Safety Assessment of Inorganic Hydroxides as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 20, 2015
Panel Meeting Date: December 14-15, 2015

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist CIR.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 20, 2015
Subject: Draft Final Report of the Safety Assessment on Inorganic Hydroxides

Enclosed is the Draft Final Report of the Safety Assessment of Inorganic Hydroxides as Used in Cosmetics. (It is identified as *inooh092015rep* in the pdf document).

At the September 2015 meeting, the Panel issued a tentative report with the conclusion that calcium hydroxide, magnesium hydroxide, potassium hydroxide, and sodium hydroxide are safe in hair straighteners under conditions of recommended use; hairdressers should avoid skin contact and minimize consumer skin exposure. These ingredients are safe for all other present practices of use and concentration described in this safety assessment when formulated to be nonirritating.

It should be noted that the Panel only discussed the safety of these ingredients for the functions of pH adjusters, depilatories, and hair straighteners. The *International Cosmetic Ingredient Dictionary and Handbook* also lists the functions of absorbent for magnesium hydroxide and denaturant for sodium hydroxide. The Panel should have a discussion about the safety of these ingredients for these other functions.

Since September, no new unpublished data have been received. Tables and associated text with example formulations of depilatories and hair straighteners from the reference *The Chemistry and Manufacture of Cosmetics Vol. II – Formulating* have been included in this draft final report (highlighted with pink shading). Does the Panel find this information useful and should it be included in the report?

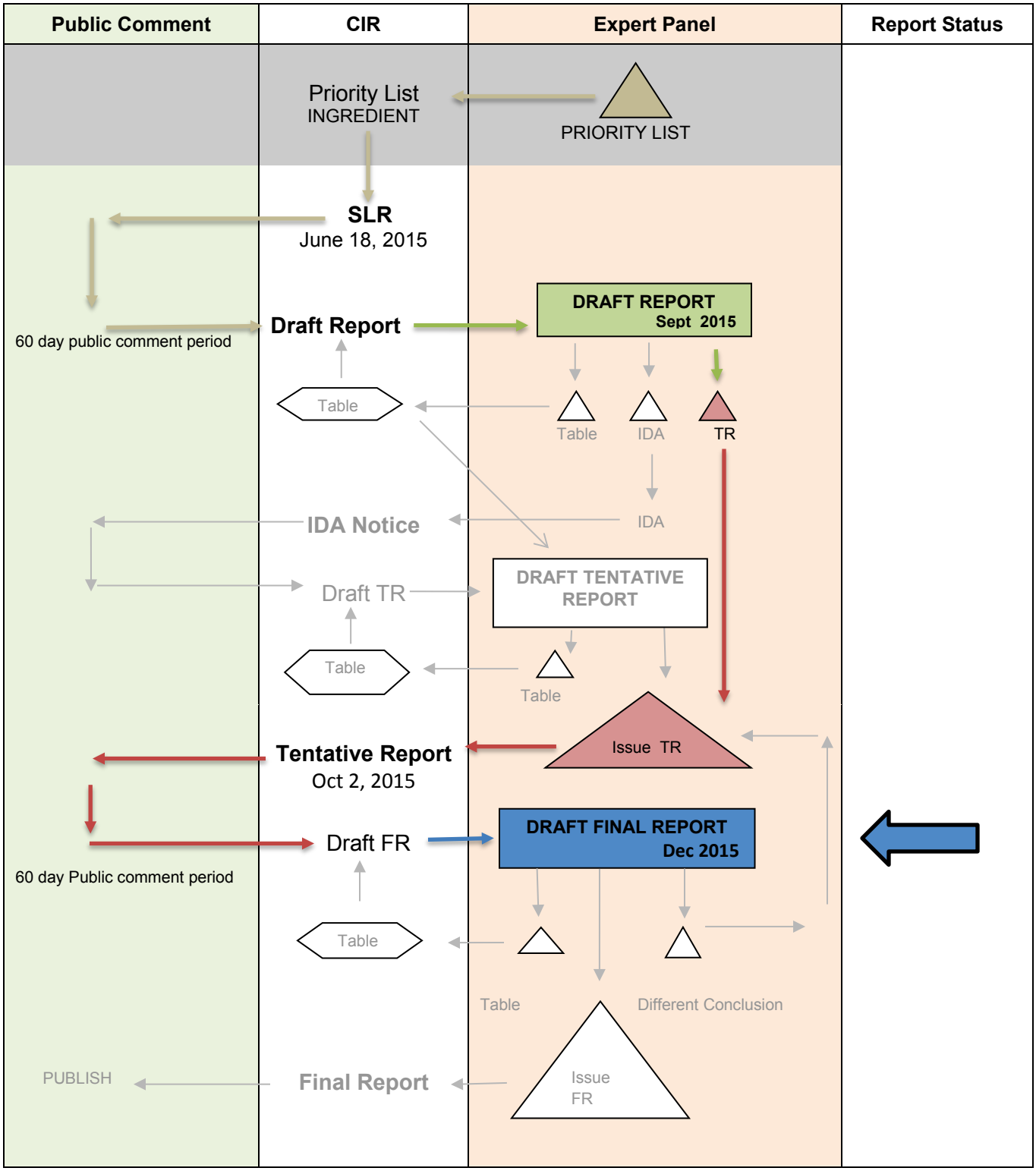
Comments provided by the Council prior to the September meeting and on the tentative report have been addressed and are included in this report package for your review (*inooh122015pcpc1* and *inooh122015pcpc2*).

The Panel should carefully review the abstract, discussion, and conclusion of this report and issue a Final Safety Assessment.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Inorganic Hydroxides

MEETING Dec 2015



Inorganic Hydroxides History

June 2015 – Scientific Literature Reviews announced for Inorganic Hydroxides.

September 2015 - The Panel issued a tentative report for public comment with the conclusion that the 4 inorganic hydroxides are safe for use as pH adjusters or depilatories when formulated to be nonirritating, and are safe for use as hair straighteners under conditions of recommended use. Hairdressers should avoid skin contact and minimize consumer skin exposure.

The Panel recognized that while these ingredients may be dermal and/or ocular irritants, their uses as pH adjustors in cosmetic formulations dictates that most of the alkalinity will be neutralized to yield various salts. Furthermore, the concentration of the inorganic hydroxides used depends on the acid content of the formulations. Therefore, the concentration of free inorganic hydroxide is expected to be low in the formulations, and systemic toxicity is not expected to be a concern. The safety of inorganic hydroxides as pH adjustors should not be based on the concentration of use, but on the amount of free inorganic hydroxide that remains after neutralizing the formulation.

While not listed as a function in the International Cosmetic Ingredient Dictionary and Handbook, the Panel discussed the use of inorganic hydroxides as depilatories and hair straighteners at very high pH values. If these hydroxides are used in hair care products, a limitation on use concentration and adequate instructions to hairdressers to avoid skin contact (such as by wearing gloves) and to minimize consumer skin exposure (by limiting the frequency of product use) would be adequate to assure that irritation is not a concern. The Panel noted that repeated applications of hair straighteners containing inorganic hydroxides by hairdressers to multiple clients over a period of time should be avoided unless adequate skin protection is provided.

Regarding the use of inorganic hydroxides in depilatories, the Panel recognized that nearly all methods of hair removal cause some degree of irritation. Based on clinical experience of the Panel, although these chemicals have the potential to be severely irritating to the skin, clinically significant adverse reactions to these ingredients used in depilatories are not commonly seen. This suggests that current products are formulated to be practically nonirritating under conditions of recommended use. Formulators should take steps necessary to assure that current practices are followed. The conclusion notes that inorganic hydroxides in depilatories are safe when formulated to be non-irritating and safe as hair straighteners under conditions of recommended use (which include avoidance of contact with skin).

Inorganic Hydroxides Data Profile – December 2015 – Writers: Christina Burnett and Bart Heldreth															
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition/Impurities**	**Toxicokinetics**	**Acute Toxicity**	**Repeated Dose Toxicity**	**Repro. /Develop. Toxicity**	**Genotoxicity**	**Carcinogenicity**	**Irritation/Sensitization – Non-Human**	**Irritation/Sensitization - Human**	**Ocular/Mucosal**	**Phototoxicity**	**Case Studies**
Calcium Hydroxide	X	X	X	X		X			X		X		X		
Magnesium Hydroxide	X	X	X	X		X		X	X		X		X		
Potassium Hydroxide	X	X	X	X		X			X		X		X		
Sodium Hydroxide	X	X	X	X		X			X		X	X	X		

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

Search Strategy for Inorganic Hydroxides (Performed by Christina Burnett)

November 2014-May 2015: SCIFINDER search for 4 inorganic hydroxide ingredients, including available CAS numbers::

- Initial search for "adverse effect, including toxicity" yielded:
  - 855 references for sodium hydroxide
    - Limits for "dermal" yielded 30 results, 20 relevant
    - Limits for "irritation" yielded 147 results, 107 relevant
    - Limits for "sensitization yielded 58 results, 31 relevant
  - 144 references for potassium hydroxide
    - Limits for "dermal" yielded 13 results, 7 relevant
    - Limits for "irritation" yielded 42 results, 36 relevant
    - Limits for "sensitization yielded 21 results, 16 relevant
  - 194 references for magnesium hydroxide
    - Limits for "dermal" yielded 2 results, 0 relevant
    - Limits for "irritation" yielded 8 results, 0 relevant
    - Limits for "sensitization" yielded 5 results, 0 relevant
  - 600 references for calcium hydroxide
    - Limits for "dermal" yielded 8 results, 1 relevant
    - Limits for "irritation" yielded 21 results, 4 relevant
    - Limits for "sensitization" yielded 35 results, 1 relevant

Search Terms	TOXLINE Hits (excluding PUBMED, English only)	PUBMED Hits	ECHA Hits
calcium hydroxide OR 1305-62-0	513	6201 dermal = 9 irritation = 23 sensitization = 7	yes
magnesium hydroxide OR 1309-42-8	361	1820 dermal = 5 irritation = 1 sensitization = 3	yes
potassium hydroxide OR 1310-58-3	514	1995 dermal = 6 irritation = 8 sensitization = 1	yes
sodium hydroxide OR 1310-73-2	2158	8568 dermal = 22 irritation = 59 sensitization = 11	yes

Total references ordered or downloaded: 67

Search updated October 22, 2015 – 0 relevant references found.

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Inorganic Hydroxides
September 21-22, 2015

Dr. Belsito's Team

DR. BELSITO: Okay. Inorganic hydroxides. First time we're looking at this. Safe as used when formulated to be non- irritating. Are we done?

SPEAKER: I think so.

MR. STEINBERG: Two --

DR. BELSITO: Yes.

MS. BURNETT: Yes.

MR. STEINBERG: There are two uses which were not mentioned which are very critical. One is --

DR. BELSITO: This is wave 3.

SPEAKER: Wave data.

SPEAKER: It was information that was on (inaudible) from just these search and from the use standard I have.

SPEAKER: That's impact as safe as used?

MR. STEINBERG: Okay, one is the use of these inorganic bases as hair relaxers, ethnic hair care products. They're basically sold with a PH around 13. Okay. And the other is depilatories.

DR. BELSITO: I guess really relaxes the hair, right?

MR. STEINBERG: Yeah.

DR. BELSITO: They're bald afterwards, is that it?

MR. STEINBERG: No, no. Because of the way it's formulated. And then depilatories, which takes all the hair off. Okay. And they both are very alkaline materials and they are made alkaline by the use of these inorganic hydroxides.

DR. BELSITO: Okay. But still are they safe as long as they're not irritating?

MR. STEINBERG: Well, they're irritating. At the PH of 13 they're irritating. They have to be used properly and labeled properly, then they're safe.

DR. BELSITO: Safe when formulated to be irritating with the instructions that they will irritate?

MR. STEINBERG: Safe if you follow the instructions.

SPEAKER: So why don't we capture those uses?

MS. BURNETT: I worked on the thioglycolates report several years ago and we had a conclusion of safe -- no -- he has --

DR. HELDRETH: So for depilatories they're safe when formulated to be non-irritating under conditions of recommended use. For the hair straightening treatment it was described that hairdressers should avoid skin contact and minimize consumer skin exposure. That was the caveat thrown into the conclusion for the straighteners. That's where very high concentration comes in.

MS. BURNETT: Our discussion has a -- robust discussion on precautions and following directions.

DR. BELSITO: Okay. So why don't we go as a tentative final, in terms of safe as used when formulated to be non-irritating as a PH adjuster, and then introduce the language from thioglycolates and the --

MR. STEINBERG: Hair relaxers.

DR. BELSITO: For the hair relaxers. And you said we had some language for thioglycolates. And what was the other one?

DR. HELDRETH: Yeah, it was also for thioglycolates when used for the hair products (inaudible) and that should avoid skin contact and minimize consumer exposure.

DR. BELSITO: Okay. So for depilatory, formulated to be non-irritating under recommended conditions of use. And for hair care, minimize skin contact. So bring that language into the report, we'll go as a tentative final, safe as used, and we'll review it. We can always revoke our approval at that point when we see it, but we'll add -- so we need to add the cosmetic functions of depilatory and hair relaxer, and then go from there. If you do that, Christina, will there be, do you think some data that you can capture in the literature that isn't in these reports in terms of safety data?

MS. BURNETT: I will go look for it, but I didn't see it the first time around.

DR. BELSITO: Okay.

MS. BURNETT: And Carol, the only thing she found in terms of hair straighteners was a case study of children swallowing it.

DR. BELSITO: Oh, nice.

MS. BURNETT: Yeah.

DR. BELSITO: I don't think that's pertinent to cosmetic use.

MS. BURNETT: No. And that's why there --

SPEAKER: That's a medical use.

MS. BURNETT: -- was no red flags on this because there weren't any cosmetic use case reports that came up. It was all --

DR. BELSITO: Right.

MS. BURNETT: Part of ingestion, you know, poison control, accident and on purpose stuff like that.

DR. SNYDER: So concentration of use -- are they used as relaxers and depilatories?

DR. BELSITO: It's probably high.

DR. KLAASSEN: High, four or five percent.

MS. BURNETT: Yeah. I think it's at six on one of them. And we were aware that was used as depilatories, but it did not set off flags I guess.

SPEAKER: Do you know how quick an exposure is (inaudible)?

SPEAKER: We have some up on 12 percent.

DR. BELSITO: For depilatories?

DR. LIEBLER: For depilatories.

DR. BELSITO: Yeah, it's like Neet and Nair. You've never used them?

SPEAKER: Never.

DR. LIEBLER: Actually, since we're done I'll tell a good story.

DR. BELSITO: So are we done now?

SPEAKER: I think so.

DR. BELSITO: So for the inorganic hydroxides we're going to say safe as used, we're going to add the function of the depilatory and hair relaxers, and we're going to bring in the language from the thioglycolate report for the discussion. And the conclusion of the safe as used according to directions and not for skin contact in hair relaxers, whatever. Okay? And it will come back as a tentative final in December. Okay, we're done.

Dr. Marks' Team

DR. MARKS: Okay. This is the first review of these four alkaline salt ingredients. They're pH adjusters. Not surprising, they're corrosives. So the four salt ingredients, okay. Same routine, Ron, Ron, and Tom, they look good? I see Ron Hill shaking his head. Ron Shank and Tom. And then are there any needs?

DR. EISENMANN: One other thing. They also work in hair relax or products. We need to consider those because those products have very high pHs. So it's not just pH adjusters. It's these hair relaxer products also which can have 11 to 14 pH. They have various warnings and various instructions for use, neutralizing shampoos to go with them. Things like that. That was a product category that also has to be considered.

DR. MARKS: Thank you for pointing that out. Christina, maybe I missed it? If not, it should be in the discussion that they can be. So what you're saying, they're in corrosive -- well, you'll see. My conclusion was that we move a tentative report with a conclusion safe when formulated to be non-irritating, so that takes care of it. If you formulate it to be non-irritating or one could say formulated to be used non-irritating would take care of that I would assume.

DR. EISENMANN: No, I don't think so. FDA has a face statement on those products which might be helpful that says to follow the directions and you shouldn't use products within several days of combing or scratching your head. A lot of details.

DR. SHANK: These are used by a consumer at pH 14?

DR. EISENMANN: Beauty salons.

DR. SHANK: On the head?

DR. EISENMANN: Yes. But I understand some of the higher pH products, the ones with lye are mostly professional products. It's the ones with calcium hydroxide, I guess, that they consider no lye relaxer. They still have high pH. Those are the ones that are used at home more.

DR. BERGFELD: But the calcium is better than the sodium and potassium.

DR. EISENMANN: I guess. But it's used with another ingredient that makes it still have a high pH.

DR. MARKS: So if we say safe when formulated to be non-irritating you're saying that the final formulation of these products are irritating. We know that. So how do we deal with that when we know it's out there being used and give guidance? Formulate to be non-irritating, does that include what you're saying all these instructions and use?

DR. EISENMANN: I think you'd have to have a separate conclusion for these additional products and say, similar to what the FDA has said or something that you follow the directions.

DR. MARKS: So that's an interesting proposal for changing for the first time having a conclusion that's a -- and these are, you said relaxers, so essentially hair straighteners?

DR. EISENMANN: Correct.

DR. BERGFELD: It doesn't appear in your concentration of use table, a straightening process. I'm just looking at it.

MS. BURNETT: I am looking at the concentration of use data the council provided for hair straighteners I see up to 3 percent.

DR. EISENMANN: The EU does have limits for those types of products too, also I think.

MS. BURNETT: I don't see --

DR. HILL: Now I know why they set them.

MS. BURNETT: -- I don't see any uses for that --

DR. HILL: What was puzzling about that.

MS. BURNETT: -- for that test with hydroxide. It's used up to 6 percent calcium hydroxide for hair straighteners. I don't see it for over 6 percent.

DR. BERGFELD: In the I studies it was 10 percent.

MS. BURNETT: So the highest for hair straighteners is 6 percent --

DR. BERGFELD: Seven.

MS. BURNETT: -- calcium hydroxide.

DR. BERGFELD: Forty two in depilatories.

MR. STEINBERG: It's also used in depilatories to get the pH way up there. I think you have to separate the use of these materials to adjust pH versus to use them as actual reactive chemicals.

DR. MARKS: So I'm still struggling with a conclusion because this will be a new twist with how we saw follow manufacturers. In the discussion we can certainly have a robust discussion about how the high pH in these hair care products, maybe we can come under that. If you're using as a depilatory and a hair straightener it's really a hair care product, per say. I don't know how you want to form. But how do we acknowledge that other than in the discussion? Formulated to be non-irritating. Usually that's the end product, so if it's formulated to be non-irritating does that also have to do with use. Although we have had in the nail products we give instruction the operator should not get it on the skin, as I recollect, something to that effect. Where we do have a conclusion that addresses use. I guess you could say formulated to be and used to be not irritating.

MR. STEINBERG: But depilatories are put directly on the skin.

DR. MARKS: Oh yes.

DR. BERGFELD: And they're put on by your hand with no glove.

MR. STEINBERG: Yes. I mean, it's just put on.

DR. MARKS: Yes. But the experience is, obviously, the vast majority of users don't get significant irritation or the product would not be on the market. I mean, I can't remember seeing a patient coming in to see me that they used a depilatory and I'm going to treat the toxic effect of that depilatory on their skin.

DR. BERGFELD: I would concur. What are the instructions in the use? Maybe those could be added?

MS. BURNETT: Several years ago we reviewed the thiogylcolate which is a depilatory, and we had --

DR. MARKS: Thank you, Christina.

MS. BURNETT: -- a specific conclusion there that they were safe for use in hair straighteners -- oh wait. As depilatories are safe when formulated to be non-irritating under conditions recommended for use.

DR. BERGFELD: Okay. That's nice.

DR. MARKS: When formulated being non-irritating and what was the rest of it?

MS. BURNETT: Under conditions of recommended use.

DR. MARKS: There you go.

DR. HILL: Can we go back to those ones that are recommended, is it Europe that says professional use only or even in this country marketed for -- or that's the ones that the FDA regulates? I'm fuzzy in my head now.

MS. BURNETT: The formaldehyde one?

DR. HILL: No, no.

MS. BURNETT: Brazilian blow out?

DR. HILL: Talking about these. I thought I heard you just say that the calcium hydroxide were readily available to the consumer, but the ones that are --

DR. MARKS: Well depilatories certainly are.

MS. BURNETT: It depends.

DR. MARKS: I don't know about hair straighteners. I --

MS. BURNETT: It looks here in one table --

DR. MARKS: -- assume --

MS. BURNETT: -- in sodium hair straighteners 2.4 percent to 3 percent. That's the sodium.

DR. MARKS: Yes.

MS. BURNETT: And the calcium I know is in here.

DR. MARKS: Yes, see calcium hydroxide.

DR. HILL: But the sodium hydroxide is a much stronger base, so it's not the concentration. I mean, that percentage of sodium hydroxide unadjusted would be lye. They're putting lye on their --

DR. MARKS: And that's -- Wilma, you're actually one of the hair experts. Presumably, this is mainly going to affect ethnic hair.

DR. BERGFELD: Yes. African American usually.

DR. MARKS: Yes, African American use. Actually, in my experience it's not irritation that's the issue. The fracture of the hair shaft --

DR. BERGFELD: Exactly.

DR. MARKS: -- and patients come in -- you know, I see patients. So I'd like the idea of safe when formulated to be non-irritating under conditions of use covers it.

DR. BERGFELD: I think that says it all.

DR. MARKS: Yes.

DR. HILL: How much precaution is given? Because if you get something like that in your eye you're in trouble. You've got to rinse profusely and for a long period of time.

DR. BERGFELD: Those would be conditions of use. They would have descriptions of how to use them.

DR. MARKS: Yes.

MR. STEINBERG: Most of the hair relaxers for the ethnic hair care the instructions start by putting petrolatum on the scalp to protect the scalp from the irritation of the relaxer.

DR. MARKS: Yes.

MR. STEINBERG: I probably, and I haven't thought this through completely, but the idea should be something to the effect, be sure you follow the instructions. Because all these products have instructions and warnings on them about how to use them correctly to prevent the irritation for the use as hair relaxers. Depilatories are another story which is more complex.

DR. MARKS: Yes. But again, I think just as we used on thioglycolate if we use that same conclusion, formulated to be non-irritating under conditions of use that covers it. You know, again, conditions of use and follow the instructions. Unless they have a high enough concentration it's not, as you well know, David, it's not going to be a depilatory.

MR. STEINBERG: It doesn't work.

DR. MARKS: Yes. It doesn't work. And we know under the instructions that are provided with these products, consumer products, that the vast majority of time they're quite safe. Ron Shank?

DR. BERGFELD: The breaking all your hair.

DR. SHANK: The depilatory I presume is formulated to be non-irritating. You say it's used to remove hair, but it doesn't irritate the skin.

DR. BERGFELD: No, it doesn't.

DR. SHANK: Okay. But the hair straightener.

DR. BERGFELD: Well, but it dissolves the hair.

DR. SHANK: If you remember the discussions we had with the Brazilian blowout.

DR. BERGFELD: That was an inhalation problem.

DR. SHANK: I think we concluded -- okay. The conclusion was even -- we didn't have confidence that it was always used the way it should be used, and that was heavily discussed. Now you're talking about something that's also potentially very threatening to the eye.

DR. BERGFELD: I can honestly say in 40 years of practice we've never seen an eye problem from it.

DR. SHANK: Why?

DR. BERGFELD: We've just seen dissolving of the hair fibers.

DR. SHANK: I don't understand. I would think if this is used by the consumer at home there's never been a reported eye incident?

DR. BERGFELD: I don't know about reported, but in the office it's never been a problem nor has skin irritation on the body for the depilatories. Unless misused. I suspect misuse, longer applications. They have timed applications of several minutes.

DR. MARKS: So I would answer two ways, Ron. I agree with Wilma, I've never seen it. But I'm a dermatologist, not an ophthalmologist, so they probably bypassed my clinic and moved down the hallway. Christina, in your review did you find anything in the ophthalmology?

MS. BURNETT: I did not find any case reports for cosmetic use. I mean, there's plenty of other ingestion incidences, purposely or accidentally, but I didn't find anything.

DR. EISENMANN: Last week I did hair relaxers. I'm certain I did find this on emergency for children that swallowed hair relaxer products.

DR. BERGFELD: Different.

DR. EISENMANN: Well, actually it almost sounds like they were surprised it wasn't worse. That there was no long term effect for these kids. So I guess they can neutralize these products fairly readily when that does happen.

DR. BERGFELD: I suppose they're neutralized with water, actually. I suspect.

DR. EISENMANN: Maybe that's why you're not seeing the eye because it hurts so much you do put water in right away and maybe that's why.

DR. MARKS: I can't imagine there isn't a disclaimer about, as with other products --

DR. EISENMANN: There is.

DR. MARKS: -- if it gets in your eye you --

DR. EISENMANN: There is.

DR. MARKS: -- flush immediately. You know it's not going to be a delayed corrosive effect.

DR. EISENMANN: One more I have. It says if relaxer goes into eyes rinse immediately and thoroughly with water and consult a physician.

DR. MARKS: Yes. Okay. Christina, did I read it correctly? Are these GRAS ingredients, Page 9?

DR. SHANK: Well, it's a food additive.

DR. MARKS: Yes.

DR. SHANK: Yes.

DR. MARKS: Yes, it's a food additive. Okay. So I would -- I didn't hear anything about the other -- we spent a great deal talking about irritation. I think we can deal with that when we use safe when formulated to be non-irritating under conditions of use. Ron, Ron, and Tom, did you have any other toxicological concerns? If not,

I'll move that we issue a tentative report with that conclusion tomorrow. In the discussion we have a robust discussion about hair straightening products.

DR. BERGFELD: And depilatories.

DR. MARKS: And depilatories, yes.

MR. BEST: I just have one question about the relationship between the concentration and the pH. So, in the European standard the pH seems to be required to be lower than, I guess, what you were saying it's used here. I was just curious what you all think about that or why they might have done that? It wasn't clear to me, I guess, how they were necessarily related? Can you have these concentrations and have a lower pH to make it safer?

DR. BERGFELD: It won't work. It won't work.

MR. BEST: Okay.

DR. BERGFELD: For the purpose that's intended, actually. You need to dissolve the hair fiber in the depilatory, and it dissolves it under the skin which is preferred by the female. On the African American who's mainly using the hair straighteners, but not only some of the curly headed other females that there's a timed relationship of how long it would be applied. The problems we get in is overuse, too frequent, or too long a time application.

MR. STEINBERG: The lower the pH the longer time it takes to remove the hair has a depilatory. So if you have a depilatory of pH-11 it will be left on the skin much longer than if the pH is a 13 where it's just put on and rinsed off in the shower almost immediately.

MR. BEST: I mean, do we know why the Europeans restricted it to that lower pH?

MR. STEINBERG: The most common reason why the most popular product on the marketplace at the time had a pH max of 12.7.

MR. BEST: So you think they may just not have been using it higher. You don't think there was like a safety reason necessarily to have it -- okay.

MR. STEINBERG: I don't believe so.

DR. HILL: Can we make sure not just in the discussion, but somewhere in the introduction that we talk about these products in the preamble to make the reader aware right up front there are these products where it's not just a pH adjustment that it's used at a very alkaline pH for the purposes. Because I didn't catch that.

MS. BURNETT: I honestly did not catch that --

DR. HILL: Yes, okay.

MS. BURNETT: -- from looking at these concentrations and the other information I had.

DR. HILL: I didn't have a whiff of that until I got down to the European restrictions --

MS. BURNETT: Right.

DR. HILL: -- on those pHs and then I said, oh.

MS. BURNETT: Right. Even the stated functions in the dictionary don't necessarily tell me that. They just say pH adjusters and absorb it which I'm not sure what that is.

DR. MARKS: Yes. So Ron Hill, I think that's exactly correct, so maybe a sentence or two in the introduction to alert the reader, and then, obviously, a more robust explanation in the discussion. Both the irritant potentially ordinate effects, but following the instructions, and a lack of case reports in the literature of any significant consumer harm by these products.

Okay. So again, I'm going to move tomorrow tentative report with a conclusion safe when formulated to be non-irritating under conditions of use. That should take care of -- Carol, thank you very much for bringing up that nuance. I don't know about Ron Hill and I, but the two of us missed this use. So thank you, Carol. Any other comments?

Okay. Let's see. Michael, I assume that's fine.

MR. BEST: Oh, yes.

DR. MARKS: The discussion was -- okay. So lots of uses in this huge amount, over 5,000.

Full Panel Meeting

DR. BERGFELD: Okay, moving on to the next ingredient, then, inorganic hydroxides, Dr. Marks.

DR. MARKS: So, this is the first time we're reviewing these four alkaline salt ingredients. They're primarily -- well, they're used as pH adjusters, but also Carol elucidated that they can be used as hair straighteners and depilatories with a high pH. So, with that twist, we decided that we could make a motion to issue a tentative report with a conclusion safe when formulated to be nonirritating under conditions of use. And we arrived at conditions of use, because we faced a similar issue with the thioglycolates, and this was how we handled it there -- is you follow the conditions of use in the package, and we know from experience that both hair straighteners and depilatories could be used safely as long as you follow the conditions of use instructions. So, again, move tentative report with conclusion safe when formulated to be nonirritating under conditions of use.

DR. MARKS: Second.

DR. BERGFELD: Any other discussion regarding this ingredient?

DR. BELSITO: Just to pretty much capture the language we used for the thioglycate report and growth in the discussion and the conclusion.

DR. BERGFELD: Thank you. I'm going to call the question then. All those in favor of safe?

GROUP: Yes.

DR. BERGFELD: Unanimous.

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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 may also function as depilating agents and hair waving/straightening agents. The Panel considered relevant data related to these ingredients. The Panel concluded that these inorganic hydroxides are safe in hair straighteners under conditions of recommended use; hairdressers should avoid skin contact and minimize consumer skin exposure. 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.

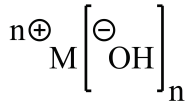

Figure 1. Inorganic Hydroxides (wherein "M" is group I or II metal)

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* each list 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 expected 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, as an absorbent for carbon dioxide, and in dehairing hides. 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: these types of data are not expected as the constituents of inorganic hydroxides (the metal cation and hydroxide anion) are normal physiological constituents. 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 effects of magnesium hydroxide (pH = 10) were 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 is 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 in in vitro tests (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 dermal rabbit 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 while 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 REPORT

No relevant (e.g., non-oral) case reports were discovered in the published literature regarding exposure to inorganic hydroxides in cosmetic products; however numerous cases of accidental occupational or industrial exposures were reported. [7,8,10,43]

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 function as depilating agents and hair waving/straightening agents at high 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 in vivo mice studies (intraperitoneal injection) at up to 0.015M.

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.

Calcium hydroxide was irritating in HET-CAM in vitro tests while 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.

No relevant (e.g. non-oral) case reports were discovered in the published literature regarding exposure to inorganic hydroxides in cosmetic products; however numerous cases of accidental occupational or industrial exposures were reported.

DISCUSSION

The Panel reviewed studies that included dermal and ocular irritation and sensitization potential of inorganic hydroxides. The available data demonstrate that the amounts of inorganic hydroxides added to many cosmetic formulations would be irritating, even caustic, to the skin and eyes, if the hydroxides were not neutralized by other ingredients in these formulations. However, these inorganic hydroxides are reported to function as pH adjusters in cosmetic products. The Panel recognized that while these ingredients may be dermal and/or ocular irritants, their uses as pH adjustors in cosmetic formulations dictates that most of the alkalinity will be neutralized into various salts.

The Panel noted that there were no carcinogenicity data; however, these ingredients are not absorbed systemically. Further, the Panel agreed that the cations of the hydroxides used in cosmetics are not expected to have any potential to cause systemic toxicity.

Furthermore, the concentration of the inorganic hydroxides used is dependent on the acid content of the formulations. Therefore, the concentration of free inorganic hydroxide is expected to be low. The safety of inorganic hydroxides as pH adjustors should not be based on the concentration of use, but on the pH of the final formulation.

While not listed in the *International Cosmetic Ingredient Dictionary and Handbook*, it was brought to the Panel's attention that these inorganic hydroxides also function as depilating agents and hair waving/straightening agents at very high pH values. If these hydroxides are used (or potentially used) in hair care products, a limitation on use concentration and adequate instructions to hairdressers to avoid skin contact (such as by wearing gloves) and to minimize consumer skin exposure (by limiting the frequency of product use) would be adequate to assure that irritation are not a concern. Without adequate skin protection, the Panel noted that repeated applications of hair straighteners containing inorganic hydroxides by hairdressers to multiple clients over a period of time should be avoided. The Panel further discussed skin irritation and sensitization with specific reference to the use of inorganic hydroxides in depilatories. The Panel recognizes that nearly all methods of hair removal cause some degree of irritation. In the experience of the Panel, although these chemicals have the potential to be severely irritating to the skin, clinically significant adverse reactions to these ingredients used in depilatories are not commonly seen. This suggests that current products are formulated to be practically nonirritating under conditions of recommended use. Formulators should take steps necessary to assure that current practices are followed. Based on this evaluation, the Panel has added language to the conclusion that specifically notes that inorganic hydroxides in depilatories are safe when formulated to be non-irritating and safe as hair straighteners under conditions of recommended use (which include avoidance of contact with skin).

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 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 under conditions of recommended use; hairdressers should avoid skin contact and minimize consumer skin exposure. 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)	44
pK_b	4.0	12
Specific gravity	2.36	44
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	44
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 formulation[3]

Ingredients	% w/w
Cetearyl alcohol (and) ethoxylated lanolins (relaxer concentrate)	12.00
Mineral oil	5.00
Triblock polymer	10.00
Petrolatum	10.00-15.00
Sodium hydroxide beads	***1.7-2.2***
Water	qs 100.00
Propylene glycol	7.00
Phosphate ester	2.00
Preservative	qs
Protein or other conditioner	0.50-2.00

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	45
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	46
potassium hydroxide	details not provided	oral gavage in 9 male/dose Charles River albino rats	$LD_{50} = 365$ mg/kg bodyweight	47
sodium hydroxide	0.2 N	oral study in rats (no further details provided)	Extensive damage to gastric mucosa observed	48
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	49
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	50
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)	51
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-physiolocial pH may yield false-positive results	52
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	53
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	52
sodium hydroxide	details not provided	Unscheduled DNA synthesis assay in E. coli strains WP2, WP67, CM871 (no further details provided)	not genotoxic	53
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	54
		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	55
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	56

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	[57]
potassium hydroxide	5% and 10%	In vitro skin corrosion – transcutaneous electrical resistance test (TER) (validation study)	Corrosive at both concentrations tested	[58]
potassium hydroxide	5% and 10%	Skin^{2}ZK1350 in vitro model (validation study)	Corrosive at 10%, non-corrosive at 5%	[58]
potassium hydroxide	5%	Leiden human reconstructed epidermal in vitro model (validation study)	Corrosive and irritant	[59]
potassium hydroxide	5% and 10%	In vitro membrane barrier test method (validation study)	Corrosive at both concentrations tested	[58]
potassium hydroxide	5%	SkinEthic in vitro model	Irritant	[60]
potassium hydroxide	5% and 10%	Episkin model (validation study)	Corrosive at both concentrations tested	[58]
potassium hydroxide	10%	SkinEthic reconstituted human epidermal model (validation study)	Corrosive	[61]
sodium hydroxide in water	4.9%	Skin^{2}ZK1350 in vitro model	Corrosive	[62]
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	[63]
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	64
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	65
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	64
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	47
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 90th 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	66
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	63
		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)	47
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	47
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	67

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2015 FDA VCRP Raw Data

AMMONIUM HYDROXIDE	03B - Eyeliner	18
AMMONIUM HYDROXIDE	03F - Mascara	17
AMMONIUM HYDROXIDE	03G - Other Eye Makeup Preparations	3
AMMONIUM HYDROXIDE	05A - Hair Conditioner	7
AMMONIUM HYDROXIDE	05C - Hair Straighteners	7
AMMONIUM HYDROXIDE	05D - Permanent Waves	28
AMMONIUM HYDROXIDE	05F - Shampoos (non-coloring)	11
AMMONIUM HYDROXIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
AMMONIUM HYDROXIDE	05I - Other Hair Preparations	3
AMMONIUM HYDROXIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	899
AMMONIUM HYDROXIDE	06B - Hair Tints	1
AMMONIUM HYDROXIDE	06F - Hair Lighteners with Color	5
AMMONIUM HYDROXIDE	06G - Hair Bleaches	8
AMMONIUM HYDROXIDE	06H - Other Hair Coloring Preparation	17
AMMONIUM HYDROXIDE	07C - Foundations	1
AMMONIUM HYDROXIDE	07I - Other Makeup Preparations	1
AMMONIUM HYDROXIDE	08E - Nail Polish and Enamel	1
AMMONIUM HYDROXIDE	08G - Other Manicuring Preparations	1
AMMONIUM HYDROXIDE	12A - Cleansing	15
AMMONIUM HYDROXIDE	12B - Depilatories	1
AMMONIUM HYDROXIDE	12C - Face and Neck (exc shave)	33
AMMONIUM HYDROXIDE	12D - Body and Hand (exc shave)	10
AMMONIUM HYDROXIDE	12F - Moisturizing	10
AMMONIUM HYDROXIDE	12G - Night	13
AMMONIUM HYDROXIDE	12H - Paste Masks (mud packs)	1
AMMONIUM HYDROXIDE	12I - Skin Fresheners	3
AMMONIUM HYDROXIDE	12J - Other Skin Care Preps	13
AMMONIUM HYDROXIDE	13A - Suntan Gels, Creams, and Liquids	1
CALCIUM HYDROXIDE	05C - Hair Straighteners	27
CALCIUM HYDROXIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
CALCIUM HYDROXIDE	07C - Foundations	13
CALCIUM HYDROXIDE	11B - Beard Softeners	1
CALCIUM HYDROXIDE	11G - Other Shaving Preparation Products	6
CALCIUM HYDROXIDE	12A - Cleansing	6
CALCIUM HYDROXIDE	12B - Depilatories	42
CALCIUM HYDROXIDE	12D - Body and Hand (exc shave)	1
CALCIUM HYDROXIDE	12I - Skin Fresheners	1
CALCIUM HYDROXIDE	12J - Other Skin Care Preps	1
MAGNESIUM HYDROXIDE	02A - Bath Oils, Tablets, and Salts	2
MAGNESIUM HYDROXIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	1

MAGNESIUM HYDROXIDE	06G - Hair Bleaches	6
MAGNESIUM HYDROXIDE	07B - Face Powders	1
MAGNESIUM HYDROXIDE	07C - Foundations	2
MAGNESIUM HYDROXIDE	12H - Paste Masks (mud packs)	1
MAGNESIUM HYDROXIDE	12J - Other Skin Care Preps	1

POTASSIUM HYDROXIDE	01B - Baby Lotions, Oils, Powders, and Creams	3
POTASSIUM HYDROXIDE	02B - Bubble Baths	3
POTASSIUM HYDROXIDE	02D - Other Bath Preparations	3
POTASSIUM HYDROXIDE	03B - Eyeliner	1
POTASSIUM HYDROXIDE	03C - Eye Shadow	5
POTASSIUM HYDROXIDE	03D - Eye Lotion	34
POTASSIUM HYDROXIDE	03E - Eye Makeup Remover	4
POTASSIUM HYDROXIDE	03F - Mascara	4
POTASSIUM HYDROXIDE	03G - Other Eye Makeup Preparations	13
POTASSIUM HYDROXIDE	04E - Other Fragrance Preparation	2
POTASSIUM HYDROXIDE	05A - Hair Conditioner	10
POTASSIUM HYDROXIDE	05B - Hair Spray (aerosol fixatives)	7
POTASSIUM HYDROXIDE	05F - Shampoos (non-coloring)	18
POTASSIUM HYDROXIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	5
POTASSIUM HYDROXIDE	05H - Wave Sets	7
POTASSIUM HYDROXIDE	05I - Other Hair Preparations	13
POTASSIUM HYDROXIDE	06H - Other Hair Coloring Preparation	1
POTASSIUM HYDROXIDE	07C - Foundations	1
POTASSIUM HYDROXIDE	07D - Leg and Body Paints	2
POTASSIUM HYDROXIDE	07E - Lipstick	2
POTASSIUM HYDROXIDE	07F - Makeup Bases	4
POTASSIUM HYDROXIDE	07I - Other Makeup Preparations	3
POTASSIUM HYDROXIDE	08B - Cuticle Softeners	7
POTASSIUM HYDROXIDE	08G - Other Manicuring Preparations	3
POTASSIUM HYDROXIDE	09A - Dentifrices	1
POTASSIUM HYDROXIDE	09C - Other Oral Hygiene Products	1
POTASSIUM HYDROXIDE	10A - Bath Soaps and Detergents	51
POTASSIUM HYDROXIDE	10B - Deodorants (underarm)	3
POTASSIUM HYDROXIDE	10E - Other Personal Cleanliness Products	41
POTASSIUM HYDROXIDE	11A - Aftershave Lotion	11
POTASSIUM HYDROXIDE	11D - Preshave Lotions (all types)	1
POTASSIUM HYDROXIDE	11E - Shaving Cream	43
POTASSIUM HYDROXIDE	11F - Shaving Soap	1
POTASSIUM HYDROXIDE	11G - Other Shaving Preparation Products	2
POTASSIUM HYDROXIDE	12A - Cleansing	168
POTASSIUM HYDROXIDE	12B - Depilatories	20
POTASSIUM HYDROXIDE	12C - Face and Neck (exc shave)	111
POTASSIUM HYDROXIDE	12D - Body and Hand (exc shave)	129
POTASSIUM HYDROXIDE	12F - Moisturizing	214
POTASSIUM HYDROXIDE	12G - Night	23
POTASSIUM HYDROXIDE	12H - Paste Masks (mud packs)	19
POTASSIUM HYDROXIDE	12I - Skin Fresheners	7

POTASSIUM HYDROXIDE	12J - Other Skin Care Preps	71
POTASSIUM HYDROXIDE	13A - Suntan Gels, Creams, and Liquids	2
POTASSIUM HYDROXIDE	13B - Indoor Tanning Preparations	1

SODIUM HYDROXIDE	01A - Baby Shampoos	6
SODIUM HYDROXIDE	01B - Baby Lotions, Oils, Powders, and Creams	16
SODIUM HYDROXIDE	01C - Other Baby Products	25
SODIUM HYDROXIDE	02A - Bath Oils, Tablets, and Salts	1
SODIUM HYDROXIDE	02B - Bubble Baths	64
SODIUM HYDROXIDE	02D - Other Bath Preparations	13
SODIUM HYDROXIDE	03A - Eyebrow Pencil	1
SODIUM HYDROXIDE	03B - Eyeliner	14
SODIUM HYDROXIDE	03C - Eye Shadow	2
SODIUM HYDROXIDE	03D - Eye Lotion	80
SODIUM HYDROXIDE	03E - Eye Makeup Remover	16
SODIUM HYDROXIDE	03F - Mascara	18
SODIUM HYDROXIDE	03G - Other Eye Makeup Preparations	60
SODIUM HYDROXIDE	04A - Cologne and Toilet waters	3
SODIUM HYDROXIDE	04B - Perfumes	4
SODIUM HYDROXIDE	04E - Other Fragrance Preparation	4
SODIUM HYDROXIDE	05A - Hair Conditioner	83
SODIUM HYDROXIDE	05B - Hair Spray (aerosol fixatives)	2
SODIUM HYDROXIDE	05C - Hair Straighteners	31
SODIUM HYDROXIDE	05D - Permanent Waves	1
SODIUM HYDROXIDE	05E - Rinses (non-coloring)	2
SODIUM HYDROXIDE	05F - Shampoos (non-coloring)	224
SODIUM HYDROXIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	55
SODIUM HYDROXIDE	05H - Wave Sets	4
SODIUM HYDROXIDE	05I - Other Hair Preparations	36
SODIUM HYDROXIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	320
SODIUM HYDROXIDE	06D - Hair Shampoos (coloring)	3
SODIUM HYDROXIDE	06H - Other Hair Coloring Preparation	6
SODIUM HYDROXIDE	07A - Blushers (all types)	1
SODIUM HYDROXIDE	07B - Face Powders	2
SODIUM HYDROXIDE	07C - Foundations	9
SODIUM HYDROXIDE	07D - Leg and Body Paints	3
SODIUM HYDROXIDE	07F - Makeup Bases	12
SODIUM HYDROXIDE	07H - Makeup Fixatives	1
SODIUM HYDROXIDE	07I - Other Makeup Preparations	26
SODIUM HYDROXIDE	08B - Cuticle Softeners	8
SODIUM HYDROXIDE	09A - Dentifrices	3
SODIUM HYDROXIDE	09C - Other Oral Hygiene Products	33
SODIUM HYDROXIDE	10A - Bath Soaps and Detergents	860
SODIUM HYDROXIDE	10B - Deodorants (underarm)	129
SODIUM HYDROXIDE	10C - Douches	2
SODIUM HYDROXIDE	10E - Other Personal Cleanliness Products	277
SODIUM HYDROXIDE	11A - Aftershave Lotion	112

SODIUM HYDROXIDE	11D - Preshave Lotions (all types)	2
SODIUM HYDROXIDE	11E - Shaving Cream	28
SODIUM HYDROXIDE	11F - Shaving Soap	1
SODIUM HYDROXIDE	11G - Other Shaving Preparation Products	14
SODIUM HYDROXIDE	12A - Cleansing	296
SODIUM HYDROXIDE	12B - Depilatories	16
SODIUM HYDROXIDE	12C - Face and Neck (exc shave)	365
SODIUM HYDROXIDE	12D - Body and Hand (exc shave)	378
SODIUM HYDROXIDE	12E - Foot Powders and Sprays	2
SODIUM HYDROXIDE	12F - Moisturizing	1078
SODIUM HYDROXIDE	12G - Night	101
SODIUM HYDROXIDE	12H - Paste Masks (mud packs)	39
SODIUM HYDROXIDE	12I - Skin Fresheners	14
SODIUM HYDROXIDE	12J - Other Skin Care Preps	205
SODIUM HYDROXIDE	13A - Suntan Gels, Creams, and Liquids	8
SODIUM HYDROXIDE	13B - Indoor Tanning Preparations	15
SODIUM HYDROXIDE	13C - Other Suntan Preparations	13

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 16, 2015

SUBJECT: Comments on the Draft Report Prepared for the September 2015 CIR Expert Panel Meeting: Safety Assessment of Inorganic Hydroxides as Used in Cosmetics

Non-Cosmetic Use- Please be more specific in describing the uses for which Calcium Hydroxide and Magnesium Hydroxide are not approved. Currently it states: "Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of this ingredient in certain drug products (21 CFR§310)." This implies that these ingredients are listed for multiple drug products. Calcium Hydroxide is listed for anti-diarrheal products and Magnesium Hydroxide is listed for digestive aid products.

Toxicokinetics - The first sentence of this section should be deleted as it implies that a relevant toxicokinetic study on these ingredient could be completed. When discussing physiological levels, it would be better to state normal blood concentrations of the ions (e.g., calcium: 9-11 mg/dl; magnesium: 1.8-3.6 mg/dl; potassium: 3.5-5.5 mEq/L; sodium 136-145 millimoles/L) rather classifying the concentrations as "low".

Repeated Dose Exposure - This section should refer the reader to the Reproductive and Developmental Toxicity section as the study completed on Magnesium Hydroxide followed OECD 422 titled "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test".

Reproductive and Developmental Toxicity, Summary - It would be helpful to state that the study followed OECD Guideline 422. The following sentence is not clear. "There were no treatment related effects on reproduction development." The offspring were sacrificed on lactation days 5 or 6 so as stated in the summary of the study, sexual maturation of the offspring was not assessed.

Summary - Please include the route of exposure for the *in vivo* genotoxicity studies (ip injection).

Table 5 - In the description of the cat study, please include the organ(s) in which the squamous mucosa was destroyed and in which thrombosis was observed (the title of reference 45 mentions esophagus).

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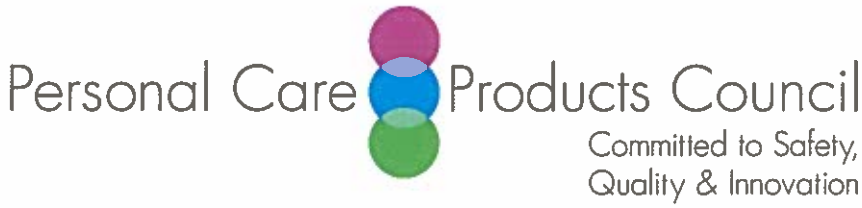

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 27, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Inorganic Hydroxides as Used in Cosmetics (reported posted October 2, 2015)

Key Issues

In describing concentrations of inorganic hydroxides in depilatory and hair straightening products, the meaning of "high" is not clear. These products have high ph values. Rather than using the term "high" to describe the use concentration, the reported use concentrations in these product categories should be stated in the Cosmetic Use section, e.g., Sodium Hydroxide is reported to be used at concentrations of 2.5-3% in hair straighteners (limit of 4.5% in professional products in Europe).

The Case Reports section and Summary indicates that "No relevant case reports were discovered in the published literature regarding exposure to inorganic hydroxides in cosmetic products." The published literature does include case series on hair relaxers such as the following references:

Mrvos R, Krenzelol. 1997. Hair relaxers: lack of morbidity despite high pH. *Am J Emerg Med* 15(2): 216.

Aronow SP, Arono HD, Blanchard T, et al. 2003. Hair relaxers: a benign caustic ingestion? *J Pediatr Gastroenterol Nutr* 36(1): 120-125.

Additional Considerations

Abstract - Rather than stating that these ingredients are use "as" depilatories and hair straighteners, it should be stated that they are used "in" depilatories and hair straighteners. For example, as suggested by the EU regulation, some hair straighteners (called "no-lye") contain both Calcium Hydroxide and a guanidine salt. Calcium Hydroxide itself is not sufficient to function as a hair straightener.

Acute Exposure - Please state the duration of exposure for the inhalation exposure studies.

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Genotoxicity - The following is not a complete sentence. "Genotoxic effects due to high non-physiological pH that may yield false-positive results"

Discussion - The first paragraph should make it clear some products containing these ingredients have high pH values and are caustic. Therefore, it is necessary to adhere to package directions.

It is not clear why the Discussion suggests that "systemic toxicity" could be a concern if concentrations of free hydroxide were high. If pH is high, local toxicity, such as dermal corrosion would be the main concern.