
Safety Assessment of Carbonate Salts as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 11, 2016
Panel Date: December 5-6, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, 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, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 11, 2016
Subject: Draft Final Report on Carbonate Salts

A Tentative Report on Carbonate Salts was issued at the June 2016 Expert Panel meeting. The Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Included in this package for your review is the Draft Final Report on Carbonate Salts (*carbon122016rep*), the CIR report history (*carbon122016hist*), Literature search strategy (*carbon122016strat*), Ingredient Data profile (*carbon122016prof*), 2016 FDA VCRP data (*carbon122016FDAdata*), Use Concentration Data received from the Council (*carbon122016data 1* and *carbon122016data2*), minutes from the June Panel meeting (*carbon122016min*), and Report Comments received from the Council (*carbon122016pcpl*). All comments have been addressed.

Referring to the report text, the Panel noted that one of the CAS numbers (8000-73-5) in the *International Cosmetic Ingredient Dictionary and Handbook* that is being used to identify Ammonium Carbonate actually represents a mixture of ammonium bicarbonate and ammonium carbamate, but is not identified as such in the *Dictionary*. The Panel agreed that the molecular chemical identity of Ammonium Carbonate needs to be clarified. In response to these concerns, the *Dictionary* monograph on Ammonium Carbonate has been revised, replacing 8000-73-5 with 8000-73-5 (mixture). The other CAS numbers are identified as 10361-29-2 (unspecified) and 506-87-6 (diammonium). Ammonium Carbonate is defined as a mixture of ammonium bicarbonate and ammonium carbamate in the *International Cosmetic Ingredient Dictionary and Handbook* as well as in the *Food Chemicals Codex* and the *Code of Federal Regulations* (21 CFR 184.1137). The CFR citation (*carbon122016CFR*) is attached for the Panel's review.

Please note that the safety assessment has been revised to include data from REACH dossiers on Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate that are accessible at the European Chemicals Agency's (ECHA) website. These data are enclosed in borders within the report text. In the absence of certain types of data from the following REACH dossiers, data on surrogate chemicals [in the dossiers] are included: Magnesium Carbonate (toxicokinetic data on magnesium sulfate, *in vitro* genotoxicity data on magnesium chloride, and short-term oral toxicity and oral reproductive/developmental toxicity data on magnesium chloride hexahydrate), Ammonium Bicarbonate (short-term oral toxicity, *in vivo* genotoxicity, and sensitization data on ammonium chloride; acute dermal toxicity and *in vitro* genotoxicity data on ammonium sulfate; and toxicokinetic, acute inhalation toxicity, and reproductive/developmental toxicity data on sodium bicarbonate), Ammonium Carbonate (tumor promotion data on sodium bicarbonate and sensitization data on ammonium acetate), Calcium Carbonate (acute dermal toxicity, short-term oral toxicity, oral reproductive/developmental toxicity, *in vitro* genotoxicity, and animal skin sensitization data on Calcium Carbonate [nano form]), and Potassium Carbonate (*in vitro* genotoxicity data on potassium chloride and ocular irritation data on sodium carbonate monohydrate).

Additionally, because Ammonium Carbonate is defined as a mixture that contains ammonium carbamate, the safety assessment has also been revised to include some additional inhalation and oral toxicity data, genotoxicity data, oral co-carcinogenicity data, and sensitization data from the REACH dossier on ammonium carbamate. Data from the published literature relating to the percutaneous absorption and ammonium carbamate are also included. Data from the REACH dossier and the published study on percutaneous absorption are also enclosed in borders within the report text.

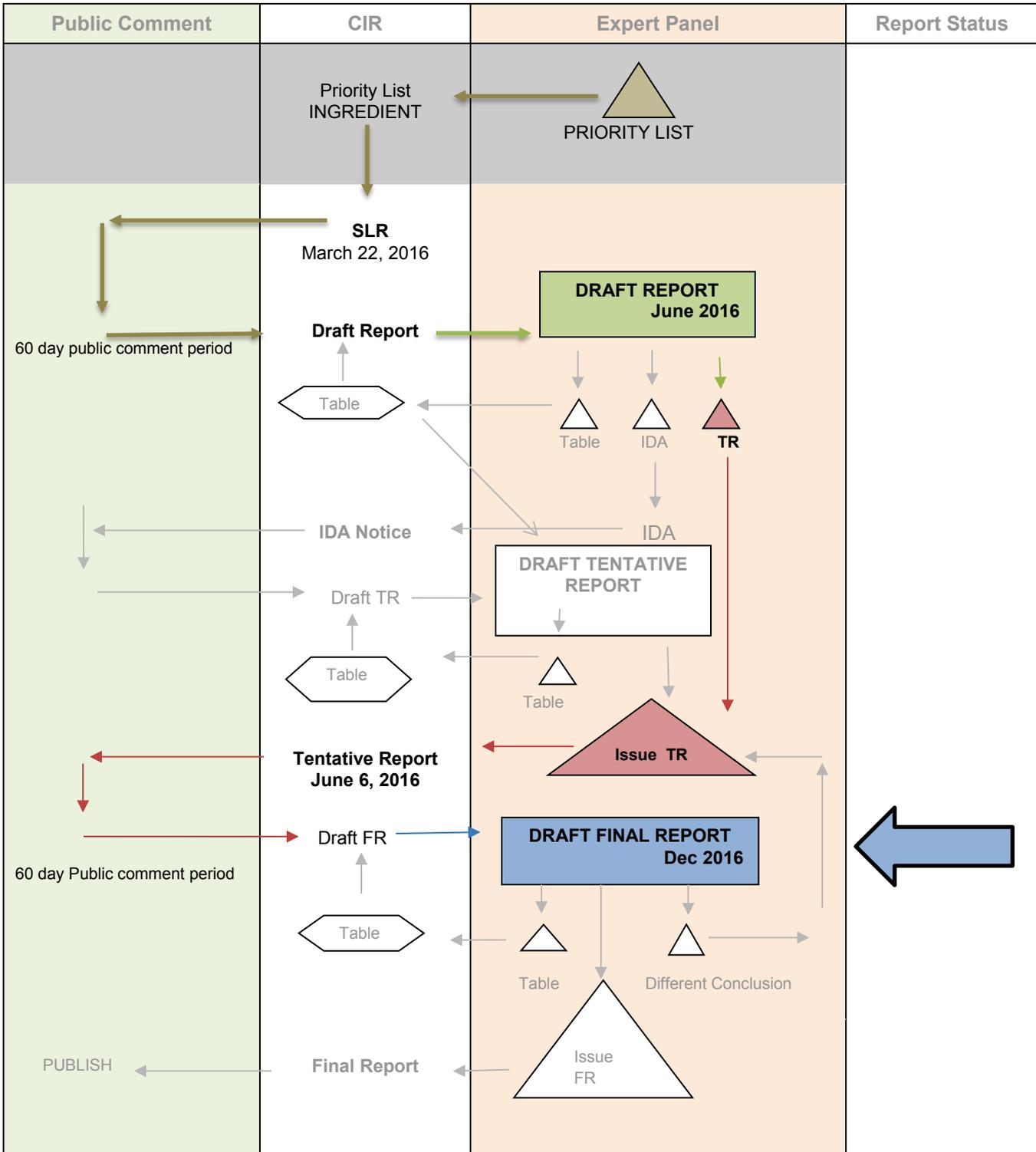
Given the Panel's concern over potential dermal reactions that could result from exposure to carbonate salts, the following additional data on irritation/sensitization potential (from the ECHA's website) have been incorporated into the safety assessment: *in vitro* skin irritation data on Magnesium Carbonate, Ammonium Bicarbonate, and Ammonium Carbonate; animal sensitization data on Calcium Carbonate and animal skin irritation/sensitization data on Potassium Bicarbonate; and ocular irritation data on Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Bicarbonate. After reviewing these data, the Panel should determine whether the first paragraph of the discussion should be revised.

After considering the data included in this safety assessment, the Panel will need to determine whether the data are sufficient for issuing a Final Report with the conclusion that cosmetic products containing carbonate salts should be formulated to be non-irritating.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Carbonate Salts

MEETING Dec 2016



CIR History of:

Simple Carbonate Salts

The Scientific Literature Review (SLR) was announced on 3-23-2016. Use concentration data were received from the Council prior to announcement of the SLR, and are included.

Draft Report, Teams/Panel: June 6-7, 2016

Comments from the Council were received, and have been incorporated.

A Tentative Report on Simple Carbonate Salts was issued at the June Panel meeting and announced on June 16, 2016. The Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

The Panel noted that one of the CAS numbers (8000-73-5) in the *International Cosmetic Ingredient Dictionary and Handbook* that is being used to identify Ammonium Carbonate actually represents a mixture of ammonium bicarbonate and ammonium carbamate, but is not identified as such in the *Dictionary*. The Panel agreed that the molecular chemical identity of Ammonium Carbonate needs to be clarified. After considering this definition of Ammonium Carbonate, the Panel agreed that the safety assessment should be revised to include safety test data on ammonium carbamate.

Draft Final Report, Teams/Panel: December 5-6, 2016

Comments received from the Council have been addressed.

The *Dictionary* monograph on Ammonium Carbonate has been revised, replacing 8000-73-5 with 8000-73-5 (mixture). The other CAS numbers are identified as 10361-29-2 (unspecified) and 506-87-6 (diammonium).

The safety assessment has been revised to include data from REACH dossiers on Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate that are accessible at the European Chemicals Agency's (ECHA) website. Furthermore, the safety assessment has been revised to include data from the REACH dossier on ammonium carbamate: acute inhalation toxicity data on ammonia (LC₅₀ values for Ammonium Bicarbonate extrapolated from these data), short-term oral toxicity data on ammonium chloride, oral developmental toxicity data on sodium bicarbonate, in vitro genotoxicity data on ammonium carbamate, oral co-carcinogenicity data on sodium bicarbonate, and sensitization data (from local lymph node assay) on ammonium carbamate. Data from the published literature relating to the percutaneous absorption and ammonium carbamate are also included.

Simple Carbonate Salts Check List for December 2016 Panel. Analyst – Wilbur Johnson																			
			Acute toxicity				Repeated dose toxicity			Irritation			Sensitization						
			ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr.	Dermal Irr Human					Sensitization Animal
Magnesium Carbonate			X														X		
Ammonium Bicarbonate				X	X		X												
Ammonium Carbonate					X	X													
Calcium Carbonate			X	X		X	X	X						X			X	X	
Potassium Bicarbonate			X	X		X	X	X									X	X	
Potassium Carbonate			X	X		X	X				X						X	X	

[Simple Carbonate Salts (10/21/2016)]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	ECETOC
Magnesium Carbonate	546-93-0 7757-69-9	1/1	18/390	18/369	18/371	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	No
Ammonium Bicarbonate	1066-33-7	1/1	13/333	13/443	13/190	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Ammonium Carbonate	10361-29-2 506-87-6 8000-73-5	1/1	3/322	25/230	25/292	Yes	No	Yes	No	No	No	No	Yes			Yes	No	No
Calcium Carbonate	471-34-1	1/1	5/28	11/6098	11/3701	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Potassium Bicarbonate	298-14-6	1/1	21/296	21/239	21/184	Yes	No	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No
Potassium Carbonate	584-08-7	1/1	18/948	18/547	18/543	Yes	No	Yes	No	No	No	Yes	Yes	No	No	Yes	No	No

Search Strategy

[document search strategy used for SciFinder, PubMed, and Toxnet]

[identify total # of hits /# hits that were useful or examined for usefulness]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - <http://www.personalcarecouncil.org/science-safety/line-infobase>
SciFinder (usually a combined search for all ingredients in report; list # of this/# useful) - <https://scifinder.cas.org/scifinder>
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - <http://www.ncbi.nlm.nih.gov/pubmed>
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – <https://toxnet.nlm.nih.gov/> (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> (CFR); then, list of all databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>; then, <http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS); <http://www.fda.gov/food/ingredientpackaginglabeling/gras/default.htm> (GRAS); <http://www.fda.gov/food/ingredientpackaginglabeling/gras/scogs/ucm2006852.htm> (SCOGS database); <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives> (indirect food additives list); <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm> (drug approvals and database); <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf> (OTC ingredient list); <http://www.accessdata.fda.gov/scripts/cder/iig/> (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - <http://ec.europa.eu/growth/tools-databases/cosing/>
ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>
IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>
HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogon>
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>
NTIS (National Technical Information Service) - <http://www.ntis.gov/>
NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/> (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - <http://www.ecetoc.org/>

Botanical Websites, if applicable

Dr. Duke's <https://phytochem.nal.usda.gov/phytochem/search>
Taxonomy database - <http://www.ncbi.nlm.nih.gov/taxonomy>
GRIN (U.S. National Plant Germplasm System) - <https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx>
Sigma Aldrich plant profiler <http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html>

Fragrance Websites, if applicable

IFRA (International Fragrance Association) – <http://www.ifraorg.org/>

RIFM (the Research Institute for Fragrance Materials) should be contacted

Day 1 of the June 6-7, 2016 CIR Expert Panel Meeting – Dr. Belsito's Team

Simple Carbonate Salts

DR. BELSITO: So then the simple carbonate salts. This is the first time five ingredients. They function as absorbents, bulking agents or pacifying agents, pH adjustors, buffering agents, abrasives and a world care agents, and I guess first question that I had for Dan is the next one we're going to look at is the dialkyl carbonates. Is there a good reason for separating these two into different reports?

DR. LIEBLER: Yeah, I mean these are totally different uses, totally different chemical structures. They have carbonates as their -- as a core piece for the dialkyl carbonates, but they're really different molecules. So, yeah, I think there's plenty of reason to have them separate.

DR. BELSITO: Okay, so then when I look through this document I thought we had a good amount of data, and my feeling was we could go safe as used possibly when formulated to be non-irritating because there were some quasi-irritation data, but I had a hard time explaining the bladder cancers and the kidney issues and had a question directed to Paul and my other colleagues. Was it just an irritant effect or --

DR. SNYDER: I think it's an irritant effect, probably getting crystals.

DR. KLAASSEN: Yes, (inaudible) formation that's well recognized but (inaudible) chronic inflammation prepared responses. (inaudible) bladder tumors. That's what you saw up there.

DR. SNYDER: So you think at those doses the crystal formation is likely --

DR. KLAASSEN: No.

DR. SNYDER: -- to be an explanation? (inaudible)

DR. LIEBLER: I thought this looked actually pretty good. You know, I'm trending toward safe as used for this, but I just had these kind of "wow" animal effects, but if it's a trivial explanation, I guess both bladder and renal could be explained by that especially (inaudible).

DR. BELSITO: So then, do we need safe as used when formulated to be non-irritating since it's used up to 93.4 percent? It's a hair bleach which would be a rinse-off, because we don't really have -- we have irritation data all when it is basically not diluted, and undiluted calcium carbonate was corrosive. Potassium carbonate was a moderate irritant at -- also undiluted, so I mean does that -- do we feel we need to cover ourselves for lack of a cutoff for sensitization with this, particularly with that high use in hair bleach and the conclusion or?

DR. LIEBLER: I don't think it would be unreasonable to do that. I mean that would be sort of erring on the safe side, I suppose, but that -- I think that the context of use there for the very high concentration is a rinse-off.

DR. BELSITO: Right.

DR. LIEBLER: And so the thing that would produce the irritation might be crystals, and you're not going to get that in a rinse-off context.

DR. BERGFELD: So why wouldn't you put that in your discussion?

DR. LIEBLER: Yeah, right, maybe the discussion as opposed to the conclusion.

DR. BELSITO: Paul, Kurt, did you have a feeling one way or the other about the irritation issues with these? I mean for non-rinse-off leave-ons I didn't write down the highest concentration, and don't know why I didn't. Okay, leave-on was 7 percent magnesium --

SPEAKER: 93.4 (inaudible).

DR. BELSITO: -- was rinse-off for ammonium bicarbonate. That's a hair bleach.

DR. SNYDER: Thirty-five percent (inaudible).

DR. BELSITO: Yeah, 35 percent for calcium carbonate which was the irritant at 100 percent in the study. I'd feel more comfortable going when formulated to be non-irritating because I don't have a cutoff level for that on a leave-on. I just have one study at 100 percent it was corrosive. So we're okay safe as used when formulated to be non-irritating, and the discussion basically I think has to center around how we interpret the kidney and bladder issues.

DR. JOHNSON: Specifically what statement would you want to address those

(inaudible)?

DR. BELSITO: Paul, Dan, do you want to create a statement?

DR. SNYDER: The data suggests that genotoxicity is all negative so likely mechanism is related to the precipitation of the compound in the urine bladder formation of crystals and resulting in physical damage to the bladder and that is the mechanism for the appropriate response.

DR. LIEBLER: So, Wilbur, I did have one question. This is in Table 1 on PDF page 20, and then also on Table 2 on PDF page 21. The ammonium carbonate lists 3 CAS numbers, and the first two of those CAS numbers are for actually ammonium carbonate which is 2-ammonium groups and a carbonate, and then the last CAS number is the mixture of ammonium bicarbonate and ammonium carbamate which is shown in Table 1.

And then in Table 2 on page 21, PDF 21, it says under ammonium carbonate commercial preparations are usually a mixture with ammonium carbamate and ammonium bicarbonate, so I guess I've got a problem with this.

First of all, is that true, and maybe Carol knows, and then second, maybe where we should list this -- I guess we're listing it by the inky name, but --

DR. BELSITO: I'm lost on your pages, Dan.

DR. LIEBLER: PDF page 20.

DR. BELSITO: Twenty-two is Table 3.

DR. LIEBLER: PDF page 20 in the middle of the third entry is ammonium carbonate.

DR. BELSITO: Right, okay.

DR. LIEBLER: And there are three CAS numbers listed on there.

DR. BELSITO: Right.

DR. LIEBLER: Okay, the third CAS number, the 8,073- is the mixture that's shown there, ammonium bicarbonate and ammonium carbamate, but the first two CAS numbers are for ammonium carbonate which is not shown by either of these structures.

And the next page, the second entry is ammonium carbonate, and it says under background information commercial preparations are usually a mixture with ammonium carbamate and ammonium bicarbonate. So I was asking for some clarification, and even if the dictionary listing is ammonium carbonate but it describes these, we need to be more explicit as to what we're considering here.

DR. EISENMANN: I was surprised when I read that, too, in the definition, and then I looked in the food chemical codex and it's also -- is that mixture, so I think that's true that the material in commerce is that mixture of --

DR. BELSITO: So calcium carbonate is not actually calcium carbonate --

DR. EISENMANN: No, it's ammonium --

DR. BELSITO: Carbonate mixed with calcium --

DR. LIEBLER: No, it's not calcium.

DR. EISENMANN: It's that ammonium that has that issue.

DR. BELSITO: Ammonium, okay.

DR. EISENMANN: It's defined as ammonium bicarbonate and ammonium carbonate, so I think that is the commercial material that's being sold under the name ammonium carbamate.

DR. BELSITO: But what you have listed as the chemical structure for ammonium carbamate looks to me to be the same -- no, I guess it is different. Sorry.

DR. LIEBLER: Right.

DR. BELSITO: The carbamate has an amine group.

DR. LIEBLER: Right.

DR. BELSITO: So, does that worry you in terms of -- I mean -- I'm not a chemist and nitrosamines --

DR. LIEBLER: No, no, no. There's no safety issue at all here. It's simply a -- describing what the chemical is, and so when you have ammonium carbonate and you have 3 CAS numbers listed, does the dictionary refer to CAS numbers?

DR. JOHNSON: Yes, it does.

DR. LIEBLER: And it refers to all three of those?

DR. JOHNSON: Yes, those CAS numbers are the ones that are listed in the dictionary.

DR. LIEBLER: So, it's possible that a commercial -- a cosmetic ingredient may also be just ammonium carbonate as chemists really understand it to be. Right?

SPEAKER: It's possible that that's true or having the three CAS suggests --

DR. EISENMANN: We'd have to go back to (inaudible) see if maybe the one should not be there based on the definition.

DR. LIEBLER: Because if it's always this mix of 200 chemicals with perfectly straight-forward chemical names it's other sort of dictionary screwed up naming issue.

DR. EISENMANN: But this time I don't think it came from the dictionary. I think this was inherited that the commercial material is this mixture.

DR. LIEBLER: But they just call it --

DR. EISENMANN: Right, and maybe the (inaudible) CAS number got added in because you look at the name and you know --

DR. LIEBLER: I think we ought to try and sort this out because it's really unclear on its face, and this is an ingredient that's used, so.

DR. BELSITO: Okay, so we're going to -- we're still going ahead as safe as used when formulated to be non-irritating, and then we want a little bit more information on exactly the ammonium carbonate issue. Is that correct?

DR. LIEBLER: Right, the actual identity of the ammonium carbonate; the molecular chemical identity needs to be clarified.

DR. BERGFELD: Are you going to put in your discussion that these are rinse-off products; the ones that might be irritating?

DR. BELSITO: No, because we don't have a cut-off for irritation for calcium, and it's used up to 34 percent in a leave-on.

DR. BERGFELD: (inaudible) at 93.

DR. BELSITO: Well, 93.4 was a rinse-off, but when we say when formulated to be non-irritating we cover all of that. Okay, so those were the two major issues; the kidney/bladder issues which we're going to explain, as Paul stated, with a crystal formation and then a little more information on the molecular identity of exactly what ammonium carbonate is, but otherwise we're happy with everything else in the document.

DR. LIEBLER: Are these added to foods? I mean are they -- there was no reference to that in the document that I could see unless I missed it. Oh, the joint (inaudible). Yeah.

DR. JOHNSON: Yes.

DR. LIEBLER: Yes, I see it.

DR. BELSITO: Yes, they are GRAS (inaudible) using.

DR. LIEBLER: Yes.

DR. BELSITO: Anything else on these? Okay.

Day 1 of the June 6-7, 2016 CIR Expert Panel Meeting – Dr. Marks' Team

Simple Carbonate Salts

DR. MARKS: Wilbur, this is a draft report, so this is the first time we will review this. I thought it was interesting -- I bring this up to the chemists -- that the title was simple carbonate salts. Are there complex carbonate salts and that's why you included the word simple in here? Because I thought you could just shorten the title to carbonate salts, but that's -- that's perhaps nitpicking. Any rate, and we can --

DR. SLAGA: (Inaudible)

DR. MARKS: -- yeah. Smart salts, yeah. There are other ones. Yeah. Exactly. Any rate, sounds like it's generated some levity here, Wilbur.

DR. HILL: No, I -- actually there's a reason for it. I assumed Wilbur was about to speak to that.

DR. MARKS: Okay.

MR. JOHNSON: No, I would mention that to Bart to see whether or not he, you know, thinks -- agrees that that title should be changed to carbonate salts.

DR. MARKS: I defer to -- as Ron Shank would say -- the chemist.

DR. HILL: So I think it -- I think it has to do with the array of counter ions that are here and the fact that they're simple in the sense of nothing so complicated as coleman or something more. Well, and so, I don't know if that's the right or best word. I will think about that overnight, but I think it relates to the fact that we're just looking at potassium, calcium, imodium, magnesium, and nothing more -- nothing more exotic than that. I assume that's what that is referring to and it works for me.

DR. MARKS: Yeah. I wouldn't spend a lot of time ruminating over it.

DR. HILL: I don't plan to.

DR. MARKS: I just thought it was an interesting title.

DR. HILL: If something pops into my head while I'm taking a shower in the morning or something, then I'll bring it tomorrow.

DR. MARKS: So do you like these salts? Ron, Ron, and Tom? The five ingredients okay?

DR. SHANK: Aren't there six?

DR. MARKS: I thought it was five. Did I miscount?

DR. HILL: I count six. I count six.

DR. MARKS: Oh, I'm sorry. Thank you. Get this thing right here.

DR. SHANK: Safe when formulated to be nonirritating.

DR. MARKS: You think there is irritation from these?

DR. SLAGA: Well, we do have some irritation data.

DR. MARKS: Yeah. I would have to --

DR. SLAGA: (Inaudible) there's carcinogenicity data that is --

DR. MARKS: Yeah. I wanted you, Tom, to comment about that. But let's take potassium carbonate at 95 percent, which is neither an irritant or a sensitizer. So I guess I was hanging -- if you have that salt at 95 percent, are we really worried about the other ones?

DR. SHANK: Let me check.

DR. MARKS: That was -- well, I don't have the pages on the page here. What?

SPEAKER: Seventeen.

DR. SLAGA: Related to the carcinogenicity, that could help because --

DR. MARKS: Oh, okay. That makes sense.

DR. SLAGA: -- the carcinogenicity data is without an initiator for a carcinogen at low dose. And so it's more like a tumor promoting type of effect. So that could be a back-up to -- for reinsurance.

DR. MARKS: Let me see what I had, too. I guess what I looked at, Ron Shank, was when I looked at the calcium carbonate not corrosive.

DR. SHANK: Okay. But potassium --

DR. MARKS: And potassium -- moderate skin irritant in the first paragraph. That was on New Zealand white rabbits. But then when they did sensitization potential in the

Buehler test, so that would be guinea pigs -- yes, ten guinea pigs -- 95 percent there was no skin irritation observed. So I sort of put my weight on the second test more than the first one.

DR. HILL: So imodium carbonate, if you just used it need is basic. If you just dissolved it in water, you've basically got weak sodium hydroxide and you're going to get irritation.

DR. MARKS: Okay.

DR. HILL: In a cosmetic ingredient, that would never be that way. It would be -- at least I'm pretty confident that that would be the case. You wouldn't see that kind of irritation happening.

DR. SLAGA: Well, it's only the potassium carbonate or bicarbonate that's a problem, right?

DR. HILL: Yeah.

DR. SHANK: Right.

DR. HILL: Did I say imodium? I didn't mean to say imodium. I meant potassium -- either carbonate or bicarbonate and potassium carbonate would be much more strongly basic, but still.

DR. MARKS: So, two -- so, Ron Shank, do you still formulate -- I hear what you're saying. That's nice. It sort of reduces the issues with carcinogenesis. But do you like that then formulate to be nonirritating? Safe when formulated to be nonirritating?

DR. SHANK: I didn't, but -- if you're content with it like that.

DR. MARKS: Let me see here. What was the --

DR. SLAGA: (Inaudible) they had the data on the potassium bicarbonate then, but we don't.

DR. SHANK: Potassium carbonate we do.

DR. MARKS: Yeah, potassium carbonate. There's another where is -- to me was a disconnect because the highest use by recorded data correctly was .0068 percent. Is that right? And it was nonirritating or sensitizing at 95 percent. So it's --

DR. HILL: So sodium bicarbonate is baking soda?

DR. SHANK: Yeah.

DR. HILL: Potassium bicarbonate is almost entirely similar?

DR. MARKS: Yeah.

DR. SHANK: It's a different --

DR. MARKS: Calcium carbonate was 35 percent use. Magnesium was seven percent use -- with lots of uses.

DR. HILL: Calcium carbonated salt is chalk.

DR. MARKS: No, Ron, I want you to be also. You are the one who brought up the -- I thought the irritation -- I saw the first one when it said it was moderate irritating. But then when I saw 90 percent was not irritating and not sensitizer, then I thought irritation was off the table. But they're different animals, too.

DR. SLAGA: The only one is potassium bicarbonate. It could be -- then they used it in a four week, 13 week, 18 week, and then 130 weeks of treatment of two and four percent. And if you look at the progression of time, there is hyperplasia and kind of irritation that comes from that. So, I don't --

DR. MARKS: So you like formulate to be nonirritating? Yeah. Okay.

DR. SLAGA: I mean it's only because of that one -- the potassium, which is the different animal.

DR. HILL: I just feel like in any cosmetic formulation that would actually be on the market and in use, unless it -- I don't think we have a situation here like we did with the hydroxides where it's being used as a depilatory or something. Do we have depilatory use?

DR. SLAGA: Of this?

DR. HILL: Any of these? We don't, do we?

DR. SLAGA: No.

DR. HILL: I didn't see that. So, yeah, I mean -- under those circumstances, any formulation is going to be neutralized with this ingredient -- with any of these ingredients in it and I don't see why there would be then irritation issue at all. But that's -- if Mr. Steinberg was in here, I would ask his take on it as well.

DR. SLAGA: It is probably not an issue. The carcinogenicity studies -- even though there were some renal cancer, kidney cancer at the extremely long 130 weeks, which is a very long, long time that given two to four percent. But you know, if you look at historic controls versus regular controls during the experiment, it kind of all neutralizes. There's really no effect. There's no really effect on transitional cell carcinomas.

If you look at pre-cancers, it's only -- these animals get a lot of renal cancer -- true -- papillomas and cancer-like. So there's really no dose response in preconditions. There's the -- if you take historical controls into consideration, there's really no effect on latency or time that appearance of tumors -- total tumors. It's only in the one experiment that some of the new results came out. It was a little significant over the existing controls. But over historical controls, then it kind of neutralizes and there's really no effect.

DR. MARKS: So that should be captured in a discussion?

DR. SLAGA: Yeah.

DR. MARKS: Okay.

DR. SLAGA: I mean we have to deal with because --

DR. MARKS: Yes. Absolutely.

DR. SLAGA: -- I mean (inaudible) does say that induces urinary bladder cancer in rats. So we have to deal with it.

MR. JOHNSON: I know in that 18-month study, the incidence of transitional cell papilloma, which was classified as benign, was two males of the urinary bladder. And you had six females. And those were -- the data in the six females were classified as statistically significant.

DR. SLAGA: Yeah.

DR. HILL: My take is --

DR. SLAGA: But if you look at historical controls, that wouldn't come out that way. I mean it's only during the experiment. And if you have an animal model that gets a lot of a -- some kind of a tumor, you have to take historical controls into consideration.

MR. JOHNSON: Okay.

DR. HILL: -- my guess is if you gave them a comparable amount of potassium for that length of time at the same levels as potassium chloride instead of potassium bicarbonate, you would see the same phenomenon. I'd be stunned if you didn't.

DR. SLAGA: I don't know.

DR. HILL: Although it would change the -- it would change the bladder pH also given that much bicarb chronically.

DR. SLAGA: Well, that's the problem. You have an increase in flow of urine and you have a tremendous increase in pH. So, which related to bladder cancer, can cause a lot of problems. It's the same type of problem so.

DR. HILL: But cosmetically, that doesn't seem exactly relevant.

DR. SLAGA: Right.

DR. MARKS: So calcium carbonate is being used in the depilatory, but is that the reason it's in there? Because I assume there is a thioglycolic in there that -- that the reason it's in there. So, to me, that still doesn't sway we need one way or another as far as irritation. Do you -- so, you're not concerned about irritation it sounds like, Ron Hill?

DR. HILL: I'm not.

DR. MARKS: Tom, from a carcinogenicity, you're aren't concerned? So, Ron, can we just go ahead and put safe as the conclusion?

DR. SHANK: Yes.

DR. MARKS: Okay. And then, Wilbur, you -- somewhere in here I have noted you wanted a comment about the antigenotox on page 4 -- 15, I mean. Is that correct? Did you want Tom to clarify?

DR. SLAGA: I would leave it in.

MR. JOHNSON: Leave it in.

DR. SLAGA: It just adds a little bit more. In a lot of cases, a lot of these things do have -- related-type compounds may have an anti-genotoxicity. The data is not that strong, but at the same time it -- it does compare to some other agents. So I would leave it in.

DR. MARKS: Okay. Good.

MR. JOHNSON: I just want to know exactly how the carcinogenicity finding is supposed to be addressed in the discussion. I know you mentioned that that wasn't true with respect to historical control data.

DR. SLAGA: Yeah. And even in the regular controls during the experiment, it was very weak so.

MR. JOHNSON: So it will weaken (inaudible).

DR. MARKS: Okay. Any other comments?

DR. HILL: I have a couple of chemistry related issues that do need to get discussed here. So --

DR. MARKS: Will they affect the conclusion?

DR. HILL: No -- don't think so.

DR. MARKS: Okay. Good.

DR. HILL: However --

DR. MARKS: Okay.

DR. HILL: -- let me -- let me deal with the one that could potentially. It has to do with information capture, which I did not address myself. If you look at ammonium carbamate -- excuse me, ammonium carbonate, and you go down to the dictionary definition and look at the structure of it and also what's else there on that line, which is page - - almost there -- page 20. There's one thing that caught my eye is the compound on the right is not ammonium carbonate or bicarbonate. It is ammonium carbamate -- or ammonium carbamate.

And then the other thing that caught my eye is we have three CAS numbers, so I didn't know exactly what those three CAS number were. And the biggest question I had is in terms of toxicology, are we capturing ammonium carbamate, per se, in the search for information? Because my guess would be if not one of those three, which I didn't look them up -- should have -- taken me about two minutes to verify. If we didn't search ammonium carbamate for toxicology information, we need to.

MR. JOHNSON: This was discussed in the other team and Carol Isim agreed to communicate with JoAnn Nikitakas, the cosmetic chemist, to see exactly, you know, which CAS numbers should actually, you know, be associated with -- with ammonium carbonate, the cosmetic ingredient.

DR. HILL: Well, what I going to say is clearly this is not a pure compound as marketed. If you look at ammonium carbonate, in fact, there is no ammonium carbonate in there. There's ammonium bicarb and ammonium carbamate, I guess. So, I -- like I said, I should have taken the 30 seconds probably to look up those three CAS numbers and see what they actually were. But I just wanted to make sure that the search has captured any toxicology information pertinent to ammonium carbamate, per se -- the one on the right -- because that's a very different beast than any of these others. And if we haven't captured it, we need to and that may cause us to have a second look.

MR. JOHNSON: That would be them because that search has not been done (inaudible).

DR. HILL: Okay. All right. So that was it. And also, in terms of the composition, you've got -- when you're up here on impurities, everything seems to be referencing for several paragraphs food codex. And so I was looking -- in magnesium carbonate, there's something like -- some high percentage of magnesium oxide -- like 40 percent. If I go back there, I could find it. So what I wanted to find out was is the cosmetic ingredients apply comparable to what we're seeing for these food codex information, or we just not have that data so far -- in terms of impurities and so forth? There are reasons for asking certain impurities. So that's really a clarification question, I believe.

MR. BOYER: Yeah. I just looked up that up -- the three CAS numbers. And they are -- all three of them are for the ammonium carbonate. Not the carbamate.

DR. HILL: So we haven't captured the carbamate at all. But clearly the commercial product, by that dictionary definition, isn't. And I can see that if you're bubbling ammonia into -- into a solution of carbonic acid, you're going to get the carbamate. There will be no avoiding it. And so then the toxicology question is have we captured that?

MS. FIUME: And I think the good thing is that actually the grass definition for the ammonium carbonate -- which is also in the food chemical codex -- is the same definition as

what's given in the dictionary for the two ingredients.

DR. HILL: Yeah. So then I had to back research how they came to the conclusion of grass -- just the remote. I don't have any concerns that are resting on my mind on this. I just feel like we haven't captured everything.

DR. MARKS: So at least at this point, you feel we could -- our team tomorrow can second as safe as used?

DR. HILL: I do.

DR. MARKS: Okay. And then we'll clarify the ammonium carbamate search for toxicologic data.

MR. JOHNSON: Just one question. I know in the developmental and reproductive toxicity data, two percent calcium carbonate in the diet resulted in hypertrophy of the heart and a tendency toward decreased thymus weight. I was just wondering if there were any concerns about developmental and reproductive toxicity in that study?

DR. SLAGA: Which one? Calcium?

MR. JOHNSON: On calcium carbonate.

DR. MARKS: That was page -- which page was that, Wilbur?

MR. JOHNSON: It's on page 13.

DR. HILL: I definitely remember reading it and not being worried.

MR. JOHNSON: The oral -- oral reproductive study.

DR. HILL: I did just now notice I didn't mark it here. Is that a daily intake of three grams per kilogram body weight?

MR. JOHNSON: I think it was in the diet.

DR. HILL: Yeah. I see it's in the diet, but yield and intake of approximately three grams per kilogram body weight. Is that per day? I didn't -- probably is. Yeah.

MR. JOHNSON: I'd have to check that.

DR. HILL: Yeah. Because a rat -- is this rat? No, mice. So they weigh about .05 kilogram? Yeah, that's probably right. That's probably per day.

DR. MARKS: Ron, Ron, any concerns?

DR. SHANK: No.

DR. MARKS: None. Okay. Wilbur, any other comments, questions?

MR. JOHNSON: In that there are no concerns, should that even -- is there any reason to mention that in the discussion, in that there are no concerns about that end point?

DR. SHANK: I think so because we get a lot of data that really don't pertain to cosmetic use. Exposure is way too high or irrelevant. If we commented every time, every report on that, it would be a lot of work for you.

DR. MARKS: Okay.

MR. JOHNSON: So that's safe when formulated to be nonirritating?

DR. MARKS: No safe.

MR. JOHNSON: Just safe (inaudible).

DR. HILL: Safe as used.

MR. JOHNSON: Okay.

Day 2 of the June 6-7, 2016 CIR Expert Panel Meeting – Full Panel

Simple Carbonate Salts

Moving on to the next ingredient. Dr. Belsito, the carbonate salts.

DR. BELSITO: Yes, so this, again, the first time we're looking at these five ingredients. And we received data that we thought was sufficient to clear them and go ahead with the safe as used when formulated to be nonirritating conclusion.

DR. BERGFELD: Okay. Marks?

DR. MARKS: Second. Is it five or six ingredients?

DR. BERGFELD: I thought it was six.

DR. BELSITO: Six.

DR. MARKS: So that was a second.

DR. BERGFELD: So you are seconding?

DR. MARKS: Yes.

DR. BERGFELD: Any other discussion, edits, comments? Seeing none. Call the question -- oh, I'm sorry, did I see one? Wilbur?

DR. JOHNSON: I know that in yesterday's team meeting, some data needs -- potential data needs were mentioned. And I'm wondering whether or not that is still the case today?

DR. MARKS: Ron Hill, do you want to mention about the ammonium carbonate search data, since it's part of the ammonium carbonate mixture?

DR. HILL: Yeah, so ammonium carbonate is not really ammonium carbonate. Ammonium carbonate seems to be a mixture of ammonium carbamate and ammonium bicarbonate. And the point was that we didn't deliberately try to capture the toxicology data and whatever is known about ammonium carbonate, and it wasn't clear that we were picking that up in the way that the information was surveyed. So I had just asked that we make sure that we go back out and do a deliberate search for the ammonium carbamate and make sure that everything had been captured before we come to a final conclusion.

DR. MARKS: It doesn't change the motion, but I ask for more data.

DR. BELSITO: I have no problem, but we're going ahead with the safe as used.

DR. MARKS: Yes.

DR. LIEBLER: Yeah, I mean I had a related point about Table 1, the third entry, that ammonium carbonate as Ron just pointed out is actually list three cast numbers, two of which are ammonium carbonate and the chemists understand ammonium carbonate to be. And then the third one in this funky mix of ammonium bicarbonate and ammonium carbamate. Then I guess it is what it is in the dictionary, and that's apparently the product that's supplied is this mixture here, which has a formula that corresponds to the name of the product. So I ask that that be clarified for us. I think regardless of whatever they are, they are safe, so I have no concerns about that. But it just -- it seems to be incorrect nomenclature for what is portrayed as the ingredient.

DR. LANGE: No, we're going to follow up with

(inaudible). It's also listed in the food chemical codex in the same way.

DR. BERGFELD: Okay. Ron hill, did you want to --

DR. HILL: No, just see if there are any other cast members that are associated with the carbonate itself. And, again, we'll make sure the search encompasses that.

DR. BERGFELD: Okay. All right. Any other comments. Let's call the question. All those in favor of safe? Unanimous. Okay with the caveats that have been -- what?

DR. SLAGA: I just want to make sure that in the discussion where there was a statement about the potassium bicarbonate causing renal cancer. We discussed that and as long as it's in the discussion, we --

DR. LIEBLER: Not relevant.

DR. SLAGA: -- it's no concern.

DR. BELSITO: Yes, we had the same issue with both the bladder and the renal affects that we thought were due to crystallization and irritation.

DR. BERGFELD: Any other comments before we move on then? Wilbur, are

we all right?

DR. JOHNSON: Yes, we are. Thank you.

DR. BERGFELD: Okay.

Safety Assessment of Carbonate Salts as Used in Cosmetics

Status: Draft Final Report for Panel Review
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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, 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, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 6 carbonate salts which function as absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients, and concluded that these carbonate salts are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

INTRODUCTION

The safety of the following 6 carbonate salts as used in cosmetics is reviewed in this safety assessment:

Magnesium Carbonate
Ammonium Bicarbonate
Ammonium Carbonate
Calcium Carbonate
Potassium Bicarbonate
Potassium Carbonate

According to the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of these ingredients in cosmetic products include: absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents (**Table 1**).¹ Ingredient definitions are also included in **Table 1**.

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) has evaluated the safety of Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate in cosmetic products, and concluded that these ingredients are safe as presently used in cosmetics.² A CIR final report with this conclusion was published in 1987. Subsequently, during a Panel re-review of the safety of these ingredients in 2004, the conclusion originally determined by the Panel was reaffirmed.³

Data from chemical registration dossiers submitted to the European Chemicals Agency (ECHA) that relate to some of the ingredients that are being reviewed were found on the ECHA website. A chemical registration dossier may contain data on the cosmetic ingredient that is being reviewed or pertinent data on a surrogate chemical. ECHA data, whether on the cosmetic ingredient or on a surrogate chemical, are included and identified as such in the report text.

CHEMISTRY

Definition and General Characterization

The carbonate salts are alkaline salts that may be formed by treating carbonic acid with an appropriate base (e.g., adding carbonic acid to sodium hydroxide will produce sodium carbonate (and water); Figure 1).

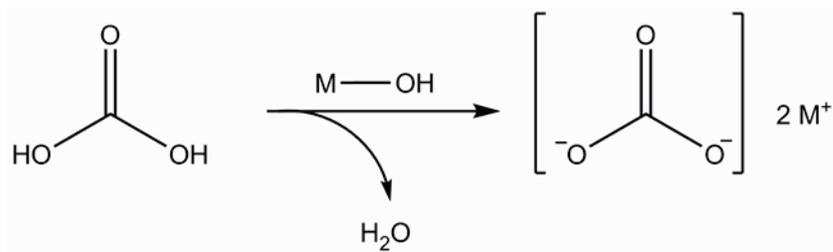


Figure 1. Carbonic Acid and Salts Thereof.

However, most of these salts are also naturally occurring as minerals. All of the ingredients in this report are related as either alkaline earth metal (column I or II) or ammonium salts of carbonic acid. This group comprises carbonate salts with differences in properties that can be attributed to differences in the cation component. Assessing the safety of all of these ingredients in a single report facilitates a coherent analysis, taking into account comparabilities and differences in properties among these ingredients. This enables a more informative and efficient safety assessment of the ingredients than would be likely in separate reports that each assesses a single ingredient. The definitions of the carbonate salts that are included in this safety assessment are presented in **Table 1**. These salts are classified as generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA) for use in food. Daily consumption of these GRAS foods would result in much larger

systemic exposures than what is expected from use in cosmetic products, even if there was 100% dermal absorption of the cosmetic product. Thus, the systemic toxicity potential of these carbonate salts via oral exposure is not addressed further in this report. The primary focus of the safety assessment is the review of the safety of topical exposure to these ingredients.

Physical and Chemical Properties

These ingredients are typically colorless or white solids with low formula weights (**Table 2**). While the carbonate salts may be fairly alkaline in concentrated solution, an acceptable pH can be easily obtained in formulation.

Method of Manufacture

Ammonium Carbonate

Ammonium Carbonate may be prepared from gaseous ammonia, carbon dioxide, and steam.⁴

Calcium Carbonate

Calcium Carbonate, as used for industrial purposes, is extracted by mining or quarrying.⁵ Pure Calcium Carbonate can be produced from marble, or it can be prepared by passing carbon dioxide into a solution of calcium hydroxide. In the latter case, Calcium Carbonate is derived from the mixture, forming a grade of product called “precipitated calcium carbonate” or PCC. PCC has a very fine and controlled particle size, diameter of 2 μ , and is particularly useful in the production of paper. The other primary type of industrial product is “ground calcium carbonate” or GCC. The production of GCC involves crushing and processing limestone to create a powdery form graded by size and other properties for many different industrial and pharmaceutical applications.

Composition/Impurities

Magnesium Carbonate

The following specifications for Magnesium Carbonate are referenced in the “Evaluation of the Health Aspects of Magnesium Salts as Food Ingredients” by the Select Committee on GRAS Substances: not less than 40% and not greater than 43.5% magnesium oxide, not greater than 3 ppm arsenic, not greater than 30 ppm heavy metals, not greater than 10 ppm lead, and not greater than 0.6% calcium oxide.⁶

The *Food Chemicals Codex* specification for Magnesium Carbonate impurities states that this chemical should contain no more than 2000 mg/kg lead and no more than 0.6% calcium oxide.⁷

Ammonium Bicarbonate

The following specifications for impurities in Ammonium Bicarbonate are stated in the *Food Chemicals Codex*: chloride ($\leq 0.003\%$), lead (≤ 3 mg/kg), and sulfate ($\leq 0.007\%$).⁷

Ammonium Carbonate

According to the *Food Chemicals Codex*, Ammonium Carbonate consists of ammonium bicarbonate (NH_4HCO_3) and ammonium carbonate ($\text{NH}_2\text{COONH}_2$), and should contain not less than 30% NH_3 and not more than 43% NH_3 . The specifications for Ammonium Carbonate impurities are as follows: chloride ($\leq 0.003\%$), lead (≤ 3 mg/kg), and sulfate ($\leq 0.005\%$).⁷

Calcium Carbonate

The following specifications for impurities in Calcium Carbonate are stated in the *Food Chemicals Codex*: acid-insoluble substances ($\leq 0.2\%$), arsenic (≤ 3 mg/kg), fluoride ($\leq 0.005\%$), lead (≤ 3 mg/kg), and magnesium and alkali salts ($\leq 1\%$).⁷

The European Commission’s purity criteria for Calcium Carbonate as a color for use in foodstuffs are as follows: loss on drying ($\leq 2\%$), acid-insoluble substances ($\leq 0.2\%$), magnesium and alkali salts ($\leq 1.5\%$), fluoride (≤ 50 mg/kg), antimony (≤ 100 mg/kg, singly or in combination), copper (≤ 100 mg/kg, singly or in combination), chromium (≤ 100 mg/kg, singly or in combination), zinc (≤ 100 mg/kg, singly or in combination), barium (≤ 100 mg/kg, singly or in combination), arsenic (≤ 3 mg/kg), lead (≤ 10 mg/kg), and cadmium (≤ 1 mg/kg).⁸

Potassium Bicarbonate and Potassium Carbonate

Potassium Bicarbonate contains no less than 99% Potassium Bicarbonate.⁴ The *Food Chemicals Codex* specification for impurities in Potassium Bicarbonate and Potassium Carbonate states that each chemical should contain no more than 2 mg/kg lead.⁷

USE

Cosmetic

The safety of the carbonate salts included in this safety assessment is evaluated based on data received from the FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data (**Table 3**) indicate that 5 of the 6 ingredients in this safety assessment are currently being used in cosmetic products; Potassium Bicarbonate is not reported as being used.

According to 2016 VCRP data, the greatest reported use frequency is for Magnesium Carbonate (317 product formulations, mostly leave-on products), followed by Calcium Carbonate (174 product formulations, mostly leave-on products) (**Table 3**).⁹ The results of a concentration of use survey conducted in 2015 indicate that Ammonium Bicarbonate has the highest maximum concentration of use; it is used at concentrations up to 93.4% in rinse-off products (hair bleaches). The maximum concentration of use in leave-on products is being reported for Calcium Carbonate (concentrations up to 35% in eyebrow pencils) (**Table 3**).¹⁰

Cosmetic products containing carbonate salts may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Calcium Carbonate at maximum use concentrations up to 35% in eye area cosmetics) and mucous membranes (e.g., Calcium Carbonate at maximum use concentrations up to 10% in dentifrices). Additionally, some of these ingredients are being used in products that may result in incidental ingestion. For example, Calcium Carbonate is being used in dentifrices at maximum use concentrations up to 10%, and in lipstick at maximum use concentrations up to 8%. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Magnesium Carbonate is used in aerosol color hair sprays at maximum use concentrations up to 0.18%, and in face powders at maximum use concentrations up to 4%. Calcium Carbonate is used in powders (dusting and talcum, excluding aftershave talc) at maximum use concentrations up to 5%, and in face powders at maximum use concentrations up to 15%. 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.^{11,12,13,14} 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.^{11,12} Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.^{15,16,17}

Calcium Carbonate and Magnesium Carbonate appear on the list of colorants allowed in cosmetic products that are marketed within the European Union.¹⁸ The purity criteria that have been established for Calcium Carbonate are presented in the Composition/Impurities section of this safety assessment.⁸ These criteria must be met for Calcium Carbonate when this ingredient is used as a colorant in cosmetic products.

Noncosmetic

The following carbonate salts are direct food additives that are classified as GRAS in the United States: Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, Potassium Bicarbonate, and Potassium Carbonate.¹⁹

The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives has determined that Magnesium Carbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate are not limited in terms of overall daily intake (mg/kg body weight).²⁰ The Committee noted that these bases are required for pH adjustment in food technology, and that the amounts and concentrations used are not likely to have

any toxicological significance. Furthermore, the Committee placed no restriction on the food-additive use of these bases, provided that the contribution made to the dietary load of potassium, calcium, and magnesium is assessed and considered to be acceptable.

A grade of Calcium Carbonate that is referred to as “precipitated calcium carbonate” or PCC is particularly useful in the production of paper.⁵ Combinations of viscous xylocaine, aluminum hydroxide-Magnesium Carbonate, and diphenhydramine hydrochloride have been used to treat mucosal toxicity resulting from chemotherapy and radiotherapy in the treatment of esophageal cancer.²¹

Carbonate salts are also used as inactive ingredients in FDA-approved drug products, and these uses are summarized below:

Magnesium Carbonate

Magnesium Carbonate is used as an inactive ingredient (maximum potency of 10 mg to 250 mg) in oral drug products that have been approved by FDA.²²

Calcium Carbonate

Calcium Carbonate is used as an inactive ingredient in drug products that have been approved by FDA for otic application (maximum ingredient potency: 0.38%), buccal application (maximum ingredient potency : 145.7 mg), and inhalation exposure (maximum ingredient potency: 4.02%).²² Calcium Carbonate is also an FDA-approved inactive ingredient in oral drug products (maximum ingredient potency: 4 mg to 550 mg).

Potassium Bicarbonate

Potassium Bicarbonate is used as an inactive ingredient (maximum potency: 1.06 mg to 500 mg) in oral drug products that have been approved by FDA.²² This ingredient is also an FDA-approved inactive ingredient (maximum potency of 8 mg) in drug products administered via the transmucosal route.

Potassium Carbonate

Potassium Carbonate is used as an inactive ingredient in oral drug products (maximum ingredient potency: up to 27.69 mg) and in topical drug products (maximum ingredient potency not stated).²²

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Ammonium Carbamate

The percutaneous absorption of 5-(dodecyloxy carbonyl)pentylammonium 5-(dodecyloxy carbonyl)pentylcarbamate (chemical has ammonium carbamate polar head) was studied *in vitro* using porcine skin in Franz diffusion cells.²³ This chemical is an ammonium carbamate formed by the reaction of 6-aminohexanoic acid dodecyl ester with carbon dioxide.²⁴ The test material (150 µl in an inert vehicle) was applied to the stratum corneum side of the skin. After the ammonium carbamate polar head penetrated into the stratum corneum intercellular lipids, it decomposed rapidly and 2 molecules of protonated dodecyl 6-aminohexanoate and carbon dioxide were released. Also, in this study, the skin penetration of the drug theophylline was enhanced in the presence of 5-(dodecyloxy carbonyl)pentylammonium 5-(dodecyloxy carbonyl)pentylcarbamate.²³

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Magnesium Sulfate

The following data on magnesium sulfate (surrogate compound) are included in a REACH dossier on Magnesium Carbonate that was submitted to ECHA.²⁵ An acid solution of magnesium chloride containing 200 μ curies of magnesium (²⁸Mg) was solution was neutralized with 1 N sodium hydroxide and the precipitate was dissolved in 1 N sulfuric acid. A slightly acidic solution of magnesium sulfate in distilled water (contained 5 meq of magnesium) was fed (in feed) to 3 groups of 6 rabbits (domestic rabbits of mixed breed). The 3 groups were treated as follows: Group 1 (feed and water withheld for 17 h), Group 2 (animals starved for 36 h), and Group 3 (animals starved for 48 h). In the 3 groups, mean urinary excretion of radioactivity in 48 h ranged between 10% and 12.5%. An external survey of group 2 animals at 24 h revealed a maximal concentration of radioactivity in the mid abdomen. Two of the animals were killed, and the cecum and its contents were found to contain 78% of the ingested dose. The results of this study indicate that poor gastrointestinal absorption of magnesium accounts for its low renal excretion. Additionally, absorption does not appear to occur from the large intestine.

Intraperitoneal

Calcium Carbonate

Calcium Carbonate (0.40 mCi of calcium ¹⁴C-carbonate pellet) was implanted intraperitoneally into a male rat.²⁶ Approximately 72% of the radioactivity was excreted as respiratory carbon dioxide between 2 h and 142 h after implantation (most after 69 h). Approximately 30% of the dose was recovered in unabsorbed pellet. Urinary radioactivity accounted for 0.27% of the dose and fecal radioactivity accounted for approximately 0.07% of the dose; 1% of the absorbed dose was retained by the tissues.

Sodium Bicarbonate

The following data on sodium bicarbonate (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ Rats (number, strain and sex not stated) received 5 i.p. injections of ¹¹C-sodium bicarbonate, made at 30-minute intervals. The dose/concentration of the test substance was not stated. The animals were killed 30 minutes after the last injection. Approximately 60% of the radioactivity was accounted for. The urine contained 1.3% of the radioactivity, and > 50% of the radioactivity occurred as respiratory ¹¹C-carbon dioxide.

Human

Oral

Calcium Carbonate

The absorbability of calcium from Calcium Carbonate and calcium citrate salts was evaluated in a study in which 37 men and women ingested 300 mg (low load) and 1000 mg (high load) calcium loads as part of a light breakfast meal.²⁸ The subjects were randomly assigned to a sequence of either Calcium Carbonate first and then calcium citrate, or vice versa. Each absorption measurement was conducted over 2 study days. On the first day, the subjects received no supplement; on the second day, the subjects received a 1000 mg calcium load. The test with the 300 mg load was performed similarly. For the high load, absorption was measured by tracer appearance in the serum and by absorptive increment in urinary calcium. For the low load, absorption was measured using the tracer method only. Test materials (in gelatin capsules) were labelled with ⁴⁵Ca. Individual tracer doses were in the range of 5 to 9 μ Ci. Relative absorption was estimated from the difference in urinary calcium following breakfast on the 2 days and true fractional absorption from the appearance of ⁴⁵Ca in the serum. Mean tracer absorption for both salts combined was 36% at the 300 mg load and 28.4% at the 1000 mg load. In both experiments, the observed mean difference in absorption between the salts was very small. By the tracer method, the within-subject difference (Calcium Carbonate less citrate) was +3.3% \pm 1.2% of the ingested dose at the high load and 3.6% \pm 2.7% at the low load.

Potassium Bicarbonate

Following ingestion, Potassium Bicarbonate rapidly dissociates in gastric juice to yield carbonate ions (bicarbonate and carbonate) and potassium ions.²⁹ At this stage, the minor alkalinity is neutralized by the stomach acid. The undissociated Potassium Bicarbonate is not expected to be systemically available in the body under normal handling and use conditions.

Potassium Carbonate

Like Potassium Bicarbonate, following ingestion, Potassium Carbonate rapidly dissociates in the gastric juice to yield carbonate ions and potassium ions.³⁰ Similarly, the dissociation into ions (in gastric juice) of the following other carbonate salts reviewed in this safety assessment would be expected: Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, and Calcium Carbonate.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Ammonium Carbonate

The acute dermal toxicity of Ammonium Carbonate was evaluated in accordance with OECD Guideline 402 using 10 (5 males, 5 females) rats of the CRL:(WI) strain.³¹ The test substance (200 mg/kg body weight) was applied to 10% of the total body surface for 24 h. The application site was covered with a gauze pad that was secured with a semi-occlusive plastic wrap. Dosing was followed by a 14-day observation period, after which necropsy was performed. None of the animals died and there were no clinical signs of toxicity. Additionally, there were no effects on body weight. It was concluded that the LD₅₀ was > 2000 mg/kg body weight.

Ammonium Carbamate

The acute dermal toxicity of ammonium carbamate (contained 43.6% ammonium and 56.3% carbon dioxide) was studied using 10 (5 males, 5 females) rats of the Crl:CD(SD) strain.³² The test substance (in water; 5000 mg/kg weight) was applied, under a semi-occlusive patch, to the back for 24 h. Dosing was followed by a 14-day observation period and necropsy. None of the animals died and there were no test substance-related clinical findings. There also were no remarkable body weight changes during the study. At necropsy, scabbing at the application site was observed in 3 animals. The reported LD₅₀ was > 5000 mg/kg. Results relating to skin irritation are included in the section on Skin Irritation and Sensitization.

Calcium Carbonate

Calcium Carbonate (nano form) was tested in an acute dermal toxicity study involving 10 (5 males, 5 females) Wistar rats.²⁸ The test substance was applied to the back and flanks (~ 10% of total body surface area; 2000 mg/kg body weight) of each animal, and the application site was covered with a semi-occlusive patch for 24 h. The animals were killed at the end of the study and subjected to gross necropsy. None of the animals died and there were no clinical signs of systemic toxicity or dermal irritation. There was no evidence of abnormalities at necropsy. The reported acute dermal LD₅₀ was > 2000 mg/kg body weight.

Potassium Bicarbonate

The acute dermal toxicity of Potassium Bicarbonate was studied using New Zealand white rabbits (5 males, 5 females).²⁹ Potassium Bicarbonate was applied to the back at a dose level of 2000 mg/kg body weight, and the application site was covered with a 10 cm x 10 cm occlusive patch. The test substance was applied to the application site at a rate of ~ 0.05 g/cm² during a 24-h exposure period. Dosing was followed by a 14-day observation period. All animals were killed and subjected to gross necropsy. None of the animals died and they all appeared clinically normal throughout the study. With the exception of an incidental dermal finding in 1 animal, there were no visible lesions at necropsy. The slight to moderate dermal irritation observed had cleared in all animals by day 10. The dermal LD₅₀ was reported to be > 2000 mg/kg body weight.

Potassium Carbonate

In a REACH dossier on Potassium Carbonate, an acute dermal toxicity evaluation using data on Potassium Carbonate containing a pesticide (identity and concentration of pesticide not stated; concentration of Potassium Carbonate not stated) was performed according to the U.S. EPA pesticide assessment guidelines.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance, moistened with distilled water, was applied to the skin

of young adult, New Zealand white rabbits (5 males, 5 females [fasted]) for 24 h. The area of application, dose per cm², and whether or not the site was covered were not stated. Application of the test substance was followed by a 14-day observation period. None of the animals died. Dermal irritation was observed at the test site; however, irritation scores were not provided. There were no gross findings at necropsy, and neither adverse pharmacologic effects nor abnormal behavior were observed. The reported dermal LD₅₀ was > 2000 mg/kg body weight for Potassium Carbonate containing a pesticide.

Ammonium Sulfate

The following data on ammonium sulfate (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ The acute dermal toxicity of ammonium sulfate was evaluated according to OECD Guideline 434 using groups of 6 (3 males, 3 females per group) Wistar rats. Ammonium sulfate (in water-acetone solution; single dose of 2000 mg/kg body weight) was applied to a 3 x 4 cm² area of the back. The application site was not covered. Dosing was followed by a 14-day observation period. The reported LD₅₀ was > 2000 mg/kg body weight.

Oral

Ammonium Bicarbonate

An LD₅₀ of 1576 mg/kg was reported for rats (number and strain not stated) in an acute oral toxicity study on Ammonium Bicarbonate.³³ Additional study details were not reported.

Ammonium Carbonate

The acute oral toxicity of Ammonium Carbonate (in 0.5% aqueous carboxymethyl cellulose) was studied using groups of 5 male and 5 female Wistar rats.²⁷ These data are included in a REACH registration dossier that was submitted to ECHA. Ammonium Carbonate was administered to 4 groups at the following oral doses, respectively: 215 mg/kg, 681 mg/kg, 1470 mg/kg, and 2150 mg/kg. The maximum dose volume per group was 10 ml. Untreated rats served as controls. Dosing was followed by a 14-day non-treatment period. Five rats dosed with 2150 mg/kg 3 rats dosed with 1470 mg/kg died. There were no mortalities in the 2 lower dose groups. Except for paresis, observed only in male rats (1470 mg/kg dose group), the following clinical signs were observed in male and female rats (number affected not stated) of the 1470 mg/kg dose group prior to death: dyspnea, apathy, abnormal position, staggering, tonic convulsions, exophthalmos, salivation, and poor general state. Necropsy findings in animals that died included general congestion of the glandular stomach (mucosa slightly red). There were no pathological findings in animals that were killed. An LD₅₀ of 1576 mg/kg was reported for male/female rats.

Ammonium Carbamate

Groups of male and female rats (1 to 5/group) were dosed orally (by gavage) with ammonium carbamate at up to 4000 mg/kg body weight.³² The 800, 1000, and 2000 mg/kg body weight groups consisted of 5 animals each; the remaining groups consisted of 1 animal per group. Deaths occurred within 30 minutes of exposure, and the clinical signs observed included apathy, convulsions, and accelerated respiration. Gross pathology data were not available. An LD₅₀ of 1380 mg/kg body weight was reported.

Calcium Carbonate

Calcium Carbonate (in arachis oil) was administered to 5 female Sprague-Dawley rats at a single oral dose of 2000 mg/kg body weight.²⁸ The dose volume was 10 ml/kg. Dosing was followed by a 14-day observation period and necropsy. None of the animals died and there were no clinical signs of systemic toxicity. Additionally, there were no adverse changes in body weight, and adverse effects were not observed at necropsy. The reported LD₅₀ was > 2000 mg/kg body weight.

Potassium Bicarbonate

A single oral dose of Potassium Bicarbonate (in distilled water; 2000 mg/kg body weight) was administered by gavage to Sprague-Dawley rats (5 males, 5 females).²⁹ Dosing was followed by a 14-day observation period and necropsy. None of the animals died. Except for piloerection in all animals during the first 30 minutes post-application, there were no treatment-related clinical signs or changes in body weight. There also were no treatment-related necropsy findings. Potassium Bicarbonate was classified as non-toxic and the reported LD₅₀ was > 2000 mg/kg body weight.

Potassium Carbonate

In an acute oral toxicity study using rats (number and strain not stated), a mean LD₅₀ of 1870 (range: 1340 to 2600) mg/kg was reported after intubation with Potassium Carbonate (0.20 g/ml).³⁴ Additional study details were not presented.

In a study summarized in a REACH dossier on Potassium Carbonate, "potash calc." (composition not stated) was evaluated in an acute oral toxicity study using a procedure that was equivalent to that of the now discontinued OECD Guideline 401.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. Fasted Sprague-Dawley rats (5 males, 5 females) were dosed with the test substance; dosing was followed by a 14-day observation period. None of the animals died, and there were no treatment-related clinical signs, necropsy findings, or changes in body weight. The LD₅₀ was > 2000 mg/kg body weight.

Inhalation

Ammonium Bicarbonate and Ammonia

The acute inhalation toxicity of ammonia was studied using 3 groups of male ICR mice (number per group not stated).³² These data are included in a REACH registration dossier that was submitted to ECHA. The 3 groups were exposed for 1 h to ammonia (method not stated) at the following concentrations: 2408 mg/m³ (3440 ppm), 2954 mg/m³ (4220 ppm), and 3402 mg/m³ (4860 ppm). Dosing was followed by a 14-day observation period and necropsy. The lungs of mice that died (number not stated) were diffusely hemorrhagic. Acute vascular congestion and diffuse intra-alveolar hemorrhage were observed microscopically. Mild to moderate chronic focal pneumonitis was also observed. In animals that survived, focal atelectasis and liver damage were observed in animals that were killed after the observation period. Other findings in surviving animals included: 3340 ppm (swelling and increased cytoplasmic granularity of hepatocytes), 4220 ppm (scattered foci of frank cellular necrosis of hepatocytes), and 4860 ppm (increased necrosis of hepatocytes), and at test concentrations(s) not stated (follicular hyperplasia in the spleen). This finding for the spleen was not observed in animals that died during exposure. It was noted that the liver lesions may have resulted from the compromised nutritional state of the mice. The LC₅₀ for Ammonium Bicarbonate was deduced using the maximum quantity of NH₃ possibly released from ammonium carbamate (i.e., 43.6%). The calculated LC₅₀ values for Ammonium Bicarbonate (in mice) were: 6.8 mg/L air (for 1 h exposure) and 1.7 mg/L air (4534 ppm [extrapolated using Haber's law]).

Calcium Carbonate

The acute inhalation toxicity of Calcium Carbonate was evaluated according to OECD Guideline 403 using 10 (5 males, 5 females) Wistar rats.²⁸ The animals were exposed for 4 h to aerosolized Calcium Carbonate using a nose-only exposure system. Exposure was interrupted for a total of 8 minutes. The flow of air in each tube was 0.97 l/minute, and the mean chemical aerosol concentration was 3 mg/l of air. Mass mean aerodynamic diameters (MMAD) were between 2.28 µm and 2.89 µm, with a geometric standard deviation between 1.5 and 3. Taking these values into consideration, it was assumed that the deposition of particles would occur in the upper and lower respiratory tract. Exposure was followed by a 14-day observation period. All animals were killed and subjected to gross necropsy. Ruffled fur was the only clinical sign that was observed. Slight body weight loss, followed by recovery, was observed. There were no macroscopic findings at necropsy. The reported LC₅₀ was > 3 mg/l of air.

Potassium Bicarbonate

The acute inhalation toxicity of Potassium Bicarbonate was evaluated using Sprague-Dawley rats (5 males, 5 females).²⁹ The animals were exposed for 45.5 h to aerosolized Potassium Bicarbonate at a mean gravimetric chamber concentration of 4.88 ± 0.6 mg/l. Approximately 1% of the particles were of a size < 1 µm; 25% were < 3 µm. The mass mean aerodynamic diameter was ~ 4.7 µm. The following signs were observed during the first hour of exposure: decreased activity, ocular discharge, and hunched posture. Similar signs as well as facial staining and/or nasal discharge were observed after removal of the animals from the exposure chamber. All of the animals recovered from these signs within 24 h. Gross necropsy findings were unremarkable, and all tissues and organs appeared normal. The LC₅₀ was reported to be > 4.88 ± 0.60 mg/l air.

Potassium Carbonate

In a REACH dossier on Potassium Carbonate, an acute inhalation toxicity evaluation using data on Potassium Carbonate containing a pesticide (identity and concentration of pesticide not stated; concentration of Potassium Carbonate not stated) was performed according to the U.S. EPA pesticide assessment guidelines.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. Sprague-Dawley rats (5 males, 5 females) were exposed to the aerosolized

test substance (mass mean aerodynamic diameter $\approx 3.6 \mu$) for 4.5 h. The gravimetric chamber concentration was 4.96 ± 1.14 mg/L, with approximately 3% of the particles below 1μ , and 38% below 3μ . Exposure was followed by a 14-day observation period. None of the animals died. Dermal necrosis and corneal opacity were observed in all animals, and damage was most severe around the mouth and on the forelimbs. There were no test substance-related gross necropsy findings. The LC_{50} was $> 4.96 \pm 1.14$ mg/L air.

Sodium Bicarbonate

The following data on sodium bicarbonate (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ The acute inhalation toxicity of sodium bicarbonate was evaluated using groups of 10 (5 males, 5 females per group) Sprague-Dawley rats. The mass mean aerodynamic diameter of the test substance was $2.9 \pm 1.77 \mu$ m. The animals were exposed to aerosolized sodium bicarbonate (4.74 ± 1.03 mg/l) for 4.5 h, followed by a 14-day observation period. None of the animals died, and necropsy was performed at the end of the observation period. Ocular/nasal discharge was observed in 6 of 10 rats. Moderately red lung tissue was reported for 1 male and 1 female. One male had slightly red lung tissue. The necropsy findings were classified as unremarkable. The reported LC_{50} was > 4.74 mg/L air.

Intravenous

Ammonium Bicarbonate

The acute intravenous (i.v.) toxicity of Ammonium Bicarbonate (in 0.03 M sodium hydroxide) was evaluated using groups of 10 young albino mice, and a mean LD_{50} value of 3.10 ± 0.28 mM/kg body weight was reported.³⁵ Additional study details were not included.

Ammonium Bicarbonate and Ammonium Carbamate

The acute i.v. toxicity of an ammonium carbamate/Ammonium Bicarbonate mixture (in 0.03 M sodium hydroxide) was evaluated using groups of 10 young albino mice,³⁵ The test substance was defined as commercial reagent grade Ammonium Carbonate, and was described as a mixture of approximately equal parts Ammonium Bicarbonate and ammonium carbamate. A mean LD_{50} value of 1.02 ± 0.11 mM/kg body weight was reported. Additional study details were not provided.

Short-Term Toxicity Studies

Oral

Magnesium Chloride Hexahydrate

The following data on magnesium chloride hexahydrate (surrogate compound) are included in a REACH dossier on Magnesium Carbonate that was submitted to ECHA.²⁵ The repeated dose toxicity of magnesium chloride hexahydrate was studied using groups of up to 30 male and female Wistar rats. The dose groups were as follows: 250 mg/kg body weight/day (10 males, 10 females), 500 mg/kg body weight/day (12 males, 12 females), and 1000 mg/kg body weight/day (15 males, 15 females). The vehicle (water) control group consisted of 12 males and 12 females. The test substance was administered orally (by gavage) to males and females daily during 14 days pre-mating and 14 days of mating. The test substance was also administered to females during gestation and up to postnatal day 3, and to males for 28 to 29 days. There were no treatment-related mortalities or major toxicological findings. There were no remarkable clinical signs or effects on hematology or clinical chemistry. The same was true for necropsy and histopathological findings relating to non-reproductive organs. It was concluded that the NOAEL for magnesium chloride hexahydrate was 1000 mg/kg body weight/day. Furthermore, it was determined that the equivalent NOAEL for Magnesium Carbonate was 414 mg/kg body weight/day. Results relating to toxic effects of magnesium chloride hexahydrate on reproductive organs are included in the section on Developmental and Reproductive Toxicity.

Calcium Carbonate

Five rats were fed ⁴⁵Ca-labeled Calcium Carbonate (0.3 g/kg body weight) in feed for 3 days.²⁶ The strain of rats tested was not identified. All of the animals remained healthy.

The oral toxicity of Calcium Carbonate (nano form) was evaluated in a 14-day study using groups of 6 (3 males, 3 females) Wistar rats.²⁸ The 4 groups consisted of the control and 250, 500, and 1000 mg/kg bodyweight/day groups. The test

substance was administered once daily by gavage at a dosage volume of 5 ml/kg. Control animals were dosed with distilled water. There were no unscheduled deaths or treatment-related toxicologically significant macroscopic abnormalities. There also were no clinical signs of toxicity or adverse effects on body weight development. The NOAEL was determined to be 1000 mg/kg body weight/day.

Potassium Bicarbonate

In a 4-week toxicity study, groups of 10 male and 10 female SPF-bred Wistar rats (CpB:WU;Wistar random) were fed unsupplemented rodent diet (control) or a diet containing 2% or 4% Potassium Bicarbonate.³⁶ The animals were killed at the end of the study. None of the animals died during the study, and no treatment-related abnormalities were reported. There were no consistent or treatment-related effects on red blood cell variables, clotting potential or total and differential white blood cell counts in any of the groups. The relative kidney weight (relative to body weight) was increased; however, this finding was not consistent or considered to be dose-related. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most of the histopathological changes observed represented background pathology that is normal for SPF-bred Wistar rats (CpB:WU; Wistar random).

Ammonium Chloride

The following data on ammonium chloride (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA. The oral toxicity of ammonium chloride was evaluated in a 28-day study involving groups of 10 male and female Wistar rats.²⁷ Ammonium chloride was fed at a concentration of 2% (2214.5 mg/kg body weight/day) or 4% (4228.5 mg/kg body weight/day) in the diet daily for 28 days. The animals were killed at the end of the study and necropsied. Organs were subjected to microscopic examination. Significant weight loss (18% to 25% below the control value; $p < 0.01$) was noted for males and females of the higher dose group; food intake was decreased. Growth was also markedly decreased ($p < 0.05$) in the lower dose group. None of the animals died and there were no treatment-related clinical signs. Urinalyses revealed a dose-dependent increase in net acid excretion. There were no consistent or treatment-related defects on red blood cell variables, clotting potential or total and differential white blood cell counts. Alkaline phosphatase activity was increased in the higher dose group (27.7% over controls, both sexes) and in low-dose males (27.7% over controls). There were no consistent or treatment-related changes in the following organ weights: liver, spleen, ovaries, pituitary, thyroid, thymus, or heart. Relative kidney weight (relative to body weight) was increased in both dose groups. Relative adrenal weight was increased only in males of the higher dose group. There were no significant differences in necropsy findings between test and control groups. Most of the histopathological changes observed were nearly equally distributed among control and test groups, and represented normal background pathology for rats of this strain and age. It was noted that most of the changes could be regarded as physiological adaptations to the feeding of acid-forming salt.

Ammonium chloride was fed (in the diet) to 10 male Sprague-Dawley rats at 684 mg/kg body weight/day (7 days per week) for 70 days.³² These data are included in a REACH registration dossier that was submitted to ECHA. Negative and positive control (tributyl phosphate) groups were included in the study. A 7-day post-exposure period was observed, and gross and microscopic examinations of the bladder were performed. There were no significant differences in food consumption among the 3 groups. The difference also was not significant when animals fed ammonium chloride were compared to the negative control group. Body weight was significantly decreased in the positive control group. Gross and microscope examination results were negative for animals fed ammonium chloride and for the negative control group. Hyperplasia of the bladder was observed in the positive control group. The NOEL for ammonium chloride was < 684 mg/kg body weight/day.

Inhalation

Potassium Carbonate

The potential for short-term toxicity and neurotoxicity of a Potassium Carbonate-based scrubbing solution (containing 30.8% (w/v) Potassium Carbonate) used in petroleum refineries was evaluated in Sprague-Dawley CrI:CD BR rats.³⁷ Inhalation exposures were to aerosols of a "used" scrubbing solution in a whole-body exposure chamber, 6 h/day for 21 consecutive days at target concentrations of 0 (filtered air – control), 0.1, 0.2, or 0.4 mg/L (30 animals/sex/group). Five rats per sex per group were allowed a 14-day recovery period (satellite recovery group) and killed on study day 35 for either systemic or neurotoxic evaluation. Functional observation battery examinations and locomotor activity tests were conducted. No apparent adverse effects were noted at any exposure level, as determined by clinical observations, food consumption

measurements, hematology, serum chemistry, ophthalmologic observations, and gross pathology evaluations. Statistically significant increases in lung weights were noted at all concentrations; all lung weights returned to control values at the end of exposure, except for the 0.4 mg/L group (females). There were no significant changes in other organ weights. Histopathologic findings were restricted to the respiratory tract and were characterized by minimal to moderate epithelial hyperplasia, epithelial necrosis, and cytoplasmic vacuolation at levels I and II of the nasal cavities. The mild cytoplasmic vacuolization of the olfactory epithelium was observed in the 0.2 and 0.4 mg/l exposure groups. Minimal epithelial necrosis on level II of the nasal cavities was observed in the 0.4 mg/l exposure group. Lung bronchiolization and alveolar macrophage infiltration were also observed in 0.2 and 0.4 mg/l exposure groups. The respiratory tract findings were considered a local response to the high alkalinity of the test material, as substantiated by the return to normal upon cessation of exposure. Exposure to the scrubbing solution had no adverse effect on functional observation battery endpoints or locomotor activity, brain weight and size, and neuropathologic assessments. The authors concluded that inhalation exposure to a Potassium Carbonate-based scrubbing solution aerosol for 21 days did not result in any persistent systemic toxicity, including neurotoxicity, in either male or female rats.

Subchronic Toxicity Studies

Oral

Potassium Bicarbonate

In a 13-week toxicity study, groups of 10 male and 10 female SPF-bred Wistar rats (CpB:WU;Wistar random) were fed unsupplemented rodent diet or a diet containing 2% or 4% Potassium Bicarbonate.³⁶ The results reported in this study were identical to those stated in the 4-week study on Potassium Bicarbonate (in the Short-term Oral Toxicity section), except for the following: Zona glomerulosa hypertrophy (classified as a non-neoplastic histopathological change) was observed at a concentration of 4%, and this finding was statistically significant ($p < 0.01$) compared to the control. The finding of oncocytic kidney tubules (also classified as non-neoplastic histopathological change) was statistically significant, compared to the control, at a concentration of 4% ($p < 0.01$).

The effect of Potassium Bicarbonate (2% or 4%) on rat urinary bladder epithelium was studied without prior exposure to a bladder tumor initiator.³⁸ In 4 studies, ranging in duration from 4 to 130 weeks, equimolar amounts of K⁺ were administered in the diet to male and female weanling, SPF-bred Wistar rats (Cpb:WU; Wistar random) (85 rats/sex/group) as Potassium Bicarbonate. Increased urinary volume and potassium levels were observed, and urinary pH was increased. Results relating to carcinogenicity are included in the Carcinogenicity section.

Groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) were fed a basal diet or diet supplemented with Potassium Bicarbonate (2.5% in the diet) for up to 13 weeks.³⁹ A group of 10 rats was also fed 6% monosodium glutamate (MSG) in the diet. Feeding with MSG induced slight growth retardation, decreased food intake (mainly with the purified diet), and increased kidney-to-body weight ratios. The addition to stock diet of 2.5% Potassium Bicarbonate, instead of MSG, induced changes in growth rate, food intake, and kidney weight that were similar to those observed with 6% MSG. Results relating to carcinogenicity are included in the Carcinogenicity section.

Another 13-week study was performed using groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) to compare the effects of 5% Potassium Bicarbonate in a stock diet and in a purified diet.³⁹ Unsupplemented stock and purified diets served as controls. The rats were gradually accustomed to the high level of Potassium Bicarbonate (5%) by feeding 1% in the diet during week 1, 2% in the diet during week 2, 3% in the diet during week 3, 4% in the diet during weeks 4 and 5, and 5% in the diet from week 6 on. Growth was retarded by 5% Potassium Bicarbonate in the groups on either basal diet, though the difference was not statistically significant for the rats fed 5% Potassium Carbonate in the stock diet but was statistically significant in the rats fed 5% Potassium Carbonate in the purified diet. None of the rats showed any abnormalities in condition or behavior. At microscopic examination, there were no treatment-related changes in the following organs: ureters, kidneys, liver, testes, thyroid with parathyroids, adrenals and. Results relating to hyperplastic changes in the bladder epithelium are included in the Carcinogenicity section.

Chronic Toxicity Studies

Oral

Potassium Bicarbonate

In an 18-month toxicity study, groups of 15 male and 15 female SPF-bred Wistar rats (CpB:WU;Wistar random) were fed unsupplemented rodent diet or a diet containing 2% or 4% Potassium Bicarbonate.³⁶ The animals were killed at the

end of the study. There were no consistent or treatment-related effects on red blood cell variables, clotting potential or total and differential white blood cell counts in any of the groups. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls, and represented normal background pathology for rats of this strain and age. The following statistically significant changes (compared to the control) were observed: zona glomerulosa hypertrophy (classified as a non-neoplastic histopathological change) was observed at a concentration in feed of 4% ($p < 0.01$); oncocytic kidney tubules (classified as a non-neoplastic histopathological change) at a concentration of 2% ($p < 0.05$) and 4% ($p < 0.01$); simple urothelial hyperplasia of the urinary bladder (classified as a non-neoplastic histopathological change) at concentrations of 2% and 4% ($p < 0.05$); and papillary/nodular hyperplasia of the urinary bladder (classified as a non-neoplastic histopathological change) at a concentration of 2% ($p < 0.01$). The papillary/nodular hyperplasia of the urinary bladder observed in the 4% dietary group was not statistically significant.

In a 30-month carcinogenicity study, groups of 50 SPF-bred weanling Wistar rats (CpB:WU;Wistar random) per sex were fed a natural ingredient diet (controls) or diet supplemented with 2% or 4% Potassium Bicarbonate.³⁶ There were no treatment-related mortalities. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls and represented normal background pathology for rats of this strain and age. Results relating to carcinogenicity are included in the Carcinogenicity section.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Magnesium Chloride Hexahydrate

The following data on magnesium chloride hexahydrate (surrogate compound) are included in a REACH dossier on Magnesium Carbonate that was submitted to ECHA.²⁵ The reproductive and developmental toxicity of magnesium chloride hexahydrate was studied using groups of up to 30 male and female Wistar rats. The dose groups were as follows: 250 mg/kg body weight/day (10 males, 10 females), 500 mg/kg body weight/day (12 males, 12 females), and 1000 mg/kg body weight/day (15 males, 15 females). The vehicle (water) control group consisted of 12 males and 12 females. The test substance was administered orally (by gavage) to males and females daily during 14 days pre-mating and 14 days of mating. The test substance was also administered to females during gestation and up to postnatal day 3, and to males for 28 to 29 days. No test substance-related histopathological lesions were observed in the reproductive organs of male or female rats dosed with the test substance (all dose groups). There were no treatment-related effects with respect to the following when compared to controls: mean number of corpora lutea, number of implantation sites, total number of pups born, number of males, number of females, sex ratio, live pups, still birth, runt on postnatal day (PND) 0, and total number of live pups and sex ratio on PND 4, pre-implantation loss and post-implantation loss. The survival of pups (in all treatment groups) from PND 0 to PND 4 was not affected by treatment. At necropsy, there were no gross external abnormalities in pups from any dose group. It was concluded that the NOAEL for reproductive/developmental toxicity of magnesium chloride hexahydrate was 1000 mg/kg body weight. Furthermore, it was determined that the equivalent NOAEL for Magnesium Carbonate was 414 mg/kg body weight/day. Additional results from this study are included in the Short-Term Oral Toxicity section of this report.

The following data on magnesium chloride hexahydrate (surrogate compound) are included in a REACH dossier on Magnesium Carbonate that was submitted to ECHA.²⁵ The teratogenicity of magnesium chloride hexahydrate (in distilled water) was evaluated using groups of 22 pregnant female Wistar rats. The 3 dose groups received oral doses (gavage) of 200, 400, and 800 mg/kg/day, respectively, on gestation days 6 to 15 (14 days). A fourth group served as the control. The animals were killed on day 20 of pregnancy. Regarding maternal toxicity, there were no clinical signs or deaths. Dosing (all groups) did not cause increased incidences of the following: number of implantations, number of corpora lutea, % implantation loss, number of offspring alive, sex ratio of offspring, offspring weight or embryo/intrauterine fetal death. Gross malformation was observed in the dose groups, but without any intergroup differences. Bone malformation was observed in one fetus of the 800 mg/kg/day dose group. There were no intergroup differences in bone abnormality, effects on lumbocostale, extra ribs, sacrococcygea, metacarpal bone or its ossification. Visceral malformations were observed in 4 to 6 fetuses from each dose group, but without intergroup differences. It was concluded that magnesium chloride hexahydrate was not teratogenic in rats dosed by gavage. The NOAEL was estimated to be > 800 mg/kg body weight/day for pregnant rats and their fetuses. The equivalent NOAEL for Magnesium Carbonate was determined to be > 331 mg/kg body weight/day.

Calcium Carbonate

Female Swiss mice were bred after feeding (number of animals/feeding duration not stated) them a diet supplemented with 0.5%, 1%, or 2% Calcium Carbonate.²⁶ First and second litters were studied. Calcium Carbonate (1% and 2% in diet) yielded an intake of approximately 3000 mg/kg body weight. When compared to the control diet, the supplemented diet significantly decreased the number and total weight of the weanling mice, and increased the proportion of deaths. Calcium Carbonate (2%) in the diet also caused hypertrophy of the heart and a tendency toward decreased thymus weight in weanling mice.

The reproductive toxicity of Calcium Carbonate (nano form) was studied using groups of 20 (10 males, 10 females per group) Wistar rats.²⁸ Three groups received oral dosage rates of 100, 300, and 1000 mg/kg body weight/day, respectively. The doses were administered daily for 48 consecutive days (including a 2-week maturation phase, pairing, gestation, and early lactation). Untreated animals served as controls. The dosage volume was 5 ml/kg. Males were killed on day 43 and females were killed on day 5 post-partum. Gross pathology and histopathology were performed. There were no test substance-related mortalities or toxicologically significant macroscopic or microscopic findings in parental animals. All offspring were subjected to a full external and internal examination; any macroscopic abnormalities were recorded. There were no test substance-related effects on reproductive performance and length of gestation. When compared to controls, there were no significant differences with respect to corpora lutea and implantation counts. Litter sizes and viability for treated groups were also comparable to controls. There also were no obvious clinical signs of toxicity in offspring from treated females, or test substance-related gross pathological findings in offspring. Because there were no treatment-related effects on reproduction, the NOEL for reproductive toxicity was considered to be 1000 mg/kg body weight per day.

In a 62-day developmental toxicity study involving 4 groups of female Charles River CD/VAF Plus rats (mated with male rats), Calcium Carbonate (in the diet) was fed at concentrations of 0.05% (control), 0.75%, 1%, and 1.25% for 6 weeks prior to mating, during mating, and for 20 days of gestation.²⁸ For each dose group, the number of females dosed prior to mating was 69 and the number of pregnant rats dosed (through mating to gestation day 20) ranged from 45 to 48. The male to female ratio per cage was 1:2. Male rats were dosed only during the mating period. On gestation day 20, the animals were killed and Cesarean sections were performed. There was no evidence of test substance-related maternal toxicity or embryotoxic/teratogenic effects. There were no dose-related changes in the average number of implantations, resorptions and viable fetuses, or fetal length or weight. When compared to the control group, there were no statistically significant increases in the litter incidence regarding specific external, visceral, or skeletal variations of the fetuses. The NOAEC for teratogenicity was > 1.25% Calcium Carbonate in the diet, and corresponded to a NOAEL between 1963 and 2188 mg/kg body weight per day.

Potassium Carbonate

The teratogenicity of Potassium Carbonate was evaluated using groups of 22 to 25 CD-1 mice, according to a protocol similar to OECD Test Guideline 414.^{30,40} These data are included in a REACH registration dossier that was submitted to ECHA. The test substance was administered, by gavage, at doses of 0, 2.9, 13.5, 62.5, or 290 mg/kg body weight/day, on gestation days 6 through 15. On day 17, Caesarean section was performed on all of the dams, and the following information was recorded: sex, numbers of corpora lutea, implantation sites, resorption sites, live and dead fetuses, and body weights of live pups. The urogenital tract of each dam was examined in detail for anatomical normality. All of the fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses in each litter were subjected to detailed visceral examinations, and the remaining two-thirds were examined for skeletal defects. There were no effects on mortality, body weight gain, or the urogenital tracts of dams. The no-observed-effect-level (NOEL) for maternal toxicity was 290 mg/kg body weight/day (i.e., the highest dose tested). There were no effects on any of the following: numbers of corpora lutea, live litters, implantations, resorptions, live and dead fetuses, the sex ratio of the fetuses, or the average fetal weight. The incidence of soft tissue and skeletal abnormalities within groups treated with Potassium Carbonate did not differ from that of sham-treated controls. The NOEL for developmental toxicity/teratogenicity was 290 mg/kg body weight/day.

The teratogenicity of Potassium Carbonate was also evaluated using groups of 22 to 25 albino rats (Wistar-derived stock).⁴⁰ The test substance was administered (by oral intubation), on gestation days 6 through 15, at dose rates of 0, 1.8, 8.4, 38.8, or 180 mg/kg body weight/day according to the procedure in the preceding experiment, except that Caesarean section was performed on day 20. There were no discernible effects on nidation or on maternal or fetal survival. Furthermore, the number of abnormalities observed in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Sodium Bicarbonate

The following data on sodium bicarbonate (surrogate compound) are included in a REACH registration dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ The embryotoxicity/teratogenicity of sodium bicarbonate was evaluated using groups of 25 female Wistar rats. After mating, groups of female rats were dosed orally (intubation) with sodium bicarbonate (in water) on gestation days 6 through 15. The following dosages were administered to the 4 groups, respectively: 3.4, 15.8, 73.3, and 340 mg/kg body weight. Two additional groups were sham-exposed and dosed with aspirin (positive control), respectively. The animals were killed on gestation day 17. There was no evidence of embryotoxicity or teratogenicity. The number of abnormalities observed in either soft or skeletal tissues of test animals did not differ from the number occurring spontaneously in sham-treated controls.

The following data on sodium bicarbonate (surrogate compound) are included in a REACH dossier on Ammonium Carbonate that was submitted to ECHA.³¹ These data are included in a REACH registration dossier that was submitted to ECHA. The embryotoxicity/teratogenicity of sodium bicarbonate was evaluated using groups of nulliparous female Sprague-Dawley rats of the Crj:CD(SD) strain. After mating was confirmed (designated as gestation day 0), the animals were dosed orally with 2% sodium bicarbonate (in drinking water) on gestation days 15 through 20. Two groups were dosed orally (by gavage) with 0.5% aqueous methylcellulose on day 16 of gestation, and were given either tap water (control group) or 2% sodium bicarbonate solution in drinking water. An untreated group served as the concurrent control. The animals were killed on gestation day 20 and fetal external examinations performed. Dosing with sodium bicarbonate had no effect on the number of implants, % resorptions, or the number of live fetuses per litter. The average body weights of the live fetuses of pregnant females treated with sodium bicarbonate were comparable to those of the control group. There were no treatment-related abnormalities in groups treated with sodium bicarbonate.

The developmental toxicity of sodium bicarbonate was studied using groups of 50 (25 males, 25 females/group) CD-1 mice.³² These data are included in a REACH registration dossier that was submitted to ECHA. Four groups were dosed orally (by gavage) with sodium bicarbonate at 5.8 mg/kg body weight, 27 mg/kg body weight, 125 mg/kg body weight, and 580 mg/kg body weight, respectively, on days 6 through 15 of gestation (17 days). A fifth group served as the sham-treated control. The number of abnormalities observed in soft or skeletal tissues of the treatment groups did not differ from the number occurring spontaneously in the sham-treated controls.

Inhalation

Potassium Carbonate

The developmental toxicity potential of a scrubbing solution containing 30.8% Potassium Carbonate, used extensively in petroleum refineries to remove CO₂ from hydrogen gas streams, was evaluated.⁴¹ Pregnant female CD (Sprague-Dawley) rats (number not stated) were exposed to aerosols of a "used" scrubbing solution at 0.05, 0.1, 0.2, or 0.3 mg/L for 6 h/day on days 6-19 of pregnancy. Control animals were exposed to filtered air under the same exposure conditions. Dams were killed on day 20 of pregnancy and a laparohysterectomy was performed. The mass median aerodynamic diameter of aerosol particles ranged from 1.6 to 2.8 μ, with geometric standard deviations between 2.0 and 2.3 μ. The overall pregnancy rate was high (> 95%) and equivalent across all groups. All pregnant dams had live litters, and 22-24 litters were examined in each group. Treatment-related clinical signs consisted of rales, observed at all exposure levels, and gasping only at the 0.3 mg/L exposure level. The occurrence of rales was presumably a localized effect on the respiratory tract, and was likely due to the irritating properties of the scrubbing solution. Maternal toxicity was exhibited in the 0.3 mg/L group, including reduced body weight, weight gain, and food consumption, and one possible treatment-related death on gestation day 17. At the scheduled necropsy, there were no treatment-related, gross pathological observations and no statistically significant differences in measurements of reproductive and developmental parameters. The incidences of fetuses with skeletal variations involving the sternum were clustered in two litters at the highest exposure level, with atypically low-term fetal body weights. Under the conditions of this investigation, Potassium Carbonate scrubbing solution was not a developmental toxicant.

GENOTOXICITY STUDIES

In Vitro

Ammonium Carbamate

Ammonium Carbonate is a mixture of Ammonium Bicarbonate and Ammonium Carbamate. The genotoxicity of ammonium carbamate was evaluated in the Ames test at concentrations up to 5000 μg/plate with and without metabolic activation.³² The positive controls were as follows: 4-nitroquinoline-*N*-oxide, 9-aminoacridine, 2-aminoanthracene (2-AA),

N-methyl-*N*-nitroso-*N*-nitrosoguanidine (MNNG), and 4-nitro-*o*-phenylenediamine. Ammonium carbamate was not genotoxic.

Calcium Carbonate

The genotoxicity of Calcium Carbonate (nano form) was studied using the mammalian chromosome aberration test, performed in accordance with OECD Guideline 473.²⁸ These data are included in a REACH registration dossier that was submitted to ECHA. Human lymphocytes were incubated with the test substance at concentrations up to 1000 µg/ml with and without metabolic activation. Cyclophosphamide and mitomycin C served as positive controls. Calcium Carbonate (nano form) did not cause a statistically significant increase in the frequency of cells with chromosome aberrations either with or without metabolic activation. The test substance was classified as non-clastogenic.

Potassium Bicarbonate

The genotoxicity of Potassium Bicarbonate was evaluated in the Ames test (with and without metabolic activation) using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, and *Saccharomyces cerevisiae* strain D4.⁴² Potassium Bicarbonate was tested at concentrations up to 0.1580% in bacteria and at concentrations up to 3.3% in yeast. Test results were negative with and without metabolic activation, and Potassium Bicarbonate was classified as non-genotoxic.

Potassium Carbonate

In the Ames test, Potassium Carbonate was not genotoxic in *Saccharomyces cerevisiae* strain D4 (yeast) or in the following bacterial strains with or without metabolic activation: *S. typhimurium* strains: TA1535, TA1537, and TA1538. Details relating to the test procedure were not included.²⁶

Potassium Chloride

The following data on potassium chloride (surrogate compound) are included in a REACH dossier on Potassium Carbonate. The genotoxicity of potassium chloride was evaluated in the L5178Y mouse lymphoma cell mutagenesis assay, at concentrations up to 5000 µg/ml with and without metabolic activation.^{30,43} These data are included in a REACH registration dossier that was submitted to ECHA. Ethyl methanesulfonate and 3-methylcholanthrene served as positive controls. Results were negative with and without metabolic activation. The positive controls were genotoxic.

Ammonium Sulfate

The following data on ammonium sulfate (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ The genotoxicity of ammonium sulfate (in acetone) was evaluated in the mammalian cell gene mutation assay using V79 Chinese hamster fibroblasts. The test procedure was consistent with OECD Guideline 476. Ammonium sulfate was tested at concentrations up to 1320 µg/ml with and without metabolic activation. Results were negative with and without metabolic activation.

Magnesium Chloride

The following data on magnesium chloride (surrogate compound) are included in a REACH dossier on Magnesium Carbonate that was submitted to ECHA.²⁵ Magnesium chloride was evaluated in the mammalian chromosome aberration test, without metabolic activation, in accordance with OECD Guideline 473. The test substance (in physiological saline) was evaluated at doses up to 2 mg/ml in Chinese hamster lung fibroblast (V79) cultures incubated for up to 48 h. Untreated and vehicle-treated cultures served as controls. The incidence of polyploid cells at 48 h was 1%, and the incidence of cells with structural chromosomal aberrations at 24 h was 2%. It was concluded that magnesium chloride was non-genotoxic in this assay.

In Vivo

Ammonium Chloride

The following data on ammonium chloride (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA.²⁷ The genotoxicity of ammonium chloride (in saline) was evaluated in the micronucleus test. Groups of 6 male mice of the ddY strain received intraperitoneal (i.p.) doses up to 500 mg/kg body weight. Control mice were injected i.p. with mitomycin C. Bone marrow from the femur was analyzed. One thousand polychromatic erythrocytes per mouse were scored and the number of micronucleated erythrocytes was recorded. Ammonium chloride was not genotoxic in this assay.

ANTI-GENOTOXICITY STUDIES

In Vitro

Magnesium Carbonate

The anti-genotoxicity of Magnesium Carbonate in the presence of hydrogen peroxide was evaluated in the Ames test using *Salmonella typhimurium* strain 102.⁴⁴ Magnesium Carbonate was tested at a concentration of 25 mM or 50 mM, and each concentration was tested in the presence of 82 mM or 164 mM hydrogen peroxide. Magnesium Carbonate did not cause a decrease in the number of revertants induced by hydrogen peroxide. The number of revertants induced by hydrogen peroxide (164 mM) alone was 695.50 ± 62.7 . The combination of Magnesium Carbonate (50 mM) + hydrogen peroxide (164 mM) yielded 746 ± 202 revertants. A control value of 334.20 ± 47.98 revertants was reported.

Magnesium Carbonate was also evaluated for anti-genotoxicity at concentrations of 50 mM and 100 mM (in the presence of hydrogen peroxide) in the suspension test using strain D7 of *Saccharomyces cerevisiae*.⁴⁴ Both stationary and logarithmic phase cells were used. The high concentration of Magnesium Carbonate (100 mM) was found to be cytotoxic only in cells in the logarithmic growth phase. Magnesium Carbonate significantly decreased the gene conversion frequency that was induced by 200 mM hydrogen peroxide. Also, the point reverse mutations induced by 200 mM and 400 mM hydrogen peroxide were statistically significantly decreased in the presence of Magnesium Carbonate. In the logarithmic growth phase, Magnesium Carbonate caused a significant decrease in the gene conversion frequency that was induced by 50 mM and 100 mM hydrogen peroxide. The anti-genotoxic effect of Magnesium Carbonate was not found to be dose-dependent.

The effects of Magnesium Carbonate on the genotoxicity induced by nickel subsulfide were examined using Chinese hamster ovary (CHO) cells and BALB/3T3 fibroblast cells.⁴⁴ The cells were incubated, with and without nickel subsulfide (at 1 $\mu\text{g}/\text{ml}$), in the presence of various concentrations of Magnesium Carbonate (0.6, 1.2, 2.4 $\mu\text{g}/\text{ml}$) to give final molar ratios of 0.25, 0.5, and 1.0. The suppression of up to 64% of the proliferation of BALB/3T3 fibroblasts by nickel subsulfide (1 $\mu\text{g}/\text{ml}$) was reversed by Magnesium Carbonate, having recovered slowly in a dose-dependent manner. The nickel compound increased not only the number of micronuclei, but also the amount of DNA-protein cross-links examined with CHO and BALB/3T3 cells, respectively. These genotoxic effects of nickel were again lessened by Magnesium Carbonate. The nickel subsulfide at 1 $\mu\text{g}/\text{ml}$ increased the number of micronuclei from 12 to 54 in controls, out of 500 binucleated cells. This number was reduced to 34 upon Magnesium Carbonate co-treatment at 2.4 $\mu\text{g}/\text{ml}$. The DNA-protein cross-links coefficient of 1.63 obtained in the presence of nickel was decreased to 1.39 with Magnesium Carbonate co-treatment at 2.4 $\mu\text{g}/\text{ml}$.

CARCINOGENICITY STUDIES

Oral

Potassium Bicarbonate

The effect of Potassium Bicarbonate (2% or 4%) on rat urinary bladder epithelium was studied without prior exposure to a bladder tumor initiator.³⁸ In 4 studies, ranging in duration from 4 to 130 weeks, equimolar amounts of potassium were administered in the diet to male and female weanling, SPF-bred Wistar rats (Cpb:WU; Wistar random) (85 rats/sex/group) as Potassium Bicarbonate. Control rats were fed a cereal-based open formula diet. The feeding of Potassium Bicarbonate (2% and 4% concentrations) resulted in simple epithelial hyperplasia and, after prolonged administration, in papillary/nodular hyperplasia, papillomas, and transitional cell carcinomas of the urinary bladder. The incidence of hyperplastic and neoplastic bladder lesions tended to be higher in rats fed 4% Potassium Bicarbonate than in those fed 2% Potassium Bicarbonate, suggesting a dose-response relationship. Based on these results, the authors concluded that Potassium Bicarbonate is capable of inducing urinary bladder cancer in rats without prior application of an initiator.

Groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) were fed a basal diet or diet supplemented with Potassium Bicarbonate (2.5% in the diet) for up to 13 weeks.³⁹ A group of 10 rats was also fed 6% monosodium glutamate (MSG) in the diet. The rats that received 6% MSG in the diet showed an increased incidence and degree of focal and diffuse hyperplasia of the bladder epithelium. The group that received Potassium Bicarbonate in the diet also had epithelial hyperplasia in the urinary bladder. Hyperplasia of the epithelium lining the renal pelvis or papilla was not observed in these animals.

Another 13-week study was performed using groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) to compare the effects of 5% Potassium Bicarbonate in a stock diet and in a purified diet.³⁹ Unsupplemented stock and purified diets served as controls. The rats were gradually accustomed to the high level of Potassium Bicarbonate (5%) by feeding 1% in the diet during week 1, 2% in the diet during week 2, 3% in the diet during week 3, 4% in the diet during weeks 4 and 5, and 5% in the diet from week 6 on. The microscopic examinations of the urinary bladder, ureters, kidneys, liver, testes, thyroid with parathyroids, adrenals and bone revealed changes considered to be related to treatment only in the bladder epithelium. These changes comprised various forms and degrees of epithelial hyperplasia and very small intra-epithelial cysts. An increased incidence and severity of hyperplasia occurred in each of the two groups that received Potassium Bicarbonate. Generally, the hyperplastic changes were diffuse, and their degree varied from minimal to moderate. More severe hyperplasia (papillomatous) was present in one rat fed Potassium Bicarbonate in the stock diet. Both the incidence and the degree of the epithelial changes indicated a more marked effect of Potassium Bicarbonate in the stock diet than in the purified diet.

In a 30-month carcinogenicity study, groups of 50 SPF-bred weanling Wistar rats (CpB:WU;Wistar random) per sex were fed a natural ingredient diet (controls) or diet supplemented with 2% or 4% Potassium Bicarbonate.³⁶ There were no treatment-related mortalities. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls and represented normal background pathology for rats of this strain and age.

Dose-related increases in the incidence of zona glomerulosa hypertrophy (classified as a non-neoplastic histopathological change) occurred in all treatment groups (both sexes) and was statistically significant ($p < 0.01$) when compared to the control. At week 13, oncocytic tubules were noted in males and females fed 2 or 4% Potassium Bicarbonate; after 30 months, the incidence of this lesion was much higher in the treated rats when compared to the background incidence in controls. No progression to oncocytomas was noted. The incidences of simple epithelial hyperplasia and of papillary/nodular hyperplasia of the urinary bladder were increased in the 2% and 4% Potassium Bicarbonate groups. Urothelial hyperplasia (classified as a non-neoplastic histopathological change) and papillary/nodular hyperplasia of the urinary bladder were statistically significant ($p < 0.01$), compared to the control. The incidence of (multiple) transitional cell papilloma (benign) in the urinary bladder was 2 (in males) and 6 (in females; $p < 0.05$) for animals dosed with 4% Potassium Bicarbonate. The incidence of transitional cell carcinoma (malignant) in the urinary bladder was 1 (in males) and 3 (in females) dosed with 4% Potassium Bicarbonate. These changes indicate an association between prolonged treatment with Potassium Bicarbonate and urinary bladder cancer. Except for the preneoplastic and neoplastic lesions in the urinary bladder, there were no treatment-related changes in any specific tumor type among the groups. In females, relatively high incidences of adenocarcinomas were found in the uterus with 4% Potassium Bicarbonate, but because these changes were not accompanied by preneoplastic alterations in this 30-month study or in the 18-month chronic oral study (in Chronic Oral Toxicity section) and because their incidences were within the range of historical control data, they were not deemed treatment-related.

Additionally, the total number of rats with tumors and the total incidence of tumors were not affected by treatment. Although the number of Potassium Bicarbonate-fed males with malignant tumors reached the level of statistical significance, the difference compared to the controls was not statistically significant when the number of urinary bladder lesions was excluded from the evaluation. In summary, apart from the effects on the urinary bladder, treatment with Potassium Bicarbonate did not affect the type, incidence, or multiplicity of tumors, or the time of tumor appearance or the ratio of benign-to-malignant tumors.³⁶

Co-Carcinogenicity

Sodium Bicarbonate

The co-carcinogenicity of sodium bicarbonate in the presence of *o*-phenylphenol was evaluated using groups of Fischer 344 male rats.³² The 6 dietary groups (31 rats/group) in this study were: Group 1 (2% sodium *p*-phenylphenol [OPP-Na] in diet), Group 2 (1.25% OPP + 0.64% sodium bicarbonate in diet), Group 3 (1.25% OPP + 0.32% sodium bicarbonate in diet), Group 4 (1.25% OPP + 0.16% sodium bicarbonate in diet), Group 5 (1.25% OPP or 0.64% sodium bicarbonate in diet), and Group 6 (1.25% OPP or 0.64% sodium bicarbonate in diet). The control group (fed plain diet) consisted of 30 rats.

The groups were fed continuously for 104 weeks. In week 104, the % survival was 84% (26 of 31 rats) for animals exposed to sodium bicarbonate and 73% (22 of 30 rats) in the control group. When compared to the control, the final body weight was statistically significantly lower in all dietary groups. The relative weight (organ/body weight %) of the kidneys and liver was statistically significantly increased when compared to the control. Also, when compared to the control group, animals fed sodium bicarbonate in the diet did not have a statistically significant increase in the number of tumors. The first bladder tumor was observed in the rat that died in week 49. The number of rats that survived for 104 weeks is unknown. Sodium bicarbonate alone in the diet did not have a carcinogenic effect on the urinary bladder of rats. Papillary or nodular hyperplasia and papilloma incidence did not differ between test animals and the control group.

Tumor Promotion

Sodium Bicarbonate

The following data on sodium bicarbonate (surrogate compound) are included in a REACH dossier on Ammonium Carbonate.³¹ The tumor promotion potential of sodium bicarbonate in male 344 rats dosed with the carcinogen *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) was evaluated in a 32-week study. Ten groups of 20 rats received drinking water with 0.05% BBN and 2 groups of 10 rats (control groups) received drinking water without BBN for the first 4 weeks of the study. At 3 days after the cessation of BBN treatment, 4 groups received a powdered basal diet containing 0.375%, 0.75%, 1.5%, and 3% sodium bicarbonate, respectively; the control group received basal diet only. The remaining 5 groups consisted of 4 groups that received powdered basal diet containing the 4 concentrations of sodium bicarbonate, respectively, + 5% ascorbic acid and the control group that received basal diet + 5% ascorbic acid for 32 weeks. The 2 groups of 10 rats (controls) that received drinking water without BBN were maintained on powdered basal diet containing 3% sodium bicarbonate or 5% ascorbic acid + 3% sodium bicarbonate for 32 weeks. The total observation period was 36 weeks and 3 days. In a second experiment, the rats were randomly divided into 4 groups of 5 rats and 4 groups received powdered basal diet with the following components, respectively: 3% sodium bicarbonate, 5% ascorbic acid, 3% sodium bicarbonate + 5% ascorbic acid. The fifth group (control) received basal diet with no added chemicals.

In 3 of the 10 groups dosed with BBN, the urinary bladder had multiple large tumors. Papillary or nodular hyperplasia and papillomas were observed. Urinary pH and sodium concentrations were increased in rats fed sodium bicarbonate only if they had been pretreated with BBN. Similar results were not reported for animals fed sodium bicarbonate only. The results of this study confirmed that the dose-dependent increase in both urinary pH and sodium concentration and the dose-dependent promotion of urinary bladder carcinogenesis were parallel effects of sodium bicarbonate. Study results also indicated that ascorbic acid administered orally acted as an amplifier (a co-promoter), though this vitamin had no promotion potential.³¹

OTHER RELEVANT STUDIES

Nephrotoxicity

The possible toxic effects of Potassium Carbonate emulsion (pH not stated) on some biomarkers of tissue damage was investigated using groups of 4 California rabbits.⁴⁵ The rabbits received Potassium Carbonate emulsion orally, via drinking, at doses of 50 mg/L and 100 mg/L for 14 consecutive days. The control group received physiological saline. At the higher concentration (100 mg/L), the emulsion significantly increased uric acid, creatinine, and urea by 126.3%, 48.6% and 458.8%, respectively, compared to the control ($P < 0.05$). Oral administration of the emulsion at a concentration of 50 mg/L caused a statistically significant increase in urea, creatinine, and uric acid by 253.8%, 38.6% and 88.8%, respectively, compared to the control. Also, Potassium Carbonate emulsion statistically significantly increased serum blood urea nitrogen (BUN) at concentrations of 50 mg/L and 100 mg/L. The results of this study suggested that oral exposure to excessive amounts Potassium Carbonate emulsion repeatedly over an extended period could precipitate kidney damage.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Skin Irritation and Sensitization

In Vitro

Magnesium Carbonate

The skin irritation potential of Magnesium Carbonate was evaluated according to OECD Guideline 431 using the reconstituted human epidermis model.²⁵ These data are included in a REACH registration dossier that was submitted to ECHA. Magnesium Carbonate (solid material, 20 mg) was applied topically to the model, followed by the addition of 0.9% w/v sodium chloride solution for wetting of the test material. Duplicate tissues were treated for exposure periods of 3, 60, and 240 minutes. The 0.9% w/v sodium chloride solution and glacial acetic acid served as negative and positive controls, respectively. Following each exposure period for Magnesium Carbonate, treated tissues appeared blue, which was indicative of viable tissue. The authors concluded that Magnesium Carbonate was non-corrosive to the skin.

Ammonium Bicarbonate

A skin corrosion and irritation test on Ammonium Bicarbonate, using a reconstructed three-dimensional human epidermis model, was performed according to OECD Guideline 431.²⁷ These data are included in a REACH registration dossier that was submitted to ECHA. Ammonium Bicarbonate (25 µL) was applied to 2 model epidermal tissue samples during 3-minute and 1-h exposure periods, respectively. The skin irritation test was performed using 3 model epidermal tissue samples that were incubated with Ammonium Bicarbonate for 1 hour, followed by a 42-h post-incubation period. Using a colorimetric test, tissue destruction was determined by measuring the metabolic activity of the tissue after exposure. The reduction of mitochondrial dehydrogenase activity, measured by reduced formazan production after incubation with a tetrazolium salt [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)] was selected as a suitable endpoint. Formazan production of the epidermal tissues treated with Ammonium Bicarbonate was compared to that of negative control tissues. Ammonium Bicarbonate was not able to reduce MTT directly in this assay. In the skin corrosion test, the mean viability of tissues treated with the test substance was determined to be 105% after an exposure period of 3 minutes, and 36% after an exposure period of 1 h. In the skin irritation test, the mean viability of treated tissues after 1 h + 42-day post-incubation period was 71%. It was concluded that Ammonium Bicarbonate was non-irritating in the skin corrosion/irritation test.

Ammonium Carbonate

The skin irritation potential of Ammonium Carbonate was evaluated *in vitro* in accordance with OECD Guideline 439 using a three-dimensional human epidermis model.³¹ These data are included in a REACH registration dossier that was submitted to ECHA. Ammonium Carbonate (50 µl) was applied to disks of the tissue samples, followed by a 15 minute incubation period and a 42-h post-incubation period. The viability of each disk was assessed by incubating the tissues for 3 h with MTT solution. Following Ammonium Carbonate treatment, the mean tissue viability was 115% and the test substance was classified as non-irritating (> 50% mean tissue viability) to the skin.

Calcium Carbonate

The dermal corrosivity potential of undiluted Calcium Carbonate was evaluated using Corrositex[®], an *in vitro* test method for assessing the dermal corrosivity potential of chemicals and chemical mixtures.⁴⁶ This methodology is based on the ability of a corrosive chemical or chemical mixture to pass through, by diffusion and/or destruction/erosion, a biobarrier and to elicit a color change in the underlying liquid Chemical Detection System (CDS). The biobarrier was composed of a hydrated collagen matrix in a supporting filter membrane, while the CDS was composed of water and pH indicator dyes. Calcium Carbonate was not a corrosive agent, based on the results of this study.

Animal

Calcium Carbonate

Undiluted Calcium Carbonate was applied to intact skin of rabbits (number and strain not stated).⁴⁶ The skin was evaluated for corrosion within 3 minutes, and at 1 h or 4 h post-application. Calcium Carbonate was not a corrosive agent.

The skin sensitization potential of Calcium Carbonate (nano form) was evaluated in the local lymph node assay in accordance with OECD Guideline 429.²⁸ These data are included in a REACH registration dossier that was submitted to ECHA. Three groups of 4 mice of the CBA/Ca (CBA/caOlaHsd) strain were exposed to concentrations of 5%, 10%, and 25% w/w, respectively. Each concentration of the test substance, in dimethyl formamide, was applied (25 µl) to the dorsal surface of each ear for 3 consecutive days. Hexyl cinnamic aldehyde served as the positive control. The proliferation response of lymph node cells was expressed as the number of radioactive disintegrations per minute per lymph node, and as the ratio of ³HTdR incorporation into lymph node cells of test nodes relative to that recorded for the control nodes (stimulation index). Results were classified as positive (sensitization) if at least one concentration of the test substance caused a 3-fold or greater increase in ³HTdR incorporation, when compared to control values. The stimulation index,

expressed as the mean radioactive incorporation for the treatment group divided by the mean radioactive incorporation of the control groups, was 5.6. Thus, Calcium Carbonate produced positive results in this assay.

Potassium Bicarbonate

The skin irritation potential of Potassium Bicarbonate was evaluated using 6 New Zealand white rabbits.²⁹ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (500 mg in saline) was applied to the dorsal area of the trunk (abraded or intact skin), and the application site was covered with a 2.5 cm² occlusive patch for 24 h. Reactions were scored for up to 48 h after patch removal. There were no signs of erythema or edema at intact skin sites at 24 h and 72 h after test substance application (i.e., 1 h and 48 h after patch removal). At abraded application sites, very slight erythema (score = 1), with slightly white discolorations, was observed in all animals at both readings. There was no evidence of edema. The primary irritation index was 0.5 (abraded and intact skin; maximum possible index = 8), and Potassium Bicarbonate was classified as mildly irritating to the skin.

The skin sensitization potential of Potassium Bicarbonate was studied using groups of Hartley guinea pigs [(CrI:HA)BR strain] according to the Buehler test procedure.²⁹ During induction, the test substance (0.2 g in deionized water) was applied, under an occlusive patch (Hill Top Chamber®, 25-mm diameter), for 6 h to the anterior left flank of 10 guinea pigs. The test substance was applied once per week for 3 weeks (total of 3 induction applications). Positive controls (4 guinea pigs) were treated with 0.3% w/v 2,4-dinitrochlorobenzene. The 10 negative control guinea pigs were not treated during induction. A 2-week non-treatment period was observed after the induction phase. During the challenge phase, Potassium Bicarbonate (0.2 g in deionized water) was applied to the anterior right flank of the 10 test animals according to the same procedure. The 10 untreated control animals were treated similarly. Reactions were scored at approximately 24 h and 48 h post-application. Dermal reactions were not found in the test group during induction or challenge phases. Reactions also were not found in untreated control animals during the challenge phase. Potassium Bicarbonate was classified as a non-sensitizer in this study.

Potassium Carbonate

Data on “potash hydrate” (composition not stated) were used to evaluate the skin irritation potential of Potassium Carbonate in 6 New Zealand white rabbits.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (500 mg, moistened with saline) was applied, under a 2.5 cm x 2.5 cm occlusive dressing, to abraded and intact dorsal skin for 24 h. Reactions were scored at 24 h and 72 h post-application using the Draize scoring system (0 to > 5 [severe irritant]). Skin irritation was not observed (scores = 0) at intact sites at 24 h or 72 h post-application. For abraded sites, an erythema score of 4 and an edema score of 2 were observed in all 6 rabbits at 24 h. At 72 h, an erythema score of 4 was observed in all rabbits; the edema score was 0. A primary irritation index of 2.5 (abraded and intact scores included; 8 = maximum index value) was reported, which enabled classifying the test substance as a moderate skin irritant.

The skin sensitization potential of a Potassium Carbonate tradename material was evaluated in the Buehler test (repeated insult patch test) using 10 guinea pigs.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (moistened with distilled water) was applied, under an occlusive patch, to the skin at a concentration of 95% w/w (minimum irritating concentration) during the 3-week induction period and challenge phase. The induction and challenge phases were separated by a 14-day non-treatment period. Challenge test sites were evaluated for erythema at 24 h and 48 h after patch application. Negative and positive (dinitrochlorobenzene) control groups consisted of 5 and 10 guinea pigs, respectively. Skin irritation was not observed in test or negative control animals during the induction phase. Additionally, skin sensitization was not observed during the challenge phase. Faint to moderate erythema was observed at positive control sites. It was concluded that the Potassium Carbonate tradename material was not a skin sensitizer in guinea pigs.

Ammonium Chloride

The following data on ammonium chloride (surrogate compound) are included in a REACH dossier on Ammonium Bicarbonate that was submitted to ECHA. The skin sensitization potential of ammonium chloride (in 0.9% saline solution) was evaluated in the maximization test using 20 Pirbright-Hartley guinea pigs.²⁷ The induction phase consisted of a single intracutaneous induction exposure to 5% ammonium chloride and a single 48-h epicutaneous induction exposure to 25% ammonium chloride. Intradermal injection occurred on day 1 and epicutaneous induction occurred on day 9. For epicutaneous induction, a 2 x 4 cm occlusive patch containing 0.5 ml of the test substance was applied to the area of the intradermal injection site. On day 22, the animals received a 24-h challenge application (occlusive patches) of 10% ammonium chloride. Reactions were scored at 24 h and 48 h after patch removal. Two of 20 animals had + reactions (barely perceptible erythema) with very slight to slight edema. Study results indicated that 10% of the animals tested had a positive

reaction after being challenged with ammonium chloride. These results were interpreted as the absence of skin sensitization potential.

Ammonium Acetate

The following data on ammonium acetate (surrogate compound) are included in a REACH dossier on Ammonium Carbonate that was submitted to ECHA.³¹ Ammonium acetate was evaluated for sensitization potential using the local lymph node assay, performed in accordance with OECD Guideline 429. Three groups of 4 CBA female mice received topical dermal applications of the following concentrations of ammonium acetate (25 µl in acetone/olive oil [4:1 v/v] mixture), respectively, on the dorsal surface of the ear: 10% w/v, 25% w/v, and 50% w/v. Hexyl cinnamic aldehyde served as the positive control, and a vehicle control group was also used. The test substance was applied for 3 consecutive days. On day 6, the cell proliferation in the local lymph nodes was measured by the incorporation of ³HTdR and stimulation indices were calculated. There were no signs of irritation at the application site in any treatment group. The observed stimulation index values were 1.6 (for 10%), 1.7 (for 25%) and 1.3 (for 50%). The stimulation index for the positive control was 10.7. It was concluded that ammonium acetate was a non-sensitizer.

Ammonium Carbamate

Skin irritation data are included in the results from an acute dermal toxicity study on ammonium carbamate (contained 43.6% ammonium and 56.3% carbon dioxide) involving 10 (5 males, 5 females) rats of the CrI:CD(SD) strain.³² These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (in water; dose = 5000 mg/kg weight) was applied, under a semi-occlusive patch, to the back for 24 h. Erythema (very slight to severe), edema (very slight to moderate), eschar, necrosis, exfoliation, scabbing, and desquamation were reported; the number of animals affected was not stated. In some of the animals at the end of the study, erythema, eschar, and scabbing were observed at the application site.

The skin irritation potential of ammonium carbamate was evaluated using 2 Vienna white rabbits.³² These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (40% or 80% aqueous; 1 ml) was applied to the skin, under an occlusive patch, for 1, 5, or 15 minutes. Application was followed by a 24-h observation period. The test substance was rinsed from the application site before reactions were scored. Neither local effects nor clinical symptoms were observed, and ammonium carbamate was classified as a non-irritant at concentrations of 40% and 80% aqueous.

The skin sensitization potential of ammonium carbamate was evaluated in the local lymph node assay in accordance with OECD Guideline 429.³² These data are included in a REACH registration dossier that was submitted to ECHA. Three groups of 5 mice of the CBA/J inbred SPF strain were exposed to concentrations of 10%, 25%, and 50%, respectively. Each concentration of the test substance, in propylene glycol, was applied (25 µl/ear) to the dorsal surface of each ear for 3 consecutive days. 1-Chloro-2,4-dinitrobenzene served as the positive control. Values for the stimulation index, expressed as the mean radioactive incorporation for the treatment group divided by the mean radioactive incorporation of the control groups, were as follows: 1.1 (for 10% ammonium carbamate), 1.2 (for 25% ammonium carbamate), and 0.6 (for 50% ammonium carbamate). Ammonium carbamate produced negative results in this assay.

OCULAR IRRITATION STUDIES

In Vitro

Magnesium Carbonate

The ocular irritation potential of Magnesium Carbonate (concentration not stated) was evaluated in the *in vitro* bovine corneal opacity and permeability test (BCOP).⁴⁷ In the BCOP test method, changes in corneal opacity caused by chemical damage are determined by measuring decreases in light transmission through the cornea. Changes in permeability of the cornea resulting from chemical damage are determined by measuring increases in the quantity of sodium fluorescein dye that passes through all corneal cell layers. Both measurements are used to calculate an *in vitro* irritancy score (IVIS), which is used to predict the *in vivo* ocular irritation/corrosion potential of a test substance. The following scores are considered positive: corneal opacity (CO) or iris (IR) score ≥ 1 or conjunctival chemosis (CC) or conjunctival redness (CR) ≥ 2 . There was no evidence of CC or CR or lesions of the iris. A CO score of 1 was reported, and the reaction cleared by day 3. Therefore, Magnesium Carbonate caused only corneal opacity in this test.

Ammonium Bicarbonate

The Hen's Egg Chorioallantoic Membrane Test (HET-CAM) was used to evaluate the ocular irritation potential of Ammonium Bicarbonate.²⁷ These data are included in a REACH registration dossier that was submitted to ECHA. Undiluted Ammonium Bicarbonate (25 µL) or 10% aqueous Ammonium Bicarbonate (0.3 mL) was applied topically to the chorioallantoic membrane of fertilized and incubated hen eggs (3 eggs per test concentration). There was no evidence of irritation at the 10% concentration. Undiluted Ammonium Bicarbonate caused moderate intravascular coagulation in all eggs within 50 seconds. Hemorrhagia was not noted during the observation period. It was concluded that, under the conditions of this test, Ammonium Bicarbonate did not produce changes that were indicative of serious eye damage.

Animal

Magnesium Carbonate

In a study involving 2 New Zealand white rabbits, the ocular irritation potential of Magnesium Carbonate (10% w/v aqueous, pH 9.9) was evaluated.²⁵ These data are included in a REACH registration dossier that was submitted to ECHA. Magnesium Carbonate (10 ml) was instilled into the conjunctival sac of the right eye. The left eye served as the untreated control. Eyes were not rinsed after instillation of the test substance. Moderate conjunctival irritation was observed at 1 h post-instillation, and minimal conjunctival irritation was observed at 24 h and 48 h post-instillation. Reactions had cleared by 72 h post-instillation. Reactions were not observed in the cornea or iris. Magnesium Carbonate was classified as non-irritating to the eyes of rabbits.

Ammonium Carbonate

The ocular irritation potential of Ammonium Carbonate was evaluated using 3 New Zealand white rabbits.³¹ These data are included in a REACH registration dossier that was submitted to ECHA. Ammonium Carbonate (0.1 ml; ~ 66 mg) was instilled into one eye. The following reactions were observed: slight corneal opacity, moderate conjunctival redness, slight to marked conjunctival chemosis, and slight to severe discharge. Additionally, discharge of blood, scleral vessels injected in a circumscribed area, or circular and marginal vascularization of the cornea in a circumscribed area were observed. The ocular reactions were reversible in 2 rabbits within 7 days and in 1 rabbit within 14 days after instillation. Ammonium Carbonate was classified as non-irritating.

Calcium Carbonate

The ocular irritation potential of Calcium Carbonate was studied using 3 male New Zealand white rabbits.²⁸ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (0.1 ml) was instilled into the right eye, and the observation period was up to 72 h. Left eyes served as controls. Ocular damage/irritation was evaluated according to the Draize scale. Corneal effects were not observed during the study. Iridial inflammation and minimal conjunctival irritation were observed in all treated eyes at 1 h post-instillation. Conjunctival irritation was also observed at 24 h and 48 h post-instillation. All reactions had cleared by 72 h post-instillation. Calcium Carbonate was classified as non-irritating to the eyes of rabbits.

Potassium Bicarbonate

Undiluted Potassium Bicarbonate (0.1 ml) was instilled into the eyes of 6 male New Zealand white rabbits.²⁹ These data are included in a REACH registration dossier that was submitted to ECHA. The eyes were not rinsed and untreated eyes served as controls. Instillation of the test substance was followed by a 7-day observation period. Mild or moderate conjunctival redness and discharge and moderate or severe chemosis were observed in all animals at 1 h post instillation. At day 4, chemosis and discharge were fully reversible in all animals. The test substance did not induce substantial corneal opacity or iritis. The study was terminated before all ocular reactions were completely reversed. However, the authors noted observations relating to the healing process indicated that the complete reversibility of ocular reactions was likely. Therefore, Potassium Bicarbonate was classified as non-irritating to the eyes of rabbits.

Sodium Carbonate Monohydrate

Data on sodium carbonate monohydrate were used to evaluate the ocular irritation potential of Potassium Carbonate in 9 New Zealand white rabbits.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. The test substance (0.1 ml; concentration not stated) was instilled into the conjunctival sac, after which the eye was either rinsed (3 rabbits) or not rinsed (6 rabbits). Untreated eyes served as controls. Reactions were scored according to the Draize scale for up to 14 days post-instillation. Conjunctival redness was observed in all 6 rabbits that were not subjected to ocular

rinsing, and in 1 rabbit after ocular rinsing. Conjunctival chemosis was observed in all 6 rabbits (no ocular rinsing) and in 2 rabbits after ocular rinsing. Corneal opacity, ulceration, and pannus were also observed in rinsed eyes. Necrosis/ulceration, alopecia, and bleeding were observed in eyes that were not rinsed. Signs of ocular irritation persisted to the end of the study in rabbits (unrinsed eyes) and in one rabbit (no ocular rinsing). It was concluded that sodium carbonate monohydrate was irritating to the eye.

CLINICAL STUDIES

Case Reports

Calcium Carbonate

A female patient (history of gastritis) at 36 weeks of gestation had ingested 5 glasses of milk and approximately 30 tablets of an antacid containing 500 mg of Calcium Carbonate daily for 2 weeks.²⁸ These data are included in a REACH registration dossier that was submitted to ECHA. A Calcium Carbonate intake of > 5.5 g/day for 14 days during pregnancy (later stages) did not cause any observable teratogenic effects.

Potassium Carbonate

A male crystal factory worker with a 1-month history of eczema on the hands, arms, and legs was patch-tested with a 1% aqueous solution of Potassium Carbonate.³⁰ These data are included in a REACH registration dossier that was submitted to ECHA. The patch test procedure was not stated. Patch test results were negative for skin sensitization.

SUMMARY

The carbonate salts have the following functions in cosmetic products: absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents.

Collectively, information supplied to FDA by industry as part of the VCRP and a survey of ingredient use concentrations conducted by the Council indicate that the following carbonate salts are being used in cosmetic products: Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate. The highest use frequency is reported for Magnesium Carbonate (317 uses). The Council survey data also indicate that the carbonate salts are being used in cosmetics at maximum ingredient use concentrations up to 93.4% (i.e., Ammonium Bicarbonate in rinse-off products [hair bleaches]). The highest maximum concentration of use in leave-on products is being reported for Calcium Carbonate (concentrations up to 35% in eyebrow pencils).

Results from an *in vitro* percutaneous absorption study indicate that ammonium carbamate penetrated into the stratum corneum intercellular lipids and decomposed rapidly to 2 molecules of protonated dodecyl 6-aminohexanoate and carbon dioxide.

Calcium Carbonate (0.40 mCi of calcium ¹⁴C-carbonate pellet) was implanted intraperitoneally into a male rat.²⁶ Approximately 72% of the radiolabeled carbonate was excreted as respiratory carbon dioxide between 2 h and 142 h after implantation.

After ²⁸MgSO₄ was fed (in the diet) to rabbits, mean urinary excretion of radioactivity ranged between 10% and 12.5% and the cecum and its contents were found to contain 78% of the ingested dose. After ¹¹C-sodium bicarbonate was injected intraperitoneally into rats, the urine contained 1.3% of the radioactivity and >50% of the radioactivity occurred as respiratory ¹¹C-carbon dioxide.

Following ingestion, Potassium Carbonate rapidly dissociates in the gastric juice to yield carbonate ions and potassium ions. Similarly, after ingestion, Potassium Bicarbonate rapidly dissociates in gastric juice to yield carbonate ions (bicarbonate and carbonate) and potassium ions. The absorbability of calcium from Calcium Carbonate and calcium citrate salts was compared in a study in which 37 men and women ingested 300 mg (low load) and 1000 mg (high load) calcium loads as part of a light breakfast meal. Relative absorption was estimated from the difference in urinary calcium following breakfast on the 2 days and true fractional absorption from the appearance of ⁴⁵Ca in the serum. Mean tracer absorption for both salts combined was 36% at the 300 mg load and 28.4% at the 1000 mg load.

In an acute dermal toxicity study on a tradename material (Potassium Carbonate containing pesticide), the LD₅₀ in rabbits was > 2000 mg/kg body weight. The same results (LD₅₀ > 2 000 mg/kg) were reported in acute dermal toxicity studies on Ammonium Carbonate, Calcium Carbonate, Potassium Bicarbonate, and Ammonium Sulfate.

An acute oral LD₅₀ of ~ 2000 mg/kg was reported for Ammonium Bicarbonate, Ammonium Carbonate and Potassium Carbonate in studies involving rats. The acute oral LD₅₀ for Calcium Carbonate and Potassium Bicarbonate was > 2000 mg/kg.

In an acute inhalation toxicity study on ammonia (1-h exposure) involving mice, the lungs of animals that died were diffusely hemorrhagic (mild to moderate pneumonitis also observed) and liver damage was observed at each concentration of exposure (3440 ppm, 4220 ppm, and 4860 ppm). It was noted that the liver lesions may have resulted from the compromised nutritional state of the mice. An acute inhalation LC₅₀ value (1-h exposure) of 6.8 mg/L air for Ammonium Bicarbonate was deduced based on the results of this study.

An acute inhalation LC₅₀ of > 3 mg/l of air was reported for rats exposed to aerosolized Calcium Carbonate. In acute inhalation toxicity studies on Potassium Bicarbonate and sodium bicarbonate, an LC₅₀ value of > 5 mg/l of air was reported. In an acute inhalation toxicity study on a tradename material (Potassium Carbonate containing pesticide), a mean LC₅₀ of > 5 mg/L air (rats) was reported.

Mean acute i.v. toxicity values of 3.10 and 1.02 mM/kg were reported for Ammonium Bicarbonate and Ammonium Carbonate, respectively, in studies involving albino rats.

An NOAEL of 1000 mg/kg body weight/day was reported in a study in which male and female rats received oral doses of magnesium chloride hexahydrate during 14 days pre-mating and 14 days of mating. The same results were reported for female rats dosed orally during gestation and up to postnatal day 3 and for male rats dosed orally for 28 to 29 days. Based on the results of the preceding 2 experiments, it was determined that the equivalent NOAEL for Magnesium Carbonate was 4128 mg/kg body weight/day. Rats fed Calcium Carbonate at 300 mg/kg for 3 days had no indication of toxicity, and the same was true for Calcium Carbonate (nano form) at oral doses up to 1000 mg/kg body weight/day for 14 days. There were no test substance-related changes in rats fed doses up to 4228.5 mg/kg body weight/day ammonium chloride for 28 days.

In repeated dose oral toxicity studies (4-week, 13-week, 18-month, and 30-month studies) of Potassium Bicarbonate (2% or 4% in diet), most of the histopathological changes observed were considered equally distributed among treatment groups, and represented normal background pathology for SPF-bred Wistar rats. Neither gross nor microscopic changes of the urinary bladder were observed in rats fed ammonium chloride (in the diet) in a short-term (70 days) oral feeding study. The NOEL was < 684 mg/kg body weight/day.

Inhalation exposure to an aerosolized Potassium Carbonate-based scrubbing solution for 21 days did not result in any persistent systemic toxicity or neurotoxicity in either male or female rats.

The results of a study in which rabbits were dosed orally (via drinking) with Potassium Carbonate emulsion (50 mg/L and 100 mg/L) for 14 consecutive days suggested that Potassium Carbonate emulsion exposure could precipitate kidney damage.

The reproductive and developmental toxicity of magnesium chloride hexahydrate was evaluated in male and female rats that received oral doses up to 1000 mg/kg body weight/day during 14 days pre-mating and 14 days of mating. Additionally, female rats received the same doses during gestation and up to postnatal day 3 and male rats were dosed similarly for 28 to 29 days. The NOAEL for the reproductive/developmental toxicity of magnesium chloride hexahydrate was 1000 mg/kg body weight/day; the equivalent NOAEL for Magnesium Carbonate was determined to be 414 mg/kg body weight/day. In another study, pregnant female rats were dosed orally with magnesium chloride hexahydrate at doses (in distilled water) up to 800 mg/kg body weight/day on gestation days 6 to 15. Visceral malformations were observed in 4 to 6 fetuses from each dose group, but without intergroup differences. The NOAEL for magnesium chloride hexahydrate was estimated to be > 800 mg/kg body weight/day; the equivalent NOAEL for Magnesium Carbonate was determined to be > 331 mg/kg body weight/day.

Female Swiss mice were bred after feeding with a diet supplemented with 0.5%, 1%, or 2% Calcium Carbonate. Calcium Carbonate (2%) in the diet caused hypertrophy of the heart and decreased thymus weight in weanling mice. In a reproductive toxicity study, rats were fed oral doses of Calcium Carbonate (nano form) up to 1000 mg/kg body weight/day for 48 consecutive days. The maximum dose administered was the NOEL in this study. In a 62-day developmental toxicity study, rats were fed Calcium Carbonate at concentrations up to 1.25% in the diet, and the NOAEL for teratogenicity was determined to be > 1.25% in the diet.

There was no evidence of embryotoxicity or teratogenicity in the offspring of rats dosed orally with sodium bicarbonate (up to 340 mg/kg body weight) on gestation days 6 through 15. In another study on sodium bicarbonate, there were no test substance-related abnormalities in the offspring of rats that received sodium bicarbonate at concentrations of 0.5% and 2% (in drinking water) on gestation days 15 through 20. The number of abnormalities observed in soft or skeletal tissues in groups of mice that received oral doses of sodium bicarbonate up to 580 mg/kg on gestation days 6 through 15 did not differ from the number occurring spontaneously in the sham-treated controls.

In teratogenicity studies involving rats and mice, NOELs of 290 mg/kg and 180 mg/kg (highest dose in each study), respectively, were reported for Potassium Carbonate. The results of an inhalation developmental toxicity study on a Potassium Carbonate scrubbing solution (up to 3 mg/l) were negative.

Teratogenic effects were not observed in a pregnant woman who ingested an antacid containing 500 mg Calcium Carbonate daily for 2 weeks.

In the chromosome aberrations assay, Calcium Carbonate was non-clastogenic to human lymphocytes and magnesium chloride and ammonium sulfate were non-genotoxic to Chinese hamster lung fibroblast (V79) cell cultures. Ames test results for ammonium carbamate, Potassium Bicarbonate, and Potassium Carbonate were negative for genotoxicity. Results were negative for potassium chloride in the L5178Y mouse lymphoma cell mutagenesis assay. In the *in vivo* micronucleus test, ammonium chloride was not genotoxic.

Additionally, anti-genotoxic effects of Magnesium Carbonate have been reported in *in vitro* tests involving *Saccharomyces cerevisiae* strain D4, Balb 3T3 fibroblast cells, or Chinese hamster ovary cells, but not in the Ames test using *S. typhimurium* strain 102.

In a co-carcinogenicity study in which rats were fed sodium bicarbonate (up to 0.64% in diet) + OPP (1.25% in the diet) continuously for 104 weeks, there was no statistically significant increase in the number of bladder tumors when compared to the control group. Also, sodium bicarbonate alone did not have a carcinogenic effect on the urinary bladder.

Bladder cancer has been associated with rats fed Potassium Bicarbonate in the diet (2% or 4%) for up to 130 weeks. The results of a 32-week tumor promotion study involving rats dosed with sodium bicarbonate (up to 3% in the diet) and 0.05% BBN confirmed that the dose-dependent increase in both urinary pH and sodium concentration and the dose-dependent promotion of urinary bladder carcinogenesis were parallel effects of sodium bicarbonate.

Undiluted Magnesium Carbonate, Ammonium Bicarbonate, and Ammonium Carbonate were non-irritating/non-corrosive to the reconstituted human epidermis model *in vitro*. Also, using an *in vitro* test for assessing dermal corrosivity potential (Corrositex®), undiluted Calcium Carbonate was not found to be a corrosive agent.

Undiluted Calcium Carbonate was not a corrosive agent when applied to the skin of rabbits. In the local lymph node assay, Calcium Carbonate (nano form) was applied to the skin of mice at concentrations up to 25%, and the results of this assay were positive.

Potassium Bicarbonate (500 mg in saline) was classified as mildly irritating to the skin of 6 rabbits. Reactions were observed at abraded sites, but not intact sites. Potassium Bicarbonate (0.2 g in deionized water) was classified as a non-sensitizer in the Buehler test (10 guinea pigs). Reactions were not observed during induction or the challenge phase. In a repeated insult patch test, a Potassium Carbonate tradename material (tested at 95% w/w) also was not a skin sensitizer in the Buehler test (10 guinea pigs). In the local lymph node assay, ammonium acetate was applied to the skin of mice at concentrations up to 50%, and the results of this assay were negative (non-sensitizer). Ammonium carbamate also produced negative results in the local lymph node assay (non-sensitizer) when applied to the skin of mice at concentrations up to 50%.

Magnesium Carbonate caused only corneal opacity in the *in vitro* bovine corneal opacity and permeability test. In the HET-CAM test, it was concluded that Ammonium Bicarbonate (undiluted or 10% aqueous) did not produce changes that were indicative of serious eye damage. Undiluted Ammonium Bicarbonate, but not the 10% concentration, caused intravascular coagulation in all eggs.

Magnesium Carbonate (10% aqueous) was classified as non-irritating to the eyes of 2 rabbits. However, transient ocular irritation was observed. Undiluted Ammonium Carbonate (3 rabbits tested), Calcium Carbonate (3 rabbits tested), and Potassium Carbonate (6 rabbits tested) were classified as non-irritating to the eyes of rabbits. The ocular reactions observed were reversible. In a study involving 9 rabbits, undiluted sodium carbonate monohydrate was classified as an ocular irritant.

DISCUSSION

The Panel expressed concern about the potential for skin and ocular irritation from exposures to carbonate salts. For example, animal studies reported that Potassium Carbonate and sodium carbonate monohydrate (a closely related chemical that is not a cosmetic ingredient) were skin and ocular irritants, respectively. Thus, the Panel determined that cosmetic products containing carbonate salts should be formulated to be non-irritating.

The Panel noted studies that reported renal toxicity and neoplastic lesions of the urinary bladder in animals fed Potassium Bicarbonate. However, the Panel concluded that the effects reported in these studies are attributable to irritation resulting from the ingredient in the urine after repeated daily exposure to high dietary concentrations of Potassium Bicarbonate over an extended period. The Panel agreed that the dietary exposures tested in these studies do not reflect the much lower exposures that can reasonably be expected from the use of carbonate salts in cosmetic products.

The Panel discussed the issue of incidental inhalation exposure from propellant hair sprays and face powders. They considered pertinent data indicating that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects, specifically, short-term (repeated exposures for 21 days) inhalation toxicity data and developmental toxicity data on a scrubbing solution containing 30.8% Potassium Carbonate in studies involving rats. The Panel also noted that droplets/particles from spray and loose-powder cosmetic products 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. 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 the following 6 carbonate salts are safe in the present practices of use and concentration, as described in this safety assessment, when formulated to be non-irritating.

Magnesium Carbonate
Ammonium Bicarbonate
Ammonium Carbonate
Calcium Carbonate
Potassium Bicarbonate*
Potassium Carbonate

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

Table 1. Definitions, Structures, and functions of the ingredients in this safety assessment (INCI Dictionary¹; CIR Staff)

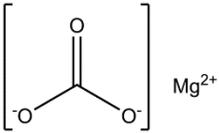
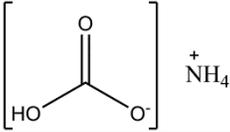
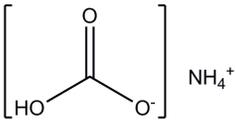
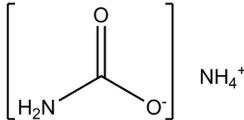
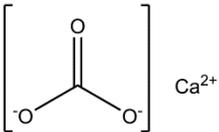
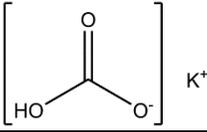
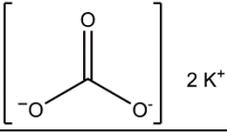
Ingredient/CAS No.	Definition & Structure	Function
Magnesium Carbonate 546-93-0 7757-69-9	Magnesium Carbonate is a basic dehydrated Magnesium Carbonate or a normal hydrated Magnesium Carbonate. 	Absorbents; Bulking Agents; Opacifying Agents; pH Adjusters
Ammonium Bicarbonate 1066-33-7	Ammonium Bicarbonate is an inorganic salt that conforms to the formula: 	pH Adjusters
Ammonium Carbonate 10361-29-2 506-87-6 8000-73-5	Ammonium Carbonate is a mixture of Ammonium Bicarbonate and ammonium carbamate.  ammonium bicarbonate  ammonium carbamate	Buffering Agents; pH Adjusters
Calcium Carbonate 471-34-1	Calcium Carbonate is the inorganic salt that conforms to the formula: 	Abrasives; Buffering Agents; Bulking Agents; Opacifying Agents; Oral Care Agents
Potassium Bicarbonate 298-14-6	Potassium Bicarbonate is the inorganic salt that conforms to the formula: 	Buffering Agents; pH Adjusters
Potassium Carbonate 584-08-7	Potassium Carbonate is the inorganic salt that conforms to the formula: 	pH Adjusters

Table 2. Properties of Carbonate Salts.⁴

Property	Value	Background Information
Magnesium Carbonate		
Formula Weight (g/mol)	84.31. ⁴⁸	
Density (g/cm ³)	3.0. ⁴⁹	
Melting Point (°C)	900. ⁴⁹	
Ammonium Bicarbonate		
Form/Odor	Shiny, hard, colorless or white prisms or crystalline mass. Faint odor of ammonia.	Comparatively stable at room temperature. Volatile with decomposition at ~60°. Decomposes in hot water.
Formula Weight (g/mol)	79.06	
Solubility	Soluble in water: 14% (10°C); 17.4% (20°C); 21.3% (30°C). Insoluble in alcohol and acetone.	
Ammonium Carbonate		
Form	Flat, columnar, prismatic crystals or elongated flakes.	Commercial preparations are usually a mixture with ammonium carbamate and Ammonium Bicarbonate.
Formula Weight (g/mol)	79.06-78.07	
Melting Point (°C)	43	
Calcium Carbonate		
Form	Odorless, tasteless powder or crystals.	Two crystal forms are of commercial importance: Aragonite (orthorhombic; melting point: 825°C (decomposes); density: 2.83; formed at temperatures above 30°; Calcite (hexagonal-rhombohedral; melting point 1339°C; density: 25.2; formed at temperatures below 30°.
Formula Weight (g/mol)	100.09	
Solubility	Soluble in 1N acetic acid, 3N hydrochloric acid, 2N nitric acid. Practically insoluble in water. Insoluble in ethanol.	
Potassium Bicarbonate		
Form	Colorless, transparent crystals, white granules or powder.	Contains not less than 99% KHCO ₃ .
Formula Weight (g/mol)	100.11	
Water Solubility (g/L)		
@ 20°C & pH 7	357	
@ 50°C & pH 7	500	
Solubility	Almost insoluble in ethanol.	
Potassium Carbonate		
Form	Hygroscopic, odorless granules or granular powder.	
Formula Weight (g/mol)	138.20	

Table 2. Properties of Carbonate Salts.⁴

Property	Value	Background Information
Potassium Carbonate		
Solubility	Soluble in 1 part cold water and in 0.7 part boiling water. Practically insoluble in alcohol.	
Density (g/ml)	2.29	
Melting Point (°C)	891	

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2016 FDA VCRP Data**Magnesium Carbonate**

01B - Baby Lotions, Oils, Powders, and Creams	3
02A - Bath Oils, Tablets, and Salts	1
02D - Other Bath Preparations	1
03B - Eyeliner	2
03C - Eye Shadow	65
03F - Mascara	2
03G - Other Eye Makeup Preparations	1
04C - Powders (dusting and talcum, excluding aftershave talc)	51
04D - Sachets	3
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	16
06E - Hair Color Sprays (aerosol)	8
06G - Hair Bleaches	2
06H - Other Hair Coloring Preparation	1
07A - Blushers (all types)	9
07B - Face Powders	52
07C - Foundations	7
07D - Leg and Body Paints	1
07E - Lipstick	1
07F - Makeup Bases	2
07H - Makeup Fixatives	2
07I - Other Makeup Preparations	3
09A - Dentifrices	1
10A - Bath Soaps and Detergents	1
11C - Mens Talcum	3
11G - Other Shaving Preparation Products	2
12D - Body and Hand (exc shave)	2
12E - Foot Powders and Sprays	1
12F - Moisturizing	1
12G - Night	1
12H - Paste Masks (mud packs)	65
12J - Other Skin Care Preps	3
Total	317

Ammonium Bicarbonate

05C - Hair Straighteners	3
05D - Permanent Waves	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	59

06G - Hair Bleaches	1
12D - Body and Hand (exc shave)	1
Total	70

Ammonium Carbonate

05G - Tonics, Dressings, and Other Hair Grooming Aids	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	24
12F - Moisturizing	1
Total	27

Calcium Carbonate

02A - Bath Oils, Tablets, and Salts	2
03B - Eyeliner	3
03C - Eye Shadow	11
03F - Mascara	2
04C - Powders (dusting and talcum, excluding aftershave talc)	17
05B - Hair Spray (aerosol fixatives)	1
07A - Blushers (all types)	8
07B - Face Powders	25
07C - Foundations	8
07D - Leg and Body Paints	1
07E - Lipstick	4
07F - Makeup Bases	5
07I - Other Makeup Preparations	5
08G - Other Manicuring Preparations	1
09A - Dentifrices	31
09C - Other Oral Hygiene Products	6
10A - Bath Soaps and Detergents	4
10E - Other Personal Cleanliness Products	7
11B - Beard Softeners	1
11G - Other Shaving Preparation Products	6
12A - Cleansing	1
12B - Depilatories	2
12C - Face and Neck (exc shave)	7
12D - Body and Hand (exc shave)	5
12E - Foot Powders and Sprays	1
12F - Moisturizing	3
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	5
Total	174

Potassium Bicarbonate - No FDA Data**Potassium Carbonate**

12A - Cleansing	1
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12F - Moisturizing	1
12H - Paste Masks (mud packs)	2
Total	4

Food and Drug Administration, HHS

§ 184.1138

(1) The ingredient is used as a dough strengthener as defined in §170.3(o)(6) of this chapter; a leavening agent as defined in §170.3(o)(17) of this chapter; a pH control agent as defined in §170.3(o)(23) of this chapter; and a texturizer as defined in §170.3(o)(32) of this chapter.

(2) The ingredient is used in food at levels not to exceed current good manufacturing practice.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[48 FR 52439, Nov. 18, 1983]

§ 184.1137 Ammonium carbonate.

(a) Ammonium carbonate ((NH₄)₂CO₃, CAS Reg. No. 8000-73-5) is a mixture of ammonium bicarbonate (NH₄HCO₃) and ammonium carbamate (NH₂COONH₄). It is prepared by the sublimation of a mixture of ammonium sulfate and calcium carbonate and occurs as a white powder or a hard, white or translucent mass.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 19, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.

(c) In accordance with §184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as a leavening agent as defined in §170.3(o)(17) of this chapter and a pH control agent as defined in §170.3(o)(23) of this chapter.

(2) The ingredient is used in food at levels not to exceed current good manufacturing practice.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[48 FR 52439, Nov. 18, 1983]

§ 184.1138 Ammonium chloride.

(a) Ammonium chloride (NH₄Cl, CAS Reg. No. 12125-02-9) is produced by the reaction of sodium chloride and an ammonium salt in solution. The less soluble sodium salt separates out at elevated temperatures, and ammonium chloride is recovered from the filtrate on cooling. Alternatively, hydrogen chloride formed by the burning of hydrogen in chlorine is dissolved in water and then reacted with gaseous ammonia. Ammonium chloride is crystallized from the solution.

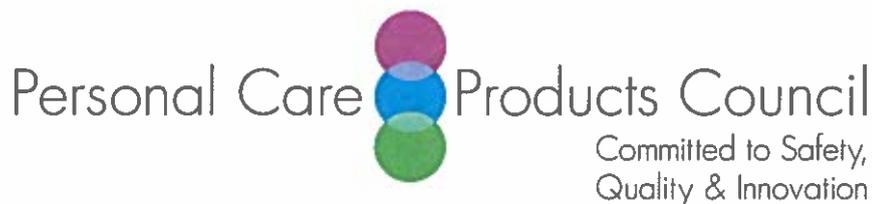
(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 20, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.

(c) In accordance with §184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as a dough strengthener as defined in §170.3(o)(6) of this chapter; a flavor enhancer as defined in §170.3(o)(11) of this chapter; a leavening agent as defined in §170.3(o)(17) of this chapter; and a processing aid as defined in §107.3(o)(24) of this chapter.

(2) The ingredient is used in food at levels not to exceed current good manufacturing practice.

(d) Prior sanctions for this ingredient different from the uses established in



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: June 23, 2016

SUBJECT: Comments on the Tentative Report: Safety Assessment of Simple Carbonate Salts as Used in Cosmetics (report posted June 16, 2016)

Key Issue

Ammonium Carbonate is defined as a mixture of Ammonium Bicarbonate and ammonium carbamate. Therefore, the ECHA dossier on ammonium carbamate that is not cited in the CIR report may be useful. For example, the dossier includes a local lymph node assay on ammonium carbamate.

Chemistry - The Chemistry section says: "Thus, the systemic toxicity potential of these carbonate salts via oral exposure is not addressed further in this report. The primary focus of the safety assessment is the review of the safety of topical exposure to these ingredients." As most of the studies described in this report are oral and inhalation studies with only one sensitization study, saying that the report is focused on topical exposure does not make sense.

Additional Considerations

Composition and Impurities - In addition to providing the *Food Chemical Codex* specifications for impurities in Ammonium Carbonate, please also indicate that the Codex says: "It consists of ammonium bicarbonate (NH_4HCO_3) and ammonium carbamate ($\text{NH}_2\text{COONH}_4$) in varying proportions." It also states that it should contain not less than 30.0% and not more than 43.0% NH_3 .

Acute, Ammonium Bicarbonate and Ammonium Carbonate - Please check reference 27. The title in the reference section says: "Toxicologic effects of ammonium carbamate and related compounds". Did the mixture they studied contain Ammonium Carbonate, or did it contain ammonium carbamate? As Ammonium Carbonate is defined as containing ammonium carbamate, studies on ammonium carbamate would be useful additions to this report.

Carcinogenicity - Please correct: "Hyperplasia of the epithelium lining the renal pelvis and of the epithelium lining the renal pelvis and papilla was not observed in these animals."

Ocular Irritation, Potassium Carbonate - The CIR Expert Panel has indicated that when a compound is used for read-across, that compound (sodium carbonate monohydrate) rather than the compound of interest (Potassium Carbonate) should be used as the section heading.

Table 2 - The description of the solubility of Potassium Bicarbonate does not make sense. It says: "Soluble in 2.8 parts water, 2 parts water at 50°C."