: I was leaving 2009 standalone. And what I thought we were at was just taking the no-brainers and adding it to the 2003, which was proposed.

DR. SLAGA: That's all we're doing.

DR. SHANK: But there are no-brainers in 2009.

MS. FIUME: My request --

DR. MARKS: Well, that's already been --

DR. SLAGA: And that's what creating a family is.

MS. FIUME: Yes. If you were going to go ahead and reopen it, then could we look at the 2009, 2005, and say yes there are actually a lot of ingredients that also belong in that family, so that they're all in one place; if it were to be reopened.

DR. SLAGA: No-brainers.

DR. ANSELL: Right. But I think you're turning it kind of upside down. The reopening justification now is to order the family. And I think that was our original question, is that worth the effort?

MS. FIUME: Well, I guess, step one would be, are there no brainers that are now listed that have not been reviewed; and is that a reason to reopen to add. And if that is, we take that step. Then can we take the next step of looking at ingredients that, yes, were reviewed, because we've done this many times, and bring them into the family as well.

So, I'm looking at it as a step process; but if you go ahead and take the first step, is there any reason not to take the second step and create a whole family.

DR. SLAGA: Maybe that's a way to bring it up, the way it was stated. That the 2003 additions, no-brainers, and then approve that, and then say there's a possibility that the others could be brought in for a family relationship.

MS. BURNETT: I would like to point out that some of the potential add-ons that have the iron included, the iron was reviewed in 2009. You wouldn't have that data from the 2003 report, if that would aide anything.

DR. HILL: What you're saying is we're not sure if iron is a no-brainer read across. And I'm sort of asserting in these kinds of materials, it pretty well should be.

MS. BURNETT: Okay.

DR. MARKS: Well, our team should at least -- there's two different issues. We're still at -- and we have a split decision among the panel as to whether we not reopen versus open 2003 report and add the ten "no brainers". I say 10, it might be 9 or 11.

DR. HILL: It's around there, somewhere in there.

DR. MARKS: Versus the idea of reopening and consolidate. I hear you, Monice. Right from the get-go we said we didn't like to consolidate. But we also hear the idea, well this is in the same family, it'd be nice to have it all on one report.

Consolidate? Because we're back to that again. And we shouldn't -- I don't think we should go into tomorrow wavering that way, if we all feel don't consolidate. And we maybe have a split concern that way. It'll be interesting to see -- the good thing for me is I'm seconding the motion.

DR. SLAGA: That's right. If they say consolidate all of them, we'd say we agree.

MS. FIUME: And as a reminder, we've done it in the past where we have reopened, and then the next time you can come back and then look at it again as an entire family, with more information and change it.

But I just wanted to lay out all the steps. And I understand if it's not reopened, you know, that's the panel's prerogative. But I just wanted to lay out the steps of how to look at the thought process.

DR. HILL: And what you just said last was what I was proposing, even if it wasn't obvious by how I said it; is put the information together and then decide. But it's staff effort and I really appreciate that.

MS. BURNETT: Already started, so it's fine.

DR. HILL: Well, I mean, the problem is if they put you on something else --

DR. SLAGA: Alright Jim, you heard that. You could either punch them tomorrow or double punch them.

DR. MARKS: No. I think it would be since we're split on it, as long as they're not split, we're going to probably agree to whichever way they want to go.

DR. SLAGA: They're probably playing in their sandbox, right?

DR. MARKS: I see the advantage -- and I have in here consider consolidating with the 2005/2009 report. But my feeling is if their team -- from what you said Christina you've already started that, that consolidating them is not going to be a huge issue from your point of view. Staffing point of view.

MS. BURNETT: No.

DR. SHANK: Am I the outlier? This is a housekeeping issue as far as I'm concerned.

DR. MARKS: Yeah, exactly.

DR. SHANK: Not a science issue.

DR. MARKS: Yeah.

DR. SHANK: So, if you want to put them together, the staff won't throw rocks at us --

MS. BURNETT: I would have thrown those rocks a long time ago at somebody else, so it's good.

MS. FIUME: She would have thrown the rocks at Bart and I.

DR. HILL: I think in putting them together and looking at subgroupings in terms of what can be read across as -- I don't know that there's such as a thing as a real no brainer but anyway -- that fit that criteria to a reasonable degree. And looking at sub -- I think some things will emerge that if we don't put them together, okay the sleeping dog will lie and there's probably no disaster to that too.

DR. MARKS: I'm going to second what I think's going to be the proposal to open the 2003 report. Put the add-ons; ten of them are we think no brainers. I'll ask you to talk about zinc tomorrow so just so, Ron Hill, you indicate --

DR. HILL: The silver?

DR. MARKS: Oh, silver. I'm sorry. Sorry, got the wrong metal. Silver, Ron Hill.

DR. HILL: I didn't bring my advance inorganic chemistry book with me to look at germanium and gold.

DR. MARKS: And then consolidate with the 2005 and 2009 reports and we'll see where it goes. I want to get to science now that we're past the procedural issues. Irritation and sensitization should be fine. It formulates to be nonirritating. That takes care of the silicates.

As I read it, there was some issues with respiratory in this. Is that true or not? And if it is, at least going forward, I wanted to get a preview of the science of the respiratory issues and how that's going to be address with these.

DR. SHANK: And where are you in all this 272 pages?

DR. MARKS: I put respiratory okay, use table 75. I guess there must have been a few things in here. I'm sorry, Ron, I just highlighted respiratory and I didn't put a page. I'm not sure where when I look through the report. Ron Hill?

DR. SLAGA: I didn't see anything.

DR. SHANK: We have four reports all in one.

DR. MARKS: Yeah, exactly. Let me see if I --

DR. HILL: I was looking at transcripts a lot and starting into this, since I wasn't around at the beginning.

DR. MARKS: Sorry, Ron. Maybe just put as an alert and as we go -- when it gets all consolidated. It seems to me it came out -- nothing stood out to you respiratory wise, Ron Hill?

DR. SHANK: Correct.

DR. MARKS: I mean, Ron Shank. Good.

MS. BURNETT: The summarized discussion from the original report mentioned --

DR. MARKS: Here it is. Page 89.

DR. SHANK: Page 89?

DR. MARKS: Page 89. This was the 2003 report. And if you look at the end of -- it says, "Panel considered that any spray containing these solids should be formulated to minimize their inhalation. With this admonition to the cosmetic industry, the CIR panel conclude that these ingredients are safe." So that must have been -- not in a conclusion, but in the discussion.

And then when you look at page 149, right above -- yeah. The conclusion doesn't mention any admonition to the cosmetic industry, which is kind of interesting. I thought that's pretty strong wording to not have in the conclusion.

And then, if you look right above the conclusion on page 149, not the note, but right before the note. The concentration of ingredients is very low. That's the respirable concentration. Even so, the panel considered that any spray containing these solids should be formulated to minimize their inhalation.

That could have been a conclusion. We do formulate to be nonirritating. Can you formulate to minimize inhalation? Or is that the way it's delivered?

DR. SLAGA: That might be coming up soon.

DR. MARKS: That's where I'm sure I got the inhalation concern.

DR. HILL: Yeah. I was reading back in the transcripts, and the discussion of talc came up which continues to remain an almost ridiculously contentious issue. But it's out there, heavily, in the consumer world, in discussion. Discussion, I use one word.

Because it mentions talc is a hydrated, magnesium silicate. And it gives the chemical composition. This is in the 149, right above the conclusion. Occurs in various forms and has unique crystalline structure. And talc is not included in this report. The significance there goes to the no-brainer contention with these add-ons.

DR. MARKS: Okay. I just wanted to, Ron, bring that up, and Ron and Tom, about I suspect at some point we're going to -- I have to address that again with it being reopened.

DR. SHANK: The respiratory issue?

DR. MARKS: Yeah. Or whether the inhalation boilerplate addresses it.

DR. SHANK: I think it does.

DR. MARKS: Yeah, okay. I think that's fine. Okay, well, we'll see what happens tomorrow. I'm planning on seconding it -- whether it's the motion or not -- opening the 2003 report with ten no-brainer add-ons. Silver, Ron Hill, has concerns. And depending on what, I'll ask you, Ron Hill, to -- and then we'll consolidate with the 2005 and 2009 reports. Does that sound okay now to everybody?

DR. SHANK: Yes.

DR. MARKS: Good. Okay. And we've taken care of the respiratory. Okay. Thank you.

Christina and Monice, that was a -- I don't know, every ingredient we've had there has been some good discussion so far. Are we going to have one where it's, yes, that's fine. Let's move on to the next one.

Full Panel Meeting – June 5, 2018

DR. BELSITO: This is a re-review coming up from 2003, and there are 16 possible add-ons that have not been assessed by the panel. There were also silicates that have been reviewed and were published in 2005, mainly potassium silicate, sodium metasilicate, and sodium silicate.

And these would be additional materials that could be incorporated, so bringing that total of 19 into this report. But then there was also in 2009, assessment of silica and related cosmetics, and that safety assessment, it turns out, was never published for some reason, and would be due in another six years.

We felt that we could reopen this report; and also in addition to what was reviewed in 2003, include the 16 possible add-ons that haven't been looked at. And include the ones from 2005, the three there, as well as the ones in 2009, that were not published. So, essentially add all of the prior reports on the silicates together, add the new ones.

We need to take a look at this because usage has increased significantly for many of these. And we need a sense of the concentration of use before we decided on the safety. So, we would like to reopen, combine all of them, and at this point our real interest is what concentration they're used at. We may not need additional data based on that.

DR. BERGFELD: So, you're asking just to reopen and add?

DR. BELSITO: Reopen, add the 16, and combine the prior reports on silicates.

DR. BERGFELD: Okay. Dr. Marks?

DR. MARKS: We second that motion. I just want to clarify. So, you don't want to move forward with either a tentative report or an insufficient data announcement with the reopening.

DR. HELDRETH: Reopening would be a tentative report.

DR. MARKS: Okay then, if it's a tentative report we have to have a conclusion, correct? And I haven't heard a conclusion.

DR. BELSITO: Well then, I would say that it's insufficient for concentration of use of what we're adding on.

DR. BERGFELD: Okay.

DR. EISENMANN: But we were never asked to do a concentration of use survey, yet, on some of the ingredients; so, it's hard to make it to be a tentative report.

DR. HELDRETH: Yeah, we can put up the insufficiency, and we could give industry time to respond with that information.

DR. MARKS: So, then it would be an insufficient data announcement.

DR. BERGFELD: Is that okay? Agreeable?

DR. BELSITO: I'm fine with whatever the procedures are. I think this will clear pretty quickly once Carol gets us the data on concentration of use. But it's hard to say "safe as used," when we don't know how the new ones are used yet.

DR. HELDRETH: Alternatively, we can concede that this can just be considered a report strategy, at this point. And if you agree with the strategy, then we will create a new report that comes back to you.

DR. BELSITO: I'm fine with that.

DR. BERGFELD: So, it's just a reopen.

DR. MARKS: And then you wanted to include, of the add-ons, Ron Hill had a question with the silver. You weren't happy with including that as a no-brainer on the add-ons?

DR. HILL: I didn't do it as a no-brainer, but if we're reopening, which we weren't clear we were doing in our session, fully reopening.

DR. MARKS: Oh yeah, we're reopening.

DR. HILL: Okay. I didn't know where we landed at the end. Okay, then I think we leave it in for now. But it's not necessarily a no-brainer, it's not clear that we will, for sure, be able to read across, but leave it in for the moment.

DR. BERGFELD: Any other comments? I'll call to question then? All those in favor of reopening, please indicate by raising your hand. Thank you. Unanimous.

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DR. BELSITO: Okay. Silica and silicates. This is the first time we're looking at this one too.

MS. BURNETT: Apologies, I'm going to hand out a last-minute submission from Women's Voices of the Earth.

DR. HELDRETH: Yeah, this one came out -- this submission came in really late, even after we put out Wave 3 to you. Since this report is only in the draft stage, feel free to wait to really go into the details of this most recent submission until the next iteration. We'll include this submission as part of the next package.

DR. BELSITO: Okay. One of the ingredients, before we even go to that, just looking at what we had, is zirconium. And it says the EU has prohibited zirconium, and zirconium silicate and its compounds, in cosmetic products. And it's not even reported as being used. Should we just delete it from the things that we're reviewing?

Or should we include it, but we have no data on it.

DR. BERGFELD: Why did they do that? They're in lots of things.

DR. BERGFELD: Zirconium?

DR. BELSITO: Zirconium. If you look at the cosmetic use, there are no reported uses for the zirconium.

DR. HELDRETH: So you could be insufficient for that one if the other ones are not a concern.

DR. BELSITO: I don't know why zirconium was a concern.

MS. BURNETT: The zirconium, that's in the report, was in the original review. It was in the original review of the silicates.

DR. LIEBLER: I'm not sure I see why it doesn't belong. I mean, chemically -- I mean, you got zinc silicate. You just incorporate the zirconium ions instead of zinc.

DR. BELSITO: And then NICNAS has recommendations for risk management for safe use, for human health or the environment, attapulgite, potassium silicate, sodium silicate, and sodium metasilicate, that I also didn't understand.

MS. BURNETT: So how they do -- if I understand, how they do their risk assessment approach, if it's a tier one -- meaning they don't consider it be a risk to human health or environment, they don't pursue a next-step risk assessment, which delves further into systemic -- they don't produce a health report. So, when you go into their database, you print an ingredient, it will spit out whether it's a tier one, tier two. If it's a tier two, you usually have a report attached to it that has data.

DR. BELSITO: Okay. So Women's Voices of the Earth. Point one, physical and chemical properties.

Morphasilica are composed of very fine particles, 20 microns which aggregate loosely in the air. Again, criticize that we're using an outdated report from 1961.

We had testimony in 2009, that when they're produced, they're 100 micros. And some applications they're milled down to 10 to 20 microns. Websites for cosmetic grade silica commonly advertise their product as having medium particle size of five microns.

DR. SNYDER: So, these are all microspheres?

DR. BELSITO: Yeah, but we state that they're fine particles which tend to aggregate in air. So, don't we already cover that claim? I mean, again, it's not particle size, it's what's coming out of the cosmetic, right?

DR. LIEBLER: I think this is one where it's probably worthwhile for Christina to go through these examples cited in Ms. Scranton's letter, and run them down their links provided at least. And to see how these relate to cosmetic ingredients that are used, in industry. And if we need to revise our particle size discussion, we can do that next time we meet.

DR. BELSITO: I mean, all the criticisms have to do with, material as supplied can have a particle size of less than ten microns, but not the material as used in a cosmetic product. So, if you look at each criticism, that's what it is.

DR. LIEBLER: Yeah, there's two issues in this letter: one is the particle size stuff, that goes the first page and a half. And the second is whether or not crystalline silica is present in cosmetic products. She points to data recorded with the California Safe Cosmetics Program that appears to contradict the assertion, in our report, that only amorphous silica is used. So, that also needs to be chased out.

MS. BURNETT: I did a little searching this morning; I went to the two links that they gave us. The one that is the California database, they have -- when you just put in silica, it comes back with both amorphous and crystalline as one ingredient. It doesn't differentiate the two.

MS. KOWCZ: Could that be the reason why they're reporting it?

MS. BURNETT: I think they're lumping it all together in California.

DR. SNYDER: We went through this before with the fumed silica versus the silica fume; one is crystalline and one's not, right? We talked about that previously.

DR. LIEBLER: So we need to -- we need to make sure that -- if this is a categorization error by lumping all silicas together, in that database, that that could be established.

MS. BURNETT: I'm not sure how to flush that out, but we'll figure --

MS. KOWCZ: I think we need to look into that, because I think if it is lumped together, then the companies that are reporting silica are just reporting silica, because they need to -- they will not take the chance of not reporting it.

MS. BURNETT: From what I can see, there's no way to designate it as one or the other, it's just one. They went ahead and categorized a thousand products with silica in it.

DR. LIEBLER: It should be possible to determine that.

MS. BURNETT: Determine?

DR. LIEBLER: It should be possible to determine whether either the entry field, for entries for those ingredients, are limited to just silica; and it includes both, and so it gets tagged both ways, automatically, upon entry, or whether or not it's just lazy reporting by the companies.

DR. KLAASSEN: Plus there are three or four other websites that she quotes here. We need to look at all of those closely. We were given the impression that what really is used in cosmetics is ten microns and larger. That when they did these studies, like in animals, they even "ground" them down to be five microns. We need to know, absolutely for sure, what's going on here. What is the size? There's a world of difference between five and ten.

DR. EISENMANN: But even if the size is five, as you put it in -- as you put it with other things -- as you put into product, final product, the particle size of the final product is what matters.

DR. KLAASSEN: In that case, we need data.

DR. LIEBLER: And that's true, but yeah, I mean, it's true and it's very reasonable to say that. But, if we don't have any data to really support that, that if you put in, let's say, ten micron distribution, plus or minus five, into a product and then you measure the particles that result in the final formulation, then it's like 50 and up.
It would be great to have data to support that. It's certainly reasonable to assume that that could happen. But in the absence of any data we can hang our hats on, it would come across as wishful thinking.

DR. SNYDER: I had a logistics question. Why didn't those come up in your search? Those ones that she found.

MS. BURNETT: They're manufacturer websites. I don't necessarily -- I have -- I'm still reorganizing a report from its original format, and I do have some outdated data sheets. But when I went to go verify that those were still good, they were no longer -- the links were no good. The thing is, is that they label -- their product manufacturers give a name to their products, so it's harder to search for them. So, it's a general Google search that you have to come up with in order to get a silica manufacturer, and it's kind of cumbersome.

DR. SNYDER: Okay. Thank you.

DR. LIEBLER: Does your search include that California Prop 65 database?

MS. BURNETT: No.

DR. LIEBLER: Okay.

MS. BURNETT: Should it?

DR. LIEBLER: I don't know. I guess that's a question I'm asking.

MS. KOWCZ: That's where she's getting the information.

MS. BURNETT: Yes.

DR. LIEBLER: Okay.

DR. HELDRETH: I think we'll have to determine if that's a credible source even.

DR. LIEBLER: Well, you know, it would be good to establish that. Because if that's a site that's being used -- you know, that would be mined and generate data that's going to contradict us over and over again, I mean, it's an unforced error not to look. So, we should be looking at that and evaluate the reliability so we can determine how to deal with this, because it will be coming up again in the future, I suspect.

MR. GREMILLION: That's a California government site. It should be fairly credible you'd think.

MS. KOWCZ: Yeah, but also, she mentions that some of the websites, of the cosmetic suppliers, are saying that's crystalline silica and it needs to require warning language. I don't think, normally, a supplier would tell a manufacturer what they need to say or not say. So, that's a question as well.

DR. HELDRETH: So, we'll include those in the response document that you see in the next panel table iteration of this report.

DR. BELSITO: When I looked at this, I was ready to go safe as used when formulated to be non-irritating, and discuss, extensively, the respiratory issues. But are we now saying that we're insufficient for information on the respiratory issues?

DR. BERGFELD: Particle size plus. Don't you have to have --?

DR. BELSITO: Well, that's the respiratory issues. Is it inhalable?

DR. BERGFELD: Okay.

DR. KLAASSEN: I agree.

DR. BELSITO: So, insufficient for understanding of particle size and formulation, which we're not going to get.

DR. EISENMANN: But in other products, is it safe when formulated to be non -- so you're concerned about spray and some powder -- and loose powder products?

DR. BELSITO: Yeah, we could say safe when formulated --

DR. EISENMANN: For like in toothpaste. I mean there's a lot -- like silica. That's a big use for si- for like sodium silicate, and sodium metasilicate were used in like hair bleaching products. It would be nice to have the insufficiency carved out, more specifically, so that the other uses are safe, or put safe when formulated to be non-irritating, if that's where you're headed.

DR. BELSITO: I mean, the real issue is, yeah, we know they can be supplied at less than ten microns. The question is, is what happens when they're put into formulation? Isn't it really a more stringent conclusion -- we're not going to get data from every single formulator for aerosol products as to what the particle diameter size is. We've been doing this for -- safe when formulated to be non-irritating, safe when formulated to be non-sensitizing, safe when formulated in aerosol products so that the final aerodynamic diameter is whatever.

DR. LIEBLER: Is non-respirable.

DR. BELSITO: Is non-respirable.

DR. LIEBLER: Yeah, we never use that, but I was just thinking the same thing. We either do that in the conclusion or we heavily emphasize it.

DR. BELSITO: No, we put it in the conclusion, because we're never going to get the data on all the products that are respirable.

DR. LIEBLER: I'm okay with that. We could have a new -- this might be something that we might need to utilize more often than a boilerplate, for aerosols. When we know we're not going to get the data; when we can't really arrive at a definition of safety. And so much of it will hinge on how the product comes out of the bottle's nozzle whatever, in the final formulated product. And that's really all up to the manufacturer.

DR. BELSITO: So, I mean, safe as used when formulated to be non-irritating and non-respirable.

MR. GREMILLION: What does non-respirable mean?

DR. BELSITO: Less than ten microns.

DR. LIEBLER: The particles can't get down into the lungs.

MR. GREMILLION: No, I understand-, but where would you draw the line on that? My understanding is that a lot of these products have at least one percent, or whatever, that's less than ten microns. Would you define that?

DR. LIEBLER: If we took this approach, we would need to probably put that into our boilerplate document that we're currently working on. And then also, probably, have that in the discussion, drawn from the boilerplate document, that would explain the relationships between particle size and respirability. And then the thing left for us to determine, is do we want to put some kind of a threshold on that?

MR. GREMILLION: It seems different than formulated to be non-irritating, where that seems like something that's either irritating or it's not irritating; whereas, respirable, everything's going to be a little bit respirable.

DR. LIEBLER: One of those endpoints are analogic.

MR. GREMILLION: Okay.

DR. HELDRETH: So, just to be clear, if it were small enough where we believe it will enter the lung, are we considering whether or not there would be some sort of systemic absorption; or are we talking about irritation or sensitization to the lung?

DR. LIEBLER: So, in the case of silica, that appears to be the issue.

DR. HELDRETH: Irritation or sensitization of the lung?

DR. LIEBLER: Oh, I'm sorry.

DR. SNYDER: Deposition into the lungs.

DR. LIEBLER: Deposition, and lung and toxicity, the results for that.

DR. SNYDER: They have a lot of data. But some of it we don't know the particle size. Or some we have particle size, some we don't. But there's clearly an effect.

DR. HELDRETH: Okay, I just want to be clear on that. Because for silica ciliate, we previously concluded safe when formulated, and delivered in final product not to be irritating or sensitizing to the respiratory tract. But, if we're talking about systemic absorption, that's a different thing.

DR. SNYDER: That's what we discussed when we talked about aerosols. There's a big difference between experimental conditions and consumer conditions of use.

DR. BELSITO: So, what are we saying tomorrow? Non-irritating, non-respirable, and we need to define non-respirable in our boilerplate?

DR. SNYDER: Correct.

DR. LIEBLER: Yes, I agree.

DR. BELSITO: Okay.

DR. SNYDER: Dr. Marks is presenting.

DR. BELSITO: All right. Good.

DR. SNYDER: We're off the hook.

DR. BELSITO: Okay. Well no, we're not off the hook.

DR. KLAASSEN: Sort of.

DR. BELSITO: Okay. We are done, unless there's anything else.

DR. BERGFELD: So, if you can't modify your boilerplate, or you can't address the inhalation -- if we can't modify your boilerplate, or you can't rectify your use and formulation, what will you do, go unsafe for that -- safe sprays or inhalation?

DR. BELSITO: Unsafe for inhalation. But I don't think we're going to need do that. We'll see.

DR. SNYDER: Insufficient.

DR. BELSITO: Insufficient, yeah.

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DR. MARKS: And let's see. The next ingredients are silica and silicates.

MS. BURNETT: Are you ready for another Wave? We had a late comment submission from Women's Voices of the Earth.

DR. SHANK: We need to have control over -- we love to have data and information, but we need time to consider it.

DR. HELDRETH: I agree. And I wanted to add the comment of, since this is not a final report, we can add this as part of the next iteration to that report package; and you can take time to consider these comments, in detail then, if you choose.

DR. SHANK: Okay. I like that.

DR. HELDRETH: We just wanted to -- since it came in, we wanted to provide it and make sure you have it.

DR. ANSELL: And we would appreciate time to read it, too.

MS. BURNETT: We did consider holding it, but one of the points that was made by them, I thought was a little -- that needed attention, potentially going into either a comment period or into an IDA period, where we could research more. But that's -- otherwise --

DR. ANSELL: Which particular one was that?

MS. BURNETT: The comment about the crystalline silica.

DR. HILL: Yeah, my concern, in general, related to what you all just said, was that we're calling this an amended report, but we're adding in a whole mess of new ingredients. And we aren't capturing, in this report, all of the information from previous ingredients in the other reports.

We're saying, here's this report. And then, if you go through the report and you look, you see information. Really, it's all silica, or -- I mean, a very restrictive set there. And we're adding in how many new ingred- -- 23, isn't it, or some large number of --

MS. BURNETT: Well, original report was the 17 silicate ingredients; and then, the panel chose to reopen to add in the three from another report, and then the nine from the silica report. Nine or Seven -- nine. And then a few just new ones that haven't been reviewed.

DR. MARKS: Well, 15. So, there are 23 additional ingredients added. Nine that were previously reviewed by the panel, 15 that have not been reviewed, so that's the 23. So, it's 17 from the original report in '03, to adding some ingredients that had previously reviewed, plus the ones that have not been reviewed.

MS. BURNETT: There was 15 that --

DR. MARKS: So, the total of 40 ingredients.

DR. HILL: And then, chemically, there's a lot of diversity in those ingredients. As I was going through it, I'm saying, this doesn't feel like an amended report anymore, it feels like a new report. And that's fine, but it --

DR. MARKS: At this point, we have in front of us, a draft-amended safety assessment of silica and silicate ingredients, containing the 40 ingredients we just talked about.

We're at the point, do we go ahead and move forward with a conclusion of the tentative amended report, safe when formulated to be non-irritating; or do we issue an insufficient data announcement? And obviously, we'll be able to address the Women's Voices for the Earth at the next review of this, if we want, unless you want to take a few minutes and look over the letter.

MS. BURNETT: While we were discussing the earlier ingredients, I did go and look at the -- for the crystalline silica comment that they made, saying that they did research and they see that it's being used in cosmetics --

DR. ANSELL: On 484, yeah.

MS. BURNETT: -- I did go to the two websites that they proposed. And the one, when you just put in silica, it comes back as only one ingredient matched, and then it goes, then, to say that they're synonyms. Crystalline is the same as amorphous, is the same silicon dioxide.

DR. ANSELL: There are many errors in the 484 database. For example, no one's actually using cadmium as an ingredient. Ethylene oxide is not an ingredient. People have -- and there's no mechanism in which to correct the filings. So, whereas I find their database quite user-friendly, the quality of the data is somewhat questionable.

MS. BURNETT: And it's also -- when you click on the word silica, silicon dioxide, amorphous silica, microcrystalline**,** it then talks about how it's manufactured from quartz and crystal (inaudible). But according to the data we have, these silicas that are used in cosmetics that are synthetically derived.

I think the CAS number is generic and it applies to both the crystalline and the amorphous type. I think I remember that somewhere in the report.

DR. ANSELL: No, no. Obviously, I've not had a chance to look at --

MS. BURNETT: Oh. So, I don't know if that's causing their error in their database.

DR. ANSELL: Well, no. I -- yeah. I mean, I've not had an opportunity to look at this. But we've looked at the California Safe Cosmetics database, quite extensively, and it has some useful information. For example, many cosmetics are white. Close to 90 percent of the filings are for titanium dioxide. But it also contains materials which should not have been reported, because they're obviously not being -- well, they best not be being used as cosmetic ingredients, heavy metals.

There's no assessment, on California's part, as to the accuracy of the any of the filings. So, we find it an interesting database, but I don't know that it's interpretive to this extent. Even the listing of materials, California points out, are listed because of data which may not be relevant to cosmetics, may contain ingredients which are not used in cosmetics, or used in cosmetics, and not present a risk, because they do not do any type of risk assessment. So, it doesn't surprise me that silica might fall well within that context on the stake or --

MS. BURNETT: Okay. I was just -- that was the main thing I was concerned about, coming out of coming out of the memo. I know, with the micron size, we were reworking the aerosol. And I didn't feel that that was an immediate need for attention by the panel. The crystalline definitely was going forward.

DR. ANSELL: But we should definitely read the letter, and prepare a thoughtful response; and hope that their response to our response is as thoughtful.

DR. HILL: So, just a general -- again, in looking at this and saying, how is this an amended report? There are quite a few substances in here. I should be able to go ingredient by ingredient if I'm going to conclude safe at some point, and say, what is this stuff?

And that got me to thinking, somebody is selling this ingredient to formulators who are formulating it. There will generally be a lot of information in their information sheets, whatever they're using for their marketing materials, about, what is this stuff? How does it behave? And I don't feel like, sometimes, we get that information. And I don't know why we don't get that information, really, from anybody who's vending -- I mean, principle.
But at least, I should be able to answer the question, substance by substance by substance, what is this stuff? I see a name. But in general, when it's sold, what is the particle size? In general, when it's sold, what's the chemical stability? In general, if you put it on mucus membranes, how will it react chemically?

All those information relate to and -- is a phagocytose. So, if macrophages are swallowing the stuff, where does it go? Do we build it up in lymph nodes? All those sorts of things. But the least fundamental question is, chemically, what is this stuff? And I don't get that, other than just, okay, it's got calcium and iron and zirconium. Probably not -- Zirconium is talked about in there, but anyway.

So, in terms of data needs, I need enough information in each ingredient if I'm being asked to read across. Because they're clearly not all silica. Silica is just silicon and oxygen and nothing else. But we do have some zeolites and clays, and so forth in there, so that does potentially allow read-across if you have more information.

DR. MARKS: Ron Shank?

DR. HILL: And again, how to capture it. Because it is -- that's the situation. What I put is, we have a lot of x's in the boxes, on the profile page, that are not captured in this particular report in any way whatsoever. It's, go out and read that report, and that report, and that report, and that report. And I'm not sure we should put together a report that way.

I mean, I realize we don't put the whole substance of the previous reports in there, but there should, some way, be data that's captured either tabulated or something, so that we can look at this report. A reader can look at this report and make conclusions about read-across, if that's what we're being asked to do, which we are. So, there are at least summaries of other ingredients in this report, so that I'm not just looking at silica, silica, silica, silica, silica. But that's me.

DR. MARKS: Tom?

DR. SLAGA: I didn't have any concerns related to the ingredients, but to me they are the type of ingredients that we had reviewed in the past. And as you said, this is a reorganized -- most of them are safe already that we have studied. And we're only dealing with 18, I felt, that were not reviewed, and that there was sufficient read across for those; not every one, but enough data to support that these are safe.

DR. MARKS: Ron Shank?

DR. SHANK: I kept the whole group together.

DR. HILL: I concur.

DR. SHANK: I thought there was very little sensitization data and we need more.

DR. MARKS: Interesting.

DR. SHANK: And some of the use concentrations are very high. 80, 100 percent, et cetera.

DR. MARKS: Yeah. Kaolin at 53 percent, silica at 82 percent. I also had very little sensitization data. But then, when I go back and look at, there are just no alerts, and silica is not a sensitizer. And those had been reviewed before.

So, I kind of felt we could go ahead as one of the conclusions in past, safe when formulated to be non-irritating. There was some concern about irritation. So, I felt sensitization would be okay in this case, even though it's not at a high concentration. But we do have sensitization data at, like, 50 percent on them, even though 83 is not 50 percent. But a local lymph node assay --

DR. SHANK: So it's not like palmitic acid -- palmitate?

DR. ANSELL: No. It's more like sand.

DR. SHANK: No, I'm just saying, the sensitization -- last ingredient, we had it --

DR. MARKS: Yeah, I know. I agree. That's it.

DR. SHANK: We had it at one level, but not a little bit higher. Now it's okay, because it's sand?

DR. MARKS: Yes. Essentially, yes.

DR. HILL: I need to qualify my earlier remarks by saying, I don't have any serious toxicological concerns with any of these, even by name only.

DR. SLAGA: It's just enough -- enough on each ingredient.

DR. HILL: But I still have the fundamental thing that if I can't answer the question, what really is this stuff, how do I read across to it and clear it? And I don't know why, if somebody's selling this, we don't have information as to what is this stuff, in every single instance that it is being reported to being use. And if it's not reported to being use, why do we clear it for safety as sufficient? We leave it insufficient until somebody comes forward with the information we need to answer the question, what is this stuff?

So it's kind of a due diligence question for me. I wrote, for example, what do we know about the thermal stability? I was even curious -- from the other end, they, apparently, have excluded the ones that have zirconium in them in Europe, I believe. And I looked and said, well, why? That zirconium's not coming out, so what's the problem? I often rail against pseudoscience because I abhor pseudoscience.

DR. MARKS: It's interesting, Ron, I had that initially. And then when I went back and reviewed, I felt the same. This is sand, even though it's not at the concentration use, I clinically didn't feel that it would be an issue.

DR. SHANK: That's fine.

DR. MARKS: Yeah. And my main, when I looked over at -- besides what you were talking about, Ron Hill -- is are we happy with the inhalation concerns that have been raised? Is there any issue?

DR. SHANK: There are a lot of studies, but most of those studies were designed to get into the deep lung. The particle sizes aren't given, but they did have alveolar effects. So, they're interesting from an inhalation toxicology point of view; but I don't think they relate to cosmetic use, because the exposure would be much, much different.

DR. ANSELL: We also have to be careful. They're looking at lung defects, but they're not truly inhalation studies. Most of them, to get these doses, were instilled.

DR. SHANK: Right.

DR. ANSELL: So, it's not really an inhalation exposure, per se.

DR. SHANK: Well, yes. The toxicologist put instillation in inhalation because, that way, they know they get it in there by ramming it down.

DR. ANSELL: Right. Yeah.

DR. HILL: But it's well to be thinking about that appropriately, because silicosis is a very real thing. And for somebody who was using fumed silica multiple times, on an almost daily basis, all the time, and be real careful how we handle it and tell the grad students how to handle it, we have to make sure that we --

DR. ANSELL: Right. It's relevant to hard rock miners.

DR. HILL: It's relevant to chemists working in labs, filling columns with silica all the time, every day, which, as I said, I was doing. So, 10 micrometer, 20 micrometer, all the time, with fines in there that are very -- go up into the air and that you don't breathe.

DR. MARKS: So, I think, for me, that needs to be explicit in the discussion, that the inhalation concerns are not relevant to the cosmetic use. Okay. I'm gonna go ahead, tomorrow, and move that a tentative amended report of these 40 ingredients, 17 previously reviewed and the 23 add-ons, are safe when formulated to be non-irritating. And we'll see if the Don's team has any concern about sensitization.

Point well taken, Ron Shank. It's a -- yeah. What can I say? I'm leaning, in that previous one, to say the clinical experience. Okay. And then, Ron Hill, you'll have comments. Okay. Let me go ahead and close this. Save it.

DR. SHANK: So what's gonna happen with this new --

DR. MARKS: Oh, we're going to -- oh, thank you. I should -- we're going to address that at the next -- at least our team is going to address it at the next meeting, unless you all want to take a few minutes and read it. But I think Christina or Bart are going to have to draft a response, just like Jinqiu has for another letter that we did get.

DR. SHANK: We could just respond that the panel will consider --

DR. MARKS: Yeah. But I think we have to go, as we've done in the past, point by point. And we'll look at that the next time. This is not the last time we see these ingredients.

DR. HILL: Right. So, in clarification, is this a draft tentative amended report? It just says draft amended report.

DR. MARKS: Just what I said, tentative amended report; which means it'll go on to the next edition, will be the final.

MS. BURNETT: We treated it as if it was a draft report. So, what it comes out of today would be -- if you feel that it's safe as used or --

DR. MARKS: Yeah. That's what I -- safe when formulated.

MS. BURNETT: It will be issued as a tentative amended report.

DR. HILL: So, the next iteration would be, essentially, a final amended report.

DR. HELDRETH: Next time you see it, it'll be a draft of the final.

MS. BURNETT: It'll be a draft.

DR. HILL: But if there was insufficiencies, it'd be a minimum of two more rounds?

DR. ANSELL: If there are insufficiencies, in a review, I would argue that the material should be removed. This is not a first iteration. So, if we've added materials, in which the data doesn't support them, then my answer would be that they shouldn't be in this report. Not that we need to find new data or materials.

DR. HILL: And that's why I asked the question, because how do I know today, when I can't answer the question, what is this stuff, for 15 ingredients that are in here? That's the point.

DR. HELDRETH: Yeah. If we do the assessment and we find that information is lacking, then certainly the assessment is already occurring and we should conclude that there's insufficiencies there.

It's at the discretion of the panel, that any specific ingredient, the review of which may otherwise be deferred, for whatever reason, shall nonetheless be included, at the discretion of the panel when other chemically related, or otherwise conveniently grouped ingredients, are considered. That's the way our procedures read.

DR. HILL: Read it again, one more time.

DR. HELDRETH: Any specific ingredient, the review of which may otherwise be deferred, should nonetheless be included at the discretion of the expert panel, when other chemically-related, or otherwise conveniently-grouped ingredients, are considered.

DR. HILL: But does that apply to amending reports? Or is that first --

DR. HELDRETH: That applies to any decision the panel wants to make. Basically, at its discretion.

DR. ANSELL: Yeah. But we can't move it to a final stage, because it's an amended, and then have materials, which there's a material deficiencies --

DR. HELDRETH: This is a draft report. It would go out as tentative if they give a conclusion. If there's insufficiencies, this would go out as an IDA.

DR. HILL: Okay.

DR. MARKS: Well, I'm gonna propose -- move that we send it out as a tentative amended report, not as an insufficient data notice. Good?

DR. SHANK: Okay.

DR. MARKS: Yeah. And then, Ron Hill, you can --

DR. HILL: I object.

DR. MARKS: Yeah. You can.

DR. HILL: But I don't think I'll be the majority opinion. I'm just -- I object.

DR. MARKS: Well, we'll find out. Let me go ahead and save this.

Full Panel Meeting – December 4, 2018

DR. MARKS: So, at the June meeting this year, we reopened a report from 2003, in which the conclusion of 17 silicate and clay ingredients were found to be safe. This amended report now would have 40 ingredients: the 17 that I mentioned we previously reviewed and 23 add-ons, of which 9 of those had already been reviewed. Our team felt we could move forward with a tentative amended report with a conclusion, safe when formulated to be non-irritating.

DR. BERGFELD: Is there a second?

DR. BELSITO: Trying to get to my --

DR. BERGFELD: Okay. We'll wait for you.

DR. BELSITO: We had some issues with respiration. And we thought safe as used when formulated to be non-irritating and non-respirable, with an extensive discussion of respiratory issues. I'll turn that reason over to Paul and Curt.

DR. BERGFELD: Paul?

DR. SNYDER: I don't recall the non-respirable component yesterday.

DR. KLAASSEN: The non-respirable really boils down to what is the size of the particles that do enter the respiratory tract. At one time, we were under the impression that they were all at least ten microns in size. But now there appears to be some information that there might five microns, at least when it leaves the nozzle.

Then the question is, do they agglomerate in the air on the way to the lung and become larger? It really is a problem of having knowledge about what is the size that we're really talking about here. It's not clear to me what it is. I think we need more information. Maybe the other team has a better handle on that than I do.

DR. LIEBLER: I think I might have been the one who floated the formulated to be non-respirable construct here. This reminds me, in a lot of ways, of the sensitization situation; where we have, for example, botanicals that we know contained a sensitizing ingredient, but may or may not be sensitizing, depending on whatever else is in the product formulation and perhaps some other conditions.

We can't really know that in all cases. We can point it out, but we want to put in the conclusion somehow, so we say formulated to be non-sensitizing. It's not that we're punting on the issue, but we realize that we don't have the data to anticipate what would be the circumstances with all of the individual products and their uses.

I think a similar situation applies to particles and inhalation. We're going to talk about the inhalation aerosol precedence in a few minutes. But it occurred to me that we're in a similar situation with the aerosols and particles; where we know that there's evidence that the distributions could include respirable particles.

What actually happens, in the product, as Curt just said, depends a whole lot on what else is in the can, or in the jar, and so forth. That's not going to be known by us, and we can't simply say it's safe or unsafe. It might be, and it might not be, it depends on the circumstances. So this seems to set up a circumstance where we might embrace a new construct, where we say formulated to be non-respirable.

It's not intended to punt on the issue; it actually highlights the issue. It essentially says to the industry, you're the people who put the silica, in this case, into your product, and you need to be aware that you could produce -- you are probably very particular about the specifications of the silica, that you order from suppliers to put into your product; but you probably need to be aware of what the particle size, and the potential for respiration of these particles, will be in your product. That's the logic behind this idea, formulated to be non-respirable. I guess, I'd better quit repeating myself.

DR. BERGFELD: Tom.

MR. GREMILLION: It's not clear to me what would be meant by formulated to be non-respirable. Would that mean like an absolute prohibition on particles less than ten microns?

DR. LIEBLER: That's impossible. Because these distributions always contain a tail that include the small number. This is something that perhaps we need to talk about more, what that might be in practice; maybe that goes into the precedence document. Is there a percentage less than ten microns, for example, that might be a useful guideline? I think practically speaking, Tom, the idea would be, the amount that would be respirable needs to be below the amount that we could reasonably anticipate would produce an adverse response in the lung.

MR. GREMILLION: I guess, how would cumulative effects play into that? Because if a lot of different manufacturers have products that, on their own, aren't making -- or contributing to an adverse effect, but people are using multiple products that have small respirable quantities, since together they could produce an adverse effect. I wouldn't know how to calculate that if I was a manufacturer.

DR. LIEBLER: Right. And the manufacturer, in that case, couldn't necessarily anticipate that Ms. Smith is using this face powder, and this spray, and this other thing; whereas, Ms. Jones is only using the face powder. That's almost beyond our purview.

If we, again, go back to the example of the botanicals and sensitization, we can specify, within a particular product, formulated to be non-sensitizing, to avoid stacking up sensitizing ingredients to a level that produces a response. But I don't think that really addresses the possibility that using six different botanical products, over the space of time, couldn't produce a response. In other words, I think there are just some things that are just beyond our ability to control.

MR. GREMILLION: I guess with the sensitizing, it seems like that's not analogous because it's either, there is a reaction or there isn't. But with something respirable, it's like you have to have a lot of something to cause an adverse reaction from breathing it in.

DR. LIEBLER: Both of these phenomena are dependent on exposure and dose.

MR. GREMILLION: I see that in very broad terms, but it seems kind of like a qualitative difference between sensitizing and respirable.

DR. HELDRETH: As it's clear, this would be a new type of conclusion that the panel's putting forth, and that's certainly the panel's prerogative to do that. However, historically, I think the way that we would have handled this, in a conclusion, is to say safe with whatever qualifications for other uses, but that the data are insufficient for use in things like sprays and powders.

DR. MARKS: I'd like Ron, Ron, and Tom to address it. Our team felt that -- at least, if I interpreted our discussion correctly yesterday -- was the inhalation concerns were not relevant to cosmetic use. Did I get that right as the bottom line?

DR. SHANK: Yes.

DR. MARKS: So, after this really robust discussion and concern about sprays and such for cosmetic use, I don't know whether, Ron Shank, you want to address why we felt that that wasn't a concern?

DR. SHANK: The inhalation toxicology data, in the report, was aimed at looking at these silicates into the lung purposefully. It wasn't the kind of study that would apply to cosmetic use. On the other hand, rather than putting that into the conclusion, that they're formulated to be non-respirable, we have to see what the boilerplate is going to be for aerosols. Because that's how we've usually handled it in the discussion, that the use is infrequent and, for the most part, large particles which are not inhaled. We've now put it into the conclusion.

If we start -- first, we add the formulated to be non-irritating; now, formulated to be non-irritating, formulated to be non-sensitizing. Now we're going to go, formulated to be non-irritating, non-sensitizing, non-respirable. Two years from now, we're going to be formulated to be nontoxic, and then we can all go home. I don't want to be facetious.

DR. LIEBLER: Ron, you're messing with my plan. I really wanted to get home.

DR. SHANK: I think it's dodging the issue. We've done it with non-sensitizing because it's usually been mixtures, where you have botanicals; and you have so many things it's hard to pick on any one chemical within the mix. Dr. Belsito explained the non-irritating. That's strictly formulation dependent. That makes sense. I think, I would rather handle this in the discussion and not put a restriction in the conclusion.

MS. BURNETT: If it helps the discussion at all, the original discussions for the 2003 silicates report, and the 2009 silica report have a respiratory component to the discussion section. If you want to look at that language, that's PDF Page 92-93, if any of that language can be reused or amplified.

DR. BERGFELD: Ron Hill.

DR. HILL: I still think that Dr. Liebler's idea is worth some serious and strong consideration, first of all. Second of all, the definition of respirable is a little bit shaky. I mean, we have some idea about that; however, in principle, with these given the idea that we are talking about solid particulates, I presume in all cases, at least we have an idea of what we're talking about. We're not talking about evaporating droplets, except as maybe in propellants, for example, in a pump spray.

My fundamental problem with this report, as it sits right now, is we've got 13 new ingredients in there for which I can't answer the question beyond the basic dictionary description, what is this stuff? I think that if we're doing an amended report here -- and I asked the question yesterday, is this an amended report or is it a new report, because we've got a number of ingredients that we can't answer the question, what is this stuff? So for me, until I get answers to that, it's insufficient on all of those that we don't have those answers.

Because that relates to, it's a difference between crystalline silica versus amorphous silica with fine (phonetic), versus the sorts of things that we actually see in cosmetic ingredients. Those are three different forms of silica. Again, I mentioned that as a chemist working many years, where almost on a daily basis, I was filling silica columns where we had to be very sure not to breathe those fines; that was a very different situation than in a cosmetic ingredient. In most cases, we know if it's face powder, they already present as higher agglomerates; there's not going to be fines in there and we don't have an issue, speaking to the cumulative problem.

But we've had a lot of discussion. We had a very robust, long discussion about the respiration issues, yesterday, to which we in the end didn't come with any firm conclusions other than some lack of information that we still need.

DR. LIEBLER: I just want to say this one thing. My inclination, originally going into this was right where Ron Shank is, that these are not respirable. But then I'm faced with the issue of saying, because why? What are the data that support that assertion, that that's not relevant to cosmetic use? That's where I felt I was tripped up. That's why I'm searching for an alternative way to deal with it.

I think you could also handle this in the discussion. If you wanted to say safe as used but, in the discussion, very clearly point out the issues and the unknowns, and the fact that this is something that manufacturers would need to take into consideration in the formulation, I can live with that too. But as again I was struck by the similarities, even if they're not complete to the formulated to be non-sensitizing, and that's why I made this suggestion. So, I'm glad we've had some discussion about it.

DR. BERGFELD: Paul and then Don.

DR. SNYDER: First, I'm going to qualify by saying, I'm not an inhalation toxicologist. But my comments are related to the fact that inhalation toxicity can be localized. It can be in upper airways, it can be all the way down in the respiratory tract. The issue with respirable particles is that they get deep into the lung, and now we have a different relative exposure for potential systemic toxicity, that may be different than oral, than pharyngeal, other mechanisms by which there could be exposure.

So, I think we're kind of -- we're not fully understanding the toxicology. And, Curt, maybe you could elaborate on this more. So, the physical properties of the formulation drive where it's going to go, and how deep it's going to go. It's not chemistry, it's not biology, it's just the physical properties of a thing. So we've always used that as a basis to be safe, to be confident that even some incidental exposure through discontinuous use or whatever, is not likely going to result in any significant toxicity. I think that's very different than saying non-respirable.

Because all of a sudden, now, if we have a conclusion that says non-respirable, because it has an aerosol use, all previous report that we've had aerosol use, and we don't have non-respirable in there, are now not compliant with use, right? I think that really opens up a huge can of worms, that I don't think we need to open. Because the old reports clearly state we had data to support that they're non-respirable; and we're not concerned about systemic toxicity from being respirable.

DR. BERGFELD: Don and then Curt.

DR. BELSITO: Just looking how we handled it before, the final sentence, in the discussions, said that the panel considered that any spray containing these solids should be formulated to minimize inhalation. It's almost like a restriction that could also occur in the conclusion.

I guess my concern -- and I brought this up with Alexandra yesterday -- is that -- and I'm, again, not a respiratory toxicologist, nor am I a spray physicist or physical engineer. But I think we've been operating under the assumption that there are hairsprays and there are pumps. Now, we're being told they are different types of delivery systems. There's some spray tanning delivery system that's different. There's liquid spray make-up that's different. And we don't have any idea what the range of particle sizes that those would deliver.

One of the things that I asked for, was that we have someone come to the panel, who understands spray delivery systems, and tells us a little bit about, you know, okay, here's the average particle size from an underarm deodorant pump. Here's the average particle size from a hairspray. We could maybe get to this issue by understanding what type of delivery system is most likely to generate the smallest number of aerodynamic particles.

I think that our assumptions that there are just two types of sprays and, you know, pumps deliver a larger aerodynamic sized particle than a hairspray, there are other spray delivery systems that we don't have information about.

DR. HILL: And the other --

DR. BERGFELD: Curt and then you can comment.

DR. KLAASSEN: Well, I think we've discussed most of the issues here. I guess I would -- the bottom line here for this report, I think, I would be more in agreement to keep it the way it was in the previous addition; that is emphasizing the possibilities here, but not putting it in the final conclusion.

DR. BERGFELD: Tom and then Ron.

DR. SLAGA: I agree with Ron Shank and Curt. I think we have to go on what we did before. And just have that, and maybe add a little bit more to the discussion that there is some little concern. But I would not put in the conclusion.

DR. HILL: Yeah, I was just going to point out, again, that one of the chronic -- no pun intended -- issues that we have, is making sure that we distinguish between solid particles of things like zeolites and the like, silica, and liquid droplets that have compounds in them. Sure, they may become solid briefly, as they're flying through the air and the solvent is evaporating, but can redissolve in the lungs; and we have -- well, we don't have any toxicology related to that.

It seems like in all these discussions of particle sizes -- and I mentioned, although technically, there is no reason that when I think of a droplet, I think of liquid, when I think of particle, I think of as a solid, which is actually not accurate, you could have a liquid particle. But anyway, we have this muddling of things.

In this particular ingredient set, I presume, we're dealing with things that are solids across the board. So, I want to go back to this particular ingredient and make sure we're thinking in that terms. Again, we have 13 things in here where all we have is the description and still no, what is this substance? So, I don't know why we're not insufficient for getting information about the properties of these compounds.

DR. BERGFELD: Thank you. Dr. Marks, you had a motion with not seconded. You want to --

MR. GREMILLION: Could I ask. There's this letter from the Women's Voices for the Earth that --

DR. BERGFELD: We're going to address that under aerosols. Thank you. Do you want to propose a motion?

DR. MARKS: I'll address the letter in a minute. I want to get to the discussion. I'll repeat the motion that our team proposed. That's that this is a tentative, amended report, 40 ingredients with a safe when formulated to be non-irritating conclusion.

DR. BERGFELD: Is there a second? Seeing none, is there another motion?

DR. BELSITO: I like Bart's idea of saying the data is insufficient to determine the safety for products that could be inhaled. I'm still very concerned that I don't understand the technology of sprays, and the size of particles that can be delivered.

DR. BERGFELD: Is there a supporting motion for this, go insufficient?

MS. BURNETT: It would have to go as an insufficient data announcement with what you need specified.

DR. BELSITO: What we need specified is the range of particle size in products that are used in sprays and face powders, that one would expect in terms of how these are being used.

DR. BERGFELD: Would you need the delivery systems?

DR. HILL: If you're asking for range of particle size, that would be implicit as far as I'm concerned.

DR. BERGFELD: Okay. All right. So, the motion has been restated. Is there a second?

DR. MARKS: I want to hear Ron Shanks comment.

DR. SHANKS: I think the issue of inhalation toxicity with these ingredients can be handled in the discussion, as we did before, and not in the conclusion. We all agree it is a concern, and I think it is how to state the conclusion. If we start putting it in the conclusion now, then we have a huge back load; every time there is a spray or aerosol, we're going to have to put this into the conclusion, because we don't have a lot of data for every ingredient. That's why we have this precedent document that discusses this in great detail. Particle size is not the only thing that determines pulmonary exposure.

DR. LIEBLER: I'd just like to say that I appreciate my collegues' thoughtful consideration of my suggestion. I think that it's not going to fly, and I've heard a lot of good reasons why it probably shouldn't. I still think the choice between us right now, is whether to say safe as used, and we'll try and craft the discussion to deal with it; or whether we should say insufficient, at this stage, for this report, and see if we can squeeze out more information that could end up helping us inform our discussion later on anyway. So, that's why I kind of lean in the direction that Don is proposing, at this point.

DR. BERGFELD: Is there a second to Don's motion?

DR. MARKS: Second. I'll withdraw our team's initial motion.

DR. BERGFELD: Well, it wasn't seconded, so it did not go forward. So, we're going to have any other discussion? You want to know --

MS. BURNETT: In addition to the range of particle size, for products that are sprays and powders, what additional items would you like in the IDA?

DR. BERGFELD: Do you want to request a characterization of the chemistry?

DR. HILL: I do want information about these ingredients.

MS. KOWCZ: Can I just make one comment?

DR. BERGFELD: Yes. Alex.

MS. KOWCZ: Well, we just really want to know, exactly, what is the ask from the panel?

DR. BERGFELD: Christina has the list, we'll let her read it.

MS. BURNETT: Range of particle size for products that are used in sprays and powders. And chemical characterization of the new add-ons.

DR. HILL: The ones for which we don't have data, new or existing, honestly.

DR. LIEBLER: So, chemical, physical properties is thin, it's just silica and hydrated silica; it's none of the zeolites, for example. Method of manufacturing is just silica and hydrated silica. Those are synthetically produced. I don't know, is everything synthetically produced now? Or is some of it mined? Composition impurities, again, is just silica. This is a big report with a lot of ingredients, and we've got just the tip of the iceberg.

DR. HILL: Well, this particular report, that was an issue I had yesterday, is relying on four or five previous reports. There's a significant number, I think, they're referencing, but it's not really brought in and captured. What I wrote in here was there were a lot of x's in the box, indicating we had data that don't directly show up in this report.

So really, some way of doing data capture without having to bring over all the language and all the information from those previous reports. I mean, we're relying on those. And whether information exists in the previous reports, just at some -- I don't know if there's any way to briefly summarize, in a table or something, to indicate what's there in the previous report so that the reader could at least use this in some self-contained fashion.

For the new ones, where we don't have information -- and there are things that are mined. There are zeolites that are mined, there are clays that are mined, there're things that are not synthetically produced, but they may be processed. I don't necessarily know what that processing is, honestly, in each of those cases. But at least some sense of what the composition of the things are, and maybe the source, if it's applicable.

DR. BERGFELD: So, a clarification on this request; physical chemistry of the unknown ingredients, are we adding methods of manufacturing impurities since we're asking?

DR. LIEBLER: Yes.

DR. BERGFELD: Anything else?

DR. HILL: Let's see what we get. If we don't get it in some case, and we decide if it's important or not.

DR. BERGFELD: Okay. And then just an editorial that we go back and tabulate all those previous studies for this document. Okay. Don and then Monice.

DR. BELSITO: Just to point out, I went back and looked at concentrations of use. For instance, silica, in an underarm deodorant, can be used up to 10.4 percent, which is not a negligible amount. And we know that underarm sprays will have lower aerodynamic particle size.

MS. KOWCZ: Can I just mention that these are amorphous-hydrated silicas, the ten percent that you're talking about. So, it is dissolved in the formula.

DR. BERGFELD: Thank you.

DR. BELSITO: That kind of information can be brought into the document?

DR. HILL: We have had past presentations on that, but then the situation is different. If it's in a spray, the particles can potentially evaporate, versus it's in a solid underarm deodorant.

DR. BERGFELD: Okay. Monice?

MS. FIUME: Just to clarify for the information on the particle size and for the ingredients; and, Alex, maybe this is what you were getting to. Is it all ingredients that are used in sprays; or are there specific ingredients from that list that you would really like to see the particle size information on? Is there more concern for some than others, or all that are used in sprays or powders?

DR. LIEBLER: I think we should ask for all that are used in sprays and powders. That maximizes our opportunity to get relevant data.

DR. BERGFELD: Thank you. Any additive remarks?

DR. MARKS: Yes. Yesterday we were given a Women's Voices of the Earth letter. Our team decided not to review that letter yesterday. We postponed it until the next meeting. It did elicit some discussion of getting Wave 3, Wave 4, and Wave 5's, at very short notice, and being able to review those thoroughly and think about our responses. I just bring up that point about yesterday. Don, I don't know whether your team felt comfortable reviewing it, but our team did not. Team members, do we have any other comments? Ron?

DR. SHANK: No, I think that the CIR can respond immediately; but I think the panel needs some time to consider how we want to respond. And we haven't had enough time to do that.

DR. BELSITO: Well, I think we discussed it, which is part of the reason why we've come to this conclusion, that we need time to digest what she said and to get a better understanding of particle size in these sprays. So, that was our response to this letter, that at this point we're going insufficient. We will consider her points and come back when we relook at the document.

DR. HELDRETH: On our end, we will make sure we respond to her and let her know exactly what we're doing. Then the next iteration of this report, when it comes back to the panel table, will have this letter and our summaries in there. And any input we get from others about the content of the letter will be included there as well.

DR. MARKS: And then the only other comment I had -- and, Don, you can respond to this if you want. There was little sensitization data with Kaolin used up to 53 percent on leave-ons, and silica at 82 percent on leave-ons. But there's no alerts in the clinical literature that would suggest these are significant sensitizers. So, I felt we could move on and not be concerned about the sensitization of these ingredients.

DR. BELSITO: I agree.

DR. BERGFELD: Paul, did you have something to say? I'm going to call the question then, to move the question of this is going out as an insufficient data announcement. All those in favor? Unanimous. All right. Thank you for that, again, very robust discussion.

APRIL 2019 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT/TABLED
Belsito's Team Meeting – April 8, 2019

DR. BELSITO: Okay. Silicates. We've got a lot of information and I thought it was okay, but it's not my area of expertise. We asked about molecular size and we got all these graphs, M, N, R, P, Q, which were 10 microns, but

then we're told that became agglomerates and it gets to larger than 100. And I just looked at them and said okay. I'm not concerned about them with skin, so I pass all of this discussion on to you three.

DR. LIEBLER: So going to those pie charts, a lot of those pie charts said that -- up to 50 -- did I read it right? Up to 50 percent were less than five microns?

DR. BELSITO: Yeah. But those were like all the original ones. And then we get this thing at the end that says, okay, that's their particle size. But then when they're put together, they agglomerate and they're all greater than 100 microns, is the way I read it, but I'm not sure. Again, as I said, it's not my area of expertise. So maybe we can have some comments from --

DR. SNYDER: And then also the grouping, because he mentioned the amorphous -- synthetic amorphous, synthetic silica aluminates, crystalline and then natural. I mean, what are the major groupings in this report? Do you have access to our document?

MR. JURD: I'm not sure which. Are you looking at like the phase three, the one that came through?

DR. BELSITO: We're looking through the CIR document.

MR. JURD: Yes.

DR. SNYDER: So we have a whole list here from activated clay all the way to zirconium silicate. And so if you look at that list, what are the high-level classifications that would capture all of those?

MR. JURD: I'm not sure about how they were lumped and how everything was kind of laced together. I can tell you, like synthetic -- I mean, there's a big difference between the synthetic versions and naturally occurring. So synthetic amorphous silica is created from primary particles; very, very small in size. They agglomerate and then aggregate. So, once they get to the larger size, it takes a tremendous amount of energy to separate those.

What the materials that are put on the market, for the most part, are larger particles, you know, between I'm going to say 10 and 80, 90 microns, type size, not in the nano range. The primary particles are typically in the nano range. There's a lot of focus on that in other areas, but those do not typically exist, or in large, easily measurable -- one of the difficulties the industry is having right now is actually measuring materials at the very, very small level.

And a lot of this is due to the definitions that are out there by a lot of various regulatory agencies looking at, you know, what defines material like nano in Europe. Silica, by at least one group, has been defined as nano structured, not a nano material, because it's composed of lots of little small things glued together.

DR. LIEBLER: So are silica and hydrated silica the only synthetically produced ingredients on our list, which on our document is PDF page 93?

So our methods of manufacture section, which is right after this, is at this point somewhat incomplete. And it does indicate that those two, silica and hydrated silica, that are used in cosmetic products are synthetically produced. But it doesn't give much information about the production of any of the others.

MR. JURD: I know for a fact that a lot of these are synthetically manufactured. We manufacture ourselves a lot of the silicates, sodium, the magnesium aluminum silicate is synthetically manufactured, along with a number of the other ones, potassium silicate. Not that I'm aware of, or anybody that I know of, has informed me that they're used in cosmetic products, but they are -- they can be synthetically manufacturing.

DR. LIEBLER: So two of the issues that we have to deal with are the particle size, and the control of contaminants. And of course, particle size and control of contaminants are under full control in the synthetically produced materials. But the materials that are mined and then worked up somehow are not, or not as controlled.

And there are some of those on our list, I would imagine things like Fuller's Earth and activated clay and zeolites, although I don't know for sure.

So we have really inadequate information to assess whether these all go together in the report, just from the standpoint of how they're produced.

DR. BELSITO: That's one of the issues that Women's Voice raises in their last paragraph.

DR. LIEBLER: Right. And the other issue about the mined material versus the synthetics are that the mined materials may contain some crystalline silica. I think you mentioned that earlier.

MR. JURD: That is -- it depends on the purity, where it is and --

DR. LIEBLER: Exactly. That's much harder to assess and control, but it's an issue that we need to be concerned about for safety. And so, you know, there are a number of other points made in this memo to Bart from the Science and Support Committee that I'm not sure I agree with, but it sure would be good for us to have enough information to make some judgments about which things actually go together in the report based on the composition and character, physical chemical characteristics of the ingredients, relevant contaminants that are particularly health concerns. And once we have that information, then perhaps we can take a swipe at the issues that are raised in this memo.

So, that's something, at least as a representative of industry, maybe if you can help disseminate that information back. Because I think our description of method of manufacture for these is really incomplete to the point that we can't make the assessment we're being asked to make.

MR. JURD: We can provide data based on what our members actually manufacture.

DR. LIEBLER: Correct.

MR. JURD: I can't go beyond that.

DR. LIEBLER: Well, that's all we care about. That's all we care about because those are the cosmetic ingredients. So silica products that are used for things other than cosmetics we don't care about, and we don't need to know that. But we do need to know about the ingredients that are used in cosmetics.

MR. JURD: We can definitely provide information. I think you've got almost everything on the silica, with some of the other reports. I don't know if that's a true statement. I mean, you might have to confirm for me.
We definitely have good contamination materials, you know, byproducts, impurities. Most of the impurities come in low levels of metals, primarily, from sodium silicate or sulfuric acid. Silicates, pretty much the same thing; low levels of metals, very, very low. And then leftover raw materials, sodium silicate, that sort of thing.

MS. BURNETT: Some of the method of manufacturing is in original report. Since this is an amended -- reopened amended -- review. The clays, it talks about being strip mined.

DR. LIEBLER: But the original report wasn't published.

MS. BURNETT: For silica and hydrated silica, this is --

DR. LIEBLER: That wasn't published.

MS. BURNETT: Yeah. So that one wasn't published. But if you go to PDF page 155 from the 2003 silicate report, it also includes like kaolin and attapulgite.

DR. LIEBLER: Zeolite.

MS. BURNETT: Bentonite.

DR. LIEBLER: Because many of these things are still used, as our survey indicated. Yeah, the method of manufacturing, the current report suggests that there's not much known, and there's actually a lot known.

MS. BURNETT: I can pull that --

DR. LIEBLER: So we need to somehow find a way to bring that in, or at least to summarize it.

MS. BURNETT: I will make sure I pull that in.

DR. LIEBLER: Okay. It could be another table.

MS. BURNETT: Okay.

MR. JURD: I guess what might be a little bit confusing, too, is most of the synthetic silicates, along with synthetic zeolites, you have naturally occurring forms too. You're running into that, I think, across the board. Whether or not naturally occurring material is used for the same sort of applications, I don't know.

I mean, zeolites is a really good example. You know, there's a lot of those manufactured for a broad range of uses. And they're lumped into a general category. I mean, zeolites are defined by the EPA as a statutory mixture. So, silica alumina, cations and anions; so it can be literally hundreds of different types of materials, which can be a challenge.

DR. LIEBLER: So in the current report version, kaolin and magnesium aluminum silicate are listed as containing quartz or crystalline silica. I don't think I'm overlooking any others, unless some of these mineral names are also crystalline silicas but don't explicitly indicate so.

So that's an issue we'll need to address by knowing the levels of impurities to be able to deal with it in our discussion.

DR. BELSITO: But we've done it. So that's an insufficiency.

DR. LIEBLER: Right, yeah. I'm putting this in legal terms. But yes, it's --

DR. SNYDER: So, essentially, we still have the same data needs that we had originally.

DR. BELSITO: Well, we need particle size for silica and silicate, don't we?

DR. SNYDER: Yeah.

DR. BELSITO: Do we need more data on that?

DR. SNYDER: I was thinking more of the composition and impurities, Dan’s point.

MR. JURD: For the silicates?

DR. BELSITO: So, basically, we get rid of the first request, which is particle size, for silicate and silica ingredients that are used. We asked for hairspray and powder formulations. We really didn’t specifically get that. We got particle size, but not for hairsprays. And we're still not done with the respiratory boilerplate, because we didn't sign off on that. Right? So how do we handle that? We really don't have the first data need either.

DR. LIEBLER: So it sounds like we have some of the information we need. It just needs to be brought into the report from the previous reports and isn't here yet.

DR. BELSITO: No, we don't have impurities or chemical characterization. We have method of manufacture, which is pretty crude. Bentonite, mined ore bentonite, is processed to remove grit and nonswelling materials.

DR. LIEBLER: Right. But Christina just told us that the previous reports have a lot of that in --

DR. BELSITO: I'm reading the prior report. This is page 155, Method of Manufacture, from the prior report. It has data in there. I mean, it has stuff in there. But are you satisfied with, "The mined ore bentonite is processed to remove grit and nonswelling materials"?

DR. LIEBLER: No.

DR. BELSITO: That's what we have for bentonite.

DR. LIEBLER: So we're still insufficient. Okay. Fair enough.

MS. BURNETT: Dr. Liebler, could I ask you, on the data that we received from SASSI, all those different graphs, should that be brought in the report? And if so, what would be a good way of presenting that data?

DR. LIEBLER: I think those data could be presented in the form of a few sentences.

MS. BURNETT: Just a few sentences.

DR. LIEBLER: Because first of all, those particle size distributions -- actually, as I recall, they don't name a particular silica form, do they?

DR. BELSITO: No, they're A, B, C, D, M, N, P, Q, R.

DR. LIEBLER: So just Product A, Company B, and distributions. So what you could do is indicate that industry reported X silica particulate size distributions that ranged from -- medians ranged from X to Y. Or the median was X and the ranges were from A to B. And that's about all you can report. And if we can't associate these with any particular silica forms for any of the ingredients in this report, that's all we can say. It becomes a piece of information that's worth a couple sentences.

MS. BURNETT: Thank you.

DR. BELSITO: So this was a draft tentative amended. So we're now saying that we really got none of the data that we asked for, except for some particle sizes on silica and silicate, but not as used in sprays and powder formulations. But then we heard that when they agglomerate it would take a tremendous amount of energy to separate them.

So, I guess if we combine that statement, we could say that they're not respirable. Could we?

DR. LIEBLER: So they're mostly not respirable. I mean, based on those distributions, it appears that they're not, because the --

DR. BELSITO: Even the small ones will agglomerate, we're told, to over 100 microns. Because some of them, you know, M, N, R, P, Q, were 10 microns.

DR. LIEBLER: Right. Yeah. My impression from looking at that summary was that they were referring to the particle size distributions of the final reduced particles which are already agglomerated. So you get --

DR. BELSITO: Is that true?

MR. JURD: That's -- yes.

DR. LIEBLER: So you get the precursor molecules. They aggregate into aggregates. And then aggregates form agglomerates or agglomerate. Right?

MR. JURD: Correct.

DR. LIEBLER: So aggregates are small-ish, agglomerates are bigger. And that's the final form of these prior to incorporation into any cosmetic formulation.

MR. JURD: Correct. Yeah, you can break apart the smaller pieces without -- well, some amount of energy is required. But once they are at -- form the larger particles?

DR. LIEBLER: Right.

MR. JURD: They're pretty robust.

DR. LIEBLER: Too many bonds.

MR. JURD: Right.

DR. LIEBLER: Too much energy.

MR. JURD: Right.

DR. LIEBLER: Whereas the small particles are smaller, and there's less energy.

MR. JURD: But these all are, you know, the way that it happens, we can't discount that there isn't a tail of smaller material.

DR. LIEBLER: Well, that's what I'm referring to also. It's almost entirely not respirable, but a tail is a tail; and it includes, you know, an indeterminate number -- well, not indeterminate. You can estimate the percentages.

DR. BELSITO: So then, when we're looking at -- like on our PDF from Wave 2, page 73, where we have a distribution curve, and the particle size seems to be peaking at around 7.5 microns, that is what's actually being supplied to the manufacturer?

Or does that further agglomerate and what's being supplied to the manufacturer is going to be over 100 microns? Because my understanding of reading further on was even these smaller ones will aggregate to larger particles. But are you now saying that whatever sample R was, was nanometers, and it's aggregated up to 10 microns?

DR. LIEBLER: No. If you -- I'm paging up in this document, past all these particle distribution graphs, to the text -- or there's a figure that shows the process?

DR. BELSITO: Yeah.

DR. LIEBLER: I remember seeing a figure for -- I think it was the nanoscale material, voluntary submission --

DR. BELSITO: Was it figure three, structural difference -- no.

DR. LIEBLER: The voluntary submission document. Ah, it's in -- hang on. Just scrolling through it.

DR. BELSITO: Wave 2 or?

DR. LIEBLER: It's in Wave 2, the Wave 2 document. I'm getting close.

DR. BELSITO: Is it page 91, reactor feed?

DR. LIEBLER: Yes. Yeah, page 91. So I'm assuming from the description -- so page 91, the figure 1-4 for is the general structure development sequenced during SAS manufacturing and reactor feed has the precursor molecules that form nuclei, which are individual molecule particles, which form primary particles, five to 50 nanometers, which then form aggregates. And that little purple cone shows that that's all happening within the spray zone, I guess.

And then I interpreted this is that these aggregates are forming the agglomerates as the aggregates are being formed. And this is all happening in the reaction vessel, and that it's not happening as --

DR. BELSITO: But some of the agglomerates are less than 10 microns.

DR. LIEBLER: Yeah. One to 250 microns, it says there.

DR. BELSITO: Right.

DR. LIEBLER: And our particle size distributions go down to about one before they appear to zero out.

DR. BELSITO: Right.

DR. LIEBLER: And then the one you just pointed to have a median of --

DR. BELSITO: 7.5 almost.

DR. LIEBLER: Yeah. Anyway, so --

DR. BELSITO: So these are small, even when they agglomerate.

DR. LIEBLER: Yeah. But that's the version of the particle, that's one of the smaller ones. Because some of these --

DR. BELSITO: I understand, but we don't know whether that particle is used in or in a pump or spray. We don't know what the particle is. So then --

DR. LIEBLER: The other unknown is when you put it into a cosmetic ingredient, if those agglomerated particles form anything larger, by combining with other ingredients in the formulation.

DR. BELSITO: And then how strongly do they agglomerate. And then what happens when you spray them out of a hairspray or whatever other sprays they're in?

DR. LIEBLER: Yeah, we don't really know --

DR. BELSITO: So, in essence, all of our data needs that we had asked for before are still unanswered. Because we now know that some of the agglomerates are down to 10 microns. And we also know that we don't know anything about what happens in terms of those that are used in sprays and powders. We don't know which ones are.

And then the next question becomes all the ones that are naturally mined, like bentonite and clay, do we keep those in the report? I mean, this is this is WVE's last question to us. Is this grouping correct?

DR. LIEBLER: I think it's a fair question. I don't know how much better characterization of those we'll have to allow us to make that determination. We've been reporting on these for years.

DR. HELDRETH: Right. So, just looking at this and looking at the history of this, we had ingredients like Fuller's Earth, and, you know, sodium magnesium silicate, already in the original report together. And it's time to review all of those ingredients again.

So really it comes down to two options, if we want to start splitting things up, if we can figure out which one's go in which report, or split them up within the report to make sure that there's clear margins between them saying, you know, we don't want to look at these together. So, I mean, either option --

DR. LIEBLER: These might be like algae.

DR. HELDRETH: Right.

DR. BELSITO: Red, brown.

DR. LIEBLER: Yeah. But I mean, we have -- it sounds like we may have a significant enough repertoire of synthetically produced silica ingredients that might constitute a report on their own, for which -- well, we'll at least have the data on method of manufacture and composition and --

DR. BELSITO: Particle size.

DR. LIEBLER: Particle size. We won't set aside the issue of is the particle size a posed risk or not, because it sounds like that might be one that's going to be hard to definitively determine. But then we will separate out the synthetically produced materials, which have certainly greater certainty about their composition and impurities --

DR. BELSITO: Well, if we could separate those out, or basically take the silica and silicates and anything that you think is actually related, could we not come to a conclusion even in the absence of our data request for aerosolized, just as we do with sensitization, since we know that some of them are down to respirable range, and some are well above respirable range.

DR. LIEBLER: Right.

DR. BELSITO: Something to the essence that, you know, should be formulated not to be respirable.

DR. LIEBLER: Respirable, yeah. I think we may have to do that, because the one other thing that those distribution figures show us is that there's a great variety. There's, you know, ten-fold variations in the median particle size, and the low-end tail is going to be dramatically different for the respirable fraction, between these different particles. And that's before you even put it into a cosmetic product with other stuff in it.

DR. HELDRETH: So that would constitute a new type of conclusion for the CIR Expert Panel to say, "when non-respirable." Comparatively, though, other types of conclusions that the panel has come to often look more towards to the product itself. So maybe we don't have enough information to say anything about an aerosolized product, or a spray product, or a powder project.

And so it may be easier for a formulator to read the conclusion of the panel if we're saying we don't have enough information and say it's safe --

DR. LIEBLER: So the data were insufficient to support the safety in sprays or products in which these ingredients may be respirable? Or sprays and -- powers and sprays. They're all powders and sprays.

DR. HELDRETH: Sprays or loose powders or whatever ones you think where the immediate problems.

DR. SNYDER: We don't know that it's insufficient; we know if it's less than 10, they're respirable, and certainly a hazard if you inhale these.

DR. BELSITO: Right.

DR. HELDRETH: I mean, we just talked about how now we have to write a -- you know, something to explain what we mean by non-sensitized, nonirritating --

DR. SNYDER: I get your point. And it sort of gets to -- both are similar responses to the problem. One requires us to introduce a new type of conclusion that we haven't used before. And the other allows us to use a type of conclusion we've used**.**

DR. BELSITO: We're told they are used and pumps and sprays. Okay? And I think we're also told that there are some of them out there where even before they go into finished products, they're greater than 100 microns.

DR. SNYDER: Less than.

DR. BELSITO: No.

DR. SNYDER: Oh, greater than.

DR. BELSITO: But there are also others that are greater. And if it's those that are used in pumps and sprays, we're not concerned. If it's the ones that are 10, we are, potentially, right?

DR. LIEBLER: Correct.

DR. BELSITO: So we have data to suggest that some of them can be used. Just as with irritation, we have data that when you take an acid and you neutralize it, it's okay. So if you put salicylic acid at 20 percent, but then you neutralize it down until it's all a salicylate salt, we don't really care. So, you know, "formulated to be non-irritating" is something we came up with, because we realize there are so many variabilities.

So when you're looking at this, you know, I don't think the data are totally insufficient to say that they can't be used in, you know, in a product that could be respirable, you know; because some of them can be, based upon the assumption that -- I mean, if you look at A, B, C, D, E, F, I think you get up to M before you get them dropping down into a respirable range.

So, I mean, there are 12, 13 right there that could easily be used in a product that is a pump or a spray. And then you get M, N, P, Q, R, which could be an issue.

So I would actually feel more comfortable saying that there are silicas, silicates out there that aren't an issue and there are others that could be. And therefore, "when formulated to be non-respirable" is a reasonable conclusion. Because if we say insufficient, you know, then a company that is using these, and they're using one that has a diameter above 100 is, you know, in two years in trouble, right?

DR. LIEBLER: Yeah, no, I mean, I agree. So, doing what you were suggesting, Bart, just floating the idea out there, that would essentially exclude perfectly reasonable products -- or perfectly reasonable ingredients for use in pumps and sprays. And really, what we need to do is in pumps and sprays, or other potentially respirable products, is reduce the respirable particles as ingredients.

So, just because we haven't ever done that conclusion before, doesn't mean we can't. There's a point at which we hadn't done formulated to be non-sensitizing, and we did it for the first time. So --

DR. SNYDER: My preference would be that we get some data, because we can have an old report that states these are all safe, even in sprays, because they're a particle size not respirable.

DR. BELSITO: But now we have data that shows --

DR. SNYDER: But now we have new data, so that's all a wash. That goes away. But what we don't have is we don't have the distribution, those tails and whatever it is, because there's no doubt that even a small amount of this material in the lungs is going to cause fibrosis and an adverse reaction.

So even though we have this distribution data, we don't have what -- those tails. You know, even in the products, how much is that? Is that one percent, five percent, ten percent?

And so I think what we need to have is we need to have very specific composition data on all the ingredients that are used in the spray and aerosolized products, period. And we cannot make any determination of safety unless we have that. And so --

DR. BELSITO: Even if we put the caveat "when formulated to be non-respirable"?

DR. SNYDER: I know what Ron is going to say. He says, why don't we just write a simple conclusion, when nontoxic, non-respirable, non-sensitizing. And so I think we can do a better job than that.

I think that if we're evaluating -- our standard has always been that we evaluate ingredients as used. And so we look at those that are used in aerosols, and say, okay, yes or no? Do we have the data? And if the data is insufficient, because we don't know what that tail is, as far as how many particles are less than 10 microns and are respirable, then we can just simply state that, and leave it at that. I'd like to get away from these bastardized conclusions.

DR. BELSITO: So let's say that we get a report and the individual ingredient has a tail where, as a toxicologist, you're concerned about even the small amounts that would be respirable. But now when you put ingredient X into that formulation of hairsprays with PVP copolymer, or whatever else is in the spray, you now get a molecule with none of those tails.

DR. SNYDER: But they've got to give us the data then, in that formulation. I mean, I really need -- we have some to be science-based, data-based.

DR. BELSITO: I understand.

DR. SNYDER: Because it actually would be better for us to say that, in this instance, using this product, an aerosol, is unsafe, because there's a significant amount that's less than 10 microns and is respirable. I think that's a better conclusion --

DR. BELSITO: But how do we know that -- what in formulation?

DR. SNYDER: We have to have --

DR. BELSITO: We just know that from the ingredient. Just like we know that --

DR. SNYDER: Let's say we do the same thing with sensitization, we wanted concentrations in use, so we want to see it with --

DR. BELSITO: Sometimes we say that is a sensitization hazard. And it really depends what product type. This is getting back to QRA. You can't just go by an HRIPT.

DR. SNYDER: I think we're getting a little ahead of the game here, because I think we've got to reopen this old report because clearly what it states as a conclusion is wrong.

DR. BELSITO: Right.

DR. SNYDER: Okay? Because it says all product is not respirable because of particle size, use that as the bar; and that's not the case now, because we know that they can be respirable.

DR. BELSITO: Right. Okay.

DR. SNYDER: So now let's go back and let's just reiterate that for aerosol use, we've got to have some of this data.

DR. BELSITO: Okay. But then we're reopening -- I can't keep straight where we are. But we reopened, we added a bunch of stuff, right? Along with the reopening. Okay. So for silica and silicates, you're saying we need to know particle size for those that are in pumps and sprays.

DR. SNYDER: I think it goes beyond -- you had some other -- composition use, right, for --

DR. BELSITO: Can we go back? I mean, are we going to split this document into natural and synthetic? And do two separate reports? I think that's -- you know, again, that's addressing Women's Voices for the Earth, their last point.

DR. LIEBLER: I think we might as well do that. I think it would help us deal with the issue -- it will help us deal with the issues of impurities and defining the compositions and particle size, or at least control knowledge of the particle size.

DR. SNYDER: It goes to our premise that we always consider the chemistry and uses to group things. And it would make more sense that the chemistry is probably different in a synthetic versus a natural.

DR. LIEBLER: Right.

DR. SNYDER: With composition of things. Right?

DR. BELSITO: Okay.

DR. SNYDER: So I think that makes sense to me initially. But I'm not at that level of a chemist and look at this huge range of things, this list, and know is that -- or is there other appropriate subclassifications?
Because I mean, he said there's synthetic amorphous, synthetic silica aluminides, the crystalline, and then the naturally occurring. So some of it --

DR. LIEBLER: This memo from the CSSC basically says don't group things that don't belong together. But they don't say what belongs together. Thank you very much.

DR. LORETZ: I think was it was the clays, the zeolites, the amorphous and silica, and then kind of another category. But it was really that kind of concern that you're kind of talking here, because each has its own kind of questions. It was kind of trying get at that, that there was just too much in one place, and sorting it out was really challenging. So I mean, that's why we were in favor of separating --

DR. BELSITO: So do you think that the idea of separating the synthetics from the non-synthetics is a good start? Or are we going to get a lot of pushback on that too?

DR. LORETZ: Well, I just mean, I think the clays, the zeolites, I think there was a sense that those should be separated within that. Then you need to separate naturals from -- I'm not sure. We hadn't discussed that. But I think those categories would be a starting point where you would separate that.

DR. LIEBLER: Yeah, I mean, it's hard for us non-silica types to even have a hint that you would separate the clays and the zeolites until somebody said, "What do you mean you're not separating the clays and zeolites?"

DR. BELSITO: So, basically, what we're talking about is taking silica and silicates and moving them into a separate report.

DR. LIEBLER: Sounds like it.

DR. BELSITO: And then that would leave us with --

DR. LIEBLER: Still a lot of other stuff.

DR. BELSITO: -- zeolite, attapulgite, bentonite, Fuller's Earth, gold zeolite, hectorite, kaolin.

DR. LIEBLER: Bentonite. Did you mention that?

DR. BELSITO: I mentioned bentonite. Montmorillonite, pyrophillite, zeolite. The zeolite in general. And so we'd basically be just staying with silicates, metasilicates.

DR. LIEBLER: Hydrated silica and silica --

DR. BELSITO: Yeah, just that. And then what do we do? Do we separate zeolite from clay from Fuller's Earth from bentonite from attapulgite? Or do we try and look at those in one chunk?

DR. LIEBLER: I think our suggestion is that we probably look at those in one chunk, unless industry returns to us with additional reasons to unchunk them further. And they need to be good reasons. Because by making this division, I think we hopefully address the issue.

DR. BELSITO: Okay. So basically, if I'm hearing things correctly, the silicates, silica, metasilicate are going to be separated out. We're going to do a separate report. But we're still with an insufficient conclusion for all the reasons we asked for before, for this entire group.

DR. LIEBLER: Mm-hmm.

DR. BELSITO: And then the remaining naturals, although I'm not sure that the zeolite --

DR. LORETZ: I think that can be synthetic or mined.

DR. BELSITO: Okay. So we'll figure it out. We'll put it in the group for now, and see what happens in that other group that is not silica or silicate, and that will go out as insufficient for method of manufacture, impurities, particle size; basically what we're asking for the silicates, except we're also going to be asking for a method of manufacture and impurities, which we --

DR. SNYDER: With an emphasis on particle size distribution for the aerosolized products.

DR. BELSITO: Right. If there are aerosolized products in those groups.

DR. SNYDER: Or powdered.

DR. LIEBLER: I'd like to come back to the issue of aerosolized particles and data, to address Paul's very strong concerns here. Those particle size distributions we got would actually allow you to calculate the fraction that is below any size threshold you want to calculate.

So it would be possible for a supplier of an ingredient to perform that analysis and provide that as part of their lot characterization to the manufacturer of cosmetic products, so that they would be able to assess the median and then the fraction below wherever we want to designate as a respirable threshold.

Then someone still needs to decide what's the limit of the amount of particles that are respirable in the product. Now, that's probably not our call, because that turns out to be a specific number. Unless we have data that says, oh, it needs to be less than X parts per million, or Y femtograms or micrograms or whatever. I don't know if we'll ever have the data to allow us to do that. But those data coming from the manufacturer to -- the supplier to the manufacturer of the cosmetic ingredient would allow them to assess the amount of respirable particle that they're incorporating into their product.

And even though we don't say, you know, here's a cutoff number, we say that information should be considered. And I would think that's one of the things you would be considering when you're deciding which silica to incorporate into your cosmetic pump spray or hairspray, something like that.

So we provide I think enough guidance, without being forced to say it has to be above or below this number. Does that help from your perspective?

DR. SNYDER: Yeah, I mean, I think --

DR. LIEBLER: And that allows us to still say "when formulated to be non-respirable," but in the discussion we would explain that that information can be determined; and that an additional consideration would be the effect of the other components of the cosmetic formulation on the final particle size.
Because I think we all agree that could change the particle size, but it's impossible for us to say how much it's going to change the particle size, and it's going to depend on what else is in the product.

DR. LORETZ: And also how it's being dispensed.

DR. LIEBLER: And how it's being --

DR. LORETZ: Which can make a big difference.

DR. LIEBLER: So I still like the idea of saying "when formulated to be non-respirable," but in the discussion explain what information industry can use to document the particle size distributions of their products that they're supplying to cosmetic ingredient producers, and then for the producers to consider in formulating products.

DR. BELSITO: Okay. So what I have is split silica and silicates from all the others, the data need has not changed, and essentially the data need we needed for that was the range of particle sizes for ingredient to be used in hairsprays and powders. So those have to be identified and get the ranges, but still come out with a conclusion formulated to be non-respirable.

Then for all the non-silica silicates, basically, we're asking what we asked before, was chemical characterization, composition, impurities, method of manufacture and source for those ingredients. And then if any of them are in aerosolized products, particle size and --

DR. LIEBLER: Particle size distributions.

DR. BELSITO: Distributions. So basically what we asked for before, except we're splitting the groups. And then we'd be interested in the scientific committee's feedback on the ones that we threw out, whether they can all be grouped or whether we should look at clay and bentonite and attapulgite and zeolite and any of those others separately or as a group of sticky, earthy subjects.

DR. LIEBLER: Correct.

DR. HELDRETH: So for silica and silicates group, I didn't hear you list method of manufacture or composition --

DR. BELSITO: No. Just particle size and materials used in powders and sprays. That's it.

DR. HELDRETH: What about the silica and silicates that are refined from naturally occurring minerals?

DR. SNYDER: That's why we still want to know the method of manufacture, as in the original request.

DR. HELDRETH: Because aluminum calcium sodium silicate is defined as coming from naturally occurring minerals.

DR. BELSITO: Okay.

DR. HELDRETH: The other ones are vague, and you don't know if it's synthetic --

DR. LIEBLER: My original suggestion was the synthetics versus the naturals.

DR. HELDRETH: But we don't know which ones are synthetic.

DR. LIEBLER: Well, we'll have to find out. We know that two of the major use ones are synthetic. And we may need to find out which others -- well, we have to find out which ones are synthetic versus natural.
And again, my feeling from a chemistry standpoint is the synthetics, you know what went into it, you know the process, you know that it was pretty well controlled, they understand what they're making to very high degree. And that separates those from the natural that are refined to some extent, but still have contaminants that are uncontrolled and maybe not even well documented.

DR. BELSITO: Okay. So we're going to split the silica from the silicates or the silica/silicates from everything else. The data needs for the silicates are going to be method of manufacture and impurities --

DR. LIEBLER: Particle size.

DR. BELSITO: For all of them essentially. Impurities will become more critical for those that aren't synthetic. Correct?

DR. LIEBLER: Right.

DR. BELSITO: But that's captured by method of manufacture and impurities. And then particle size and materials that are used in powders and sprays. And then, despite that, we probably still say, "formulated to be non-respirable."

DR. LIEBLER: Right.

DR. BELSITO: And then for the others, the bentonite, essentially the same thing.

DR. LIEBLER: Do we want to see one report, then the other, or two reports in parallel at the same time? I'm trying to see if Christine is staring daggers at me.

DR. BELSITO: I think what we have the most information on are the silicates/silica. I'd like to see that one probably come first, then see that goes.

DR. SNYDER: From that old report. I think that's where we have the most data, that old report.

DR. HELDRETH: And doing them sequentially, we give the CIR Science and Support Committee time to evaluate the second group.

DR. BELSITO: Yeah, the second group.

MS. BURNETT: This wouldn't come back at least until September anyway, just due to the meeting scheduling this year. I have no preference.

DR. LIEBLER: Okay. Well, I think one then the other makes sense.

MS. BURNETT: Probably silica first.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. So then that's what we're doing. So now can we go back to Women's Voices for the Earth letter and decide how we're responding to them?

DR. SNYDER: The 25th? Which one are we looking at first?

DR. BELSITO: April 8th is the date.

DR. LORETZ: There's two. I dated the Wave 3 as today. Their submission came in on the 25th of March.

DR. BELSITO: There are so many handouts here.

DR. LORETZ: I think you had it.

DR. BELSITO: I've got it. So the first is about crystalline and amorphous silica. Crystalline silica is on Prop 65, amorphous is not. How are we addressing that, by saying we're looking at the respiratory issue?

DR. LIEBLER: I think this letter, at least the whole first page and much of the second page, is about the issue of reporting the presence of crystalline silica. And I'm not familiar with how the California Safe Cosmetics database works, but basically, what Ms. Scranton is pointing out is that they're only required on that database to report ingredients that are on the Proposition 65 carcinogen list, which includes crystalline silica but not amorphous silica.

So the products containing amorphous silica aren't on there. And the ones that contain or may contain crystalline silica are. And she then lists on the next page a number of producers and cosmetics companies that have reported presence of crystalline silica in the state's Safe Cosmetics Program database.

Did I paraphrase that correctly?

DR. BELSITO: Yeah.

DR. LIEBLER: Okay. The next issue is particle size, we come back to that; but the presence of crystalline silica is obviously some -- is of concern.

DR. LORETZ: I wish Jay were here. I totally forgot about that issue, because he was the one who looked into it. And I think some of that is in error. So I think we looked at that and didn't agree with what they were saying; that some of those reports, in fact, were not what Women's Voices for the Earth mistakenly thought they were.

DR. LIEBLER: Okay. I mean, when we see this report again -- so I think it probably should be noted at this discussion in the minutes that this was discussed and acknowledged, and that we agreed that there was apparently some -- potentially some conflict between what Ms. Scranton is reporting to us and what the council has determined, and we need to reconcile that for the next look at this report.

DR. BELSITO: Let me clarify. So what she's saying, companies reporting to California that they contain crystalline silica, that may be inaccurate?

DR. LORETZ: I believe so.

DR. BELSITO: I sort of do, too, because I know -- for instance, if a product contains tar, it has to have a carcinogenic label in California. Neutrogena does not sell their T/Gel shampoo in California, because they would have to label it. They do sell T/Sal, which has no tar in it.

So they're one company who won't label for California and just will restrict sale of products in that state. So I'm surprised to see them on the list as a company that would do that, since their practice, at least up until now, has not been to label for Prop 65.

DR. LIEBLER: So let's just hypothetically say that the council is able to resolve this list down to one company that reports this; what do we do then? If there are one or two or five instead of whatever?

DR. BELSITO: Well, it doesn't really matter, because it begs the question as to whether they're using crystalline silica, as opposed to amorphous. And it begs the question as to whether we agree with the State of California that it's carcinogenic.

MR. JURD: California actually does define it also as respirable. It's not just crystalline. They actually go further in defining, in the Prop 65 list, that it is respirable.

DR. BELSITO: Okay.

DR. LIEBLER: Respirable crystalline silica, not just crystalline silica.

MR. JURD: Not just crystalline silica, yes.

DR. LIEBLER: Okay, but not referring to respirable amorphous.

MR. JURD: Not respirable amorphous.

DR. SNYDER: Okay. We have to get some of this clarified. And I think, as Dan said, Jay sounds like he's on it. So we just want to make sure that he reads the minutes of our concern, and addresses the issues, and brings some clarity to that.

DR. LORETZ: Yes. We'll bring that one back, definitely.

MR. JURD: There was discussion this morning at the other panel meeting, also, on the same point. And I think they were mistaken. There was a mention that maybe we're looking at Ti02 and not --

DR. LORETZ: Yeah. That's exactly what I remember, that it turned out it was actually Ti02 that they were talking about. But I didn't want to say that because I'm not clear on the details.

MR. JURD: Yeah, I think that's what it was. I'm not clear on the details, but that's what they mentioned maybe in the source --

DR. SNYDER: What's Ti02?

DR. BELSITO: Titanium dioxide.

DR. SNYDER: Okay.

DR. LIEBLER: Which is really low (inaudible).

DR. HELDRETH: So from the standpoint of this letter, it came in later than the publication of the report, and pretty late to even make it into our Wave 2. Since this is going to come back to the panel, likely in September, this could be incorporated as part of the report package.

DR. LIEBLER: Sure.

DR. HELDRETH: And the panel will have time to fully consider this more. We'll have Council's input on it by then. And I can write to Ms. Scranton letting her know the panel has seen it, they want to evaluate it in full detail, see you in September.

DR. LIEBLER: Next time this is reviewed.

DR. BELSITO: Okay. So there will be no detailed specific response, rather than simply saying, thank you, it's under consideration. The panel will be looking at this as well as other information that we've requested. You can see our discussion and our document online.

DR. HELDRETH: Once the panel reviews it --

DR. BELSITO: Right.

DR. HELDRETH: -- then we'll get back to you again.

DR. BELSITO: Okay. I'm fine with that response. Anything else on silicates? So splitting them, but the data needs remain the same for both groups. And our recommendation is to come back with silica/silicates first, but we're open to trying to tackle all of them at the same meeting as well. If there's some thought that the data will help cross the boundaries, help us out.

Marks' Team Meeting – April 8, 2019

DR. MARKS: Okay. Any other comments about the fatty acids? Next is the silicates, and I'm going to refer to the information we found on our desks this morning as Wave 3. And there's some pretty significant issues. There's a memo from the CIR Science and Support Committee, and then Christina also sent us a memo about silicon silicates. So Tom and Ron, perhaps you first want to read those? And then when you're done reading those, we can open the discussion. Tom and Ron, have you had enough time?

DR. SLAGA: I'm still reading, but you can proceed if you'd like.

DR. MARKS: No, I think that letter is important, so continue to read.

DR. HILL: In the next two minutes I should be done.

DR. MARKS: Sure. So Christina, I think it's going to be interesting. We may need Bart to help clear up the chemistry of all this, but we'll see where we go. So this is a draft tentative amended safety assessment of silica and silicate ingredients. At the December 2018 meeting, the panel issued an insufficient data announcement for the 40 silica and silicate ingredients. The additional data were a range of particle size, particularly in sprays and powder formation.

We have comments about the importance of particles in these communications since this meeting. The chemical characterization, except for silica -- and that's also been a question of what really are the composition of this group of ingredients, and are they really similar enough to group together in method of manufacture for the ingredients? Our team thought that, in December, we could issue a conclusion of formulate to be non-irritating and assess the respiratory concerns at discussion. But since then, we've gotten a letter in Wave 2 from the SASSI, which is the Synthetic Amorphous Silica and Silicate Industry, concerning SAS, which is synthetic amorphous silica, discussing the inhalation and chemistry.

And then today, we've gotten information from the Personal Care Products Science and Safety Support Committee for the CIR concerning the grouping and concerns that these are not structurally related and about the composition in ingredients and, particularly, a number of the ingredients that contain other components like germanium and zirconium and silver. And Ron Hill, you expressed concern about silver in the past.

So they suggest reconsidering a large number of silicate ingredients in this report because the ingredients are not sufficiently related structurally to form a useful ingredient family. And then their comment was the particle size in the finished cosmetic product is not the same as the particle size in ingredients. So the lack of particle size should not lead to an insufficient conclusion. The memo from Christina, date April the 8th, includes the Women's Voice for the Earth letter, and their first point related to confusion about the CA -- I assume that means California -- Safe Cosmetics Database and the manufacturers who have reported the use of crystalline silica. And they recommend --

MS. KOWCZ: We have -- Dr. Marks?

DR. EISENMANN: We have looked at that database over the last --

DR. MARKS: Okay. Let me finish the letter, and then we can address all this. And then the second was the particle size, again, of the ingredients are highly relevant. So I think they were the two main points from the letter. Okay. So it's gotten, perhaps, more complicated since the last meeting. Carol, Alex?

DR. EISENMANN: We looked at that data -- California's database, and we believe the companies are reporting titanium dioxide, not silica. Silica and titanium dioxide both have this non -- the same qualifier. And for some reason, when you search silica, these companies reporting titanium dioxide are coming up. The name silica, if it's seen on a label, means a more synthetic amorphous silica. It's not a crystalline silica. Under the name silica, they're not using crystalline silica, they're using an amorphous silica.

DR. MARKS: And just for general public importance, what is the significance of the difference, in terms of toxicology and safety?

DR. EISENMANN: Crystalline silica, when it's taken up by -- as I understand it, when it's taken up by microphages, it causes them to burst and then results in adverse lung effects which leads to cancer. Whereas, synthetic amorphous silica can be cleared from the lungs without causing any additional problems.

DR. MARKS: Okay. Good. That's the way I interpret it, but I wanted to hear it from you. Okay. So I think that addresses the California issue with the Women's Voice of the Earth point.

DR. HILL: Can I just ask a follow up clarification question? So what she's saying in here, if I understand correctly, is that there are companies that make lots of silica containing compounds, but they are only selectively reporting. And what she's asserting is that, presumably, because of the requirements of Proposition 5 -- or excuse me, 65, which would relate to carcinogenic potential, that they're reporting specific ones because they have something in there of concern. So what you're saying is the products that they're reporting all, without exception, seem to have titanium dioxide and that the labeling -- or the reporting is based on that and not silica. And you can't tell from the way the database is constructed?

DR. EISENMANN: Correct. When we looked at the database, we could only find that they were reporting titanium dioxide and not silica. Because the silica they're using -- if they're using the name silica, it's synthetic amorphous silica.

DR. HILL: Okay. And then the other question I had in this document is related to what she's addressing on the last page, which is the jet milled powder issue. But then it finishes off with powder presses. And so then I thought what in the cosmetic or personal care product would they be using powder press -- to press jet milled powder, except that this is an article in the cosmetics and toiletries news -- some news publication from 2012.

So that concerns me because if there are jet milled powders that are being included in powdered products, that could be potentially inhaled with those particle sizes -- and I have a lack of clarity in terms of what those particles are like and whether they present the same issues as crystalline silica. I'm guessing not because it would then be crystalline product, which would be more along the lines of nuisance dust; but it would sure be nice to have confirmation of that.

In terms of your letter about the ingredient grouping, you're preaching to a member of the proverbial choir because I would like the ingredient groupings -- I understand the convenience of administratively grouping them, but I think it occludes and obfuscates the ability to see clearly the issues that are there. And I just don't understand -- other than administrative convenience and some similarity in the elements that are in there -- why you would group clays with a synthetic amorphous silica.

I would break out the different clays even, or at least make sure that they're very clear in the subcategories. But I didn't have any problem with that because we already had a clay report a few years back, and I was fine with all of that. But putting it together with silica just didn't sit well with me.

DR. EISENMANN: And if you don't separate in different reports, at least within the report, it'd be helpful to have them separate, rather than one paragraph that has silica and clay in one sentence. And then the next sentence is -- and you don't know which -- do you support which ingredient.

DR. HILL: Within the body of the report, you can segregate the information, and that's fine. But then the problem comes when you get cumbersome conclusions where you have to split out conclusions based on large differences in the ingredients. And I think when you have ingredients that don't belong together based on how you would arrive at the conclusion -- and maybe I'm not thinking thoroughly through this enough -- then, to me, that's a good enough reason to split them out. But that's just my take on this, in reading all the information here.

DR. MARKS: So Ron, you would reconsider the numbers and split it out. Tom, how do you feel about that, too?

DR. SLAGA: There's no doubt that they have a good point, and the groupings are different. As Ron said, the elements are the same, but there is structural difference. Are we saying, now, to have these two groups within one report? Because I think we can come up with the same conclusion, can't we?

DR. MARKS: I would think so. The last time -- and again, Ron Hill, you probably have the exception. Our team was actually ready to move on and say safe when formulated to be non-irritating but address the respiratory concerns in a discussion, as I recall in the minutes. In the last meeting, the Belsito team really had the concerns about the inhalation, and that's why the insufficient.

So I guess one way to address the different ingredients is to acknowledge that they're structurally different through the groupings. And the two groupings you're talking about now -- you said silicas and clays. Is that what we mean in terms of the chemical groupings? Because Bart -- I'm sure Christina was the one who put this all together. I wish Bart was here so he could -- but maybe, Monice, you could comment.

DR. HILL: Well, let me just dispute what you said about the elements are the same because, in silica, there is silicon. There is oxygen, nothing else. But the clays typically have iron, other elements that are in there besides silicon and oxygen and nothing else.

DR. MARKS: Is that where the zirconium, the silver and all that --

DR. HILL: Yeah. So then you get other metals. And the ones I raised, I wasn't necessarily sure that there was any problem, but we were lacking data to cross read to the things that are more exceptional, like silver and gold, germanium -- there was one other -- zirconium.

DR. MARKS: Yeah. Zirconium was mentioned.

DR. HILL: I wasn't as concerned about zirconium because I think that's fairly pervasively occurring in some kinds of clays and such. But I think, when you get into some of these ones that have -- they're higher atomic weight and have different redox properties than some of the other elements, then that's different.

DR. MARKS: And then, to be consistent, when we say silica, we're talking about synthetic amorphous silica. Yeah. And that'll have to be very clear in the document that that's what we're talking about.

DR. HILL: And that was interesting because the 2004 SIDs that's referenced includes synthetic amorphous silica but also silicic acid, which again, is oxygen and silica, calcium salt. So there is calcium besides the oxygen and silica, and salicylic acid, aluminum and sodium salt, that's also apparently in that same report. I'm not sure why they grouped that in there, as well, but there must have been a reason. I didn't go back and research that because it didn't jump out in my mind until this.

DR. EISENMANN: They considered the solubilities similar. That's low water solubility is why they can group them together.

DR. HILL: I see.

DR. MARKS: Monice?

MS. FIUME: First, I'd just like to respond to one of the paragraphs in the comments that were received today regarding groupings. Yes, often when we group ingredients, it is for read across, but that is not the only reason that we create groupings.

If a family seems to belong together for several different reasons, they can go into a report. When we do our botanicals, they're grouped because they're all the same genus species, but they don't necessarily support each other. So I did want to clarify that read across is not the only reason to group ingredients. But I do understand the concerns about these being different.

In the past, Christina can definitely go through and break out the clays versus the silicates to make it easier for you to read. We've done this several times in the past, especially when the information in the report is leading to a similar conclusion. If the conclusion is going to be safe for all of the ingredients, we can explain that in the discussion how the different aspects in the report came to the same conclusion, even though what we're looking at might not chemically be specifically the same.

Dr. Hill, I know you said you don't have a problem with the zirconium, but the zirconium being raised -- that ingredient was reviewed before. So somehow or another, it has to be addressed because this is a rereview of a report that had the zirconium ingredient in that 2003 report. So that can't really come out. It has to be addressed, but we definitely can break down the groupings.

We can have a mixed conclusion if some of the ingredients that are in there are not considered safe, but the others are. We've done mixed conclusions. And we have done reports where we have split them by different families and brought you all the information, and then bring it all back together in the discussion as to how the conclusions were reached.

DR. HILL: But we've also split out into separate reports when we thought there was good reason to do that, and I don't really understand what the big difficulty is with creating three different reports, as opposed to trying to get everything properly grouped within one report. And when I came on the panel, the idea behind groupings was that we would be using that for read across; and they should be no brainer read acrosses or we wouldn't put them together in one report. So we've certainly departed from that quite a way.

Botanicals are different. I don't think we should even think about botanicals in the same way as we think about other classes of agents, such as silicas, such as polymers, such as like that. Even some of the polymer groupings

have been very cumbersome in terms of putting them together all in one report, but at least -- I think, from a physicochemical properties point of view, it makes sense.

So I mean, it's not up to me. But if it were up to me, there would be probably two, and maybe three, separate reports here. And I realize we may leave some strays that have, again, silver, gold -- some of these other elements well and good. If they're not in use, then strays are just strays. If they are in use or we've reviewed them before, like zirconium -- which I think was one of the reasons it was sticking out in my mind, and you just put words to it. No problem there. But to me, that would group with clays and not with silica.

MS. FIUME: Again, it's always a prerogative of the panel. That's why we bring the rereview groupings to you to be approved. With the rereview, you do have the option to change your mind. But having the whole panel weigh in on it would be great. And as I said, we have done it where it's separate reports; but generally, in the past, we've broken them out into different groupings by different families and kept it within the same document.

DR. SLAGA: So we're going to table it until --

DR. HILL: We're not deciding anything today.

DR. MARKS: Let's -- before we get to what I will move tomorrow, I just want to clarify. I've heard two groups and I've heard three groups. So again, we'll need direction for Christina what our team feels. So Ron, you said two or three? I initially heard the two groups being silica, which is synthetic amorphous silica, and then clays. Is there another one you would put in there, besides those two?

DR. HILL: If we were going to split our reports, then a starting point for me would probably be -- although, I have to revisit this -- would probably be silica, and we could decide if there are a couple of others -- again, if it's just silica and oxygen, we can put silicic acid -- those things in there. I think calcium soluble silica still should be fine, but that and everything else -- if we're going to keep them in the same report, then I don't think groupings -- they're major groupings.

And we can decide, then, how within the report to group. But the fundamental issue is, does it all stay in one report, or do we create a separate report? What was in the silica report, again? There were two that we reopened. There was one that was silicas.

MS. BURNETT: The original silica report contained silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate.

DR. HILL: All right. And so the question would be those ones -- for example, the one with the iron in it, does that stay there or go with the clays? I'm not willing to make an off the cuff comment on that one without looking again.

DR. MARKS: Okay. Carol, Alex, how do you like the idea of having the same report and just groupings within it? I mean, we've done that, not just with the botanicals. I think we've done that with other groups of ingredients. Do you see a problem from your point of view?

MS. KOWCZ: I think the one thing that we are trying to address with Monice is, if we are going to have one report, then we do have to have specific delineations or differentiations of this chemical class versus that chemical class, because it is different based on the physical chemical properties, as Ron has stated as well.

So if we can do that with a mixed conclusion, as you've said you've done in the past, we just feel that they're very different materials and that they should not be all grouped together. But if that's an opportunity to do it in one report, with different conclusions and really showing that the data goes to which group, I think we'd be fine with that.

MS. FIUME: And I guess the reason I was pushing for the one report with the subgroupings, is because that 2003 report that initiated the rereview does have a mix. For example, kaolin is in that 2003 report, as well as the silicates. So it is very mixed.

So it seems, in order to take that rereview forward of that report -- if we could create subgroupings in this rereview document and, therefore, address the ingredients that were looked at in 2003, that would keep the family from the 2003 report in the same rereview, but also explain the different groupings that were included originally and how they're being looked at now.

DR. HILL: So if it were up to me -- if I ran the zoo, we would create new reports. And one would be silicas, and one would be clays, and one would be zeolite and maybe a diatomaceous earth; and one would be other things, that aren't silica, that aren't clay, that aren't zeolite, that aren't diatomaceous earth.

And I'm thinking, in terms of zeolite and how I know those are used industrially, I think it's interesting they end up in cosmetic ingredients. So we would have strays, but I'm pretty sure I would create four reports, maybe five, if I ran the zoo. And I don't. And they would be new reports, and then that would give the opportunity -- because I think there are still some issues out there in the wind, no pun intended, but maybe about aerosol sprays, for example.

Because again, I think we're still missing -- and we identified them as we were trying to put to bed the aerosol report, which I still don't think we've ever -- our guidance document -- I don't think we've finalized that, have we? And promulgated it. But there were some pieces of issue out there, such as if you have an aerosol spray and then the solvent evaporates as they're flying through the air, and you start with the glomerates, depending on what the substance is in there -- what happens between there and it gets to my nose?

So it would provide a little bit of time, as well, to make sure we've revisited each of those as relates to the specific categories of ingredients. Because when you're mixing things like the flow chart -- that's very nice that they gave us. It's fairly near the end of the PDF here that was from the SASSI -- shows with the synthetic amorphous silica and how that relates to the others that are silicates. And there's nothing else in there by silicon.

Those things all grouped together -- and then you could add, again, things that are only silica and oxygen, maybe a calcium salt, and then decide from there do we include aluminum-containing compounds or does that go in a different report. But I'm just looking at, if the issues are necessarily the same, can you discuss them all in the same report? I'm sure you can find a way to do that.

But having to keep the same ingredients together in a rereview, to me, seems to be artificial. There's no good scientific logic. I wasn't around when the 2003 report was put together and the grouping was established, so I don't know why I should be stuck with it, I guess, is one way of saying it.

MS. KOWCZ: Would it be difficult to separate them now with the 2003 report already established?

MS. FIUME: It can be done, and we've had ingredients that have been pulled out. I can't speak to any of the chemistry as to why Bart put this together. So I would really rather let Bart comment on his feelings on keeping them in one report versus separate, because he builds the documents based on his chemical knowledge. So I would prefer to let him comment on it, if that's okay.

DR. MARKS: Sure. Tom, what's your feeling about this? You proposed tabling it, but I'd like to get back to the discussion. Perhaps, we know where Ron Hill stands with having multiple reports. You had previously -- and I'm certainly fine with having one report. We do many reports where we have split conclusions. So I think Bart's input is going to be very important.

I kind of like the idea of tabling it because I think we've gotten enough new information. In terms of particularly handling the structure, I don't know how we can move forward with a tentative amended report if we don't have it clarified as far as what are we going to do with these different structurally chemically different ingredients and how we're going to group them.

And I actually kind of liked, Ron Hill, your approach. You have the silica. you have the clays, and then you could have an "other" group or a "miscellaneous" group, and still have it all in the same report. I guess then it'd be up to Bart to name what that miscellaneous new report would be.

Whereas -- would the title of this still be silica and silicate ingredients, or would it be silica and clay ingredients? Or would the title change now since we're -- so that's another thing to think about, because it doesn't sound like silica and silicate ingredients really cover these structurally different ingredients.

DR. HILL: And honestly, when I read the SASSI -- the most recent input, I thought, okay, they have some things in process currently, as well, related to all of this. And that if we were able to table and have just a little bit of space and time to think about how better -- it could come back as quickly as June, perhaps, if we get information from the industry group. But I was around for 2008 when we got that first -- I was here in 2009 when we were still looking at the SASSI input data, and I remember we had at least one of those individuals from that organization come and give us a presentation, if I'm not mistaken.

So I just felt like my take on reading that was could we table this and have a look at those issues seriously; discuss with the industry groups, and decide what this should look like in the end? And the other thing I was going to mention while I've got the mic -- and then I'm going to shut up and shut it down -- is there any chance we can get Bart in for this discussion? Can we table for the moment and sometime between now and the end of the afternoon, if we're the ones that have to move tomorrow, get Bart in for some of the discussion? Or do we have that all happen overnight?

DR. MARKS: I feel comfortable moving tomorrow table, and raise the reason that we feel we table it because we had a structural ingredients difference. The issues have been raised by the Science and Support Committee and actually also -- now, I guess it wasn't raised by the Women's Voice of the Earth. They will remain particle size.

DR. HILL: I wanted clarification about this jet milling thing, because I think we're still okay just because it's not crystalline at that point. But I wanted to feel a little better about that.

MS. KOWCZ: Dr. Marks, can we just ask -- we have a representative from SASSI -- because this is the perfect opportunity to ask any questions. And we do have the industry expert.

DR. MARKS: Excellent. So would you please introduce yourself, and you can use SASSI but also tell us what that means -- meaning the full name of it. I know what it is here -- the Synthetic Amorphous Silica and Silicate Industry. But for those of us who may not be within that industry, SASSI doesn't mean a lot. It could have other meanings, if you're sassy.

MR. JURD: Brett Jurd. I am currently the chairperson of SASSI, which is a trade association actually formed in -- about 20 years ago to differentiate synthetic amorphous silica from crystalline silica because it was, at that time, being lumped together.

We are and work with a similar associate that's part of CEFIC in Europe, called ASASP. The organizations have very close memberships. We represent, basically, the eight to ten major synthetic amorphous silica producers globally. We're missing one or two companies there, but for the most part of -- all the major companies, PQ, PPG, are all members of our association.

We do a number of things, including supporting studies. If you know it or not, there's a lot of activity going on in Europe right now. We would be more than willing to provide whatever support you need to come to the correct conclusion. A lot of our members also are involved in other silicates; you know, manufacturing, the ones that you said were in the initial report.

And we also, for one reason or another, the companies -- and I actually am with W.R. Grace. We actually do mine clays and also put on the market zeolites, although not for cosmetic purposes. But we have chemistry experts, within our organizations, that can help differentiate those kinds of materials.

The one thing we feel very strongly about with synthetic amorphous silica -- and I think the points made earlier about the differentiation between the crystalline form, which is classified as carcinogenic, particularly the respirable, the less than ten-micron particle size, and synthetic, is there's a significant health difference between the crystalline. Even California differentiates crystalline amorphous respirable silica as the carcinogenic version, not just larger particle sizes.

DR. MARKS: I don't know whether you want to -- since you're here and you may add -- we had a rather robust discussion prior to you coming into the room about the structurally different ingredients, which are grouped together in this tentative report. And that was also raised by the association manager in a letter -- that clarification on the scope of the 40 ingredients. And this was authored by David Pavlich?

MR. JURD: Yes.

DR. MARKS: So I guess what our team is struggling with, or discussing, is whether to have one report dividing these ingredients into two or three groups, a silica group, a clay group, and another group, which would be a miscellaneous group of ingredients in the same report, versus having multiple reports. This was also pointed out by the CIR Science and Support Committee of the PCPC. What's your feelings about splitting it out and how you would do that? One might be the report just on silica, which we now -- when I say silica, I refer to synthetic amorphous silica, SAS.

MR. JURD: We would agree. We would like separate reports. Particularly, as was mentioned, I think clays fit into a different class. There can be a lot of contaminants -- other materials in clay, including crystalline silica. So you've got that component that could potentially be in there and could be an inhalation hazard in certain types of formulations in cosmetic products. That's an opinion on my part not supported by any scientific evidence.

I think you would have to look at maybe -- like zeolites, you could do an aluminum silicate or alumina silicate kind of grouping. A synthetic amorphous silica, which I think is the majority of the silica, if not all the silica that's found in cosmetic products, I think is chemical synthesized rather than naturally occurring. And then, as you mentioned, a miscellaneous, because there were some very unusual materials kind of lumped in that category.

And I think if you look at -- at the very high level, it's like where else could they fit? Ah, this makes sense. We can lump them in to here. But if you look at the data that's out there -- and I think you talked a little bit about read across -- I'm not sure if you could do read acrosses at this point in time because I don't think the data is necessarily there to be able to afford that conclusion.

DR. MARKS: Okay. That helps us -- reinforces that we need to have different groups. I think the question will be do these different groups occur in the same report, or do we split it out as different reports? And we'll handle that in the future. So tomorrow, I'm going to move that we table this because of the ingredients that are structurally different, and I'll kind of summarize what we talked about, Tom and Ron. And obviously, feel free to add into that. Any other comments from our --

DR. SADRIEH: I'd like to just mention that, regardless of what's done in the end, I'd like for the issue of magnesium calcium silicate to be addressed, which is asbestos. So that's something that -- whatever conclusion you come to, I think the potential for any kind of asbestos contamination would have to be addressed.

MS. BURNETT: Did you say magnesium calcium silicate is not an ingredient in this report?

DR. SADRIEH: Correct. But you could have contamination. Asbestos contamination is not an ingredient. You're looking at ingredients.

DR. MARKS: Yes. That obviously gets to the impurities portion of these ingredients. So just as we've heard that clays may have crystalline silica as a contaminant in it or a component impurity, so the same way we'd have to deal with asbestos, too. Thanks for bringing up that point. Yes?

MS. BURNETT: Before we move on, in the Wave 2, I asked -- I know there was a lot of data points. How would you like to have that data represented in the report, if at all? It was SASSI provided different particle size readouts for different samples of -- I think some of them were cosmetic products. Some of them were straight.

DR. HILL: Excuse me. It came to my comment about making sure that we revisit our inhalation/aerosols document and where we landed two meetings ago. I think we looked at some of that in December, didn't we?

MS. FIUME: Right, it had not reached finalization yet.

DR. HILL: Because I don't think there's any really new information. They sent us a data dump is what it appeared to be, with some particle size characterizations, which is helpful. But I don't know that there's any new information in there whatsoever. I think where I still have data gaps is -- we had a pretty good summary, and I think a lot of it came in that SASSI report from 2000 -- S-A-S-S-I report from 2008 about the issue of agglomeration in finished cosmetic products.

But once a manufacturer of an ingredient sends it to the formulators, then it's really on the formulators to figure out what happens from there and if I spray it in an aerosol spray -- and now we have different aerosol devices. So that was something else that came to the floor in that last round -- the last rounds of data we had is that, well, there's not just one kind of aerosol can and one kind of pump spray.

There are these other things that we hadn't maybe fully considered. And any given ingredient, I'm not sure we have the full scope of everything, but we're supposed to be getting it and reviewing based on what information we do get, what kinds of devices do we have? Are they for sure larger particulate agglomerations? Because the particle sizes that I gave us are, I think, are the raw ingredient before it ever goes into a product, if I'm not mistaken, in that Wave 2 data dump that we got. So that doesn't really give us the full picture because -- unless that was added to a face powder.

They talked about the feel of these jet milled powders, and that's what got my attention; is what's added and what's actually being sold to the consumer, and what particle sizes are in there. And is there anything crystalline as an impurity is the immediate concern. And beyond that, is it nuisance dust or something else we have to worry about? And we have these inhalation documents. We've got these face powder and loose powder, and then we have some statement about exposures are thus and such related to workplace exposure. And I'm thinking, well, yes, but what's the stuff? If it's just nuisance dust and it's innocuous, and we don't have to worry about anything that might happen -- sensitization in the bronchials, for example, or something like that -- that's one thing.

But there's disconnect every time I read that statement right now. And we talked about that as our -- not boilerplate, that's the wrong -- our guidance document is being updated. That we had these issues that were still out there. I don't know if we could ever actually resolve them because the science keeps improving in terms of what we know. But the other thing that came to the floor is it actually assessing how much of what size of particles come into somebody's breathing zone and what the actual exposure is daggone hard, if not almost totally impossible.

I just know if my wife's using hairspray in the bathroom -- where she hasn't much used aerosol sprays anymore. But if she is, I can't walk in there because I'm going to be coughing for the next ten minutes. That's a sentinel. That's my defense mechanism. I don't worry about any danger to me, but it doesn't take much to trigger that cough reflex. So I know there's particles, and I'm breathing them.

MR. GERMILLION: This is reminding me. There was a discussion at the last meeting, or two meetings ago, about formulas being non-respirable and a decision not to go that route. Am I remembering that --

DR. MARKS: Yeah. That's correct. Ultimately, it turned out to be issuing this insufficient data announcement and asking for the particle size. But you're absolutely right. Our team felt that we could handle the issue with inhalation in the discussion and not put that in the conclusion, but we lit on doing the insufficient data announcement.

Now, we have gotten more data. Obviously, synthetic amorphous silica is not an issue with inhalation. It's not a respiratory toxin. And then we have this memo from the CIR Science and Support Committee. And basically, in referring to particle size, the finished product -- cosmetic product is not the same as the particle size of the ingredients.

So it's the end product which we should be, again, addressing, and that needs to be addressed in the discussion, I think. So the lack of ingredient particle size should not lead to an insufficient data conclusion. I don't know if that answers your question, but you're absolutely right. Actually, that was one of the big discussant points last time. Not so much the structural differences among these different ingredients, which we've lit on in this meeting, but the previous one was really the respiratory issue.

MR. GERMILLION: Yeah. And I remember that back and forth, and then I'm looking at this Women's Voice for the Earth letter. And she starts another reference to particle size and the manufacturer representing particle size at some level.

DR. MARKS: So I think we will address that in this. We're going to have another crack at this, if not multiple cracks at it or reviews. Because if indeed we table it tomorrow -- and that's what our team will move -- then not only will we deal with the issue of structurally different ingredients, whether it's in the same report or multiple reports, but we'll also, I'm sure, go back and address the inhalation toxicity. And for SAS, that does not seem to be an issue. It's going to be these others, perhaps, and particularly the clays where you could have contamination with crystalline silica and asbestos, too, if that's an impurity.

DR. SLAGA: All the data in Wave 2 on particle distribution could be summarized in the report. I don't think we need all -- Ron should be able to help with that.

DR. MARKS: Well, and Ron Shank did.

DR. HILL: And it strikes me in listening to this -- we have language, for example, formulators should take caution not to put a penetration enhancer in the same formula when dermal absorption was our index of safety or lack of dermal absorption was our index of safety.

And I think we need -- and it will probably depend on the exact ingredient and situation -- comparable language here that it shouldn't be formulated to set up this scenario, which potentially sets a risk. And that could probably even include crystalline silica, provided it's in some cream where there's zero chance that it will ever be volatilized versus an aerosol can where perhaps we're not quite sure in some cases.

DR. MARKS: Robust discussion. Any other comments? So Tom and Ron, I'm going to move that we table these ingredients tomorrow. We'll, I'm sure, in the discussion tomorrow decide whether or not we're going to move forward; for the time being, at least it's a single report with split out ingredients within that or multiple reports. And I suspect we will touch on inhalation again, perhaps. Certainly, that'll come up again multiple times. Thank you for your comments.

Full Panel Meeting – April 9, 2019

DR. MARKS: So in December's meeting, the panel issued an insufficient data announcement for the 40 silica and silicate ingredients. The needs were listed in Christina's March 15th memo, particle size, chemical characterization, method of manufacturing.

Since that, particularly in Wave 2 data, we received a letter from the Synthetic Amorphous Silica and Silicate Industry (SASSI) concerning synthetic amorphous silica (SAS). And that that wasn't anywhere near the same as crystalline silica, didn't have the toxicity of crystalline silica.

And then also, in Wave 3, as I'll refer to what we received yesterday, was Women's Voices for the Earth letter, and the CIR Science and Support Committee letters, all concerned about the grouping of these different ingredients, and that they were dissimilar.

So, that elicited a significant amount of discussion on our team. We move that these ingredients be tabled and be represented to us. And what we suggested, we weren't sure whether it be three separate reports or in one report. Personally, I was fine with one report. But the groups would be the silica group, which is the synthetic amorphous silica, clays, which may have contamination with crystalline silica, and then other ingredients, such as that contain silver zirconium. And look at these different groups separately.

So our motion is to table it and relook at this once these have been divided up by structural groups.

DR. BERGFELD: Is there a second, or a discussion or a comment?

DR. BELSITO: Well, I don't know if we said table or not, but we agree with splitting the report into silica and silicates from all the others, and then trying to look at all the others separately but start with silica and silicates. And our data needs haven't changed, method of manufacture and impurities, and particle size in materials that are used in powders and sprays.

So I guess if that's a table, then it's a table. But I think of a table as the report just staying as it is, and that's not what we're requesting. We're requesting that it actually be split, for now, into two, that silica/silicates be a separate report addressed first.

DR. BERGFELD: Bart, you want to comment on that?

DR. HELDRETH: Either process is possible for the panel to take. I think if we're not waiting for some new data, or some new information to come in, then it does make sense to proceed and not put it in a table mode where we don't know where it's coming back.

Also, yesterday, I heard from the Belsito team that we would do these sequentially. And do the silica and silicates -- immediately return as a new report in the process, whereas the rest would constitute another report. And this would give us time to focus on the silica and silicates, and also give industry time to take a look at that grouping and let us know their thoughts on those materials.

DR. BERGFELD: So it sounds like this is just an administrative movement that we do not have to go out as insufficient, we don't have to table, but we will take it as a tentative -- a draft amended?

DR. BELSITO: It's still insufficient, though.

DR. BERGFELD: Yeah.

DR. BELSITO: Because we still want method of manufacture, impurities, and particle size for use in powders and sprays. So there are data requests that are there.

DR. BERGFELD: So, do we send this out again, as an insufficient data request?

DR. MARKS: I guess one could send it out as a revised draft tentative amended safety, because that's what we're doing, really revising it, and that would be the next iteration.

Just to go back to particle size, both from the manufacture SASSI, the industry, association of manufacturers, and then also from the Science and Support Committee, they address the particle size. And from the Science and Support Committee, particle size as finished cosmetic products are not the same as a particle size of the ingredients. The lack of ingredient particle size should not lead to an insufficient data conclusion.

So I don't know whether industry wants to address that; but if we send out an insufficient for particle size, I guess we're ignoring what the Science and Support Committee has responded to that request.

DR. BERGFELD: Alex, you want to respond?

DR. BELSITO: I'll let Paul respond, but I mean, I don't think we have to agree with what the committee says. We didn't yesterday.

DR. MARKS: On, no. I agree. I just think we need to rationalize, you know, why we're still saying --

DR. SNYDER: I think we were taking an ultraconservative approach because there is a risk if these are inhaled, because it will cause a hazard. And so we want to fully understand the particle size distribution and have better appreciation for that before we approve. And so I think it's a high-level approach. We'll ask for the data and then once we see their justification for needing or not, then we can make our final conclusion at that appropriate stage.

DR. MARKS: Paul, would it be -- I'm kind of just thinking out aloud here -- would it be similar to the monomers? And when we look at those ingredients, how much free monomer is left? How much free of the small particle size? Because it seems like what we're getting is that these aggregate in the finished product; so therefore, whatever we start as a particle sizes is irrelevant. Unless, to my mind, there are residual small particles, I guess. Is that reasoning correct?

DR. SNYDER: That's correct. And we were assured that once they've aggregated or agglomerated, whatever you refer to it as, that it's nearly impossible for them to dissociate. But again, we don't have the data to know how much of what impurity in regard to any smaller particles that might be in there.

DR. BERGFELD: Carol, do you wish to speak?

DR. EISENMANN: I still think there's a -- synthetic amorphous silica is so different -- and those two, the hydrated silica -- and so different from the others, they can control the composition more carefully, if there is some solubility. It's not an inhalation. If you inhale it, some of it will dissolve and get removed from the lungs, versus other silicates. And I'd hate to see you keep putting those two ingredients, lumping them with the rest, because there is a big difference between them.

DR. BELSITO: And I think we'll probably get a better understanding of that when we separate the silica and silicates out. But it doesn't hurt to ask for now, and we may determine that it's not needed after looking at it.

DR. EISENMANN: And that's the information you've gotten in Wave 2, that they've already provided. And not only that, there's an OECD summary, that the data is in the report, but within the report that hasn't come to the CIR report yet, particle size and surface area is listed for a lot of the ingredients, that the data is in, that still has to be added. So you have a lot of that already for SAS and the hydrated silica.

DR. BELSITO: Yeah, and we'll look at it. But I mean, I don't think we're prepared to withdraw our recommendations at this point for additional data needs. Again, when we look at it, we may determine that we really didn't need these, as we often do.

DR. BERGFELD: I'm going to ask Bart to respond, because administratively we can handle this a number of ways. So will you elucidate those or just explain the possibilities?

DR. HELDRETH: Sure. I think that the possibility that seems most in line with the consensus that I'm hearing is that we will bring back, at a future meeting, this draft tentative report, which will be revised. It won't be a new report that's going to go out for public comment.

The silica and silicates draft tentative report will come back to the panel, and then there will be opportunity for the panel to address the new report and the comment period will open thereafter.

DR. BERGFELD: So everyone understands, we -- just a minute, Ron -- we will not be voting on this. It's a consensus opinion, that it will go back to the staff, divided up separate items -- or ingredient groupings -- and then come back to us again for discussion and vote. Ron Hill.

DR. HILL: Actually, was not my concern that was discussed yesterday. But we asked about the implications of removing ingredients, given that this started as a re-review or reopen. And that's where we came and said, well, does this need to be then a new report, or a series of new reports, number to be determined.

And I was only asking that question, because I was sitting here pondering what if the report that comes back is that we only look at synthetic amorphous silica, which as we understand it, that's the only silica that should be used in cosmetic products at this point; and then everything else, where we could keep silicates in with clays and so forth, because some of the issues in terms of safety would be the same.

And I just, I don't know if that's an option or not. How far can you cut down before it's not a new report, I guess is what I'm driving at.

DR. HELDRETH: I don't think anything is going to be left out here. All those ingredients that we've looked at before are going to get reviewed. We're just reorganizing the format.

DR. HILL: But into one report, or are we breaking out into separate reports? Because that's what matters, I think, in terms of technicality of procedures.

DR. BERGFELD: It's my understanding that they'll first break it out into the different categories that we've explained. And then the next meeting, we will decide how we're going to handle them.

DR. HILL: Okay, I wasn't clear on that, but got it.

DR. BERGFELD: Okay. Dan?

DR. LIEBLER: I want to clarify that the breakdown needs to include all the synthetics together. So, I don't know if the synthetics are limited to hydrated silica and silica, or if there are any other ingredients on our current list that are the synthetics.

But those are the ones where the composition and structure can be exclusively controlled. Many of our issues with possible contamination with crystalline silica, or other things, that is already handled in the production of those.

So I just want to make sure that the grouping, the reorganization, puts those synthetics together, and doesn't contaminate them, so to speak, with the mined or other silicas.

DR. HELDRETH: So then, to that point, which ingredients are those?

DR. LIEBLER: That is my question. And there's somebody here who knows, and it's not me.

DR. HILL: We got, at least -- and you weren't in this group yesterday -- Brett, from the SASSI, who also clearly has expertise in many of these other areas and was aware that crystalline silica as an impurity in mined powders could be a problem. Whereas synthetic, you're exactly right, when they can control what's there, then those issues should go away.

But then the question will be, I still think the silica grouping, whatever it is, should at least be restricted to things that have silicon, oxygen, and maybe salts, thereof, calcium, aluminum, like that.

DR. HELDRETH: I don't disagree with that. But unfortunately, we don't know which ones are synthetic and which ones are not. For example, some of the salts that are listed in Table 1 would seem to be something that could be made synthetically, but the definition says that they are mined.

DR. HILL: Yeah.

DR. HELDRETH: And the other ones, it's unclear of the source, or whether it's --

DR. HILL: So that's an insufficiency, really.

DR. BERGFELD: Well, I think that we can proceed and perhaps have some consultation with the CIR SSC committee and see if we can figure this out.

DR. SADRIEH: I just wanted to mention that, you know, yesterday you brought up the issue of potentially evaluating as a contaminant, asbestos, which is magnesium calcium silicate. And so, I just wanted to make sure that, for the record, that it was mentioned right now.

DR. BERGFELD: Thank you. All right, I think we will move on then. Administratively we're taking this back, reorganizing it, and bringing it forth again, in the next meeting or so.

DECEMBER 2019 PANEL MEETING – GROUPING STRATEGY
Belsito's Team – December 9, 2019

DR. BELSITO: Okay. So, we're going to the silicates and whether we were -- this is also in Admin, whether we're happy with how things were broken down here. As you remember, there was the amorphous and now we're into the mined. I guess the questions I had all were to Dan, and anyone else who can explain why calcium silicate is okay, but calcium magnesium silicate got struck.

DR. LIEBLER: Yeah, that was the question I had.

DR. BELSITO: Sodium magnesium aluminum silicate got struck. It didn't really seem to me that these were so different.

DR. LIEBLER: Yeah, I had the same question. I don't know.

MS. BURNETT: We can add them back in. It was just that they were suggested add-ons. And since the add-ons kind of caused a quagmire, we thought, well these are no-brainers, so we pulled all of them out. But we can easily add back in whatever ones you want added in.

DR. BELSITO: But how is lithium magnesium silicate a no-brainer, and calcium magnesium silicate is not a no-brainer?

MS. BURNETT: Those were reviewed originally. So, those were part of the re-review that we reopened, so they already have a conclusion. So we still --

DR. BELSITO: I understand. But if we're looking at them, and now we've all of a sudden gotten concerned about inhalation, da, da, da, da, how is calcium -- I mean, I would be more concerned about lithium magnesium sulfate silicate than I would about calcium magnesium silicate.

DR. LIEBLER: So, these strike-outs are basically not because of some inside knowledge of chemical distinct likelihood of being problems, but they're simply because they weren't previously reviewed, and we didn't want to add them in?

MS. BURNETT: Yes.

DR. LIEBLER: Okay. I think that I --

MS. BURNETT: If you want to keep them all in, we can.

DR. LIEBLER: Right. I agree. I think we can keep them all in, and I like the three-report strategy.

MS. BURNETT: Okay.

DR. BELSITO: Okay. So, you're happy with what's under silicates, Dan?

DR. LIEBLER: Yes sir.

DR. BELSITO: Okay.

MS. BURNETT: What about the clays --

DR. BELSITO: Yes, private. What about clays?

DR. LIEBLER: Yes.

DR. BELSITO: Okay. And zeolites?

DR. EISENMANN: One comment on clays, is there's an ingredient in the dictionary called clay that was 100 uses. And there are also a bunch of site-specific clays that I think you should ignore. But the one ingredient that is called clay --

DR. LIEBLER: I think the issue before us right now is the three-report strategy or something else.

DR. EISENMANN: Okay.

DR. LIEBLER: So, I like the three-report strategy and if anybody doesn't, I'll see them out back.

DR. BELSITO: Oooh, okay.

DR. LIEBLER: But anyway, I mean, think that's fine. And then we can finesse the individual ingredients as we get through these reports.

DR. BELSITO: Okay. Good.

MS. BURNETT: And keep all zeolites, then, too?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay.

DR. BERGFELD: I'm confused about the three-report strategy. You're going to have three more reports?

DR. LIEBLER: Three different reports, instead of having all these grouped together. There will be a report on silicates and a report on clays and a report on zeolites.

DR. BERGFELD: So, you're not accepting this?

DR. LIEBLER: That is what's proposed.

DR. BELSITO: We are. What we're saying is, that they were striking out ingredients that had not been reviewed and just keeping in those that were reviewed. And we're saying, no, if they're in the dictionary, let's put them all in and see where it falls, because Dan feels he can potentially read across. I mean, it's again, to get rid of calcium magnesium silicate, and keep in lithium magnesium silicate, that would make no sense to me.

MS. FIUME: So, it's just the difference of an add-on versus an existing ingredient?

DR. BELSITO: So, are we going to take these up all at one time then?

DR. BELSITO: Right. I understand. But it looks silly.

MS. FIUME: Yeah. Okay.

DR. SNYDER: Well, they're basically already written; they just got to par out the data, pretty much, right?

DR. BELSITO: Right. Yeah.

MS. BURNETT: I'll do another search to make sure there is --

DR. BELSITO: Right. Nothing new.

MS. FIUME: So, we're not going to approve this, we're just going to bring this back the three --

DR. BELSITO: No, just before Christina wasted her time putting them together, are we happy with this way of separating them?

DR. KLAASSEN: Yes.

DR. BELSITO: We're saying we are. Okay.

Marks' Team – December 9, 2019

DR. MARKS: Silicates. Let me see, where is that? Is that in the Admin too?

DR. PETERSON: Yep.

DR. HELDRETH: Yes, it is. PDF Page 61.

DR. MARKS: Oh, good. Thank you. I shouldn't have gotten ahold of the admin folder so quickly. So that's on Page 61 of the admin folder.

And the big toxicity concern was inhalation silicosis, and that's from mined silicates. So, the reason at the June meeting this year -- Lisa, I don't know how much of this you got from this memo in looking back.

But in June of this year, the Panel issued a final safety assessment of synthetically manufactured anamorphous silica and hydrated silica are safe when formulated to be nonirritating. And we were reassured with that, that there was no evidence of inhalation toxicity by those two ingredients.

And then we were going to have these other silicate ingredients included, but then it became evident that part of them, potentially, could be, mined. And then, now, we were in the inhalation toxicity issue. So, then, there was a suggestion that we divide these in three groups.

And I think also -- let's see in your memo, Christina. Did it say constitute impurities -- so, first was, do you like these three groups? And I guess, do we really need three separate safety assessments, or can we have one safety assessment which has these three groups in it?

So, the first question is, do you like the three groups? I don't think we have anything more than making an assessment. Do we like the groups?

DR. SLAGA: I like them, but I wouldn't put them in one report.

DR. MARKS: Okay. Yeah, I think that's important.

DR. SHANK: The three groups are fine with me. I leave that to the chemists. And if there are one report or three, it doesn't matter to me.

DR. MARKS: Lisa, you're the chemist. Ron is now really putting you on the spot.

DR. PETERSON: Yeah, I thought that they were fine. The three groups were fine.

What I didn't understand was why, like, zirconium silicate was included when it was no longer used; in that it's because there's safety issues associated with that?

And then there's one that was still in use, the -- I think it's -- I'm still learning how to notate in the PDF file, but the ammonium silver zinc aluminum silicate was still in use, so why was it crossed out?

MS. BURNETT: So, for our history, the ingredients that are not crossed out in those lists were already reviewed by the Panel. So, back in June 2018, the re-review came up and we proposed these add-on ingredients, which are the red cross-outs. And we reopened the report to add all these ingredients in.

And then, through the process, we've determined that these reports weren't as no-brainery as we usually go for add-ons, so we're proposing to remove them. So, all the ingredients that are in black, without the strikeout, were reviewed in the same report and have the same safety conclusion.

DR. PETERSON: Okay.

MS. BURNETT: Now, the Panel does not have to remove those ingredients. If you feel that they all should be still reviewed together, we can still go ahead with our review. Some of them may be closer in similarity than some of the others, but it's up to you guys to determine whether they should be removed or added.

It just was our suggestion that, oh, maybe these weren't no brainers after all. We still have to go forward with the re-review process, because these are now hanging out there. So, it's up to you.

DR. HELDRETH: Yeah, we used the frequency of use and concentration of use to inform us on which previously unreviewed ingredients to pick and look at. But for those ingredients we've reviewed before, whether or not there's reported use for them is somewhat inconsequential when we're doing a re-review, which is what we're doing here.

The Panel's looked at them before. It's now been at least 15 years since the Panel's looked at it, and it's time to take another look at it and say, has the science changed? Has the concentration of use changed, the frequency of use changed, and do we need to come up with a new conclusion or not?

So, that's why those ones, like the zirconium silicate, that you pointed out, remain in our list here because they're due for re-review, even though they may not be reported to be in use at this point.

DR. MARKS: So, instead of Freudian slip, Christina, in that last sentence right above the three groups of silicates, "CIR staff suggested that the remining ingredients be presented." Because that was the big issue was, when we got the composition at least, Lisa, the representatives from the amorphous silica industry -- SASSI, I think it was, so whatever that is -- that they couldn't tell us with a surety that these didn't have mined silica in them, as part of their composition.

So, I think they have to be reopened just for that issue alone. It's already reopened. But the ones that are in red and you crossed out, if they're similar ingredients, is there a reason not to include those from a --

DR. HELDRETH: Those were proposed add-ons that we made.

DR. MARKS: Yeah, now it says the remaining ingredients be presented in three separate reports. Yeah. Okay.

DR. HELDRETH: And so, we proposed taking them out just because it seems like it's been so arduous to try to finish these re-reviews. So, we've tried to simplify it, and take it down just to those ingredients that we really had to take a look at.

DR. MARKS: Hm. Oh, I understand the reasoning.

DR. HELDRETH: So, it was just a matter of trying to make this as simple as possible because it's been an ordeal. You know? And we've even brought in -- like you said, even the SASSI folks have come in and are still confused as to which goes with which. That's why we --

MS. BURNETT: I mean, certainly we could keep them in. I mean, I've done an initial search and I will do another search and see if there's anything new.

So, it's totally up to you. If you think it's going to cause more headache, then we can take them out. If you think that we've already gone through the headache, we can just pop a couple aspirins and keep going.

DR. MARKS: Well, I don't -- Ron and Tom? Was there anything when we looked at these before other than really in the inhalation issue and silicosis?

DR. SHANK: That was all. That was all we had.

DR. MARKS: And it's going to be interesting, because I think, ultimately, it's going to be an insufficient data -- or insufficient because we won't be able to get the composition, probably with a surety, that there's no mined silica. If we got that, I think we could move forward in any and all of these. Is my interpretation correct?

DR. SHANK: You could say safe as used if there's no mined product.

DR. MARKS: Yeah, there you go. So, you see how we word it around? And that's -- why didn't I think of that? But I was only thinking off the top of my head. Exactly.

DR. ANSELL: Isn't that where we divided this into three groups? Because, each silicate group, we have expansive inhalation toxicology and were prepared to move them forward; but not so for -- but we're uncertain about some of the other groups?

DR. MARKS: Okay, Jay. So, which group do you think -- do we have enough inhalation tox we can say that by reading across -- I think, whether we put that in the conclusion, Ron, or not, it will certainly be in the discussion in great detail.

So, we'll be looking at this again with -- but that's a good point you bring up. Obviously, it's back to our -- the data is what we want first. And if we have inhalation data that suggests in the present use and concentration, it's safe, then mined becomes almost a new subject.

Is there anything more, Christina, you wanted from us other than moving that the three groups are okay and to proceed? And I would say include everything you have here, even the red, and then sort it out later.

DR. PETERSON: Yeah, I guess that makes sense to me, too.

DR. MARKS: Does that sound good, Lisa?

DR. PETERSON: Yeah, I got very confused by the "no brainer" statement, and then why some things were crossed out and some things weren't.

MS. BURNETT: Yeah.

DR. PETERSON: I tried to figure it out, and I couldn't.

MS. BURNETT: Sorry.

DR. ANSELL: Only because it is confusing.

DR. PETERSON: Yes.

DR. MARKS: Okay.

DR. HELDRETH: Yeah. Just for Dr. Peterson's benefit -- so, when we use that phrase "no brainer," that's something that the Panel has kind of used as a measurement for when we do a re-review document and we consider

adding in additional ingredients that weren't reviewed before. And the idea being that the data already in the current report would support the safety of those add-ons, even if we never got any data about those new ones.

So, that's the idea here is --

DR. SHANK: No brainer.

DR. HELDRETH: -- do we know that these -- or do we think -- does the Panel think -- I'm sorry -- that these are no brainers? Are they so similar to the ingredients in the current report that we don't need new data to call them safe or have the same conclusion?

DR. PETERSON: Okay, I understand.

DR. HELDRETH: So, that's the idea behind that.

DR. ANSELL: And we fully support that approach. But if you put in an ingredient and then have to reopen the report, because you can't decide whether that ingredient is safe or not, then it falls outside of what we would consider to be a no brainer. So, it has to slip in -- all the data in the current report has to fully support the safety of the add-ins.

DR. HELDRETH: Right. So that's part of the reason why when -- it fell back to CIR staff to come up with groups. That's why we suggested removing these ones, because it's still completely and utterly unclear which ones of these ingredients are synthetic amorphous and which ones are potentially mined.

And we remember back when we looked at the hydrated silica and -- hydrated silica. They suggested to us that it was synthetic. But then you read the details of the synthesis, and the first step is, it's a mined silica and then chemically modified. Not exactly de novo synthesis; and there is potential for having crystalline silica.

DR. ANSELL: Right.

DR. HELDRETH: So, we don't know for any of these. Is the cosmetic ingredient only amorphous? Does it have some crystalline potentially? Is it potentially mined, we don't know. And that's why we suggested deleting any potential add-ons, because we don't know anything about those ones either.

DR. MARKS: Well, I think the conclusion's going to be the same for all of them. And that uncertainty is going to lead us to either an insufficient conclusion or a conclusion, safe as long as it contains no mined silica or crystalline silica.

And that's another way of -- unless, Jay, you have the inhalation toxicity studies on individual ingredients here that would support its safety.

DR. ANSELL: Well, yes. The presence of crystalline silica is a real issue.

DR. MARKS: Yeah.

DR. ANSELL: And that's why we fully support the separation of these.

DR. SLAGA: That's why I think they should be in separate reports.

DR. ANSELL: Right.

DR. SLAGA: I don't like to mix strong against safe.

DR. MARKS: Pardon?

DR. SLAGA: I don't like to mix something that has really potential health problems with something that is safe. That kind of dilutes the safe.

DR. MARKS: Well, that's why we split out in silica and hydrolyzed. But do you want to, right now, go to three separate reports? Or you want to kind of move forward and then let's see what it comes down to with --

DR. SLAGA: Let's see what it comes down to.

DR. MARKS: Okay. Is that okay, Ron?

DR. SHANK: Yes.

DR. MARKS: And Lisa, okay with you? Okay. So, move three groups okay, one report, include all the ingredients including the add-ons. And then we'll see where we go.

MS. BURNETT: And you said separate reports or one?

DR. MARKS: No. One report at this point.

MS. BURNETT: Okay.

DR. MARKS: We don't care.

DR. HELDRETH: I think, separation within the report.

DR. MARKS: Oh, yeah. Absolutely. To me, it just makes it easier in some ways if it's all grouped together.

DR. SLAGA: It makes it easy. Right. It does.

DR. MARKS: Oh, listen.

DR. SLAGA: Yeah.

DR. MARKS: Christina's fine, if she can get through citrus. This is a piece of cake compared to citrus and all that stuff, huh?

MS. BURNETT: Yeah.

DR. MARKS: Okay. Any other comments? So, I'll move three groups are fine, one report at this stage. Include all the ingredients including the add-ons, and then we'll see where we go from there. Okay. Let me save this. So, we'll see what the Belsito team thinks tomorrow. Okay.

DR. HELDRETH: One more thing on this one.

DR. MARKS: Sure.

DR. HELDRETH: I think industry had suggested, if we were keeping any of the stuff in clay groups, that we actually review the ingredient clay since some of these things, like hectorite or whatever, are just subgroups of that one in there.

Should we go ahead and throw that one in there since we're going to be reviewing all these clays anyway?

DR. MARKS: I think that's fine.

DR. SHANK: Okay.

DR. MARKS: Let's include it now, and we could always -- I guess part of that is thinking of you, Christina. If we throw clay in there, does that add a lot more work for you? Although, if it's a safety concern, work is not the issue.

MS. BURNETT: It won't be a problem. I'm more worried about generic searches and --

DR. MARKS: On clay?

MS. BURNETT: Yeah. But we'll figure it out. It's got to be done at some point, so why not now?

DR. MARKS: Yeah. Okay.

DR. HELDRETH: Thank you.

DR. MARKS: Maybe adding clay, Tom, will then force us to go into three groups. Clay will be too big. Okay.

Full Panel Meeting – December 10, 2019

DR. MARKS: So, this is on Page 61 of the Admin folder. And, what is being proposed is that we have three groupings of the silicate ingredients. As you recall, in the September meeting a final safety assessment of synthetically manufactured amorphous silica and hydrated silica are safe when formulated to be non-irritating.

The other silicate ingredients, we were concerned about chemical characterization, method of manufacturing, source if mined and whether it's amorphous or not. And that all led to obviously the potential toxic inhalation effect of the silicosis.

So, we have already opened these ingredients. Christina listed them under the group, silicates, clays and zeolites, and we concur with that grouping.

There was a discussion whether or not to add the proposed ingredients, they were in red and crossed out. We liked adding them since we're going to look at these different groups.

And then there was a discussion as to whether or not -- so we liked the three groups; do we do one report or multiple reports? And we fell on the side of doing one report just divided in the three sections, but that's not a hard and fast.

DR. BERGFELD: Belsito response?

DR. BELSITO: Well, we liked the groupings. We agree not to include those that were suggested to be eliminated. We didn't see the reason for eliminating them.

We did not specifically discuss the issue of putting them into one report and three separate headings. But just thinking about how mind-boggling this is going to be, I would prefer to have three separate reports, personally.

DR. LIEBLER: If we have one report we'd effectively be converting silicates to algae.

DR. MARKS: I've likened it to citrus. Christina, she did such a good job with citrus, I figure she could have handled it.

DR. LIEBLER: We've been there and done that.

DR. MARKS: Yeah, as I said, we didn't have any strong feelings one way or another, so separate reports are fine with our team.

DR. BERGFELD: So, acceptance of the list with the deletion, three different categories and three different reports.

DR. MARKS: Yes.

DR. BERGFELD: I call the question, all those in favor of that decision? Thank you, unanimous.

MARCH 2022 PANEL MEETING – DRAFT AMENDED REPORT

Belsito's Team Meeting – March 7, 2022

Dr. Donald Belsito: So we're moving on to Clays. So this is the last of the group that we split out from silicates via (inaudible) clays, and really this is the first time we're looking at it. We split it out. We asked for mean and range of particle sizes. And corresponding sizes in final formulation, particles, chemical characterization, composition, impurities and method of manufacture, source data. But that was just I guess a wish list really so now we've got to look at what data we have here. There's also wave three comments from the Council, and we know that Kaolin is used in airbrush device. From wave 2. So in the ingredients listed activated clay and clay. We have absolutely no data. And the definition of activated clay as it it's chemically synthesized aluminum silicate and sulfuric acid and heat. And the question I have is this forming crystalline silica? And for clay, we have zero data and just the main ingredients being hydrated silica and aluminum. We don't have a clue what the other ingredients are.

Dr. Dan Liebler: So I think that considering the structure of clay is helpful here. You know which starts at the top of PDF 82 with that diagram. With a multi-layer silicate sheets. And then some coordinated other atoms.

That this sheet like structure is distinct from the hexagonal crystalline structure of crystalline silica, such as quartz. And I think that we should not necessarily assume that these mined ingredients are toxicologically equivalent to mined crystalline silica. Like quartz. So it's a similar concern I had to our interpretation of the chemistry as in the diatomaceous earth report. It's not all. Not all silica containing materials are created equal.

Dr. Donald Belsito: OK. And are you happy with the method of manufacturing that is given this is PDF 82 going on to 83? Or do we need better data for cosmetic grade materials? More complete composition for clay.

Dr. Dan Liebler: Well, I mean, I think these are all essentially. At least the ones that are listed are all mined, washed, filtered, ground. etc. So that's what we're given with these. Let me look at the full list. So we got attapulgite and bentonite. Kaolin. Yeah. Bentonite Hectorite Montmorillonite. So you got virtually all of them listed as mined, essentially, mined washed and or I'm sorry that that's the descriptions. Yeah, I'd like to. Now, let me see here. So we don't have any explicit description. Of the manufacturer for the ones other than the ones that are listed. So we've got attapulgite. Kaolin. And I think it's hectorite?

Dr. Donald Belsito: Bentonite.

Dr. Dan Liebler: Bentonite. OK, so the others? We should be able to at least confirm that they are mined, and not synthetically produced.

Dr. Donald Belsito: Well, activated clays, apparently synthetically produced.

Dr. Dan Liebler: Are you getting that out of table one?

Dr. Donald Belsito: Yeah, I think so.

Christina Burnett (CIR): Based on the definition.

Dr. Donald Belsito: Yeah.

Dr. Dan Liebler: Oh, inorganic compound obtained by heating natural aluminum silicate with sulfuric acid. Yeah, if this isn't mined and it's not demonstrably structurally similar or identical with the other clays. It probably should be deleted from the report.

Christina Burnett (CIR): So delete activated clay?

Dr. Dan Liebler: Yeah, we delete it unless we can show that it belongs with the other ingredients. Either by virtue of its structure. You know, well characterized information on the structure or the method of manufacture beyond what's in the table. It's an entry in the table suggests that it doesn't belong.

Dr. Paul Snyder: We thought the botanicals were a ******.

Christina Burnett (CIR): Oh my God.

Dr. Paul Snyder: So I had. I thought these were all safe as used because clay is GRA in indirect food additives. Except for inhalation, and I think the inhalation issues surrounds the insufficient date announcement that mean range of particles, the chemical composition, impurities, data and method of manufacturing source data. I thought we were

still stuck there because I don't think we have any data on some of these. Or insufficient data, but I thought for only for inhalation. Incidental inhalation, I thought for. Although the uses that either were OK, it goes safe as you.

Dr. Dan Liebler: Yep.

Dr. Paul Snyder: Kind of the same. I mean, it's the same ****** to me.

Dr. Dan Liebler: Yes, we don't have any inhalation tox on these.

Dr. Donald Belsito: Right.

Dr. Dan Liebler: Yeah. So that's what that's what saved us with the, with the diatomaceous earth report, because we did. Here we don't and I wouldn't support the same approach that we took at diatomaceous earth. I think we would need to raise a concern about inhalation. Safe is insufficient for (inaudible) potentially inhaled products. I mean, we do know on the other hand that clays are structurally distinct. From the silicate structures that we associate with pulmonary toxicity, but if we don't have. You know, then it's just a question of, do you? I think the analogy to silicates. Doesn't necessarily hold up chemically. But then the lack of any inhalation tox still raises a, I think a legitimate concern. Is that where you are, Paul?

Dr. Paul Snyder: Yeah, I mean, I mean, I. Yeah, I mean it's just the same, same old, same old, you know, it's just there's just no inhalation data and there's no impurity data or chemical composition or reap range of particle size or anything.

Dr. Donald Belsito: Well, we know that Bentonite can contain crystalline, it says from the documents.

Dr. Curtis Klaassen: I think there was an intratracheal study I remember.

Dr. Donald Belsito: Or yeah, we had carcinogenesis studies. This is the one Paul where all the inhalation carcinogenicity.

Dr. Dan Liebler: PDF 86-88.

Christina Burnett (CIR): No, it's for Attapuligite (inaudible). And Attapulgite has the IARC designation for at different fiber lengths.

Dr. Donald Belsito: We also have montmorillonite (inaudible).

Christina Burnett (CIR): That's the *(inaudible) study.

Dr. Donald Belsito: We also Christina need to update the concentrations of use. The last data we have is 2018.

Christina Burnett (CIR): I forget to do that? The concentration of use means… that's the data that I have. Council will have to do a new survey.

Dr. Donald Belsito: Yep. Do we know if that's under works?

Christina Burnett (CIR): I don't.

Dr. Carol Eisenmann (PCPC): It is not in the works.

Dr. Donald Belsito: Thank you, Carol.

Dr. Donald Belsito: So where are we with these here? With this, with these carcinogenicity studies? Are they helpful? And should they be moved to the toxicity section?

Dr. Dan Liebler: We awaiting judgment by Paul or Kurt.

Dr. Curtis Klaassen: Well, I think it's appropriate, but have it where they are at because, they really are. This attapulgite. Is ah. You know, I think they this this group of chemicals maybe have a greater concern in regard to lung and lung cancers and some of the other components that we've been looking at. I mean, you can see here that.

Dr. Paul Snyder: A lot of lung cancer.

Dr. Curtis Klaassen: They did a yeah, and there's some nasty ones. You know, they got a parenteral, mesothelioma, adenocarcinoma, three bronchiolar hyperplasia and not so bad. Ah. And the mesothelioma.

Dr. Dan Liebler: Yeah.

Dr. Curtis Klaassen: Like mentality, older neoplasia. I mean, I think. They had a fall guy that we definitely don't want to have.

Dr. Paul Snyder: Can you send me that study, Christina, please? Report.

Christina Burnett (CIR): I will have to find it because these are from the original report, yeah.

Dr. Paul Snyder: Oh, OK, that's right.

Christina Burnett (CIR): But I can look.

Dr. Curtis Klaassen: Panel that says under the kaolin right underneath it is it was used as the negative control.

Christina Burnett (CIR): Correct.

Dr. Curtis Klaassen: Ah. And they. They had two bronchiolar alveolar tumors were reported.

Dr. Donald Belsito: OK.

Dr. Dan Liebler: So Don, the previous discussion which is on PDF 96 is kind of interesting. It was put up there for our consideration. A panel. I'm just reading a little bit panel did note concern about inhalation of these ingredients due to a report in case of pneumoconiosis and fibrosis in humans and pulmonary lesions in animals. However, extensive damage in humans was the result of direct occupational inhalation of a dust and lesions and animals were affected by particle size, fiber length and concentration. So the panel basically said that most of these formulations aren't respirable and the preparations that are respirable the concentration of the ingredients are low. So even so, the panel considered spray containing these solids should be formulated to minimize inhalation. So, in other words, on all sides of the issue.

Dr. Donald Belsito: I mean, this is not my area of purview, by the way, we have no sensitization data, but it's not going to pass the stratum corneum so we can argue that in the discussion. So, I wouldn't push for that.

Dr. Dan Liebler: I mean in, you know, given the data that we have in, in, in front of us at this stage of the report. I suppose. You know, I guess we could consider an IDA. More inhalation tox. I don't know if that's needed it, given the data that we already have from the old report. The data from the old report, I think we would probably now have a conclusion that says safe as used except for products where incidental inhalation may occur.

Dr. Donald Belsito: Right.

Dr. Paul Snyder: In the absence of Impurities, composition and Inhalation tox toxicity studies, right.

Dr. Dan Liebler: Yeah.

Dr. Donald Belsito: Well, we have products where incidental inhalation, we have products that may have incidental inhalation. So. I mean, this is a first pass, so I guess the first question I have is, are we getting rid of activated clay because it's manufactured and not mined?

Dr. Dan Liebler: We don't have enough description of the final material to show that it actually belongs with the rest of these. It's called activated clay, but it may not really be like the other clays.

Dr. Paul Snyder: So we should.

Dr. Donald Belsito: OK, so we're getting rid of this.

Dr. Paul Snyder: So should the title, be natural, naturally sourced clays.

Dr. Donald Belsito: Sure. OK. So, we're going to get rid of the activated clay, we're happy with the manufacturing?

Dr. Dan Liebler: I think other than that, we are. Interestingly, activated clay has no reported uses no concentrations.

Dr. Donald Belsito: Right. Right. So we're happy with manufacturing. What about impurities?

Dr. Dan Liebler: Taking another look real quick. I think we're satisfactory on it. Composition, impurities.

Dr. Donald Belsito: The bentonite has cristobalite.

Dr. Dan Liebler: Right.

Dr. Donald Belsito: OK and carcinogenicity data. How are we dealing with that?

Dr. Paul Snyder: Well, I think this one, this is I think a little bit different here is that for these, we really want to know the particles, mean and range of particle size distributions, right? More so than the more so than impurities.

Dr. Donald Belsito: OK. So is it insufficient for mean and range of particle size distribution?

Dr. Paul Snyder: I think at this stage, yes.

Dr. Donald Belsito: There as long as we're asking for that, we can ask for skin sensitization. We don't have any.

Dr. Dan Liebler: Yeah. For Bentonite, we do have some particle size information on PDF 83. It says 90% of the particles were smaller than 68 microns, 50% smaller than five microns.

Dr. Donald Belsito: Yeah.

Dr. Dan Liebler: I don't think it will boil out like incidental inhalation.

Dr. Donald Belsito: It'll be the heavy metal boilerplate in discussion. OK, so we are insufficient for mean and range of particle distribution except for Bentonite?

Dr. Dan Liebler: Right.

Dr. Paul Snyder: Well. Yeah. I mean, it's 60% of them are for sure under 10 microns.

Dr. Dan Liebler: That's for bentonite.

Dr. Paul Snyder: Yeah.

Dr. Dan Liebler: Yeah, I mean it, I don't object to asking for it even if we have it, but it doesn't mean it doesn't tell us what the particle size distribution would be in the product that contains you know, the clay.

Dr. Donald Belsito: We want particle distribution and final product.

Dr. Dan Liebler: Yeah, nobody is going to have that.

Dr. Donald Belsito: Right.

Dr. Bart Heldreth (CIR): You actually asked for that before. At the top of the memo, on PDF Page 3.

Dr. Donald Belsito: Yeah.

Dr. Dan Liebler: Yeah.

Dr. Bart Heldreth (CIR): It's the first data need.

Dr. Dan Liebler: Alright, well we can keep it in and then decide whether we you know. But I mean our discussions public record so.

Dr. Paul Snyder: I mean, like I said before, it's for me there's safe as used. Other than that incidental inhalation

Dr. Dan Liebler: Yeah because, you've got all this tracheal installation, carcinogenesis carcinogenicity, right. So that's that's the fly in the ointment right there.

Dr. Donald Belsito: OK so. We're asking for particle size. This range and distribution for all except Bentonite and then.

What are we asking to clear the inhalation that we're saying is the issue. We have these carcinogenicity studies.

Christina Burnett (CIR): You have it on one, not the others, correct

Dr. Donald Belsito: Right, we have it on attapulgite?

Dr. Paul Snyder: It's just going back to the previous discussion, Don, on Page 96 where we want to, we want to say the that the formulations are not respirable. So, we need to know what the range of particle sizes are and product preparations are respirable the concentration in the ingredients is very low.

Which I think is not quite how we've handled it now is it updated? But.

Dr. Donald Belsito: We pretty much know that attapulgite should not be in products that could be inhaled.

Dr. Paul Snyder: Bentonite because most of the particles are less than. Less than 10 microns.

Dr. Donald Belsito: Or. And it also has a lot of cristobalite. Kaolin seems to be OK. It was the negative control.

Dr. Paul Snyder: But is it Kaolin and the one that's used in airbrushes?

Dr. Dan Liebler: So we'll just need our airbrush discussion boilerplate once we adopt it.

Dr. Donald Belsito: Heavy metal. So what I have here is insufficient for median range of particle distribution for all except Bentonite. Which leaves what all except Attapulgite. No. All except Bentonite, right?

Dr. Dan Liebler: Yep.

Christina Burnett (CIR): Correct.

Dr. Donald Belsito: Attapulgite and bentonite should not be in products that could be inhaled. And airbrush discussion boilerplate. Dermal all we have is a negative irritant study in hectorites. So, we want sensitization irritation and concentration of use as long as we're going forward.

Dr. Dan Liebler: I think the inhalation data requirement is everything except Kaolin, right?

Dr. Donald Belsito: Well, do we want them to repeat that attapulgite?

Dr. Dan Liebler: Oh no. Right. Unless you think that tracheal (inaudible). Actually, the data we have and the carcinogenicity section for attapulgite includes inhalation and parenteral OK, yeah.

Dr. Donald Belsito: And Bentonite contains cristobalite. We want an inhalation study on that.

Dr. Dan Liebler: Yeah.

Dr. Donald Belsito: We do.

Dr. Dan Liebler: I think so.

Dr. Paul Snyder: Yeah, at this pass, yes.

Dr. Donald Belsito: So it's…

Dr. Dan Liebler: I mean, you know, we will have an inhalation reason to dissociate any of them. Without having data and Kaolin is the one that was inhalation as a negative control and it behaved that way. So we don't have that kind of data for anything else. So Attapulgite's documented with respect to producing tumors and so forth, the others have no data one way or the other. So, I think they, you know, they belong with an insufficient data requirement.

Dr. Donald Belsito: So maybe we need. Excuse me, do we need chronic inhalation for kaolin? Was used as the negative control and was negative.

Christina Burnett (CIR): I did find that study.

Dr. Dan Liebler: Yeah.

Christina Burnett (CIR): I could send it on to whomever would like it.

Dr. Paul Snyder: I would like it please.

Christina Burnett (CIR): OK, Dr Snyder, right.

Dr. Paul Snyder: Yes, please. Thank you, Christina.

Dr. Donald Belsito: Well, chronic inhalation for all except attapulgite and kaolin right now.

Dr. Dan Liebler: So. Right.

Dr. Donald Belsito: So we're dropping activated clay. We're asking for mean and range of particle distribution for all except Bentonite. We're asking for chronic inhalation for all except attapulgite and Kaolin. And we're asking for sensitization, irritation and the maximum concentration of use. Which is what 7% is that right?

Monice Fiume (CIR): I'm sorry, Kaolin is used that up to 53% in manicuring preparations.

Dr. Paul Snyder: Those are manicure preparation.

Monice Fiume (CIR): Bentonite 15% in skin care preparations.

Dr. Paul Snyder: Yeah.

Dr. Donald Belsito: So (inaudible) at 15% in Bentonite? And the discussion, heavy metals? And Airbrush technology and that attapulgite and bentonite should not be used in products that could be inhaled based upon the carcinogenicity studies. Without attapulgite and the cristobalite concentration in bentonite. Is that correct?

Dr. Paul Snyder: And particle size distribution in bentonite also. So that for the other ones, if we get particle size distribution says not respirable, then we don't need the chronic inhalation studies.

Dr. Donald Belsito: Yep. For bentonite, it's because of cristobalite and particle size.

Dr. Paul Snyder: Correct.

Dr. Donald Belsito: And for attapulgite, it's because of data.

Dr. Paul Snyder: Correct.

Dr. Donald Belsito: Anything else for this?

Dr. Curtis Klaassen: So eventually with attapulgite it we know that it can cause tumors. So in the end, will we most likely say that it's OK to use, but we just need to minimize the inhalation exposure?

Dr. Donald Belsito: We're already saying that in the discussion.

Dr. Curtis Klaassen: OK.

Dr. Donald Belsito: They both attapulgite and bentonite should not be in product.

Dr. Curtis Klaassen: So yeah. Being the Devil's advocate a little. Done with all of the other compounds. Why do we want to do a chronic study of carcinogenicity. Because they'll have the same conclusion one way or the other.

Dr. Donald Belsito: Well, we have Kaolin and it's negative. So, we don't know what the others are going to be.

Dr. Curtis Klaassen: Then we could. We won't say anything about *(inaudible).

Dr. Paul Snyder: We could have a *(inaudible) size, Curt, then we don't have to worry about it.

Dr. Curtis Klaassen: But they're all going to be in the right size.

Dr. Paul Snyder: I think you're right.

Dr. Donald Belsito: Well, let's see what we got. I mean, it's, it's insufficient. Do we need any other data needs so insufficient mean and range of particle distribution for all except Bentonite? The chronic inhalation for all except Attapulgite and Kaolin. And dermal sensitization irritation at 15%, Bentonite and already in the discussion heavy metals, the attapulgite and bentonite not in products that could be inhaled, attapulgite because of the carcinogenicity studies, bentonite because its cristobalite content, particle size and also discussing airbrush technology discussion boilerplate. That's what I have.

Dr. Paul Snyder: I think you have it.

Dr. Donald Belsito: OK. Let's move on, folks. It's 3:15. We still have two. One being, botanicals.

Dr. Curtis Klaassen: Thanks.

Dr. Donald Belsito: Christina, any questions?

Christina Burnett (CIR): No.

Cohen's Team Meeting – March 7, 2022

Dr. David Cohen: OK. Yeah. Look, I told you the out of the gate with these were a little tough, so we have let's we want to move on to Clay.

Christina Burnett (CIR): Sure.

Dr. David Cohen: So, this is used as a skin conditioning agent and it's used a fair amount and in 2018 the panel reopened a 2003 safety assessments for several silicates, clays and zeolites. At I think that meeting Don had suggested splitting off clays on their own. That was probably a very good recommendation. And at that meeting but insufficient data was described for eight clay ingredients, asking for particle size ranges that are used in sprays and

powders, chemical characterization of composition, method of manufacturing. We have updated VCRP information. And there's a mention about this discussion about pneumoconiosis. And the second wave data, we see clays used in airbrushes. And in impurities, there's no mention of crystalline silica, but I think there's a comment about it in the bentonites section. So, and the third wave of edits from PCPC were great. The constituents didn't seem to alarm me for irritants or allergens. What do you think, Tom you want to start?

Dr. Thomas Slaga: Ah, yeah, well, since the last meeting, we really haven't received any new data. So you know particle size and all of that, the chemical characterization, etcetera. It's the same, so same conclusion as last time. Unless I missed data? But what I see is that we didn't receive any.

Christina Burnett (CIR): No, we didn't.

Dr. Carol Eisenmann (PCPC): But, this is Carol. Sorry to interrupt, but, method of manufacture for this doesn't make sense. Mainly you dig it out of the ground and clean it up. I mean, what, what more can you say about Clay?

Dr. Thomas Slaga: Ah. I didn't ask for that. I think the 1st 2. The particle size and chemical characterization that's more important. The method I agree with the method of manufacturing, it's not really needed.

Dr. David Cohen: I put it since this predated me it if we had this and this was new for us. This was just a new report on clay. Without the prior IDA or bias from that. What would you? How would you come out on this? What? What would you want to know? And if we knew it was being used in a spray product in an airbrush, we would simply split the conclusion out that there's insufficient data for airbrush. But what part of this report do you still need or want irrespective of the idea in the past?

Dr. Thomas Slaga: I don't think I would need any.

Dr. Wilma Bergfeld: I thought it was missing the molecular weight.

Dr. Thomas Slaga: *(inaudible) That's where I would go. So but we do have the IDA with those requirements and we have to you know either get something or find a reason why we don't need it. That's where we're at right now.

Dr. David Cohen: Well, no. You said something that you need we needed something?

Dr. Wilma Bergfeld: Well, I just said that I had the old document that I was reviewing and a lot of the chemical information is in the old document including molecular weights. And I didn't really see all of that in the new document.

Which may or may not help the chemists, but they are ranging from 100 to 350 in molecular weight. And they have full description of the actual chemicals in the old document. We're still missing some of the human stuff. Sensitization, I recall.

Christina Burnett (CIR): Right. There is no, there's no sensitization data.

Dr. Ron Shank: Yeah, we don't have it.

Dr. Wilma Bergfeld: No, no. Yeah, I have it listed here.

Dr. Ron Shank: We didn't ask for it last time. Why?

Christina Burnett (CIR): Well, last time you looked at it was all lumped together with the silicates and silica. I felt the focus at that time was on those ingredients. And these were kind of not really discussed at that time.

Dr. Ron Shank: OK.

Christina Burnett (CIR): It was a big report last time, so I understand.

Dr. David Cohen: So.

Dr. Ron Shank: Well. I thought there was, these are large, large molecules are not likely to penetrate the epidermis. So I don't have a systemic toxicity concern, apparently they can be formulated, or the formulators can choose. Clays. That can be, I don't know if it's certified. But claimed to be free of crystalline silicate. I understood that from the report. I think the inhalation can be handled by the boiler plate. So the. The only serious lack I saw was sensitization.

Dr. David Cohen: Right, so when I.

Dr. Ron Shank: That'll probably surprise everybody.

Dr. Wilma Bergfeld: I would think irritation too.

Dr. Ron Shank: OK, I put those together.

Dr. Wilma Bergfeld: Yeah. OK.

Dr. David Cohen: Yeah, I mean, I think when I looked at the constituents, I'm like I don't. Expect much in the way of sensitization, but it's possible here because there's some minerals there, so we'll ask for sensitization and irritation and sensitization.

Dr. Thomas Slaga: Yes.

Dr. Ron Shank: Yes.

Christina Burnett (CIR): Yes. If you would like, you can just, when you issue the new IDA, you can ask for the previous items again to minus the method of manufacturing. If you believe that's not needed.

Dr. Ron Shank: Well, I thought we had that.

Dr. David Cohen: And then.

Dr. Thomas Slaga: Yeah.

Christina Burnett (CIR): Yeah.

Dr. David Cohen: Wait, so do we?

Christina Burnett (CIR): We have the method of manufacturing for attapulgite, bentonite and kaolin. Strip mined and then cleaned up a little bit.

Dr. David Cohen: OK so as same as before last method of manufacturing for the ones we have. And we want irritation and sensitization data and would we still split the conclusion, I mean it it's in, it's in airbrush material.

Dr. Wilma Bergfeld: Correct.

Dr. Bart Heldreth: Well, and since you're putting out an insufficient data announcement, you don't really have to put out a conclusion yet.

Dr. David Cohen: No. I know I think just during tomorrow we would discuss airbrush, right? We're not going to split anything because there's no conclusion to split. But this this data. Anything else on this one?

Dr. Thomas Slaga: No.

Christina Burnett (CIR): Because it will come up eventually.

Dr. Wilma Bergfeld: Well.

Christina Burnett (CIR): Possibly. I don't know, I mean. I did note in the report that the IARC and the California board had flagged attapulgite for fiber lengths greater than five micrometers. Is that anything that will need to be discussed in the future?

Dr. Ron Shank: Yes.

Christina Burnett (CIR): OK. Do we have anything to actually…How did you want to state anything? Did you want it similar to eronite where you expect that it's not to be used or controlled?

Dr. Wilma Bergfeld: Should be similar.

Dr. Ron Shank: Well, long fibers. It's a matter of fiber length.

Christina Burnett (CIR): Yes it appears.

Dr. Ron Shank: So long fibers should not be used and apparently of the formulators can choose (inaudible) that don't have long fiber. Attapulgite.

Christina Burnett (CIR): OK.

Dr. David Cohen: In it may come up also on page 95 under Bentonite. I think it's in the occupational exposure section.

It says, however, because some forms may contain variable amounts of respirable crystalline silica, prudent management, inherent occupational exposure limits as appropriate. So are we going to get into the crystalline silica thing here for Bentonite?

Dr. Wilma Bergfeld: I think so.

Dr. Ron Shank: Yes.

Dr. Wilma Bergfeld: You have to discuss it at least.

Dr. David Cohen: Yeah.

Dr. Wilma Bergfeld: In the old document it also says that clay has a great ability to absorb.

Christina Burnett (CIR): So yeah, it there was a very long section on how they use it to clean up, you know, pollution and use it in all sorts of things just to pull toxins out.

Dr. Wilma Bergfeld: Adsorbed then.

Christina Burnett (CIR): Adsorbed yeah.

Dr. David Cohen: Message not otherwise specified.

Christina Burnett (CIR): Yes, so that information.

Dr. Ron Shank: That's not a cosmetic use.

Christina Burnett (CIR): Correct. It was included in the old report, I believe, you know, we put a lot of information that we don't use anymore in those.

Dr. Wilma Bergfeld: Well, that I don't think that I think we conclude I think that there could be used in a cosmetic.

Dr. David Cohen: Oil absorption. Yeah, oil absorbing.

Dr. Wilma Bergfeld: There, yeah.

Dr. David Cohen: Oil absorption, providing a matte sheen right, and that's maybe all part of clay.

Dr. Wilma Bergfeld: That's what the masks do.

Christina Burnett (CIR): I can't remember if, did I completely remove that because I can just... Yeah, I put just it's good adsorption performance in the non cosmetic use section. Is that sufficient? OK.

Dr. Ron Shank: Yeah, that's alright.

Dr. Wilma Bergfeld: Right. The other thing is that I I'm trying to think where I wrote this down at some of these are GRAS ingredients and the question was whether they're used as nanoclays in cosmetics. And that kaolin is food grade. So we have maybe to deal with the GRAS ingredients in the in the discussion.

Dr. Ron Shank: Yeah. Well, we don't need systemic tox data.

Dr. Wilma Bergfeld: Bentonite. What? No. That's right, Bentonite. Yeah, I was the one, I think.

Dr. David Cohen: Bentonite was the oral one.

Dr. Wilma Bergfeld: Yeah. So one of the GRAS and the food additives are indirect are the silicates.

Dr. David Cohen: OK. So we're going to go with the IDA as we suggested, they'll be a lively discussion about other components of this. And the report will proceed along. OK.

Full Panel Meeting – March 8, 2022

Dr. Don Belsito: OK so basically this was split out of the silicates, clay, and zeolite report in 2018 and it's really the first time that we're seeing this package on Clay. We do have a good amount of information in the package, which we viewed. And basically inhalation and heavy metals are going to be the focus with this report. The first thing is that activated clay appears not to be mined, but rather manufactured and Dan recommended it be dropped from the group and then for the other remaining clays, they're insufficient for mean and range of particle distributions. For all except bentonite. Attapulgite or bentonite should not be in products that could be inhaled. Attapulgite because of

the carcinogenicity data, bentonite because of its content of cristobalite. The airbrush discussion in the boiler plate that we've discussed. Dermal, all we have is a negative irritant study on hectorite. So we want sensitization and irritation of 15% bentonite, which is the highest uses and we want chronic inhalation for all except attapulgite and kaolin Attapulgite already known to be positive and kaolin was used as a negative control in those studies. So get rid of activated clay and insufficient. For the reasons that I gave.

Dr. Wilma Bergfeld: David, comment?

Dr. David Cohen: Digesting. That was very comprehensive and I think checked off everything we had. Don, you mentioned the respirable Crystalline silica in the bentonite.

Dr. Don Belsito: Yeah.

Dr. David Cohen: While the constituents don't necessarily alarm us for allergens, we wanted irritation and sensitization, how you mentioned it.

Dr. Don Belsito: Yeah, I mean it's a wish list. We asked for it.

Dr. David Cohen: So. Yeah. Yeah, I would second the Belsito team motion.

Dr. Wilma Bergfeld: Any other comments about pulling out the activated clays?

Dr. David Cohen: We didn't discuss that and that was interesting. Ron and any comments that seems to make sense to me because we commented on the method of manufacturing which is pulling clay at the ground and cleaning it up. Ron, Tom, what do you think? I'm OK with pulling that out.

Dr. Ron Shank: Great.

Dr. Thomas Slaga: I am too.

Dr. Ron Shank: I have no objection.

Dr. Wilma Bergfeld: Ron. Dan, could you describe why you pulled it out?

Dr. Dan Liebler: From the definition of briefly indicated in table one, I think it is. It's an inorganic compound obtained by heating natural aluminum silicate with sulfuric acid. So, this is really distinguishes it from all of the other mined ingredients and because there's not much description of what it is, does it have the same kind of lattice structure and everything? I felt that there, you know, the burden would be on industry to demonstrate that this material belongs in the same category as these others.

Dr. Ron Shank: OK.

Dr. Wilma Bergfeld: OK.

Dr. Paul Snyder: We also discussed changing the title then to naturally sourced clays.

Dr. Don Belsito: Right.

Dr. Wilma Bergfeld: OK.

Dr. David Cohen: Ah, that's a that's a good idea.

Dr. Wilma Bergfeld: Yeah. It's so general agreement changing the title. Yes, I gather. OK.

Dr. Dan Liebler: Yep.

Dr. Wilma Bergfeld: OK, so we had a second on a data, a conclusion of insufficient data with all the insufficiencies described and pulling out the activated clay. Christina, do you have a comment?

Christina Burnett (CIR): Yeah, I just want to read back what the data needs are to make sure I got it done right. I have dermal irritation and sensitization at maximum concentration of use, which was the one for bentonite.

Dr. Don Belsito: 15%.

Christina Burnett (CIR): 30%. Chronic inhalation studies on all except attapulgite and kaolin. And then particle size distribution for all of them. Except for bentonite. Is that correct?

Dr. Don Belsito: I'm. I'm just checking here. Yeah, I mean, and range of particle size distribution for all except bentonite, right, Christina?

Dr. Paul Snyder: That's correct.

Christina Burnett (CIR) : OK.

Dr. David Cohen: And on this is going to be perfect for your new inclusion in cosmetic uses, because this is going to come up for the airbrush.

Dr. Don Belsito: Right.

Dr. Wilma Bergfeld: Yeah. OK. Any further discussion will call the question. All those opposed. Approved.

SEPTEMBER 2022 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT

Belsito's Team Meeting – September 26, 2022

Minutes not captured.

Cohen's Team Meeting – September 26, 2022

Dr. David Cohen - We were doing well. And now we have Clay. At the March at the March 22 meeting, we determined that we had an IDA for the safety of seven clay ingredients. We asked for particle size distribution except for bentonite, chronic inhalation data, except for attapulgite and kaolin. And then irritation and sensitization at max use. We received a considerable amount of information since then. We also received some information, comments from the Women's Voices for the Earth. And some commentary on nanoclays. And also some information in the second wave about illite. Or illite, or yeah, illite. So there's a lot to discuss here. I don't know. I don't know if I can corral it all at once. So why don't we just go through this specific data that we did get. What comments do we have on the received information so far? Or you know what? Let's get more specific. The Women's Voices for the Earth discussed some issues with kaolin and crystalline silica. Yeah. And I thought the discussion, it dealt with that sufficiently. Tom, what were your thoughts on their comments? You're still on mute. Tom. You're on mute still.

Dr. Wilma Bergfeld - And hear you.

Dr. Tom Slaga – Sorry. I'm trying to keep back the back door was slamming earlier when you thought it was.

Dr. David Cohen - A hammer.

Dr. Tom Slaga - OK, so uh, the winds picking up but. Well anyway. I thought her comments were pretty good, actually. You know, they're they put a lot of work into those and you know, we always have to be very careful to, you know, make sure we respond to them and you know the, I don't know how I am. This is a very tough one to decide if we have sufficient to go forward or this insufficient to forward only on that and what we need, I, you know, we don't have everything we need yet. So.

Dr. David Cohen - Well look, the issue is does the discussion point where we already put in that attapulgite and bentonite should not be used in cosmetic formulations that may be incidentally inhaled in one of their…

Dr. Tom Slaga – Right.

Dr. David Cohen – Points. Are do we include kaolin and hectorite in that?

Dr. David Ross - Could I make a comment here? I felt,

Dr. David Cohen - Please.

Dr. David Ross - You know where we're back into your silicates discussion and there was an exchange, I think, between probably Christina and Ron Shank, which, on the diatomaceous earth discussion, hence my comment last time. And I think the wording went something like this, "When the potential for incidental inhalation of silica exist due to crystalline silica impurities and the cosmetic, the concentration of silica and the product the concentration of use of the product and the repeat dose inhalation data were safe." OK, so that's one comment which one in the discussion. And you know what I would say is that what I think you have is because of the, those chronic inhalation data, I went back to that original MRC study in the 1987 with kaolin. And it looked there and I think that's the one that in your last discussion you characterize this coming up essentially clean. I think they came up with couple of the chronic studies in animals that you had it listed in your report as coming up, I think with two bronchial tumors. If

you actually look back in that original report, they don't class them as tumors, they said the response that irritation from dust that bronchial alveolar hyperplasia. So anyway, the point is that kaolin came up clean and that's so how do you deal with that. Have the chronic inhalation data. So I would suggest you know without preamble of that sentence, that Christina and Ron discussed having a sentence something like because of the presence of crystalline silicon impurities and the absence of negative repeat dose inhalation data there's insufficient information to reach a conclusion of the safety of products containing X. So that would apply to bentonite, hectorite and any others that arise in the future, but it wouldn't arrive apply to kaolin because you have that negative. You have that negative.

Dr. Tom Slaga - Negative results, yeah.

Dr. David Ross - Yeah, I mean, so that's how I read it and I might be misinterpreting this. So please correct me. I'm off.

Dr. Tom Slaga - I think you're right on.

Dr. David Cohen - So expanding what Christina already had in the discussion. Adding bentonite in there but not kaolin?

Dr. David Ross - I think that was the end point of the previous discussion that you had because kaolin had that negative repeat dose inhalation study now.

Dr. Tom Slaga - Yeah.

Dr. David Ross – There was a comment on the inhalation. Women's Voices for the Earth did send a wave three data through and it was very tough to find that reference, but I got a list, Saturday night from Jinqiu on the staff and took a look at that. That seemed to that was with specific manufactured fibers that would, including kaolin, but there were manufactured to be 20 microns long to, you know, to be a specific fiber length for insulation. And it's an occupational type relevance, so I'm not sure that one was entirely relevant to the studies we're looking at, but that I didn't have much time to look at it that came in late, but that's my understanding of it. So yeah, so I think kaolin and at this point based on that early MRC study as that chronic (*inaudible) data.

Dr. Susan Tilton - So I agree on the conclusion for kaolin. But I'm trying to, it's hectorite we're discussing adding or bentonite?

Christina Burnett (CIR) - Illite is the one that would be potentially added. Illite. And it's part of the clay composition.

Dr. Susan Tilton - OK.

Dr. David Ross - That's a different question.

Dr. David Cohen - Yeah, that, different than the we have to get to that one because that's the whole new. Addition to it. But what about?

Dr. Susan Tilton Susan Tilton - Oh, (*inaudible).

Dr. David Cohen - It we would be adding bentonite to the discussion point correct.

Dr. Tom Slaga - Correct.

Dr. David Ross - Yeah. And I think I think your original conclusion in the previous discussion looked great to me that. Attapulgite, I'm not quite sure how you pronounce that, but attapulgite, that conclusion I think looked pretty straightforward. You know, it should not be used in formulations which may be inhaled. Period. I think you got that right on with that tumor data.

Dr. Tom Slaga - Yeah. Period.

Dr. David Cohen - Right.

Dr. David Ross - And very yeah, that should be clear. And then there's other statements would be applied to the compounds that have the crystalline silicate impurities. Most of them look like they were lower than 5%. Is that correct, Christina?

Christina Burnett (CIR)- And so you have bentonite and attapulgite, currently and then so I'm...

Dr. David Cohen - Oh wait, we're not adding bentonite, we would be adding…

Christina Burnett (CIR)- Yeah, it's ... You mean to the ones that?

Dr. David Cohen - Hectorite we'd add. Heck.

Christina Burnett (CIR)- Like the ones that aren't sufficient, right. So hectorite?

Dr. David Ross - Bentonite and hectorite. But I think attapulgite you know, based on that tumor data should be in a different classification from my perspective it should be, should not be used. Period. In formulations that can be inhaled.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - That's already in the discussion.

Christina Burnett (CIR)- Right.

Dr. David Ross - Yeah.

Christina Burnett (CIR)- And that's… and you have the exception, yeah. So in the one on PDF page 113 in the fourth paragraph. 3rd and 4th paragraph you just have the inhalations discussion. Or, you know, the crystalline silica. And attapulgite and bentonite, and if you feel to add hectorite, we could do that for sure.

Dr. Tom Slaga - In the discussion, right?

Christina Burnett (CIR)- Correct.

Dr. David Cohen - Yes.

Dr. David Ross - But I think you should be (*inaudbile) lack of chronic negative toxicity data. I think those two statements I said earlier would sort that out, but that's…

Dr. David Cohen - So David, your statement before, I have because of the presence of crystalline silica and negative inhalation studies, this is for kaolin, right?

Dr. Tom Slaga - Kaolin.

Dr. David Ross - But that would be it would be all of them where you didn't have the negative inhalation studies, which would then, I mean kaolin, you've got the negative inhalation study. But with bentonite and hectorite, I guess you don't.

Dr. David Cohen - But, but what's the follow through the negative because of the presence of crystalline silicon negative inhalation studies. What's the proviso? What are you following it with?

Dr. David Ross - I mean that was the first statement which I think you used and you know, ordered it in the silica statement. That document, so you got that statement, which says because of the presence of silica, all the potential presence of silica. You need composition, impurities, data, quantification of crystalline silica, and you need negative repeat was inhalation data on naturally sourced so on the compound being new. And I think the second aspect of that is you put in a sentence which says when the potential for incidental inhalation silica exists, due to crystalline silica impurities and cosmetic product, the concentration of silica in the product. Well, actually I'm repeating myself. Yeah, that's the same statement that me go to let me go to the second segment because of the presence of crystalline. And this is in a different part because of the presence of crystalline silicon and purities and the absence of negative repeat those inhalation data.

Dr. David Cohen - The absence of negative, that's a double negative, right? So not having negative data.

Dr. David Ross - Well, the absence of repeated dose inhalation data you could.

Dr. David Cohen - OK.

Dr. David Ross - There is insufficient information to reach a conclusion of the safety of products containing X that may be inhaled. And so that is one approach to it, but you don't have that chronic repeat dose inhalation data which is cleared here for kaolin. Kaolin wouldn't be enough group. But bentonite, hectorite and any others that arise would be. You know how that is going to be used. Something like that.

Dr. Susan Tilton – So that statement would apply to hectorite, but we've already (*inaudible) benonite because it's potentially carcinogenic is already stated that it should not be used in formulations that would be inhaled.

Dr. David Ross - I thought there was a big difference between (*inaudible).

Dr. David Cohen - Well, either way, or are we going with the same conclusion?

Dr. Tom Slaga - Yeah.

Dr. David Cohen - Right.

Dr. David Ross - So you have attapulgite…it's not being used and these are the shouldn't be you have a negative tonic. We don't have that (*inaudible) data.

Dr. David Cohen - Well, I think what Christina has in there, which has the brevity on its side. Right because of the potential of adverse health effects from inhalation of carcinogenic material to panel, determine that attapulgite, hectorite and bentonite should not be using cosmetic formulations, which may be incidentally inhaled.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - I mean, I think it's simple, but it really it says what we need it to say.

Dr. Susan Tilton - Yeah.

Dr. Tom Slaga - Right.

Dr. David Cohen - Thomas, I know you had your hand up, so I'm sorry.

Thomas Gremillion (CFA) - Yeah. No, thank you. Doctor Cohen. So it sounds like the four studies that Women's Voices for the Earth brought to the panel's attention, they don't change the conclusion that or that they that whatever hazard they demonstrate, it's not so much as to overcome the inhalation studies that are already cited in the report is that. And I guess in another question I wanted to ask. Was just whether those there's a note in here. So whether the four studies, will, you know, should be incorporated into the report. And I wondered about that.

Dr. David Cohen - Was there any reason not to include those in the report?

Dr. David Ross - Which specific study?

Christina Burnett (CIR) - The ones that WVE provided in wave three. Sorry I'm getting feedback. There were I think 3, you know, tox studies and one was an intratracheal study in mice.

Dr. Carol Eisenmann (PCPC) - Wasn't the one intratracheal ceramic material?

Christina Burnett (CIR) - I believe so, yes. It

Dr. Carol Eisenmann (PCPC) - If it's a ceramic material, should not be included because that means it's heated to very high temperatures and changes the properties of the material, so it's not really what you're studying, so that one should not be in in the report.

Dr. David Cohen - Yeah.

Christina Burnett (CIR) - Kato at all, 2017.

Dr. David Cohen - That's a ceramic one.

Christina Burnett (CIR) - I believe so. It says in Jinqiu summary, it says two types of kaolin which was kaolin S. And kaolin P.

Dr. David Cohen - Hold on. Oh boy I'm in the wrong document.

Dr. Susan Tilton - So that's helpful to understand that those are different formulations. And even so, they were also intratracheal installations. As opposed to the inhalation exposure. And so we've already discussed based on formulation that we wouldn't expect these to be respirable. It would certainly have concern if we had no inhalation data. Like we have with the others.

Dr. David Cohen - So. Are, are, we going to include those three in the report, are we inclined to do that?

Christina Burnett (CIR)-The (*inaudible) all.

Dr. Wilma Bergfeld - Is there any reason not to?

Dr. David Cohen - Right. That's the question. We had one good reason not to include the ceramic one?

Dr. Susan Tilton - Yeah, I would say if it's included, we should make sure that that distinction is made clear.

Christina Burnett (CIR)- OK.

Dr. Susan Tilton -But. It could also.

Dr. David Cohen - OK.

Thomas Gremillion (CFA) - Sorry, can I? I just wanted to make sure I understood that so. The it's a matter of the particle size that's used in these studies and what's understood that instead of be a larger particle size and the cosmetics that are that are in use, so there's not an inhalation risk? But do I understand that correctly?

Dr. David Cohen - Susan, could you comment on that?

Dr. Susan Tilton - Let's. Yeah, that, I mean, that's my understanding of based on the formulation for cosmetics.

Thomas Gremillion (CFA) - OK. Thank you.

Dr. David Cohen - David, any other comments on those on that?

Dr. David Ross - Yeah. No, I think that's, that's fine, I think including those, if you want them.

Dr. David Cohen - OK.

Dr. Wilma Bergfeld - But David, can I ask you a question? This is called the amended safety assessment. And what are we amending? Let's be clear on what we're amending.

Christina Burnett (CIR)- The amendment comes from the fact that this belongs to a large silica silicate report several years ago and this is.. we broke off silica and hydrated silica and silicates and this is the third part of that… clays. So that's why this is called an amended report. Because it had a conclusion previously back in 2003.

Dr. David Cohen - Thank you, Wilma. That'll be an important point if when I open it tomorrow, why we're calling it that.

Dr. Wilma Bergfeld - Right.

Dr. David Cohen - OK. We should move on to the to the comment and these really were very thoughtful comments.

Dr. David Cohen - About nanoclays. I'm I need to rely on our respiratory tox experience in the team to comment on this. Is this something that should go in the discussion? Is there any reason to amend? Any conclusion, change any conclusions we might make because of this? What do we do with this nanoclay discussion?

Dr. Tom Slaga - I think they have to come up with a discussion point, but it's not going to change that conclusion in my eyes.

Dr. David Ross - Yeah, I would agree with that. I thought you could include it as a discussion item, but it wouldn't change what the end conclusion you were (*inaudible).

Dr. David Cohen - And before Christina asks, what would we put in the discussion regarding the nanoclays? What would we say?

Dr. Tom Slaga - I don't.

Dr. Wilma Bergfeld - I'd say that they may have a greater hazard in as an inhalation product. I mean the smaller particles go deeper. I don't think we can conclude that and what we have.

Dr. Tom Slaga - Yeah.

Dr. Wilma Bergfeld - Just on the general concept.

Christina Burnett (CIR) - Does that somehow link up or connect to the airbrush technology…

Dr. Wilma Bergfeld - Good.

Christina Burnett (CIR) - …language.

Dr. David Cohen - It could, but next to it. The other thing is I think this is mention that this 4% of the nanoclay market goes into cosmetics, but then there's a comment about the meeting used in lipsticks, eyeliners and toothpaste. Which to me has a lower inhalational risk, right? Those products are specific, but since these reports (*inaudible) for

decades sometimes, I don't want to rely on that right that the nanoclay in those products didn't immediately trigger an inhalational risk, but perhaps an absorption or ingestion component but I'm not sure what those risks would be, huh?

Dr. Wilma Bergfeld - Pretty large particles. Pretty large particles.

Dr. David Cohen - But nanoclays would be really small, right? And.

Dr. Wilma Bergfeld - Right.

Dr. David Cohen - Do they get into your gums and, you know, into the recesses of your teeth? I'm not sure?

Dr. Wilma Bergfeld - That's Pandora's box.

Dr. David Cohen - I know. No, I get it. I just. There's not enough data.

Dr. Wilma Bergfeld - That's what held up the sunscreen. FDA's final on the sunscreens, where the nanoparticles of zinc and titanium they did penetrate.

Dr. Tom Slaga - Yeah, we don't have any data. I don't know.

Dr. David Cohen - But we do know they're being used in those locations, so at least in the discussion, we might indicate that we don't really have a good read on that the health effects of nanoclays.

Dr. Tom Slaga - Right.

Dr. David Cohen - When you used in the mouth or on the lips, or by the eyes, we just we don't know.

Dr. Tom Slaga - Yeah. I agree with that.

Dr. David Cohen - Right. I mean it's right in in the sunscreens if they can percutaneously penetrate right when you're brushing them into your mouth, right. They may have a polishing effect. Maybe that's what they're used for, but I don't know what the long term effect is. I'm just suggesting we put it in the discussion somehow that we really can't comment on very much on the use of nanoclays in cosmetics and what the implications of that are.

Dr. Wilma Bergfeld - We're going to have to say insufficient information.

Dr. David Cohen - But it's not a conclusion though, right? It's just in the discussion I like that Wilma.

Dr. Wilma Bergfeld - No, no, no Yeah.

Dr. David Cohen - That's sort of the insufficient data on the safety of nanoclays.

Dr. Wilma Bergfeld - Right.

Dr. David Cohen - OK. Another item we have is the illite. Said that's being added or the question is, should we add it? It seemed logical that we added, but we don't have a lot of data on it, do we?

Dr. Tom Slaga - No.

Christina Burnett (CIR)- I have not done a search on it because I didn't want to do a lot of work and then find out you didn't want to add it. So after this meeting, if you decide to add, I will be researching and adding it to the report.

Dr. David Cohen - So Christina, just to that point. Were there reasons that you contemplated where we wouldn't add it like it? This is a clay, right? This seems like a clay.

Christina Burnett (CIR)- It is it, it's more it's based on geological description. They associate it to be a mica, but it's still a silicate. Based clay or composition type. So it technically can fit.

Dr. Carol Eisenmann (PCPC) - When I wrote this the suppliers of ingredients that are listed under the INCI name clay, that's the response I got. So this company is selling, they go dig this clay out and it contains 75% illite I was kind of surprised by it but that's how it ended up. That's how you got the information. When I wrote the companies that are supplying clay the INCI name, clay. That's how the that's the response that came in.

Dr. David Ross - So it was mined, and processed. There was no other way, you know, because in this previous version of this report, apparently activated clays were removed because they are chemically treated. So this material is mined and processed,

Christina Burnett (CIR)- Correct

Dr. Tom Slaga - Yeah.

Dr. David Ross - That's what I'm hearing. So basically. It would. Based on your faction in there.

Dr. Carol Eisenmann (PCPC) - Right. They're not taking the three different components in mixing them together. They're mining it. And that's what it is.

Dr. David Ross - Yeah. So the USGS says it's a clay yeah. Some minor structural differences in the crystal lattice, but I didn't see a huge difference there. So I came down as including it. I'm not sure where else you would put it, but the wise and but you know it's in a lot of these products anyway. (*inaudible). Yeah, I have including it. That's where I am.

Dr. David Cohen – Susan?

Dr. Susan Tilton - I would I support including it however it sounds like it's essentially synonymous with clay when we are already considering the you know, data from the mixture of the three ingredients that's predominantly illite. And is reported for clay. But if there is data for it independently, I think it should be included.

Dr. David Cohen - To a good point, 3/4 of what we're calling clay is this. But so what happens mechanistically if we add this on what happens to this the status of this report?

Christina Burnett (CIR) - It will, you will still see it at a future meeting as the draft final. Amended report. It just might not be December. It might be next year, March.

Dr. David Cohen - OK. Yeah, no rush, but. But I think we should put the illite in case if we if we have to bring this in as a separate report, we're going to go through the same machinations that we've been doing now and we might as well put it all together. And as Susan mentioned, I, I mean it was a great summary remark is we won't be seeing probably much new information, but if there is some, you know, independent stuff in it. We should put it in here.

Christina Burnett (CIR) – Yeah. I will note that in Council data, in the data supplement, or that was attached to this report package data 8, which is the updated concentration of use they already performed a survey on it. So you do have that the maximum use concentration is 3.8% in skin cleansing. 1 to 2% in masks. And then it goes lower than that, so soaps .34%. Probably not knowing what other baby products, if that's a leave on I'm guessing is it might be. It's pretty low concentration.

Dr. David Cohen - So I think it's important we swing back to the IDA questions that we asked for and then check those off. So I'll go through each one and I'd ask you guys to just comment on whether you think the IDA was fulfilled. Particle size distribution of all ingredients except bentonite, we got a lot of particle size information, but was it sufficient for the team?

Dr. David Ross - I think it could D50 and distributions for at the ones we ask for, correct? So yeah, I thought it was OK.

Dr. David Cohen - Tom, Susan?

Dr. Tom Slaga - Yeah, I agree.

Dr. Susan Tilton - Yes.

Dr. David Cohen - OK. Chronic inhalation data on all ingredients.

Dr. Susan Tilton - So that was not provided.

Dr. David Ross - And that's why I think you still need that statement somewhere in the discussion.

Dr. David Cohen - So how do how do we handle this IDA for chronic inhalation data? Does our discussion comment fulfill the needs that we ask for here? I mean, in the we didn't get it, but then we make a comment in the discussion that we're not supporting really its usage incidentally inhaled products, except kaolin, right?

Dr. Tom Slaga - Right.

Dr. David Cohen - So.

Dr. David Ross - Yeah.

Dr. David Cohen - We don't hold out on that data then any further that question.

Dr. David Ross - Yeah, you make that statement. If you don't have a chronic inhalation data, so therefore you don't support. You know you can't reach your conclusion on the safety of the use of those products in our cosmetic products that would be inhaled.

Dr. Tom Slaga - Yeah, without the data, can't interpret it. No matter what it is.

Dr. David Cohen - Right. And we got a tremendous amount of new irritation and sensitization data.

I think the totality of that suggests that these are not a big sensitization risks. There was one kaolin mask where there might have been some redness in the induction period, but. I'm not sure I think. I think our data needs were met here.

Dr. David Ross - Apart from the inhalation, I have two notes. One was the dermal sensitization and as usual it said, ask David but I have that down as OK and then the other note was the ocular. And they had with kaolin in that data was with cultures basically using MTT assays. No data in animals and kaolin is used up to 8 1/2%. According to the Table 201 uses. Around the eye area.

Dr. David Cohen - Which so I are you talking about the EPI ocular data?

Dr. David Ross - Yeah. You think the EPI ocular? OK? I mean, they're used it up to 14% in the EPI ocular data. So they're above maximum concentration of use, but that was the only data they had with kaolin.

Dr. David Cohen - That may be the best we get for ocular data some times.

Dr. Tom Slaga - I think it's over to get.

Dr. David Cohen - So. Did I miss any other points that we needed to address? So are we, going out with the conclusion of safe as used?

Dr. David Ross - Well, with the exceptions that you've noted.

Christina Burnett (CIR) - So you could say kaolin is safe as used in.

Dr. Tom Slaga - Right.

Christina Burnett (CIR) – The others are safe when not used in incidentally inhaled products or something to that effect is that. Correct?

Dr. Tom Slaga - Right.

Dr. David Ross - I see.

Dr. David Cohen - Yeah, it's technically correct, but do we conclude that way or do we have in the discussion that these should be in that they shouldn't be incidentally inhaled? So that conclusion has a provision of not being incidentally inhaled? Is that a conclusion?

Dr. Carol Eisenmann (PCPC) – Data Insufficient for products that maybe incidentally inhaled.

Dr. Tom Slaga - Right.

Dr. David Ross – I think that's the conclusion as long as you have that statement down, lack of chronic inhalation data.

Dr. David Cohen – So kaolin, safe as used. And the others are safe as used, but not, insufficient data to support when incidentally inhaled?

Dr. Tom Slaga – Right.

Dr. David Ross – Yeah, basically that's what we are saying (*inaudible).

Dr. Tom Slaga – That's what we're saying.

Dr. Wilma Bergfeld – What are you going to do about the addition of illite? Is it going into this document?

Dr. David Ross – Yeah.

Dr. David Cohen - We have to yeah. So there's still insufficient data on illite, right? So can I add that as a third point, Wilma, from a procedural standpoint, kaolin safe as used. The others, except illite safe as used, but insufficient data to support the use when incidentally inhaled. And insufficient.

Dr. Wilma Bergfeld - I would think that would be a temporary one. I think that the reality is you haven't sought out the illite, whatever. You're going to call it, you haven't done a resource.

Haven't asked for it, so you might want to table this until you get that.

Christina Burnett (CIR)- You do have what the data that you received on clay and you have the knowledge that the clay is 75% illite and 16% kaolin and 9% montmorillonite. You do have data in that respect. But yes, see we don't have data on, just illite by itself.

Dr. David Ross - But you don't have chronic inhalation data on that mixture either?

Christina Burnett (CIR)- Correct.

Dr. David Ross - So I think that's the key, that's the key delineated here.

Dr. David Cohen - But that would be rolled into insufficient data to support use when incidentally inhaled.

Dr. David Ross - Right.

Dr. David Cohen - So I get but Wilma's points important right? Like I don't know what we would see from new illite data that may change this but I won't know that till I see it. Well.

Christina Burnett (CIR)- And it's sufficient.

Dr. David Cohen - I just want to. I wanted.

Christina Burnett (CIR)- Sorry, I was just going to say.

Dr. David Cohen - Insufficient data for illite.

Christina Burnett (CIR)- It well, I mean.

Dr. Wilma Bergfeld - You have to ask for it. You have ask for it.

Christina Burnett (CIR)- That will allow Council the opportunity to do a survey to ask for any data that might be out there.

Dr. David Cohen - Alright, so it an insufficient data on illite, but we have to remind ourselves when we come back to this, that if we don't get any new data on it or it's minimal that we really have to remember that this is being rolled into clay. Right. Because we can get wrapped around the axle in this in six months.

Dr. Wilma Bergfeld - Right. Remember, you can always table. Until you get the data. If it's begun, if they've sent out the survey. Already.

Dr. David Cohen - The surveys out?

Christina Burnett (CIR) - Well, they included it in their concentration of use survey. I'm not sure if we…Carol, will have to speak to it.

Dr. Carol Eisenmann (PCPC) - I have. I have not contacted the suppliers of illite itself and I don't know how many there are. But I did the concentration of use survey.

Dr. David Cohen - So well know what's the downside of putting insufficient data for llite it? It would.

Dr. Wilma Bergfeld - I think that, if you want to move forward with it and do something with it this time, You'd have to just in your comments so the other option is to table till we have this and to see how the group goes.

Dr. David Cohen - OK.

Dr. Wilma Bergfeld - But we our team is supporting those, yeah.

Dr. David Cohen - OK, I like that.

Dr. Wilma Bergfeld - What you probably, since Carol told us the update on the survey, you can repeat that there a survey is anticipated. It's not random.

Dr. David Cohen - OK. I did we miss anything else on clays, Christina, were there open items we didn't cover? We looked at the IDA. We looked at the WVE comments. We did nanos. We did illite.

Christina Burnett (CIR) - Thank you, had them all.

Dr. David Cohen - OK.

Dr. Wilma Bergfeld - That was harder than yeast.

Dr. David Cohen - All right, we'll move. I'm not sure I they were different.

Dr. Wilma Bergfeld - Yeah, but they were more discussion.

Dr. David Cohen - Yeah. OK.

Dr. David Ross - So we can I just ask you include that statement that you had in the silica, you know the lack of chronic inhalation didn't give you included (*inaudible) quite strong.

Dr. David Cohen - I had it. So I had it written and then I crossed it out. But Dave, would you mind emailing me the clip and I could bring it up for discussion tomorrow?

Dr. David Ross - Yeah, I can send you an e-mail of.

Dr. David Cohen - Just a clip that the sentence or two, so it'll just reduce my fishing time.

Dr. David Ross - I can send you that and suggested one why (*inaudible).

Dr. David Cohen - And it won't change the motion.

Dr. David Ross - No.

Dr. David Cohen - It'll just be brought up during the discussion, which I think would be lively and very helpful.

Dr. Tom Slaga - Right.

Dr. David Ross - But as you said, a lot of these you know these things stay in place for decades. So I think it's important that, you know, I think in this delineated in the discussion of why we did what we did was clear.

Dr. David Cohen - I like that. I'll look out for that e-mail and I'll read that off tomorrow after the motion is seconded or it's not seconded and there's a discussion anyway.

Dr. Wilma Bergfeld - Do you have his e-mail?

Dr. David Ross - Yeah, it's, it's in the list of.

Dr. Wilma Bergfeld - OK.

Dr. David Cohen – It's in the group.

Dr. David Ross - Yeah.

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Dr. Wilma Bergfeld - All right. So moving on to the next big one, which is clays, Doctor Cohen.

Dr. Dr. David Cohen - Yes, this is a very intense re-review here. I'm sorry… an amended report and this is an amended report because clays were splintered off from a larger category of silicates in the past. I think Don spearheaded that, which was a really good idea in March. The panel determined that the data were insufficient to support the seven clay ingredients and the additional data needs were particle size distribution, except for bentonite, chronic inhalation data on all ingredients except attapulgite and kaolin and human dermal irritation and sensitization at max use concentration. While I have a number of points to discuss, I'm going to go right to a motion and then we can go back into discussion. Our conclusion is. With number one, we believe that we've received the requested information. Our conclusion is safe as used for kaolin. Then safe as used for the others with insufficient data to support the use when incidentally inhaled.

Dr. Don Belsito - That's exactly what we agreed on.

Dr. Wilma Bergfeld - So you're seconding it?

Dr. Don Belsito - Yeah.

Dr. Wilma Bergfeld - OK.

Dr. David Cohen - I love that, Don.

Dr. Wilma Bergfeld - Good. OK. Two minds act together. What are your comments on, David?

Dr. David Cohen - I think that we received very insightful and helpful feedback from the Women's Voices for the Earth regarding crystalline silica and hectorite and kaolin. And we had a lively discussion about that and kaolin. We have inhalation data that's we believe supported our conclusion. We also wanted to add in the discussion some issue about safety or the insufficient data on the use of nanoclays in cosmetics. Lastly, we would like to add illite to the review, understanding that 3/4 of clay had illite in it and we had a couple of options that we went through. One was to either issue insufficient data for illite and wait for the information, if we have anything specific for it. Or to just table that discussion until it comes around until this report may come around again to us.

Dr. Don Belsito - We actually felt that we could add illite in because we have a lot of data on it. I mean everything that was kaolin was actually clay with 75% illite. We also discussed the issue of clay and the possibility that clay that could be mined from other areas might be different from this French clay. But as always our reports say as so our definition of clay has become the definition that's in the report. If your clay differs significantly from the clay that we've reported, then you need to go out and get your own safety data. We had a discussion about the nanoparticles as well. We also discussed DART data, but we determined that dermal absorption wasn't going to be an issue for these. The fact that we had very little data on Fuller's Earth, but it essentially appears to be attapulgite, from our report. And those I think were the major issues and then of course the airbrush technology we did discuss also want to discuss that in the discussion that intratracheal exposures which were the sort of inhalation that we got bypass all the protective mechanisms of the lungs and certainly the exposures there would exceed what you would get then in cosmetics. But we felt we could just add illite in and that the writer would go out and see if there's additional data just on that. But we really had sufficient data. Looking at the information we had on the clay, clay ingredient.

Dr. David Cohen - We were strikingly well harmonized on that. One quick comment from Dave Ross on our team. He went into the silica review and there's a sentence that we might consider putting in here and I'll read it. It's a bit long, but when the potential for incidental inhalation exists, the additional data needed to determine safety of naturally sourced ingredients, i.e. potentially containing crystalline silica and cosmetics, that may be incidentally inhaled or composition and impurities, data, especially quantification of crystalline silica and concentration of use of naturally sourced silicate ingredients or negative repeat dose inhalation data on naturally sourced silicate ingredients. What Don, what do you think about having that in the discussion?

Dr. David Ross - That's the just the...

Dr. Don Belsito - I'm fine with that, but I'm going to pass that off to my other team members too.

Dr. David Ross - That statement came from Ron Shank in the silicate discussion you.

Dr. Don Belsito - Can't hear you, David.

Dr. David Ross - That statement came from Ron Shank in the silicate discussion. So you know that you know, it just seemed to me that the important thing here was the lack of the negative repeat dose inhalation data and that was the reason we went ahead and approved kaolin. We had that negative data. And I just felt that it should be clear to why we did what we did with respect to these compounds. So that's the obvious logical thing.

Dr. Wilma Bergfeld - Other comments.

Dr. Don Belsito - Someone has their hand up in the audience.

Dr. Curtis Klaassen - Tom.

Thomas Gremillion (CFA) - Hey, thank you. I just wanted to confirm my understanding with respect to the Women's Voices for the Earth letter these studies that they cite, the exposure levels are higher than what you're expecting with cosmetics. And if I understand correctly and so my question is, will the study still go into the safety assessment because maybe they speak to the inhalation rest from airbrush cosmetics or, are they not relevant at all?

Dr. Wilma Bergfeld - Are David, you want to respond to that?

Dr. David Cohen - I thought we had some discussion about this, right, that we were going to include these in the report that except 1 right.

Dr. Wilma Bergfeld - The trachea.

Dr. David Ross - Yeah, correct.

Thomas Gremillion (CFA) - And I guess I follow up question is there is it just that like the universe of this research is so large that that inevitably studies are going to be left out or do these studies come from kind of obscure journals or is there?

Dr. David Cohen - Thomas is the question why weren't they there before or?

Thomas Gremillion (CFA) - Yeah, yeah, yeah.

Dr. David Cohen - I imagine you've answered part of it. I might ask the CIR staff to comment on that as well.

Christina Burnett (CIR) - Partially with especially the ones with the genotoxic tox, they were specific to nanoparticles and in the past we haven't included nanoparticle studies. It could be that the Panel wants to change that way moving forward just because of usage but, just the past SOP was staff was to not include ones that were targeted on nanoparticles because they weren't quite the same as the ingredient itself.

Thomas Gremillion (CFA) - And that that's because there's some boilerplate that that advises against using nanoparticles in the formulations.

Dr. David Cohen - Well, we are going to comment about nanoparticles in the discussion. I think you know this is the start of more discussion on nanoparticles, because these clays I recall nanoclays are used in lipsticks and toothpastes and we really don't have a good read on how they're absorbed or what their impact is. So I think you bring up a good point and we may need to evaluate how we're dealing with nanoparticles.

Dr. Curtis Klaassen - I think the nanoparticle, I think the.

Dr. Don Belsito - Alex, I know their cosmetic industry is doing a lot of work on this. I mean, as far as I'm aware so far, the toxicology of nanoparticles have not seemed to significantly differ as that your understanding? Alexan**dra?** Someone from the PCPC want to comment.

Dr. Wilma Bergfeld – Bart?

Alex Kowcz (PCPC) - How would we handle it in the past, Bart?

Dr. Bart Heldreth - We we've just, uh, not focused so much on the issue of it being nano specifically by itself, but whether or not something would be respirable or whether it would be absorbed instead of focusing on nano is kind of a buzzword. And there's plenty of particles that are much smaller and even more respirable, but don't get the nano buzzword attached to it. So we've kind of tried to shy away from focusing so much on nano per se and just looking at is just going to absorb, is this going to be respirable? And if it's respirable, is that actually a problem because not everything that's respirable as a problem?

Dr. Daniel Liebler - I think. I think the evaluation needs to focus on the chemical substance that comprises the ingredient, and if nanoparticles were excluded for from searches for some other reason, I think they prevent us from accessing data that we should be looking at. And so, you know, there are, there are certainly differences with nanoparticles, but not enough to make the substance on a nanoparticle or formulate as a nanoparticle not to be relevant to our evaluations.

Dr. Bart Heldreth - Right. Didn't you could you further elaborate on your viewpoint on these studies?

Jinqiu Zhu (**CIR)-** So the nanoparticles are studies. Based on their particle size. It's relevant to the report, but somehow, we do not examine the details because, (*inaudible), searching the papers in the future.

Dr. David Cohen - I guess the question is in, the in our search model, right? Whenever you're going to do a search, would the presence or absence of the word nano if you're looking for clays, would we miss a nanoparticle? Probably not, because you search clays, it would still come up and maybe we at, depending as Dan said, depending on the specific chemical we reviewing we should not wholesale discount on article on that has nano in it and look at it and see if it makes sense and is does it speak to the need for dermal tox, inhalational tox, additional oral tox?

Dr. Don Belsito - Yeah. I mean, I think as a Panel member, I want all the data you know, sometimes we get data and we got God, this is totally irrelevant to cosmetics. But let us make that decision, get us all the data and let us look at it whether it's nano or micro or milligrams or whatever. I think we should have it and not be provided with it by someone else.

Christina Burnett (CIR) - OK. OK, I will. I'm sorry. I'll include these. I do want clarification though on the one that was intratracheal…that one was specifically on a kaolin that was heated to become a ceramic.

Dr. David Cohen - Yeah, it was a ceramic and we thought it wasn't relevant to this. That was a highly processed clay.

Christina Burnett (CIR) - OK, so that one won't be included.

Dr. Don Belsito - Right. And we just. We put, you know all of being true tracheal that we got in the discussion, that it's bypassing all the protective mechanisms of inhalation and but we've looked at the data and I think that's what's critical here. We should have all the data and then let us decide how to deal with it.

Christina Burnett (CIR) - OK.

Dr. Don Belsito - Someone else has their hand up.

Donald Bjerke (P&G) - Yeah, this is Don Bjerke, I completely agree with Doctor Belsito and Doctor Cohen that all the data should be looked at. Some things to consider is that although a raw material may be nano as the raw material, you'll also have to consider what the exposure is in the product. And oftentimes these things, these things agglomerate and the actual exposure from the product is not nano at all. But look at all the data. And I think in this particular case even if it is nano, I think your conclusion covers that for the incidental inhalation exposure. So I think you're in really good shape here.

Dr. Bart Heldreth - Right. Yeah. I just want to reiterate, we, we're not excluding anything for nano. We're not out there looking and searching for nano specifically, but we were not excluding these papers on purpose.

Dr. David Cohen - Then we are aligned and just one comment I agree we want all the data, but we certainly want the expertise of the staff members to filter things that are really not related right, because it's very you know you could do a search and put clay in and we may get you know ten, 20,000 returns on that or you know when you when you do a lot very broad searches, so we do want them relevant to the situation at hand, right?

Dr. Dr. Bart Heldreth – Right.

Dr. Wilma Bergfeld - I think that we've come to the end of our discussion. I believe Doctor Cohen, can you restate where we stand now because there was a little bit of discussion between you and Don?

Dr. David Cohen - Yes. Of course, our motion is that a kaolin is safe as used in the current concentration of practices and the other clay ingredients are safe as used with insufficient data to support their use when incidentally inhaled.

Dr. Wilma Bergfeld - And Don, are you agreeing to that or seconding that?

Dr. Don Belsito - Yes, I seconded it and then there were just some discussion issues.

Dr. Wilma Bergfeld - All right. And do we have all those discussion issues that we've decided upon or do you want to restate them?

Dr. Don Belsito - I believe Christina has, I think Christina has them all from our panel meeting.

Dr. Paul Snyder - So Bart, this is a this will go to a draft final report. The next stage. We'll see it one more time.

Dr. Bart Heldreth - That's correct. It will go out as a tentative amended report for public comment and then it'll come back to the panel at a future meeting as a draft final amended report.

Dr. Paul Snyder - OK. Because I have some questions about David's discussion about the impurities issue and related to I mean the biggest issue for us is particle size distribution is not just whether it contains crystalline silica so. I would like to I want to see that and make sure we don't kind of go down a rat hole there because there's other issues. These are insoluble and inhalation and any capacity would be depending on the particle size so. I would like to…I want to see that and make sure we don't kind of go down a rat hole there because there's other issues. These are insoluble and inhalation and any capacity would be depending on the particle size so that's my only comment.

Dr. David Ross - Yeah.

Dr. Wilma Bergfeld - Excellent. All right. Any other discussion points that want to bring forward now?

Dr. David Ross - I had a discussion point that I sent along to Christina last night regarding the negative data on kaolin and then the original MRC study, and it hasn't changed the conclusion it's still negative and it just how that was represented in our discussion.

Dr. Wilma Bergfeld - OK. Well, I will call the question then all those opposing? Abstaining? The clays are approved as stated.

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.

Amended Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	February 10, 2023
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Ronald C. Shank, Ph.D. and Daniel C. Liebler, PhD. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

16HBE	human bronchial epithelial cell line 16HBE14o-
AICIS	Australian Industrial Chemicals Introduction Scheme
BAL	bronchoalveolar lavage
CCK-8	cell counting kit-8
cfu	colony forming units
cGMPs	current good manufacturing practices
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
ECVAM	European Centre for the Validation of Alternative Methods
EU	European Union
FDA	Food and Drug Administration
β-GLUC	β-glucuronidase
GRAS	generally recognized as safe
HRIPT	human repeated insult patch test
IARC	International Agency for Research on Cancer
ICP-OES	inductively coupled plasma-optical emission spectrometry
IL-1	interleukin-1
LDH	lactate dehydrogenase
MDGF	macrophages-derived growth factor
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
mU	milli units
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
OTC	over-the-counter
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PEL	permissible exposure limit
$PM_{2.5}$	particulate matter with aerodynamic equivalent diameter of 2.5 μm or less
PMN	polymorphonuclear
REL	recommended exposure limit
t_{50}	50% decrease of tissue viability
TG	test guideline
UDS	unscheduled DNA synthesis
UV	ultraviolet light
VCRP	Voluntary Cosmetic Registration Program
wINCI *Dictionary*	web-based International Cosmetic Ingredient Dictionary and Handbook

ABSTRACT

The Expert Panel for Cosmetic Safety (Panel) assessed the safety of 8 naturally-sourced clay ingredients, of which 6 were previously reviewed, as used in cosmetic formulations. All of these ingredients are reported to function in cosmetics as absorbents and bulking agents; other cosmetic functions are also reported. The Panel reviewed all relevant data and concluded that Kaolin is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The remaining 7 naturally-sourced clay ingredients are safe in cosmetics in the present practices of use and concentration, with the exception that the available data are insufficient to make a determination that these ingredients are safe in products that may be incidentally inhaled.

INTRODUCTION

The Expert Panel for Cosmetic Ingredient Safety (Panel) previously reviewed the safety of 6 naturally-sourced clay ingredients in a report that was published in 2003.[1] At that time, the Panel concluded that these ingredients are safe as used in cosmetic products. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. This report has been reopened to reassess the safety of the 6 clays included in that original report, and also includes 2 additional ingredients, i.e., Clay and Illite. In total, this report assesses the safety of 8 naturally-sourced clay ingredients (listed below) as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1), all of these ingredients are reported to function in cosmetics as absorbents and bulking agents; other cosmetic functions are also reported. [2]

Attapulgite*
Bentonite*
Clay
Fuller's Earth*
Hectorite*
Illite
Kaolin*
Montmorillonite*

**Previously reviewed by the Panel.*

The Panel has also reviewed related ingredients. In a report that was finalized in 2019, the Panel concluded that synthetically-manufactured amorphous silica and hydrated silica are safe in the present practices of use and concentration when formulated to be non-irritating.[3] In 2021, the Panel concluded that silicate ingredients, including aluminum silicate and magnesium aluminum silicate, are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating, with the exception that the data are insufficient to make a determination that naturally-sourced (i.e., mined) silicate ingredients are safe for use in products that may be incidentally inhaled.[4] (The reports on these ingredients are available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients). Although the clay ingredients comprise silica and/or silicates, silicates, synthetically-manufactured amorphous silica, and hydrated silica are neither part of this safety assessment, nor are data from those reports included in this assessment.

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 the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://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 summaries of the previous report on clay ingredients are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.)

CHEMISTRY

Definition and Structure

The definitions of Clay (CAS No. 53801-44-8) and the other clay ingredients included in this review are provided in Table 1.[2] These inorganic oxide ingredients, comprising in part silicon dioxide, are solids derived from naturally occurring minerals.

Clays in general have atomic lattices consisting of two structural units.[1] One unit consists of two sheets of closely packed oxygens or hydroxyls. 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. 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.*

Figure 1 depicts the general structure of clay ingredients. Clays are composed of magnesium, lithium, aluminum, and/or iron silicate sheets with various exchangeable cations. These sheet-like structures are in sharp contrast to the hexagonal crystalline structure of crystalline silica (e.g., quartz).

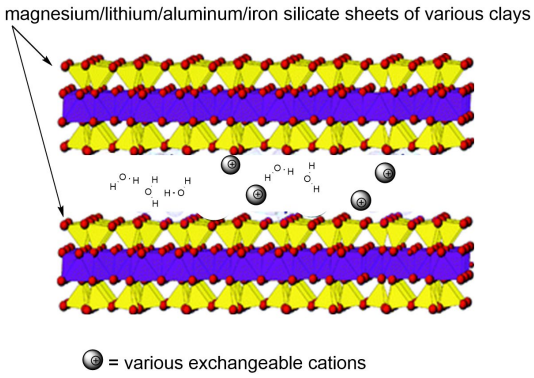

Figure 1. General structure of clay ingredients.[CIR Staff]

Attapulgite

The structurally important element is the amphibole double silica chain oriented with its long direction parallel to the c-axis.[1] Attapulgite 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 are considered probable.

Bentonite, Hectorite, and Montmorillonite

Bentonite, Hectorite, and Montmorillonite (also known as smectites) units comprise of two silica tetrahedral sheets with a central alumina octahedral sheet.[1] 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 are 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 these clay ingredients is the ability of water and 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 of these clay ingredients have substitutions within their lattices: aluminum or phosphorous for silicon in the tetrahedral coordination and/or magnesium, iron, zinc, nickel, lithium, etc. for aluminum in the octahedral sheet.

Illite

Illite is a non-expanding, clay-sized, dioctahedral mineral that is considered part of the mica group.[5,6] It is a layered alumino-silicate, known as a phyllosilicate. Its basic unit is a layer composed of two inward-pointing silica tetragonal sheets with a central alumina octahedral sheet. Poorly hydrated potassium cations occupy the space between the sequence of layers, which prevents swelling or the expansion of the layers. Illite is very similar structurally to common mica (muscovite), with slightly more silicon, magnesium, iron, and water, and slightly less tetrahedral aluminum and interlayer potassium.

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.[1] 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.

Chemical Properties

Chemical properties for clay ingredients are described in Table 2.[1,7-9] Clay ingredients are generally described as insoluble in water.

A supplier has reported the particle size distribution at D_{50} for Bentonite and Kaolin to be 61.1 µm and 3.1 µm, respectively.[10] The mean particle sizes for 5 different Hectorite products were 19.9 - 25.4 µm, and the particle ranges for these products were 2.9 - 131.7 µm.[11] Another supplier provided specifications for a Clay raw material containing 75% Illite, 19% Kaolin, and 6% Montmorillonite (see Clay in Table 2); however, there is no information therein to indicate the particle size of resultant final cosmetic formulations.[9]

Method of Manufacture

Attapulgite

Attapulgite is produced through an opencast mining technique, stripping layers with heavy machinery.[1] The clay is then transported to a processing plant where crushing, drying, classification, and pulverizing take place. High-heat drying to remove water may occur to enhance absorbent qualities. Attapulgite is mined in 10 countries: Australia, China, France, India, Russia, Senegal, South Africa, Spain, Turkey, and the US.

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 post-Soviet states, and the US.[1] The mine ore of Bentonite is processed to remove grit and non-swelling materials.

A supplier has reported that Bentonite is mined mineral.[12] The material is then washed, filtered, dried, treated, and tested for quality.

Clay

A supplier has reported that Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) is naturally sourced, mechanically refined, and not chemically processed.[9] A dehydration process is used to eliminate bacteria prior to sorting through induction.

Illite

Illite is formed by the weathering of silicates (feldspar), by the alteration of other clay minerals, or during the degradation of muscovite.[5,6] The formation of Illite is generally favored by alkaline conditions and by high concentrations of aluminum and potassium. Deposits of Illite are widely distributed globally: it is commonly found in soil and argillaceous sedimentary rocks, as well as in some low-grade metamorphic rocks.[5,6,8]

Kaolin

Deposits of Kaolin have been found in England, the US, France, the Czech Republic and Slovakia, Germany, and Japan.[1] Kaolin is extracted from kaolinized granite by washing it out with powerful 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.

Composition/Impurities

Attapulgite

Attapulgite commonly is found with smectites, amorphous silica, chert, and other minerals.[1] A typical mineral composition of Attapulgite is approximately 55% silicon dioxide, 10% aluminum oxide, 3.5% iron (III) oxide, 10.5% magnesium oxide, 0.5% potassium oxide, and 20% water.

Bentonite

The principal constituent of Bentonite is Montmorillonite.[1] 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. A typical mineral composition of Bentonite is approximately 60% silicon dioxide, 20% aluminum oxide, 3% iron (II) oxide, 1.5% magnesium oxide, 0.6% calcium oxide, 0.6% potassium oxide, and 21% sodium oxide.

According to the *Food Chemicals Codex*, Bentonite is composed of natural smectite clays consisting primarily of colloidal hydrated aluminum silicates of the Montmorillonite or Hectorite type of minerals with varying quantities of alkalis, alkaline earths, and iron.[7] Food-grade Bentonite should contain no more than 5 mg/kg arsenic, no more than 15 mg/kg lead, and no more than 1000 colony-forming units (cfu)/g aerobic microbes. Bentonite should be negative for *Escherichia coli* in 25 g.

In particle size analysis of Bentonite, 90% of the particles were smaller than 68 µm, 50% were smaller than 5µm, and 10% were smaller than 2 µm.[13] No particles were smaller than 0.9 µm. A second analysis of Bentonite showed that 90% of the particles were smaller than 25 µm, 50% were smaller than 6.5 µm, and 10% were smaller than 1.6 µm.[14] No particles were smaller than 0.5 µm.

Clay

A supplier has reported that Clay contains 75% Illite, 19% Kaolin, and 6% Montmorillonite and does not contain quartz.[9] Trace heavy metals may be present: < 0.5 ppm antimony, < 17 ppm arsenic, < 0.5 ppm cadmium, < 7 ppm cobalt, < 0.5 ppm tin, < 0.05 ppm mercury, < 20 ppm nickel, and < 20 ppm lead were detected using inductively coupled plasma-optical emission spectrometry (ICP-OES). Bacterial, yeast, and mold content were below the threshold of detection. Dioxin and polychlorinated biphenyl "results are near zero."

Fuller's Earth

Principal deposits of Fuller's Earth include Montmorillonite, Bentonite, Attapulgite, and sepiolite.[1]

Hectorite

Principal impurities of Hectorite include calcite, dolomite, silica crystals, and grit.[1] *A typical mineral composition of Hectorite is approximately 56% silicon dioxide, 0.1% aluminum oxide, 0.03% iron (III) oxide, 25% magnesium oxide, 0.1% potassium oxide, 3% sodium oxide, 1% lithium dioxide, 6% fluorine, and 12% water.*

According to some suppliers of Hectorite products (97 - 100% pure), crystalline silica (also described as quartz and/or CAS# 14808-6-7) may be an impurity.[15,16] Quantities of crystalline silica were reported to be 1-3%.

Illite

The sheets of Illite are composed of silicon, magnesium, iron, aluminum, potassium, and water.[6] In analysis of 0.5 kg samples of 3 clay products containing Illite, the major element composition (as mean concentration) comprises silicon (23.02%), aluminum (8.80%), calcium (4.55%), iron (4.22%), potassium (3.19%), titanium (0.48%), sulfur (0.21%), phosphorus (0.10%), and manganese (0.041%).[17] Trace element impurities (as mean concentration) were identified as barium (426.70 mg/kg), rubidium (253.7 mg/kg), strontium (227.07 mg/kg), zinc (100.97 mg/kg), cesium (65.93 mg/kg), nickel (35.37 mg/kg), neodymium (30.23 mg/kg), lanthanum (28.00 mg/kg), lead (26.77 mg/kg), copper (25.07 mg/kg), arsenic (16.33 mg/kg), thorium (8.83 mg/kg), uranium (3.78 mg/kg), and bromine (< 1 mg/kg). Bulk composition analysis indicated the samples contained calcite and quartz.

Kaolin

Quartz, mica, and feldspar are often found associated with Kaolin as the crude mineral and are often removed through screening and elutriation.[1] *Potentially pathogenic organisms were absent. The bacteria present were mostly gram-positive aerobic spore-formers. A typical mineral composition of Kaolin (reported as kaolinite) is approximately 45% silicon dioxide, 39% aluminum oxide, 0.8% iron (III) oxide, 0.08% magnesium oxide, 0.08% calcium oxide, 0.1% potassium oxide, 0.7% sodium oxide, 0.2% titanium (IV) oxide, and 14% water.*

According to the *Food Chemicals Codex*, Kaolin is a purified clay consisting mainly of alumina, silica, and water.[7] Food-grade Kaolin should contain no more than 3 mg/kg arsenic and no more than 10 mg/kg lead.

According to some suppliers of Kaolin products (up to 100% pure), crystalline silica (described as quartz, free respirable silica, and/or CAS # 14808-6-7) may be an impurity.[18,19] Quantities of crystalline silica were reported to be ≤ 2%.

Montmorillonite

A typical mineral composition of Montmorillonite is approximately 51% silicon dioxide, 20% aluminum oxide, 0.8% iron (III) oxide, 3% magnesium oxide, 2% calcium oxide, 0.1% potassium oxide, 0.04% sodium oxide, 0.1% zinc oxide, and 23% water.[1]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or

particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP survey data, Kaolin has the most reported uses in cosmetic products, with a total of 1046; the majority of uses are in leave-on formulations (Table 3).[20] Bentonite has the second most reported uses in cosmetic products, with a total of 262; half are reported in leave-on formulations. The frequencies of use for both of these ingredients have greatly changed since the original safety assessment was finalized; in 1998, Kaolin was reported to have 509 uses, and Bentonite was reported to have 94.[1] The results of concentration of use surveys conducted by the Council in 2022 indicate Kaolin has the highest maximum concentration of use in leave-on formulations; it is used at up to 53.2% in manicuring preparations.[21] For leave-on dermal preparations, specifically, Kaolin also has the highest reported maximum concentration of use, at 16% in face and neck products, and Bentonite has the next highest, at 8% in face and neck preparations. According to the original safety assessment, the maximum leave-on use concentration in 1999 for Kaolin was 100% in skin care preparations; the maximum leave-on use concentration for Bentonite was 8% in makeup foundations.[1]

Clay ingredients may be used in products that can be incidentally ingested; for example, Kaolin is used in lipstick (at up to 14.5%).[21] Additionally, clay ingredients have been reported to be used in products that may come into contact with the eyes and mucous membranes; for example, Kaolin is used at up to 8.5% in eye shadows and at up to 5% in bath soaps and detergents.

Moreover, clay ingredients are used in cosmetic formulations that could possibly be inhaled; for example, Bentonite is reported to be used at 0.9% in spray suntan products and Kaolin is reported to be used at up to 15% in face powders.[21] In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

While no data have been submitted from the cosmetics industry indicating that these clay ingredients are used in nanoform in cosmetic formulation, a report from a nanotechnology research company provides statistical data showing that nanoclays can be used as cosmetic additives for lipsticks, eyeliners, and toothpaste, functioning for rheology modification, viscosity control, thixotropic effect, as well as increased stability and pigment dispersibility.[22]

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

In regulations regarding cosmetic products in the European Union (EU), no restrictions were listed for Attapulgite, Clay, Fuller's Earth, Hectorite, Illite, or Montmorillonite.[23] Bentonite and Kaolin are listed in Annex IV-Allowed Colorants under CI 77004 with the chemical name of "natural hydrated aluminum silicate…containing calcium, magnesium or iron carbonate, ferric hydroxide, quartz-sand, mica, etc. as impurities;" the remaining clay ingredients named in this report are not restricted from cosmetic use in any way. Note, these ingredients are not approved as colorants in the US.[2] Bentonite, Hectorite, and Kaolin were included in the scientific opinion by the EU Scientific Committee on Consumer Safety (SCCS) on the safety of aluminum in cosmetic products.[24] The SCCS concluded that the use of aluminum compounds is safe at the following equivalent aluminum concentrations up to 6.25% in non-spray deodorants/antiperspirants, 10.60% in spray deodorants/antiperspirants, 2.65% in toothpaste, and 14% in lipstick.

According to the Australian Industrial Chemicals Introduction Scheme (AICIS), the following ingredients are Tier I chemicals (not considered to pose an unreasonable risk to the health of workers and public health): Bentonite, Fuller's Earth, Kaolin, and Montmorillonite.[25] Attapulgite is a Tier II chemical (requires risk management measures to be instituted for safe use for human health). Hectorite is listed as a chemical unlikely to require further regulation to manage risks to human health.

Non-Cosmetic

Based on the properties of broad surface area, rich porosity, diverse morphology, good adsorption performance, and high ion exchange capacity, nanoclays have been widely applied in many fields, such as drug delivery systems,[26] food and beverage packaging,[27] paper manufacturing,[28] and constructional material.[29]

Attapulgite

Attapulgite is reported to be used in absorbents, pesticides, oil and petroleum treatment, and as a filler in many products.[1]

Bentonite

Bentonite is reported to be 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.[1]

Bentonite is generally recognized as safe (GRAS) as a direct food additive for humans (21 CFR§184.1155) and animals (21 CFR§582.1155). Bentonite is also GRAS as an indirect food additive in adhesives and components of coatings (21 CFR§175.105), in paper and paperboard components (as a colorant only, 21 CFR§176.170), in adjuvants as a colorant for polymers (21 CFR§178.3297),

Clay

Clay (natural) is GRAS as an indirect food additive in polymers (cellophane; 21 CFR§177.1200).

Fuller's Earth

Fuller's Earth is reported to be used as a military decontaminant for removal of hazardous materials from the skin.[30]

Hectorite

Hectorite has been approved for use in internally and externally applied products, as well as dentifrices and externally approved pharmaceuticals.[1]

Hectorite is reported to be used as drug-delivery system in anticancer therapy because of its biocompatibility, mechanical strength, and natural availability.[31]

Illite

Illite has been studied for use in environmental remediation of contaminated soils and water as an adsorbent.[32-35] It also has been studied for use in veterinary applications, such as dietary supplements for swine[36] and topical therapeutic treatment in equine injuries.[37]

Kaolin

Kaolin is reported to be used in the paper industry to fill and coat the surface of paper, as a filler in rubber and plastics, paint extender, ceramics manufacture, ink, adhesives, insecticides, medicines, food additives, bleaching, adsorbents, cement, fertilizers, crayons, pencils, detergents, porcelain enamels, paste, foundries, linoleum, floor tiles, and textiles.[1] *It has been classified by the National Formulary as a tablet and/or capsule diluent.*

Kaolin clay is GRAS as an indirect food additive with no limitation other than current good manufacturing practice (21 CFR§186.1256). It is used in the manufacture of paper and paperboard that contact food. Kaolin (colloidal) is an approved over-the-counter (OTC) drug as an antidiarrheal active ingredient (21 CFR§335.10), an anorectal active ingredient (21 CFR§346.14), and a skin protectant active ingredient (from 4% to 20%; 21 CFR§347.10). Kaolin is used as a digestive aid (21 CFR§310.545); however, the data are currently inadequate to establish general recognition of the safety and effectiveness of this ingredient for this specified use. Kaolin is exempted from the requirement of a tolerance for pesticide residues when used on or in food commodities to aid in the control of insects, fungi, and bacteria (food/feed use; 40 CFR§180.1180).

Kaolin minerals (specifically kaolinite) have been studied for use in environmental remediation of contaminated soils and water.[34,35] This clay material has also been studied for use in veterinary applications, such as dietary supplements for swine[36] and topical therapeutic treatment in equine injuries.[37]

Montmorillonite

Montmorillonite is reported to be used for food packaging and in paper manufacturing.[27,28] It also has been studied for use in environmental remediation of contaminated soils and water[34,35] and in veterinary applications, such as use in dietary supplements for swine.[36]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Clay

In ex vitro bioavailability studies using human skin models, the ability of transcutaneous passage of heavy metals (vanadium, lead, arsenic, barium, nickel, chromium, and aluminum) in 3 clay pastes was analyzed.[38] The clay pastes were white Montmorillonite, Kaolin, and Clay (composed of 75% Illite, 19% Kaolin, and 6% Montmorillonite). Approximately 150 g of each product were tested with human skin samples in Franz cells and incubated for 24 h. The tested products, the diffusion liquids, and the storage liquids were then analyzed for metal content (details not provided). No detectable quantities of heavy metals were found in the diffusion or storage liquids. It was determined that the traces of heavy metal in the clay pastes did not penetrate cutaneous tissue.

Kaolin

In a dietary study, a group of 10 male Sprague-Dawley rats were fed a control diet plus 0.5 ml 20% Kaolin – 1% pectin for 48 h.[1] Stool samples were collected 72 h later and analyzed for volume, sodium, potassium, and fat content. The results were a 103% increase in sodium, a 184% increase in potassium, and fat excretion remained at baseline.

Montmorillonite

Polydisperse and monodisperse [^{134}Cs]-fused Montmorillonite suspensions were administered to groups of 40 rats and mice and to 120 beagle dogs by a multiport nose-only inhalation exposure system.[1] Aerosol concentrations ranged from 0.1 to 0.001 mg of fused Montmorillonite/l 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. Five rats and 5 mice from each group were killed 4 h after exposure. The remaining rats and mice were killed at various times after exposure. Tissues from rats and mice were collected on post-exposure days 2, 4, 8, 16, 32, 64, 128, 256, 365, 512, 730, and 850. Tissues and excreta from the dogs were also collected on the same schedule, but also at 4, 5, 7, and 9 yr after inhalation exposure. Two dogs were scheduled for termination at times ranging from 4 h to 9 yr. All animals were necropsied and tissues from lungs, lung-associated lymph nodes, gastrointestinal tract, spleen, kidneys, abdominal lymph nodes, blood, skeleton, muscle, and skin were prepared for analysis of [^{134}Cs]-exposure. 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/g 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 deposits 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 lung-associated lymph nodes 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-d half-time in the lymph nodes and 6900-d half-time clearance in the gastrointestinal tract. The transport rate of the particles in the dog was 0.0002/d of the lung burden. The long-term biological clearance half-term day was 690 d for rats and 490 d for mice. The lymph node accumulation process was modeled by a short-term process that became negligible after a few days.

Radiolabeled, [^{134}Cs]-fused Montmorillonite particles were instilled into specific lung lobes or injected intraperitoneally into 32 beagle dogs.[1] Necropsy was performed 34, 182, and 365 d 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 for 29 dogs and from 42 to 64 µCi lung burdens for the other 3 dogs. Effective translocation half-time of lung instillations was 390 d. The accumulation rate of [^{134}Cs]-fused particles in the lymph nodes was 0.03% per day. Individual lung lobes cleared particles to 1 - 2 lymph nodes, and specific lymph nodes accumulated particles from 1 - 3 lung lobes. Lymph nodes that collected particles from the lung included the left mediastinal node and the left, left-middle, right, and right-middle tracheobronchial lymph nodes. The destination for translocated particles was primarily the nodes proximate to the tracheal bifurcation. Particles injected into the peritoneal cavity were translocated mainly to mesenteric lymph nodes and left and right sternal lymph nodes. A small percentage of particles went to the left tracheobronchial lymph node.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Clay

In an acute dermal toxicity study performed in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 402, rats received 2000 mg/kg bw of Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) on clipped skin.[38] The test material was moistened with 0.2 ml distilled water. A control group received only distilled water. The rats were observed for 14 d. No mortality or clinical signs of toxicity were observed. The LD_{50} was greater than 2000 mg/kg. No further details were provided.

Oral

Clay

In an acute oral study performed in accordance with OECD TG 423, rats were exposed to a single dose of 2000 mg/kg bw of Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) in distilled water.[38] No mortality or clinical signs of toxicity were observed. Visceral examination did not reveal any lesions of pathological significance except uterine distension in one rat, which was not considered to be treatment-related. The LD_{50} was greater than 2000 mg/kg bw. No further details were provided.

Hectorite

Five male and 5 female Sprague-Dawley rats were administered a single dose of 5 g/kg of Hectorite by gavage.[1] None of the animals died; the acute oral LD_{50} was > 5.0 g/kg bw.

Kaolin

In an acute oral study, 120 rats were fed doses of Kaolin ranging from 100 to 210 g/kg.[1] Fourteen rats were controls. Kaolin was inert and non-static except for the danger of bowel obstruction resulting in perforation. The clinical signs were listlessness, anorexia, oliguria, hypothermia, and dyspnea. These were pathological reactions from overdistention 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.

Inhalation

Clay

In an acute inhalation study performed in accordance with OECD TG 403, rats were exposed to 3.856 mg/l air of Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite).[38] A control group was exposed to air passed through inert bed material (iron grit). Both groups of rats were exposed for 4 h and then observed for 14 d. No mortality or clinical signs of toxicity were observed. The LC_{50} was greater than 3.856 mg/l. No further details were provided.

Illite, Montmorillonite, Kaolin

The inhalation toxicity of a naturally-occurring dust containing Illite, Montmorillonite, Kaolin and α-quartz was determined in a group of 6 male CD(SD)BR rats exposed to an aerosol of the dust (12 mg/m^3, ~ 10 µm mean diameter) for 3 h in open cages.[39] The dust was composed of approximately 75% of the 3 clay aluminum-silicates and approximately 20% α-quartz. A control group of 6 male rats were exposed to room air only. Animals were killed at recovery periods of 0 h, 24 h, 8 d, and 30 d. Lung tissues underwent microscopic and histopathological examination. Rats that were exposed to the dust exhibited preferential particle deposition at the first alveolar duct bifurcations after the terminal bronchiole immediately after the 3 h exposure. No extracellular particles were observed in the recovery periods after this point, in either treated or control animals. The average number of particles observed at the first bifurcation after the 3 h exposure (recovery time 0 h) was 4.6 ± 1.0 particles per bifurcation. Histological sections showed prominent first bifurcation characterized by accumulation of mononuclear cells 24 h after exposure. The presence of macrophages with ingested aluminum silicate particles were observed. Macrophage migration to the bifurcations was observed to a lesser degree immediately after exposure. At 24 h, 87 ± 12% of the first bifurcation contained a significantly increased number of macrophages. After 8 and 30 d, particles and alveolar macrophages were not significantly elevated and histology was back to normal.

Parenteral

Illite, Montmorillonite, Kaolin

In a study of the naturally-occurring dust described above, 6 male albino Wistar rats were instilled with 50 mg of the dust (3.2 µm mean diameter) in 300 µl of sterile phosphate-buffered saline (PBS).[39] The dust particles were injected into the trachea. Control animals (groups of 6) received either 300 µl of PBS, 50 mg of carbonyl iron in 300 µl PBS, or 50 mg of α-quartz in 300 µl PBS. The animals were killed 30 d later. Tissues, particularly the lungs and trachea, underwent microscopic and histopathological examination. Multifocal interstitial lung disease was observed using light microscopy. Mononuclear cell infiltrates, composed of macrophages and lymphocytes located mainly around the small airways and alveolar walls, were identified during examination of all lung sections. No nodules or granulomata were observed. Collagen fibers were observed in the interstitial lesions. The α-quartz instillation resulted in multiple silicotic nodules, iron instillation did not produce any interstitial lesions (some alveolar macrophages with intracellular iron spheres were identified), and no alterations were observed in the animals that received PBS alone.

Short-Term Toxicity Studies

Parenteral

Kaolin

Nano-sized Kaolin (primary particle size 4.8 µm) was instilled intratracheally in groups of 4 male *gpt* delta mice as either a single dose of 0.2 mg/animal or multiple doses of 0.2 mg/animal/wk for 4 consecutive instillations.[40] Control mice received solvent alone intratracheally. The mice were killed at 12 wk after instillation (for a single dose) or 8 wk after the last instillation (for multiple doses). Tissues, particularly the lungs and kidneys, underwent histopathological examination. Kaolin-phagocytized alveolar macrophages were found, diffusely distributed in the lungs. Focal granulomatous formation, with or without phagocytized alveolar macrophages, were also frequently observed in the lungs of mice that received multiple instillations. Similar observations were made in the mice that received a single instillation, but with a slight degree of particle accumulation and granuloma formation in the lungs. No abnormalities were observed in the kidneys.

Subchronic Toxicity Studies

Oral

Montmorillonite

In a 90-d feed study, 10 male Wistar rats received a Montmorillonite clay (40 mg/kg/d; modified with hexadecyltrimethylammonium bromide) in the diet.[41] Another 10 male rats received only standard diet as control. During the treatment period, clinical signs, body weight, and feed and water consumption were recorded weekly. At the end of the treatment period, the rats were fasted for 18 h before being killed. Histopathological examinations were performed, and liver, kidneys, lungs, spleen, brain, testes, gastrointestinal tract, and heart were weighed. Blood samples were obtained for analysis. No rats died during the treatment period and no remarkable clinical signs were observed. Body weight gains and feed and water consumption were comparable to controls. No significant changes were noted in clinical biochemistry, organ weights, or in the histopathological examinations when compared to controls.

Parenteral

Kaolin

Toxicity of some of the minerals present in coal-mine dust was examined in groups of 10 SPF Sprague-Dawley rats.[1] The rats were exposed over a period of 3 mo to 50 mg/animal 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 bronchovascular lymphoid sheaths. No information regarding nonexposed lungs was presented. The opinion of the investigators was that exposure to Kaolin results in "pulmonary toxicity" and possesses "fibrogenic capacity."

Chronic Toxicity Studies

Oral

Montmorillonite

The potential toxicity of a naturally-occurring calcium Montmorillonite clay was studied using groups of 10 male and 10 female Sprague-Dawley rats for 28 wk.[42] The rats received the test material at 0, 0.25, 0.5, 1.0, or 2.0% w/w in their feed. Rats were observed daily for clinical signs and deaths. Feed consumption was recorded daily for the first month and then every fourth day. Body weights were measured weekly. At the treatment end, final body weights were recorded and blood was drawn for analysis. After the rats were killed, histopathological examinations were performed, and select organs were weighed. Total feed consumption, cumulative feed consumption, body weight, total body weight gain, and relative organ weights were not affected in either sex at any dose tested. No differences in relative organ weights or gross or histopathological changes compared to controls were observed. Non-dose-dependent significant changes were observed in mean corpuscular hemoglobin, serum calcium, serum vitamin A, and serum iron.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Kaolin

Groups of 12 Sprague-Dawley female rats were fed a control diet, 20% Kaolin diet, or iron-supplemented 20% Kaolin diet.[1] The diets were fed for 37 to 86 d, 69 to 85 d, and 96 to 117 d 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 red blood cell 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 red blood cell levels.

In a study of 12 fetal lambs and 6 fetal rhesus monkeys, sterile suspensions of 2% Kaolin in saline were injected into the cisterna magna.[1] Fetal lambs received 1 to 3 ml of Kaolin and fetal monkeys received 0.5 to 1.0 ml of Kaolin. 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 gestation days 140 to 145 for the sheep and gestation days 160 to 165 for the 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 1 monkey underwent ventriculoamniotic shunting at 120 d after gestation. Ventricular dilatation was apparent at 1 wk 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 µm compared to 1225 µ in control animals. The corpus callosum was an average of 125 µm in thickness in the sheep compared to 475 µm in control animals. Microscopic examination found the cortical neurons 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 5 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.

GENOTOXICITY STUDIES

In vitro and in vivo genotoxicity studies summarized here are described in Table 4.

Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite; 5000 µg) was not mutagenic in an Ames test, with or without metabolic activation.[38] Unmodified Montmorillonite clay (at up to 125 µg/ml) and one type of cation-exchanged (hexadecyltrimethyl-ammonium) montmorillonite clay (at up to 250 µg/ml) also were not mutagenic in an Ames test with or without metabolic activation, but significant increases in revertant colonies were observed in one strain with metabolic activation in 2 other cation-exchanged montmorillonite clays.[43] No mutagenic activity was observed in a *Salmonella*/microsome assay with and without metabolic activation when tested in Montmorillonite and cation-exchanged montmorillonite in both nano- and non-nano-sized material at up to 141 µg/ml and up to 14.1 µg/plate, respectively.[44] However, the cation-exchanged montmorillonite material (both nano- and non-nano-sized, at up to 226 µg/ml and 170 µg/ml, respectively) in this study was genotoxic in a concentration-related manner in a Comet assay with Caco-2 cells. The natural clay was not considered genotoxic. Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cell cultures when tested at up to 5000 µg/ml, with or without metabolic activation.[38] Micronucleus induction was observed in a dose-dependent manner to micro- and nano-sized Kaolin in CHO AA8 and primary normal human diploid epidermal keratinocytes and fibroblasts, with fine particles having a higher genotoxic potency than coarse particles.[45] A 4-fold increased frequency of micronucleated cells was observed in human lung cancer A549 cells following exposure to nano-sized Kaolin.[40] Statistically significant increases in the frequency of micronuclei were induced by Montmorillonite clay at 62.5 µg/ml in a cytokinesis block micronucleus cytome assay in human hepatoma cell lines, but this effect was not observed at a concentration of 31.25 µg/ml or lower.[46] No effects in nucleoplastic bridges or nuclear buds were observed at any concentration in this study. In an in vitro micronucleus assay and kinetochore analysis using human lung fibroblasts, the genotoxic potential of Bentonite at up to 15 µg/cm^2 was determined to be generally low, but could be altered by the content of quartz and available transition metals.[47] In an in vitro Comet assay with micro- and nano-sized Kaolin in CHO AA8 and primary normal human diploid epidermal keratinocytes and fibroblasts, the test materials promoted DNA damage in a dose-dependent manner, and the particles that were 200 nm had a higher DNA-damaging potency than those that were 4.8 µm.[45]

In an in vivo Comet assay with nano-sized Kaolin intratracheally instilled in mice, DNA damage was induced with 0.2 mg/mouse, but not with 0.05 mg/mouse, after a 3-h exposure. No difference in induction was observed after the 24 h exposure compared to the 3 h exposure.[40] Increased *gpt* and Spi$^-$ mutant frequencies were observed in the lungs of the mice following intratracheal instillation with either single or multiple doses of 0.2 mg nano-sized Kaolin. A mutation spectra analysis showed > 60% of G:C to C:G transversion occurred in the *gpt* genes. In another Comet assay, rats were given 2 oral doses of up to 1000 mg/kg bw cation-exchanged montmorillonite clay.[48] There was no statistically significant difference in % tail DNA between the negative controls and the different treatment groups for any of the cells (liver, kidneys, colon) tested.

Attapulgite

In 2 studies looking at unscheduled DNA synthesis (UDS) in rat hepatocytes, Attapulgite did not cause a significant increase in DNA-specific activity at up to 10 µg/ml with no cytotoxicity.[49] However, in another UDS study using rat pleural mesothelial cells, Attapulgite tested at 2, 4, or 10 µg/cm^2 produced a significant increase in UDS and inhibited cell growth at 10 µg/cm^2. Attapulgite did not induce point mutations in a third DNA study.

Hectorite

In the Salmonella typhimurium LT2 spot test (TA98, TA100, TA1535, TA1537, and TA1538) with or without metabolic activation, Hectorite was found to be non-mutagenic.[49] In primary hepatocyte cultures, the addition of Attapulgite at 10 µg/cm^2 caused significant increases in UDS in rat pleural mesothelial cells.

CARCINOGENICITY STUDIES

The International Agency for Research on Cancer (IARC) has determined there is inadequate evidence in humans for the carcinogenicity of Attapulgite (IARC uses the mineralogical term "palygorskite" for Attapulgite).[50] Further, IARC has determined there is insufficient evidence in experimental animals for the carcinogenicity of short Attapulgite fibers (< 5 µm); however, there is sufficient evidence in experimental animals for the carcinogenicity of long Attapulgite fibers (> 5 µm). Overall, long Attapulgite fibers (> 5 µm) are possibly carcinogenic to humans (Group 2B) and short Attapulgite fibers (< 5 µm) cannot be classified as to their carcinogenicity to humans (Group 3).

Attapulgite (palygorskite fibers > 5 µm in length) is listed by California Proposition 65 as a carcinogen.[51]

Inhalation

Attapulgite

In a rat inhalation study, groups of 40 (20 male and 20 female) SPF Fischer rats were exposed to samples of Attapulgite dust mined in Lebrija or Leicester in inhalation chambers at a concentration of 10 mg/m^3 for 6 h/d for 5 d/wk until they were killed.[1] Negative and positive control groups received Kaolin and crocidolite, respectively, at 10 mg/m^3. Four

animals were killed at 3, 6, and 12 mo, and the 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. At microscopic examination, 1 peritoneal mesothelioma, 1 adenocarcinoma, and 3 bronchoalveolar hyperplasia were found in rats treated with Lebrija Attapulgite. Thirty-five rats had no proliferative changes. In rats treated with Leicester Attapulgite, proliferative lesions observed included 2 mesothelioma, 1 peritoneal mesothelioma, 1 malignant alveolar neoplasm, 2 benign alveolar neoplasms, and 8 bronchoalveolar hyperplasias. Twenty-seven rats had no proliferative lesions. Rats exposed to the negative-control Kaolin had 2 bronchoalveolar hyperplasias. Rats in the positive-control crocidolite group had 1 adenocarcinoma and 3 bronchoalveolar hyperplasias.

Kaolin

Kaolin was reported to be the negative control in the above rat inhalation study.[1] The rats received 10 mg/m^3 Kaolin for 6 h/d for 5 d/wk. Two bronchoalveolar hyperplasias were reported.

Parenteral

Attapulgite

In an intratracheal study, groups of 5 rats received a single instillation of Attapulgite at 1, 5, and 10 mg.[1] One month after treatment, bronchoalveolar lavage and microscopic examination of the lungs were performed. The average length of the fibers was 0.8 µm, and 100% of the fibers were less than 3 µm. Every test animal had type A lesions, which 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 bronchoalveolar lavage (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.

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 1 of 2 Attapulgite samples.[1] 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 yr. 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 the positive control, crocidolite, 14/29 developed pleural mesotheliomas.

Attapulgite (20 mg/ml of 0.9% sodium chloride) was injected into the pleural cavities of 36 Sprague-Dawley rats.[1] The median fiber length was 0.77 µm. 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.

Attapulgite was injected intrapleurally as a single dose of 0.5, 2, 4, 8, 16, or 32 mg into 6 groups of 25 Fischer 344 rats.[1] 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.

In another intrapleural study, injections of 20 mg of different Attapulgite fiber samples in 1 ml of saline were given to 2-mo-old Sprague-Dawley rats.[1] 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. The researchers concluded Attapulgite was not carcinogenic in this study.

Samples of Attapulgite from Lebrija, Torrejon, and Leicester were injected intrapleurally as a single injection in groups of 20 male and 20 female SPF Fischer rats.[1] Concentrations were not reported; however, fiber length was reported as < 2 µm, for Lebrija Attapulgite, at most 0.54% > 6 µm for Torrejon Attapulgite, and 19% > 6 µm for Leicester Attapulgite. Kaolin and saline were used as negative controls, and crocidolite was used as a positive control. 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. Mesotheliomas were reported in 2, 14, 30, and 34 rats for Lebrija Attapulgite, Torrejon Attapulgite, Leicester Attapulgite, and crocidolite, respectively. In the negative controls, no mesotheliomas were reported for the Kaolin and 1 mesothelioma was reported for the saline group. Lebrija Attapulgite dust extracted from the lung had fibers < 2 µm. Material examined from Torrejon Attapulgite was fibrous and had fiber length up to 8 µm. Leicester Attapulgite fibers from extracted lungs were up to 25 µm. The investigators considered these fibers to be tumorigenic.

Three samples of 25 mg of Attapulgite dust were injected intraperitoneally into 40 Wistar rats.[1] 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%.

In a carcinogenicity study conducted with 3 samples of Attapulgite labeled Georgia, Lebrija, and Morimoiron, female Wistar rats (112, 115, and 114 per sample type, respectively) were injected intraperitoneally.[1] Each sample was injected 1/wk for 9 wk at 60 mg per injection. Fiber dimensions for each of the samples Morimoiron, Georgia, and Lebrija were as follows: <50% fiber length was 0.7, 0.5, and 0.8 µm, respectively and <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 yr after treatment for necropsy. At necropsy, neoplasms or organs with suspected neoplasm tissue were fixed for microscopic examination. The percentage of rats with tumors were 3.5%, 3.5%, and 3.6% for the Morimoiron, Lebrija, and Georgia samples, respectively. These 3 samples were determined to be noncarcinogenic.

In another experiment by the same investigators, a fourth sample of Attapulgite from Caceres was tested in 30 rats.[1] Intraperitoneal injections of 2, 4, and 4 mg were administered consecutively for 3 wk. 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. Forty percent of the rats had tumors. The results were considered moderate in relation to the dose.

Montmorillonite

Heat-treated Montmorillonite in doses of 5, 15, and 45 mg was given to groups of 4 Sprague-Dawley rats by intratracheal instillation.[1] Following a 3-mo 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 alveolar macrophages. 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.

OTHER RELEVANT STUDIES

Adsorption

Clay ingredients are reported to adsorb various chemicals, molecules, and microorganisms.[1] These compounds include, but are not limited to, strychnine, quinine, atropine, ampicillin, amoxycillin, Agrobacterium radiobacter, Escherichia coli, Serratia marcescens, Bacillus species, bacterial endotoxins and enterotoxins, and aflatoxins.

Cytotoxicity

Numerous studies with various cell lines on the cytotoxic and hemolytic effects of clay ingredients have been reported.[1] Results varied and may have been dependent on different factors, including mineral composition of the test materials.

Illite and Montmorillonite

The protective effect of Illite and Montmorillonite (up to 1 mg/ml each) on alterations in cell viability and epithelial barrier function induced by mycotoxins was evaluated using Caco-2 cells in a colorimetric 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay and a lactate dehydrogenase (LDH) assay.[52] Both clays provided protection against mycotoxin effects. Aflatoxin B1- and fumonisin B1-induced cytotoxicity were completely abolished by Illite. Decreases in the gene expression of specific claudin isoforms and the reduction of trans-epithelial electrical resistance of cell monolayers (an indicator of the epithelial barrier integrity) induced by mycotoxins were reversed by Illite. Montmorillonite also provided protection against mycotoxin effects, but at a lesser degree.

Illite, Montmorillonite, Kaolin

The cytotoxicity of a naturally-occurring dust (dust samples collected from a Mexican city) comprising approximately 75% Illite, Montmorillonite, and Kaolin, and approximately 20% α-quartz was studied in alveolar macrophages obtained from male albino Wistar rats.[39] LDH release was used as an indicator of cell membrane disruption. The alveolar macrophages were incubated with and without the dust (3.2 µm mean diameter) for up to 2 h. LDH was measured in the supernatant at 0, 1, and 2 h, with controls run in parallel. Rat alveolar macrophages incubated with the dust released increasing amount of LDH into the medium as a function of time. Significant levels above control values (2.2 ± 2.6 LDH U/l) were observed by 1 h (19.5 ± 2.6 LDH U/l) and 2 h (29.5± 4.0 LDH U/li) of incubation.

The hemolytic activity of the dust was also investigated by incubating different particle concentrations (0.1, 0.5, 1.0, 1.5, and 2.0 mg/ml) with a 0.6% suspension of human red blood cells obtained from normal donors. Cell-particle suspensions were incubated at 37°C in PBS for 1 h under moderate agitation. The results indicated the dust was highly hemolytic. An amount of 2 mg/ml produced 95 ± 3% hemolysis. The effect was observed starting at 1 mg/ml in a dose-related manner.

Kaolin

In a study examining the toxic mechanisms of typical fine particulate air pollution ($PM_{2.5}$), human bronchial epithelial (16HBE) cells were treated with nano-scale Kaolin at concentrations of 40 to 240 µg/ml.[53] The particle size information was not available; however, the authors stated the nano-scale Kaolin utilized in the study was to imitate Kaolin in atmospheric fine particles ($PM_{2.5}$). Cytotoxicity results of the cell counting kit-8 (CCK-8) assay showed the 16HBE cells had high viability after exposure to 40 µg/ml nano-sized Kaolin, but cell viability decreased significantly at doses greater than 80 µg/ml. A lactate dehydrogenase assay indicated that nano-sized Kaolin caused membrane disruption in a dose-dependent manner.

Hemostatic Response

Bentonite

The ability for Bentonite (2/3 weight) and a zeolite (type not specified; 1/3 weight) to act as a hemostatic agent was studied in 12 male Sprague-Dawley rats.[54] Another 12 rats served as controls. Approximately 8 g of the material was applied on wounded skin. Wounds were circular, full-thickness and 2 cm in diameter; skin samples were excised and evaluated stereologically after scarification. On days 12 and 21, 6 rats from the test group and 6 rats from the control group were killed. At day 12 termination, a 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. The researchers concluded the hemostatic agent containing Bentonite may cause vasoconstriction and inhibition of neoangiogenesis.

Other Parenteral Studies

Attapulgite

In an intratracheal study, groups of 5 rats received a single instillation of Attapulgite at 1, 5, and 10 mg.[1] One month after treatment, BAL and microscopic examination of the lungs were performed. The average length of the fibers was 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.

Groups of 5 male Wistar rats received 1, 5, or 10 mg of Attapulgite by transtracheal injection to examine alveolar macrophage production of interleukin-1 (IL-1) and macrophages-derived growth factor (MDGF) from fibroblasts.[1] Saline and chrysotile B asbestos were used as controls. At 1 mo, Attapulgite produced granulomas and the chrysotile B produced fibrosis. At 8 mo, 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 chrysotile B. Enhanced production of IL-1 was seen in all treated groups. MDGF production was only seen in animals with lung fibrosis.

Attapulgite with a mean fiber length of 0.8 µm and diameter of 0.02 µm was delivered to the lungs of sheep by bronchioscopic cannulation.[1] The tracheal lobe of 16 sheep was subjected to a single exposure of 100 mg of Attapulgite in 100 ml of saline. A BAL was conducted at 2, 12, 24, 40, and 60 d, and necropsy was conducted on day 60. Total BAL cells, macrophages, and neutrophils, fibronectin content, and LDH and β-glucuronidase (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.

Bentonite

The ability of Bentonite to increase susceptibility to bacterial pneumonia was studied in mice.[1] The animals were injected intratracheally with 1, 10, or 100 µg Bentonite. 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-d period. Control animals were exposed to titanium dioxide. 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.

The effects of Bentonite dust in rats was analyzed in a 2-part intratracheal study.[1] A 0.5 mg dose of Bentonite with a mean size of 0.3 µm was instilled. Control animals were injected with sterile saline and titanium dioxide. Animals were killed at 1, 2, 6, 24, and 48 h and 4 and 7 d after instillation. Bronchopulmonary lavage was carried out and alveolar

macrophages and polymorphonuclear leukocytes were recovered. The activity of LDH and protein content of the lavage fluid were also determined. In the first experiment, a rapid influx of polymorphonuclear (PMN) leukocytes was detected at 6 h. PMN leukocyte response peaked at approximately 19 x 10^6 cells after instillation and started declining more slowly up to 4 d. At 7 d, the polymorphonuclear leukocyte numbers were 2.5 x 10^6. The greatest increase in the numbers of alveolar macrophages recovered occurred at 4 and 7 d. 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 d. LDH activity at 24 h was maintained at 40 milli units (mU)/ml and then increased (73 mU/ml) with the influx of polymorphonuclear 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, after instillation of 5 mg of Bentonite, the animals were killed at 1, 7, 49, and 100 d.[1] In addition to the above measured parameters, peroxidase and lysozyme activity were also measured. A large number of polymorphonuclear leukocytes were recovered at day 1. However, the severity of the response did not differ significantly from the 0.5 mg dose. By 7 d, the numbers had decreased and were similar to control values. A significant decrease in the number of alveolar macrophages compared to controls was observed at 24 h after instillation. This decrease was followed by a sharp increase that exceeded control values by 7 d. Total number estimates were similar to those of the first experiment. LDH activity and protein concentration from Bentonite and titanium dioxide 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 d, but returned to control values at 49 and 100 d.

In an intratracheal study, a single dose of 40 mg of Bentonite suspended in 1 ml of physiological saline containing 40,000 IU of crystalline penicillin was administered to male CFY rats.[1] The Bentonite 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 d after exposure. Body and lung weights 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 d, 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 24 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 48 and 72 h. After 90 d of exposure, Bentonite caused storage focal tissue reaction (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 increased but distribution remained the same. After 90 d, the value was the same as seen at 72 h.

In another study by the same research group, male CFY rats were given a single intratracheal dose of 60 mg of Bentonite in 1 ml of physiological saline containing 40,000 IU crystalline penicillin.[1] 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, weeks 2 and 4, and months 3, 6, and 12. The acid phosphatase activity and the progression of fibrosis were determined. The lungs were processed for microscopic examination and fibrosis determined by Belt and King's classification. Acid phosphatase activity was increased at 72 h and had returned to normal by the first month. Loose reticulin fibrils, but no collagen, were observed after months 1 - 12.

Bentonite dust was administered intratracheally as a single 60-mg dose to Sprague-Dawley rats.[1] The animals were killed 3, 6, and 12 mo after exposure. The right lung was studied microscopically and the lipids, phospholipids, and hydroxyproline values 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 mo, 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 difference was detected at 6 and 12 mo. Hydroxyproline content of treated rats (mg/g lung wet weight) was very similar to controls at 3, 6, and 12 mo.

Subplantar injections of 0.05 ml of a 5% solution of Bentonite were given to male Wistar rats.[1] The rats either received Bentonite injections in both hind paws 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 (control). 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.

Kaolin

The ability of Kaolin to increase susceptibility to bacterial pneumonia was studied in mice.[1] The animals were injected intratracheally with 100 µg Kaolin. 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-d period. Control animals were exposed to titanium dioxide. 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.

DERMAL IRRITATION AND SENSITIZATION

In vitro, animal, and human dermal irritation, sensitization, and photoallergy studies are summarized in Table 5.

A formulation containing 38% Montmorillonite was predicted to be non-irritating in an EpiDerm™ skin model when tested neat.[55] Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) was not irritating to rabbit skin when tested at 500 mg in distilled water.[38] A formulation containing 1.75% Bentonite was not irritating to 25 human subjects in a 14-d cumulative irritation assay, nor was a mud mask containing 8% Bentonite irritating in a single-insult occlusive patch test in 19 subjects.[56,57] No visible irritation was observed in a 4-wk clinical use test (50 subjects) of a facial cleanser containing 2% Bentonite and 2% Kaolin; however, some subjects reported perceived discomfort and/or irritation.[58]

A formulation containing 38% Montmorillonite was predicted to be non-sensitizing in a KeratinoSens™ assay.[55] No sensitization was observed in guinea pig studies of 50% Hectorite (Buehler test, details not provided) or of Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite; intradermal induction at 5%; no further information on dosing for topical induction or challenge provided).[11,38] Dermal sensitization was not reported in human repeated insult patch tests (HRIPTs) with a foot mask containing 3.5% Bentonite (102 subjects), a clay mask containing 3.8% Bentonite (108 subjects), or in a face cream containing 7.5% Bentonite (52 subjects).[59-61] No sensitization was observed in HRIPTs with a lip product containing 14.5% Kaolin (54 subjects) or a clay mask containing 40% Kaolin (51 subjects); however, one subject in a study of a clay mask containing 14.5% Kaolin (103 subjects) had moderate erythema progressing to erythema and edema with papules through the induction and challenge phase.[62-64] A sunscreen with 1.75% Bentonite was not a photosensitizer in 23 human subjects.[65]

Hectorite

A primary irritation study patterned after the Draize method was conducted using 6 white rabbits.[1] 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. Hectorite was nonirritating to the skin of rabbits.

OCULAR IRRITATION STUDIES

Animal

Clay

In an ocular irritation study performed in accordance with OECD TG 405, 100 mg of Clay (75% Illite, 16% Kaolin, and 9% Montmorillonite) was instilled into one eye of rabbits.[38] The other eye served as a control and was instilled with 0.1 ml normal saline. No adverse effects were noted following treatment up to 72 h after instillation. The test material was considered to be non-irritating to rabbit eyes. No further details were provided.

Hectorite

In a primary eye irritation study using 9 New Zealand white rabbits, a 0.1 ml liquid or semisolid (100 mg of the solid) sample was instilled into the one eye of each rabbit.[1] The eyes of 6 rabbits were not rinsed, and the eyes of 3 rabbits 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 d. 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.

Kaolin

The potential for ocular irritation from a clay mask with 14.5% Kaolin was investigated in a tissue equivalent assay with EpiOcular™ cultures.[66] The EpiOcular™ human cell constructs were exposed to 100 µl test material under standard culture conditions for 4, 8, 16, and 24 h. Tissue viabilities were then examined by MTT assay. The duration of exposure resulting in a 50% decrease of tissue viability (t_{50}) was calculated to be 5.2 h (at 4 h, tissue viability was 63.4%). The positive control yielded expected results. As residual test article may bind to the tissue and result in a false MTT reduction signal, a freeze-killed tissue control was used, and calculations were performed to correct for the amount of MTT reduced directly by the test article residues in the tissues. The clay mask with 14.5% Kaolin was predicted not to be an ocular irritant in this assay.

CLINICAL STUDIES

In a study of total pulmonary non-asbestos mineral content in lung tissue from 20 individuals with no occupational dust exposure, Attapulgite and Kaolin were identified in 12 individuals.[1] No correlations were made between numbers or types of fibers and age, sex, or smoking. Approximately 8400 out of 106,000 fibers (7.9%) were identified as Attapulgite and approximately 3500 out of 106,000 fibers (3.3%) were identified as Kaolin. Mineralogical analysis found that 100% of the Attapulgite fibers and 94% of the Kaolin fibers were 1 - 4.9 µm in length.

Oral

Montmorillonite

The effect of oral ingestion of Montmorillonite on protection against the adverse effects of the ingestion of aflatoxins were studied in 23 male and 27 female human subjects.[67] The subjects received 1.5 g/d or 3.0 g/d in capsules. A total of 9 capsules were ingested over a 2-wk period. The study was randomized and double-blinded. Blood and urine samples were collected before and after the study. Mild gastrointestinal effects were reported with no statistical significance found between the treatment groups. No significant differences in hematology, liver and kidney function, or electrolytes were reported in either group.

Case Reports

Bentonite

Several case studies involving Bentonite workers have been reported.[1] Some milling plants had dangerous concentrations of silica that ranged from 2 to 10 times the safe maximal concentration according to the US Bureau of Mines. Silicotuberculosis developed in four patients studied.

Fuller's Earth

A patient that reported working no more than 15 yr in a Fuller's Earth plant as a young man was diagnosed with terminal aspiration pneumonia, pneumoconiosis due to Fuller's Earth exposure, bilateral emphysema, and fibrous pleural adhesions.[1] The 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%).

Two additional cases of pneumoconiosis in employees that worked in processing or milling Fuller's Earth for at least 28 yr were reported.[1]

Kaolin

A patient was reported with multiple pulmonary Kaolin granulomas.[1] 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.

In another investigation, the death of a 62-yr-old man who worked in a cotton textile mill for 43 yr was reported.[1] 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.

The lungs and chest x-ray films were evaluated in a pair of case studies of men who worked in a Kaolin-processing plant for many years.[1] The first case was a 36-yr-old man who worked on the plant for 17 yr. 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-yr-old man who worked in the Kaolin-processing plant for 21 yr. Within his last 3 yr, he had dyspnea and a slight cough with small 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).

A 35-yr-old man who worked at a Kaolin-processing plant for 17 yr presented with chest pain and was hospitalized.[1] For the previous 2 yr 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 cm x 12 cm x 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.

Pulmonary tissue was obtained from 5 Kaolin workers with advanced pneumoconiosis.[1] 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 composed 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.

Six additional cases of pneumoconiosis in employees of 12 yr in Kaolin processing or milling facilities were reported.[1]

Montmorillonite

A 73-yr-old Montmorillonite worker developed signs of pneumoconiosis, but subsequently died of acute gastrointestinal hemorrhage from a benign gastric ulcer.[1] A chest radiograph taken 2 yr before his death showed a bilateral fine reticulonodular shadowing, while another radiograph taken a few weeks before his death 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 - 5 mm in diameter were observed occupying most of the lungs. 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. A slight degree of fibrosis associated with the dust lesions was observed, and the neoplasm was a poorly differentiated adenocarcinoma containing giant cell areas. Mineralogical analysis showed a large amount of calcium Montmorillonite.

OCCUPATIONAL EXPOSURE

Attapulgite

A cohort of 2302 men employed for at least 1 mo between January 1, 1940 and December 31, 1975 at an Attapulgite mining and milling facility was studied.[1] A significant deficit of mortality from nonmalignant respiratory disease was observed based on age, calendar year, and rates. A marked deficit of nonmalignant respiratory disease 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 yr in high-exposure level jobs. An increased mortality was observed for gastric cancer (6 observed) and a deficit due to nonmalignant respiratory disease was observed (9 observed).

Kaolin

A study was performed on the prevalence of ventilatory impairment, chest symptoms, and radiographic abnormalities in over 2000 Kaolin workers representing over 95% of the employees in the industry at the time.[1] Of the participants, 19% admitted having a cough. Of those participants with a cough, 17% had an abnormal forced expiratory volume and 14% had an abnormal vital capacity. Of those without a cough, 5.5% had an abnormal forced expiratory volume and 7% had an abnormal vital capacity. Also, 18% of the participants admitted to chronic sputum production. Of those with sputum production, 16% had abnormal forced expiratory volume, and 12.5% had abnormal vital capacity. Of those without sputum production, 6% had an abnormal forced expiratory volume, and 7.5% had an abnormal vital capacity. About 30% of the participants complained of shortness of breath, 3.1% of the cases were 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. Eighteen subjects (0.89%) had complicated pneumoconiosis. 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 forced expiratory volume and forced vital capacity, 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 forced expiratory volume 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.

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.[1] Fifty-four of the 62 men worked with Kaolin or related kaolinized mineral stone. All the test subjects were employed in the mining industry. 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. An increasing quartz concentration appears to be related to nodular fibrosis. The degree of interstitial fibrosis appeared to be more related to dust lung concentrations, although these results failed to reach statistical significance.

The Occupational Safety and Health Administration (OSHA) lists the following permissible exposure limit (PEL) for 8 h work shifts for Kaolin: total dust - 15 mg/m^3 and respirable fraction - 5 mg/m^3.[68,69] The National Institute for Occupational Safety and Health (NIOSH) lists the following recommended exposure limit (REL) for up to 10 h time weighted average for Kaolin: total dust - 10 mg/m^3 and respirable fraction - 5 mg/m^3.

Bentonite

In a toxicological and occupational epidemiological review of Bentonite, the authors concluded Bentonite is probably not more toxic than any other inert insoluble dusts.[70] However, because some forms may contain variable amounts of respirable crystalline silica, prudent management and adherence to occupational exposure limits is appropriate.

SUMMARY

This report assesses the safety of 8 clay ingredients as used in cosmetics. All of these ingredients are reported to function as absorbents and bulking agents; other cosmetic functions are also reported. The Panel previously reviewed the safety of Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, and Montmorillonite in a report that was published in 2003. In that report, the Panel concluded that these ingredients were safe as used in cosmetic ingredients. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 yr, and it has been at least 15 yr since this assessment has been issued.

According to 2022 VCRP survey data, Kaolin has the most reported uses in cosmetic products, with a total of 1046; the majority of uses are in leave-on formulations. Bentonite has the second most reported uses in cosmetic products, with a total of 262; a little more than half are reported in leave-on formulations. The frequencies of use for both of these ingredients have greatly changed since the original safety assessment was finalized; in 1998, Kaolin was reported to have 509 uses and Bentonite was reported to have 94. The results of concentration of use surveys conducted by the Council in 2022 indicate Kaolin also has the highest maximum concentration of use in leave-on formulations; it is used at up to 53.2% in manicuring preparations. For leave-on dermal preparations, specifically, Kaolin also has the highest reported maximum concentration of use, at 16% in face and neck products, and Bentonite has the next highest, at 8% in face and neck preparations. According to the original safety assessment, the maximum leave-on use concentration in 1999 for Kaolin was 100% in skin care preparations; the maximum leave-on use concentration for Bentonite was 8% in makeup foundations.

Several of these clay ingredients are GRAS as direct and/or indirect food additives. Kaolin is also an approved OTC drug.

Ex vitro bioavailability studies were performed using human skin models. Trace heavy metals in 3 clay pastes (white Montmorillonite, Kaolin, and Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite)) did not penetrate cutaneous tissue.

In acute dermal and oral toxicity studies in rats, Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) had an LD_{50} greater than 2000 mg/kg. The same product was tested in an acute inhalation study in rats and had an LC_{50} greater than 3.856 mg/l. Inhalation studies in rats with a naturally-occurring dust containing Illite, Montmorillonite, and Kaolin (comprising 75% of the mixture) demonstrated that the majority of particles were deposited at the first alveolar duct bifurcations, and at 24-h later, numerous particles had been ingested by alveolar macrophages. Rats instilled intratracheally with the same dust developed a multifocal interstitial lung disease.

Nano-sized Kaolin (primary particle size 4.8 µm) instilled intratracheally in mice (single and multiple (4) instillations) produced diffuse alveolar macrophages containing Kaolin in the lungs. Focal granulomatous formation, with or without alveolar macrophages containing Kaolin, were also frequently observed in the lungs of mice that received multiple instillations. Similar observations were made in mice that received a single instillation, but with a slight degree of particle accumulation and granuloma formation in the lungs. No abnormalities were observed in the kidneys.

In a 90-d oral study in male rats, a modified Montmorillonite clay at 40 mg/kg/d did not cause any deaths during treatment, and no significant changes were noted in clinical biochemistry, organ weights, or in histopathological examinations when compared to controls. A naturally-occurring calcium Montmorillonite clay produced non-dose-dependent significant changes in mean corpuscular hemoglobin, serum calcium, serum vitamin A, and serum iron when tested at up to 2.0% w/w in rats in a dietary study; however, no adverse effects were noted in feed consumption, body weight, organ weights, or in gross or histopathological exams.

Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite; 5000 µg) was not mutagenic in an Ames test, with or without metabolic activation. Unmodified Montmorillonite clay (at up to 125 µg/ml) and one type of cation-exchanged Montmorillonite clay (at up to 250 µg/ml) also were not mutagenic in an Ames test with or without metabolic activation, but significant increases in revertant colonies were observed in one strain with metabolic activation in 2 other cation-exchanged Montmorillonite clays. No mutagenic activity was observed in a *Salmonella*/microsome assay with and without metabolic activation when tested in Montmorillonite and cation-exchanged montmorillonite in both nano- and non-nano-sized material at up to 141 µg/ml and up to 14.1 µg/plate, respectively. However, the cation-exchanged Montmorillonite material (both nano- and non-nano-sized, at up to 226 µg/ml and 170 µg/ml, respectively) in this study was genotoxic in a concentration-related manner in a Comet assay with Caco-2 cells. Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cell cultures when tested at up to 5000 µg/ml, with or without metabolic activation. Micronucleus induction was observed in a dose-dependent manner to micro- and nano-sized Kaolin in CHO AA8 and primary normal human diploid epidermal keratinocytes and fibroblasts, with fine particles having a higher genotoxic potency than coarse particles. A 4-fold increased frequency of micronucleated cells was observed in human lung cancer A549 cells following exposure to nano-sized Kaolin. Statistically significant increases in the frequency of micronuclei were induced by Montmorillonite clay at 62.5 µg/ml in a cytokinesis block micronucleus cytome assay in human hepatoma cell lines, but this effect was not observed at a concentration of 31.25 µg/ml or lower. No effects in nucleoplastic bridges or nuclear buds were observed at any concentration in this study. In an in vitro micronucleus assay and kinetochore analysis using human lung fibroblasts, the genotoxic potential of Bentonite at up to 15 µg/cm^2 was determined to be generally low, but could be altered by the content of quartz and available transition metals. In an in vitro Comet assay with micro- and nano-sized Kaolin in CHO AA8 and primary normal human diploid epidermal keratinocytes and fibroblasts, the test materials promoted DNA damage in a dose-dependent manner, with greater DNA-damaging potency in the nano-sized Kaolin than in the micro-sized Kaolin.

In an in vivo Comet assay with nano-sized Kaolin intratracheally instilled in mice, DNA damage was induced at 0.2 mg/mouse but not at 0.05 mg/mouse after 3 h exposure. No difference in induction was observed after 24 h exposure compared to the 3 h exposure. Increased *gpt* and Spi- mutant frequencies were observed in the lungs of the mice following intratracheal instillation with either single or multiple doses of 0.2 mg nano-sized Kaolin. A mutation spectra analysis showed > 60% of G:C to C:G transversion occurred in the *gpt* genes. In another Comet assay, rats were given 2 oral doses of up to 1000 mg/kg bw cation-exchanged montmorillonite clay. There was no statistically significant difference in % tail DNA between the negative controls and the different treatment groups for any of the cells (liver, kidneys, colon) tested.

IARC has determined there is inadequate evidence in humans for the carcinogenicity of Attapulgite. Further, IARC has determined there is insufficient evidence in experimental animals for the carcinogenicity of short Attapulgite fibers (< 5 µm); however, there is sufficient evidence in experimental animals for the carcinogenicity of long Attapulgite fibers (> 5 µm). Overall, long Attapulgite fibers (> 5 µm) are possibly carcinogenic to humans (Group 2B) and short Attapulgite fibers (< 5 µm) cannot be classified as to its carcinogenicity to humans (Group 3). Attapulgite (palygorskite fibers > 5 µm in length) is listed by California Proposition 65 as a carcinogen.

The ability for Bentonite (2/3 weight) and a zeolite (type not specified; 1/3 weight) to act as a hemostatic agent was studied in 12 male Sprague-Dawley rats. This hemostatic agent may cause vasoconstriction and inhibition of neoangiogenesis. Illite and Montmorillonite were observed to have protective effects on cytotoxicity induced by mycotoxins in MTT and LDH assays. A naturally-occurring dust containing Illite, Montmorillonite, and Kaolin induced LDH release from alveolar macrophages of rats, and showed hemolytic effects on human red blood cells. Cytotoxicity results of the CCK-8 assay showed the 16HBE cells had high viability after exposure to 40 µg/ml nano-sized Kaolin, but cell viability decreased significantly at doses greater than 80 µg/ml. A LDH assay indicated that nano-sized Kaolin caused membrane disruption in a dose-dependent manner.

A formulation containing 38% Montmorillonite was predicted to be non-irritating in an EpiDerm™ skin model when tested neat. Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) was not irritating to rabbit skin when tested at 500 mg in distilled water. A formulation containing 1.75% Bentonite was not irritating to 25 human subjects in a 14-d cumulative irritation assay, nor was a mud mask containing 8% Bentonite irritating in a single-insult patch test in 19 subjects. No visible irritation was observed in a 4-wk clinical use test (50 subjects) of a facial cleanser containing 2% Bentonite and 2% Kaolin; however, some subjects reported perceived discomfort and/ or irritation.

A formulation containing 38% Montmorillonite was predicted to be non-sensitizing in a KeratinoSens™ assay. No sensitization was observed in guinea pig studies of 50% Hectorite (further dosing information not provided) or Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite; intradermal induction at 5%, no further information on dosing for topical induction or challenge provided). Dermal sensitization was not reported in HRIPTs with a foot mask containing 3.5% Bentonite (102 subjects), a clay mask containing 3.8% Bentonite (108 subjects), or in a face cream containing 7.5% Bentonite (52 subjects). No sensitization was observed in HRIPTs with a lip product containing 14.5% Kaolin (54 subjects) or a clay mask containing 40% Kaolin (51 subjects); however, one subject in a study of a clay mask containing 14.5% Kaolin 103 subjects) had moderate erythema progressing to erythema and edema with papules through the induction and challenge phase. A sunscreen with 1.75% Bentonite was not a photosensitizer in 23 human subjects.

A clay mask with 14.5% Kaolin was predicted to not be an ocular irritant in a tissue equivalent assay with EpiOcular™ . In an ocular irritation study in rabbits, Clay (75% Illite, 19% Kaolin, and 6% Montmorillonite) produced no adverse effects and was considered to be non-irritating.

Nine capsules containing Montmorillonite (up to 3.0 g/d) were administered to 50 human subjects over a 2-wk period. Only mild gastrointestinal effects were reported.

OSHA lists the following PEL for 8-h work shifts for Kaolin: total dust - 15 mg/m^3 and respirable fraction - 5 mg/m^3. NIOSH lists the following REL for up to 10-h time weighted average for Kaolin: total dust - 10 mg/m^3 and respirable fraction - 5 mg/m^3. 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.

DISCUSSION

In 2003, the Panel published a final report that included Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, and Montmorillonite, and concluded that the ingredients named in that report were safe as used in cosmetic products. In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years, and when appropriate, additional ingredients are included in the resulting re-review. Accordingly, the Panel re-reviewed the safety of these 6 clays, with the addition of 2 related ingredients (Clay and Illite), and concluded that the available data are sufficient to determine that Kaolin is safe in cosmetics in the present practices of use and concentration as described in this safety assessment. Furthermore, the Panel concluded that the remaining 7 naturally-sourced clay ingredients are safe in cosmetics in the present practices of use and concentration, except for those products that may be incidentally inhaled, for which the available data are insufficient.

The Panel expressed concern regarding heavy metals that may be present in these ingredients. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities in cosmetic formulations.

The Panel was made aware that nanoforms of clay ingredients could potentially be used in cosmetic formulations, including those that could result in incidental ingestion (e.g., lipstick and toothpaste; categories of sprayable products were not reported based on current available data). However, use of nanoform ingredients is unlikely to translate into nanoparticle form within final formulations under in-use conditions (or under in-use exposure scenarios). In these formulations, low concentrations of use (e.g., maximum reported use concentration of Kaolin in lipstick is 14.5%) and processing would be expected to result in much larger particle sizes (by, for example, agglomeration) in the consumer product.

Additionally, some naturally-sourced clay ingredients were reported to be used in spray and powder products that could possibly be inhaled. For example, Bentonite is reported to be used at 0.9% in spray suntan products and Kaolin is reported to be used at up to 15% in face powders. For Kaolin, the data available from inhalation studies, including acute, chronic, and carcinogenicity data, suggest little potential for adverse respiratory effects at relevant doses for this naturally-sourced clay ingredient. These data have mitigated the concern of the use of Kaolin in cosmetic products which may be incidentally inhaled.

Conversely, the data are insufficient to determine the safety of the remaining 7 naturally-sourced clays for use in formulations which may be incidentally inhaled. The Panel noted that Bentonite and Hectorite may contain crystalline silica (cristobalite), which is a human carcinogen, as an impurity. Furthermore, the Panel noted that Attapulgite with long fibers (> 5 μm) is possibly carcinogenic to humans and animals. The additional data needed to determine safety of these 7 ingredients for such use are composition and impurities data, especially quantification of crystalline silica, and negative repeated-dose inhalation data on naturally-sourced clay ingredients.

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Therefore, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Kaolin is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the following 7 ingredients are safe in cosmetics in the present practice of use and concentration described in this safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

Attapulgite	Fuller's Earth	Montmorillonite
Bentonite	Hectorite	
Clay	Illite	

TABLES

Table 1. Definitions and reported cosmetic functions of the ingredients in this safety assessment.[2]

Ingredient, CAS No.	Definition	Reported Functions
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
Clay 53801-44-8	Clay is a group of phyllosilicate minerals produced by the chemical and physical weathering of rock. It consists chiefly of varying amounts of hydrated silica and alumina, and is characterized by a particle size of less than 2 micrometers.	Absorbents; Binders; Bulking Agents; Skin-Conditioning Agents - Misc.; Viscosity Increasing Agents - Aqueous
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
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
Illite 12173-60-3	Illite refers to a group of clay sized micas that have a higher lattice water content and lower potassium content than mica.	Abrasives; Absorbents; Anticaking Agents; Bulking Agents
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
Montmorillonite 1318-93-0	Montmorillonite is a complex aluminum/magnesium silicate clay.	Abrasives; Absorbents; Bulking Agents; Emulsion Stabilizers; Opacifying Agents; Viscosity Increasing Agents - Aqueous

Table 2. Chemical properties

Property	Value	Reference
	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]
Chemical Formula	$Mg(Al_{0.5\text{-}1}Fe_{0\text{-}0.5})Si_4O_{10}(OH)\cdot 4H_2O$	[1]
Density (g/ml)	2.2	[1]
Solubility	Insoluble in water	[1]
Particle Size/Length (µm)	< 5	[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]
Chemical Formula	$Al_2O_3\cdot 4SiO\cdot 2H_2O$	[1]
Formula Weight (Da)	359.16	[1]
Solubility	Insoluble in water, alcohol, fixed oils, glycerin, dilute acid, and alkali solutions	[1,7]
Particle Size/Length (µm)	Mainly 50-150 with some 1-2	[1]
	Clay	
Physical Form	Beige green powder	[9]
pH	Between 8 and 9	[9]
Grain size	Variation 1: 80% < 5 µm; 100% < 10 µm Variation 2: 90% < 20 µm; 100% < 40 µm Variation 3: 90% < 77 µm; 100% < 100 µm Variation 4: 90% < 750 µm; 100% < 1100 µm	[9]
	Fuller's Earth	
Physical Form	Non-plastic variety of Kaolin; sheet structure	[1]
	Hectorite	
Physical Form	Translucent colorless mineral when mined and turns white when dried; tridecahedral	[1]
Chemical Formula	$Na_{0.33}(Mg_{2.67}Li_{0.33})Si_4O_{10}(OH)_2$	[1]
Specific Gravity (g/ml)	2.65	[1]
	Illite	
Physical Form	Gray-white to silvery-white, greenish-gray claylike material; waxy, greasy, earthy, or dull luster; dioctahedral	[8]
Chemical Formula	$K_{0.65}Al_{2.0}[Al_{0.65}Si_{3.35}O_{10}](OH)_2$	[8]
Specific Gravity (g/ml)	2.79 - 2.80	[8]
	Kaolin	
Physical Form	White or yellowish white, earthy mass or white powder; unctuous when moist	[1]
Chemical Formula	$Al_2O_3\cdot 2SiO_2\cdot 2H_2O$	[1]
Formula Weight (Da)	258.2	[1]
Solubility	Insoluble in water, alcohol, dilute acids, and alkali solutions	[1,7]
	Montmorillonite	
Chemical Formula	$R^+_{0.33}(Al, Mg)_2Si_4O_{10}(OH)_2$, where $R^+ = Na^+, K^+, Mg^{2+}$ or Ca^{2+}	[1]

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
	Attapulgite				**Bentonite**			
Totals	**3**	**10**	**NR**	**8**	**262**	**94**	**0.00025-17.3**	**0.5-80**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*NR*	*5*	*NR*	*8*	*131*	*37*	*0.00025-8*	*0.8-8*
Rinse-Off	*3*	*5*	*NR*	*8*	*118*	*57*	*0.22-17.3*	*0.5-80*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*13*	*NR*	*NR*	*5*
Exposure Type*								
Eye Area	NR	NR	NR	NR	19	8	0.00025-4.5	0.8-5
Incidental Ingestion	NR	NR	NR	NR	8	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	8[b]	23[a]; 42[b]	5[a]; 7[b]	0.9	1-3[a]; 2-5[b]
Incidental Inhalation-Powder	NR	5	NR	8[b]	1; 42[b]	7[b]	8[c]	2-5[b]
Dermal Contact	3	10	NR	8	212	88	0.00025-10	0.5-80
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	8	4	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	17.3	NR
Nail	NR	NR	NR	NR	24	1	2.8	1
Mucous Membrane	NR	NR	NR	NR	30	3	0.22-4.7	0.5-5
Baby Products	NR	NR	NR	NR	2	NR	NR	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Other Baby Products					2	NR	NR	NR
Bath Preparations (diluted for use)								
Bath Oils, Tablets, and Salts					11	NR	NR	5
Bath Capsules								
Other Bath Preparations					2	NR	NR	NR
Eye Makeup Preparations								
Eyebrow Pencil					1	NR	NR	NR
Eyeliner					4	6	0.00025	5
Eye Shadow					1	NR	4.5	NR
Eye Lotion					1	NR	NR	NR
Eye Makeup Remover					1	NR	NR	NR
Mascara					10	1	1.5	0.8
Other Eye Makeup Preparations					1	1	NR	NR
Fragrance Preparations								
Powders (dusting/talcum, excl aftershave talc)	NR	5	NR	NR				
Hair Preparations (non-coloring)								
Hair Conditioner					NR	1	NR	NR
Hair Sprays (aerosol fixatives)								
Hair Straighteners					NR	3	NR	NR
Rinses (non-coloring)								
Shampoos (non-coloring_								
Tonics, Dressings, and Other Hair Grooming Aids					6	NR	NR	NR
Wave Sets								
Other Hair Preparations					2	NR	NR	NR
Hair Coloring Preparations								
Hair Tints								
Hair Shampoos (coloring)								
Hair Lighteners with Color								
Hair Bleaches					NR	NR	17.3	NR
Makeup Preparations								
Blushers (all types)					2	NR	4	NR
Face Powders					1	NR	NR	NR
Foundations					3	5	NR	2 – 8
Leg and Body Paints								

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
Lipstick								
Makeup Bases					1	3	NR	1
Rouges								
Makeup Fixatives								
Other Makeup Preparations					1	NR	0.6	NR
Manicuring Preparations (Nail)								
Basecoats and Undercoats								
Cuticle Softeners					NR	1	NR	1
Nail Polish and Enamel					22	NR	NR	NR
Nail Polish and Enamel Removers					1	NR	NR	NR
Other Manicuring Preparations					1	NR	2.8	NR
Oral Hygiene Products								
Dentifrices					5	NR	NR	NR
Other Oral Hygiene Products					3	NR	NR	NR
Personal Cleanliness Products								
Bath Soaps and Detergents					7	1	0.22 - 4.7	0.5
Deodorants (underarm)								
Other Personal Cleanliness Products					2	2	NR	NR
Shaving Preparations								
Beard Softeners								
Mens Talcum								
Preshave Lotions (all types)					1	NR	NR	NR
Shaving Cream								
Shaving Soap								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing					18	6	1.3 - 7	NR
Depilatories								
Face and Neck (exc shave)					39	1	8	2 - 5
Body and Hand (exc shave)	NR	NR	NR	8	3	6	NR	2 - 5
Moisturizing					16	2	NR	3
Night					NR	1	NR	NR
Paste Masks (mud packs)	3	5	NR	8	80	44	1.5 - 10	12 - 80
Skin Fresheners					1	1	NR	NR
Other Skin Care Preparations					13	8	NR	NR
Suntan Preparations								
Suntan Gels, Creams, and Liquids					NR	1	2.5 (not spray) 0.9 (spray)	NR
Other Suntan Preparations					NR	NR	NR	1
	Clay				**Fuller's Earth**			
Totals	**59**	**NA**	**4.5**	**NA**	**9**	**3**	**NR**	**NR**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*40*	*NA*	*NR*	*NA*	*2*	*1*	*NR*	*NR*
Rinse-Off	*17*	*NA*	*4.5*	*NA*	*7*	*2*	*NR*	*NR*
Diluted for (Bath) Use	*2*	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*
Exposure Type*								
Eye Area	12	NA	NR	NA	NR	NR	NR	NR
Incidental Ingestion	10	NA	NR	NA	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]; 11[b]	NA	NR	NA	1[a]	NR	NR	NR
Incidental Inhalation-Powder	1; 11[b]	NA	NR	NA	NR	NR	NR	NR
Dermal Contact	42	NA	4.5	NA	8	3	NR	NR
Deodorant (underarm)	2[a]	NA	NR	NA	NR	NR	NR	NR
Hair - Non-Coloring	4	NA	NR	NA	1	NR	NR	NR
Hair-Coloring	NR	NA	NR	NA	NR	NR	NR	NR
Nail	NR	NA	NR	NA	NR	NR	NR	NR
Mucous Membrane	16	NA	NR	NA	1	NR	NR	NR
Baby Products	NR	NA	NR	NA	NR	NR	NR	NR

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Other Baby Products								
Bath Preparations (diluted for use)								
Bath Oils, Tablets, and Salts	2	NA	NR	NA				
Bath Capsules								
Other Bath Preparations								
Eye Makeup Preparations								
Eyebrow Pencil	1	NA	NR	NA				
Eyeliner								
Eye Shadow	8	NA	NR	NA				
Eye Lotion								
Eye Makeup Remover								
Mascara	3	NA	NR	NA				
Other Eye Makeup Preparations								
Fragrance Preparations								
Powders (dusting/talcum, excl aftershave talc)								
Hair Preparations (non-coloring)								
Hair Conditioner	1	NA	NR	NA				
Hair Sprays (aerosol fixatives)								
Hair Straighteners								
Rinses (non-coloring)								
Shampoos (non-coloring)	2	NA	NR	NA				
Tonics, Dressings, and Other Hair Grooming Aids					1	NR	NR	NR
Wave Sets								
Other Hair Preparations	1	NA	NR	NA				
Hair Coloring Preparations								
Hair Tints								
Hair Shampoos (coloring)								
Hair Lighteners with Color								
Hair Bleaches								
Makeup Preparations								
Blushers (all types)	3	NA	NR	NA				
Face Powders	1	NA	NR	NA				
Foundations	1	NA	NR	NA				
Leg and Body Paints								
Lipstick	6	NA	NR	NA				
Makeup Bases	1	NA	NR	NA				
Rouges								
Makeup Fixatives								
Other Makeup Preparations								
Manicuring Preparations (Nail)								
Basecoats and Undercoats								
Cuticle Softeners								
Nail Polish and Enamel								
Nail Polish and Enamel Removers								
Other Manicuring Preparations								
Oral Hygiene Products								
Dentifrices	1	NA	NR	NA				
Other Oral Hygiene Products	3	NA	NR	NA				
Personal Cleanliness Products								
Bath Soaps and Detergents	4	NA	NR	NA	1	NR	NR	NR
Deodorants (underarm)	2	NA	NR	NA				
Other Personal Cleanliness Products								

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
Shaving Preparations								
Beard Softeners								
Mens Talcum								
Preshave Lotions (all types)								
Shaving Cream								
Shaving Soap								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing	2	NA	4.5	NA				
Depilatories								
Face and Neck (exc shave)	10	NA	NR	NA				
Body and Hand (exc shave)	1	NA	NR	NA				
Moisturizing	1	NA	NR	NA				
Night								
Paste Masks (mud packs)	4	NA	NR	NA	6	2	NR	NR
Skin Fresheners								
Other Skin Care Preparations	1	NA	NR	NA	1	1	NR	NR
Suntan Preparations								
Suntan Gels, Creams, and Liquids								
Other Suntan Preparations								
	Hectorite				**Illite**			
Totals	**50**	**18**	**0.057-1.5**	**0.4-100**	**59**	**NA**	**0.0015-3.8**	**NA**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*34*	*10*	*0.057-1.5*	*0.7-15*	*31*	*NA*	*0.0015-0.025*	*NA*
Rinse-Off	*16*	*8*	*0.1-0.13*	*0.4-100*	*26*	*NA*	*0.34-3.8*	*NA*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*NA*	*NR*	*NA*
Exposure Type*								
Eye Area	17	4	0.057	0.7	NR	NA	NR	NA
Incidental Ingestion	NR	NR	NR	NR	1	NA	NR	NA
Incidental Inhalation-Spray	3[a]; 5[b]	1[a]	NR	8[b]	4[a]; 18[b]	NA	0.25[a]	NA
Incidental Inhalation-Powder	1; 5[b]; 1[c]	NR	0.1[c]	8[b]	2; 18[b]	NA	NR	NA
Dermal Contact	35	10	0.057-1.5	0.4-100	55	NA	0.0015-3.8	NA
Deodorant (underarm)	NR	1[a]	NR	0.7[a]	NR	NA	NR	NA
Hair - Non-Coloring	5	NR	0.1-0.13	1	3	NA	0.25	NA
Hair-Coloring	1	5	0.1	NR	NR	NA	NR	NA
Nail	1	2	NR	NR	NR	NA	NR	NA
Mucous Membrane	NR	1	NR	NR	4	NA	0.34	NA
Baby Products	1	NR	NR	NR	NR	NA	0.0015	NA
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams	1	NR	NR	NR				
Other Baby Products					NR	NA	0.0015	NA
Bath Preparations (diluted for use)								
Bath Oils, Tablets, and Salts					1	NA	NR	NA
Bath Capsules								
Other Bath Preparations					1	NA	NR	NA
Eye Makeup Preparations								
Eyebrow Pencil								
Eyeliner	7	3	0.057	NR				
Eye Shadow	1	NR	NR	NR				
Eye Lotion								
Eye Makeup Remover								
Mascara	8	1	NR	0.7				
Other Eye Makeup Preparations	1	NR	NR	NR				
Fragrance Preparations								
Powders (dusting/talcum, excl aftershave talc)								

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
Hair Preparations (non-coloring)								
Hair Conditioner	3	NR	0.13	NR				
Hair Sprays (aerosol fixatives)								
Hair Straighteners								
Rinses (non-coloring)	1	NR	NR	NR				
Shampoos (non-coloring)	NR	NR	0.1	1	1	NA	NR	NA
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	0.13 (not spray)	NR	2	NA	0.025	NA
Wave Sets								
Other Hair Preparations	1	NR	NR	NR				
Hair Coloring Preparations								
Hair Tints								
Hair Shampoos (coloring)	1	NR	0.1	NR				
Hair Lighteners with Color								
Hair Bleaches	NR	5	NR	NR				
Makeup Preparations								
Blushers (all types)								
Face Powders	1	NR	NR	NR	2	NA	NR	NA
Foundations	1	NR	1.5	15	1	NA	NR	NA
Leg and Body Paints	1	NR	NR	NR				
Lipstick								
Makeup Bases	1	NR	NR	NR				
Rouges								
Makeup Fixatives								
Other Makeup Preparations	1	1	NR	NR				
Manicuring Preparations (Nail)								
Basecoats and Undercoats	NR	1	NR	NR				
Cuticle Softeners								
Nail Polish and Enamel	NR	1	NR	NR				
Nail Polish and Enamel Removers								
Other Manicuring Preparations	1	NR	NR	NR				
Oral Hygiene Products								
Dentifrices	NR	NR	NR	NR	1	NA	NR	NA
Other Oral Hygiene Products								
Personal Cleanliness Products								
Bath Soaps and Detergents					1	NA	0.34	NA
Deodorants (underarm)	NR	1	NR	0.7				
Other Personal Cleanliness Products	NR	1	NR	NR				
Shaving Preparations								
Beard Softeners								
Mens Talcum								
Preshave Lotions (all types)								
Shaving Cream								
Shaving Soap								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing	7	NR	NR	100	6	NA	3.8	NA
Depilatories								
Face and Neck (exc shave)	5	NR	0.1 (not spray)	NR	18	NA	NR	NA
Body and Hand (exc shave)	NR	NR	NR	8				
Moisturizing					2	NA	NR	NA
Night	3	NR	NR	NR				
Paste Masks (mud packs)	4	2	NR	0.4 - 8	17	NA	1 - 2	NA
Skin Fresheners								
Other Skin Care Preparations	1	1	NR	NR	6	NA	NR	NA
Suntan Preparations								
Other Suntan Preparations	NR	1	NR	NR				

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
Other Suntan Preparations								
	Kaolin				**Montmorillonite**			
Totals	**1046‡**	**509**	**0.0005-53.2**	**0.01-100**	**75**	**NR**	**0.1-3**	**NR**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*707*	*501*	*0.0015-53.2*	*2-100*	*26*	*NR*	*1.2-2*	*NR*
Rinse-Off	*320*	*7*	*0.0005-33*	*0.01-84*	*47*	*NR*	*0.1-3*	*NR*
Diluted for (Bath) Use	*19*	*1*	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Exposure Type*								
Eye Area	201	231	0.001-8.5	3-48	2	NR	NR	NR
Incidental Ingestion	150	6	0.0053-14.5	12-30	1	NR	NR	NR
Incidental Inhalation-Spray	1; 50[a]; 87[b]	NR	0.0015-25[a]	2-25[a]; 3[b]	7[a]; 11[b]	NR	NR	NR
Incidental Inhalation-Powder	53; 87[b]; 1[c]	98	0.01-15; 0.11-16[c]	5-30; 3[b]	11[b]	NR	1.2-2[c]	NR
Dermal Contact	798	466	0.001-33	0.01-100	68	NR	0.1-3	NR
Deodorant (underarm)	7[a]	NR	2.6	NR	NR	NR	NR	NR
Hair - Non-Coloring	47	5	0.0005-26	4-15	6	NR	NR	NR
Hair-Coloring	13	1	5-19.5	NR	NR	NR	NR	NR
Nail	9	NR	0.023-53.2	53-54	NR	NR	NR	NR
Mucous Membrane	193	8	0.0053-14.5	3-30	12	NR	NR	NR
Baby Products	1	NR	0.0085	NR	NR	NR	NR	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams	1	NR	NR	NR				
Other Baby Products	NR	NR	0.0085	NR				
Bath Preparations (diluted for use)								
Bath Oils, Tablets, and Salts	17	NR	NR	NR	1	NR	NR	NR
Bath Capsules	1	NR	NR	NR	NR	NR	NR	NR
Other Bath Preparations	1	1	NR	NR	1	NR	NR	NR
Eye Makeup Preparations								
Eyebrow Pencil	6	5	4.3	15 - 17	1	NR	NR	NR
Eyeliner	6	9	0.82 - 2	25 - 48				
Eye Shadow	137	171	0.35 - 8.5	3 - 29				
Eye Makeup Remover	NR	NR	0.001	NR	1	NR	NR	NR
Mascara	29	31	0.5 - 4.7	8 - 18				
Other Eye Makeup Preparations	23	15	NR	20				
Fragrance Preparations								
Powders (dusting/talcum, excl aftershave talc)	5	40	NR	5				
Hair Preparations (non-coloring)								
Hair Conditioner	7	5	0.0005 - 26	4	1	NR	NR	NR
Hair Spray (aerosol fixatives)	1	NR	NR	NR				
Hair Straighteners								
Rinses (non-coloring)								
Shampoos (non-coloring)	17	NR	0.058 - 0.14	NR	4	NR	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids	14	NR	0.0015 - 25	15	1	NR	NR	
Wave Sets	1	NR	NR	NR				
Other Hair Preparations	7	1	0.1	5				
Hair Coloring Preparations								
Hair Tints	NR	NR	5	NR				
Hair Shampoos (coloring)								
Hair Lighteners with Color	1	NR	19.3	NR				
Hair Bleaches	12	NR	19.5	NR				
Makeup Preparations								
Blushers (all types)	39	72	0.05 - 15	14 - 20				
Face Powders	47	58	0.01 - 15	30				
Foundations	36	45	0.5 - 6	6 - 36	1	NR	NR	NR
Leg and Body Paints	3	NR	NR	NR				

Table 3. 2022 and historical frequency and concentration of use according to duration and exposure and by product category.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022[20]	**1998**[1]	**2022**[21]	**1999**[1]	**2022**[20]	**1998**[1]	**2022**[21]	**1999**[1]
Lipstick	134	6	0.0053 - 14.5	12 - 30				
Makeup Bases	3	24	1	7 - 25				
Rouges	2	2	NR	NR				
Makeup Fixatives	1	3	NR	NR				
Other Makeup Preparations	12	20	2 - 4	10 - 24				
Manicuring Preparations (Nail)								
Basecoats and Undercoats	1	NR	NR	NR				
Cuticle Softeners								
Nail Polish and Enamel	7	NR	0.023	NR				
Nail Polish and Enamel Removers								
Other Manicuring Preparations	1	NR	35.5 - 53.2	53 - 54				
Oral Hygiene Products								
Dentifrices	16	NR	NR	NR	1	NR	NR	NR
Other Oral Hygiene Products								
Personal Cleanliness Products								
Bath Soaps and Detergents	15	1	1 - 5	3	6	NR	NR	NR
Deodorants (underarm)	7	NR	2.6 (not spray)	NR				
Other Personal Cleanliness Products	9	NR	NR	NR	3	NR	NR	NR
Shaving Preparations								
Beard Softeners	1	NR	NR	NR				
Mens Talcum	1	NR	NR	NR				
Preshave Lotions (all types)								
Shaving Cream	NR	NR	0.25	NR				
Shaving Soap	1	NR	NR	NR				
Other Shaving Preparations	1	NR	NR	NR				
Skin Care Preparations								
Cleansing	85	NR	3.4 - 20	0.01	15	NR	0.3	NR
Depilatories	NR	NR	4	NR				
Face and Neck (exc shave)	73	NR	0.11 - 16 (not spray)	3	8	NR	1.2 - 2 (not spray)	NR
Body and Hand (exc shave)	14	NR	3.3 - 12 (not spray)	NR	3	NR	NR	NR
Moisturizing	30	NR	0.2 – 1 (not spray)	25	6	NR	NR	NR
Night	3	NR	NR	NR				
Paste Masks (mud packs)	155	NR	5 - 33	12 - 84	16	NR	0.1-3	NR
Skin Fresheners	3	NR	0.25	2	NR	NR	NR	NR
Other Skin Care Preparations	60	NR	10 - 20.4	3 - 100	6	NR	NR	NR
Suntan Preparations								
Suntan Gels, Creams, and Liquids	NR	NR	NR	25				
Other Suntan Preparations								

NR – not reported
NA – not applicable
*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
**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 are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
ǂ Includes entries for Kaolinite from the VCRP database.

Table 4. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Bentonite particles with α-quartz content (up to 6%) and with different chemical modifications (acid, alkaline, organic, untreated); gypsum and quartz were negative and positive controls	1 to 15 µg/cm^2	isotonic NaCl solution	Human lung fibroblasts (IMR90)	Micronucleus assay and kinetochore analysis; treated cells incubated for 36, 48, or 72 h	In acidic sample, formation of micronuclei was only slightly increased after exposure to samples with a quartz content of 4% - 5% for 36 h (15 µg/cm^2), 48 h (5 µg/cm^2), and 72 h (1 µg/cm^2); and with a quartz content of 1% for 72 h (1 µg/cm^2). In the alkaline sample, the formation of micronuclei was only slightly increased after exposure to sample with a quartz content of 5% for 48 h and 72 h (15 µg/cm^2). Untreated and organic activated Bentonite particles did not show genotoxic effects; Bentonite particles with a quartz content of < 1% were in negative in the micronucleus assay. Statistically significant reductions in kinetochore-positive micronuclei were not observed with the Bentonite samples	47
Clay (75% Illite, 16% Kaolin, and 9% Montmorillonite)	5000 µg	Not reported	*S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	Ames test in accordance with OECD TG 471; with and without metabolic activation	Not mutagenic with or without metabolic activation	38
Clay (75% Illite, 16% Kaolin, and 9% Montmorillonite)	156.25, 312.5, 625, 1250, 2500, or 5000 µg/ml	culture medium	CHO - K1 cell cultures	Mammalian chromosome aberration test in accordance with OECD TG 473; with and without metabolic activation	Test material did not induce chromosomal aberrations, with or without metabolic activation	38
Kaolin; particle size 4.8 µm and 200 nm	0.2 - 200 µg/ml	particles suspended in saline containing 0.05% Tween 80; suspensions then mixed with culture medium supplemented with 10% fetal bovine serum prior to treating cells	CHO AA8 cells; primary normal human diploid epidermal keratinocytes and fibroblasts	Micronucleus assay; cells were incubated with test materials for 6 h; mitomycin C was positive control	Micronucleus induction in a dose-dependent manner, with frequencies of micronucleated cells increased 3- to 4-fold at 200 µg/ml in all cell types; fine particles of Kaolin had higher genotoxic potency than coarse particles, with no significant differences detected among the 3 cell types	45
Kaolin; primary particle size 4.8 µm	0.02 - 200 µg/ml	particles suspended in saline containing 0.05% Tween 80; suspensions then mixed with culture medium supplemented with 10% fetal bovine serum prior to treating cells	Human lung cancer A549 cells	Micronucleus assay; cells were incubated with test materials for 6 h	A 4-fold increased frequency of micronucleated cells was observed	40

Table 4. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
Kaolin; particle size 4.8 µm and 200 nm	0.2 - 200 µg/ml	particles suspended in saline containing 0.05% Tween 80; suspensions then mixed with culture medium supplemented with 10% fetal bovine serum prior to treating cells	CHO AA8 cells; primary normal human diploid epidermal keratinocytes and fibroblasts	Comet assay; 1-h treatment	Kaolin particles promoted DNA damage in a dose-dependent manner; %tail DNA was increased 8- to 20-fold by exposure to the particles at 200 µg/ml for all cells tested; 200 nm particles had a higher DNA-damaging potency than the 4.8 µm particles, while no significant difference was detected among three cell types	[45]
Montmorillonite-based clay minerals (1 unmodified clay and 3 cation-exchanged clays	unmodified clay tested at up to 125 µg/ml; modified clays tested at up to 250 µg/ml	MilliQ water	*S. typhimurium* strains TA97A, TA98, TA100, TA102, TA104	Ames test; with and without metabolic activation	No significant increases in revertant colonies observed in the unmodified clay (tested at up to 125 µg/ml) or in one of the modified clays (tested at up to 250 µg/ml); however, significant increases in revertant colonies observed in S9 in strain TA98 in the other two modified clays (tested at up to 8 µg/ml and 125 µg/ml, respectively); no changes observed for the same strain without S9 or in the rest of the strains for these 2 modified clays	[43]
Montmorillonite, natural and organo-modified	0-14.1 µg/plate for unfiltered material; 0-141 µg/ml for filtered material (particles larger than nano-range removed)	MilliQ water	*S. typhimurium* TA98 and TA100	*Salmonella*/microsome assay; with and without metabolic activation; suspensions were tested both filtered (removing particle larger than nano-range) and unfiltered material	No mutagenic activity observed with or without metabolic activation	[44]
Montmorillonite, natural and cation-exchanged	56.5, 85, 113, or 170 µg/ml for unfiltered material; up to 226 µg/ml for filtered material (particles larger than nano-range removed)	culture medium	Caco-2 cells	Comet assay; suspensions were tested both filtered (removing particle larger than nano-range) and unfiltered material	Unfiltered and filtered modified Montmorillonite was genotoxic in a concentration-related manner, with statistical significance at the 2 highest concentrations tested for each, when compared to negative controls; no genotoxic effects were observed in the unfiltered and unfiltered natural Montmorillonite	[44]
Unmodified Montmorillonite clay	15.65, 31.25, or 62.5 µg/ml	serum-free medium supplemented with B27 (no further details on supplement)	Human hepatoma cell lines (HepG2)	Cytokinesis block micronucleus cytome assay; cells were incubated with test material for 4 or 24 h; positive controls were benzo(α)pyrene and etoposide	Test material induced statistically significant increases ($p < 0.0001$) only in the frequency of micronuclei in 1000 binucleated cells at the highest concentration tested; no effects observed in nucleoplasmic bridges or nuclear buds; positive controls yielded expected results	[46]

Table 4. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VIVO			
Kaolin; primary particle size 4.8 µm (major peak average 357.6 ± 199.4 nm)	Single dose of 0.05 or 0.2 mg/animal	particles suspended in saline containing 0.05% Tween 80; particles agglomeration in suspensions observed (low-density tabular structures with rectangular or hexagonal shape were observed)	Groups of 5 male C57BL/6J mice	Comet assay; mice were intratracheally instilled with particles; negative control received solvent; 3 h after instillation, mice were killed and lungs were removed for analysis; additional exposure time also examined (24 h)	DNA damage was induced at 0.2 mg/mouse (up to 2 - 3-fold), but not at 0.05 mg/mouse, after 3 h exposure; DNA damage induced at 24 h did not differ from 3 h exposure	[40]
Kaolin; primary particle size 4.8 µm (major peak average 357.6 ± 199.4 nm)	Single dose or multiple doses (4x) of 0.2 mg/animal	particles suspended in saline containing 0.05% Tween 80; particles agglomeration in suspensions observed (low-density tabular structures with rectangular or hexagonal shape were observed)	Groups of 10 male *gpt* delta transgenic mice	*gpt* mutagenesis assay; mice were intratracheally instilled with particles; negative control received solvent; mice killed at 12 (single dose) or 8 (multiple doses) wk; lungs and kidneys removed for analysis	Increased *gpt* and Spi^- mutant frequencies observed in the lungs of the mice; mutation spectra analysis showed > 60% of the base substitution occurred in the *gpt* genes	[40]
cation-exchanged Montmorillonite	0, 250, 500, or 1000 mg/kg bw; 1000 mg/kg bw in range finding study	Water or cell-culture medium	Groups of 3 male and 3 female Wistar Hannover Galas rats; 2 rats of each sex in a range finding study	Comet assay; rats received 2 single doses of test material by gavage 24 h apart; 3 h after dosing, rats were killed and examined macroscopically, and liver, kidneys, and colon were dissected and analyzed for DNA damage; water or cell-culture medium was negative control and ethylmethanesulfonate was positive control	No statistically significant difference in % tail DNA between the negative controls and the different treatment groups for any of the organs tested for DNA damage; positive control yielded expected results; all rats survived during treatment period with no clinical signs of abnormalities	[48]

Table 5. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
IN VITRO						
Formulation containing 38% Montmorillonite	25 µl calcium and magnesium free Dulbecco's phosphate buffered saline	Tested neat; 25 mg	EpiDerm™ tissues	EpiDerm™ skin model in accordance with OECD TG 439	Not an irritant; mean viability = 105.7%	[55]
ANIMAL						
Clay (75% Illite, 16% Kaolin, and 9% Montmorillonite)	0.5 ml distilled water	500 mg	rabbits (no further details)	Acute dermal irritation study in accordance with OECD TG 404; patches were applied to intact skin with gauze patch for 4 h; after exposure period, residual test substance was removed with cotton soaked in distilled water; skin reactions scored at 1, 24, 48, and 72 h post-patch removal	Not irritating; mean dermal irritation scores for erythema and edema were 0.0	[38]
HUMAN						
Formulation containing 1.75% Bentonite	none	0.05 ml	25 subjects	14-d cumulative irritation assay under occlusive patches; test sites on the back or upper arm and patches were 15 mm diameter disks; positive control site received 0.05 ml of 0.25% sodium lauryl sulfate and negative control site was a plain patch	Irritation potential was negligible; no adverse events reported	[56]
Mud mask containing 8% Bentonite	none	As supplied	19 subjects	Single-insult occlusive patch test	No irritation; primary irritation index = 0.0	[57]
Facial cleanser containing 2% Bentonite and 2% Kaolin	none	As supplied	50 subjects	4-wk clinical use test; single-blind baseline controlled monadic design; subjects instructed to use test material daily in the morning as a facial cleanser, twice weekly in the evening as an exfoliating scrub, twice weekly in the evening as a purifying mask, and 3 times weekly in the evening as a facial cleanser	No visible irritation; however, 8 subjects reported perceived discomfort and/or irritation, including burning/stinging and/or redness/dryness while using the test material; 6/8 subject responses were not considered related to the use of the test material and 2/8 subject responses were not sufficient intensity to warrant discontinuation of product	[58]
SENSITIZATION						
IN VITRO						
Formulation containing 38% Montmorillonite	Cell culture medium	Not reported	KeratinoSens™ cells	KeratinoSens™ assay (validated by the European Centre for the Validation of Alternative Methods (ECVAM)); 12 concentrations in 3 repetitions, in 3 replicates (details not reported); luciferase induction and cellular viability determined after 48 h incubation time	Not a sensitizer; test material weakly toxic to cells	[55]
ANIMAL						
Clay (75% Illite, 16% Kaolin, and 9% Montmorillonite)	Distilled water	5% (w/v) for intradermal injection; concentration details not provided for topical induction or challenge; topical dose was 100 mg test material in 0.2 ml vehicle	10 guinea pigs/sex	Skin sensitization study in accordance with OECD TG 406; no further details provided	Negative for sensitization; no positive skin responses at 24 or 48 h post-patch removal at challenge; no clinical signs during treatment	38
50% Hectorite	Not reported	Not reported	Guinea pigs; number/sex not provided	Buehler test; no further details provided	Non-sensitizing	11

Table 5. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN			
Foot mask containing 3.5% Bentonite	As supplied	0.2 g	102 subjects	HRIPT under occlusive patches; induction patch applied on the back for 9 total applications; 10-15 d non-treatment period followed by challenge patch applied to naïve site and scored at 48 h and 72 h post-application; patch was ~ 2 cm^2	No dermal sensitization; no adverse events reported	[61]
Clay mask containing 3.8% Bentonite	As supplied	0.1 - 0.15 g	108 subjects; 25% with self-perceived sensitive skin	HRIPT under semi-occlusive patches; induction patch applied on the back for 9 total applications; after a 2-wk non-treatment period, challenge patch applied to naïve site and scored at 24 h and 72 h post-application; patch was ~ 2 cm^2 and contained ~ 25 - 38 mg/cm^2 test material	No dermal irritation or sensitization	[59]
Face cream containing 7.5% Bentonite	As supplied	0.1 - 0.15 g; volatilized for 30-90 min prior to application	52 subjects	HRIPT under occlusive patches; induction patch applied on the back for 9 total applications; after a 2-wk non-treatment period, challenge patch applied to naïve site and scored at 24 h and 72 h post-application; no further details on patches provided	No dermal irritation or sensitization	[60]
Lip product containing 14.5% Kaolin	As supplied	0.1 - 0.15 g	54 subjects	HRIPT under occlusive patches; induction patch applied on the back for 9 total applications; after a 2-wk non-treatment period, challenge patch applied to naïve site and score at 24 h and 72 h post-application; patch contained ~ 25 - 38 mg/cm^2 test material	No dermal irritation or sensitization	[62]
Clay mask containing 14.5% Kaolin	Neat	0.1 ml	103 subjects	HRIPT under occlusive patches; induction patch applied on the back or upper arm ;after a 10-15 d non-treatment period, challenge patch applied to naïve site and scored at 48 and 72 h post-application; material was applied to a 2 x 2 cm^2 Webril pad	Not sensitizing; moderate erythema at the first induction in one subject mildly progressed through the induction period to erythema and edema with papules; no other adverse events reported during study	[64]
Clay mask containing 40% Kaolin	As supplied	0.1 - 0.15 g	51 subjects	HRIPT under occlusive patches; induction patch applied on the back for 9 total applications; after a 2-wk non-treatment period, challenge patch applied to naïve site and scored at 24 h and 72 h post-application; no further details on patches provided	No dermal irritation or sensitization	[63]
			PHOTOSENSITIZATION			
			HUMAN			
Sunscreen containing 1.75% Bentonite	As supplied	0.2 ml	23 subjects	Photoallergy test under occlusive patch; on day 1, subjects received test material on 2 sites on the back for 24 h, after which, subjects received a total of 6 applications (twice weekly) on the back; 24 h after application, one site was irradiated with UVB + UVA with full Xenon lamp spectrum, other site was non-irradiated control; after a non-treatment period of 10-17 d, challenge patches on naïve sites were placed and one site was irradiated with 6 J/cm^2 UVA and ½ the minimal erythemal dose of UVB; sites were evaluated at 24, 48, and 72 h after irradiation	Not a photosensitizer	[65]

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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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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Amy R. Elmore, former Scientific Analyst and Writer. Address correspondence to F. Alan Andersen, Cosmetic Ingredient Review Director, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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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

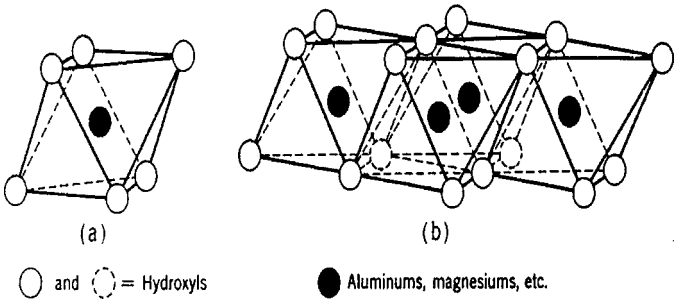

FIGURE 1
(*a*) Single octahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

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).

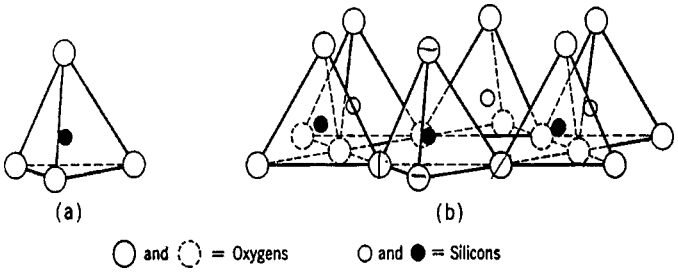

FIGURE 2
(*a*) Single tetrahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

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
	$0.8 \times 0.8 \times 0.01$ 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

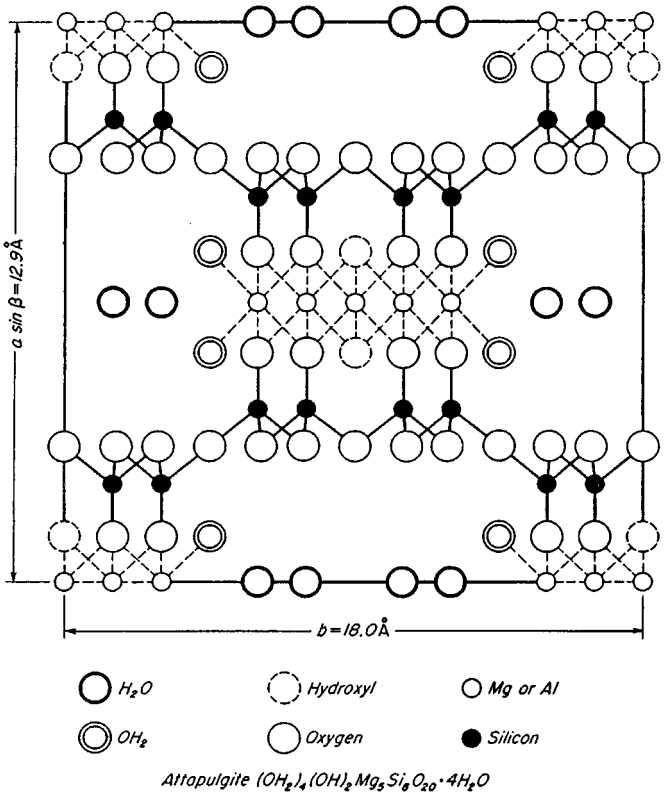

FIGURE 3
Attapulgite structure (taken from Grim 1967 with permission).

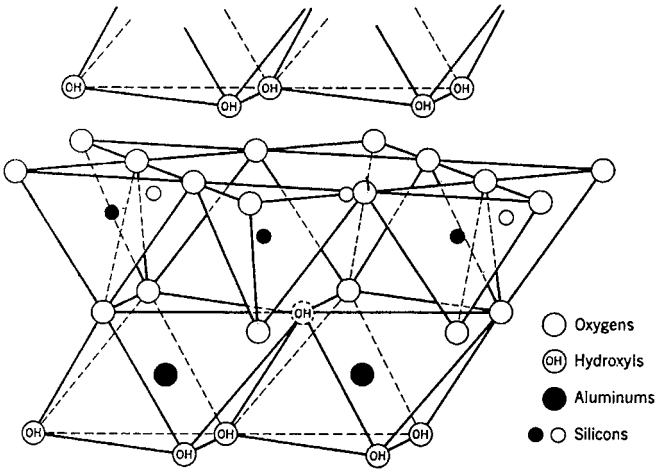

FIGURE 4
Kaolin layer (taken from Grim 1967 with permission).

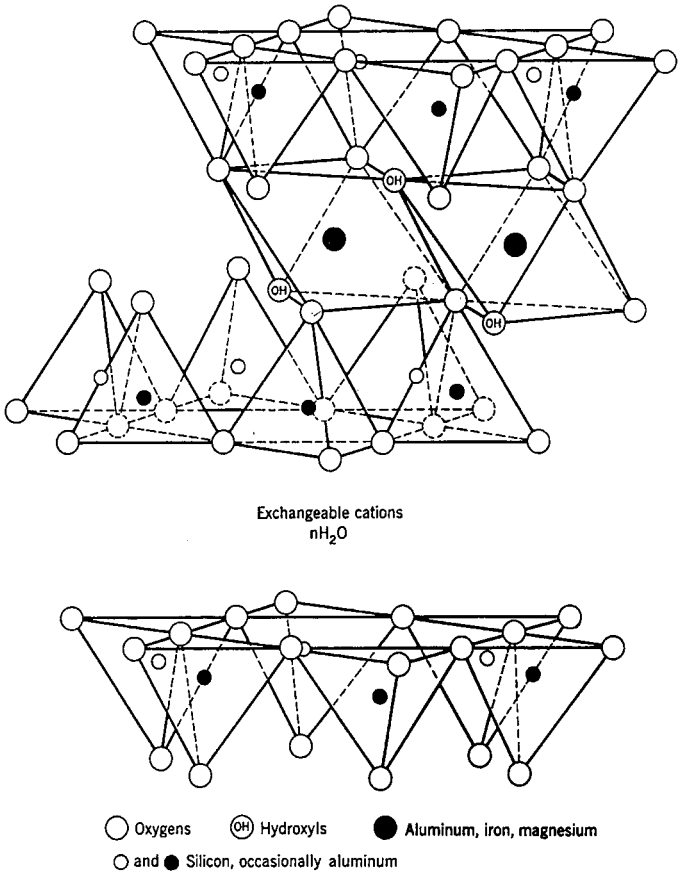

FIGURE 5
Smectite structure (taken from Grim 1967 with permission).

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 74×10^3/6 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

(Continued on next page)

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)	50% hemolysis in 1 ml of a 2% erythrocyte suspension as function of: 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%) $\pm$ the standard deviation. The 20-μg/ml dose of Kaolin (K-1) resulted in a 101.4% $\pm$ 6.7% viability and the 80-μg/ml dose produced a 69.5% $\pm$ 6.5% viability. With a 20-μg/ml dose of Kaolin (K-2), viability was 93.6% $\pm$ 4.5%, with the 80 μg/ml dose, it was 60.0% $\pm$ 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 $\times$ 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 μm, 6.5%; 5 μm, 5.9%; 10 μm, 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 μm, 14.5%; 10–30 μm, 32.8%; 50–70 μm, 16%; ≥ 100 μm, 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 $\geq$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 $8 \times 12 \times 10$-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 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.

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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