Amended Safety Assessment of Zeolites as Used in Cosmetics

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ABBREVIATIONS

CHO = Chinese hamster ovary
CIR = Cosmetic Ingredient Review
Council = Personal Care Products Council
CPSC = Consumer Product Safety Council
D_{50} = the median value of the particle size distribution
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
LTA = Linde Type A
MPE = micronucleated polychromatic erythrocytes
NCE = normochromatic erythrocyte
NOAEL = no-observable-adverse-effect-level
OECD = Organization for Economic Co-operation and Development
Panel = Expert Panel for Cosmetic Ingredient Safety
PCE = polychromatic erythrocytes
TG = test guideline
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).

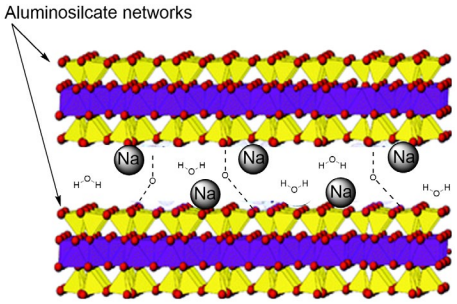

Figure 1. Zeolite

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.

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 life-time 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 at 141 wk. 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.

Antimicrobial Properties

The antimicrobial properties of synthetic Zeolite with different Al/Si ratios and with ions exchanged with Ag^+, Zn^{2+}, and Cu^{2+} were studied against a broad range of microorganisms.[17] The zeolites were synthesized from sodium aluminate, sodium hydroxide, sodium metasilicate pentahydrate, and ludox. Silver nitrate, zinc chloride, copper sulfate pentahydrate, and anhydrous copper sulfate were used for the ion-exchange process. The resulting metal ion-embedded zeolites were individually tested against 4 bacteria species (*Staphylococcus aureus, E. coli*, *Bacillus cereus*, and *Pseudomonas aeruginosa*) 2 fungus species (*Aspergillus niger* and *Penicillium vinaceum*), and 2 yeast species (*Candida albicans* and *C. glabrata*). The zeolites were suspended at a concentration of 2048 µg/ml in 10 ml tryptic soy broth (for bacteria) and sabouraud dextrose broth (for fungi), and 2-fold dilutions were conducted. Suspensions of the microbial species were prepared from fresh cultures, and then 0.5 ml of inocula was added to 45 ml of serially diluted zeolite suspensions. The inoculated suspensions were incubated for 24 - 72 h. The minimum inhibition concentration was then determined at the lowest concentration in which microbial growth was inhibited. Zeolites that were Ag^+ ion-loaded exhibited more antibacterial activity when compared to Zn^{2+} and Cu^{2+} ion-embedded zeolite samples, with inhibition at concentrations as low as 16 µg/ml. Yeast and fungal growth were inhibited at concentrations as high as 1024 µg/ml; however, the Zn^{2+} and Cu^{2+} ion-embedded zeolite samples were found to display more antifungal and anticandidal characteristics.

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.[18] 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 synthetic Zeolite (details not provided) and an unspecified Zeolite at 7.907% in a mixture were not sensitizing to 71 subjects in a human patch test and to 53 subjects in a human repeated insult patch test (HRIPT), respectively.[3,19]

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 fibrosis 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.[20] 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 mg/kg bw 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. In 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 were observed up to 11 mo, treatment-related aseptic superficial inflammation of abdominal organs was observed with deposits of the test material found 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 were 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/m^3 in a whole-body inhalation study of Zeolite (synthetic) in male and female monkeys.

In bacterial reverse mutation assays with *S. typhimurium* and *E. 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 *S. 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.

Synthetic zeolites embedded with metal ions have antimicrobial properties. Zeolites that were Ag^+ ion-loaded exhibited more antibacterial activity when compared to Zn^{2+} and Cu^{2+} ion-embedded zeolite samples; however, the Zn^{2+} and Cu^{2+} ion-embedded zeolite samples were found to display more antifungal and anticandidal characteristics.

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 synthetic Zeolite (details not provided) and an unspecified Zeolite at 7.907% in a mixture were not sensitizing to subjects in a human patch test and a HRIPT, respectively.

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 used 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 free metal ions contamination of these ingredients. The metals in Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite would have limited phase exchange into solution due to the nature of the zeolite framework. The zeolites are also not likely to absorb through the skin. Although heavy metal contaminates (e.g., lead, mercury, nickel) may be present during mining, those should be readily separable. Accordingly, the Panel stressed that the cosmetics industry should continue to use cGMPs to limit these heavy metal contaminates, 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 low 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. 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).

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that 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 $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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	[18]
			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	[19]

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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