Safety Assessment of Inorganic Hydroxides as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of inorganic hydroxides, which function in cosmetics primarily as pH adjusters. Industry has indicated these ingredients are used in depilating and hair waving/straightening formulations to raise pH values. The Panel considered relevant data related to these ingredients. The Panel concluded that these inorganic hydroxides are safe in hair straighteners and depilatories under conditions of recommended use; users should minimize skin contact. These ingredients are safe for all other present practices of use and concentration described in this safety assessment when formulated to be nonirritating.

INTRODUCTION

This report addresses the safety of the inorganic hydroxides calcium hydroxide (also known as calcium hydrate or slaked lime), magnesium hydroxide, potassium hydroxide (potassium hydrate or potash), and sodium hydroxide (sodium hydrate, lye, or caustic soda). These ingredients are all alkaline salts and are reported in the *International Cosmetic Ingredient Dictionary and Handbook* to function as pH adjusters in cosmetics; however, representatives from the cosmetics industry and formulary references have stated that the inorganic hydroxides are also used at very high pH values in hair straighteners and depilatories.[1-5] Additionally, sodium hydroxide has been reacted with fats to form soap for millennia.

The inorganic hydroxides in this report, with the exception of magnesium hydroxide, are well-known caustic agents that can cause severe burns and corrosion with acute exposures. Sodium hydroxide is commonly used as a positive control in efficacy studies of skin protective creams and in other studies of irritant contact dermatitis.[6]

Some chemical and toxicological data on the inorganic hydroxides included in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. These data summaries are available on the ECHA website.[7-10]

CHEMISTRY

Definition

Inorganic hydroxides are alkaline salts formed by treating oxides with water or via decomposing salts by adding other soluble hydroxides to a solution thereof (e.g., adding sodium hydroxide to magnesium sulfate will produce magnesium hydroxide). The formation of an inorganic hydroxide, such as specifically lime or calcium hydroxide, by reaction of an oxide with water is known as slaking.[11] The resulting highly water soluble ingredients only vary structurally by the metal cation. These variations result in different degrees of basicity across these four ingredients, ranging in pK_b values from 0.2 to 4.0. Used primarily as pH adjusters (to increase the pH of an otherwise acidic formulation), the caustic nature of these ingredients is unlikely to be observable in typical, final cosmetic formulations, except when used in depilatory or hair straightener product types.

Figure 1. Inorganic Hydroxides (wherein "M" is group I or II metal)

The definitions, structures, and functions of the inorganic hydroxides included in this report are provided in Table 1.

Chemical and Physical Properties

The inorganic hydroxides are all highly water-soluble, white solids with specific gravities around 2. Physical and chemical properties of the inorganic hydroxides in this report are provided in Table 2.

Method of Manufacturing

Calcium Hydroxide

Calcium hydroxide may be formed by the hydration of lime or by treating an aqueous solution of a calcium salt with alkali.[12]

Magnesium Hydroxide

Magnesium hydroxide may be formed by reacting magnesium chloride or sulfate with sodium hydroxide.[12] Most commercial-grade magnesium hydroxide is obtained from seawater or brine using lime or dolomitic lime.[11]

Potassium Hydroxide

Potassium hydroxide may be produced by treating oxides with water, a process known as brine electrolysis.[11,12]

Sodium Hydroxide

Sodium hydroxide is formed by brine electrolysis.[11]

$2\ NaCl + 2\ H_2O \rightarrow 2\ NaOH + Cl_2 + H_2$

Process 1. Brine Electrolysis

Sodium hydroxide may also be formed by reacting lime with soda ash.[11]

$Ca(OH)_2 + Na_2CO_3 \rightarrow CaCO_3 + 2\ NaOH$

Process 2. Slaking

Impurities

The *U.S. Pharmacopeia* and *Food Chemicals Codex* provide specifications for acceptable levels of impurities for the inorganic hydroxides named in this report.[13,14] These specifications are provided in Table 3.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the reported use in cosmetics using the data received from the Food and Drug Administration (FDA) and the cosmetics industry. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Personal Care Products Council (Council).

According to the 2015 VCRP data, sodium hydroxide has the most reported uses in cosmetic formulations of the ingredients listed in this safety assessment, with a total of 5147; about half of the uses are in leave-on skin care formulations (Table 4).[15] Potassium hydroxide has the second greatest number of overall uses reported, with a total of 1074; the majority of the uses also are in leave-on skin care formulations. The results of the concentration of use survey conducted in 2014 by the Council indicate calcium hydroxide has the highest reported maximum concentration of use; it is used at up to 13.2% in rinse-off shaving preparations; however, it is only used at up to 0.5% in leave-on formulations (deodorants).[16] Sodium hydroxide is used at up to 10% in an "other" skin care preparation, which may or may not be a leave-on formulation. The next highest concentration of use reported for sodium hydroxide in a leave-on formulation is 6.9% in a face or neck formulation. Potassium hydroxide is used at up to 7% in a leave-on body and hand formulation. Examples of depilatory and hair straightening formulations containing inorganic hydroxides are found in Tables 5 and 6.

Some of these ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes. For example, sodium hydroxide is used in lipstick (at least one use at up to 0.26%) and in bath soaps and detergents (860 uses at up to 12.9%). Additionally, some of these ingredients were reported to be used in hair sprays and body and hand sprays and could possibly be inhaled. For example, potassium hydroxide was reported to be used in hair sprays at a maximum concentration of 0.69%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[17-20] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[18,19]

Europe's Scientific Committee on Consumer Safety (SCCS) opined that potassium hydroxide is safe for use as a callosity softener/remover with a concentration of up to 1.5%.[21] A proposed change to the European Commission's regulation under Annex III List of Substances Which Cosmetic Products Must Not Contain Except Subject to the Restrictions Laid Down has been sent to the World Trade Organization (WTO) for consideration. Currently, sodium hydroxide, potassium hydroxide, and calcium hydroxide are listed on Annex III with the restrictions listed here.[22] The uses of sodium hydroxide and potassium hydroxide may not exceed 5% in nail cuticle solvents; 2% for general use and 4.5% in professional use of hair straighteners; must have a pH below 12.7 when used as a pH adjuster in depilatories; and must have pH below 11 in other uses. The use of calcium hydroxide may

not exceed 7% in hair straighteners containing calcium hydroxide and a guanidine salt, must have a pH below 12.7 when used as a pH adjuster in depilatories, and must have a pH below 11 in all other uses.

Magnesium hydroxide is not restricted from use in any way under the rules governing cosmetic products in the European Union.[22]

Non-Cosmetic

According to FDA, the inorganic hydroxides in this report are generally recognized as safe (GRAS) in the U.S. as direct food substances based upon following current good manufacturing practice conditions of use (21CFR§184). Additionally, they are GRAS as feed additives for animals (21CFR§582). The FDA has also separately reviewed calcium hydroxide and magnesium hydroxide for use as active ingredients in over-the-counter (OTC) drugs. Calcium hydroxide is listed for anti-diarrheal products and magnesium hydroxide is listed for digestive aid products (21CFR §310).

Calcium hydroxide is used in mortar, plaster, cement and other building and paving materials.[12] It is also used in lubricants, drilling fluids, pesticides, fireproofing coatings, water paints, as egg preservative, in the manufacture of paper pulp, in rubber vulcanization in water treatment, in dehairing hides, and as an absorbent for carbon dioxide. Therapeutically, it is used as an astringent.

Magnesium hydroxide may be used therapeutically as an antacid, cathartic, or laxative.[12] It is an approved OTC active ingredient (21 CFR§ 331.11).

Non-cosmetic uses of potassium hydroxide include as a mordant for wood, for mercerizing cotton, for absorbing carbon dioxide, for removing paint and varnish, for electroplating, for photoengraving and lithography, in printing inks, for debudding calves' horns, and for dissolving scales and hair in skin scrapings.[12]

Sodium hydroxide is a strong base and is extremely corrosive. Sodium hydroxide solutions are used to neutralize acids and to make sodium salts (for example, in petroleum refining to remove sulfuric and organic acids); to treat cellulose during viscose rayon and cellophane production; to reclaim rubber; in plastics manufacturing; and in dehorning calves.[11,12]

TOXICOKINETICS

No relevant published toxicokinetics studies on inorganic hydroxides were identified in a literature search for these ingredients and no unpublished data were submitted. Data on the kinetics of the metal ions of these ingredients are abundant in the published literature, but these data are not useful in assessing the safety of these ingredients as they are used in cosmetics.

TOXICOLOGICAL STUDIES

Acute Toxicity

Animal acute toxicity studies are presented in Table 7.[7-10,23-26] In oral toxicity studies, calcium hydroxide had an LD_{50} > 7300 mg/kg bodyweight in rats and mice and magnesium hydroxide had an LD_{50} > 2000 mg/kg bodyweight in rats. An LD_{50} of 1230 mg/kg body weight was observed in rats that received potassium hydroxide at doses that increased in log fashion by a factor of 2 starting at 0.1 mg/ml solution. Other oral studies of potassium hydroxide in rats have LD_{50} results of 333 to 388 mg/kg bodyweight. Oral studies of sodium hydroxide led to extensive gastric damages in the animal tested. In dermal toxicity studies, calcium hydroxide had an LD_{50} >2.5 g/kg bodyweight in rabbits, and mice treated with 50% sodium hydroxide had better survival rates when the test compound was washed off within an hour of application. In inhalation studies in rats, the LC_{50}s for magnesium hydroxide and sodium hydroxide were > 2.1 mg/l (4-h exposure) and > 0.75 mg/l (2-h exposure), respectively.

Repeated Dose Toxicity

A combined repeated dose toxicity study and reproductive and developmental toxicity screening test was performed with magnesium hydroxide in accordance with Organisation for Economic Co-operation and Development (OECD) guideline 422.[9] These results are described in the Reproductive and Developmental Toxicity section of this report. No other relevant published repeated dose toxicity studies on inorganic hydroxides were identified in a literature search for these ingredients and no unpublished data were submitted.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Magnesium Hydroxide

The reproductive toxicity of magnesium hydroxide (pH = 10) was studied in rats that received the test material via gavage.[9] The study followed OECD guideline 422. Groups of 10 male and 10 female Wistar rats

received 0, 110, 330, or 1000 mg/kg bw/day magnesium hydroxide in water daily. Males were exposed for 29 days (i.e., 2 weeks prior to mating, during mating, and up until treatment end) and females were exposed for 41-45 days (i.e., 2 weeks prior to mating, during mating, during gestation, and during at least 4 days of lactation). No treatment-related effects were observed on clinical signs, body weight or weight gain, feed consumption, or hematology. In parental males, lower total protein levels (330 and 1000 mg/kg dose groups), lower albumin levels (1000 mg/kg dose group), and lower calcium levels (330 and 1000 mg/kg dose groups) in the blood, and lower sodium and potassium excretion (1000 mg/kg dose group) and higher calcium concentration in urine (1000 mg/kg dose group) were observed; however, these changes only just exceeded or remained within normal ranges and there were no corresponding histopathological changes. No toxicologically relevant changes from the test material were observed in parental organ weights or in gross pathology. There were no treatment-related effects on offspring development. The no observed adverse effect level (NOAEL) for parental systemic effects, parental reproductive effects, and offspring effects in this one generation rat study of magnesium hydroxide was 1000 mg/kg bw/day.

GENOTOXICITY

Genotoxicity studies are presented in Table 8.[7-10,27] Calcium hydroxide, magnesium hydroxide, and sodium hydroxide were not genotoxic in several different in vitro assays. Potassium hydroxide was not genotoxic in one Ames test, but results were ambiguous in another Ames test and a chromosome aberration test. Sodium hydroxide was not genotoxic in an in vivo mouse oocyte aneuploidy induction study at up to 0.015M. High non-physiological pH may yield false-positive results in genotoxicity studies.

CARCINOGENICITY

No relevant published carcinogenicity data on inorganic hydroxides were identified in a literature search for these ingredients and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Dermal Irritation

Sodium hydroxide is a corrosive material that can produce immediate coagulative necrosis resulting in considerable tissue damage with ulceration and sloughing.[28] Toxicity is a function of pH, with greater toxicity associated with increasing pH values. High pH (strong alkalinity) can cause deep burns and readily denatures keratin. Following exposure, the chemical must be removed quickly and completely in order to avoid further damage to the skin or possible systemic injury.

A representative sampling of dermal irritation studies are presented in Table 9.[6-10,29-38] Magnesium hydroxide was not irritating or corrosive when tested in vitro (concentrations not reported); however, potassium hydroxide and sodium hydroxide were corrosive at concentrations as low as 1%. Calcium hydroxide was generally irritating but not corrosive in rabbit dermal studies (concentrations not reported). Potassium hydroxide was irritating and/or corrosive in rabbit (at 2% or greater) and guinea pig (at 10%) studies. Sodium hydroxide was irritating/corrosive in a concentration-dependent manner in rat, rabbit, and pig studies. In humans, sodium hydroxide was irritating at concentrations as low as 0.5%. Because of the large number of studies that include sodium hydroxide as a positive control, only a sampling has been presented in this safety assessment.

Ocular Irritation

Caustic chemicals like sodium hydroxide can rapidly penetrate ocular tissues.[28] Toxicity is a function of pH, with greater toxicity associated with increasing pH values. The concentration of the solution and duration of contact with the eye are important determinants of the eventual clinical outcome.

A representative sampling of ocular irritation studies are presented in Table 10.[7-10,38-42] Calcium hydroxide was predicted to be irritating in hen's egg test-chorioallantoic membrane (HET-CAM) in vitro tests while magnesium hydroxide was predicted not to be irritating in a bovine corneal opacity and permeability (BCOP) in vitro test. In rabbit studies, calcium hydroxide was severely irritating at a concentration as low as 10% and pH of 9. Potassium hydroxide and sodium hydroxide were severely irritating and/or corrosive in a concentration-dependent manner in rodents. Magnesium hydroxide was not irritating in a rabbit study.

Dermal Sensitization

Dermal sensitization studies are summarized in Table 11.[8-10] Potassium hydroxide (0.1%) was not sensitizing in a guinea pig study, whereas magnesium hydroxide in propylene glycol was sensitizing in a local

lymph node assay (LLNA) when tested at up to 50%. In a human repeat insult patch test (HRIPT), sodium hydroxide was not sensitizing when induced at up to 1.0% and challenged at 0.125%, but irritation was observed.

CASE REPORTS

There were no case reports discovered in the published literature indicating adverse events that could be associated specifically with the presence of inorganic hydroxide ingredients in cosmetic products. However, there are numerous case reports suggesting an association between the use of depilatory and hair straightening products that contain active ingredients like thioglycolates (Table 5) as well as inorganic hydroxides.[43-50]

SUMMARY

The inorganic hydroxides, calcium hydroxide, magnesium hydroxide, potassium hydroxide, and sodium hydroxide, are all alkaline salts and are reported in the *International Cosmetic Ingredient Dictionary and Handbook* to function most commonly as pH adjusters in cosmetics; however, representatives from the cosmetics industry have stated that the inorganic hydroxides are added to depilating and hair waving/straightening formulations to raise pH values. Inorganic hydroxides, with the exception of magnesium hydroxide, are well known caustic agents that can cause severe burns and corrosion in acute exposures. Sodium hydroxide is commonly used as a positive control in efficacy studies of skin protective creams and in other studies of irritant contact dermatitis.

According to the 2015 VCRP data, sodium hydroxide has the most reported uses of the ingredients listed in this safety assessment in cosmetic products, with a total of 5147; about half of the uses are in leave-on skin care products. Potassium hydroxide has the second greatest number of overall uses reported, with a total of 1074; the majority of the uses also are in leave-on skin care products. The results of the concentration of use survey conducted in 2014 by the Council indicate calcium hydroxide has the highest reported maximum concentration of use; it is used at up to 13.2% in rinse-off shaving preparations. However, it is only used up to 0.5% in leave-on products (deodorants). Sodium hydroxide is used at up to 10% in an "other" skin care preparation, which may or may not be a leave-on product. The next highest concentration of use for a leave-on product for sodium hydroxide is 6.9% in a face or neck product.

The inorganic hydroxides in this report are GRAS as direct food substances and as feed additives for animals. The FDA has also reviewed calcium hydroxide and magnesium hydroxide for use as an active ingredient in over-the-counter drugs. Inorganic hydroxides have numerous non-cosmetic uses.

In oral toxicity studies, calcium hydroxide had an LD_{50} > 7300 mg/kg bodyweight in rats and mice and magnesium hydroxide had an LD_{50} > 2000 mg/kg bodyweight in rats. An LD_{50} of 1230 mg/kg bodyweight was observed in rats that received potassium hydroxide at doses that increased in log fashion by a factor of 2 starting at 0.1 mg/ml solution. Other oral studies of potassium hydroxide in rats have LD_{50} results of 333 to 388 mg/kg bodyweight. Oral studies of sodium hydroxide led to extensive gastric damages in the animal tested. In dermal toxicity studies, calcium hydroxide had an LD_{50} >2.5 g/kg bodyweight in rabbits, and mice treated with 50% sodium hydroxide had better survival rates when the test compound was washed off within an hour of application. In inhalation studies in rats, the LC_{50}s for magnesium hydroxide and sodium hydroxide were > 2.1 mg/l (4-h exposure) and > 750 µg/l (2-h exposure), respectively.

The NOAEL for parental and offspring effects following oral exposure to magnesium hydroxide (pH = 10) was 1000 mg/kg bw/day. No treatment-related effects were observed on clinical signs, body weight or weight gain, feed consumption, or hematology. No toxicologically relevant changes from the test material were observed in parental organ weights or in gross pathology. There were no treatment-related effects on offspring development.

Calcium hydroxide, magnesium hydroxide, and sodium hydroxide were not genotoxic in several different in vitro assays. Potassium hydroxide was not genotoxic in one Ames test, but results were ambiguous in another Ames test and a chromosome aberration test. Sodium hydroxide was not genotoxic in mice studies (intraperitoneal injection) at up to 0.015 M.

Magnesium hydroxide was not irritating or corrosive in in vitro tests; however, potassium hydroxide and sodium hydroxide were corrosive at concentrations as low as 5%. Calcium hydroxide was irritating but not corrosive in dermal rabbit studies. Potassium hydroxide was irritating and/or corrosive in rabbit and guinea pig studies at concentrations of 2% or greater. Sodium hydroxide was irritating and/or corrosive in a concentration-dependent manner in rat, rabbit, and pig studies. In humans, sodium hydroxide was irritating at concentrations as low as 0.5%. Because of the large number of studies that include sodium hydroxide as a positive control, only a sampling has been presented in this safety assessment.

In ocular studies, calcium hydroxide was irritating in HET-CAM in vitro tests, whereas magnesium hydroxide was not irritating in a bovine corneal opacity and permeability BCOP in vitro test. In rabbit studies, calcium hydroxide was severely irritating at a concentration of 10% and pH of 9. Potassium hydroxide and sodium

hydroxide were severely irritating and/or corrosive in a concentration-dependent manner. Magnesium hydroxide was not irritating in a rabbit study.

Potassium hydroxide (0.1%) was not sensitizing in a guinea pig study while magnesium hydroxide in propylene glycol was sensitizing in an LLNA when tested at up to 50%. In an HRIPT, sodium hydroxide was not sensitizing when induced at up to 1.0% and challenged at 0.125%, but irritation was observed.

There were no case reports discovered in the published literature indicating adverse events that could be associated specifically with the presence of inorganic hydroxide ingredients in cosmetic products. However, there are numerous case reports suggesting an association between the use of depilatory and hair straightening products that contain active ingredients like thioglycolates, as well as inorganic hydroxides.

DISCUSSION

The Panel reviewed studies performed to assess the dermal and ocular irritation and sensitization potential of the inorganic hydroxide ingredients. The Panel recognized that these ingredients can cause dermal and/or ocular irritation when used to adjust the pH of highly alkaline cosmetic formulations, specifically depilatory and hair straightening products. However, most of the alkalinity of the inorganic hydroxides in other types of cosmetic products will be neutralized by other ingredients in the formulation. Thus, neither local nor systemic toxicity is expected to be a concern for the use of the inorganic hydroxide ingredients in such formulations.

The safety of inorganic hydroxide ingredients as pH adjusters should not be based on the concentration of use, but on the concentration of free hydroxide ions that remain in a formulation. In general, the concentration of free hydroxide ion in a formulation depends on the acidity of the other ingredients in the formulation. The concentration of free hydroxide ions is expected to be low in cosmetic formulations, except in some depilatory and hair-straightening formulations.

The inorganic hydroxide ingredients are not listed in the *International Cosmetic Ingredient Dictionary and Handbook* as depilating or hair waving/straightening agents. However, inorganic hydroxides are added to some depilating and waving/straightening products to enable or enhance the depilatory and waving/straightening action of these products by increasing the pH of the formulations to high values. If the inorganic hydroxides are used in hair waving/straightening products, use concentrations should be limited and adequate instructions should be provided to users to prevent skin contact on the hands (such as by wearing gloves) and to minimize skin exposure (such as by limiting the frequency of product use) to ensure that irritation is not a concern. The Panel noted, for example, that hair dressers should use adequate measures to protect their skin before repeatedly applying hair straighteners containing inorganic hydroxides to multiple clients over a short period. In addition, users should avoid prolonged skin exposures on hands and scalp. The Panel emphasized that following manufacturers' instructions on the proper application and use is especially important if these products are used on children.

The Panel further discussed the potential for skin irritation and sensitization specifically from the use of inorganic hydroxides in depilatories. The Panel recognized that nearly all methods of hair removal may cause some irritation. However, clinically significant adverse reactions to the ingredients in depilatories are not commonly seen in the experience of the Panel. This indicates that current products are formulated to be practically nonirritating under conditions of recommended use.

No case reports were discovered indicating that topical exposures to inorganic hydroxides in cosmetic products are generally associated with adverse health effects. However, there are numerous case reports of adverse events associated with the use of depilatory or hair-straightening products containing inorganic hydroxides. These events were not clearly attributable to the inorganic hydroxides rather than to other ingredients, such as thioglycolates, in such products.

These ingredients are also reported to function as absorbents (magnesium hydroxide) and denaturants (sodium hydroxide) in cosmetic products. The Panel had no concerns about the safe use of these ingredients when used for these purposes in cosmetic products that are formulated to be nonirritating.

No carcinogenicity data were discovered. However, the Panel agreed that the cations of the hydroxides used in cosmetics are not expected to cause cancer or other local or systemic toxicity

The Panel discussed the issue of incidental inhalation exposure from hair sprays and body and hand sprays, hair color sprays, fragrance preparations and foot powders. Limited data are available from acute inhalation toxicity studies on magnesium hydroxide and sodium hydroxide. There were no inhalation toxicity data available on the remaining ingredients. These ingredients are reportedly used at concentrations up to 0.69% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available

to characterize the potential for inorganic hydroxides to cause irritation and sensitization, and as noted above, recognize that these potentially irritating substances would be neutralized in formulation and are unlikely to cause local effects in the respiratory tract. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that calcium hydroxide, magnesium hydroxide, potassium hydroxide, and sodium hydroxide are safe in hair straighteners and depilatories under conditions of recommended use; users should minimize skin contact. These ingredients are safe for all other present practices of use and concentration described in this safety assessment when formulated to be nonirritating.

TABLES

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

Ingredient/CAS No.	Definition & Structure	Function
Calcium Hydroxide 1305-62-0	Calcium Hydroxide is the inorganic base that conforms to the formula Ca^{2+} ^{-}OH	pH adjuster
Magnesium Hydroxide 1309-42-8	Magnesium Hydroxide is an inorganic base that conforms to the formula Mg^{2+} ^{-}OH	absorbent; pH adjuster
Potassium Hydroxide 1310-58-3	Potassium Hydroxide is the inorganic base that conforms to the formula K^{+} ^{-}OH	pH adjuster
Sodium Hydroxide 1310-73-2	Sodium Hydroxide is the inorganic base that conforms to the formula Na^{+} ^{-}OH	denaturant; pH adjuster

Table 2. Physical and chemical properties of inorganic hydroxides

Property	Value	Reference
Calcium Hydroxide		
Physical form	crystals or soft, odorless granules or powder with a slight bitter or alkaline taste	[12]
Formula weight (g/mol)	74.09	[12]
pK_b	2.4	[12]
Specific gravity	2.08-2.34	[12]
Solubility at 25 °C, g/L	1.59	[14]
Magnesium Hydroxide		
Physical form	bulky white, amorphous powder	[12]
Formula weight (g/mol)	58.32	[12]
Melting point (°C)	350 (decomposes)	[51]
pK_b	4.0	[12]
Specific gravity	2.36	[51]
Solubility at 25 °C, g/L	0.0117	[11]
Potassium Hydroxide		
Physical form	White or slightly yellow lumps, rods, pellets	[12]
Formula weight (g/mol)	56.11	[12]
Melting point (°C)	360	[12]
Boiling point (°C)	1327	[21]
pK_b	0.5	[12]
Specific gravity	2.044	[51]
Solubility at 25 °C g/L	1100	[21]
Sodium Hydroxide		
Physical Form	Brittle, white, translucent crystalline solid	[11]
Formula weight (g/mol)	39.998	[11]
Melting point (°C)	318	[11]
Boiling point (°C at 760 mm Hg)	1388	[11]
pK_b	0.2	[12]
Specific gravity at 20 °C	2.13	[11]
Solubility at 25 °C g/L	1000	[14]

Table 3. Impurities acceptance criteria by the *US Pharmacopeia* and *Food Chemicals Codex* [13,14]

Calcium Hydroxide	
Acid-insoluble substances	NMT 0.5%
Arsenic (for 1 g sample)	NMT 3 mg/kg
Carbonate (for 2 g sample)	NMT a slight effervescence observed
Fluoride (for 1 g sample)	NMT 0.005%
Heavy metals (for 2 g sample)	NMT 20 µg/g
Lead (for 1 g sample)	NMT 2 mg/kg
Magnesium and alkali salts (for 500 mg sample)	NMT 4.8%
Magnesium Hydroxide	
Calcium Oxide (for 500 mg sample)	NMT 1%
Carbonate (for 0.1g sample)	NMT a slight effervescence observed
Lead	NMT 2 mg/kg
Heavy metals (for 1 g sample)	NMT 20 µg/g
Potassium Hydroxide	
Carbonate (as K_2CO_3)	NMT 3.5%
Lead (for 1 g sample)	NMT 2 mg/kg
Mercury (for 10 g sample)	NMT 0.1 mg/kg
Sodium Hydroxide	
Arsenic (for 1 g sample)	NMT 3 mg/kg
Carbonate (as Na_2CO_3)	NMT 3.0%
Lead (for 1 g sample)	NMT 2 mg/kg
Mercury (for 10 g sample)	NMT 0.1 mg/kg

NMT = no more than

Table 4. Frequency and concentration of use according to duration and type of exposure for inorganic hydroxide.[15,16]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Calcium Hydroxide		**Magnesium Hydroxide**	
Totals†	**99**	**0.1-13.2**	**14**	**1.1-1.6**
Duration of Use				
Leave-On	18	0.11-0.5	4	NR
Rinse Off	81	0.1-13.2	8	1.1-1.6
Diluted for (Bath) Use	NR	NR	2	NR
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation -Sprays	spray: NR possible: 2[a]; 1[b]	spray: NR possible: 0.18[a]	NR	NR
Incidental Inhalation - Powders	powder: NR possible: 1[b]	NR	powder: 1	NR
Dermal Contact	71	0.1-13.2	7	1.1
Deodorant (underarm)	NR	spray: NR possible: NR not spray: 0.5	NR	NR
Hair - Non-Coloring	28	0.18-6	NR	NR
Hair-Coloring	NR	NR	7	1.6
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	1.1
Baby Products	NR	NR	NR	NR

	Potassium Hydroxide		**Sodium Hydroxide**	
Totals†	**1074**	**0.0000049-10**	**5147**	**0.0000083-12.9**
Duration of Use				
Leave-On	681	0.0000049-7	2802	0.0000083-10
Rinse Off	387	0.00048-10	2267	0.00002-12.9
Diluted for (Bath) Use	6	0.3-6.4	78	0.00002-0.28
Exposure Type				
Eye Area	61	0.000049-0.5	191	0.0000083-0.86
Incidental Ingestion	4	0.00049-0.005	36	0.00083-0.26
Incidental Inhalation -Sprays	spray: 9 possible: 252[a]; 240[b]	spray: 0.00049-0.69 possible: 0.0045-0.77[a]; 0.3-10[b]	spray: 13 possible: 1284[a]; 745[b]	spray: 0.000025-0.35 possible: 0.0025-0.93[a]; 0.09-2[b]
Incidental Inhalation - Powders	powder: NR possible: 240[b]; 3[c]	powder: 0.0000049 possible: 0.3-10[b]	powder: 2 possible: 745[b]; 16[c]	powder: 0.0000083-0.25 possible: 0.09-2[b]
Dermal Contact	995	0.0000049-10	4310	0.0000083-12.9
Deodorant (underarm)	spray: NR possible: 3[a]	NR	spray: NR: possible: 129[a]	spray: 0.4 possible: NR not spray: 0.01-1.1
Hair - Non-Coloring	60	0.005-0.77	444	0.00002-3
Hair-Coloring	1	0.31	329	0.001-1.7
Nail	10	0.02-1.7	8	0.13-1
Mucous Membrane	102	0.00049-6.4	1253	0.00002-12.9
Baby Products	3	0.19-0.21	47	0.13-0.16

NR = Not reported.

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

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

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

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

Table 5. Example depilatory formulations[5]

Ingredients	Cream % w/w	Lotion % w/w
Calcium thioglycolate	5.40	5.40
Calcium hydroxide	***4.00***	***4.00***
Sodium hydroxide, to pH 12.0-12.5	***qs***	***qs***
Ceteareth 20	1.50	1.00
Cetearyl alcohol	3.50	3.00
Stearyl alcohol	1.00	-
Silica	0.25	-
Propylene glycol	2.00	1.00
Sweet almond (prunus amygdalus dulcis) oil	1.00	-
Mineral oil	5.00	5.00
Cocoa butter	1.00	-
Jojoba (buxus chinensis) oil	-	0.50
Fragrance	0.50	0.70
Water	qs 100.00	qs 100.00

qs = quantum satis (amount which is needed)

Table 6. Example hair relaxer/straightener formulations[3]

Ingredients	Lye Relaxer % w/w	No-Lye Relaxer (cream + activator) % w/w
Cetearyl alcohol (and) ethoxylated lanolins (relaxer concentrate)	12.00	-
Relaxer concentrate (type not specified)	-	15.00 (in cream)
Mineral oil	5.00	15.00 (in cream)
Triblock polymer	10.00	-
Petrolatum	10.00-15.00	10.00 (in cream)
Sodium hydroxide beads	***1.7-2.2***	-
Calcium hydroxide powder	-	***5.00 (in cream)***
Guanidine carbonate	-	30.00 (in activator)
Water	qs 100.00	49.50 (in cream) and qs 100.00 (in activator)
Propylene glycol	7.00	5.00 (in cream) and 0.50 (in activator)
Phosphate ester	2.00	-
Polyquaternium 11	-	0.40 (in activator)
Preservative	qs	qs (in activator)
Xantham gum	-	1.00 (in activator)
Protein or other conditioner	0.50-2.00	-
Fragrance	-	0.50 (in cream)

qs = quantum satis (amount which is needed)

Table 7. Acute toxicity studies

Ingredient	Concentration/Dose	Study Protocol	Results	Reference
		Oral		
calcium hydroxide	details not provided	oral study in mice and rats (no further details provided)	$LD_{50} \geq 7300$ mg/kg bodyweight	[7]
magnesium hydroxide in water	2000 mg/kg	oral gavage (10 ml/kg dose volume) in 3 female Wistar rats	$LD_{50} > 2000$ mg/kg bodyweight	[9]
magnesium hydroxide	details not provided	oral study in rats (no further details provided)	$LD_{50} = 8500$ mg/kg	[52]
potassium hydroxide	details not provided	oral gavage in male Sprague Dawley rats 14 day conventional test (10 animals/dose) or 1 week up-and-down test (1 animal/dose)	$LD_{50} = 333$ mg/kg bodyweight in conventional method, $LD_{50} = 388$ mg/kg bodyweight in up-and-down test	[23]
potassium hydroxide in water	0.1 mg/ml solution with doses increased in log fashion by factor of 2	oral gavage in 5 male/dose Carwoth-Wistar rats	$LD_{50} = 1230$ mg/kg bodyweight	[53]
potassium hydroxide	details not provided	oral gavage in 9 male/dose Charles River albino rats	$LD_{50} = 365$ mg/kg bodyweight	[54]
sodium hydroxide	0.2 N	oral study in rats (no further details provided)	Extensive damage to gastric mucosa observed	[55]
sodium hydroxide	8.3%	oral study in 2-4 mongrel cats	Superficial layer of squamous mucosa was destroyed in the esophagus; submucosal and transmural thrombosis observed in the blood vessels	[56]
sodium hydroxide	7 ml of 0.5 N	oral gavage in 26 Wistar rats (no further details provided)	Entire gastric mucosa fell off; intestinal metaplasia in 18/26 rats	[57]
sodium hydroxide in water	0.4%, 0.5%, or 0.62% corresponding to 20, 25, or 31 mg/kg bodyweight	oral study in male rats (no further details provided)	Increasing concentrations resulted in increasing gastric injury; erosion scores were 10%, 65%, and 70% for 0.4%, 0.5%, and 0.62% NaOH, respectively	[24]
		Dermal		
calcium hydroxide	2.5 g/kg bodyweight	dermal exposure to 5 male and 5 female New Zealand White rabbits; patches semi-occluded; test area 100 cm^2; test site rinsed with water after 24 h	$LD_{50} > 2.5$ g/kg bodyweight	[7]
sodium hydroxide in water	50%	Dermal exposure in groups of 27 54A/He and C57 black mice, test sites were irrigated immediately, or after 30 min, 1 h, 2 h, or not at all (no further details provided)	Mortality rate of the mice was 0%, 20%, 40%, 80%, and 71% when application sites were irrigated immediately, after 30 min, after 1 h, after 2 h, or not at all	[25]
		Inhalation		
magnesium hydroxide	2.1 mg/l	4-h whole-body inhalation of aerosol in groups of 5 male and female Wistar rats	$LC_{50} > 2.1$ mg/l	[9]
sodium hydroxide	0.75 mg/l	whole body exposure of aerosol for 2 h in 24 male Wistar rats, microscopic examinations performed on cross sections of nose, larynx, trachea with esophagus, and lungs at 1 h and 24 h post-exposure	No mortalities during test; acute laryngitis observed in 11 animals after 1 h and after 24 h; average severity of lesions was 1.58 (very slight) at 1 h and 1.25 (very slight) at 24 h	[26]

Table 8. Genotoxicity studies

Ingredient	Concentration/Dose	Study Protocol	Results	Reference
		In Vitro		
calcium hydroxide	0.3 to 3750 µg/plate	Ames test in *Salmonella typhimurium* strains TA 98, TA100, TA 1535, and TA 1537 and *Escherichia coli* strain WP2 uvr A, with and without metabolic activation	-not mutagenic	[7]
calcium hydroxide in glycerol	30, 100, or 300 mM	-chromosome aberration study, with and without metabolic activation, in human dental pulp cells -test material was incubated with cells in one of 3 scenarios: 30 h continuous treatment with colcemid added 3 h before harvest; 3 h treatment with 27 h recovery and colcemid added 3 h before harvest; or 2 h treatment with a 28 h recovery and colcemid added 3 h before harvest (metabolic activation scenario)	-not genotoxic	[27]
magnesium hydroxide in dimethyl sulfoxide (DMSO)	100 to 5000 µg/plate	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and *E. coli* strain WP2 uvr A, with and without metabolic activation	-not mutagenic	[9]
magnesium hydroxide in DMSO	1, 3, 10, or 33 µg/ml	mouse lymphoma L5178Y/TK mutation test, with and without metabolic activation	-not mutagenic -test material precipitated at concentrations greater than 33 µg/ml	[9]
magnesium hydroxide in DMSO	3, 10, or 33 µg/ml	chromosome aberration test in human lymphocytes, with and without metabolic activation	-not clastogenic -test material precipitated at concentrations greater than 33 µg/ml	[9]
potassium hydroxide in distilled water	0.01, 0.05, 0.1, 0.5, or 1 mg/plate	Ames test in *S. typhimurium* strains TA 97 and TA 102, with and without metabolic activation	not genotoxic	[10]
potassium hydroxide in distilled water	0.00945% to 0.019%	Ames test in *E. coli* strains B/Sd-4/3,4 and B/Sd-4/1,3,4,5 without metabolic activation	-ambiguous results (no further details)	[58]
potassium hydroxide	0, 4, 8, 12, 16, or 20 mM	Chinese hamster ovary (CHO) chromosome aberration test, with and without metabolic activation	-ambiguous results: positive with metabolic activation at 12 mM and pH 10.4 but negative without metabolic activation -high non-physiological pH may yield false-positive results	[59]
sodium hydroxide	details not provided	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 (no further details provided)	not genotoxic	[60]
sodium hydroxide	0, 4, 8, or 16 mM with corresponding pH values of 7.4, 9.1, 9.7, or 10.6, respectively	CHO-K1 cell chromosomal aberration test, with and without metabolic activation	not clastogenic	[59]
sodium hydroxide	details not provided	Unscheduled DNA synthesis assay in E. coli strains WP2, WP67, CM871 (no further details provided)	not genotoxic	[60]
sodium hydroxide	details not provided	Unscheduled DNA synthesis assay in E. coli strains WP2, WP2uvrA,WP67, CM611, WP100, W3110polA+, p3478pola-, with and without metabolic activation (no further details provided)	not genotoxic	[61]
		In Vivo		
sodium hydroxide (as a control substance)	10 mg/kg of 15 mM	Chromosome aberration bone marrow micronucleus assay in 5 male and 5 female CD- mice via a single intraperitoneal dose	-no significant increase of nuclei was observed	[62]
sodium hydroxide (as a control substance)	0.3-0.4 ml of 0.01 M	Aneuploidy induction study in female Swiss mice oocytes; mice injected intraperitoneally and chromosome spreads were made 12 h after injection (no further details provided)	-no non-disjunction observed	[63]

Table 9. Dermal irritation studies

Ingredient	Concentration/	Study Protocol	Results	Reference
		In Vitro		
magnesium hydroxide	details not provided	Human three dimensional epidermal model using 10 mg test material moistened with 25 µl purified water	Not irritating	[9]
magnesium hydroxide	details not provided	Human three dimensional epidermal model using 25 mg test material moistened with 25 µl purified water	Not corrosive	[9]
potassium hydroxide	10%	Epiderm and Skin^{2}ZS1301 in vitro models (validation study)	Corrosive	[64]
potassium hydroxide	5% and 10%	In vitro skin corrosion – transcutaneous electrical resistance test (TER) (validation study)	Corrosive at both concentrations tested	[65]
potassium hydroxide	5% and 10%	Skin^{2}ZK1350 in vitro model (validation study)	Corrosive at 10%, non-corrosive at 5%	[65]
potassium hydroxide	5%	Leiden human reconstructed epidermal in vitro model (validation study)	Corrosive and irritant	[66]
potassium hydroxide	5% and 10%	In vitro membrane barrier test method (validation study)	Corrosive at both concentrations tested	[65]
potassium hydroxide	5%	SkinEthic in vitro model	Irritant	[67]
potassium hydroxide	5% and 10%	Episkin model (validation study)	Corrosive at both concentrations tested	[65]
potassium hydroxide	10%	SkinEthic reconstituted human epidermal model (validation study)	Corrosive	[68]
sodium hydroxide in water	4.9%	Skin^{2}ZK1350 in vitro model	Corrosive	[69]
sodium hydroxide in water	16% and 24%	-irritation study in Yorkshire weanling pigs skin flaps -test area was 5 cm^2 area on the lower abdominal skin -dose volume = 200 µl	Severe necrosis of all epidermal cell layers and dermis, with some lesions extending into the subcutaneous layers. A decrease in glucose utilization and changes in vascular resistance were observed	[70]
sodium hydroxide	1%	-in vitro study using human breast or abdominal tissues -test material (150 µl) applied to the epidermis of at least 6 skin discs for 24 h before rinsing with water -transcutaneous electrical resistance (TER) was measured	Corrosive effects observed (TER was below 11.0 kohms/disc at 7.7)	[30]
		Non-Human In Vivo		
calcium hydroxide	details not provided	-irritation study in 3 Himalayan rabbits -treated skin was cleaned with soap and water immediately after exposure -0.5 g test material applied to shaved skin for 4 h -sites graded immediately and at 1, 24, 48, and 72 h and on days 7 and 4 post-exposure	Irritating but not corrosive	[7]
calcium hydroxide	details not provided	-Draize irritation study in 3 New Zealand White rabbits -0.5 g test material applied to shaved skin and semi-occluded for 4 h -sites graded at 1, 24, 48, and 72 h post-patch removal	Not irritating	[7]
calcium hydroxide	details not provided	-5 male and 5 female New Zealand White rabbits -2500 mg/kg applied via semi-occluded patches on shaved skin for 24 h -treated skin was rinsed with water 24 h after application	Irritating; redness followed by scabbing, was observed at the test site following rinsing	[7]

Table 9. Dermal irritation studies

Ingredient	Concentration/	Study Protocol	Results	Reference
potassium hydroxide	1% and 2%	-Draize irritation study in 6 rabbits -occlusive 1 in^2 patches on clipped skin -0.5 ml applied for 4 h	Not corrosive at 1%, corrosive at 2%	[37]
potassium hydroxide	10%	-irritation study in 6 Hartley guinea pigs -0.5 ml test material on intact and abraded skin for 4 h, patches occluded -sites graded after 4, 24, and 48 h	Corrosive	[71]
potassium hydroxide	5% and 10%	-6 rabbits exposed to 0.2 ml test material in 19 mm diameter Hill Top chamber for 1 or 4 h or 0.5 ml on Webril gauze patches for 4 h -patches occluded -sites graded 30 min, 24, 48, and 72 h after patch removal	Severe irritation at both concentrations tested	[72]
potassium hydroxide	10%	-irritation study in 6 rabbits -0.5 ml test material applied under occlusive patches on abraded and intact skin for 4 h -sites observed after 4, 24, and 48 h	Corrosive	[71]
potassium hydroxide	5%	-modified Draize study in 6 albino rabbits -0.1 ml test material applied to area of 20 mm^2 for 24 h under occlusive patches on abraded and intact skin	Mild irritant on intact skin, extreme irritant on abraded skin	[54]
sodium hydroxide	details not provided	-stepwise screening test for skin irritation in mice (no further details provided)	-minimum concentration for skin irritation was 5% (50 mg/kg) -minimum intradermal test response was 0.25% to 0.3% (1.25-1.5 mg/kg)	[38]
sodium hydroxide	8%	-test material was applied for 1 min with 2 cm diameter filter paper to the abdomens of 20 SD rats -test area was washed with 500 ml distilled water at 1, 10, or 30 min post-exposure -test sites examined at 1-min intervals for up to 90 min	-subcutaneous tissue pH did not recover to pre-experiment values by the 90^{th} min -tissue pH value did not exceed 8.0 (at 1 min) -no difference in effects were observed when washing was at 10 or 30 min	[73]
sodium hydroxide	0.36% and 5%	-test material (0.5 ml) was applied for 4 h to 4 New Zealand White rabbits -semi-occluded patches on clipped dorso-lumbar skin -test sites washed after patch removal -test sites examined 1, 24, 48, 72, and 144 h after patches were removed	-test material was corrosive at 5% when tested in 1 rabbit, scores of 4 for erythema were recorded up to 168 h post-patch removal, edema scores of 1 were recorded at 24 and 48 h -no irritation was observed in 3 rabbits at 0.36%	[8]
sodium hydroxide	4.9% by weight	Irritation study in 3 Vienna White rabbits (1 male, 2 females); patches were occlusive and applied to shaved skin (one intact and one abraded site) for 24 h; sites observed for reactions at 24 and 72 h post-application with last check after 8 days	Moderately irritating with a primary irritation index (PII) score of 5.6; mild necrosis was observed after 24 h and parchment-like/leather-like necrosis was observed after 72 h that was observed after 8 days	[8]
sodium hydroxide	1% w/v aq. solution	Irritation study in 6 New Zealand White rabbits; patches were 2.5 cm^2 and the shaved sites were occluded for 2 h; sites observed for reactions at 1, 24, 48, 72 h and 7 days	Slight skin irritant; very slight erythema in 2 animals at 1 h, well-defined reaction observed in 1 animal and same very slight irritation in 2 other animals at 24 h; very slight irritation observed in 3 animals at 48 and 72 h that persisted in 1 animal until day 7	[8]

Table 9. Dermal irritation studies

Ingredient	Concentration/	Study Protocol	Results	Reference
sodium hydroxide	0.95% by weight	Irritation study in 3 female Vienna White rabbits; patches were occlusive and applied to shaved skin (one intact and one abraded site); sites observed for reactions at 24 and 72 h post-application with last check after 8 days	Mildly irritating with a PII score of 2.7; fully reversible erythema in 2 rabbits with spot-like necrosis observed at 72 h for 2 animals	[8]
sodium hydroxide	5% aqueous	Irritation study in 6 New Zealand White rabbits exposed for 2 h to 0.5 ml test material; test site was 2.5 cm^2, shaved and occluded; sites were scored at 24, 48, and 72 h and on day 7	Skin irritant; Slight dermal irritation observed in 3 animals 1 h post-patch removal; 1 rabbit had caustic burn with "in depth" skin damage and small dermal hemorrhages; 2 rabbits had small dermal hemorrhages with some slight tissue necrosis; similar reaction observed at 24, 48, and 72 h and on day 7; one patch had poor skin contact during the 2 h patching	[8]
sodium hydroxide in water	8%, 16% or 24%	-irritation study in 4 Yorkshire weanling pigs -200 µl on a 5 cm^2 area on the lower abdominal skin for 30 min	-highly irritating at 8% and 16%, corrosive at 24% -gross blisters developed within 15 min of application -8% and 16% produced severe necrosis in all epidermal layers -24% produced numerous and severe blisters with necrosis extending into the subcutaneous tissue	[70]
		Human		
sodium hydroxide	0.5% in aq. solution	-test material (50 µl) used as a positive control and irritation inducer in an efficacy study of skin protective creams in 20 human subjects -test material applied on 18 mm diameter area on 5/13 test sites	-yielded expected irritation as a positive control	[6]
sodium hydroxide	0.5%	Patch test in 30 subjects with 0.2 ml of the test substance on a 25 mm Plain Hill Top Chamber containing a Webril pad for 15 and 30 min, 1, 2, 3, and 4 h.	Irritating to the skin, maximum exposure time was limited to 1 h due to strong level of response	[30]
sodium hydroxide	2% in distilled water	Closed patch test in 12 mm diameter Finn chambers of experimental irritants in 16 subjects; patch was removed after 1h	Visual median score after 24 h and 96 h was 1 out 3 (weak positive reaction), respectively	[31]

Table 9. Dermal irritation studies

Ingredient	Concentration/	Study Protocol	Results	Reference
sodium hydroxide	up to 5% aq.	-patch test in healthy male volunteers of 7 known irritants to determine the optimum concentration to produce mild to moderate reactions in ~75% of individuals tested; -test substance (30 µl/cm^2) applied to the volar area of the forearm with 8 mm Finn chambers; -patches removed after 48 h and reactions assessed 1 h later.	-0% of the subjects had a positive reaction at 1%, 29% of the subjects had a positive reaction at 2%, and 100% of the subjects had a positive reaction at 4%; -at 2%, 4 subjects had +/- reactions; -at 3%, 2 subjects had +/- reactions, 1 subject had 1+ reaction, and 4 subjects had 2+ reaction; -at 5%, 2 subjects had 3+ reaction and 1 subject had 4+ reaction; -the severity of irritant reactions to sodium hydroxide rose sharply with increasing concentration, with considerable pain in some volunteers, that led to removing the patches before 48 h.	[33]
sodium hydroxide	0.5% dissolved in water	-test material was used as a positive control and irritation inducer in an efficacy study of perflurorpolyethers as protective preparations; -7 male and 3 female subjects; -irritant application of 0.05 ml occurred 30 min after pretreatment with protective preparation in 12 mm diameter Finn chambers; -chambers removed after 30 min of exposure and the skin was rubbed dry; -subjects were treated over a 12-day period.	-sodium hydroxide yielded expected irritation as a positive control	[34]
sodium hydroxide	0.5% dissolved in water	-test material was used as a positive control and irritation inducer in an efficacy study of perflurorpolyethers as protective preparations; -7 male and 13 female subjects; -irritant application of 0.05 ml occurred 30 min after pretreatment with protective preparation in 12 mm diameter Finn chambers; -chambers removed after 30 min of exposure and the skin dried; -subjects were treated over a 12-day period.	-sodium hydroxide induced significant irritant reaction from day 1 until the end of the first week, and to a smaller extent from end of week1 to the end of week 2, as indicated by visual score values, transepidermal water loss (TEWL), and chromametry of the control sites.	[29]
sodium hydroxide	2% in sterile water, pH 13.7	-closed patch test of different irritants in 16 volunteers (10 female, 6 male) on both arms using 12 mm diameter Finn chambers; -skin damage was evaluated visually and by polysulfide rubber replica; -sodium hydroxide patch was removed at the most 1 h post-application; -visual assessments of the test sites were performed 24, 48, and 96 h post-application; -skin surface imprints with polysulfide rubber were made.	-at 24 h, reactions were observed in 12 subjects with 3 being scored a 3; -at 48 h, reactions were observed in 9 subjects with 5 being scored a 3; -at 96 h, reactions were observed in 11 subjects with 4 being scored a 3; -in 31% of the imprints, skin damage was observed	[32]

Table 9. Dermal irritation studies

Ingredient	Concentration/	Study Protocol	Results	Reference
sodium hydroxide	1 g/v% in distilled water, pH 12.7	-test of barrier function of the skin following exposure to low concentrations of known irritants; -allergic patch testing in 42 subjects with miscellaneous diseases; -test sites were on unaffected skin of the volar forearm; -test substance (100 µl) was applied for 48 h by 12 mm Finn chambers; -24 h post-exposure, the skin water vapor loss was measured.	-sodium hydroxide was observed to increase skin water vapor loss when compared to unexposed skin ($3.6\ g/m^2\ h \pm 2.0$, $p < 0.05$).	[36]
sodium hydroxide	0.5 mol/l	-19 subjects received two 30 min exposures/day with a 3-h interval for 4 days -50 µl test material via occlusive (Finn Chambers or Scanpor 12 mm diameter discs) and non-occlusive patches -test sites were rinsed with 10 ml of tap water and dried after the 30 min applications	-highly irritating -application of test material was discontinued after the 3rd day because of the severity of the reactions -increased in TEWL values observed at day 3 -visual scores showed highly significant irritation	[35]

Table 10. Ocular irritation studies

Ingredient	Concentration	Study Protocol	Results	Reference
		Non-Human – In Vitro		
calcium hydroxide	50 mg, no further details provided	-HET-CAM in vitro test	-irritating	[7]
calcium hydroxide	250 mg, no further details provided	-HET-CAM in vitro test	-irritating	[7]
magnesium hydroxide in physiological saline	details not provided	-BCOP in vitro test	-not irritating -irritancy score was 501 after 240 min of treatment	[9]
		Non-Human – In Vivo		
calcium hydroxide	150g/l	-acute eye irritation/corrosion study in 3 male New Zealand White rabbits -0.1 ml instilled into the conjunctival sac of one eye, eye was not rinsed -observations made at 1, 24, 48, and 72 h after treatment up to 21 days	-irritating	[7]
calcium hydroxide	10%, pH 9	-acute eye irritation/corrosion study in 1 male New Zealand White rabbit -100 mg instilled into the conjunctival sac -eyes examine after 1 h	-irritating -very severe reactions were observed 1 h after exposure, with pronounced chemosis, necrotized appearance of the conjunctiva, whitish watering and total opacity of the cornea, showing nacreous appearance -iris became totally obscured -test was discontinued after treatment with 1 rabbit for humanitarian reasons.	[7]
calcium hydroxide	0.01, 0.03, or 0.10 g, no further details provided	-acute eye irritation/corrosion study in New Zealand White rabbits -9 rabbits received low dose, 6 rabbits each received medium and high doses -test material applied directly to the cornea of one eye of each rabbit -observations made a 1, 3, 7, 14, and 21 days after treatment	-irritating -study halted at 14 days for the medium and high dose groups due to severe eye irritation -expected return to normalcy in the eye of the low dose group was greater than 21 days.	[39]
magnesium hydroxide	details not provided	-acute eye irritation/corrosion study in 3 male New Zealand White rabbits -rabbits received an average instillation of 57.3 mg (dose volume 0.1 ml) of the test substance in the conjunctival sac of one eye, eye was not rinsed -observations made at 1, 24, 48, and 72 h after instillation	-not irritating -slight dulling of normal luster and/or epithelial damage in 2 rabbits resolved within 24 or 48 h -iridial irritation grade 1 observed in all rabbits resolved within 24h -irritation of the conjunctivae consisting of redness, chemosis, and discharge in all rabbits resolved within 72 h	[9]
potassium hydroxide in water	0.1%, 0.5%, 1%, 5%	- acute eye irritation/corrosion study in 10 albino rabbit eye -0.1 ml instilled for 5 min or 24 h, with observations performed at 1, 24, 48, and 72 h and 7 days -eyes rinsed following exposure	-highly corrosive at 5% for 5 min (1 rabbit) -irritant at1% for 5 min (3 rabbits) -marginal irritant at 0.5% for 24 h (3 rabbits) -no ocular reactions at 0.1% for 24 h (3 rabbits)	[54]
sodium hydroxide in water	1.0% or 2.0%	- acute eye irritation/corrosion study in 6 New Zealand White rabbits -0.1 ml instilled into lower conjunctival sac -observations made a 4, 24, 48, 72, and 96 h	-2% caused moderate corneal injury (score = 2.0 out of 4); severe conjunctival irritation was observed between 4 and 96 h -lesser effects were observed with the 1% solution (no further details provided)	[40]

Table 10. Ocular irritation studies

Ingredient	Concentration	Study Protocol	Results	Reference
sodium hydroxide in water	0.5% or 10%	- acute eye irritation/corrosion study in New Zealand White rabbits -3 groups of 3 rabbits for 0.5%; 4 groups of 3 rabbits for 10% -0.5% groups received 0.01, 0.03, or 0.1 ml -10% groups received 0.003, 0.01, 0.05 ml, or 0.1 ml -observations made at 1 h and 1, 2, 3, 4, 7, 14, and 21 days -eyes were not washed	-slight eye irritant at 0.5%, corrosive at 10% -at 0.5%, no corneal effects at 0.01-0.1 ml; grade 1 iridial effects observed in 2/3 animals that cleared by day 1 at 0.1ml -at 10%, irreversible effects on the eye at 0.05 and 0.1 ml	[8]
sodium hydroxide	details not provided	-eye irritation study in rats (no details provided)	-eye irritation observed at a concentration of 1.25%	[38]
sodium hydroxide in distilled water	0.004% (0.001 M) , 0.04% (0.01 M), 0.2% (0.05 M), 0.4% (0.1M), 1.2% (0.3 M)	- acute eye irritation/corrosion study in a minimum of 7 Stauffland albino rabbits -0.1 ml instilled into the lower conjunctival sac -observations made 1, 2, 3, 4, 7 days, then every 3-4 days up to 21 days post-treatment	-non-irritating at 0.004%-0.2% -mild irritation at 0.4% -corrosive at 1.2%	[41]
sodium hydroxide in water	0.1%, 0.3%, 1.0%, or 3.0% corresponding to pH values of 12.3, 12.8, 13.1, or 13.5	- acute eye irritation/corrosion study in New Zealand albino rabbits -2 groups of 6 rabbits; eyes were washed 30 sec after exposure for 2 min with 300 ml tap water and eyes were unwashed after exposure in the second -0.1 ml instilled into conjunctival sac -observations made 1 h and 1, 2, 3, and 7 days post-treatment	-conjunctivitis observed at 1.0% and 3.0% that lasted through day 7 -duration of corneal opacities produced by 1.0% reduced as a result of washing test eyes 30 s after instillation	[42]

Table 11. Sensitization studies

Ingredient	Concentration	Study Protocol	Results	Reference
		Non-Human		
potassium hydroxide in water	0.1%	Intracutaneous repeat insult test in 5 male albino guinea pigs	not sensitizing	[54]
magnesium hydroxide in propylene glycol	0%, 10%, 25%, or 50%	Local lymph node assay (LLNA) in groups of 5 female CBA/J mice	-sensitizing -SI values for 10%, 25%, and 50% were 2.0, 3.6, and 5.9, respectively -EC_3 value calculated to be 19.4% -very slight erythema was observed in all animals treated at 50%	[9]
		Human		
sodium hydroxide	induction 0.63% to 1.0%; challenge 0.125%	modified HRIPT in 15 male subjects	-not sensitizing -irritation response well correlated with the concentration of the irritant	[74]

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