Amended Safety Assessment of Zeolites as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	May 23, 2022
Panel Meeting Date:	June 16-17, 2022

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.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Lisa A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/ Writer, CIR.

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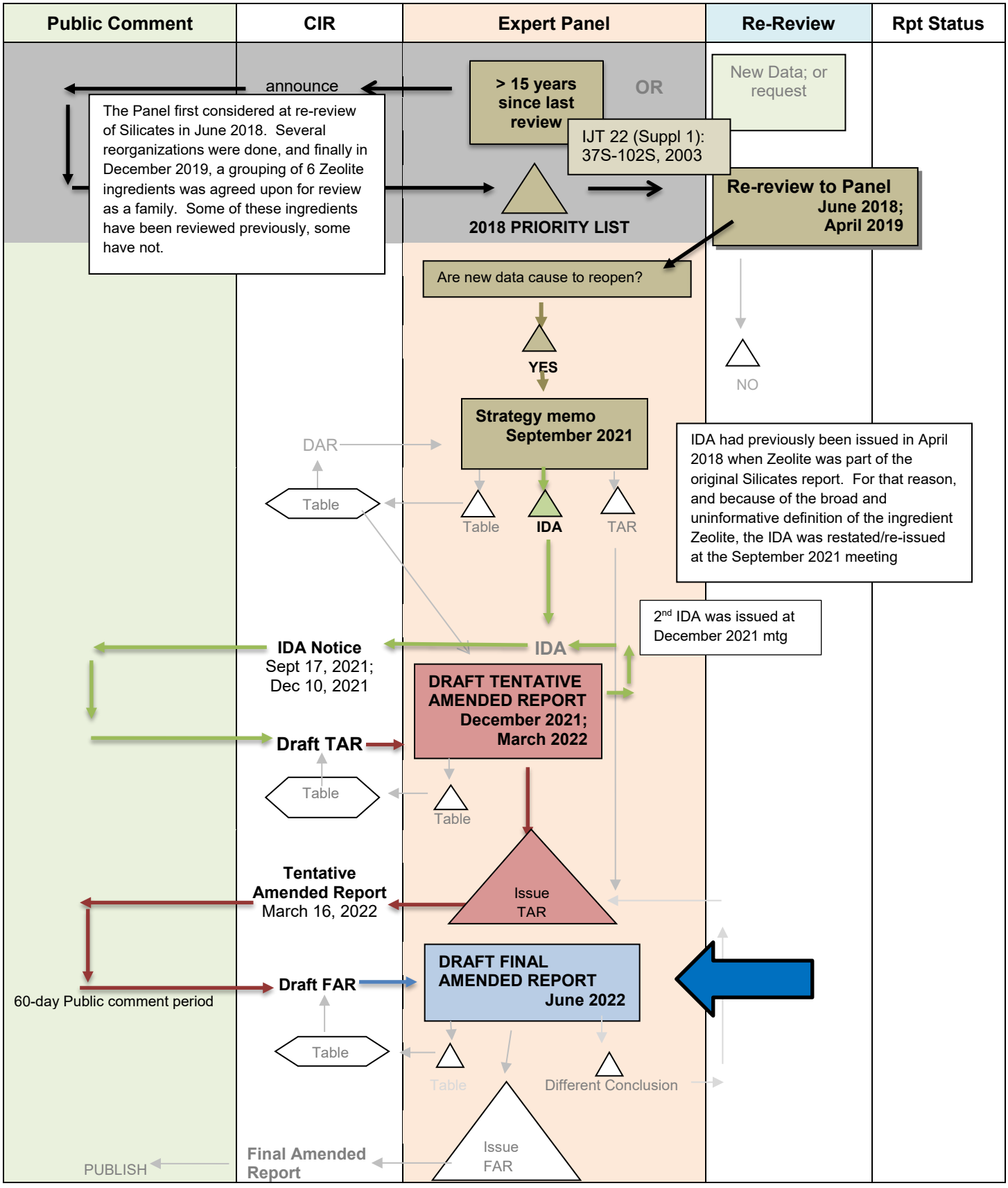
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Zeolites

MEETING June 2022



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

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: May 23, 2022
Subject: Amended Safety Assessment of Zeolites as Used in Cosmetics

Enclosed is the Draft Final Amended Report of the Safety Assessment of Zeolites as Used in Cosmetics. (It is identified as *report_Zeolites_062022* in the pdf document.) At the March 2022 meeting, the Panel issued a Tentative Amended Report with the conclusion that the 6 zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Since the issuance of the Tentative Amended Report, CIR has received no new unpublished data. The attached Council comments on the Tentative Report have been addressed (*PCPCcomments_Zeolites_062022*), as noted in the check sheet immediately following the comments (*response-PCPCcomments_Zeolites_062022*). Changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

The previously published report that included Zeolite 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) [*2003originalreport_Zeolites_062022*]

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

- June 2018 through March 2022 – Minutes for the Panel's deliberations since June 2018 when the re-review commenced [*transcripts1-reopenedRR_Zeolites_062022*]
- 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 [*transcripts2-originalreport_Zeolites_062022*]

Additional supporting documents for this report package include a flow chart (*flow_Zeolites_062022*), report history (*history_Zeolites_062022*), search strategy (*search_Zeolites_062022*), data profile (*dataprofile_Zeolites_062022*), and 2022 VCRP data (*VCRP_Zeolites_062022*).

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

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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: April 4, 2022

SUBJECT: Tentative Report: Safety Assessment of Zeolites as Used in Cosmetics (release date March 16, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Zeolites as Used in Cosmetics.

Composition/Impurities, old report summary – Please correct: "a natural Zeolite from Russian found" (either delete "n" from "Russian", or add something after "Russian")

Non-Cosmetic Use, old report summary – The meaning of the following is not clear: "aromatic separates, dimension stones", and it is not clear what Zeolites have to do with "petroleum solvents".

Toxicokinetics – Please correct "AU;C", and "form the oral dosage forms" (needs to be corrected to "from the oral dosage forms")

Short-Term, Subchronic and Chronic; Table 6 – As the dietary concentrations are expressed as % for all oral studies, except a 13-week rat study, it would be helpful to also indicate dietary concentrations as % in addition to ppm for the 13-week rat study. Please state the "mid-dose" used in the monkey inhalation study.

Genotoxicity; Summary – The descriptions of the host (mouse)-mediated studies should state the organisms (*Saccharomyces cerevisiae* and *S. typhimurium*) in which the genotoxic potential was assessed.

Summary – Please revise: "an oral LD_{50}s" (delete "s')

Discussion – In the paragraph regarding metals, does it make sense to state that the metals specifically associated with the Zeolite ingredients, e.g., silver in Ammonium Silver Zeolite, are

not easily released, then to state that in the mined zeolites, the heavy metals "should be readily avoidable/separable"?

Table 3 – The text states that there were no uses of Zeolite reported in the earlier CIR report. The columns in Table 3 with only NR and only NA should be deleted.

Table 5 – Rather than using the trade name Tylose, please use carboxymethylcellulose (third oral study). In the Results column of the third parenteral study, "mortality rats" needs to be corrected to "mortality rates"

Table 6 – In the Results column of the fourth oral study, please revise: "urine pH values of the urine 3% and 10% dose groups". In the sixth study, please also state the dietary concentrations as % to be consistent with the other studies. In the protocol column of the seventh study, please correct "mt/kg" (to mg/kg). In the Results column of the monkey inhalation study, please correct: "fibrosis observed n the quartz positive control group" (add "i") and "2 monkeys exposed to 55 wk" ("to" should be "for").

Table 8 – In the description of the dominant lethal study, please state how long the male rats were treated before mating started. Please consider adding a separate section in this table for the host-mediated studies. The cells (*Saccharomyces cerevisiae*, *S. typhimurium*) used to assess genotoxicity in the host-mediated studies should be presented in the test system column.

Table 9 – PDII should be defined the first time it appears (first animal study) rather than in the sixth study. In the fourth animal irritation study, please correct "shave" to "shaved". In the nineth animal study, please correct "sited" to "sites". The human study in 71 subjects from the ECHA dossier indicated that the test substance was a 5% aqueous paste. Although the results were "not sensitizing", this appears to be an irritation rather than a sensitization study.

Table 10 – In the Results column of the thirteenth study, please correct: "hyperemia up between 1-24 h post-administration"

Zeolites – June 2022 – Christina Burnett	
Comment Submitter: Personal Care Products Council **Date of Submission: 4/4/2022**	
Comment	**Response/Action**
Composition/Impurities, old report summary – Please correct: "a natural Zeolite from Russian found" (either delete "n" from "Russian", or add something after "Russian")	Correction made (deleted "n").
Non-Cosmetic Use, old report summary – The meaning of the following is not clear: "aromatic separates, dimension stones", and it is not clear what Zeolites have to do with "petroleum solvents".	As written in the original report. No further details provided.
Toxicokinetics – Please correct "AU;C", and "form the oral dosage forms" (needs to be corrected to "from the oral dosage forms")	Corrections made.
Short-Term, Subchronic and Chronic; Table 6 – As the dietary concentrations are expressed as % for all oral studies, except a 13-week rat study, it would be helpful to also indicate dietary concentrations as % in addition to ppm for the 13-week rat study. Please state the "mid-dose" used in the monkey inhalation study.	Suggestions accepted.
Genotoxicity; Summary – The descriptions of the host (mouse)-mediated studies should state the organisms (*Saccharomyces cerevisiae* and *S. typhimurium*) in which the genotoxic potential was assessed.	Corrections made.
Summary – Please revise: "an oral LD_{50}s" (delete "s')	Correction made.
Discussion – In the paragraph regarding metals, does it make sense to state that the metals specifically associated with the Zeolite ingredients, e.g., silver in Ammonium Silver Zeolite, are not easily released, then to state that in the mined zeolites, the heavy metals "should be readily avoidable/separable"?	CIR would like the Panel's input prior to changing wording in the Discussion.
Table 3 – The text states that there were no uses of Zeolite reported in the earlier CIR report. The columns in Table 3 with only NR and only NA should be deleted.	Table 3 is presented in standard protocol for CIR.
Table 5 – Rather than using the trade name Tylose, please use carboxymethylcellulose (third oral study). In the Results column of the third parenteral study, "mortality rats" needs to be corrected to "mortality rates"	Corrections made.
Table 6 – In the Results column of the fourth oral study, please revise: "urine pH values of the urine 3% and 10% dose groups". In the sixth study, please also state the dietary concentrations as % to be consistent with the other studies. In the protocol column of the seventh study, please correct "mt/kg" (to mg/kg). In the Results column of the monkey inhalation study, please correct: "fibrosis observed n the quartz positive control group" (add "i") and "2 monkeys exposed to 55 wk" ("to" should be "for").	Corrections made.

Table 8 – In the description of the dominant lethal study, please state how long the male rats were treated before mating started. Please consider adding a separate section in this table for the host-mediated studies. The cells (*Saccharomyces cerevisiae*, *S. typhimurium*) used to assess genotoxicity in the host-mediated studies should be presented in the test system column.	Male rats received a single oral dose in the dominant lethal study, time period between dosing and mating not reported. For host-mediated studies, cell information was moved to the test system column with the rodent information. No new section was created.
Table 9 – PDII should be defined the first time it appears (first animal study) rather than in the sixth study. In the fourth animal irritation study, please correct "shave" to "shaved". In the nineth animal study, please correct "sited" to "sites". The human study in 71 subjects from the ECHA dossier indicated that the test substance was a 5% aqueous paste. Although the results were "not sensitizing", this appears to be an irritation rather than a sensitization study.	Corrections made with exception to the comment on the human study. As there is not enough detail to discern the nature of the test, quotes were added around "not sensitizing" and the study was kept in the Human Sensitization section of the table.
Table 10 – In the Results column of the thirteenth study, please correct: "hyperemia up between 1-24 h post-administration"	Correction made.

Zeolites 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.

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.

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

Post-December 2019 - CIR staff determined the definition of Zeolite in the Dictionary is extremely broad and uninformative for the purposes of researching this cosmetic ingredient in relation to safety. Searches by CIR staff found that zeolite refers to a class of minerals that are crystalline solids with structures made of silicon, aluminum, and oxygen, and these structures form a framework with cavities and channels inside wherein cations, water, and/or small molecules may reside. Zeolites occur naturally or may be produced synthetically. According to the Structure Commission of the International Zeolite Association, well over 200 unique zeolite frameworks have been identified.

To help narrow the search for information that would be useful to the Panel so that they can conclude on the safety of Zeolite, CIR staff sought guidance from the International Cosmetic Ingredient Nomenclature Committee. Specifically, CIR asked whether the ingredient is naturally-sourced or synthetically-derived; if naturally-sourced, what specific minerals are mined (and from where); and, if synthetically-derived, which zeolite structures are used. The Committee was not able to provide clarity on these points.

September 2021 – CIR staff, via a strategy memo, sought guidance from the Panel as to what information they would find useful and necessary to determine the safety of Zeolite. The staff also asked the Panel if the 5 add-on ingredients should remain the in the report. The Panel confirmed that the add-on ingredients should remain in the report. The Panel also reissued an IDA with the following data needs:

- Method of manufacturing and/or source data
- Chemical characterization, including specific framework(s), and composition and impurities data
    - Depending on the composition, additional toxicity data as needed
- The range of particle sizes that is used in spray and powder formulations
- Dermal irritation and sensitization data at maximum use concentrations

October 2021 – CIR received unpublished HRIPT and in vitro primary cutaneous tolerance test data on a Zeolite material of unknown type.

December 2021 – The Panel issued a new IDA on the 6 zeolite ingredients. The additional data needs are:

- Maximum use concentration for both mined and synthetic zeolites
- Method of manufacturing and/or source data for Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite
- Chemical characterization, including specific framework(s), and composition and impurities data for mined Zeolite, Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite
    - Depending on composition, additional toxicity data may be needed
- The range of particle sizes that is used in spray and powder formulations
- Human dermal irritation and sensitization data at maximum use concentrations

March 2022 - The Panel issued a Tentative Amended Report with the conclusion that the 6 zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel noted that erionite is a naturally occurring fibrous material that is carcinogenic to humans and animals and is significantly more structurally similar to asbestos than the zeolite ingredients discussed in this report (i.e., the superstructures of the zeolites in this report comprise layered sheets, while erionite (and by comparison, asbestos) is fibrous). The Panel also expressed concern about the presence of heavy metals and free metal ions in zeolite ingredients. The metals in Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite are unavailable (i.e., not easily released) due to the nature of the zeolite framework. The zeolites are also not likely to absorb through the skin. Although other heavy metals may be present during mining, those should be readily avoidable/separable. Accordingly, the Panel stressed that the cosmetics industry should continue to use current good manufacturing processes (cGMPs) to ensure erionite and available heavy metals are not present in cosmetic formulations.

Zeolites Data Profile – June 2022, 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**
Zeolite (synthetic)	#		X O	X		O	X	X	X		X O	X O		X O	X O	X O		O	X	#	X	X		X	X #			X		
Zeolite (natural)	#		O	XO			X	X						O	X	O				#	X				#			X		O
Ammonium Siliver Zeolite																														
Gold Zeolite																														
Silver Copper Zeolite																														
Titanium Zeolite																														
Zinc Zeolite	X																													

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

Data not distinguished as synthetic or natural.

Zeolites

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Ammonium Silver Zeolite		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Gold Zeolite		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Silver Copper Zeolite	130328-19-7; 168042-42-0 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Titanium Zeolite		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Zeolite	1318-02-1	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Zinc Zeolite		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy (from 1999 for re-review)

PubMed

General search for “zeolite” resulted in over 11,000 hits. General search for “1318-02-1” resulted in over 4000 hits. No results for other CAS #.
Discovered “zeolite” refers to numerous unique types, *Dictionary* definition was not helpful in determining limits of search.

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) - http://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 - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

JUNE 2018 PANEL MEETING – RE-REVIEW

Belsito's Team Meeting – June 4, 2019

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.

DECEMBER 2018 PANEL MEETING – DRAFT AMENDED REPORT/IDA

Belsito's Team Meeting – December 3, 2018

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.

DR. 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.

Marks' Team Meeting – December 3, 2018

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 tablize 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.

DR. 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.

SEPTEMBER 2021 PANEL MEETING – Zeolites – Strategy Memo

Belsito's Team – September 13, 2021

DR. BELSITO: Anything else on this? Okay. Okey-doke. So then we're moving on to Zeolites. Okay, so basically in response to a strategy memo from December 2019, we approved a new grouping for these ingredients, including the zeolite grouping. So the definition in the *INCI Dictionary* is extremely broad and uninformative for researching cosmetic ingredients, great, and it's defined as "hydrated alkali aluminum silicate that functions as an absorbent and deodorant agent."

Zeolite actually refers to a class of minerals that are crystalline solids with structures of silicon, aluminum, and oxygen to form a framework with cavities and channels inside wherein cations, water and small molecules reside. They're like everything else, synthetic or natural, and the International Zeolite Association classifies over 200 unique zeolite frameworks. So they narrowed the search to look for information useful for us, get some guidance from the nomenclature committee specifically whether the ingredient is natural or synthetic.

If natural, what specific minerals are mined and from where. Synthetic, what's the structure, and they got nothing. So they're seeking guidance from us as to what information we would find useful and necessary to determine the safety of the zeolites.

DR. LIEBLER: So, Don, my first question is, is it used? There are no reported uses in the old document on page 90. There was an old Wenninger, 2000. It functions as an absorbent and deodorant agent in cosmetic formulations. There were no current uses reported.

MS. BURNETT: According to VCRP data, the generic term zeolite has 28 uses and is used up to 35.7 percent in leave-on products.

DR. SNYDER: What was the highest concentration again?

MS. BURNETT: 35.7 in leave-ons, hair tonics, and dressings.

DR. SNYDER: Okay.

DR. ANSELL: So it's my understanding that this was left over from another family that's proceeding.

DR. BELSITO: Yeah, we split it out, Jay.

DR. ANSELL: Yeah. With the 20 some uses, I don't think this makes the cut. We would presume that it would just go into the hopper of all unreviewed ingredients and come up when it's appropriate as opposed to being reprioritized just because it was in another family.

MS. BURNETT: It was reopened and currently has an IDA on it.

MS. FIUME: It also was part of the report that was published in 2003, so it's up for rereview either way.

DR. SNYDER: But it has been reopened?

MS. FIUME: It was previously reviewed. It was part of the large silica/silicates document and then split out.

DR. SNYDER: So the train has left the station?

DR. BELSITO: Yes.

MS. BURNETT: Unfortunately.

DR. SNYDER: Okay.

DR. BELSITO: So basically, I personally can't tell you where to go with this. We sort of need everything. It has some uses, but we have no concentration of use. We have no information of how it's made. We don't even really know what it is, so I'm just going to open it up and it'll become insufficient across the board unless people provide us with information. We have opened it up, right, so we have to proceed and it's also on a 2003 timeline.

MS. BURNETT: Yes. So it was originally concluded to be safe in 2003 and then when we reopened this back in 2018 or 2019 with the silicates, that's during those proceedings that these ingredients were determined to be insufficient. So you've technically already issued an IDA I would say, so I don't know if you would like me to still put together some kind of little report and go ahead and put a stamp of insufficient on it.

DR. BELSITO: Yeah, I mean, it's been 18 years and our whole approach to safety has changed significantly. Particularly this is going to be another product if it has any uses in aerosolized products, it's going to be an issue.

MS. BURNETT: Right.

DR. BELSITO: So, yeah, I mean we just go insufficient and find out what is out there. It sounds like nothing, and we go insufficient for a whole boatload of needs.

DR. SNYDER: Which largely can be driven by the constituent that's attached to it.

DR. BELSITO: Right.

DR. LIEBLER: I think we're going to end up with probably a group of the zeolite plus the five addons, which I don't see any reason to exclude.

MS. BURNETT: Go ahead and keep them?

DR. LIEBLER: Yeah, I would say go ahead and keep them. Then you're going to have the information you had in the old report.

MS. BURNETT: Right.

DR. LIEBLER: And then the new concerns primarily revolve around incidental inhalation, and we're probably going to come out insufficient on that. We're probably going to reaffirm the other conclusions.

MS. BURNETT: Right. So, because I have no guidance on what to search, I can't search anything in all honesty. I mean, when I started searching, I go down rabbit holes of if it's a naturally sourced one. Some of them are very similar to asbestos in nature and have all sorts of carcinogenicity data. I could write a whole report on those two alone, so I cannot feel confident in trying to perform any additional searches for data without knowing what I'm working with at all.

DR. LIEBLER: Mm-hmm.

DR. BELSITO: So can we simply state that? We can (audio gap) because of manufacturing, composition, and impurities. Put the information you have pointing you in multiple different directions including one that includes content of asbestos, and then just put a discussion after that. Say, in the absence of this information, it's impossible to determine the safety of a specific zeolite product used in cosmetic ingredients.

MS. BURNETT: Okay.

DR. BELSITO: And the data needed would be method of manufacture, impurity, and composition, and, based upon that, additional data.

DR. LIEBLER: Yeah, I agree with that.

MS. BURNETT: Okay, I can do that.

DR. BELSITO: I mean, short and sweet, if we don't have information.

MS. BURNETT: I think that's it, then.

Cohen's Team – September 13, 2021

DR. COHEN: And, again, for me this was a little bit different than what I've been used to. I saw the manuscript on it, and I see that there were five add-on ingredients: ammonium silver, gold, silver copper, titanium, and zinc zeolite might be added to this.

What are the comments on the team on this? What do we need at this point? And how is this presented? Is this presented just like all the other chemicals? Or is this something different?

DR. HELDRETH: So this is just a strategy memo. There doesn't need to be a vote. It doesn't form an iteration of a report. It's just a report that we, the staff, are trying to gauge the consensus of the Panel on these issues because we were struggling with exactly how to move forward on this broad class of chemicals that are listed under one ingredient, zeolites.

DR. COHEN: Yeah.

DR. HELDRETH: It's just a matter of getting Panel input at this point and getting a consensus on it. That's all that's asked here.

The five ingredients were, actually, already approved by the Panel to include in this group. But, as we're kind of modernizing the way we look at ingredients with CIR where we don't add in ingredients that aren't helpful to the report, we thought, since we haven't started this full report yet, it might be useful to ask the Panel if they want to take back the inclusion and not include these ingredients that don't have any uses and don't have data to be helpful.

DR. COHEN: It's a pretty big list of products. Maybe I'm being old school, but if we can add them in now, why not?

DR. HELDRETH: That's totally fine. That's the Panel's prerogative. Their choice.

DR. COHEN: Lisa, what do you think?

DR. PETERSON: I mean, I guess I was of the opinion that if there's no uses -- unless you think by asking you find out if there's uses -- but if there's currently no uses, I'm not sure what the value is by adding. The only one I would consider would be the zincs as zeolite.

DR. SLAGA: That's what I had, too. Jut eliminate the others and only use zinc.

DR. COHEN: So, just hypothetically, if someone wanted to use these other ones in the future, we would need to revisit the whole thing again, right?

DR. HELDRETH: Potentially, the Panel could choose to re-open this report once it's formed and finished and finalized and include those ingredients. Or a separate report could be generated. Let's say, for example, we deleted, right now, ammonium silver zeolite, gold zeolite, silver copper zeolite, and titanium zeolite, and five years from now somebody says, hey, I'm using ammonium silver zeolite and the frequency of use, the concentration of use, and all the data are available, we would likely bring that to the Panel and say, do you want do a report on this separate or do you want to re-open your report on zeolite and zinc zeolite and include this in it? Probably in a very similar strategy memo like you have before you.

DR. COHEN: Okay.

DR. HELDRETH: I think Carol has some input here.

DR. EISENMANN: My question is, with only 28 uses of zeolite, is it really necessary to re-review this at all, at this point? It seems like an awful lot of work because of the great structural variation: natural and synthetic.

And I also thought that in the original report that there's a fairly good description of it. I'm not sure you're going to find much more information than you have already found on it. Whether or not you really need to re-review it with just 28 uses. You've orphaned a few other ingredients that were in original reports and then got dropped in a re-review. So this would be one of those.

MS. BURNETT: Well, the problem is it was re-opened and currently has a hanging insufficient data announcement on it. When we reviewed the silicate package with the clays, we re-opened that in 2018, 2019, and that's when we started splicing these off. So we've done silica, we're doing the silcates. Now we're down to clays and the zeolites that were part of that report. The Panel re-opened those, and now we have these ingredients that are hanging open with an insufficient data announcement.

DR. EISENMANN: Well, you would have to publish something that would say that you decided not to review zeolite based on lack of use.

DR. HELDRETH: Yeah, and then the Panel would have to reaffirm their old conclusion, which I don't know if that's something they feel comfortable doing without looking at the available data.

DR. SHANK Right

MS. BURNETT: Right. And my problem is I don't know how to research it because it's such a complex thing. I don't know what I'm researching. So that's why I'm seeking guidance because I put in a search term for "zeolites," and I get a lot of stuff.

And you can go down rabbit holes. Some of these natural ones are related to asbestos. And I could write a 20-page report on that alone.

DR. COHEN: I was going to ask about the presence of crystalline silica in any of these.

MS. BURNETT: The "A" word is worse than that word.

DR. COHEN: Lisa, so in the figure on what these zeolites look like, there's a metal sitting in the center of these. What is the capacity of those metals to dissociate, form ions that are reactive with skin proteins?

DR. PETERSON: I'm a non-inorganic chemist, so I don't really know the answer to that.

DR. COHEN: Some of the metals are going to be sensitizers.

DR. PETERSON: Zeolites are going to be really hard. What?

DR. COHEN: Some of the metals can be sensitizers if they're ionic.

DR. HELDRETH: I'm not a zeolite expert either, however, looking at lots of the different similar materials, like, some of the clays, like the bentonites, and these other things that we've looked at before, it is possible to swap the ions out. You do ion exchange with these things. And, in fact, chemists and formulators often do this on purpose and will flush out whatever ions are there to put in some other ion. It gives the clay a property that they were looking for.

But how easily, say, for zinc zeolite -- how easily is the zinc flushed out onto the skin and cause a reaction for somebody that's already sensitized to zinc? I don't know.

DR. COHEN: So, Christina, can you just help us articulate what questions we need to answer because I reviewed this and I was all over the place. What do you need from us?

MS. BURNETT: So a possible solution is that, because we already have announced an IDA in this report, there was a structure of a report when the Panel saw it not that long ago, a couple of years ago, that was a re-review. You could just go ahead and push on through with a report with the insufficient conclusion. Or you can ask if -- further push industry to ask them, what zeolites you guys are using in your products? What is this?

The producer of the 28 might know. I don't know. As it is now, I can't just go and search zeolites to see what new data there is because there's too much to sort through.

DR. BERGFELD: Can you do it by natural versus synthetic?

MS. BURNETT: Not really. I mean, you could say you would prefer the industry only uses synthetic. But, even then, we still have lots of different configurations that you can put together.

It was when I first started searching that I realized how problematic it was. And that's why this is before you now just because it's just -- I don't know what direction to turn, to be honest with you.

DR. COHEN: So we have a hanging IDA on this?

MS. BURNETT: Yes.

DR. COHEN: And in the IDA, you'll always push us to say, what are we looking for? What did that IDA originally ask for?

MS. BURNETT: Good question. Bart, do you remember? I can look real quick.

DR. BERGFELD: It's not in our materials. I was looking.

MS. BURNETT: Yeah, that's a good question. I'll look for it unless Bart --

DR. COHEN: Because according to the last conversation, if it's the same questions we have a insufficient data conclusion. But if it's different -- different from what? We don't have a different list. It's another IDA. And, if we do have different questions, such as sensitization, irritation, then it creates a new IDA that would allow this to not be tabled but to postponed.

Is that an accurate play on the technicalities?

DR. BERGFELD: Bart has to answer that.

DR. HELDRETH: I'm thinking.

MS. BURNETT: I'm familiar with that sigh he makes when he's thinking.

DR. HELDRETH: So, ultimately, if we're talking about -- I don't know what the IDA says. I don't remember.

MS. BURNETT: I'm pulling it up. Hold on. It's coming.

DR. HELDRETH: But depending on what it says, if we agree that that's all that's needed, right now to continue with a re-review, then I feel we've already done the waiting. I mean, it's so long ago we don't remember it. I mean, it's been at least two years, maybe a good bit more, since that insufficient data announcement came out.

It may be useful to go with what Christina was suggesting was to continue with what's left of the original report as a re-review document. That would take care of zeolite and the other ingredients that were, essentially, left behind in the original silica and silicates and zeolite and all of these other materials in one re-review.

And we'll have that IDA has part of the report package. And the Panel can start from that point to move forward. Nothing would have to be decided today except for, yes, we have to look at the re-review package as it comes out.

And one thing we would need input on is whether or not the Panel wants to keep those add-ons. If it's just zinc or none of the add-ons.

DR. COHEN: I'll proffer tomorrow that we keep zinc and not the others because there's no use. It wasn't my original intent, but it sounds like adding additional ones could just mire us even further down than we already are.

DR. HELDRETH: Yes, and that's why we propose that you might want to delete them.

DR. COHEN: Okay. Yeah, I didn't have a sense of what the quicksand looked like. But, you know, there's a lot of discussion about the pneumoconiosis. But I didn't see anything about sensitization.

Ron, do you have any curiosity about the sensitization issue? Ron? Thomas, you had a question?

DR. SLAGA: No.

MR. GREMILLION: Sorry, can you hear me? I guess this is obvious, but I just wanted to confirm -- it says one of these is used at 35.7 percent in leave-on products. It seems like a high concentration. I don't know if that has any bearing on your (inaudible)

DR. COHEN: Were you referring to irritancy or sensitization?

MR. GREMILLION: Yeah. Just whatever bad things might happen to us with the high concentrations.

MS. BURNETT: I found what the insufficient data was.

DR. COHEN: Okay.

MS. BURNETT: It took a little while. So the data needs were mean and range particle sizes and corresponding sizes for final formulation particles that are used in spray and powder formulations; chemical characterization, composition, and impurities data for all ingredients; and method of manufacturing and/or source data for all ingredients.

DR. COHEN: All right. So we had mean and range of particle sizes. What was the next one after that?

MS. BURNETT: Chemical characterization, composition, and impurities.

DR. COHEN: Okay.

MS. BURNETT: And then the last one is method of manufacturing or source.

DR. COHEN: And from two or plus years ago, did we get anything?

DR. SHANK: No.

MS. BURNETT: No, not for this.

DR. BERGFELD: That remind me, we had split out silicates.

MS. BURNETT: Correct. But I found this in the post-panel meeting from April 2019, and the data means was for all: for silica, silicates, and all the other natural zeolites and the clays.

DR. BERGFELD: Wouldn't we just send this again to say now we're working on this?

DR. COHEN: I might suggest -- I don't have any sense of sensitization information on this. I just don't have a feel for it.

MS. BURNETT: Okay.

DR. COHEN: If we added sensitization, we are adding new requests from the existing IDA which would make this a new IDA.

MS. BURNETT: Correct.

DR. HELDRETH: Yeah, and that's totally fine.

DR. COHEN: And I really would like to à propos to what Thomas said and how I've been looking at this. There's aluminum, a potential sensitizer; titanium, a very rare sensitizer; manganese, a rare sensitizer, but they're in there. And I just don't know how they interact with the skin proteins to form a hapten. You know, a hapten to form a total allergen. So, maybe, I'd go with that.

MS. BURNETT: So, you do want to keep the add-ons then if under that description? Or do you want to just focus on the zeolite?

DR. COHEN: You mean the add-ons? The gold? The silver? The titanium? I thought we were going to just add the zinc.

MS. BURNETT: Okay.

DR. COHEN: Add zinc and then add a request for sensitization data to the prior IDA question list that was not addressed thus far.

MS. BURNETT: Okay. Got it.

DR. COHEN: How does that work for the team?

DR. SLAGA: Great.

DR. BERGFELD: The question is, if you add the zinc, does that change the character of the IDA? Does that make it a second IDA?

MS. BURNETT: It was already in the first --

DR. BERGFELD: Iteration. Yeah. Okay.

DR. HELDRETH: Right, but the request for sensitization does make it a second IDA.

MS. BURNETT: Yes, that does.

DR. BERGFELD: In some ways, that's good because it's a forgotten IDA for now.

DR. COHEN: It's a renewed, refreshed IDA.

MS. BURNETT: Version 2.0.

DR. COHEN: So that gets us through our agenda. Any comments? Tom? Lisa? Ron?

DR. SHANK: No.

DR. SLAGA: Nothing additional.

DR. COHEN: And then I'd ask advise from Wilma and Bart tomorrow.

DR. BERGFELD: Be prepared.

DR. COHEN: Eat your Wheaties.

DR. BERGFELD: I think that you've condensed after each presentation what you were going to say, so you just have to write it down. And I think that we have to stand to be flexible with whatever the Belsito team comes up with and decide if we agree with what they say.

DR. SLAGA: Yeah. Agreed.

DR. COHEN: Now, they're a sharp team, and they have swayed us before, appropriately.

DR. BERGFELD: Yeah. Vice versa, though.

DR. COHEN: Yes.

Full Panel Meeting – September 14, 2021

DR. BELSITO: So, in response to a strategy memo from December of 2019, we looked at regrouping a family of cosmetic ingredients that were previously grouped all together. And, they were then bucketed into three, and those were Silicate that we reviewed at this meeting, Clays, and Zeolites.

So now we're being asked, how do we deal with these Zeolites? So in preparation of the safety assessment, Christina found that the definition of Zeolite in the INCI Dictionary and Handbook is broad and uninformative for doing any type of research on what this Zeolite cosmetic ingredient specifically is. According to the dictionary, Zeolite is defined as the hydrated alkaline within the silicate that functions as an absorbent deodorant agent.

Searches found that Zeolite refers to a class of minerals that are crystalline solids with structures made of silicone, aluminum, oxygen, and these structures form a framework with various cavities, channels containing cations, water, et cetera, et cetera. Zeolite can be natural or synthetic. And that there are over 200 (audio skip) zeolite frameworks identified.

So, basically the CIR staff is coming back to us and saying, hey, help us out, what are we looking for, how do we approach this, because we don't even know what this material is, number one. And number two, should we keep all of the add-on ingredients to Zeolites. So the ammonium silver, the gold, the silver copper, the titanium and zinc.

The easiest answer was keep the add-ons. The more difficult one was how to proceed. And, we thought that the easiest way to proceed was to go back to industry and ask them specifically what are the chemical composition and method of manufacturing and the impurities in the Zeolite that they used.

And the other insufficiency is depending upon that information additional data may be needed. If we can't get clarification on exactly what we're talking about with Zeolite, then there's no way that we can put our arms around (audio skip) and assess its safety.

DR. BERGFELD: David, do you want to comment?

DR. COHEN: Yeah. Thank you. Don, we wrestle with the same issues. We had come to a conclusion just to add zinc, as the others had no use data at this point. We learned that there was an IDA from a few years ago, and that IDA asked for mean and range of particle size, characterization of the particles, composition and impurities, method of manufacturing, or source information.

And at the time that IDA was issued until today we don't have any additional information provided. One of our conversations related to sensitization and whether those cations can participate and interact with epidermal proteins. Some of those cations could be allergen, right, so, or haptens. So we were suggesting asking for sensitization data on their max use concentration, because their max concentrations can be very high, in high 30's. The addition of this new requested information would convert an insufficient data conclusion, because the IDA was never answered, to a new IDA, by asking for sensitization data.

DR. BERGFELD: May I add that the silicates were peeled off this group, so we're left with the Clays and the Zeolites. So it was reduced and they did respond to the silicates.

DR. COHEN: Yeah, the ones left behind in this Zeolites, apparently we didn't get any response. That's the information I have. And maybe get some more information about the ones that are in there, their use. So, you know, Don, I thought maybe some of those high concentrations of use could potentially have sensitization issues if that cation could disassociate.

DR. BELSITO: We don't even know what the structures are.

DR. COHEN: Yeah.

DR. BELSITO: I mean, that's why I said depending upon this information. And the feeling I got from Christina is that she's already tried to find that information, and it's not going to be available. So, you know, rather than beginning to spin our wheels, first of all this is not even a document yet, right, I mean, she's asking what do we need, where do we need to start with, what do I need to do.

Well, what we need is to find out method of manufacturing, composition and impurities. And then once we have that, we can ask -- other data needs may be needed. You know, we're floating in the dark. We've got something with a name that we don't know anything about.

DR. BERGFELD: We can't find it?

DR. COHEN: Those data needs that you mention, Don, are included in the prior IDA, and there was even more information requested in the prior IDA.

DR. BELSITO: And the expectation is that we won't get them and then we'll just go insufficient and we won't have to have done all of this additional work for that insufficient announcement. Keep all of the ingredients in there. And in five and two years -- or whatever the timeline for an insufficient -- it'll become use not support.

DR. BERGFELD: How about the option, if the others aren't used but the zinc is that we go for the zinc right now?

DR. BELSITO: Let's get rid of all of them, because my understanding is, you know, we've had this IDA out, as David pointed out, for a long time. We haven't gotten that information. You know, Christina's been trying to assess this, hasn't gotten this information. I don't think we're ever going to get any information on exactly what Zeolite is, and if we do that's good. But then we can start directing her.

So, you know, put out the call for scientific literature review with a primary endpoint being, hey, tell us what the structure is, tell us how you manufacture this, tell us what the impurities are, then we can tell you what else may be needed.

DR. BERGFELD: David? Paul?

DR. SNYDER: I think we have to step back here. Remember this is in reference to an original report that was split with the Silicates, the Clays and the Zeolites. So the problem is we have a Zeolite report out there that says safe as used. So, I think we need to reopen, and she should pull all the Zeolite information from that old report and expand it with any new information that's been published since then or can be provided to us and made available to us and then we go from there. This is not, are we looking to review Zeolite. We've already reviewed it and we have a safe as used out there. Okay, so, it's come around now we need to revisit it for a re-review. So I think it's a little different approach we need to take here.

DR. BELSITO: Particularly if we find the information isn't appropriate to clear it as safe as used.

DR. SNYDER: Well, because that would be a significant deviation from our original conclusion, yes.

DR. BELSITO: Yeah, but, I mean, that's why you have re-reviews, Paul, right?

DR. SNYDER: Yeah, I agree.

DR. BERGFELD: So I'm not understanding what we're really going to do here. It all sounds pretty good. Bart?

DR. HELDRETH: So, technically the panel has already seen a draft report. That was the draft report that had Zeolites and silica and all those Silicates in it at that point. And, an IDA has been sitting out there as Dr. Cohen mentioned for a couple of years at this point. So, I believe the next step would be to possibly issue, you know, maybe we don't formally call it an IDA, but remind those interested parties that we're still waiting on that information. And, that the panel will see a new document, basically a draft tentative report in the future.

DR. BELSITO: That's fine.

DR. HELDRETH: Okay.

DR. COHEN: So, if that's the case I would ask for sensitization data then.

DR. BELSITO: I'm fine with that. We can ask for anything we want at this point.

DR. SLAGA: Right.

DR. LIEBLER: Yeah. That's good.

DR. BERGFELD: So, it looks like consensus is that we send an IDA, similar to the one that was sent, reminding them to respond. And add the human I and S information.

DR. BELSITO: Yeah.

DR. BERGFELD: Okay, start there. Sounds good. We don't have to vote on that.

DECEMBER 2021 Panel Meeting – Zeolites - Review of Tentative Amended Draft

Belsito's Team – December 6, 2021

DR. BELSITO: In 2018, we reopened this 2003 safety assessment, and we split out zeolites. We had an insufficient data announcement on the six zeolite ingredients that included method of manufacturing, chemical composition, particle size data, dermal irritation and sensitization.

We received an HRIPT and in vitro primary cutaneous tolerance test on its Zeolite material unknown type. We found the ECHA database has been updated with zeolite with a specific CAS number 1318-02-1, which is the CAS number associated with zeolite in the dictionary. We've got a description of what that is. It's synthetic and non-fibrous according to ECHA. Those data were incorporated in the report.

Now, this is what we're looking at. We did get some comments in Wave 2 from a manufacturer of zeolite A that I thought were very helpful. That was from H.R. Grace. Looking at this now, where are we with this report? The

maximum leave-on concentration is 35.7 percent. It also has aerosol use where we got some acute toxicity data and some good respiratory data on the synthetic zeolites.

I was of the opinion that, with a statement in the discussion about airbrush as I've been pushing, that we probably could go ahead with safety as used for the synthetic zeolites, and the naturals would be insufficient for -- unless we agreed with the Russian data that I didn't think was very good on that Russian zeolite -- manufacturing, impurities, chemical characterization, chronic respiratory and other endpoints, depending on these results. But we'll open it up to other individuals.

MS. BURNETT: Dr. Belsito, I wanted to make note that, in the Wave 2 along with the unpublished data, there was an updated use concentration table from the council. The maximum concentration of use has gone down dramatically.

DR. SNYDER: To what?

MS. BURNETT: 0.9 percent for synthetic zeolite in aerosol hairspray is the maximum. In the Wave 2 supplement, it's PDF page 61.

DR. LIEBLER: So down from 37.8 to 0.9?

MS. BURNETT: Yes, correct.

DR. BELSITO: In hairspray.

DR. LIEBLER: Yeah.

MS. BURNETT: We do have concentrations reported for both natural and synthetic. They divided them out for us.

DR. BELSITO: Right. I saw that.

DR. SNYDER: How did they do a sensitization on a product that's at 0.9 percent?

MS. BURNETT: Well, they might have been used at that concentration at one time.

DR. EISENMANN: That was old product, and they didn't have the information about what type anymore.

DR. BELSITO: Okay. The maximum now is 0.9 in aerosol hairspray and 0.6 in leave-on. Is that correct?

MS. BURNETT: Yes.

DR. BELSITO: I saw this. I just didn't pull it over. Maybe I actually probably reviewed zeolites before we got Wave 2, and I didn't update it. Okay. But I still think that we can clear the synthetics, but we can't clear the naturals. Again, I'd open it up for comments.

DR. LIEBLER: Well, Don, my thoughts were similar to yours. I came down with -- the points in the previous discussion, I think are largely still valid. I came down to saying that we can clear the zeolite and zinc zeolite, but the data are insufficient for uses in which product may be incidentally inhaled. Otherwise, I don't think we have a problem with either the zeolite or the zinc zeolite. I'm not sure that the difference between synthetic and mined zeolite is relevant. We can deal with it, essentially, by saying "not insufficient for incidental inhalation."

DR. BELSITO: Across all categories?

DR. LIEBLER: Yep.

DR. BELSITO: Paul, Curt, if you are able to talk.

DR. SNYDER: What about the titanium and the respiratory for titanium zeolite? Is there any concern there?

DR. LIEBLER: You mean the titanium metal, per se?

DR. SNYDER: Yeah.

DR. LIEBLER: That's not ringing a bell with me as a toxicant. Curt, is titanium hitting your radar? I think your phone is muted, Curt. Not hearing you. We're not hearing you, Curt.

MS. BURNETT: You might need to unplug it from your source. That might interfere with the phone. If you can, do that just briefly. Dr. Klaassen, we still can't hear you. Just unplug the power cord from your iPhone. No, it's still not working. Sorry.

DR. BELSITO: The way that I understood how these metals are locked in, are we really concerned given now the percentages that we're told are being used about the availability of free titanium?

DR. SNYDER: That's kind of what I am agreeing about, Don. Do we have the method of manufacturing and the impurities to show there's not free titanium?

MS. BURNETT: We don't have any information on those at all.

DR. LIEBLER: Yeah. They're not used. I think it would be an almost impossible measurement to make simply because, how do you determine what's free in a product like this? I don't know what the sample preparation processing could be that would give you a reliable measure of that. Titanium is interspersed in the structure; the metal part is interspersed in the structure. It's there, but it is coordinated with the other elements of the structure, the rest of the matrix.

There may be a small amount of titanium that is not bound in the structure at any given moment. I don't really have any feel for how dynamic this is. I don't know, Curt, if you can hold up one finger if titanium is a red flag for you tox-wise or two fingers if it's not. I don't know if that's a -- and three fingers if that's a bad question. Okay, thank you.

DR. KLAASSEN: I'm not concerned.

DR. LIEBLER: Okay. Gotcha.

MS. BURNETT: We have some hands up. I don't know if the people that have their hands up might be able to shed some information or not.

DR. KLAASSEN: Yes, while you're waiting for that, I have one point. That is that we have been here. I think on page 93 that the -- let me check. The dominant lethal test, that is the genotoxicity test and not a reproductive test, so just move that down.

DR. LIEBLER: Okay. Then we have the comments from the two people with their hands up, Demetrius Michos and Brett.

DR. MICHOS: Yes, hello. This is Demetrius Michos, and I am with W.R. Grace. I'm the author of the note that I submitted for the synthesis of zeolite A. I want to make a comment that, for the leave-on products, we certainly want to keep the usage level over 35 percent because, for the self-heating masks, we need a very high percentage of zeolite in order to create the effect. I do not know where that below one percent or so datapoint came. In order for the product to be functional in this area, it should be 35 plus. Thank you.

MR. JURD: Brett Jurd, also from W.R. Grace. I have the same comment as Dr. Michos.

DR. LIEBLER: Christina, can follow up to clarify that and make sure our maximum use concentration is correct.

MR. JURD: Great. Thanks.

DR. BELSITO: I guess I wonder who's making these masks and why we got this lower information. In the absence of Carol being able to get that data from her query, can we have a letter from one of you gentlemen stating that, for self-heating masks, a certain concentration is needed of the zeolites?

DR. MICHOS: Yes. We'll get that and provide that.

DR. BELSITO: Okay. Great, thank you. We're back into the 30 percent range for zeolites, at least for these masks. We're still comfortable with the conclusion that we're rendering? I was, and I obviously reviewed this before I saw Wave 2 because I didn't pick up the concentrations.

DR. LIEBLER: So we're safe as used on zeolite and zinc zeolite. Insufficient for inhalation exposures?

DR. BELSITO: Yes. You're just doing zeolite and zinc zeolite? You're tossing out the others?

DR. LIEBLER: Actually, I had it safe as used for all of them. Yeah.

DR. BELSITO: Paul, Curt, you comfortable with that?

DR. SNYDER: Yea, I was. My only query, Don, was, was the eight percent HRIPT adequate enough for what I thought was the 36 percent max use. That was my only suggestion.

DR. BELSITO: Yeah. These are huge molecules. They're not really going to get through the stratum corneum.

DR. LIEBLER: I'm fine. Safe as used, all of them.

DR. BELSITO: Curt?

DR. KLAASSEN: No additional comments.

DR. BELSITO: Okay. Good. Let's move on, then, to basic yellow.

DR. HELDRETH: I believe Carol has her hand up.

DR. BELSITO: Who has a hand up?

DR. HELDRETH: I believe Carol.

MS. BURNETT: So it will be similar to the silicates in that it is safe except for use in --

DR. BELSITO: Inhalation.

MS. BURNETT: -- inhalation, and that's insufficient? Data needs, just prior tox data?

DR. BELSITO: Chronic respiratory tox and particle size distribution.

DR. EISENMANN: That was my point. You can't get better than a 24-month monkey study where they have positive quartz control and there's no fibrosis in the zeolite study and there was fibrosis in the quartz study. You can't get better than that, so I don't know how more inhalation data -- this is on the synthetic. I'm not arguing about anything other than the synthetic.

DR. BELSITO: Yeah. That was my point originally. I said that I thought the respiratory and other data cleared synthetic zeolites for all uses, but the naturals were insufficient. That's not what I heard from my teammates.

DR. EISENMANN: I'm just saying you can't ask for more inhalation data because you got the --

DR. BELSITO: I agree.

DR. EISENMANN: -- (audio skip) study.

DR. BELSITO: Can we push this back to Paul, Dan, and Curt?

DR. SNYDER: I said, "safe as used." I wasn't wary of the discussion having the inhalation restriction. I'm trying to find that now.

DR. LIEBLER: I said safe as used for all, regardless of their source, with an inhalation restriction insufficient.

DR. BELSITO: Okay, but what about the synthetics? Is it insufficient for inhalation?

DR. LIEBLER: Right. I'm sorry. They could be the naturals.

DR. BELSITO: Right, but what about synthetics, safe as used?

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: It's consistent with our other conclusions for these kinds of ingredients.

DR. BELSITO: Okay. Paul, are you okay with that?

DR. SNYDER: Yes.

DR. BELSITO: Christina, if I can summarize -- and correct me if I'm wrong -- we're going for all of the ingredients safe as used for the synthetic zeolites, safe as used except for products that could be incidentally inhaled for the naturals.

MS. BURNETT: Then, for the data needs for the naturals would be chronic inhalation?

DR. BELSITO: Well, I think, for me, manufacturing, impurities, chemical characterization, unless we thought the Russian zeolite data was sufficient for all of them, and chronic respiratory depending upon these other data endpoints.

MS. BURNETT: Okay.

DR. BELSITO: Any comments on our needs for the naturals? Okay.

Cohen's Team – December 6, 2021

DR. COHEN: So, at the September meeting, we reviewed the rather broad definitions of the zeolite ingredients. We issued an IDA on six zeolite ingredients and asked for information about method of manufacturing chemical composition, particle size, and dermal irritation and sensitization. We received patch tests on a zeolite synthetic without any other details at 7.9 percent that was not sensitizing. In the second wave data we got information on maximum concentration for a synthetic zeolite at 0.9 percent in an aerosol hairspray and 0.6 percent in a powder and foundation.

And we received a detailed letter from Grace with information about a zeolite with method of manufacturing and chemical characterization. So, I'll open it up. I have a little trouble because we keep calling it a zeolite, but it's not very specific on which one we're talking about when we're referring to specific information. So maybe the team can help me understand this a bit better.

MS. BURNETT: I did want to mention something. So, in the Wave II that we received, the use concentrations were updated to reflect both synthetic and natural use. And as indicated in the survey, the concentrations appear to be lower, but we were informed in the other team by some guest in the audience that they are still being up to 30-some percent in masks because they will not perform without being used at higher concentrations. So we will hopefully get that tidbit of data actually in a memo sent to us. But, as far as we know, at least I think it was one of the synthetic manufacturers indicated that they were used at 30 percent in face masks.

DR. COHEN: So that might need an inhalation discussion?

MS. BURNETT: For face masks, I'm not sure. I think those are applied wet.

DR. COHEN: Yes, but they're often allowed to dry.

MS. BURNETT: Correct.

DR. COHEN: And then they crack, and they're often used under the nose, around the nostrils and the lips.

MS. BURNETT: Correct.

DR. COHEN: So, I'm just going to round the bend here with everybody. What are your comments? Lisa.

DR. PETERSON: I think from a chemistry perspective we have everything we need. We have method of manufacturing, impurities, and composition. We need to deal with the inhalation issue, but I'll wait. That discussion can come later.

DR. BERGFELD: With all the ingredients that aren't used, are they okay to keep there or to keep an insufficient status, or what? There are several at the bottom.

DR. COHEN: Wilma, did you say the zeolites that are not used?

DR. BERGFELD: Yeah, that are not used.

DR. SLAGA: Not used.

DR. BERGFELD: It said there were five.

DR. COHEN: Yeah, there was a table of not used ones.

DR. PETERSON: Yeah, I guess the not used ones stay insufficient for those things. I don't know why I was focusing on just the main ones.

DR. COHEN: So insufficient for the not used. And so, it's insufficient across the board?

DR. PETERSON: No, the natural and synthetic zeolites are fine. It's the ammonia and silver zeolite, gold zeolite, silver/copper zeolite, the titanium zeolite, zinc zeolite. Why did I say --

DR. COHEN: That's what I'm getting at. Are those insufficient across -- we're not reading across at all with the natural and synthetic zeolites above in that table?

MS. BURNETT: It would be the four ingredients that are not currently used.

DR. BERGFELD: There are only four? I thought there were five.

MS. PETERSON: Let me just make sure I understand. So --

DR. SLAGA: Five.

DR. PETERSON: -- zinc has the hydrated crystalline ammonium silicates, and then it has the ability to exchange out. So, I mean, honestly, I don't know enough about the chemistry of these to --

MS. BURNETT: So, zinc zeolite has two reported uses but no reported use concentration.

DR. PETERSON: We would need the use concentration on that.

MS. BURNETT: Okay.

DR. PETERSON: But we are missing method of manufacturing on the ammonium silver, gold, silver/copper, titanium, and zinc.

MS. BURNETT: Okay. I'm sorry. I missed what you said. The insufficiencies would be the same?

DR. PETERSON: Method of manufacturing and composition of impurities, and you actually are lacking anything on any toxicology.

MS. BURNETT: Okay.

DR. PETERSON: And I guess that you also are lacking the concentration of use on the zinc.

MS. FIUME: I do see two people in the audience have their hands up.

DR. COHEN: I can't see that.

DR. SHANK: I have a question. What's the relationship between erionite and zeolite? Erionite is listed as a Class III carcinogen.

MS. BURNETT: So erionite is a form of natural zeolite that is very similar to asbestos. It's fibrous, and it has its own IARC notation saying that it is a --

DR. SLAGA: Carcinogen.

MS. BURNETT: -- carcinogen, whereas the other ones were evaluated separately.

DR. COHEN: Can the discussion -- we would specifically call out that this is not part of this safety assessment?

DR. SLAGA: Right.

DR. SHANK: But is it very similar to the cosmetic ingredients? I couldn't find anything.

DR. COHEN: I see Dr. Michos from Grace has got his hand raised. Maybe we can get some more information.

DR. MICHOS: Yes, thank you. I just wanted to point out that the letter we provide to you explains the synthesis and the properties of the synthetic zeolite Type A. And the ingredients -- or the ions that can be exchanged in that framework is sodium, potassium, and calcium. Those are the ones that we have data on, and we supply commercially. Anything else, except those elements, we do not have any data. So as a material we have silicon, aluminum, oxygen, potassium, sodium, and calcium.

That's it. Anything else, it's outside the letter we provide you in terms of synthesis. I hope that answers your question.

DR. COHEN: Yeah, so that HRIPT at almost 8 percent was for this Type A synthetic zeolite?

MS. BURNETT: It's for a synthetic zeolite, but the manufacturer could not specify which type of synthetic it was. And I don't believe they said it was A. It's probably similar to A but not A. From what I understand, the synthetics -- it's the proportion of the calcium and potassium. It changes slightly.

DR. MICHOS: And also, for the zeolite A, the silicon to aluminum is fixed, and once you move away from the A zeolite, the silicon to aluminum ratio changes. And then you go to other type of zeolites, for example, X, Y. But those were not familiar that they're used in cosmetics, but sadly we cannot provide those in the cosmetic industry. Only Type A synthetic.

DR. COHEN: Okay. So, Lisa, you had what you needed except for the five that were not being used?

DR. PETERSON: Well, the zinc -- let me get back to the list.

DR. COHEN: I guess if we're going to have insufficient data --

DR. PETERSON: Yeah, so the ones that we need method of manufacturing and composition are on the ammonium silver, gold, silver/copper, titanium, and zinc. It's the five at the bottom. If you take the list on page 6, it's the five lower ones.

DR. SLAGA: Right.

DR. COHEN: Okay, and Tom?

DR. SLAGA: Yeah, and I think we can go with safe with the synthetic. Any agreements?

DR. COHEN: Well, Christina, that mask at 30 percent was a synthetic?

MS. BURNETT: I believe so. The gentlemen that just spoke was the one that informed us.

DR. COHEN: Oh, Dr. Michos, you are aware of 30 percent max use concentration in a mask?

DR. MICHOS: Absolutely, absolutely. And in order for the zeolite to be effective it needs to be at these high concentrations, and we're aware of masks where those -- the self-heating masks where the person wets the face. And then they apply the cream on it, and then the zeolite absorbs the water and releases heat. So, these are the main use, self-heating masks.

DR. BERGFELD: Is this 30 percent or 37 percent? 37 percent is in our document on face masks under uses.

DR. MICHOS: Correct. People are trying to use as much as possible in order to have the most noticeable heating effect.

DR. COHEN: So, Tom, we have sensitization data at 7.9 percent.

DR. SLAGA: So, do you want to put a limit on it -- is what you're saying?

DR. COHEN: No, we would just perhaps ask for max use.

DR. SLAGA: Yeah, I think we have sufficient data for the synthetic, don't we?

DR. COHEN: Well, if the synthetic is going to 37 percent in a face mask and our highest HRIPT is 7.9 percent and they're both synthetic, I'm not sure we don't have a gap there.

DR. SLAGA: Well, can we set the limit? I mean, we have no data for the 30-some right?

DR. COHEN: Right, but we already know going into it that it has use at that high concentration, so do we just go out with insufficient without safe as used up to a certain percent? I'm asking, really.

DR. SLAGA: Yeah, I know.

DR. COHEN: Ron?

DR. SLAGA: That's a tough one.

DR. SHANK: I'm still -- when the report says zeolite, can we use that to cover all of the, what is it, five or six others? Like for read across --

DR. COHEN: Are you talking about the non-use ones?

DR. SHANK: -- most of the time it just says zeolite unspecified or unknown type I guess it says. And in our previous report zeolite was okay.

DR. SLAGA: Yeah.

MS. BERGFELD: Did it include the mask?

DR. SLAGA: I don't remember that. I can't recall if it had the mask or not. I don't think it did. I don't remember seeing it.

MS. FIUME: David, can I ask a question? On PDF page 110 animal testing, it looks like the synthetic zeolite was tested in a dealer test up to 50 percent. Is that at all helpful for what --

DR. COHEN: What page?

MS. FIUME: PDF page 110.

DR. SHANK: 110, Table 9.

DR. ANSELL: And covered in PDF 95.

DR. COHEN: So, you're talking about an animal study?

MS. FIUME: Yes, is that at all helpful in determining sensitization potential, or do you need it to be in a human study?

DR. COHEN: Let me -- and Jay, what was the other one?

DR. ANSELL: Synthetic zeolite 3 percent intradermal, 25 percent topical induction, 40 percent challenge was not sensitizing in guinea pig maximization.

DR. BERGFELD: It will allow you to go to 40.

DR. COHEN: Yeah, you know, aluminum can be a contact sensitizer. And obviously I'm not worried about the sodium/potassium, the calcium and silicone so much, but it's a big space between 8 percent and 37 percent.

MS. BURNETT: Dr. Cohen, you have another hand up. Mr. Jurd.

MR. JURD: Yes, hi, my colleague Dr. Michos already spoke, and we're both with W.R. Grace. I'm looking for that data right now in our work portfolio, so if I can't find it today, I will try to get back to you as soon as I possibly can.

DR. COHEN: That's perfect then. Why don't we just ask for that tomorrow?

DR. SLAGA: Yeah.

DR. COHEN: And it'll come back, this is -- I'm trying to remember what the disposition of this report is. It's a draft tentative amended report. So, we get another round of this at the next meeting?

DR. BERGFELD: You can table it. You can request table.

DR. SLAGA: Table, yeah.

DR. COHEN: Okay. So that's a motion, Wilma? I can ask to table it?

DR. BERGFELD: Yeah, no discussion. You have to call for second, vote in or out. Yeah.

DR. COHEN: Oh, so, when I present it, I could give some background information and then ask for a table?

DR. BERGFELD: Yeah.

DR. COHEN: Okay. Would that be satisfying to the rest of the group?

DR. SLAGA: Yes.

DR. PETERSON: Yup.

DR. COHEN: Okay.

DR. BERGFELD: So, it's going to be depending on what the Grace cooperation can get back to you on the information regarding the concentrations in masks and their safety. Is that what we're asking?

DR. COHEN: Yes.

MR. JURD: Right, we'll get the concentration information, and I'm not going to guarantee we have the sensitization data. But I do want to look through our registrations because I know that that dossier is currently under evaluation in Europe. I will search and see what I can find if that's the data gap. But for the cosmetic products themselves, of course, we wouldn't have that being only a manufacture of zeolite.

DR. BERGFELD: Okay.

DR. COHEN: Okay.

MS. FIUME: I see Dr. Michos also has his hand up. I don't know if he has additional information.

DR. MICHOS: Yeah, I just wanted to address Dr. Cohen's question on the aluminum. We do not have free aluminum that can enter the skin. This is aluminum that is bonded with silicone in an aluminum silicate structure.

So, it's not something like the aluminum chloride or aluminum chlorohydro. It is aluminum, oxygen, silicone, aluminum, oxygen in a chain. So, there's no free aluminum.

DR. COHEN: And under use -- under typical use, you would not expect the aluminum to exchange for any other ion?

DR. MICHOS: No, no. The aluminum, it is called a framework aluminum along with the silicone, but the sodium, potassium, and calcium, those are the exchangeable ions. You can think of the critical structure as a very large anion, but they're fixed in place and it's a crystalline. But the potassium, calcium, and any other cat ions are free to exchange in order to bond with the charge.

DR. COHEN: Yeah, that is helpful.

DR. MICHOS: Thank you.

DR. COHEN: All right. So I can give that background information tomorrow, ask for a table, get the material back from Grace, and then we can bring it up at the next meeting?

DR. SLAGA: Sounds good.

DR. COHEN: Wilma, does that --

DR. BERGFELD: That's a way of solving it. You'll have to wait and see what the Belsito team wants to do but still.

DR. COHEN: Yeah, I think we'll be able to have a flexible conversation tomorrow about it.

DR. SLAGA: Okay.

DR. BERGFELD: Now, I think that whatever we get from Grace obviously needs to go into our minutes because they will give us more information about the chemistry and the stability of their molecules.

MR. JURD: Yes, yes, thank you.

Full Panel Meeting – December 7, 2021

DR. COHEN: Okay. At the September meeting the Panel discussed the broad and vague definition of the ingredient zeolite and issued an IDA for synthetic natural ammonium silver, gold, silver cooper, titanium, and zinc zeolite. Our additional needs were method of manufacturing, chemical composition, particle size data and dermal irritation and sensitization data. We received information on HRIPT of an unspecified zeolite at 7.9 percent in a mixture. That was not sensitizing in human subjects, and we received substantial information on a synthetic type A zeolite from the manufacturer.

In the second wave data we got maximum concentration of use for synthetic zeolite at 0.9 percent in an aerosol hairspray and maximum concentration for a natural zeolite in 0.6 percent in a face powder and foundation. Yesterday, though, during the discussion we heard about the max use of a synthetic zeolite at 37 percent in a self-heating mask. Our motion is to table the vote until additional information is provided by the manufacturer to corroborate max concentration of the face mask, irritation and sensitization data if available and notes on the chemistry of the synthetic zeolite.

I think specifically that a type A aluminum silicon zeolite does not have aluminum as an exchangeable ion. So that's our motion is to table based on that information. We expected to have that information shortly and certainly before the next meeting.

DR. BERGFELD: There's no discussion on a table. If there's a second, it is tabled. So is there a second to table this ingredient for the needed information as recorded by Dr. Cohen?

DR. SHANK: Second.

DR. BERGFELD: Second. Bart?

DR. HELDRETH: Would it be acceptable to the Panel instead of tabling this to issue an insufficient data announcement for those needs? I think that'll keep the process moving along and get the information in time for the next iteration.

DR. BERGFELD: That's a consideration. David, you want to rescind your motion and go with IDA?

DR. COHEN: Yes. We can issue an IDA asking specifically for the material before. We want max use concentration, irritation and sensitization, and additional notes on the chemistry. That's what I would put in the IDA, and we still have insufficient data for the zeolites not in use, which were ammonium silver, gold, silver cooper, titanium, and zinc. We still don't have any of the information from the original IDA.

DR. BERGFELD: Okay. Ron, I need to have you rescind your second.

DR. SHANK: I rescind my second.

DR. BERGFELD: Okay. So what is on the table is an IDA with a noted request. Don, do you have a comment?

DR. BELSITO: Yeah. So our group actually felt that the synthetics were okay and the naturally mined were insufficient for the original data needs, so I would just like to throw that out for comments from my team members. The concentration for the face mask is actually very interesting because when we first looked at it, we were looking at those concentrations. And then it got lowered with, I guess, the Wave II data for concentration of use, and then it was pointed out that it has to be in the 30 percent range to have a heated face mask.

So our original look at this was actually at such a high level. We do have an irritation in in vitro epi skin test at 28 percent of zeolite, the type of which was unknown. There's really nothing about these to me that would suggest they're sensitizers. And I guess I'll ask Dan to comment on the ion exchange. We actually had that discussion in our team yesterday, so, Dan, if you could comment on that.

DR. LIEBLER: Well, I mean, these are all involving coordinate bonds between the metals and the rest of the matrix, so it's not that none of the metals can get out but that the metals are present largely in the substance -- in the zeolite substance. So I didn't think whether or not the free metal got out was the big driver of concern for me unless there was some unique skin sensitization risk with any of these metals, and they didn't ring a bell like nickel would for example.

So I think that when I read the latest version of the report, I felt that we could go safe as used, and then we had the comment about the face mask requiring such a high concentration. And honestly, Don, that's when I had some uncertainty because part of the safe as used was at the relatively lower concentrations that appeared to be listed in the report. If indeed we've got these very high concentrations in these face masks, then I'm more receptive to the idea of going out with the IDA as the Cohen team suggests. So that's where I am. I don't know, Paul or Curt, what you guys think.

DR. SNYDER: Yeah. I mean, we reviewed it thinking that the leave on percentage was much lower, and then this was a new twist that -- it went from 37.5 to 0.9. Now, we're back up to greater than 35 percent, so I'll concur with the majority.

DR. SLAGA: Yes, and I'll go along with that as well.

DR. BELSITO: Okay. So with the IDA, though, should be all of our requests for the mined as well, not just the new requests for the synthetic.

DR. SNYDER: Correct.

DR. SHANK: Christina has her hand up.

MS. BURNETT: Yes. So currently we do have guinea pig maximization tests at up to 50 percent.

DR. BELSITO: Yes.

MS. BURNETT: You want more specifically an HRIPT at the higher percent?

DR. BELSITO: I thought it was okay. David?

DR. COHEN: Listen, I'd like to see what we have. I got an impression that it's possible that that data exists, and if it does, I want to see it. We're aware of this mask at 37 percent, and we want to see if there's any additional human testing on it. One other thing I wanted to throw out for just advice actually, if it's used as a heating mask that might dry, are there any inhalation issues we might need to think about being around the face and it drying and cracking? Don?

DR. BELSITO: You know, inhalation is my weak point, so I'll pass it on to my teammates.

DR. SNYDER: Yeah. I think that would be quite extraordinary to get a significant (inaudible).

DR. LIEBLER: I think cracked face mask pieces go on the large size of the particle distribution.

DR. COHEN: I can buy that, Dan. I just wanted to just have that discussion.

DR. LIEBLER: I think Brett Jurd has a comment.

MR. JURD: Can I speak? Is that okay?

DR. COHEN: Yeah.

MR. JURD: Regarding the data with Dr. Cohen's question, I looked at it and talked to my team. There's not available data out there that we have direct access to that can share. It's all data currently owned by the consortia in REACH. There was, however, information in the HERA zeolite A report, which is the human and environmental risk assessment. It's a focus on cleaning products, but there was data in there on sensitization. And then I talked to our chemists and toxicologists in Europe, and I asked if there was anything that we could do going forward.

And they said, unfortunately, if you tried to do OECD 442 and/or 429, there were issues with solubility for 442 and then metals interference with 429, which kind of pushes you to OECD 406, which will become an animal welfare issue. And they weren't in favor of doing that, and they said probably it's best just to refer back to the HERA report, which I think you guys may have received. So there was some information there. I think -- go ahead, I'm sorry.

DR. BELSITO: I think Brett's point is that Europe has banned animal testing for anything that's used in cosmetics, so since we're a Panel that looks at cosmetics, we're either into in vitro tests. Or you would have to ask for an HRIPT. We're not going to get any additional animal tests on this material for use as a cosmetic.

MR. JURD: Correct.

DR. SHANK: Wilma, you're on mute.

DR. BERGFELD: I didn't do that. Can the chemists define when it's dry and it cracks off what exposure to this kind of compound would be? Are the particle size pretty big?

DR. BELSITO: Big flakes.

DR. BERGFELD: Big flakes, yeah. Maybe it can be discussed in that light in the discussion.

DR. BELSITO: I don't even know that we need to bring it into the discussion, do we?

DR. BERGFELD: Well, you're going to have that high percentage, and it deals with the face mask specifically. You're going to have to explain that, why it mainly is the lower percentage in the usual cosmetic product.

DR. BELSITO: Would you expect a face mask to be respirable?

DR. SLAGA: Well, you're pulling air through it, so particles could come off through breathing. You know, to create a vacuum depending on the quality of the face mask, you could pull some stuff in.

DR. LIEBLER: I think it takes a lot of work --

DR. SLAGA: It's not going to be all big stuff. Some of it could -- the big flakes, obviously, you're not going to worry about, but if air goes over it, you possibly could pull something. I don't know, but it's not as simple as it sounds.

DR. LIEBLER: What we think of as fine particles are really hard to produce. You know the bits of powder flake off from something like that is probably in the at least tens if not hundreds of microns in diameter.

DR. BELSITO: Lisa, your thoughts?

DR. PETERSON: My thoughts were how have you handled this issue before? I mean, there's been face masks before. It's not a big concern. I agree that to get the really tiny particles you probably would need some special manipulation, but there could be some.

DR. SNYDER: We have never considered face masks as a potential for inhalation exposure, and I think that could be a very, very bad precedent.

DR. PETERSON: Yeah. That was sort of my thought is that if you've not dealt with this before, then why bring it up now? Because then it's an issue, and it's quite honestly -- I mean, when you do a mask, that's not something you think about in terms of what comes off.

DR. COHEN: Well, I think it came up with the very high concentration -- 37 percent of this particular product. And probably in the context of other face mask discussions it's not like that, but they're fractions of a percent.

DR. BERGFELD: At 50, they're very high --

DR. SNYDER: I would estimate that the report was split from clay and --

DR. BERGFELD: Yeah.

DR. BELSITO: I mean, face masks are going to be clays and these types of materials which we've reviewed which are in very high concentrations.

DR. COHEN: Yeah. So the question is does it go in the discussion or not. Don, your suggesting it doesn't; right?

DR. BELSITO: Yeah. I was just throwing that out for --

DR. SNYDER: I support that.

DR. BERGFELD: Well, I want to have you discuss it only because there's such a wide variance in concentrations in what is usually used in cosmetic ingredient and what is used in a mask that could just be addressed in a sentence.

DR. BELSITO: We dealt with materials. I mean, all of the other materials that were broken out of this original big group are used in masks at very high concentrations. That's the nature of a mask. It's a clay-like material that dries on the skin.

DR. BERGFELD: I understand.

DR. BELSITO: It's never brought up this issue before.

DR. BERGFELD: I just think it's a variance, and also I'd like to remind you all that this inhalation resource document is only a few years old, so we've only been looking at inhalation as a problematic area for us for a few years and really honing in on it the last couple years. So it's very possible that some of these are very old documents that we dealt with that had masks in them. I think the clay, though, was maybe five years ago -- three years ago. Anyway, let us proceed. It sounds like the opinion is not to put in the discussion the difference in the large concentration (inaudible).

MS. BURNETT: Just an FYI, the clays were part of the silicates massive report that was split off, so you will be looking at those soon.

DR. BERGFELD: Okay.

DR. COHEN: Okay.

DR. BERGFELD: So it sounds like we have an IDA going forward, some discussion on what should go in the discussion. It sounds like there was a deletion of inhalation information and also a deletion of anything mentioning clay masks. Would that be correct?

DR. COHEN: As it stands now.

DR. BERGFELD: Okay.

MS. BURNETT: So currently we're going out with a new IDA with a different list of needs.

DR. BERGFELD: Yes.

MS. BURNETT: So could you repeat that list again to make sure I have it correct?

DR. BERGFELD: Dr. Cohen, can you do that?

DR. COHEN: Yes. We want maximum concentration of use for synthetic zeolites, irritation and sensitization, and we maintain the IDA on the prior zeolites. That IDA's never been satisfied, so those carry.

DR. BELSITO: So, David, do you still want irritation and sensitization since we have in vitro irritation on epi skin? We have a guinea pig max test, and we just heard we're not going to get sensitization because the lack of solubility precludes use of in vitro testing.

DR. COHEN: So, Don, the face mask that's 37 percent, I'm not sure -- maybe I was reading between the lines, but I'm not sure there isn't any skin testing on that product or not. I just don't know, so if it exists, I'd like to see it.

DR. BELSITO: Human?

DR. COHEN: Yeah. Human.

Dr. BELSITO: Okay. Fine. I mean, this is a wish list. We can always reconsider when we see the final product.

DR. COHEN: Absolutely, Don. Yes.

MS. BURNETT: And you stated that these insufficiencies are only for the synthetic versions or for both mined and synthetic as used?

DR. BELSITO: Both.

DR. COHEN: Both.

MS. BURNETT: Okay.

DR. BERGFELD: So we appear to have consensus on this IDA and consensus on the needs that we're going to be requesting, so I'll assume unanimous approval of this. All right. Anything else to be said about the zeolites? Nothing? All right.

March 2022 Panel Meeting – Review of 2nd Draft Amended Tentative Report

Belsito's Team – March 7, 2022

DR. BELSITO: OK, great. So let's move on to zeolites. Yes. So this is Christina. Hi, Christina. You got all the easy ones this time I see. So, these are six ingredients and in December we asked for additional needs, maximum use concentration for mined and synthetic, method of manufacturing or source data for ammonium silver, gold, silver, copper, titanium, and zinc zeolite. Chemical characterization, including specific frameworks and compositions and impurities for the mined zeolite, ammonium silver, gold, silver, copper, titanium, and zinc zeolite. And depending upon that, additional tox may be needed. We wanted particle size as used in sprays and powders, and irritation and sensitization at concentration of use. None of the data has been received, and since the last meeting published data on erionite, which is a carcinogen…its relation to natural zeolite was added, there have been updates to the VCRP, including data on aerosol hairspray and concentrations. And the point it's gone back and forth is the self-heating masks or one point the concentration was lowered and they were told they had to be used about 30% to generate the heat and we finally got that letter back and wave two, wave three, one of the waves said that yes, they are used at higher concentrations, otherwise they cannot generate heat. So let's look at the documents with that as background and see where we are with these. There's wave two and wave three. Yes. Wave two. We learned that synthetic zeolites, namely grace sylosiv A3? It's a synthetic zeolite and it's used up to 30% in a self-heating cream mask.

DR. SNYDER: Not in that same way. We did not receive confirmation of that. There's no confirmation documents. That being true, is that right? Monice, Christina?

DR. BELSITO: We got a letter. Is that wave three?

MS. FIUME: In wave two, it was, it should be the last page of the supplement in wave two.

DR. SNYDER: I have a question.

MS. FIUME: Page 18, I think.

DR. KLAASSEN: Christina, we can't hear you. No.

MS. BURNETT: Great.

DR. KLAASSEN: There you go. It's OK.

MS. BURNETT: There you go. Oh yeah.

DR. LIEBLER: Yep.

MS. BURNETT: OK, wave two was the note from the supplier. Wave three was council comments.

DR. LIEBLER: So we were asking about the load in the masks. And the response from the letter from Bob Woods that was forwarded by Carol refers to self-heating creams and lotions. I don't know if that also includes what we've been talking about as masks. Christina, do you know if that is the same thing or if it's a different kind of product?

DR. BELSITO: No, it's a mask then.

DR. LIEBLER: It is OK.

DR. BELSITO: Yep.

MS. BURNETT: Thanks.

DR. LIEBLER: So one of the things we got hung up on last time was the issue of whether or not there's an added concern for mask, particularly from inhalation exposure from powdered zeolite chipping off and being respirable during the removal of the mask after it's dried. But, you know.

DR. BELSITO: Sort of addressed that in his letter now.

DR. LIEBLER: Yeah, well. I don't remember seeing that, but you know the way, these are the way these are taken off after they've dried, you wash them off with hot water. You don't take like a hammer and chisel to your own face. So I think the issue of you know powdered zeolite from masks being respirable as a non-issue. I watched a couple of videos on YouTube about using these and taking them off. I tried to hide my IP address so people wouldn't know that's the kind of content I'm viewing, but anyway. From what I saw it really removed any concern I had about that issue.

DR. BELSITO: Yeah, and that's pretty much what he said.

DR. LIEBLER: And I also was not worried about the metals. The metal components. I think that was one of the requests for concentration of free metal in the zeolite ingredients that contain some of the some of the different metal forms? Yeah. That would be an experiment. I mean, a measurement there would be essentially impossible to make. Because I don't see how you could possibly work up a sample to get the free metal versus the zeolite bound metal, so I mean, I think we're asking for something. Gosh, in principle, it would be nice to know if you could only make the measurement, but there's no way you could really realistically make that measurement. And then, you know, for example, processing could even disrupt these, possibly releasing some metals. But I think being worried about this sort of ignores what we know about the structures of these, ingredients in that in that the metals are integrated into this lattice structure, so they're not just, it's not like a simple coordination complex where they could be coming and going according to some equilibrium and they're part of these structures and I think they're largely unavailable. I think they're, you know, based on the known chemistry and structures of these, they should not be available to exert direct effects independent of the overall, you know, zeolite structure. So, I think that that issue kind of goes away. And with those two issues gone, I end up safe as used for the whole group.

DR. BELSITO: Paul?

DR. SNYDER: Sorry, I was looking at that. There is we only issue I had…was on that…there's that one inhalation study where they had to…where they treated the animals, and they had a particle size distribution. Did you see that?

How much? There was a large percentage of particles that were less than 10 microns. On page 107. Particle size distribution would be like…because we'd ask for particle size distribution before. In our insufficient data announcement.

DR. BELSITO: Which page you are on, Paul?

DR. SNYDER: Page 107.

DR. BELSITO: OK.

DR. SNYDER: There was an inhalation study there were they treated fifteen male and female rats for 22 months and I was struck by the particle size distribution. Zeolite A was point five to one microns, 15.7% one to two, 14.8, two to five, six to two. We didn't receive any particle size distribution did we?

DR. BELSITO: No, we did not.

DR. ANSELL: Yeah, but that's an outcome of the experiment. You don't run an inhalation experiment where the particles aren't respirable. So, they are specifically manipulated to all be in the respirable size. And if you look at the concentrations and the effects are…particularly the long term monkey exposure. The synthetic material effects were not observed over visible. So you can't interpret the experimental data particle size to what people would be exposed to in a product.

MS. BURNETT: On PDF page 103 we do have information of a range from a supplier. Under chemical properties.

DR. BELSITO: Typical particle. Particle size, not partial signs.

MS. BURNETT: Thank you.

DR. BELSITO: 6 to 10 microns.

DR. LIEBLER: Hey, course, this is the zeolite material as opposed to particles of the product that would contain the zeolite material.

DR. BELSITO: Right. Dan, if we were to go safe as used. If you go to PDF page 103 at the bottom, it says natural zeolite, specifically clinoptilolite and phillipsite, may contain erionite. So, would we need to say something about the naturals needing the levels of erionite to be undetectable? Since that's been reported to have health effects similar to asbestos.

DR. LIEBLER: I think that could be incorporated into the discussion. Come and it should say something along the lines of natural zeolites should not contain erionite.

MS. BURNETT: I do have wording in the discussion already? It's there, OK. Or would you like it to be modified? Second paragraph.

DR. BELSITO: PDF, Christina, please.

MS. BURNETT: Page 111. OK.

DR. LIEBLER: Yep, last paragraph. The second yellow paragraph. Yes, I think that's perfect, Christina.

DR. BELSITO: OK, so I had synthetics were safe and if there was concern for silver, gold, copper, titanium bound into these matrices. I didn't think so, but I think Lisa had raised that previously.

DR. LIEBLER: Yeah. And when I went over the Minutes from the Cohen team. And I think maybe at least as comments in the full panel discussion, my impression was it was sort of well since we're at an early stage, let's ask for it.

DR. BELSITO: OK, now we have a lot of great inhalation data for this synthetics. We have nothing on the mined zeolites. Does that give you pause, Dan?

DR. LIEBLER: No.

DR. BELSITO: Ok as long as we make them erionite free?

DR. LIEBLER: I mean, the thing about zeolites that's different from the silicates is that you know that. In in the Silicates we had this kind of synthetic versus mind where the synthetic was all amorphous and the mine had potentially large amounts of crystalline, and we were worried about the crystalline because, the documented health hazard. We don't have that same situation with the zeolites. I mean, there is a greater propensity for contamination with crystalline material in the zeolites, but the zeolites tend to have, you know, a different structure distribution, then, then the, then the silicates.

DR. BELSITO: Ok.

DR. LIEBLER: It's so…I just don't think that's an issue that should, you know, mined versus synthetic that should drive our thinking on this category as it did with the silicates report.

DR. BELSITO: OK. And then so we've got use, we know at least up to 3% we have negative irritation data at 28%. I'm really not concerned about these. We have a 40% guinea pig max study. So, I mean, I think we clear the sensitization and irritation endpoints too. So we're going to go safe as used?

DR. SNYDER: Can we look at the wording on page 110 for a minute? That IARC paragraph. Is there something that's missing in there or something? Doesn't naturally occurring zeolite erionite? Its carcinogenic, humans group one.

MS. BURNETT: That's the summary data. The full paragraph is on PDF page 107 following the summarized material.

DR. SNYDER: So that statement on page 110 is inaccurate. It's the erionite, not zeolite.

DR. BELSITO: Where, Paul? I'm confused.

DR. KLAASSEN: Yeah, I understand.

MS. BURNETT: So zeolite is the Group 3, the first sentence and then the eronite which is the naturally occurring zeolite is Group One. That's what's in the paragraph.

DR. SNYDER: Oh, OK. I got you. OK, I got it. OK. That's just with that. With the parentheses. Yeah. OK, I see. I got it. We may need to make that a little clearer. Yeah.

MS. BURNETT: There's a double. I need to close the second yeah. I need to close the second.

DR. SNYDER: Yeah. Yeah, exactly. Thank you.

DR. BELSITO: And we need the respiratory boilerplate. Right? Is it in the discussion.

MS. BURNETT: Not currently. I will add it.

DR. BELSITO: And respiratory boilerplate that I think I saw an email come over across when I was on the phone at lunch. Dan, did you craft an email?

DR. LIEBLER: Yes, I sent it. I sent it to Monice and copied you.

DR. BELSITO: So did the (indistinguishable) hairspray?

DR. LIEBLER: You want me to read it?

DR. BELSITO: Sure.

DR. LIEBLER: OK, hang on a second. OK. The panel noted that the VCRP did not provide uses or use concentration for these ingredients as delivered by airbrush application although products containing some of these ingredients are marketed for airbrush application.

DR. BELSITO: Maybe marketing?

DR. LIEBLER: OK, fine. We won't wordsmith at the moment. The CIR inhalation resource documents noted that airbrush technology presents a potential safety concern without information regarding the uses and use concentrations of these ingredients. The panel cannot evaluate their safety in airbrush applications.

DR. BELSITO: OK. So, I guess it's been called to our attention that they used those words work well when we just don't (indistinguishable). Are we going to include that because no one has said that the zeolites are used in airbrush. We will get into it when we get into the clays with kaolin.

DR. LIEBLER: I see, so maybe marketed I think would be.

DR. BELSITO: Or it could be.

DR. LIEBLER: Either those. I'll defer to my colleagues on the right wording, please feel free to use this as a template to further edit.

DR. BELSITO: So I would just add that in, Christina, and we can discuss it tomorrow.

MS. BURNETT: OK. Are there any other discussion points that you wanted added?

DR. BELSITO: No, I didn't have any - Paul, Curt, Dan?

DR. LIEBLER: I just put in some language about the masks and how they're taken off.

MS. BURNETT: OK.

DR. LIEBLER: Are applied and how they're taken off. You know that they're aqueous slurries and which are rinsed off after use.

DR. SNYDER: Yeah. My only comment was on the erionite. And I can we say there should contain no instead of limiting the amount.

MS. BURNETT: OK.

DR. SNYDER: Because, I think that's a little different than the metals, right?

DR. LIEBLER: Yep.

MS. BURNETT: OK.

DR. SNYDER: There's none that would be acceptable.

MS. BURNETT: OK.

DR. BELSITO: Like this? No margin of safety, OK. We need to go back. You're saying no erionite. So where was that in the current discussion?

DR. SNYDER: Page 111 Don.

DR. BELSITO: Yeah. OK, it's not.

MS. BURNETT: It's all in the last sentence.

DR. BELSITO: (indistinguishable). Yes, the panel was concerned over…cosmetic industry should continue. So how did you want to change that to limit impurities?

DR. SNYDER: Well, I would, I would split out the heavy metals versus the erionite because I think that erionite is a known carcinogen. We shouldn't be any in there.

MS. BURNETT: Or I'll split the sentence out into 2.

DR. BELSITO: So erionite in one sentence. And then those heavy metals in the other.

MS. BURNETT: Right.

DR. SNYDER: Yeah, I didn't put in the same classification as heavy metals, Donald, so.

DR. BELSITO: Right.

DR. SNYDER: So going back to this discussion about the airbrush use. Monice, would it work to have a footnote in every one of the tables for use for the inhalation that whether this was reported to be used in airbrush or not reported here? Used in airbrush is the footnote… says kind of the stuff that that Dan alluded to that is not under the purview of the panel because that application is outside the purview of the Cosmetic Ingredient Panel or something like that?

DR. BELSITO: Well, it's not outside of our purview, we just don't understand the technology and we don't have the data. Right.

MS. FIUME: I would like to go to the panel...if you think it's going to get the attention it needs in the table, or you just prefer to have it in the discussion without, I leave it up to the panel's discretion.

DR. SNYDER: I just don't think…I think we run into a problem if we put it in our resource documents. It's kind of buried over there. It's not really brought out in that in the report. And I agree with Jay. That putting it in every one of the conclusions I think is highly inappropriate. And so, I was just trying to figure out (indistinguishable). You know, compromise or how we could say we acknowledge this, but it's, you know, it's not under our purview because there is no data. And there won't be any data.

MS. FIUME: I'm sorry, I guess I thought that that was going to go into most of the discussions, not the conclusions. Did I misunderstand earlier?

DR. BELSITO: No. What Paul is saying is that an put it as an asterisk to the use table. Paul, is that where you want it?

DR. SNYDER: Well, I was thinking that that might be, yeah, kind of as a compromise that it's acknowledging it but not over emphasizing it. Because I think we're going to run into trouble. Where? Because you know, the Women's Voices of the Earth are going to come back and say here's where this data is used, you know, I mean in these products.

DR. BELSITO: Right. That's why we're drafting a when we know it's used and when for all the others where we don't have information, then once called our attention. But if they were to be used in an air spray device, the data does not support the safety or something like that in the discussion.

DR. SNYDER: Yeah, but that's again, that's why I thought it be good in that table. That it could be in the table, in the narrative, both. But I guess I'm fine. Well, I guess we'll just have to see how it plays out.

DR. BELSITO: Dan, you looked like you were going to say something.

DR. LIEBLER: Nope, nothing else to add.

DR. BELSITO: OK. We're all set with zeolites, Christina?

MS. BURNETT: Yep.

Cohen's Team – March 7, 2022

DR. COHEN: We are starting with a tough one. We are starting with zeolites. So at the December 2021 meeting, we issued an IDA on six zeolite ingredients and we asked for both max use concentration for both mined and synthetics, method of manufacturing, chemical characterization, particle size range in HRIPT. I see we have new VCRP data that's been listed. We went a little back and forth whether we were dealing with a .9% max use and our discussion at the last meeting, industry was present suggested there was a much higher concentration, self-heating face mask at 35%. But then we got late breaking information from Univar, that the self-heating mask had a synthetic zeolite at 30%. There's also a new entry for erionite, which seemed to be rather asbestos-like. We have HRIPT for 7% in max and the max used concentration now is in the 30s, and I needed input on what are we going to do with the wording for synthetic versus mined, material and silica. So I really need everyone's help on this one. I could have spent 10 hours on or you know an hour on which is more like it. So Ron, what do you think?

DR. SHANK: Pardon me. OK. I thought we had sufficient data on the zeolites, synthetic and natural, to support their safety. But there are no data on the remaining five. The ammonium silver, the gold, the silver, copper, the titanium, and the zinc. So those would be insufficient to support their use. The skin sensitization data I thought were sufficient for zeolites synthetic and zeolites natural. Even for face masks, which have a (indistinguishable)… they were tested at 50% concentration in the guinea pig maximization tests. And neat for some kind of zeolite, either natural or synthetic. It wasn't clear in an HRIPT, so I thought the zeolites synthetic and natural were safe for use. The other five were insufficient. We didn't have any data on those.

DR. SLAGA: I agree with Ron.

DR. COHEN: OK. Hey, you know, looking at the human data it's just hard to tell exactly what they're testing. This is such a heterogeneous group. It's like, I'm not sure you know how to read across, but we're going to read across and so will come out with a split conclusion, yeah. So it's going to be safe for synthetic and natural.

DR. SHANK: Yes.

DR. COHEN: Except. The ammonium silver, gold, silver, copper, titanium, and zinc.

DR. SHANK: Correct.

DR. COHEN: Any comment that we have on this erionite. What do we do with that from a safety perspective, if this is going to be applied, in a face powder or something like that?

DR. SHANK:
Well, in the discussion, right now, that is handled. It says the erionite is naturally occurring. And it's a known carcinogen. Oh, and that we're concerned about that. And stressed that industry should make sure that their sources of zeolites don't contain appreciable levels of erionite. That's already in the discussion.

DR. COHEN: Yeah, and that's sufficient for us and some of this is just me still being a little bit new here. We're including it in this report. Right?

DR. SHANK: I think it should be in the report.

DR. COHEN: But we're suggesting not to have it in products, right?

DR. SHANK: Yes, it's a potential impurity for cosmetic ingredients. But, apparently, they can find sources as zeolites that don't contain this. That was my understanding. So industry should take this into account and make every effort to make sure that the zeolites that are used in cosmetics do not contain erionite.

DR. COHEN: OK. Tom and anyone else. So what we're basically in the discussion pulling erionite out of use by let's say it shouldn't be in there?

DR. SLAGA: Right.

DR. SHANK: Right.

DR. SLAGA: No, I agree with that too. As long as it's in the discussion. I think it's OK.

DR. BERGFELD: I agree with that.

DR. SHANK: I think…I think somewhere in the report. I suggested the bottom of page 104 which is the use section we should indicate that these are used as face masks. And they can, the face mask, flake. So there is a potential for inhalation exposure. And that the size of the flakes would be too large for respiration. I think that should be in the report.

DR. COHEN: Yeah. Yes. Right where that came up at the last meeting that we suspected the flake size would be large.

DR. SHANK: Yes.

DR. COHEN: There are also…it's also being rinsed off. It's in an aqueous phase. Often OK. OK. And any other comments, so we'll go with the split conclusion.

DR. BERGFELD: I just wanted to clarify - you're putting that particular statement into the discussion regarding the flakes?

DR. SHANK: Yes.

DR. COHEN: That's what we intended to do, yeah.

DR. BERGFELD: Yeah.

MS. BURNETT: Do you have any other discussion points that you would like in the report?

DR. BERGFELD: I have none.

DR. COHEN: Ron, anything, I didn't either.

DR. SHANK: I don't. No.

DR. COHEN: Tom, any other discussion points?

DR. SLAGA: Oh no.

MS. BURNETT: OK Thank you.

Full Panel Meeting – March 8, 2022

DR. COHEN: OK, at the December meeting, the panel issued a new insufficient data announcement on many zeolites. We wanted a max use concentration for both mined and synthetic, method of manufacturing for five, specifically ammonium, silver, gold, silver, copper, titanium, and zinc. Chemical characterization range of particle size and irritation and sensitization. We have some new VCRP data with max use concentrations that were low at the last meeting. We heard about a zeolite used in a self-heating mask at 35% and in late breaking package too. We received confirmation from (indistinguishable) that there's a self-heating mask with a synthetic zeolite at 30%. We thought the late breaker package in wave three had some edits that were reasonable. There's some new discussion about erionite having physical properties and health implications similar to asbestos. We have HRIPT up to 7.9%. And we had a discussion about how these molecules might interact with the skin and Dan gave us a nice description of how the metals are fairly locked up. So we came to a conclusion as safe as used for this synthetic and natural zeolites and insufficient for ammonium, silver, gold, silver, copper, titanium and zinc. That's our motion.

DR. BERGFELD: Comment on or second.

DR. BELSITO: We felt that they were all safe as used and I'll let Dan discuss why we did not feel that the metals were an issue.

DR. LIEBLER: Yeah, we had. We had asked about the getting, I guess, releasable forms of the other metals. I think that that would actually be just about an impossible analysis to do, because I think you would, you know, anything you did to the sample to perturb it, you know, would make it very difficult to measure separately as released metal from the zeolite contained metal. The other thing is that the structure of this with the sheets and within metals interspersed in between the sheets suggests to me that, you know, they these metals are, as you just said, David, locked up. That's probably a pretty good way to put it. So I didn't feel that there was a basis to exclude the other metal containing zeolites.

DR. SLAGA: Thanks.

DR. COHEN: Yeah. So glad we had that. I'm glad you had that discussion because we were at an impasse there. Ron and Dr. Slaga, are you OK amending our recommendation to roll them all up or Ron, did you have an issue with some of the insufficient data?

DR. SLAGA: Yeah.

DR. SHANK: I'm looking at (indistinguishable) maybe the metals. And I'm trying to look. So yeah. If the metals stay tied up in the complex and are not available to penetrate the skin, then they would all be safe as used.

DR. SLAGA: I go with that too. But they're all tied up.

DR. BERGFELD: Good. So you remember your conclusion?

DR. COHEN: So. Well, I'd like to amend the conclusion that…we will conclude that these are safe as used in present practice for the entire report.

DR. BERGFELD: Now we have a motion, is there a second?

DR. BELSITO: Second.

DR. BERGFELD: OK. And we have any comment or discussion regarding it, specifically the discussion area?

DR. BELSITO: Yeah. So we want the respiratory boilerplate and including, airbrush there? How masks are removed, as David pointed out, they're not pulverized out there, washed. We wanted to split this sentence with the erionite and heavy metals. They shouldn't be grouped together. I'm trying to figure out which (indistinguishable).

DR. COHEN: I think I know what you mean.

DR. BELSITO: In the discussion, the panel expressed concern. Yeah, the last sentence in the discussion. As currently written, the panel expressed concern about this potential impurity erionite and heavy metals, right, and two sentences and panel expressed concern about presence of erionite. Period. Paul, you I think you said there should be none present, right?

DR. SNYDER: Yeah, like that's what I…that's where we stayed.

DR. BELSITO: Right, yeah.

DR. SNYDER: Not present, yeah.

DR. BELSITO: Erionite should not present right and heavy metals should be limited.

DR. SNYDER: Yeah. Final formulation, yes.

DR. BELSITO: Or two sentences.

DR. COHEN: That we agree with that.

DR. BERGFELD: That's editorial, yes.

DR. SHANK: Yes.

DR. BERGFELD: Any other comments to be made on this ingredient group? Hearing none, all those opposed. Abstaining. Approved. OK, moving on to the next big ingredient wave.

DR. COHEN: So, Wilma, I mean, that's it's…this is a quite an accomplishment. Getting this through after all these years.

DR. BERGFELD: Right. Yeah Congratulations to everyone.. Thank you, David.

DR. SHANK: You can say that again.

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 Zeolites as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 23, 2022
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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.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Lisa A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/ Writer, CIR.

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ABBREVIATIONS

CHO = Chinese hamster ovary
CIR = Cosmetic Ingredient Review
Council = Personal Care Products Council
CPSC = Consumer Product Safety Council
DART = developmental and reproductive toxicity
ECHA = European Chemicals Agency
FDA = Food and Drug Administration
HRIPT = human repeated insult patch test
IARC = International Agency for Research on Cancer
LOAEL = lowest-observable-adverse-effect-level
MPE = micronucleated polychromatic erythrocytes
NCE = normochromatic erythrocyte
NOAEL = no-observable-adverse-effect-level
OECD TG = Organization for Economic Co-operation and Development test guideline
Panel = Expert Panel for Cosmetic Ingredient Safety
PCE = polychromatic erythrocytes
US = United States
VCRP = Voluntary Cosmetic Registration Program
wINCI *Dictionary* = web-based International Cosmetic Ingredient Dictionary and Handbook

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 6 zeolite ingredients that are hydrated alkali aluminum silicates that can be derived from naturally-occurring minerals or can be produced synthetically. All of these ingredients are reported to function in cosmetics as absorbents. The Panel reviewed all relevant data, and concluded that these zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

Zeolite is an ingredient that was included in a safety assessment previously published by the Expert Panel for Cosmetic Ingredient Safety (Panel) in 2003.[1] At that time, the Panel concluded that this Zeolite was safe as used in cosmetic products. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued. (The other ingredients included in that original report have been categorized and re-reviewed in other reports.)

This re-review of Zeolite includes additional zeolite ingredients; in total, this report assesses the safety of 6 zeolite 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; other reported uses include cosmetic astringents, deodorant agents, light stabilizers, preservatives, skin protectants, and/or skin-conditioning agents.[2]

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

**Previously reviewed by the Panel.*

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 Cosmetic Ingredient Review (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.

Zeolites is a broad term used to represent a large group of hydrated aluminosilicates that have exchangeable cations. Zeolites can be naturally sourced or synthetically produced. For simplification, the various sub-types of synthetic zeolite (e.g. Zeolite A, Zeolite X, Zeolite NaY, etc.) will be described simply as Zeolite (synthetic). Data for natural zeolites will be described as Zeolite (natural) with the specific type named when the information is known.

The majority of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website for a zeolite with the listed CAS number (1318-02-1); it is described as cuboidal, crystalline, synthetic, non-fibrous.[3] This CAS number is the same as the one used for Zeolite in the *Dictionary*. Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

Excerpts from the summaries of the previous report on Zeolite 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

Zeolites are defined as a group of hydrated, crystalline aluminosilicates containing exchangeable cations of group IA and IIA elements such as sodium, potassium, magnesium, and calcium.[1] Numerous structural types of Zeolites, both natural and synthetic, have been reported.

The definitions of the ingredients included in this review are provided in Table 1. Various sub-types of synthetic Zeolite are used in detergent formulations (Figure 1).[4] These sub-types each comprise hydrated, crystalline, sodium aluminosilicates; these vary by slight differences in the ratios of silicon/aluminum (within aluminosilicate networks, sodium (Na), and water (H_2O)). These variations result in performance changes towards binding with other elements (e.g., magnesium).

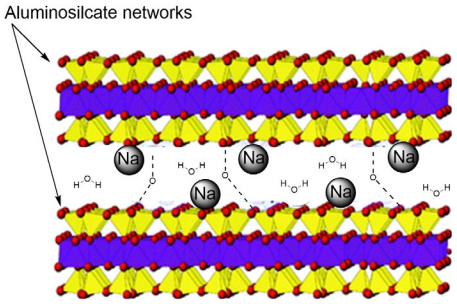

Figure 1. Zeolite

Zeolites are microporous, 3-dimensional aluminosilicate networks with 4-coordinate silicon and aluminum atoms linked by oxygen bridges.[4,5] These networks are negatively charged and the pores contain cations which compensate this negative charge. The water molecules and cations are able to diffuse through the pore network; the cations can exchange with other cations in the surrounding electrolyte. In accord with these factors, the elements in these pores can be exchanged to achieve Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite.

Chemical Properties

Chemical properties for various subtypes of Zeolite are described in Table 2. These zeolites are synthetic, fine white powders, pastes, or granulates that are poorly soluble in water.[4,5] A supplier of a synthetic Zeolite subtype known as Zeolite A (Linde Type A (LTA) framework) reported that typical partial sizes have a D_{50} (by volume) in the 6 – 10 µm range.[6]

Method of Manufacture

Zeolites may be naturally-sourced from mines in the United States, Cuba, Japan, Hungary, Bulgaria, Cuba, Italy, and South Africa.[1] Natural zeolites are recovered from deposits by selective opencast or strip-mining processes. The raw material is then processed by crushing, drying, powdering, and screening. Synthetic zeolite manufacturing 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.

Synthetic zeolites are manufactured from silicon dioxide- and aluminum oxide- containing substances, at temperatures greater than 50 °C and with alkali hydroxides as catalysts.[4,5] All detergent zeolites are manufactured under similar conditions, being crystallized at high pH from sodium silicate, sodium aluminate and caustic soda.

A supplier of a synthetic Zeolite subtype as a sodium salt states that water, sodium silicate, sodium aluminate, and sodium hydroxide are combined and heated to promote the formation of the Zeolite, which precipitates out of the solution.[6] Pure particles are recovered via filtration and washing with water. The resultant material (hydrated) has the following formula: $(Na_2O)\cdot(Al_2O_3)\cdot 2(SiO_2)\cdot wH_2O$, where w represents the variable amount of water in the material. The materials can be dehydrated via exposure to high temperatures.

The same supplier reports that a synthetic Zeolite subtype (sodium, potassium and/or calcium forms) is produced by combining the above resultant hydrated sodium salt material to a water solution of potassium salt (e.g. potassium chloride) and/or calcium salt (e.g. calcium chloride).[6] Following the ion exchange of the potassium and/or calcium ions with the sodium ions, the material is washed with water to remove free salts. The resultant hydrated material has the following formula: $x(Na_2O)\cdot y(K_2O)\cdot z(CaO)\cdot(Al_2O_3)\cdot 2(SiO_2)\cdot wH_2O$, where $x + y + z = 1$. This material can also be dehydrated through exposure to high temperatures.

Composition/Impurities

Analyses of samples of a natural Zeolite from Russia found the purity ranged from 50.6% - 83%.[1] The composition was determined to be 62.64% - 70.92% silicon dioxide, 12.11% - 14.17% aluminum oxide 0.2% - 4% iron (III) oxide, 0.53% - 1.53% magnesium oxide, 1.93% - 4.15% calcium oxide, 0.15% - 64% sodium oxide, and 0 - 3.6 µg/kg benzo[a]pyrene.

Zeolites used as builders in detergent formulations are synthetic sodium aluminum silicates.[4,5] According to one source, a subtype of Zeolite (synthetic) is reported to have a purity of $\geq$ 99%.[5] Trace impurities may consist of iron (III) oxide ($\leq$ 0.2%) and amorphous aluminosilicates. The compositions of various subtypes of Zeolite (synthetic) are reported to be very similar, with the Si/Al ratio differing slightly: 0.7 - 2.5.[4] Moisture content may vary from 10% to 20%.

A supplier of a subtype of Zeolite (synthetic) reported that there may be residual levels of free sodium, potassium, and calcium salts in the finished product.[6] Synthetic Zeolite is tested for the presence of heavy metals.

Natural zeolites, specifically clinoptilolite and phillipsite, may contain erionite.[7,8] Erionite is a unique, naturally occurring fibrous mineral that belongs to the zeolite mineral group, but has physical and health effects similar to asbestos.[7-9]

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. Therefore, airbrush application of cosmetic products is not assessed by the Panel.

According to 2022 VCRP survey data, Zeolite is reported to be used in 33 cosmetic formulations, with the majority of uses being in leave-on formulations (Table 3).[10] Zinc Zeolite is reported to be used in 2 rinse-off formulations. In the concentration of use survey conducted by the Council in 2021, results were provided for synthetic, natural, and unspecified-source zeolite ingredients. The survey indicated the maximum concentration of use for synthetic Zeolite is 0.9% in aerosol hair spray.[11] The maximum concentration of use for natural Zeolite is 0.6% in face powders and foundations. However a supplier reported to the Panel that synthetic Zeolite is used at up to 30% in self-heating cosmetic creams and lotions.[12] No uses or concentrations of use were reported for Zeolite during the original safety assessment.[1] There were no reported uses in the VCRP or the industry survey for the remaining 4 zeolite ingredients (Table 4).[10,11]

Zeolite ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, Zeolite is reported to be used in lipsticks (concentration not reported), and Zinc Zeolite is reported to be used in personal cleanliness products (concentration not reported).[10] Additionally, Zeolite has been reported to be used in products that may come into contact with the eyes; for example, it is used at up to 0.6% in eye makeup preparations.[10,11]

Moreover, Zeolite is used in cosmetic sprays and powders, and could possibly be inhaled; for example, synthetic Zeolite is reported to be used at up to 0.9% in hair spray, and natural Zeolite is reported to be used in face powders at concentrations up to 0.6%.[10,11] 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.

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.

The zeolite ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[13]

Non-Cosmetic

Zeolites are reported as being used in carbon dioxide 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.[1] The three main uses of synthetic Zeolite are as detergents, catalysts, and adsorbents or desiccants.

Zeolite (described as Zeolite Na-A (a synthetic zeolite); CAS No. 68989-22-0) is listed in 21 CFR§176.170 as a substance that may be safely used as component of paper and paperboard that may be in contact with aqueous and fatty foods as a pigment extender at a level not to exceed 5.4% by weight in finished paper and paperboard. The use of a Zeolite (described as clinoptilolite (a natural zeolite)) has been investigated for use in oral drug delivery of acidic medications, such as aspirin.[14] The results showed that adsorption and desorption of aspirin on this zeolite are particle size- and pH-dependent.

Synthetic sub-types of Zeolite are used in household detergents to decrease water hardness.[4,5] Synthetic Zeolite is also used as a catalyst or as molecular sieves.

TOXICOKINETIC STUDIES

Zeolite (synthetic) was administered in a single 20 mg/kg dose to determine the oral bioavailability of silicon and aluminum in 12 female beagle dogs.[1] Blood was sampled at intervals up to 24 h after dosing. The plasma samples were

assayed for silicon and aluminum by graphite furnace atomic adsorption. No dogs displayed emesis but 4 had soft stool. The area under the curve (AUC (mg · h/l), maximum concentration (C_{max}: mg/l), and the time to reach C_{max} (T_{max} ; h) for silicon absorption were 9.5, 1.07, 7.9, respectively. The AUC (mg · h/l), C_{max} (mg/l), and T_{max} (h) for aluminum absorption were 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 another study to determine the bioavailability of silicon and aluminum in Zeolite (synthetic), 12 beagle dogs received a single dose of 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.[1] 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 from the oral dosage forms was less than 0.1% relative to the intravenous infusion.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In a single intratracheal study of a Zeolite dust (50 mg) in male rats that were observed 1 and 3 d and 1 and 3 mo after injection, time-dependent increases in phagocytosis were observed and morphological changes in the lungs were described as exogenous fibrous alveolitis.[1] In another study of a single intratracheal instillation of 50 mg Zeolite (natural; clinoptilolite) in male rats, lung tissues were examined histopathologically on days 1, 3-5, and 18 after injection. 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.

Acute dermal, oral, inhalation, and parenteral studies summarized here are described in Table 5.[3] The dermal LD_{50} for Zeolite (various synthetic subtypes and natural - smellerite) was > 16,000 mg/kg bw in studies with rabbits. Mild erythema that resolved within 4 d of application was noted in rabbits that received 2000 mg/kg bw on both intact and abraded skin.

In oral studies in mice of Zeolite (synthetic) and a modified zeolite described as H-mordenite, the LD_{50}s were > 10,000 mg/kg bw and > 9000 mg/kg bw, respectively, with no clinical signs of toxicity observed.[3] One synthetic Zeolite had an oral LD_{50} > 16,520 in rats, while rats that received various subtypes of synthetic Zeolite orally had an oral LD_{50} > 32,000 mg/kg bw. An extremely low order of toxicity was observed in rats that received up to 32,000 mg/kg bw Zeolite (synthetic bonded with bentonite). Other various synthetic subtypes of Zeolite had an oral LD_{50}s > 31,600 mg/kg in rat studies. An oral study of Zeolite (natural; smellerite) in rats reported an LD_{50} > 16,000 mg/kg bw. An oral study of Zeolite (synthetic) in dogs reported an LD_{50} > 1000 mg/kg bw: emesis occurred within 5 min of dosing.

In inhalation studies in rats, various subtypes of synthetic Zeolite had LC_{50}s >18.3 mg/l.[3] Mice that received Zeolite (synthetic) via a single 10 mg intraperitoneal dose, 2 different forms of cellular accumulation were observed in the omentum; however, additional formation of connective tissue or other mesenchymal activity was not induced by these accumulations. In rats that received a single intraperitoneal dose of Zeolite (synthetic; up to 50 mg) and observed up to 11 mo, treatment-related aseptic superficial inflammation of abdominal organs was observed with deposits of the test material observed in the regional lymph nodes, abdominal cavity, and mediastinum without fibrogeneous or silicogeneous. A similar study with a dose of 200 mg/kg and an observation period of up to 24 mo noted collagen fibers reticulating the alveolar macrophages 3 mo after application that were predominantly surrounded by narrow, concentric dense fibrous layers. No effects noted to local lymph nodes. Fibroid effects were reversible during the study course, so that 18 mo after treatment a progression of the effects was excluded. No treatment-related findings observed at 24 mo.

Short-Term, Subchronic, and Chronic Toxicity Studies

In a 6-wk dietary feed study in pigs, 0.3% Zeolite (synthetic) or 0.5% Zeolite (natural) did not affect average daily weight gain, average daily feed intake, and feed:weight gain ratio.[1] An 84-d dietary feed study in castrated male pigs found that Zeolite (clinoptilolite) had no effect on daily weight gain, daily feed intake, or the ratio of weight gain:feed intake of growing pigs. Sheep fed a diet containing 0.15 g/kg bw of Zeolite for 3 mo had no adverse health effects in parameters including 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. In a 148-d feed-lot experiment, cross-bred steers fed a sorghum diet with Zeolite (clinoptilolite) substituted at 0%, 1.25%, and 2.5% of the diet dry matter exhibited no differences among treatments in average daily weight gain, feed intake or feed efficiency.

In inhalation studies, male and female rats exposed to 0 or 20 mg/m^3 Zeolite (synthetic; particle size 0.5 to 10 μm) for 5 h/d, 3 times/wk for 22 mo had moderate to extensive respiratory disease in both treated and control groups. No neoplasms were observed in any group.[1] In another chronic inhalation study of Zeolite, groups of male and female hamsters and male

and female rats were exposed for 5-h periods 3 times/wk for 12 mo for hamsters and 22 mo for rats. Both species had moderate signs of respiratory disease in the treated and controls. The researchers noted the animals had deaths attributed to a specific infection. 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.

Repeated dose toxicity studies summarized here are described in Table 6.

In short-term oral studies, rats that received various subtypes of synthetic Zeolite daily at up to 5000 mg/kg bw for up to 1 wk had no adverse effects.[3] Zeolite (synthetic) at up to 10% in dietary feed in rats and dogs affected the kidneys and the urinary bladder (including pustules on kidneys, interstitial nephritis, transitional hyperplasia or thickening of the bladder) at concentrations as low as 1% in 32 – 35-d studies. In a 13-wk dietary feed study in rats, the lowest-observable-adverse-effect-level (LOAEL) for Zeolite (synthetic) was 0.5%, with significant effects observed in bladder and reproductive tissues. A similar 13-wk study of Zeolite (synthetic) in rats had a no-observable-adverse-effect-level (NOAEL) of 5000 ppm (0.5%) and an LOAEL of 10,000 ppm (1.0%) that resulted in effects to the kidneys and urinary bladder, including urinary calculi and wall thickening. In further rat dietary studies of Zeolite (synthetic) at up to 2.0%, the NOAEL was 0.125% when the animals were dosed for up to 24 wk. A 24-wk dietary study of Zeolite (synthetic) in rats had an NOAEL of 0.2%; renal pelvic epithelial hyperplasia was noted in both males and females treated with the maximum concentration tested of 0.5%. A synthetic Zeolite had an NOAEL $\geq$ 20 mg/m^3 in a 4-wk whole-body inhalation study in rats. In a 24-mo whole-body inhalation study in monkeys exposed to up to 50 mg/m^3 Zeolite (synthetic), the LOAEL was 1 mg/m^3; high-dose monkeys had nonsuppurative inflammatory reactions of the lungs and mid-dose (6 mg/m^3) monkeys had nonsuppurative bronchiolitis and alveolitis. Fibrosis was observed in monkeys of the positive control group treated with 50 mg/m^3 quartz, but not in the monkeys treated with Zeolite.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

In gavage DART studies of Zeolite (synthetic) in distilled water, no adverse effects on the dam, embryo or fetus were observed in Sprague-Dawley rats that received 74 or 1600 mg/kg test material on days 6 to 15 of gestation or in New Zealand rabbits that received 74, 345, or 1600 mg/kg test material on gestation days 6 to 18.[1] In a long-term ingestion study of Zeolite (natural; clinoptilolite; dosing information not provided), reproductive performance in rats was unaffected although reduced body weight gains were observed during gestation.

DART studies summarized here are described in Table 7.

In oral developmental studies of Zeolite (synthetic) in mice (gestation days 6-15), hamsters (gestation days 6-10), rats (gestation days 6-15), and rabbits (gestations days 6-18), the NOAEL for both maternal and fetal toxicity for all species was $\geq$ 1600 mg/kg.[3] In an oral reproductive study of Zeolite (synthetic) in male rats, the NOAEL was $\geq$ 1250.8 mg/kg bw/d. The NOAEL for reproductive effects was $\geq$ 50 mg/m^3 in a whole-body inhalation study of Zeolite (synthetic) in male and female monkeys.

GENOTOXICITY STUDIES

In an in vitro study of the clastogenic potential of Zeolite in human peripheral blood lymphocytes, statistically significant increases in the percentage of aberrant metaphases, mostly from chromatid breaks, were noted.[1] In a chromosomal aberration study in C57BL/6 mice that received an intraperitoneal injection of 100 µg/mouse Zeolite (natural) particles, Zeolite induced a statistically significant increase in aberrant metaphases after 7 and 28 days in the peritoneal lavage cells. Intraperitoneal injection of 5 different Zeolite dust samples in BALB/C mice resulted in clastogenic effects on bone marrow cells.

In vitro and in vivo genotoxicity studies summarized here are described in Table 8.

In bacterial reverse mutation assays with *Salmonella typhimurium* and *Escherichia coli*, a Zeolite described as H-mordenite (natural; up to 5 mg/plate), and various subtypes of synthetic Zeolite (up to 10 mg/plate) were negative for genotoxicity, with and without metabolic activation.[3] Zeolite (synthetic; concentration not reported) was not mutagenic in *Saccharomyces cerevisiae* in a gene mutation assay with and without metabolic activation. Zeolite (synthetic) was not genotoxic in mouse lymphoma gene mutation assay at up to 0.16 mg/ml with and without metabolic activation, but chromosomal aberrations were observed in Chinese hamster ovary (CHO) cells at up to 0.4 mg/ml with and without metabolic activation. Zeolite (synthetic) was not genotoxic in human embryonic lung cells at up to 0.1 mg/ml without metabolic activation. Zeolite (synthetic) at up to 5000 mg/kg was not genotoxic in a rat bone marrow chromosome aberration test, rat dominant lethal assay, or in mouse-mediated mitotic recombination (with *S. cerevisiae*) and reverse mutation (with *S. typhimurium*) assays. Synthetic Zeolite at up to 5000 mg/kg was not genotoxic in a mouse micronucleus assay.

CARCINOGENICITY STUDIES

No neoplastic changes were observed in groups of male and female Wistar rats that received 1, 10, 100, or 1000 mg/kg Zeolite (synthetic) in diet for 104 wk.[1] In a 12-mo inhalation study, groups of male and 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 non-fibrous Zeolite. Exposures were for 7 h/d, 5 d/wk. One pleural mesothelioma and one pulmonary adenocarcinoma were seen in Zeolite-exposed rats. No neoplasms were found in negative controls.

No mesothelioma was observed up to 23 mo following a single intraperitoneal injection of 10 mg of Zeolite (synthetic) in male mice.[1] No neoplastic changes were observed in male mice that received a single intraperitoneal injection of Zeolite (10 or 30 mg) in a 10 mo study. In mice that received a single injection of 10 mg of Zeolite (natural; mordenite), 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 mo.

In a study of single intrapleural injections of non-fibrous Zeolite (natural; 20 mg) in male and female Fischer 344 rats, mean survival time for control animals was 720 d and 715 d for treated animals.[1] One pleural mesothelioma was found in the control group and one pleural and one peritoneal mesothelioma was found in the treated group. In a 141-wk study in which groups of Sprague-Dawley rats received a single intraperitoneal injection of 25 mg of Zeolite (synthetic), one peritoneal mesothelioma was observed in a treated rat. In a study by the same research group, single intrapleural injections and single subcutaneous injections of 25 mg of Zeolite (synthetic) were given to groups of male and female Sprague-Dawley rats. No difference in incidences of tumors was found among control and treated animals. Three intra-pleural injections of 20 mg Zeolite (natural; clinoptilolite) were given in monthly increments to a group of 44 male and 49 female rats. Control animals received only saline injections. 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. In a similar study in rats with 20 mg Zeolite (natural - potassium and calcium exchanged; phillipsite), neoplasms were found in 41/101 Zeolite-treated rats (50 tumors). Tumor types included 1 pleural mesothelioma, 2 pulmonary adeno-carcinoma, 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.

Intratracheal instillations of 60 mg Zeolite (natural; mordenite) were made in groups of rats that were killed at 1 wk, and 1, 3, 6, and 12 mo after treatment.[1] Nonspecific confluent bronchopneumonia was observed at 1 week after exposure and sequestration of macrophages at 1 mo after exposure. Mild fibrosis was observed at later times. After 12 mo, the aluminum:silicon ratio in macrophages was similar to the ratio in natural Zeolites. 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. In a 104-wk study of a single intratracheal dose of 30 or 60 mg Zeolite (clinoptilolite; suspended in crystalline penicillin) in male and female rats, 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.

The International Agency for Research on Cancer (IARC) has determined there is inadequate evidence in humans for the carcinogenicity of zeolites, other than the naturally occurring erionite.[15] (IARC has found there is sufficient evidence that erionite is carcinogenic to humans and animals (Group 1); erionite causes mesothelioma.[8]) IARC also determined there is inadequate evidence in experimental animals for the carcinogenicity of the natural zeolites (specifically clinoptilolite, mordenite, phillipsite, and non-fibrous Japanese zeolite) and synthetic zeolites. Overall, clinoptilolite, mordenite, phillipsite, non-fibrous Japanese zeolite, and synthetic zeolites cannot be evaluated as to their carcinogenicity to humans (Group 3).

Inhalation

The fibrogenic, silicogenic, and carcinogenic potential of Zeolite (synthetic) through inhalation was studied in groups of 15 male and 15 female Wistar rats.[3] The rats were exposed 5 h/d, 3 times/wk to 20 mg/m^3 Zeolite for 22 mo. A group of 30 untreated males served as control. After 1 yr, two further groups were assigned: a group of 25 animals for control and another group of 24 animals that were exposed to the test material for 8 m. The particle size distribution for Zeolite A was 0.5 - 1 µm (15.7%), 1 - 2 µm (14.8%), 2 - 5 µm (62.0%) and 5 - 10 µm (7.3%). Animals were observed daily for signs of toxicity and mortality. Body weights were measured weekly until study week 24, then bi-weekly until week 32, and then monthly until study end. All animals were killed at study end, necropsied, and underwent histopathological examination.

Treated animals kept eyelids closed during exposure and cleansing of the fur was observed more often in the treated group than in the controls. Body weight and body weight gains in the treated groups were similar to controls. After 10 mo of exposure, rats in both the treated and control groups had signs of dyspnea. At study month 22, nearly all animals exhibited signs of chronic pneumonia. Rats in the treated and the control groups had moderate to extensive respiratory disease. No treatment-related tumors were observed.[3]

Intrapleural

In a whole-life (up to 3 yr) study, groups of 100 male and female rats received a single intrapleural injection of 20 mg Zeolite (synthetic) in sterile saline in the 8th week of life.[3] Control groups included saline (20 mg/rat), crocidolite (20 mg or 40 mg in 60 rats), natural fibrous erionite (a crystalline zeolite; 20 mg in 60 rats), non-fibrous erionite (20 mg), and titanium dioxide (20 mg in 60 rats). Co-treatment groups included crocidolite (20 mg) combined with Zeolite (20 mg; in 60 rats), titanium dioxide combined with crocidolite (20 mg in 60 rats), and quartz with crocidolite (20 mg in 60 rats). The animals were observed daily for signs of toxicity and were weighed on the day of treatment, immediately after treatment, and then weekly). Animals were humanely killed when considered necessary. Necropsy and histopathological examinations were performed, and organ weights were measured.

The highest mortality was observed in the rats that received natural fibrous erionite: all rats in this group died of pleural mesotheliomas between weeks 38 and 71. In the other groups, the main factor determining survival was if the animals received crocidolite or not. The majority of the animals that received crocidolite died due to mesotheliomas and very few survived past week 126. No statistically significant increase in mortality was observed in treatment groups that received non-fibrous erionite or Zeolite. In gross pathological findings of non-fibrous erionite and Zeolite, white test material was present in the intra-thoracic region with occasional slight adhesions. Non-fibrous erionite and Zeolite were occasionally present and infrequent pleural pericardial thickening composed of macrophages with or without connective tissues were noted in histological findings. When non-fibrous erionite or Zeolite was given in conjunction with crocidolite, no evidence of co-carcinogenicity was observed.[3]

OTHER RELEVANT STUDIES

Cytotoxicity

Zeolite (synthetic; 0.1 to 100 µg/ml) incubated for 48 h with normal human osteoblast-like cells induced a dose-dependent increase in DNA synthesis and the proportion of cells in mitosis.[1] Total degradation of rat peritoneal macrophages incubated with Zeolite (natural; clinoptilolite) dust particles occurred during 15- and 30-min time periods at concentrations of 1.0 and 0.5 mg/ml, respectively. Thirty-eight percent of macrophages and 57.5% of red blood cells were killed within 30 min at a Zeolite concentration of 0.25 mg/ml. In Syrian hamster and rat alveolar macrophages exposed to nontoxic concentrations of Zeolite (natural; mordenite) and other fibrous particles (positive controls), Zeolite was less active at comparable concentrations when compared to the positive controls. Compared to the positive control of crocidolite and erionite samples, non-fibrous Zeolite (natural; 5 to 100 µg/ml) incubated in Chinese hamster V79-4 and A579 cells had a much greater LD_{50} value and was nontoxic in the A549 assay.

Hemostatic Response

The ability for Zeolite (type not specified; 1/3 weight) and bentonite clay (2/3 weight) to act as a hemostatic agent was studied in 12 male Sprague-Dawley rats.[16] 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, 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 Zeolite may cause vasoconstriction and inhibition of neoangiogenesis.

DERMAL IRRITATION AND SENSITIZATION

Dermal irritation and sensitization studies summarized here are described in Table 9.

A mixture containing 28% Zeolite (unknown type) was predicted to be not irritating in an EpiSkin® in vitro MTT conversion assay.[17] In rabbit dermal irritation studies, Zeolite (synthetic; 500 mg) and another synthetic subtype of Zeolite (2000 mg/kg) were not irritating in 4-h exposure and 24-h exposure tests, respectively.[3] Zeolite (synthetic; 2000 mg/kg) was not irritating in a 24-h exposure test, nor was another synthetic subtype Zeolite (500 mg) irritating in a 4-h dermal study, both in rabbits. A Zeolite (natural; smellerite) was not irritating in a 24-h dermal irritation study in rabbits (dose/concentration not provided). In multiple dermal irritation studies of various synthetic subtypes of Zeolite in rabbits, no or mild irritation responses were noted after 4- or 24-h exposures, except in a 4-h study where sodium oxide was noted as an impurity (irritation was observed). Zeolite (synthetic; up to 660 mg/ml) was not irritating in single application patch tests in 54 human subjects. Synthetic Zeolite (3% intradermal induction, 25% topical induction, and 40% challenge) was not sensitizing in a guinea pig maximization test of 15 animals. Various synthetic subtypes of Zeolite were also not sensitizing in guinea pig studies (20 animals in each test) when the animals were induced and challenged at up to 50% of the test materials. A human patch test of a Zeolite (synthetic; details not provided) in 71 subjects and a human repeated insult patch test (HRIPT) in 53 subjects of an unspecified Zeolite at 7.907% in a mixture were not sensitizing .[3,18]

OCULAR IRRITATION STUDIES

Ocular irritation studies summarized here are described in Table 10.

No to slight ocular irritation was observed in rabbit studies of various synthetic subtypes of Zeolite at up to 100 mg (undiluted and in water).[3] Natural Zeolite (smellerite; dose/concentration not reported; in water) was not irritating in rabbit eye studies. Slight irritation was observed in the eyes of Rhesus monkeys that received Zeolite (synthetic).

CLINICAL STUDIES

Case Reports

A patient living in the Nevada desert was reported to have developed extensive pleural thickening and interstitial fibrous associated with the pulmonary deposition of Zeolite.[1] An open biopsy of the right lung and pleura was performed on the 52-yr-old man. Mycobacterial and fungal cultures were negative. Histopathological evaluation established lesions of chronic inflammation and fibrosis and presence of many fibrous and non-fibrous 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.

Occupational Exposure

In a safety assessment of synthetic Zeolites used in detergents, the researcher concluded that these ingredients are safe for consumers under the conditions of recommended use.[19] The author further stated that due to irritant effects of undiluted Zeolite on mucous membranes and the respiratory tract, the exposure of workers should be controlled.

SUMMARY

This report assesses the safety of 6 zeolite ingredients as used in cosmetics. All of these ingredients are reported to function in cosmetics as absorbents; other reported uses include cosmetic astringents, deodorant agents, light stabilizers, preservatives, skin protectants, and/or skin-conditioning agents. The Panel previously reviewed the safety of Zeolite in a report that was published in 2003; the Panel concluded that this ingredient was 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 add additional ingredients.

According to 2022 VCRP survey data, Zeolite is reported to be used in 33 formulations, with the majority of uses being in leave-on formulations. Zinc Zeolite is reported to be used in 2 rinse-off formulations. The results of the concentration of use survey conducted by the Council in 2021 indicate the maximum concentration of use for synthetic Zeolite is 0.9% in aerosol hair spray. The maximum concentration of use for natural Zeolite is 0.6% in face powders and foundations. However, a supplier reported to the Panel that synthetic Zeolite is used at up to 30% in self-heating cosmetic creams and lotions. No uses or concentrations of use were reported for Zeolite during the original safety assessment. There were no reported uses in the VCRP or the industry survey for the remaining zeolite ingredient.

The acute dermal LD_{50} for Zeolite (various synthetic subtypes and natural - smellerite) was > 16,000 mg/kg bw in studies with rabbits. Mild erythema that resolved within 4 days of application was noted in rabbits that received 2000 mg/kg bw on both intact and abraded skin.

In acute oral studies in mice of Zeolite (synthetic) and a modified zeolite described as H-mordenite, the LD_{50}s were > 10,000 mg/kg bw and > 9000 mg/kg bw, respectively, with no clinical signs of toxicity observed. One synthetic Zeolite had an oral LD_{50} > 16,520 in rats, while rats that received various subtypes of synthetic Zeolite orally had an oral LD_{50} > 32,000 mg/kg bw. An extremely low order of toxicity was observed in rats that received up to 32,000 mg/kg bw Zeolite (synthetic bonded with bentonite). Other various synthetic subtypes of Zeolite had an oral LD_{50} > 31,600 mg/kg in rat studies. An oral study of Zeolite (natural; smellerite) in rats reported an LD_{50} > 16,000 mg/kg bw. An oral study of Zeolite (synthetic) in dogs reported an LD_{50} > 1000 mg/kg bw: emesis occurred within 5 min of dosing.

In acute inhalation studies in rats, various subtypes of synthetic Zeolite had LC_{50}s > 18.3 mg/l. Mice that received Zeolite (synthetic) via a single 10 mg intraperitoneal dose, 2 different forms of cellular accumulation were observed in the omentum; however, additional formation of connective tissue or other mesenchymal activity was not induced by these accumulations. In rats that received a single intraperitoneal dose of Zeolite (synthetic; up to 50 mg) and observed up to 11 mo, treatment-related aseptic superficial inflammation of abdominal organs was observed with deposits of the test material observed in the regional lymph nodes, abdominal cavity, and mediastinum without fibrogeneous or silicogeneous. A similar study with a dose of 200 mg/kg and an observation period of up to 24 mo noted collagen fibers reticulating the alveolar macrophages 3 mo after application that were predominantly surrounded by narrow, concentric dense fibrous layers. No effects noted to local lymph nodes. Fibroid effects were reversible during the study course, so that 18 mo after treatment a progression of the effects was excluded. No treatment-related findings observed at 24 mo.

In short-term oral studies, rats that received various subtypes of synthetic Zeolite daily at up to 5000 mg/kg bw for up to 1 wk had no adverse effects. Zeolite (synthetic) at up to 10% in dietary feed in rats and dogs affected the kidneys and the urinary bladder at concentrations as low as 1% in 32 – 35-d studies. In a 13-wk dietary feed study in rats, the LOAEL for

Zeolite (synthetic) was 0.5%, with significant effects observed in bladder and reproductive tissues. A similar 13-wk study of Zeolite (synthetic) in rats had a NOAEL of 5000 ppm (0.5%) and a LOAEL of 10,000 ppm (1.0%) that resulted in effects to the kidneys and urinary bladder. In further rat dietary studies of Zeolite (synthetic) at up to 2.0%, the NOAEL was 0.125% when the animals were dosed for up to 24 wk. A 24-wk dietary study of Zeolite (synthetic) in rats had a NOAEL of 0.2%; renal pelvic epithelial hyperplasia was noted in both males and females treated with the maximum concentration tested of 0.5%. A synthetic Zeolite had a NOAEL $\geq$ 20 mg/m^3 in a 4-wk whole-body inhalation study in rats. In a 24-mo whole-body inhalation study in monkeys exposed to up to 50 mg/m^3 Zeolite (synthetic), the LOAEL was 1 mg/m^3; high-dose monkeys had nonsuppurative inflammatory reactions of the lungs and mid-dose (6 mg/m^3) monkeys had nonsuppurative bronchiolitis and alveolitis. Fibrosis was not observed in the monkeys exposed to Zeolite (synthetic).

In oral developmental studies of Zeolite (synthetic) in mice, hamsters, rats, and rabbits, the NOAEL for both maternal and fetal toxicity for all species was > 1600 mg/kg. Treatment started on gestation day 6 in these studies and lasted until day 10 – 18, depending on the species. In an oral reproductive study of Zeolite (synthetic) in male rats, the NOAEL was > 1250.8 mg/kg bw/d. The NOAEL for reproductive effects was > 50 mg/m3 in a whole-body inhalation study of Zeolite (synthetic) in male and female monkeys.

In bacterial reverse mutation assays with Salmonella typhimurium and Escherichia coli, a Zeolite described as H-mordenite (natural; up to 5 mg/plate), and various subtypes of synthetic Zeolite (up to 10 mg/plate) were negative for genotoxicity, with and without metabolic activation. Zeolite (synthetic; concentration not reported) was not mutagenic in Saccharomyces cerevisiae in a gene mutation assay with and without metabolic activation. Zeolite (synthetic) was not genotoxic in mouse lymphoma gene mutation assay at up to 0.16 mg/ml with and without metabolic activation, but chromosomal aberrations were observed in CHO cells at up to 0.4 mg/ml with and without metabolic activation. Zeolite (synthetic) was not genotoxic in human embryonic lung cells at up to 0.1 mg/ml without metabolic activation. Zeolite (synthetic) at up to 5000 mg/kg was not genotoxic in a rat bone marrow chromosome aberration test, rat dominant lethal assay, or in mouse-mediated mitotic recombination (with *S. cerevisiae*) and reverse mutation (with *S. typhimurium*) assays. Synthetic Zeolite at up to 5000 mg/kg was not genotoxic in a mouse micronucleus assay.

IARC has determined that there is insufficient evidence to classify natural and synthetic zeolites, other than erionite, as carcinogens in humans (Group 3) (The naturally occurring zeolite, erionite, is carcinogenic to humans (Group 1). In a 22 mo inhalation study of Zeolite (synthetic; 20 mg/m^3) in rats, no treatment-related tumors were observed. There was no statistically significant increase in mortality in rats that received non-fibrous erionite or synthetic Zeolite via a single 20 mg intrapleural injection; these materials were occasionally present and infrequent pleural pericardial thickening compose of macrophages with or without connective tissues were observed. When given in conjunction with crocidolite, non-fibrous erionite or synthetic Zeolite were not co-carcinogens.

The use of Zeolite (type not specified) and bentonite clay as a hemostatic agent was studied in rats with wounded skin. The researchers concluded that the test material may cause vasoconstriction and inhibition of neoangiogenesis.

A mixture containing 28% Zeolite (unknown type) was predicted to be not irritating in an EpiSkin® in vitro MTT conversion assay. In rabbit dermal irritation studies, Zeolite (synthetic; 500 mg) and another synthetic subtype of Zeolite (2000 mg/kg) were not irritating in 4 h exposure and 24 h exposure tests, respectively. Zeolite (synthetic; 2000 mg/kg) was not irritating in a 24 h exposure test, nor was another synthetic subtype Zeolite (500 mg) irritating in a 4 h dermal study, both in rabbits. A Zeolite (natural; smellerite) was not irritating in a 24 h dermal irritation study in rabbits (dose/concentration not provided). In multiple dermal irritation studies of various synthetic subtypes of Zeolite in rabbits, no or mild irritation responses were noted after 4¬- or 24 h exposures, except in a 4 h study where sodium oxide was noted as an impurity (irritation was observed). Zeolite (synthetic; up to 660 mg/ml) was not irritating in single application patch tests in human subjects. Synthetic Zeolite (3% intradermal induction, 25% topical induction, and 40% challenge) was not sensitizing in a guinea pig maximization test. Various synthetic subtypes of Zeolite were also not sensitizing in guinea pig studies when the animals were induced and challenged at up to 50% of the test materials. A human patch test of a Zeolite (synthetic; details not provided) and a human repeated insult patch test (HRIPT) of an unspecified Zeolite at 7.907% in a mixture were not sensitizing in human subjects.

No to slight ocular irritation was observed in rabbit studies of various synthetic subtypes of Zeolite at up to 100 mg (undiluted and in water). Natural Zeolite (smellerite; dose/concentration not reported; in water) was not irritating in rabbit eye studies. Slight irritation was observed in the eyes of Rhesus monkeys that received Zeolite (synthetic).

In a safety assessment of synthetic Zeolites used in detergents, the researcher concluded that these ingredients are safe for consumers under the conditions of recommended use. The author further stated that due to irritant effects of undiluted Zeolite material on mucous membranes and the respiratory tract, the exposure of workers should be controlled.

DISCUSSION

In accordance with the CIR Procedures & Support to the Expert Panel for Cosmetic Ingredient Safety, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years. In 2003, the Panel published a final report on Zeolite, and concluded that the ingredients named in that report were safe as used in cosmetic products. This report has been reopened to include additional ingredients. Thus, this current assessment reviews the safety of 6 zeolite ingredients

as used in cosmetic formulations. In this amended report, the Panel concluded that the available data are sufficient for determining the safety of these 6 zeolite ingredients as reportedly use in cosmetics.

The Panel noted that erionite is a naturally-occurring fibrous material that is carcinogenic to humans and animals, and is significantly more structurally similar to asbestos than the zeolite ingredients discussed in this report (i.e., the superstructures of the zeolites in this report comprise layered sheets, while erionite (and by comparison, asbestos) is fibrous). The Panel stressed that the cosmetics industry should continue to use current good manufacturing processes (cGMPs) to ensure erionite is not present in cosmetic formulations.

The Panel also expressed concern about the presence of heavy metals and free metal ions in zeolite ingredients. The metals in Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite are unavailable (i.e., not easily released) due to the nature of the zeolite framework. The zeolites are also not likely to absorb through the skin. Although other heavy metals may be present during mining, those should be readily avoidable/separable. Accordingly, the Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredients before blending into cosmetic formulations.

Additionally, some zeolite ingredients were reported to be used in spray and powder products that could possibly be inhaled. For example, synthetic Zeolite is reported to be used at up to 0.9% in hair spray, and natural Zeolite is reported to be used in face powders at concentrations up to 0.6%. The limited data available from inhalation studies, including acute, chronic, and carcinogenicity data, suggest little potential for respiratory effects at relevant doses. The Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the lows concentrations at which the ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. As indicated in the respiratory exposure resource document and in the Cosmetic Use section of this report, airbrush application of cosmetic products is not assessed by the Panel. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients also included in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings).

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

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

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions and reported functions of the ingredients in this safety assessment.[2]

Ingredient, CAS No.	Definition	Reported Functions
Ammonium Silver Zeolite	Ammonium Silver Zeolite is the ammonium salt of the product obtained by the cation exchange of silver nitrate and Zeolite.	Absorbent, Deodorant Agent, Preservative
Gold Zeolite	Gold Zeolite is the product obtained by the cation exchange of gold chloride with Zeolite.	Absorbent, Cosmetic Astringent, Skin Protectant, Skin-Conditioning Agent-Misc.
Silver Copper Zeolite, 130328-19-7; 168042-42-0 (generic)	Silver Copper Zeolite is the product obtained by the cation exchange of Zeolite with silver nitrate and cupric nitrate.	Absorbent, Deodorant Agent
Titanium Zeolite	Titanium Zeolite is the product obtained by the cation exchange of Zeolite with titanium tetrachloride.	Absorbent, Light Stabilizer, Skin – Conditioning Agent-Misc.
Zeolite, 1318-02-1	Zeolite is a hydrated alkali aluminum silicate.	Absorbent, Deodorant Agent
Zinc Zeolite	Zinc Zeolite is the product obtained by the cation exchange of Zeolite with zinc chloride.	Absorbent, Cosmetic Astringent, Skin Protectant, Skin – Conditioning Agent-Misc.

Table 2. Chemical properties

Property	Value	Reference
	Zeolite (synthetic – subtype A)	
Physical Form	Fine powder, paste or granulate	4,5
Color	White	4,5
Particle Size (µm)	3-5	4
Density (g/ml)	1.99	4
Melting Point (ºC)	1700	4,5
Water Solubility (mg/l)	< 10; poorly soluble	4,5
	Zeolite (synthetic - subtype P)	
Physical Form	Fine powder, paste or granulate	4
Color	White	4
Particle Size (µm)	2-3	4
Density (g/ml)	2.01	4
Water Solubility	poorly soluble	4
	Zeolite (synthetic - subtype X)	
Physical Form	Fine powder, paste or granulate	4
Color	White	4
Particle Size (µm)	3-5	4
Density (g/ml)	1.93	4
Water Solubility	poorly soluble	4

Table 3. Frequency and concentration according to duration and type of exposure for zeolite ingredients.[1,10-12]

	Zeolite				Zinc Zeolite			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2022	**1998**	**2021**	**1999**	**2022**	**NA**	**2021**	**NA**
Totals*	**33**	**NR**	**nat; 0.6 syn: 0.03-30 gen: 0.0043-0.6**	**NR**	**2**	**NA**	**NR**	**NA**
Leave-On	26	NR	0.03-30	NR	NR	NA	NR	NA
Rinse-Off	7	NR	0.0043	NR	2	NA	NR	NA
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NA	NR	NA
Eye Area	3	NR	0.6	NR	NR	NA	NR	NA
Incidental Ingestion	3	NR	NR	NR	NR	NA	NR	NA
Incidental Inhalation-Spray	4; 6[a]; 3[b]	NR	0.25-0.9	NR	NR	NA	NR	NA
Incidental Inhalation-Powder	1; 3[b]	NR	0.6; 0.03[c]	NR	NR	NA	NR	NA
Dermal Contact	18	NR	0.0043-30	NR	1	NA	NR	NA
Deodorant (underarm)	NR	NR	NR	NR	NR	NA	NR	NA
Hair - Non-Coloring	12	NR	0.25-0.9	NR	1	NA	NR	NA
Hair-Coloring	NR	NR	NR	NR	NR	NA	NR	NA
Nail	NR	NR	NR	NR	NR	NA	NR	NA
Mucous Membrane	3	NR	NR	NR	1	NA	NR	NA
Baby Products	NR	NR	NR	NR	NR	NA	NR	NA

NR = Not reported. NA = Not applicable.

*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.

nat = naturally-sourced Zeolite, reported to be used at 0.6% in face powders and foundations.

syn = synthetically made Zeolite, reported to be used at 0.9% in a hair spray, 0.42-0.5% in foundations, 0.03% in body and hand skin care preparations, and 30% in self-heating creams and lotions.

gen = source unknown (generic), reported to be used at 0.6% in other eye makeup preparations, 0.25% in a hair spray, and 0.0043% in skin cleansing preparations.

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

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

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

Table 4. Ingredients not reported to be in use.[10,11]

Ammonium Silver Zeolite	Gold Zeolite
Silver Copper Zeolite	Titanium Zeolite

Table 5. Acute toxicity studies[3]

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results
DERMAL					
Zeolite (synthetic)	Female New Zealand White rabbits	10	Not reported	2000 mg/kg bw; skin abraded in 5 animals and all patches were occluded; 24 h exposure; in accordance with OECD TG 402	> 2000 mg/kg bw; no deaths or adverse skin reactions observed; body weight gains within normal parameters; no abnormalities at necropsy
Zeolite (synthetic)	Male and female New Zealand White rabbits	5 per sex	Water	16,000 mg/kg bw; skin was clipped and intact and all patches were occluded; 24 h; test sites observed for 14 d post-dosing	> 16,000 mg/kg bw; 1 male rabbit died during study with no signs of toxicity, necropsy showed dark pink lungs; no other deaths or signs of toxicity observed in the remaining rabbits; one female rabbit had white foci on the kidneys (no further details provided)
Zeolite (synthetic)	New Zealand Albino rabbits (no further details provided)	10	Not reported	2000 mg/kg; skin abraded in 5 animals and all patches were occluded; 24 h exposure; animals were observed for mortality for up to 48 h; in accordance with Department of Transportation 49CFR173	> 2000 mg/kg bw; no deaths or adverse skin reactions observed (no further details provided)
Zeolite (synthetic)	Male and females New Zealand White rabbits	3 per sex	Not reported	2000 mg/kg; skin abraded in 3 animals and all patches were occluded; 24 h exposure; test sites observed for 14 d post-dosing	> 2000 mg/kg bw; no deaths observed; mild erythema on both abraded and intact sites at 24 h that resolved by day 4
Zeolite (natural - smellerite)	Male and female New Zealand White rabbits	5 per sex	Water	2000 mg/kg bw; 24 h exposure; standard acute method	> 2000 mg/kg bw; no adverse skin reactions; 1 male that died after day 4, had red discharge from perinasal area and necropsy showed mottled, light to dark pink lungs; no other deaths; 1 female had diarrhea at the end of the observation period and a liquid-filled stomach and gas-filled intestines at necropsy; 1 other female had dark red lungs at necropsy but no clinical signs
ORAL					
Zeolite (natural - H-mordenite)	Male and female ICR mice	5 per sex	gum Arabic (250 mg/ml suspension)	6250, 7500, or 9000 mg/kg via gavage; in accordance with OECD TG 401	> 9000 mg/kg bw; no deaths or clinical signs of toxicity observed; body weight gains within normal parameters; no abnormalities at necropsy.
Zeolite (synthetic)	Male CF-2 mice	10	Water	10,000 mg/kg bw; via gavage; performed following the Henkel-Limit TG (no further details provided)	> 10,000 mg/kg bw; no mortalities or sign of toxic effects were observed
Zeolite (synthetic)	Male and female Wistar Bor:WISW (SPFTNO) rats	5 per sex	0.5% carboxymethylcellulose solution	5110 mg/kg bw via gavage with a volume of 21.5 ml/kg; in accordance with OECD TG 401	> 5110 mg/kg bw; no deaths or clinical signs of toxicity observed; body weight gains within normal parameters; no abnormalities at necropsy
Zeolite (synthetic)	Male and female Cox CD rats	10 per sex	Water	3070, 6020, or 16,520 mg/kg (no further details provided)	> 16,520 mg/kg bw; no mortalities; moderate symptoms observed at the 2 and 4 h observation period in the high dose group; 24 h after dosing 3 rats had slight to moderate hemorrhagic rhinitis (no further details provided); no abnormalities observed at necropsy
Zeolite (synthetic)	Male and female Sprague-Dawley rats	5 per sex	Tested as a 20% solution (no further details provided)	5000 mg/kg bw; performed following the Comparable to Limit TG (no further details provided)	> 5000 mg/kg bw (no further details provided)
Zeolite (2 synthetic forms)	Male Wistar-derived rats	Not reported	Agar	4000, 16,000, or 32,000 mg/kg bw; via gavage (no further details provided)	> 32,000 mg/kg bw (no further details provided)
Zeolite (synthetic)	Male Wistar-derived rats	5 in high dose group, 3 each in middle and low dose groups	Agar	4000, 16,000, or 32,000 mg/kg bw; via gavage (no further details provided)	> 32,000 mg/kg bw (no further details provided)
Zeolite (synthetic bonded to bentonite)	Male Wistar-derived rats	5 in high dose group, 3 each in middle and low dose groups	Agar	4000, 16,000, or 32,000 mg/kg bw; via gavage (no further details provided)	Extremely low order of toxicity (no further details provided)

Table 5. Acute toxicity studies[3]

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results
Zeolite (synthetic)	Male and female Sprague-Dawley rats	5 per sex	Arachis oil	2000 mg/kg bw via gavage; in accordance with OECD TG 401	> 2000 mg/kg bw; 1 female killed in extremis on day 6 that had hunched posture, lethargy, decreased respiration, and many other signs of toxicity, and at necropsy, hemorrhagic lungs, dark liver and kidneys, and hemorrhage of the intestines were noted; no other rats had signs of systemic toxicity or abnormalities at necropsy; surviving rats had expected body weight gains
Zeolite (synthetic)	Male and female Sprague-Dawley rats	5 per sex	0.5% methylcellulose	2000 mg/kg bw via gavage with a volume of 10 ml/kg; in accordance with OECD TG 401	> 2000 mg/kg bw; no deaths observed; no effects on general behavior or body weight gains; no abnormalities at necropsy
Zeolite (synthetic)	Male and female Sprague-Dawley rats	5 per sex	Not reported	3980, 6320, or 10,000 mg/kg in range finding study and 31,600 mg/kg in main study; via gavage; in accordance with Department of Transportation 49CFR173	> 31,600 mg/kg bw; no deaths or abnormal behavior observed; no macroscopic changes observed in viscera
Zeolite (synthetic)	Male and female Bor:WISW (SPFCpb) rats	5 per sex	1% carboxymethyl cellulose	5110 mg/kg bw via gavage with a volume of 21.5 ml/kg bw; in accordance with OECD TG 401	>5110 mg/kg bw; no deaths or signs of toxicity observed; body weight gains within normal parameters; no abnormalities at necropsy
Zeolite (synthetic)	Male and female Sprague-Dawley rats	5 per sex	Water	16,000 mg/kg via gavage; animals observed for 14 d after dosing; necropsy performed at study end	> 16,000 mg/kg bw; no deaths or clinical signs of toxicity observed; no abnormalities at necropsy
Zeolite (synthetic)	Male Sprague-Dawley rats	5 in first trial, 10 in second trial	0.85% saline	10, 100, 500, 1000, 2000, or 5000 mg/kg in first trial and 5000 mg/kg in second trail; performed via gavage	1050 mg/kg bw in first trial; > 5000 mg/kg bw in second trial; 3 or more deaths occurred at 1000 mg/kg or greater in first triall, with dark patches in the intestine and distended stomachs; no deaths or clinical signs of toxicity in the second trial, no gross findings at necropsy
Zeolite (synthetic)	Male and female Cox-SD rats	5 per sex	Water	7100, 14,000, or 27,400 mg/kg bw; in accordance with OECD TG 401	> 27,400 mg/kg bw; no deaths observed; decreased motor activity noticed in higher dose groups; body weight gains within normal parameters; moderate to severe congestion of the liver, kidneys, and adrenal glands (no further details provided)
Zeolite (natural - smellerite)	Male and female Sprague-Dawley rats	5 per sex	In 50% suspension with distilled water	16,000 mg/kg bw via gavage with a volume of 7.0-7.3 ml; because large volumes required, doses were divided into 2 portions administered at least 1 h apart; animals observed for 14 d after dosing; necropsy performed at study end	> 16,000 mg/kg bw; no deaths or clinical signs of toxicity observed; body weight gains within normal parameters; no abnormalities at necropsy
Zeolite (synthetic)	Male and female dogs (no further details provided)	1 per sex	Water	1000 mg/kg bw (no further details provided)	> 1000 mg/kg bw; emesis occurred within 5 min of dosing (no further details provided)
INHALATION					
Zeolite (synthetic)	Male Sprague-Dawley rats	10	Air	2.8 mg/l (mean measured); whole body exposure for 1 h followed by 14 d observation period; necropsy at study end	> 2.8 mg/l; no deaths or signs of toxicity observed; body weight gains within normal parameters; increased incidence of pulmonary abnormalities (no further details provided)
Zeolite (synthetic)	Male Sprague-Dawley rats	10	Air	2.3 mg/l (mean measured); whole body exposure for 1 h followed by 14 d observation period; necropsy at study end	> 2.3 mg/l; no deaths or signs of toxicity observed; body weight gains within normal parameters (no further details provided)
Zeolite (synthetic)	Male and female rats (no further details provided)	5 per sex	Air	3.35 mg/l; whole body exposure for 4 h; 14 d observation post-dosing; necropsy at study end	>3.35 mg/l; no deaths or signs of toxicity observed; no abnormalities at necropsy
Zeolite (synthetic)	Male Sprague-Dawley rats	10	Air	2.4 or 18.3 mg/l; 1 h exposure (no further details provided	> 18.3 mg/l; no deaths or signs of toxicity observed; body weight gains within normal parameters; no abnormalities at necropsy

Table 5. Acute toxicity studies[3]

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results
Zeolite (synthetic)	Male Sprague-Dawley rats	10	Air	0.08 or 0.14 mg/l; whole body exposure for 4 h followed by 14 d observation period; ophthalmoscopic examination and necropsy performed at study end	> 0.14 mg/l; no deaths or signs of toxicity; body weight gains within normal parameters; no abnormalities observed in ophthalmoscopic examinations or at necropsy
			PARENTERAL		
Zeolite (synthetic)	Male mice; strain not reported	Not reported	Tyrode solution	Single intraperitoneal dose; 0 or 10 mg/animal; quartz DQ 12 was positive control; mice observed for 3, 6 or 18 mo; animals killed at each time period underwent necropsy and histopathologic examination	For mice receiving Zeolite, 2 different forms of cellular accumulation observed in the omentum, additional formation of connective tissue or other mesenchymal activity not induced by these accumulations; spots of connective tissue occurred on the parenchymatous organs, especially the spleen, but substantial deposits observed only on the spleen
Zeolite (synthetic)	Male Wistar rats	20	Tyrode solution	Single intraperitoneal dose; 1, 2.5, 5, 10, or 50 mg/animal; animals observed for 3, 6, or 11 mo; 5 animals each in the 3 and 6 mo time period and 10 animals in the 11 mo time period were killed and underwent necropsy and macroscopic and histopathologic examinations; quartz DQ 12 was positive control	Absolute increase in organ weight observed in all test groups when compared to positive control; treatment-related aseptic superficial inflammation of abdominal organs observed; deposits of the test material were observed in the regional lymph nodes, abdominal cavity, and mediastinum without fibrogeneous or silicogeneous, these effects were reversible at 11 m except for the 50 mg dose group
Zeolite (synthetic)	Male Wistar rats	134 total used in treatment, positive and negative controls	Not reported	Single intraperitoneal dose; 200 mg/kg bw; animals daily observed up to 2 yr; rats killed at 3, 6, 18 or 24 mo after dosing; gross observation performed on all rats and histopathological examinations observed in 3 rats/ treatment group; body weights measured weekly for 77 wk, then monthly; positive (quartz) and negative (not reported) controls used	After 2 years, mortality rates were 2.5% for negative control, 15% for Zeolite, and 10% for quartz; no behavioral abnormalities observed in rats treated with Zeolite; mesenteric fat deposits were observed in both the negative control and Zeolite groups 3 mo post-dosing; at 18 mo post-dosing, no differences in Zeolite treated mesenteries concerning weight and fat deposits when compared to negative control; 3 mo after application in rats treated with Zeolite, small deposits were observed in the greater omentum (collagen fibers reticulating the alveolar macrophages) that were predominantly surrounded by a narrow, concentric dense fibrous layer; local lymph nodes revealed no effects; fibroid effects were reversible during the study course, so that 18 mo after treatment a progression of the effects was excluded; no Zeolite related findings observed at 24 mo
Zeolite (2 synthetic forms)	Male Sprague-Dawley rats	10	Water	Single intratracheal administration; up to 300 mg/ml in 1 ml; 14 d observation period	12-40 mg/kg bw; in the first material, 4/10 animals died at 50 mg/ml, 2/10 died at 100 mg/ml and all animals died at 300 mg/ml; in the second material, 9/10 animals died at 10 mg/ml and all animals died at higher doses; body weight gains were within normal parameters in the second group; in the second group, only one animal had lung abnormalities at 3 mg/ml (no further details provided)

Table 6. Repeated dose toxicity studies[3]

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results
			ORAL		
Zeolite (synthetic)	5 male Sprague-Dawley rats	5 d	28.5% (w/v) in 0.85% saline	5000 mg/kg bw once daily via gavage; observed for deaths and clinical signs of toxicity for 14 d; necropsy performed	LD_{50} > 5000 mg/kg bw/d; no deaths observed; slight signs of rough fur, reduced activities, and pale appearing feces observed; no abnormalities observed in gross pathology
Zeolite (synthetic)	5 male and 5 female Wistar rats per dose group	7 d	Dietary feed	0, 800, 2000, or 5000 mg/kg/d; animals observed daily for signs of toxicity and weighed 3 times during the week; necropsy performed at study end	NOAEL > 5000 mg/kg bw/d; no deaths or clinical signs of toxicity observed; body weight gains within normal parameters; no effects observed on organ weights
Zeolite (synthetic)	10 male and 10 female Wistar rats per dose group	32 d	Dietary feed	0%, 1%, 3%, or 10%; animals observed daily for signs of toxicity; body weight recorded 7 times during study; feed consumption recorded; hematological and clinical biochemistry studies performed; urinalysis performed on high dose group; necropsy and histopathological evaluation performed	One death occurred in the 3% dose group after 18 doses; no effects observed on feed consumption; body weight gains were significantly decreased in treated groups; water consumption was increased in treated groups; urinary pH and volume was high in both sexes of the treated groups, while urine specific gravity was decreased in treated males; grossly yellow pustules on kidneys observed in 1 female of the 3% dose group and in 2 males and 3 females in the 10% dose group; interstitial nephritis observed in 6 males and 5 females in 10% dose group and 2 males and 2 females in 3% dose group; transitional hyperplasia of the urinary bladder was observed in 2, 6, and 4 males in the 1%, 3%, and 10% dose groups, respectively and in 1 female in the 10% dose group
Zeolite (synthetic)	3 male and 3 female Beagle dogs per dose group	5 wk	Dietary feed	0%, 1%, 3%, or 10%; dogs were killed for necropsy and histopathological evaluation 36 d after the last dose; hematological, clinical biochemistry evaluations performed; urinalysis performed	No deaths or clinical signs of toxicity observed; no effects on feed consumption; water consumption of the 3% and 10% dose groups greater than control; urine volumes of the 3% males and 10% males and females greater than compared to controls; urine specific values decreased in 3% males and in both sexes in the 10% dose group; urine pH values of the 3% and 10% dose groups were increased compared to controls; body weight gains of the 10% males were statistically significantly lower than controls; increased kidney weight compared to % body weight in the 10% females, increased blood urea nitrogen values in 10% males, increased % of monocytes of the 3% an 10% males, and a decreased % of eosinophils in the 1% and 3% females were significant compared to controls; interstitial nephritis present in all dogs in the 10% dose group, in all males and 2/3 females of the 3% dose group, and in 1 male of the 1% dose group; thickened walls of the urinary bladder observed in 2/3 females of the 3% dose group and in 2/3 males and 2/3 females in the 10% dose group; tiny calculi observed in the urinary bladder of 3/3 males in the 3% dose group and 2/3 males in the 10% dose group
Zeolite (synthetic)	20 male and female Cox-SD rats per dose group	91 d (13 wk), with some rats killed on day 163	Dietary feed	0%, 0.5%, 1.0%, or 2.0%; animals observed daily for deaths and signs of toxicity; body weight and feed consumption recorded weekly; urinalysis, hematological, and clinical biochemistry studies performed; animals killed on day 28 (5/sex/group) and day 91 (5/sex/group), remaining killed on day 163; necropsy performed	LOAEL = 0.5%; 4/20 rats in high dose group died before day 91 compared to 2/20 in control group no clinical signs of toxicity observed; body weight gains and feed consumption within normal parameters; no effects observed on hematology, clinical biochemistry, or urinalysis; no effects observed on organ weights; bladder stones were observed in the high dose group; in 2 males that died in the high dose group, significant pathology occurred in the bladder and reproductive tissue; because of the bladder lesions, remaining animals were continued until day 163; in rats that were killed on day 163, bladder stones were noted in 1 male each of the low- and mid-dose groups and 3 males in the high-dose group; no significant histological findings reported in the animals that were killed on day 163 that were treatment-related

Table 6. Repeated dose toxicity studies[3]

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results
Zeolite (synthetic)	20 male and 20 female Wistar rats per dose group	90 d	Dietary feed	0, 1000, 5000, or 10,000 ppm (0, 50-60, 250-300, or 500-600 mg/kg bw/d, corresponding to 0%, 0.1%, 0.5%, or 1.0%, respectively); Henkel-method; animals observed daily for mortality and signs of toxicity; body weight and feed consumption recorded weekly; urinalysis, blood chemistry, and hematology performed; necropsy performed at study end	NOAEL = 5000 ppm, LOAEL = 10,000 ppm; no deaths or clinical signs of toxicity observed; body weight gains and feed consumption within normal parameters; no effects observed on blood chemistry or hematology; diminished urine secretion, hematuria, and ketone bodies in the urine of the 10,000 ppm dose group, with 12/20 males having urinary calculi in the bladder in addition to bladder wall thickening; in the 10,000 ppm dose group, hyperplastic reaction of the transitional epithelium was observed in the rats with calculi
Zeolite (synthetic)	40 male Cox-SD rats per dose group	160 or 200 d	Dietary feed	0%, 0.125% or 2.0% (0, 75.14, or 1250.79 mg/kg bw/d); animals observed daily for mortality and signs of toxicity; body weight and feed consumption recorded weekly; urinalysis and bacteriological evaluation performed; whole body X-rays made on day 90 in surviving animals to evaluate genital urinary system; representative animals selected at random and killed on day 160, remaining animals killed on day 200; gross pathology and necropsy performed	NOAEL = 0.125% (75.14 mg/kg bw/d); no effects were observed in body weight gains, feed consumption, or urinalysis; no gross signs of adverse systemic effects were observed; no signs of urinary infection in bacterial evaluation; a significant increase in bladder and kidney stones were observed in the high dose group; histological changes in kidneys and bladders found in the high dose group but not the low dose group; microscopic alterations observed in kidneys; an increase in the incidence and severity of transitional epithelial hyperplasia was observed in the bladder; no detectable alterations observed in X-rays
Zeolite (synthetic)	male and female Long-Evans rats; number per dose group not provided	24 wk	Dietary feed	0%, 0.125%, 0.5%, or 2.0%; animals observed daily for deaths and signs of toxicity; body weight and feed consumption recorded weekly; urinalysis performed at weeks 13 and 24; necropsy and histopathological evaluation performed	NOAEL = 0.125%, LOAEL = 0.5%; no deaths or clinical signs of toxicity observed; feed consumption within normal parameters; body weight gains were slightly decreased in high dose males between weeks 6-15; when compared to controls, alterations in urinalysis parameters occurred in both sexes of the high dose group; high dose males had a low incidence of urinary crystals at 24 wk and a slight increase in leukocytes in the urine at 13 wk; dose-dependent alterations in kidneys observed including interstitial nephritis, regenerative epithelium, tubular degeneration and necrosis, purulent pyelonephritis, pelvic epithelial hyperplasia, and crystals in the tubules or lumen of the pelvis; no treatment-related microscopic alterations observed in ureters or bladders of the treated rats
Zeolite (synthetic)	20 male and 20 female Wistar rats per dose group	24 wk	Dietary feed	0%, 0.05%, 0.1%, 0.2%, or 0.5%; animals observed daily for signs of toxicity; feed consumption and body weight recorded "regularly"; urinalysis performed on days 60, 120, and 160; necropsy and histopathological evaluation performed	NOAEL = 0.2%; no deaths or clinical signs of toxicity observed; feed consumption and body weight gains were within normal parameters; dose-related increase in total silicon mean mass and mean concentration noted in urine; no treatment-related stone formations observed in urinary tracts of either sex in any dose group; treatment-related crystals observed in the renal pelvis in high dose group; 6 males and 10 females in the high dose group had renal pelvic epithelial hyperplasia
INHALATION					
Zeolite (synthetic)	25 male Wistar rats per dose group	4+ wk (13 exposures total)	air	0 or 20 mg/m^3 whole-body inhalation; rats exposed 5 h/d, 3d/wk for total of 13 exposures; body weight recorded and necropsy performed with macroscopic evaluations (no further details provided)	NOAEL = > 20 mg/m^3; no treatment-related effects noted; body weight gain within normal parameters; no macroscopic changes in inner organs; significant increase in silica content of lungs observed (no further details provided)

Table 6. Repeated dose toxicity studies[3]

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results
Zeolite (synthetic)	3 male and 3 female *Macaca fascicularis* monkeys per dose group	24 m	air	0, 1, 6, or 50 mg/m^3 whole-body inhalation; monkeys exposed 6 h/d, 5d/wk in 6000 l glass chambers with an airflow of 1000 l/min; positive control was 50 mg/m^3 quartz dust; interim killing at 6 and 12 m; positive control and high dose group discontinued after 55 wk; 3 m recovery for some monkeys at study end; physical examinations monthly until study end; pharmacotoxic signs recorded daily; hematological and serum chemistry evaluations and urinalysis tri-monthly until study end; necropsy and histopathological evaluation performed	LOAEL = 1 mg/m^3; 2 monkeys killed at 6 m due to broken arms; no treatment-related effects on body weight gain, hematology, serum chemistry, urinalysis, ophthalmic parameters, or organ/body weight ratios at any dose group; treatment-related histo-morphological changes not observed in upper airways or in any non-respiratory tract organs examined; no evidence of progressive pulmonary fibrosis observed; dose-related nonsuppurative inflammatory reactions observed in animals of all dose groups that diminished in severity in the mid and high dose group; in 1 mg/m^3 dose group, these effects were not evident after the 90-day recovery period; fibrosis observed in the quartz positive control group. -high dose group had some focal nonsuppurative inflammatory reactions of the lungs after 29 and 55 wk of exposure which were not completely resolved in individual monkeys after a 90-d recovery (sporadic inflammatory changes in one monkey after 29-wk of exposure, little change other than macrophage accumulation after the last exposure at 55 wk; however, 3 m after exposure 1/3 monkeys had multifocal to diffuse nonsuppurative bronchiolitis and alveolitis; the other 2 monkeys exposed for 55 wk and held 3 m had no treatment-related inflammatory response to the macrophage accumulations). -mid-dose group had free alveolar and septal wall macrophages after 26 wk, with similar macrophage accumulations after 52 and 104 wk; sporadic nonsuppurative bronchiolitis and alveolitis observed in the lungs of 3/6 monkeys exposed for 52 wk and 1 monkey exposed for 104 wk; changes were not completely reversed after the recovery period in 2/4 monkeys; no treatment-related inflammatory reaction observed after the recovery period in the 2 other monkeys. -low dose group had free alveolar and septal wall macrophage accumulations after 26, 52 and 104 wk; sporadic areas of nonsuppurative bronchiolitis and alveolitis observed in lungs of 3/4 monkeys; following the recovery period, primarily macrophage accumulations without any inflammatory response observed; sporadic non-suppurative inflammatory reactions, which occurred in individual monkeys after 104 wk, were not evident after the recovery period.

Table 7. DART studies[3]

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results
			ORAL		
Zeolite (synthetic)	Female CD-1 mice; number/group not reported	Not reported	0. 16, 74.3, 345, or 1600 mg/kg	Developmental toxicity study in accordance with OECD TG 414; mated female mice received test material daily via gavage on gestation days 6-15 and were killed on day 17; animals observed daily for clinical signs of toxicity and feed consumption; Caesarean section performed on day 20 and number of implantation sites, resorption sites, and live and dead fetuses recorded; body weights of live pups recorded; all fetuses underwent gross examinations, 1/3 of each litter underwent visceral examinations and 2/3 of each litter underwent skeletal examinations	NOAEL for both maternal and fetal toxicity ≥ 1600 mg/kg bw/day; no maternal toxic effects observed; no embryotoxic or teratogenic effects observed
Zeolite (synthetic)	Female Syrian hamsters; number/group not reported	Not reported	0. 16, 74.3, 345, or 1600 mg/kg	Developmental toxicity study in accordance with OECD TG 414; mated female rats received test material daily via gavage on gestation days 6-10 and were killed on day 14; observations and examinations performed in a similar manner as described above	NOAEL for both maternal and fetal toxicity ≥ 1600 mg/kg bw/day; no maternal toxic effects observed; no embryotoxic or teratogenic effects observed
Zeolite (synthetic)	Female Wistar rats; number/group not reported	Not reported	0. 16, 74.3, 345, or 1600 mg/kg	Developmental toxicity study in accordance with OECD TG 414; mated female rats received test material daily via gavage on gestation days 6-15 and were killed on day 20; observations and examinations performed in a similar manner as described above	NOAEL for both maternal and fetal toxicity ≥ 1600 mg/kg bw/day; no maternal toxic effects observed; no embryotoxic or teratogenic effects observed
Zeolite (synthetic)	Female Dutch rabbits; number/group not reported	Not reported	0. 16, 74.3, 345, or 1600 mg/kg	Developmental toxicity study in accordance with OECD TG 414; rabbits artificially inseminated and injected with human chorionic gonadotropin on day 0; test material given daily via gavage on gestation days 6-18 and rabbits were killed on day 29; observations and examinations performed in a similar manner as described above	NOAEL for both maternal and fetal toxicity ≥ 1600 mg/kg bw/day; no maternal toxic effects observed; no embryotoxic or teratogenic effects observed
Zeolite (synthetic)	Groups of 40 male COX-SD rats	Diet	0%, 0.125%, or 2.0%	Animals received treatment daily for 160 or 200 d; animals observed daily for clinical signs of toxicity and mortality; feed consumption and body weights recorded weekly; urinalysis performed; whole body X-ray taken at day 90; males selected at random and killed on day 160 while remaining animals continued with daily treatment; at study end, gross pathology and necropsy performed with special attention on the urogenital system	NOAEL ≥ 2.0% (1250.79 mg/ kg bw/d); no treatment-related effects observed in testes; body weights, body weight gains, and feed consumption comparable to the controls; no clinical signs of toxicity
			INHALATION		
Zeolite (synthetic)	3 male and 3 female *Macaca fascicularis* monkeys per dose group	Air	0, 1, 6, or 50 mg/m^3	Whole body inhalation study (see Repeated Dose Toxicity Studies above); monkeys exposed 6 h/d, 5d/wk for 24 m in 6000 l glass chambers with an airflow of 1000 l/min; positive control was quartz dust; interim killing at 6 and 12 m; necropsy and histopathological evaluations included study of the gonads	NOAEL ≥ 50 mg/m^3; no treatment related changes observed in the male or female genital organs (see Repeated Dose Toxicity Studies above for other results)

Table 8. Genotoxicity studies[3]

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results
			IN VITRO		
Zeolite (synthetic)	0.0003, 0.0033, 0.033, 0.1, 0.33, 1.0, 3.3, or 10 mg/plate	0.067 M potassium phosphate buffer	*S. typhimurium* TA98, TA100, TA1335, TA1537, TA1538 or *E. coli* WP2 (uvrA); target gene: his operon	Bacterial reverse mutation assay in accordance with OECD TG 471, with and without S9 metabolic activation; positive and negative controls used	Negative with no cytotoxicity; controls gave expected results
Zeolite (synthetic)	Microdrop of a solution of 0.01 to 0.25 ml or small crystal; no further details provided	Vehicle not described	*S. typhimurium* TA`530 and G-46	Bacterial reverse mutation assay without S9 metabolic activation; positive control used	Negative; no further details provided
Zeolite (synthetic)	Not reported	Vehicle not described	*Saccharomyces cerevisiae* D-3	Gene mutation assay without metabolic activation; positive and negative controls used; no further details provided	Negative; 0, 0.001, and 0.01 dose groups had 2%, 1%, and0% acentric fragments, respectively; the high dose group had1% acentric fragments with 1% bridge, which was not considered significant; positive controls gave expected results
Zeolite (natural: H-mordenite)	0.156, 0.313, 0.625, 1.25, 2.5, or 5 mg/plate	Distilled water	*S. typhimurium* TA98, TA100, TA1335, TA1537, or *E. coli* WP2 (uvrA)	Bacterial reverse mutation assay, with and without S9 metabolic activation; positive and negative controls used	Negative with no cytotoxicity; controls gave expected results
Zeolite (synthetic)	Range finder: 0.008 - 5 mg/plate Exp 1 with and without S9: 0.00032, 0.00016, 0.0008, 0.004, 0.02 and 0.1 mg/plate Exp 2 with S9: 0.00009766, 0.00039063, 0.0015625, 0.00625, 0.025 and 0.1 mg/plate Exp 2 without S9 in TA98 and TA 100: 0.00003906, 0.00015625, 0.000625, 0.0025 and 0.01 mg/plate Exp 2 without S9 in all other strains: 0.00007813, 0.0003125, 0.00125, 0.005 and 0.02 mg/plate	Dimethyl sulfoxide	*S. typhimurium* TA98, TA100, TA102, TA1335, TA1537	Bacterial reverse mutation assay in accordance with OECD TG 471, with and without S9 metabolic activation; positive and negative controls used	Negative; cytotoxicity observed at the 2 highest test concentrations without S9 and only at the highest test concentration with S9; controls gave expected results
Zeolite (synthetic)	Exp 1 without S9 = up to 0.04 mg/ml Exp 1 with S9 = up to 0.16 mg/ml Exp 2 without S9 = up to 0.025 mg/ml Exp 2 with S9 = up to 0.09 mg/ml	Vehicle not described; however, study notes test material was poorly soluble and undissolved material was observed at all test concentrations	Mouse lymphoma L5178Y cells; target gene: tk locus	Mammalian cell gene mutation assay in accordance with OECD TG 476, with and without S9 metabolic activation; positive and negative controls used	Negative; cytotoxicity observed above 0.02 mg/ml without S9 and above 0.08 mg/ml with S9; controls gave expected results
Zeolite (synthetic)	Without S9: between 0.0275 and 0.0725 mg/ml With S9: between 0.164 and 0.4 mg/ml	Vehicle not described; however, study notes test material was poorly soluble and undissolved material was observed at all test concentrations	CHO cells	Mammalian chromosome aberration test in accordance with OECD TG 473, with and without S9 metabolic activation; positive and negative controls used	Positive; cytotoxicity observed; increased frequencies of cells with aberrations at medium and high doses, with and without S9
Zeolite (synthetic)	0.001, 0.01, or 0.1 mg/ml	0.85% saline	Human embryonic lung cells (Wi-38)	Cytogenetic assay; without metabolic activation	Negative; cytotoxicity greater than 0.1 mg/ml; 0, 0.001, and 0.01 dose groups had 2%, 1%, and0% acentric fragments, respectively; the high dose group had1% acentric fragments with 1% bridge, which was not considered significant; positive controls gave expected results

Table 8. Genotoxicity studies[3]

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results
			IN VIVO		
Zeolite (synthetic)	0, 4.25, 42.5, 425, or 5000 mg/kg	0.85% saline	Groups of 5 male Sprague-Dawley rats	Mammalian bone marrow chromosome aberration test in accordance with OECD TG 475; rats received test material via oral gavage; positive and negative controls used	Negative; negative controls and the treated groups were within normal limits of break observed; mitotic indices were slightly but not significantly depressed, number of mitotic indices were comparable to negative controls in remaining test group; positive control gave expected results
Zeolite (synthetic)	0, 4.25, 42.5, 425, or 5000 mg/kg	0.85% saline	Groups of up to 10 male rats; strain not specified; each male was mated with 2 virgin females/wk for 8 wk	Rodent dominant lethal assay in accordance with OECD TG 478; male rats received test material via a single oral gavage treatment; time between dosing and mating was not reported; female rats were killed at day 14 after separating and the uteri were studied for early death, late fetal death, and total implantations; positive and negative controls used	Negative; no dose- or time-related effects indicating a potential for inducting dominant lethal mutations observed; significant decreases in average corpora lutea and pre-implantation losses were observed in the 4.25, 42.5, or the 425 mg/kg treatment groups at weeks 4 and 5, the average resorption in these treatment groups showed a significant increase at week 3; in the 5000 mg/kg dose group, these values did not vary from the negative controls (no further details provided)
Zeolite (synthetic)	0, 4.25, 42.5, 425, or 5000 mg/kg	0.85% saline	Groups of 10 male ICR mice hosting *Saccharomyces cerevisiae* D-3	Host mediated mitotic recombination; mice received test material via oral gavage 5 times at 24-h intervals; following dosing, mice received 2 ml intraperitoneal injection of exponential log-phase growing yeast; mice killed 3 h after last dosing and yeast cells were removed from peritoneal cavity and plated; positive and negative controls used	Negative; controls gave expected results
Zeolite (synthetic)	0, 4.25, 42.5, 425, or 5000 mg/kg	0.85% saline	Groups of 10 male ICR mice hosting *S. typhimurium* strain TA1530	Host mediated reverse mutation assay; mice received test material via oral gavage 5 times at 24-h intervals; following dosing, mice received 2 ml intraperitoneal injection of exponential log-phase growing bacteria and his G-46; mice killed 3 h after last dosing and bacterial cells were removed from peritoneal cavity and plated; positive and negative controls used	Negative; controls gave expected results
Zeolite (synthetic)	0, 1250, 2500, or 5000 mg/kg	0.5% methylcellulose	Groups of 5 male and 5 female Swiss mice	Micronucleus assay in accordance with OECD TG 474; mice received test material via oral gavage 4 times at 24-h intervals; positive and negative controls used	Negative; in males, mean values of micronucleated polychromatic erythrocytes (MPE) in treated groups were comparable to negative control group; in the 5000 mg/kg dose group males, the polychromatic and normochromatic erythrocyte (PCE/NCE) ratio was significantly lower ($p < 0.05$) when compared to the negative control group, showing that the bone marrow cells were effectively exposed to the test substance; for females, mean values of MPE as well as PCE/NCE ratio in treated groups were comparable to the negative control group and no significant difference was observed; controls gave expected results

Table 9. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IRRITATION		
			IN VITRO		
Zeolite (unknown type)	28% in a mixture	EpiSkin® reconstructed human epidermis model	MTT conversion assay (in vitro primary cutaneous tolerance)	Predicted to be not irritating; mean % viability 95.4	[17]
			ANIMAL		
Zeolite (synthetic)	500 mg moistened with 0.25 ml demineralized water	3 rabbits; further details not provided	4 h exposure; occluded patch on shaved skin; sites observed for 72 h; in accordance with OECD TG 404	Not irritating; no cutaneous reactions observed during study; primary dermal irritation index (PDII) = 0; no systemic effects observed	[3]
Zeolite (synthetic)	2000 mg/kg; vehicle not provided	10 rabbits; further details not provided	24 h exposure; semi-occluded patch on shaved skin; test sites were abraded in 5 animals and intact in the remaining 5; sites observed for 14 d; in accordance with OECD TG 404	Not irritating; slight erythema in 3/5 intact rabbits until day 2; erythema in 3/5 abraded rabbits with it persisting until day 7 in one animal	[3]
Zeolite (synthetic)	2000 mg/kg; vehicle not provided	10 rabbits; further details not provided	24 h exposure; occluded patch on shaved skin; test sites were abraded in 5 animals and intact in the remaining 5; sites observed 48 h; in accordance with Department of Transportation 49CFR173	Not irritating; no cutaneous reactions or deaths observed during the study; PDII = 0	[3]
Zeolite (synthetic)	500 mg in water	6 Japanese White rabbits; sex not provided	4 h exposure; occluded patch on shaved skin; sites observed for 96 h	Not irritating; very slight erythema in 1 animal at 28 h post-patch removal that was present through 96 h; PDII = 0	[3]
Zeolite (natural; smellerite)	Amount not provided; in water	6 New Zealand White rabbits; sex not provided	24 h exposure; occluded patch on shaved skin; sites observed for 7 d	Not irritating; PDII = 0	[3]
Zeolite (synthetic)	500 mg in water	3 male New Zealand White rabbits	4 h exposure; semi-occluded, 6 cm^2 patch on shaved skin; sites observed for 72 h; in accordance with OECD TG 404	Not irritating; no cutaneous reactions observed during study; PDII = 0	[3]
Zeolite (synthetic)	500 mg moistened with 0.5 ml demineralized water	2 male and 1 female rabbits; strain not provided	4 h exposure; occluded patch on shaved skin; sites observed for 72 h; in accordance with OECD TG 404	Not irritating; very slight erythema in 1 animal at 1 h post-patch removal; PDII = 0.1; no systemic effects observed	[3]
Zeolite (synthetic)	2000 mg/kg; vehicle not provided	10 rabbits; further details not provided	24 h exposure; occluded patch on shaved skin; test sites were abraded in 5 animals and intact in the remaining 5; sites observed for 48 h; animals observed for mortality and dermal signs of irritation	Not irritating; no cutaneous reaction or deaths observed during study; PDII = 0	[3]
Zeolite (synthetic); impurities included sodium oxide	Applied undiluted	4 male rabbits; strain not provided	4 h exposure; occluded patch on shaved skin; sites observed for 17 d; in accordance with OECD TG 404	Irritating; maximum erythema score (3.0, mean) after 72 h post-patch removal and edema maximum score after 24 h post-patch removal; PDII = 1.75; effects ascribed to impurities in test material	[3]
Zeolite (synthetic)	20% in water	3 New Zealand Albino rabbits; sex not provided	24 h exposure; occluded patch on shaved skin; patches placed on intact and abraded skin; sites observed for 72 h	Mildly irritating; abraded site erythema score = 0.33, edema score = 0; intact site erythema score = 0.17, edema score = 0; PDII = 0.25	[3]
Zeolite (synthetic)	500 mg moistened with distilled water	3 male and 3 female rabbits; strain not provided	4 h exposure; semi-occluded patch on shaved skin; sites observed for 7 d	Not irritating; no cutaneous reactions; PDII = 0	[3]
Zeolite (synthetic)	Amount not provided; in water	6 New Zealand White rabbits; sex not provided	4 h exposure; occluded patch on shaved skin; sites observed for 14 d; in accordance with OECD TG 404	Mean erythema score after 1 h = 0.67, after 24 h = 0.33, resolved by 48 h; mean edema scores at all observation points = 0	[3]
Zeolite (synthetic)	Amount not provided; in water	6 New Zealand White rabbits; sex not provided	4 h exposure; occluded patch on shaved skin; sites observed for 14 d; in accordance with OECD TG 404	Mean erythema score after 1 h = 1.0, after 24 h = 0.33, resolved by 48 h; mean edema score after 1 h = 0.17, resolved by 24 h	[3]
			HUMAN		
Zeolite (synthetic)	330 and 660 mg/ml with deionized distilled water	54 subjects	Test material applied with a 1.8 cm^2 occlusive bandage on the back; patches removed after 48 h; sites graded shortly after patch removal and at 24 h post-removal, some sites were read again at 48 h	No reactions observed	[3]

Table 9. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Zeolite (synthetic)	330 and 660 mg/ml with deionized distilled water	54 subjects	Same as the procedure described above	One subject had minimal reaction that resolved after 48 h of patch removal; no other reactions observed	[3]
Zeolite (synthetic)	Details not provided	Details not provided	Single application patch test	Not irritating	[3]
			SENSITIZATION		
			ANIMAL		
Zeolite (synthetic)	Intradermal induction = 3.0% w/v dermal induction = 25% w/v challenge = 40% w/v; in olive oil	15 female Hartley guinea pigs induced and challenged, additional 5 were controls that were only challenged	Maximization test; intradermal induction followed by 24 h treatment with 10% SDS and occlusive dermal applications; challenge patches occlusive; in accordance with OECD TG 406	Not sensitizing	[3]
Zeolite (synthetic)	Induction, challenge = 50%; in water	20 Hartley guinea pigs induced and challenged, additional 10 served as control; sex not provided	Buehler test; occlusive dermal induction and challenge applications; in accordance with OECD TG 406	Not sensitizing	[3]
Zeolite (synthetic)	Induction = 10% solution (1:1 with Freund's adjuvant) challenge = 50% suspension	20 male Pirbright-Hartley guinea pigs induced and challenged, additional 10 served as control	Adjuvant-type test; 10 dermal induction patches followed by a 2-wk rest and a 24 h challenge patch	Not sensitizing; reversible erythema observed during induction phase due to Freund's adjuvant	[3]
			HUMAN		
Zeolite (synthetic)	5% aqueous paste	71 subjects	Human patch test (no further details provided)	"Not sensitizing"	[3]
Zeolite (type not specified)	7.907% in a mixture	53 subjects	HRIPT; approximately 00.2 g applied to upper back with a ¾ in^2 absorbent pad and occluded; 9 induction patches over a 3 week period followed by a 2 week rest and then a challenge patch on a virgin site; challenge sites scored 24 and 72 h post-application	Not irritating or sensitizing	[18]

Table 10. Ocular irritation studies[3]

Test Article	Concentration/Dose	Test Population	Procedure	Results
			ANIMAL	
Zeolite (synthetic)	100 mg, undiluted	1 male and 2 female White Russian Albino rabbits	Acute ocular irritation study in accordance with OECD TG 405; single instillation of test material in 1 conjunctival sac; observations made at 1, 24, 48, and 72 h and on day 4, 7, and 8 post-administration	Slightly irritating; cornea opacity reversible in 1 animal after 7 d, remaining 2 animals healthy within 4 d; affects to the iris and conjunctivae chemosis were resolved within 4 d in all animals; redness of the conjunctivae reversible in 1 animal after 4 d, remaining 2 animals healthy with 5 d; all eyes appeared normal by day 8
Zeolite (synthetic)	60 mg, undiluted	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; minor, transient, diffuse corneal injury observed in 1/6 eyes; transient iritis observed in 5/6 eyes; minor to moderate conjunctival irritation with substantial discharge observed in 6/6 eyes at 1 h; all eyes healed by 48 h
Zeolite (synthetic)	0.1 ml/10 mg of solids, undiluted	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; 1 rabbit died from unknown causes not thought to be due to treatment; iritis observed in all 6 eyes, at 24 h only iritis in 1 eye; minor to moderate conjunctival irritation observed in 6 eyes with 5/6 eyes exhibiting large amount of discharge at 1 h; all eyes appeared normal by 72 h
Zeolite (synthetic)	100 mg, undiluted	6 New Zealand Albino rabbits; sex not provided	Acute ocular irritation study in accordance with Department of Transportation 49CFR173; test performed in manner similar as described above	Not irritating; cornea and iris appeared normal during observation period; 3 animals had slight redness of the conjunctivae on day 3; slight corneal chemosis observed in 1 animal that resolved by day 3

Table 10. Ocular irritation studies[3]

Test Article	Concentration/Dose	Test Population	Procedure	Results
Zeolite (synthetic)	60 mg, undiluted	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; no corneal injury observed; transient iritis and moderate conjunctival irritation developed in all 6 eyes, iritis resolved after 24 h but minor conjunctival effects persisted; all eyes appeared normal by 48 h
Zeolite (synthetic)	70 mg, undiluted	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; no corneal injury in any eye; transient iritis observed in 5/6 eyes; substantial discharge observed in all animals at 1 h; all effects resolved by 24 h
Zeolite (synthetic)	0.1 ml, undiluted	8 Japanese White rabbits; sex not provided	5 rabbits in group 1 received instillation of test material that was rinsed within 5 min, 3 rabbits in group 2 had eyes rinsed after 24 h; observations made at 1, 24, 48, and 72 h and up to 7 d post-administration	Not irritating; reaction in conjunctiva observed at 1 h post-administration that resolved within 48 h; no other treatment-related effects reported
Zeolite (synthetic)	0.1 ml of solids, undiluted	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; minor diffuse corneal injury in 5/6 animals; iritis in 5/6 animals; minor to moderate conjunctival irritation with substantial discharge in 6/6 animals; all eyes healed at 72 h
Zeolite (natural; smellerite)	amount not reported, in water	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study; details not provided	Not irritating; no corneal opacity or iridal effects observed; mean conjunctivae score as high as 1 at 1 h, fully reversible within 48 h; mean chemosis score as high as 1 at 1 h, fully reversible within 48 h
Zeolite (synthetic)	100 mg, undiluted	3 male New Zealand White rabbits	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; very slight to marked conjunctival reactions noted between day 1 and day 6; slight iritis observed on day 3 in 2 animals that persisted for 48 h in 1 animal; very slight or slight corneal opacity noted in all animals on day 2 that persisted in 1 animal for 24 h and for 48 in the other 2; reversibility of ocular lesions noted on day 5 in 2 animals and on day 7 in the other 1
Zeolite (synthetic)	90 mg, undiluted	3 female White Russian Albino rabbits	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; overall irritation score = 0; no treatment-related effects to the cornea or iris in any animal during observation period; grade 1 hyperemia of the conjunctiva in 1 animal that resolved by 24 h post-administration; discharge occurred in all 3 animals only on day of application
Zeolite (synthetic)	100 mg, undiluted	6 New Zealand Albino rabbits, sex not provided	Acute ocular irritation study in accordance with Department of Transportation 49CFR173; test performed in manner similar as described above	Not irritating; no treatment-related effects to the cornea or iris in any animal during observation period; slight redness in the conjunctiva of 2/6 animals at 24 h that persisted in 1 animal until 72 h
Zeolite (synthetic)	30 or 80 mg, undiluted	2 male and 1 female White Russian Albino rabbits	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; no systemic effects observed; no adverse effects observed in the cornea or iris at observation period; all 3 animals at grade 1 hyperemia between 1-24 h post-administration; discharge occurred in all 3 animals 1 h post-administration, with grade 3 moistening in 2 animals and grade 2 in 1 animal; the irritation index was 2
Zeolite (synthetic)	3 mg or 0.1 ml of a 10% aqueous test solution with no rinse; undiluted	3 rabbits/dosing régime; strain and sex not provided	Single instillation of test material in 1 conjunctival sac, other eye served as a control; 3 rabbits treated in each dosing régime: 3 mg followed by no rinse, 3 mg with rinsing performed 4 sec post-administration, 0.1 mL of a 10% w/v test solution with no rinse); observations made at 1 and 24 h post-administration	No abnormalities observed at either observation period
Zeolite (synthetic)	100 mg, undiluted	6 female New Zealand Albino rabbits	Test performed in manner similar as described above	1/6 animals had grade 1 corneal effects at 24 h; 4/6 animals had grade 1 conjunctival redness at 24-72 h, while 1/6 had grade 2 reaction at 24 h; grade 2 conjunctival chemosis was observed in 2/6 animals at 24 h; no further details provided
Zeolite (synthetic)	100 mg, undiluted	6 female New Zealand Albino rabbits	Single instillation of test material in the left conjunctival sac, other eye served as a control; 3 treated eyes were rinsed with 20 ml of distilled water 2 sec after instillation and the remining 3 treated eyes were rinsed after 4 sec; observations made at 24, 48, and 72 h and 7 d post-administration	No toxic effects; 1 animal had slight redness at 24 h and another had corneal abrasion at 24 h – both effects were resolved by 72 h

Table 10. Ocular irritation studies[3]

Test Article	Concentration/Dose	Test Population	Procedure	Results
Zeolite (synthetic)	100 mg, undiluted	3 male New Zealand White rabbits	Acute ocular irritation study in accordance with OECD TG 405 performed in manner similar as described above	Not irritating; between day 1 and day 4, very slight to slight chemosis, very slight to slight conjunctival redness and clear ocular discharge observed; slight iritis observed on day 2 in all animals that persisted for 24 h in 1 animal; slight corneal opacity noted in 2 animals on day 2 that persisted for 48 h in 1 animal; ocular lesions had reversed by day 5 in all animals
Zeolite (synthetic)	60 mg in water	6 New Zealand White rabbits; sex not provided	Acute ocular irritation study performed in manner similar as described above	Not irritating; mean cornea opacity score as high as 0.5 at 4 h, fully reversible within 48 h; mean iris score as high as 0.5 at 4 h, fully reversible within 24 h; mean conjunctivae score as high as 1.5 at 4 h, fully reversible within 72 h; mean chemosis score as high as 2 at 4 h, fully reversible within 48 h
Zeolite (synthetic)	35 mg, undiluted	2 Rhesus monkeys	Single instillation of test material in the left conjunctival sac, other eye served as a control; observations made at 24, 48, and 72 h and 7 d post-administration	Slightly irritating; corneal dullness and slight conjunctival redness observed at 24 h; signs of irritation had completely resolved by 48 h

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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

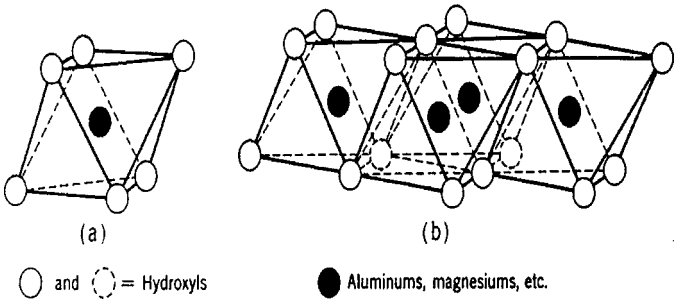

FIGURE 1
(*a*) Single octahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

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).

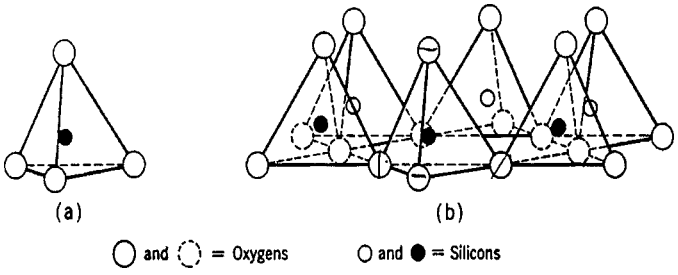

FIGURE 2
(*a*) Single tetrahedral unit; (*b*) Sheet of units (taken from Grim 1967 with permission).

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

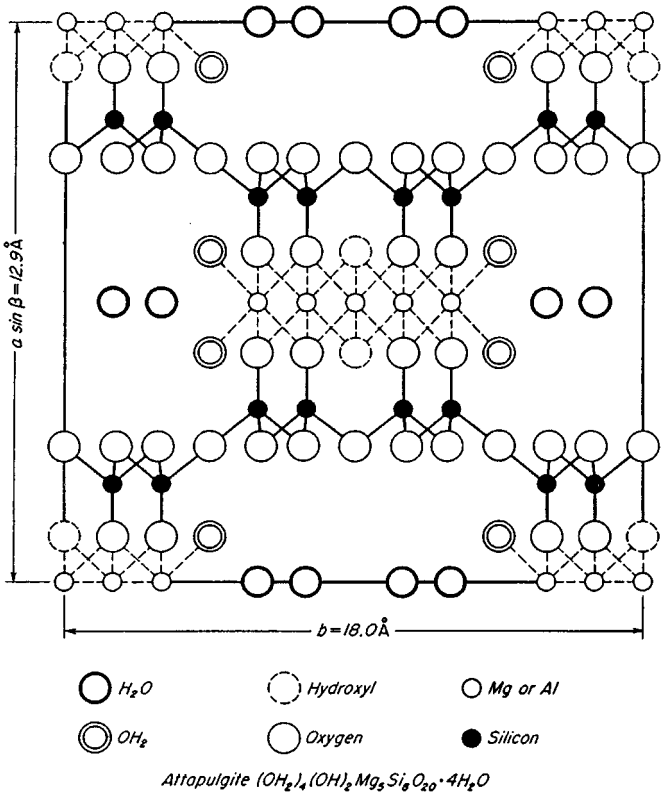

FIGURE 3
Attapulgite structure (taken from Grim 1967 with permission).

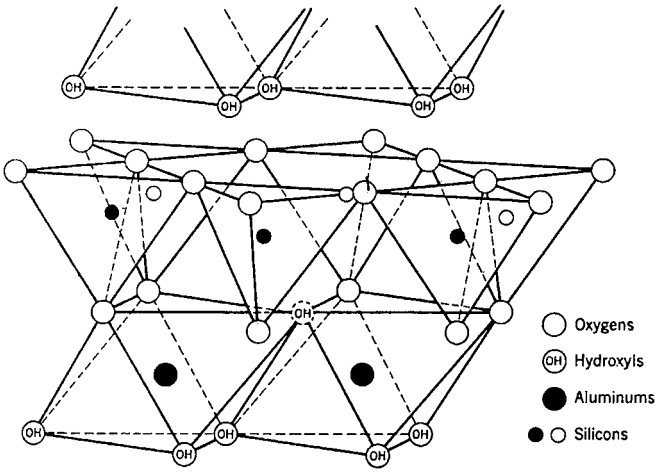

FIGURE 4
Kaolin layer (taken from Grim 1967 with permission).

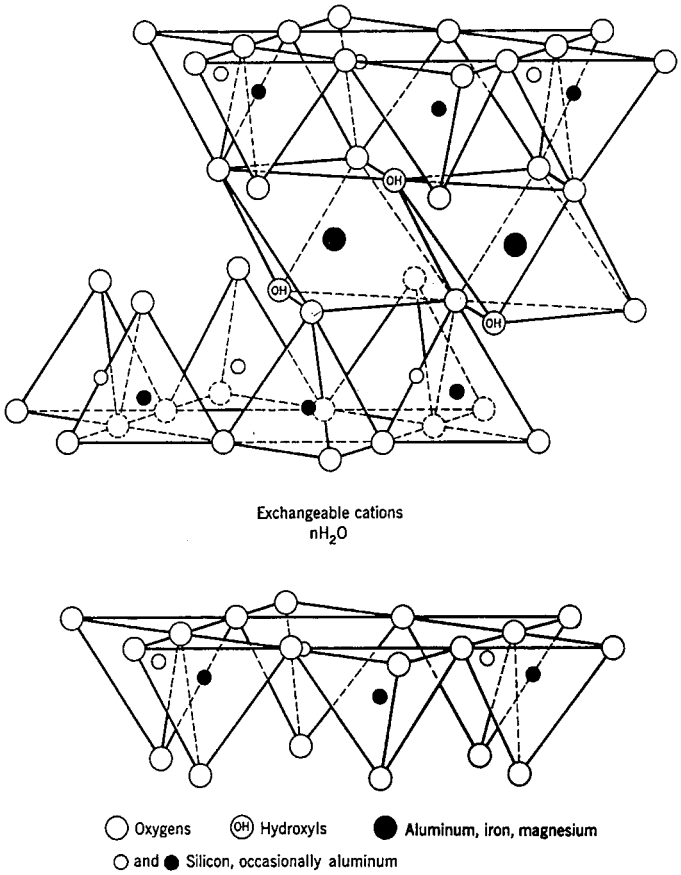

FIGURE 5
Smectite structure (taken from Grim 1967 with permission).

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

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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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2022 FDA VCRP Raw Data

ZEOLITE	03A	Eyebrow Pencil	1
ZEOLITE	03B	Eyeliner	1
ZEOLITE	03C	Eye Shadow	1
ZEOLITE	05B	Hair Spray (aerosol fixatives)	4
ZEOLITE	05F	Shampoos (non-coloring)	5
ZEOLITE	05G	Tonics, Dressings, and Other Hair Grooming Aids	1
ZEOLITE	05I	Other Hair Preparations	2
ZEOLITE	07A	Blushers (all types)	1
ZEOLITE	07B	Face Powders	1
ZEOLITE	07E	Lipstick	3
ZEOLITE	07I	Other Makeup Preparations	3
ZEOLITE	12A	Cleansing	1
ZEOLITE	12C	Face and Neck (exc shave)	3
ZEOLITE	12F	Moisturizing	5
ZEOLITE	12H	Paste Masks (mud packs)	1
ZINC ZEOLITE	05F	Shampoos (non-coloring)	1
ZINC ZEOLITE	10E	Other Personal Cleanliness Products	1