Safety Assessment of Sodium Benzotriazolyl Butylphenol Sulfonate as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 20, 2015
Panel Meeting Date:	March 16-17, 2015

The 2015 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 Lillian C. Becker, Scientific Analyst/Writer.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: February 20, 2015

Subject: Safety Assessment of Sodium Benzotriazolyl Butylphenol Sulfonate As Used In Cosmetics

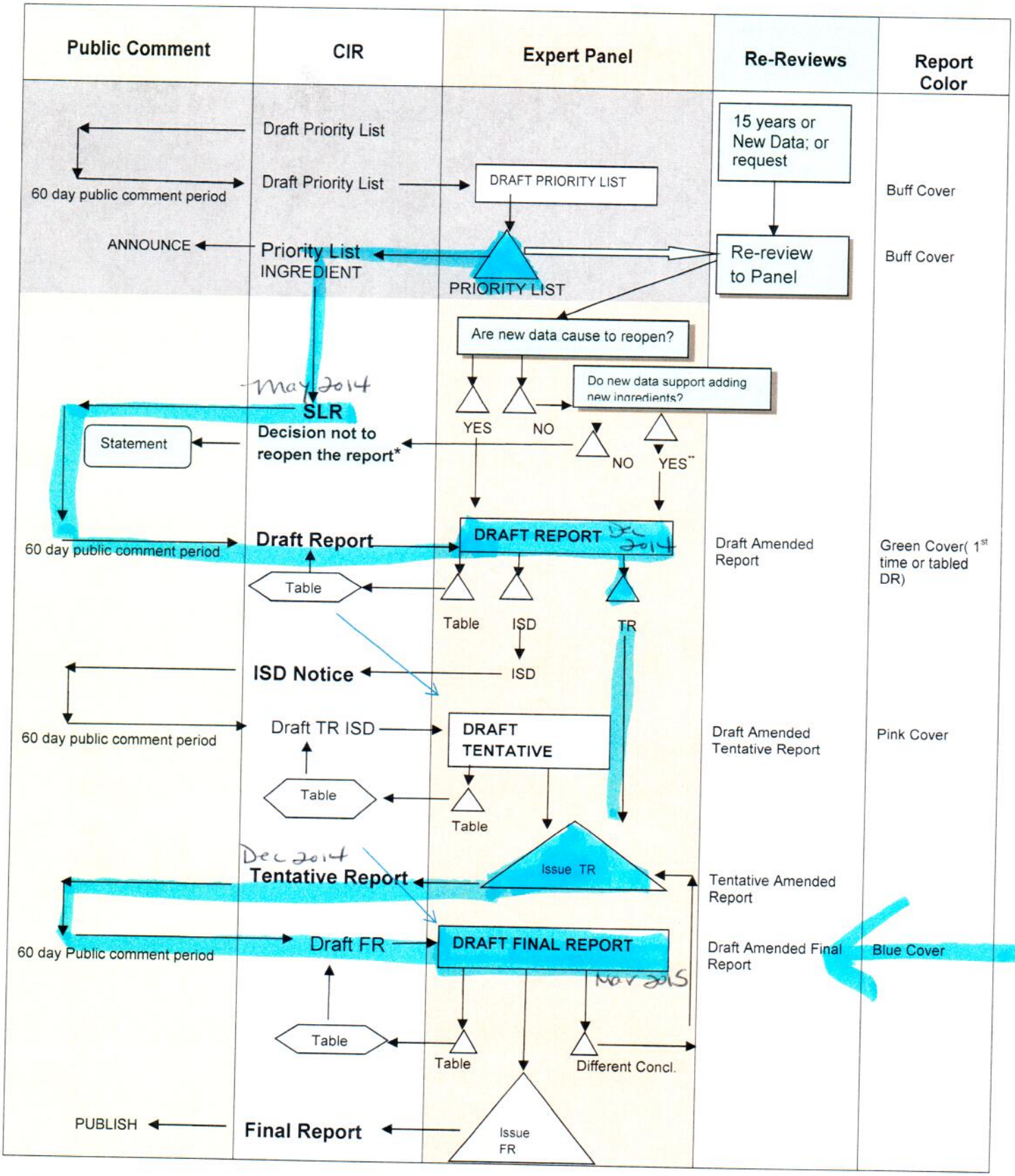
Attached is the draft final report of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. [*SBBSul_032015_Rep*] The Panel concluded that this ingredient was safe as used based mostly on data from the ECHA database. No new data have been discovered or submitted by industry. Council comments have been addressed. [*SBBSul_032015_Council*]

The Panel is to review the Abstract, Discussion, and Conclusion to ensure that they reflect the Panel's thinking. The Panel is to issue a Final Report.

Sodium Benzotriazolyl Butylphenol Sulfonate

SAFETY ASSESSMENT FLOW CHART

Mar 2015



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

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

Report History of
Sodium Benzotriazolyl Butylphenol Sulfonate

June, 2014 – The SLR was posted to the CIR website.

September, 2014 – Due to the number of reports going to the September Panel meeting, this report was postponed to the December meeting.

December, 2014 – The Panel examined the Draft Report and concluded that this ingredient is safe as used.

Sodium Benzotriazolyl Butylphenol Sulfonate Data Profile for March, 2015. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
SBBS	X	est	X	X	X		X			X	X		X		X	X		X

Search Strategy
Sodium Benzotriazolyl Butylphenol Sulfonate

SciFinder – CAS No. and Name – 109 hits. Culled for toxicity, preparation, properties, - 48 hits. Removed patents – 48 hits. 2 might be useful.

EPA High Production Volume Information System – no hits.

Web Search – Some chemical properties. Nothing else useful.

ECHA search – Found several unpublished studies.

Minutes - Sodium Benzotriazolyl Butylphenol Sulfonate
December, 2014

DR. MARKS: Okay. If no other comments we'll move forward. So now we have the sodium benzotriazolyl butylphenol sulfonate. And this is a draft report. This is the first review. It's one ingredient. We see ultraviolet --

DR. SLAGA: Which is, we should celebrate.

DR. MARKS: (Laughter) I was --

DR. HILL: Refrain from commenting.

DR. MARKS: Yes. It's used as a UV -- ultra violet light stablizer in cosmetics. Tom, let me see what Ron -- Ron Shank is always on the line now because I read his comments first. Ron Shank says, "This ingredient poorly penetrates the epidermis. The available toxicity data do not indicate significant systemic toxicity. It is an eye irritant, but there are no reports of use around the eyes. There should be some discussion about the reliability of data taken from ECHA Reports, since almost all the tox data comes from that source."

DR. SLAGA: That was my only concern.

SPEAKER: Did we -- we skipped --

DR. BERGFELD: That was mine too, and (inaudible).

DR. MARKS: Did I skip one? No. I didn't skip any.

DR. SLAGA: I mean, if we use all of that data, that's safe as used.

DR. MARKS: Hmm?

SPEAKER: Yes. It's final; final with editorial.

DR. MARKS: Hey, Jay, you can't lose concentration for even --

DR. ANSELL: I can't. No. It's true.

MS. BECKER: No. No blinking.

DR. ANSELL: I look down at my phone and the next I know we are --

DR. HILL: That's it.

DR. ANSELL: Ah-ha, always a cell phone.

DR. MARKS: So, the European Chemical Agency -- You know, let's -- Tom?

DR. SLAGA: Yes. Again, it's safe as used if we meet all of their data; I mean there is except -- you know, we have the methods of manufacturing, we have impurities. We have all the toxicological, including genotox irritation, sensitivity --

DR. MARKS: Yes. That's another further toxin?

DR. SLAGA: So based on that, you'd have to say it's --

DR. BERGFELD: Can you use somebody else's data like that?

DR. MARKS: Well, that's the issue.

DR. GILL: Have we done that before?

DR. HILL: No. We got permission, didn't we?

DR. GILL: Where the majority of the data in the reports come from ECHA Summary Data.

DR. BERGFELD: And then that has references?

DR. GILL: Yes.

DR. BERGFELD: Original references?

DR. GILL: Some of it does, not -- most of it does not. It's the summary information.

DR. SLAGA: Safe as used.

DR. ANSELL: They are robust summaries, and I think if the data had showed the material was unsafe, there would be no question as to whether we could use it or not.

DR. BERGFELD: Okay. All right.

DR. ANSELL: Right.

DR. GILL: And, Jay, if I understand Carol correctly, we will see more of this in the future, where it's a robust summary data. We won't actually get the data. We'll be referred to the robust summary data at the website.

DR. ANSELL: Right, the robust summary data is public. The studies themselves which could be used for regulatory purposes and registrations are property, but the conclusions are not. And so Carol's comments, typically, only relate to the reference that the REACH Reports -- REACH is not the author of the reports, but simply the place that they post it, but she makes that pretty much with everything.

SPEAKER: Mm-hmm. Who changed that?

DR. BERGFELD: Now, if we could use their stuff, are they using ours?

DR. MARKS: We would hope s...

DR. SLAGA: Yeah, we would.

DR. BERGFELD: I mean, is there a reciprocal using of materials?

DR. MARKS: Well, at least I have the published reports.

DR. BERGFELD: Or are they just strictly one- lined?

DR. ANSELL: Those are published (inaudible)

DR. BERGFELD: I know. But are we -- are we referenced in any of their material?

DR. ANSELL: I really don't know. I haven't --

DR. LORETZ: (Inaudible) on the website, but it's study, so it's pure studies and nothing more. I mean, it's just pure data.

DR. BERGFELD: Yes. But we have unpublished data on ours.

DR. LORETZ: I think that -- Yes, I think we are (inaudible) to submit.

DR. BERGFELD: I think it would be an interesting look.

DR. ANSELL: I have not been involved in any of the consortia in the -- in pulling together a rich dossier, but --

DR. LORETZ: I think they -- and they could sort of submit that data.

DR. ANSELL: Yea.

DR. LORETZ: Yes. As part of their dossier; whether they do or not, I don't know.

DR. ANSELL: Have you done any of the REACH dossiers?

DR. GILL: But I would think that the original data wouldn't -- they would be citing the studies, which we also cite in our report. So they could go back to the original studies to cite.

DR. LORETZ: Right. Exactly! Not citing the (inaudible), right.

DR. BERGFELD: But they can't when they are unpublished.

SPEAKER: Correct.

DR. LORETZ: I don't know. It would be interesting.

DR. BERGFELD: And what's the source of the unpublished.

DR. LORETZ: Yes. We have good source.

DR. ANSELL: No. No. The company would be the source.

MS. BECKER: Yes. The company; the company that's submitting it might be the source and then they would just give it their (inaudible), the same thing that they gave us.

DR. BERGFELD: But they don't usually allow all that material to go out.

DR. ANSELL: They have to. I mean, you can't -- I mean the REACH is a structural framework, and they have rules in there about not repeating data, to double count. And you can submit data but it's compensable; you know, it's owned. But whether they would cite CIR as a primary resource, or as a secondary, I'm not sure about that.

But I know they would reach out to the companies to get the data. REACH is all full of that, that you're not supposed to -- you need special permission to rerun a study, so the

company would have to refuse to make the data available. It would be very awkward.

DR. BERGFELD: Well, I mean we have trouble enough getting the data. I wonder how they get it; if they do reach out to the companies.

DR. GILL: But aren't they submitting the (inaudible).

DR. ANSELL: Because it's a legal obligation, and we are voluntary.

DR. BERGFELD: But they would only get European, would they not, or companies that deal in the European market?

DR. ANSELL: Not necessarily. I mean, the consortia is made up of multinational companies, I think the regional (inaudible).

DR. LORETZ: It's called the European Technical Agency.

DR. ANSELL: That's where it's posted. That's not the author. That's what Carol keeps reminding us, is that the author is a consortia of companies.

DR. LORETZ: The consortium of companies that are putting together a dossier.

DR. BERGFELD: It will be interesting just to see.

DR. ANSELL: Yes. Yes. But it's an interesting question.

DR. MARKS: So before I move on with this one, Ron Hill, I didn't give you a chance to -- or you haven't commented -- I shouldn't say that. I gave you chance to make a comment (inaudible).

DR. HILL: No. I haven't been able to get a word in edgewise at the moment but -- All right, so I'm a little perplexed. It said -- the statement in the report was; no concentration of use data for compounds used in the vicinity of -- formulations used in the vicinity of the eye. And I don't find any on the listing other than face preparations that would necessarily be. So why is that statement in there the way it's in there?

MS. BECKER: Because there's a lot eye irritation data or at least there is eye irritation data; and I want to make sure you guys paid attention to the connection.

DR. HILL: Okay. The way the sentence is written suggests that they were used around the eye, and we didn't have any concentration of use data for that. So it would be just to have a look at that.

MS. BECKER: Okay.

DR. HILL: Since we're talking about robust summaries, it says, "Robust summaries from the ECHA database are presented below. Does that mean you are capturing their summaries and plugging them in? Or these are your robust summaries of their data? And what is the hallmark of a robust summary?

MS. BECKER: Robust summary is not my word. That's what we've come up with in CIR to characterize the ECHA data. And it is my summaries of their summaries, because they don't have it in paragraph form. We got these (inaudible) and we've got that much, and I'm putting it in paragraphs for you.

DR. HILL: Okay. So then we need to make sure that that wording says that they are your robust summaries. Then I have a lot of places where I picked the toxicokinetics data section. But I don't necessarily think we need to pick about that here. I just want to make sure that you -- So the next time we will get a draft final report?

MS. BECKER: Mm-hmm.

DR. HILL: Okay. So just before next time maybe we can -- and then everybody can be looking at that toxicokinetic section because there are several sentences in there that don't make good sense, so that's what I pointed out.

MS. BECKER: Okay.

DR. GILL: Ron, I want to go back to a point you made earlier about, you don't say that there are no products used around the eye. There is a sentence that says they are not used around the eye. And also say in the following paragraph that there's no constant transition

of use data, of product use around the eye. I think we could explain why we have that there though.

DR. GILL: It could be extreme. Yes.

DR. HILL: And I agree. Yes. Because the sentence in there reads, "There were no concentrations of use reported for products used around the eye." That's what the sentence says.

DR. GILL: Correct. Okay. You've clarified it.

DR. HILL: It suggests that there are products used around the eye which I guess, you know, face preparations maybe, but --

DR. GILL: Mm-hmm.

DR. MARKS: Okay. Actually I had that the use concentration was 0.64, we are at the highest, and the ocular hearing it was 100 percent. So that was really a big -- that's why I think you could use it in a facial cream and not worry.

DR. HILL: I wasn't worried about it. It was the way it was stated that worried me.

DR. MARKS: Okay. So tomorrow, presumably, I will second a motion to issue a tentative report with a safe conclusion.

SPEAKER: Great.

DR. MARKS: Okay.

MS. BECKER: Did you want to say anything about the eye use, or just leave it in the discussion?

DR. MARKS: I'd just leave it in the discussion, yes.

MS. BECKER: It wasn't really valuable.

DR. HILL: And while we're on there, on the skin fresheners they list the concentration of 0.64 percent, which is way out of line with all the rest of them. So I'm wondering if that might be one of those deals where they are giving the result -- the percentage in the raw material rather than finished products. I'm not sure. And I'm not sure we can even know that because it's a survey data, but I'm wondering if the industry could be contacted and checked and see if that 0.64 percent is actually correct or not. We've done that before, I wouldn't bring that up.

MS. BECKER: Did we do that Jay?

DR. MARKS: I may have forgotten to read Ron Shank's most important sentence on this ingredient. "I see no data needs, and therefore support a-safe-as-used condition." Okay, let's move on. Now we are to the PEG diesters.

Dr. Belsito's Team

DR. BELSITO: Okay, sodium benzotria -- so are we done with the poly siloxanes? Okay. Sodium benzotriazolyl butylphenyl sulfonate. So this is the first time we're looking at this ingredient, and it's under benzotriazolyl. And it's a stand alone ingredient. So the first comment I had was, given the method of manufacture, and we don't have any impurity data, but given how it's made and the low concentration of use in cosmetics, is anyone concerned about the lack of impurity data?

DR. SNYDER: At 9.64 [sic] percent leave on.

DR. BELSITO: Right, okay. I mean, I'm just raising these questions. And then on page 11 of the document, with the in vitro animal assays, are we okay with the one chromosome aberration, the Chinese hamster lung fiber blast, it was a high concentration with high cytotoxicity. I didn't think so.

On the sensitization data, I had really -- I had problems. Five percent -- so this is a guinea pig maximization test on ten animals, and they noted at twenty- four hours, three of the animals had reactions, and at forty-eight, two. So 30 percent at 25 hours and 20 percent at 48 hours. And they concluded that it wasn't a dermal sensitizer, which I found hard to understand

that conclusion.

This is page 12 of the PDF. I mean, there's some data there, and it certainly looks like it'd be a nice binder to skin protein.

DR. LIEBLER: So the question I had was whether Don thought we needed sensitization on this. Because I thought that result was kind of equivocal and --

DR. BELSITO: Yeah, I mean, it's a high level. I mean, this is a guinea pig maximization test, and they're using five percent intradermal induction and a twenty-five percent dermal induction. But it's sort of all we have. Then we have a photosensitization and phototoxicity data, and that was --

DR. EISENMANN: There is the local lymph node assay also.

DR. BELSITO: Right. I didn't -- I mean, I just disagreed with it. I don't know how you could get that number of animals reacting and saying it wasn't a sensitizer in your test system. I mean, that was just my point. The LLNA is where that's -- I mean, I didn't -- I mean, I pretty much was comfortable going with the safe as used. These were just points that I was bringing out that I was concerned in the document.

And in that photo data, given the percentage that was used, 30 percent in the photo study and 5 and 25 in the guinea pig maximization, it looks like these are separate tests. And I didn't reference -- is the same?

MS. BECKER: For the phototoxicity? Yeah, they're both the same reference.

DR. BELSITO: So they just used different concentrations for the photo than they did for the guinea pig maximization?

MS. BECKER: That's ECHA data, so they're two separate experiments given ECHA.

DR. BELSITO: So you're just summarizing it from the ECHA data, okay.

MS. BECKER: Yes.

DR. BELSITO: So I understand now. Okay, so actually in that paragraph on page 12, so it says, "In an acute dermal photo irritation response, 30 percent and then were not found to be photo irritating." That's really not a photo irritation study. It's a photo sensitization study.

So it was not photo irritating or phototoxic or photo irritating, and I basically said safe as used. So I must have looked at the LLNA data and also the very high levels.

DR. KLAASEN: If you're okay, I'm okay.

DR. BELSITO: Kurt, Paul?

DR. KLAASEN: Yeah, that was my only concern was that section and if you felt okay with it, I feel okay. In regard to -- just for my gratification, in regard to the local lymph node, what is kind of considered a positive response? It says, the stimulation indexes were 0.7, 0.57 and 2.06.

DR. BELSITO: You want a stimulation index of three?

DR. KLAASEN: That's what I thought.

DR. BELSITO: So you usually extrapolate out to see what it would be at three. And if you don't get to three and you're not interested in pursuing it at higher concentrations, companies usually will just give up and say, look it, we're using it at a much lower concentration, and at these concentrations we didn't get to three.

So they looked at up to 30 percent. Right. Anything else?

MS. BECKER [sic]: I just had question. This ingredient is a light stabilizer. How does it work actually?

DR. BELSITO: So it's like a sunscreen. So basically if you have a photo reactive chemical in a clear bottle that light could get through, UVA light, you want to protect it from photo degradation.

DR. SADRIEH: So does it interact with the color additive then?

DR. BELSITO: I don't know. I mean, it basically absorbs light and emits heat energy, is typically how sunscreening agents work. So it would work like benzoquinone 3 put on your skin. It absorbs the UV wavelengths and --

DR. SADRIEH: But it's intended to protect the formulation, right?

DR. BELSITO: Right.

DR. SADRIEH: So the degradation of it --

DR. BELSITO: From photo degradation.

DR. SADRIEH: Okay, by absorbing the -- but does it interact actually with the color additive to somehow modify it to not be affected by that. That's what I was just wondering.

DR. BELSITO: I don't know. I mean, I don't know what they're trying to protect from photo degradation. All we know is that this is a sunscreening agent and that it's used in cosmetics for -- to prevent photo degradation of what, I don't know. It would be like adding an antioxidant to prevent formation of hydroperoxides in a perfume containing litadol where you're concerned about hydroperoxides of litadol or something. So there must be some cosmetic chemicals out there that are degraded by light, that need to be protected, is what I assume.

DR. SNYDER: (Inaudible) protect coatings and plastics and things.

DR. BELSITO: Resins, yeah. Yeah, the way that the ingredient dictionary defines these light stabilizers is, are employed in cosmetics to protect the product from chemical or physical deterioration induced by the light. So it's not a matter of reaction, but it's a matter of protection of the product.

DR. SADRIEH: Okay, I was just thinking about whether it modifies that actual color additive or not.

SPEAKER: (Inaudible).

DR. GILL: Yeah, changing colors of the product.

DR. LIEBLER: Neither (inaudible) or electrical (inaudible) on those ones.

DR. BELSITO: Okay, any more comments?

DAY TWO

DR. BELSITO: Yeah, so this is sodium benzotriazolyl butylphenol sulfonate. It's used in 67 leave-on products, 377 rinse-off products, and 29 bath products up to a highest concentration of .64 percent in leave-on products. There was one baby product, a hair product, some other dermal products. There is no eye use.

We received a good amount of summary data from the ECHA website and based upon the data we received, we felt that this ingredient was safe as used in cosmetics.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: Any further discussion regarding this ingredient? Ron?

DR. HILL: I just made the comment yesterday, and I wanted to reiterate, there were a few bits of language in the section that's called toxicokinetics that the statements didn't make good sense and so I think I gave guidance yesterday about the clean up on that.

DR. BERGFELD: Thank you. Any other comments regarding the document itself? Anything major? If not, call the vote then, all those in favor please indicate by raising your hands. Unanimous. Good, decision approval of safety.

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ABSTRACT

This is a safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. It is reported to function as a light stabilizer in cosmetics. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant animal and human data related to the ingredient. The Panel concluded that sodium benzotriazolyl butylphenol sulfonate is safe in cosmetics in the present practices of use and concentration.

INTRODUCTION

This report presents the CIR Panel safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. This ingredient is reported to function as a light stabilizer (ie, protecting the product from chemical or physical deterioration induced by light) in cosmetics.[1]

A comprehensive search of the literature identified little published data relevant to this safety assessment. No toxicity data have been submitted by industry. However, pertinent data were discovered in the European Chemicals Agency (ECHA) database.[2] Robust summaries from the ECHA database are presented below.

CHEMISTRY

Definition and Structure

Sodium benzotriazolyl butylphenol sulfonate (CAS No. 92484-48-5) is an organic compound (Figure 1).[1] It is also referred to as sodium 3-(2*H*-benzotriazol-2-yl)-5-*sec*-butyl-4-hydroxybenzenesulfonate in the literature.

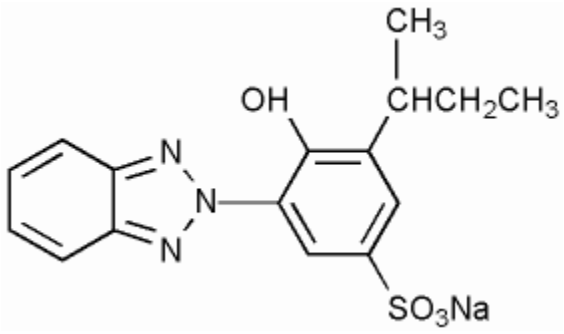

Figure 1. Sodium benzotriazolyl butylphenol sulfonate.

Physical and Chemical Properties

Sodium benzotriazolyl butylphenol sulfonate is a light beige to white powder with a trace characteristic odor (Table 1). It is an ultraviolet (UV) absorber, which converts the energy of absorbed UV light to heat through a mechanism analogous to ‘‘keto-enol’’ tautomerization.[3]

The UV absorption spectrum of sodium benzotriazolyl butylphenol sulfonate shows 2 peaks at wavelengths of approximately 290 and 335 nm and demonstrates no absorption above approximately 390 nm.[4]

Sodium benzotriazolyl butylphenol sulfonate is a sodium sulfonate salt and is reported to be soluble in water and alcohol.[4] It is hydrolytically stable at 50°C.[2,4]

Method of Manufacture

Sodium benzotriazolyl butylphenol sulfonate is prepared by warming 2-(2'*H*-benzotriazol-2'-yl)phenols containing *t*-alkyl substituents in a toluene solution with an aluminum chloride/nitro-methane catalyst resulting in the releasing of the *t*-alkyl groups to the solvent, leaving 2-[2’*H*-benzotriazol-(2)-yl]phenol.[5] The 2-[2’*H*-benzotriazol-(2)-yl]phenol is then treated with chlorosulfonic acid to give sodium benzotriazolyl butylphenol sulfonate.

A patent for the manufacture of sodium benzotriazolyl butylphenol sulfonate describes the following procedure.[6] 2-(2’-Hydroxy-3’-*sec*-butyl-5’-*tert*-butylphenyl)benzotriazole is combined with oleum at cool temperatures. This solution is stirred at room temperature, and then poured into ice water. The precipitate is heated, cooled, and filtered. The acid is well pressed, then suspended in water. The pH is adjusted to 7 with sodium hydroxide. The resulting crystal slurry is heated, cooled, and then filtered. The product is heat-dried under vacuum.

Impurities

A supplier reported that the purity of sodium benzotriazolyl butylphenol sulfonate was between 98.6% to 99.4%.[2] The impurities were not specified.

USE

Cosmetic

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP).[7] In 2014, sodium benzotriazolyl butylphenol sulfonate was reported to be used in a total of 473 cosmetic formulations, consisting of 67 leave-on products, 377 rinse-off products, and 29 products for the bath (Table 2). These products include one baby product, hair products (coloring and non-coloring), perfumes, and other dermal products; 311 products have the potential for mucus membrane exposures.

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for this ingredient.[8] Sodium benzotriazolyl butylphenol sulfonate was reported to be used up to a highest maximum concentration of 0.64% in leave-on products, with its highest maximum concentration identified in skin fresheners. It is used in rinse-off products up to 0.1%, the highest maximum concentration in skin cleansing products. It is also used up to 0.033% in bubble baths.

Sodium benzotriazolyl butylphenol sulfonate was reported to be used in aerosol/spray products that could possibly be inhaled, eg, perfumes and body and hand products. This ingredient is reportedly used at concentrations up to 0.1%. 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.[9-12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[9,12]

Sodium benzotriazolyl butylphenol sulfonate is not restricted from use in any way under the rules governing cosmetic products in the European Union.[13]

Non-Cosmetic

Sodium benzotriazolyl butylphenol sulfonate is a UV absorber used to protect coatings, plastics, paint, wood, wool and other items that degrade when exposed to UV light.[3,14]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Overview Analysis

An analysis of the toxicokinetics of sodium benzotriazolyl butylphenol sulfonate stated that generally, compounds with molecular weights below 500 Da are expected to be absorbed after oral ingestion; however, sodium benzotriazolyl butylphenol sulfonate (mw 369.37) has ionizable groups that may reduce its absorption in the gastrointestinal tract, especially in the small intestines.[2] The solubility in water (100-10,000 mg/L) and very low log P_{ow} (-0.24) of this ingredient suggest absorption through passive diffusion. However, the rate of absorption by this mechanism may be limited by the rate at which this substance partitions from the gastrointestinal fluid.

This analysis also states that the low vapor pressure of this ingredient indicates that inhalation exposure to the vapor is not likely.[2] Sodium benzotriazolyl butylphenol sulfonate is not expected to be rapidly absorbed from the lungs, and not likely to penetrate the skin to any significant extent because of its high hydrophilic and polar nature.

This analysis also states that any sodium benzotriazolyl butylphenol sulfonate that is absorbed into the body is expected to distribute throughout the interstitial fluid, when absorbed sytemically.[2] The chemical structure and physicochemical properties of this ingredient suggest that it will undergo mainly phase-II metabolism, yielding water-soluble metabolites that are readily excreted in both urine and bile. Metabolic activation is not likely.

Dermal/Percutaneous

Two formulations of sodium benzotriazolyl butylphenol sulfonate (composition of the formulations not provided) showed minimal penetration into cadaver skin using Franz cells (n=3) and the finite dose approach.[2] Most of the test substance remained on the surface of the skin; there was no evidence of accumulation in the skin. Total absorption was 0.037, 0.029, 0.016 µg, respectively, for the 3 groups of Franz cells described below. The skin for these experiments was collected from 3 donors within 24 h of death; 6 replicas per donor were used. In the first group of cells, the test substance (0.1%; 0.8 mg/0.8 cm^2; formulation not specified) was placed on the skin for 30 min; then the surface of the skin was washed with deionized water. In the second group (0.5%; 0.8 mg/0.8 cm^2; same unspecified formulation as for the first group) and third group (0.5%; 1.6 mg/0.8 cm^2 in an emulsion; formulation not specified) of Franz cells, the test substance was placed on the cadaver skin, and the phosphate-buffered saline was replaced in the receptor cells at 2, 4, 8, 12, 24, 32, and 48 h. Receptor cell fluids were analyzed by diode-array ultraviolet detector. Following the last receptor solution collection, the skin samples were surface washed with deionized water. The skin was then removed from each chamber, tape stripped 20 times to collect the stratum corneum (10 strips/vial), separated into epidermis and dermis, and extracted with a solvent (solvent not specified) for no less than 24 h.

In another study, sodium benzotriazolyl butylphenol sulfonate was not detected in the receptors of Franz cells (n=10; 3 donors) after 24 h; the permeation rate of the test substance through the skin was <5 ng/cm^2 (ie, the limit of detection) or approximately 0.08 % of the administered dose.[2] The total amount of the test substance recovered from the

deeper layers of the skin was 0.026 µg/cm^2 (<0.4 % of the administered dose). The experimental protocol of this study included administering an oxidative hair dye containing sodium benzotriazolyl butylphenol sulfonate (0.67% mixed with developer for a final concentration of 0.33%; 2 mg/cm^2) to the epidermal membranes with a glass rod. The doses ranged from 1.6-2.6 mg/cm^2 (mean 2.1 ± 0.1 mg/cm^2; 6.9 ± 0.3 µg/cm^2 of the test substance). The receptor cells were sampled at 2, 4, 6, 12 and 24 h and the samples tested by HPLC. The diffusion cells were dismantled, any formulation remaining on the skin surface was removed by gentle wiping with a cotton bud, and the epidermal membrane was tape stripped (tape-strip fractions collected: 1-3, 4-6, 7-12 and 13-20 times).

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal – Non-Human

The dermal LD_{50} of sodium benzotriazolyl butylphenol sulfonate was shown to be >2000 mg/kg when administered to the shaved backs of KFM-Han Wistar rats (n=5/sex) in carboxymethyl cellulose (4 mL) under occlusion for 24 h.[2] The test was conducted in accordance with Organization for Economic Co-operation and Development (OECD) Guideline 402. The test material was administered to 10% of the body surface. The rats were observed for 15 days and then killed and necropsied. The necropsies were unremarkable.

When sodium benzotriazolyl butylphenol sulfonate (100%; 0.5 g moistened with distilled water) was dermally administered to the shaved skin (3 cm x 3 cm) of New Zealand White rabbits (n=1 male, 2 females) under semiocclusion for 4 h, no discoloration or toxic signs were observed.[2] The test site was then washed with lukewarm tap water. The rabbits were observed for 72 h.

Oral – Non-Human

The oral LD_{50} of sodium benzotriazolyl butylphenol sulfonate was found to be >5000 mg/kg when administered to KFM-Han Wistar rats (n=5/sex) by gavage in carboxymethyl cellulose (20 mL).[2] The test was conducted in accordance with OECD guideline 401. The rats were observed for 15 days after exposure and then necropsied. One female rat died on day 2 of observation. Clinical signs were sedation, dyspnea, hunched posture, diarrhea, and ruffled fur, all of which were resolved by day 8. At necropsy, the lungs of the rat that died had reddish discoloration and dark-red foci. The rest of the necropsies were unremarkable.

Repeated Dose Toxicity

Oral – Non-Human

There were no clinical signs that could be attributed to the test material in any group in a range finding study where sodium benzotriazolyl butylphenol sulfonate (0, 200, or 1000 mg/kg in 4% carboxymethyl cellulose; 10 mL/kg) was administered by gavage to Wistar rats (n=3/sex) for 5 days.[2] There was an increase in absolute liver weights in male rats and in liver-to-body weight ratios in male and female rats in the high-dose group when compared to controls and to the low-dose group. The absolute and relative adrenal weights of the female rats of the high-dose group were decreased compared to those of the rats of other groups. Compared to male rats in the control and low-dose group, the males of the high-dose group had decreased feed consumption during the first 3 days of treatment. Feed consumption was comparable to that of the other groups at termination of treatment. The feed consumption of the females was similar among the groups. No differences in body weight gains were observed between rats in the control and treatment groups. The ophthalmoscopic examinations at termination were unremarkable.

The oral no-observed-adverse-effects level (NOAEL) for sodium benzotriazolyl butylphenol sulfonate was 200 mg/kg/d for rats in a 28-day gavage study.[2] The test was conducted in accordance with OECD Guideline 407. In this study, benzotriazolyl butylphenol sulfonate (0, 20, 50, 200, 800 mg/kg/d in carboxymethyl cellulose 4% in distilled water; 10 mL/kg) was administered by gavage to Wistar rats (n=5/sex; controls=10/sex) for 28 days. The rats were then killed and necropsied. A second high-dose group was allowed a recovery period (time not specified) before they were killed and necropsied. There was 1 death of a female in the high-dose group due to intubation error. There were no reported changes in clinical condition, body weights, or feed consumption. There were increases in absolute and relative liver weights in male and female rats at termination of the treatment period in the 200 mg/kg group. These findings were considered to be adaptive and not adverse because no histopathological lesions were observed in the livers. No other effects were observed at 200 mg/kg/d. In the high-dose groups, the absolute weights of the adrenal glands were decreased in males at the termination of treatment and following the recovery period. There was no evidence of abnormal histopathological findings resulting from treatment with the test material. No effects were observed in clinical laboratory investigations (hematology, clinical biochemistry, and urinalysis). There were no ophthalmoscopic effects.[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

One study reported the oral NOAEL for reproductive and developmental toxicity for Wistar rats as 800 mg/kg/d sodium benzotriazolyl butylphenol sulfonate administered by gavage throughout gestation.[2] The NOAEL for parental toxicity was 200 mg/kg/d because salivation and increased water consumption were noted for animals in the 800 mg/kg/d group. Wistar rats (n=10/sex) were dosed by gavage with sodium benzotriazolyl butylphenol sulfonate (0, 50, 200 and 800

mg/kg/d in 1% carboxymethyl cellulose) in accordance with OECD Guideline 421. The males were treated for a total of 29 days and the dams for a total of 43-55 days starting on day 1 of pairing. Parents and pups were killed and necropsied. No further details on the methods were provided.

During this experiment, there were no mortalities in the parental groups. There were no changes in body weights or body weight gain. There were no changes in feed consumption. In the high-dose group, water consumption was increased for males and females during the entire experiment, which may be a behavioral adaption in response to increased salivation observed in all rats in this group. Mating, fertility and conception indices, precoital time, and number of corpora lutea and implantation sites were similar in all groups. No macroscopic treatment-related findings were observed at necropsy, and there were no treatment-related microscopic findings. There were no toxicologically relevant effects on the gestation index and duration, parturition, maternal care or early postnatal pup development (mortality, clinical signs, body weight and macroscopic findings).[2]

GENOTOXICITY

In Vitro

In a bacterial reverse mutation assay using *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537), sodium benzotriazolyl butylphenol sulfonate (10, 33.3, 100, 333.3, 1000, and 5000 µg/plate; vehicle not provided) was not mutagenic with or without metabolic activation.[2] Results of the positive control were as expected. The test was conducted in accordance with OECD guideline 471 and Guideline EU Method B.13/14.

In a mammalian chromosomal aberration assay using Chinese hamster lung fibroblasts (V79), sodium benzotriazolyl butylphenol sulfonate (8, 80, and 110 µg/plate without metabolic activation; 10, 50, 120, 130 µg/plate with metabolic activation; in dimethyl sulfoxide [DMSO]) was genotoxic with and without metabolic activation at the highest test concentrations.[2] There were increased numbers of cells with structural aberrations after treatment with the test material with metabolic activation. Without metabolic activation, an increase of the aberration rate was observed only at the incubation time of 18 h. Treatment of the cells with 110 µg/mL (without metabolic activation) and 130 µg/mL (with metabolic activation) reduced the plating efficiency of the V79 cells. The highest concentrations yielded 18% survival (110 µg/mL; without metabolic activation) and 67.1 % survival (130 µg/mL; with metabolic activation). Results of the positive control were as expected. The test was conducted in accordance with OECD Guideline 473 and Guideline EU Method B.10.

In a mammalian cell gene mutation assay using V79 fibroblasts targeting the hypoxanthine-guanine phosphoribosyl transferase gene, sodium benzotriazolyl butylphenol sulfonate (10, 30, 45, 60, 70, 80, and 100 µg/plate in saline, with and without metabolic activation) was not genotoxic up to 80 µg/plate.[2] The highest concentration was cytotoxic; 100 µg/plate reduced the survival rate of the cells by 13.2 % without metabolic activation and 22.7 % with metabolic activation. Results of the positive control were as expected. The test was conducted according to OECD Guideline 476.

In Vivo

In a mammalian erythrocyte micronucleus assay, a single dose of sodium benzotriazolyl butylphenol sulfonate (3000 mg/kg in 0.5% methocel; 20 mL/kg) was not genotoxic to NMRI mice (n=6/sex) when administered by gavage.[2] The test was conducted in accordance with OECD Guideline 474 and Guideline EU Method B.12. The mice were killed 24, 48 and 72 h after administration of the test material, and the bone marrow was collected. The positive control was cyclophosphamide (30 mg/kg). When examining the marrow, 1000 polychromatic erythrocytes (PCE) were analyzed per animal for micronuclei.

In an unscheduled DNA synthesis assay, a single dose of sodium benzotriazolyl butylphenol sulfonate (100, 330, 1000 mg/kg in 1% carboxymethylcellulose suspension; 10 mL/kg) was not genotoxic to male Wistar rats (n=5) when administered by gavage.[2] In the high-dose group, the viability of the isolated hepatocytes of 2 rats was slightly decreased. The in vitro attachment of the hepatocytes was not affected by the in vivo pre-treatment with the test article. The test was conducted in accordance with OECD Guideline 486 and Guideline EU Method B.39. The rats were killed 12-14 h after administration of the test material. The positive control was 2-acetylaminofluorene (100 mg/kg).

CARCINOGENICITY

No published carcinogenicity studies were discovered in the literature and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

No irritation, erythema, or edema was observed when sodium benzotriazolyl butylphenol sulfonate (100%; 0.5 g moistened with distilled water) was administered to the shaved skin (3 cm x 3 cm) of New Zealand White rabbits (n=1 male, 2 females) under semi-occlusion for 4 h.[2] After exposure, the test site was washed with lukewarm tap water. The rabbits were observed for 72 h. The test was conducted in accordance with OECD Guideline 404 and EU method B.4.

When sodium benzotriazolyl butylphenol sulfonate was administered to the shaved backs of KFM-Han Wistar rats (n=5/sex) in carboxymethyl cellulose (4%; 4 mL) under occlusion for 24 h, all rats had erythema that resolved by day 8.[2] The test material was administered to 10% of the body surface.

Ocular

Sodium benzotriazolyl butylphenol sulfonate (0.1 g; 100%) was an ocular irritant causing irreversible corneal damage in one of the rabbits tested in a study in which this substance was instilled into the conjunctival sac of the left eye of New Zealand White rabbits (n=1 female, 2 males).[2] The test was conducted in accordance with OECD Guideline 405. The damage to the cornea was irreversible over 21 days of observation. The primary irritation score was 4.3 out of 5. The ocular irritation/corrosion was observed at 24, 48, and 72 h. The untreated eyes served as the control.

Sodium benzotriazolyl butylphenol sulfonate (30%; composition of the remainding 70% of the test substance was not provided; 0.01 mL) caused irreversible ocular damage in a New Zealand White rabbit.[2] The test was conducted in accordance with OECD Guideline 405 and EU Method B.5. At administration, no signs of initial pain (class 1 on a 0-5 scale) were observed. Slight or mild corneal opacity, involving the whole cornea, was observed on day 1 and remained after 21 days. There were no iridial effects. Conjunctival effects consisted of slight or moderate redness for up to 4 days, slight or mild chemosis for up to 4 days, and a slight or moderate discharge for up to 7 days. Additional signs of irritation consisted of lachrymatory, mucoid and Harderian discharge, irregular corneal surface and raised corneal opacity, erythema, edema, thickening and convolution of the eyelids, dried secretion around the periorbital skin, and neovascularization. Irritation was still apparent 21 days after instillation and there was little evidence of recovery. No further rabbits were tested because of the severity of these results.

Sensitization

Dermal – Non-Human

Sodium benzotriazolyl butylphenol sulfonate (0, 3%, 10%, or 30% w/v; 25 µL in propylene glycol) was not found to be a potential dermal sensitizer in a mouse local lymph node assay (LLNA) using male CBA/Ca/Ola/Hsd mice (n=4).[2] The test was conducted in accordance with OECD Guideline 429. The Stimulation Indices were 0.78, 0.57, and 2.06 for the concentrations of 3%, 10%, and 30%, respectively. Hexyl cinnamic aldehyde (1%, 3%, and 10%) was the positive control and gave the expected results.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 25% dermal induction) was not a dermal sensitizer in a guinea pig maximization test using Dunkin-Hartley guinea pigs (n=10/sex; control=5/sex) when challenged and re-challenged at 25%.[2] The test was conducted in accordance with OECD Guideline 406. Edema, erythema, and necrosis were similar in both the control and test groups. Edema, erythema, and necrosis were observed after the first challenge in 3 and 2 guinea pigs at 24 and 48 h, respectively. When challenged the second time, positive reactions were observed in 2 and 1 guinea pigs at 24 and 48 h, respectively. The intradermal induction was performed at 5% in physiological saline and in an emulsion of Freund's Complete Adjuvant (FCA)/physiological saline. The dermal induction patch was conducted under occlusion with the test substance at 25% in physiological saline. Two weeks after induction, the challenge was conducted by dermal administration of the test material at 25% in physiological saline under occlusive dressing for approximately 24 h. A second challenge was performed 2 weeks after the first challenge. The guinea pigs were observed at 24 and 48 h after each dermal administration.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 50% dermal induction) was not a dermal sensitizer in a guinea pig maximization test using female Ibm: GOHI, SPF-quality guinea pigs (n=20; control=10) when challenged at 10%.[2] The test was conducted in accordance with OECD Guideline 406. There was no erythema or edema formation observed at 24 and 48 h after removal of the induction patch in either the control or test group. The intradermal induction was performed with a 5% dilution of the test article in distilled water and in an emulsion of FCA/physiological saline. The dermal induction was conducted under occlusion with the test article at 50% in distilled water for approximately 24 h. Two weeks after induction, the challenge was completed by dermal administration of the test material at a concentration of 10% in distilled water under occlusion. The control group was exposed to distilled water and FCA/physiological saline during the induction phase and challenged in the same manner as that of the test group.

Photosensitization and Phototoxicity

Sodium benzotriazolyl butylphenol sulfonate (0, 10%, 15%, 25%, or 30% in distilled water; 0.025 mL/2 cm^2) was not phototoxic when the test article was administered dermally to the shaved skin of anesthetized Dunkin-Hartley guinea pigs (n=10; control=5) for 30 min and the test site then exposed to UVA (20 J/cm^2; exposure time not specified).[2] On the irradiated flanks, 1 guinea pig in each of the 30% and the 25% groups exhibited erythema at 24 h, which was resolved at 48 h. On the non-irradiated flank, 2 guinea pigs in the 30% group and 1 in the 25% group exhibited erythema, which was resolved at 48 h. All concentrations of the test substance were administered to both flanks of the guinea pigs, and the irradiation was administered only to the left flank. The test sites were pretreated with DMSO (2% in ethanol; 0.025 mL/2 cm^2) to enhance the dermal penetration of the test substance. The test was conducted 30 min later. The guinea pigs were observed for 72 h.

In an acute dermal phototoxicity dose-response test using female albino Dunkin-Hartley guinea pigs (n=20; control=10), sodium benzotriazolyl butylphenol sulfonate (30%; 0.1 mL in bi-distilled water) was not photosensitizing when challenged at 1%, 5%, 10% and 15% (0.025 mL/2 cm^2).[2] No signs of toxicity were evident in the guinea pigs of the control or test group. Induction was accomplished through epicutaneous injections of sodium benzotriazolyl butylphenol sulfonate

(30%) to an 8 cm^2 area of shaved skin (marked previously with 4 intradermal injections of FCA/physiological saline). The test sites were then exposed to 1.8 J/cm^2 UVB and 10 J/cm^2 UVA irradiation 4 times over the 2 weeks of the induction phase. Control animals were intradermally injected with FCA/physiological saline only. The challenge was performed 3 weeks after the beginning of the induction period. The test sites on both flanks were treated epicutaneously with the test material at concentrations of 1%, 5%, 10%, and 15%. The treated sites were then either exposed to 10 J/cm^2 UVA irradiation (left flank) or remained unirradiated (right flank). Erythema and edema formation were evaluated at 24, 48 and 72 h after the challenge exposure.

SUMMARY

This is a safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. This ingredient is reported to function as a light stabilizer in cosmetics.

Sodium benzotriazolyl butylphenol sulfonate was reported to be used in a total of 473 cosmetic formulations, consisting of 67 leave-on cosmetic products, 377 rinse-off products, and 29 products diluted for the bath. This ingredient is used at concentrations up to 0.64% in leave-on products (skin fresheners), 0.1% in rinse-off products, and 0.033% in bubble baths.

There was minimal dermal penetration by sodium benzotriazolyl butylphenol sulfonate in in vitro assays using human skin.

In rats, the dermal LD_{50} of sodium benzotriazolyl butylphenol sulfonate was >2000 mg/kg and the oral LD_{50} was >5000 mg/kg. The oral NOAEL for sodium benzotriazolyl butylphenol sulfonate was 200 mg/kg/d for rats when administered over 28 days.

The oral NOAEL for reproduction and development for rats was 800 mg/kg/d sodium benzotriazolyl butylphenol sulfonate. The oral NOAEL for parental toxicity was 200 mg/kg.

In a bacterial reverse mutation assay using *S. typhimurium*, sodium benzotriazolyl butylphenol sulfonate was not mutagenic up to 5000 µg/plate with and without metabolic activation. In a mammalian chromosomal aberration assay using V79 fibroblasts, sodium benzotriazolyl butylphenol sulfonate was mutagenic with metabolic activation at 130 (but not at 120 µg/plate) and at 110 µg/plate (but not at 80 µg/plate) without metabolic activation. In a mammalian cell gene mutation assay using V79 fibroblasts, sodium benzotriazolyl butylphenol sulfonate was not mutagenic up to 80 µg/plate with and without metabolic activation; it was cytotoxic at 100 µg/plate. In a mammalian erythrocyte micronucleus assay, sodium benzotriazolyl butylphenol sulfonate at 3000 mg/kg was not genotoxic to mice when administered by gavage. In an unscheduled DNA synthesis assay, up to 1000 mg/kg sodium benzotriazolyl butylphenol sulfonate was not genotoxic to rats when administered by gavage.

Sodium benzotriazolyl butylphenol sulfonate at 100% was not dermally irritating to rabbit skin. In a study in rats, erythema was observed at 4%, which resolved by day 8.

Sodium benzotriazolyl butylphenol sulfonate, at concentrations up to 30% w/v, was not a potential dermal sensitizer in an LLNA.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 25% dermal induction) was not found to be a dermal sensitizer in a guinea pig maximization test when challenged and re-challenged at 25%. Edema, erythema, and necrosis were observed after the first challenge in 3 and 2 guinea pigs at 24 and 48 h, respectively. When challenged the second time, positive reactions were observed in 2 and 1 guinea pigs at 24 and 48 h, respectively. These results were similar to the control group. In another test, sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 50% dermal induction) was not a dermal sensitizer in a guinea pig maximization test when challenged at 10%.

Sodium benzotriazolyl butylphenol sulfonate at 30% and 100% was an ocular irritant and caused irreversible eye damage to the cornea in 1 of 3 rabbits and the single rabbit tested, respectively, when administered to the conjuctival sac of rabbits.

Sodium benzotriazolyl butylphenol sulfonate at 30% was not phototoxic or photosensitizing when dermally administered to the shaved skin of guinea pigs for 30 min, and the test site was then exposed to UVA.

DISCUSSION

The majority of the data in this safety assessment were from robust summaries found in the ECHA database. The Panel determined that data from these summaries was applicable for use in reviewing the ingredient in this report.

The Panel expressed concern about studies that indicated the potential for ocular irritation. However, the Panel noted that the test concentrations that resulted in ocular damage were much greater than the concentrations reported to be used in cosmetics including those that are used on the face, thus possibly near the eyes.

Studies showed no evidence of systemic toxicity and negative sensitization studies were at concentrations well above the reported concentrations of use. Although there were no carcinogenicity studies available for this ingredient, the Panel determined that the lack of systemic toxicity, the negative in vivo genotoxicity data, and lack of dermal penetration indicated that carcinogenicity was not a concern.

The limited impurity data was noted. The Panel was concluded that the manufacturing process would minimize any impurities in the source material. Also, the low concentration of use and the lack of genotoxicity at high concentrations assured the Panel that impurities were not a concern.

The Panel discussed the issue of incidental inhalation exposure from sodium benzotriazolyl butylphenol sulfonate in fragrance preparations up to 0.1% and spray body and hand product(s) up to 0.05%. There were no inhalation toxicity data available. The Panel noted that 95%-99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel noted the lack of systemic toxicity in single- and repeated-dose oral exposure studies, little or no irritation or sensitization in tests of dermal exposure, the absence of genotoxicity in an Ames tests, and a mammalian cell gene mutation assay as well as mammalian erythrocyte micronucleus assay and an unscheduled DNA synthesis assay. This ingredient did not penetrate cadaver skin. In addition, this ingredient is insoluble in water, and has a low estimated vapor pressure value of 6.06×10^{-18} Pa which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that sodium benzotriazolyl butylphenol sulfonate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical and physical properties of Sodium Benzotriazolyl Butylphenol Sulfonate.

Property	Value	Reference
Physical Form	Solid; powder Fine powder	[2] [15]
Color	Light-beige Light-beige/white	[2] [15]
Odor	Trace characteristic odor	[15]
Molecular Weight	369.37	[16]
Density/Specific Gravity @ 22°C	1.39	[2]
Vapor pressure (mmHg) @ 25°C	< 0.000000001	[2]
Melting Point (°C)	Decomposes before melting at >170 138-141	[2] [4]
Water Solubility (g/L) @ 20°C & pH 6 @ 20°C	9.8 1.0	[2] [4]
Other solubility (g/L) @ 20°C		[4]
PEG-7 glyceryl cocoate	4.10	
Propylene glycol	2.20	
Sodium laureth sulfate	0.90	
Cocamido propyl betaine	0.80	
Ethanol	0.40	
2-Propanol	0.30	
log K_{ow}	-0.55 est.	[16]
logP_{ow} @ 25°C & pH 6.1	-0.24	[2]
Acid dissociation constants (pKa) @ 25°C	7.93	[2]
UV Absorption (λ) nm	290, 335	[4]

Table 2. Frequency of use according to duration and exposure of sodium benzotriazolyl butylphenol sulfonate.[7,8]

Use type	Uses	Maximum Concentration (%)
Total/range	**473**	**0.0033-0.64**
Duration of use		
Leave-on	67	0.033-0.64
Rinse-off	377	0.0033-0.1
Diluted for (bath) use	29	0.033
Exposure type[a]		
Eye area	NR	NR
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	36; 19[b]; 7[d]	0.05-0.1[e] 0.035-0.64[b]
Incidental inhalation-powders	1[c];7[d]	0.033-0.09[c]
Dermal contact	392	0.0033-0.64
Deodorant (underarm)	NR	NR
Hair-noncoloring	18	NR
Hair-coloring	62	NR
Nail	1	0.17
Mucous Membrane	311	0.033-0.035
Baby	1	NR

NR=Not Reported; Totals=Rinse-off + Leave-on + Diluted Product Uses.

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

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

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

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

[e] Body and hand spray product 0.05%; perfumes 0.05%-0.1%.

REFERENCES

1. Nikitakis, J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 *ed*. Washington, DC: Personal Care Products Council, 2014.

2. European Chemicals Agency. Sodium 3-(2*H*-benzotriazol-2-yl)-5-*sec*-butyl-4-hydroxybenzenesulfonate. http://echa.europa.eu/.

3. Schaller, C, Rogez, D, and Braig, A. Organic vs inorganic light stabilizers for waterborne clear coats: a fair comparison. *Journal of Coatings Technology and Research*. 2012;9(4):433-441.

4. BASF. 2012. Technical information: Light stabilizers Tinogard ® HS Sodium Benzotriazolyl Butylphenol Sulfonate. Unpublished data submitted by Personal Care Products Council.

5. Rosevear, J and Wilshire, JFK. Preparation of some 2-("*H*-benxotriazol-2'-yl)phenol ultraviolet absorbers: Application of the transalkylation reaction. *Austrailian Journal of Chemistry*. 1985;38:1163-1176.

6. Burdeska, K and Göttel, OR; inventor. Process for the preparation of 3-[2'H-benzotriazol-(2')-yl]-4-hydroxybenzenesulfonic acids and the salts thereof. United States 4,937,349. 1990.

7. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2014. Washington, DC: FDA.

8. Personal Care Products Council. 4-18-2014. Concentration of Use Information for Sodium Benzotriazolyl Butylphenol Sulfonate. Unpublished data submitted by Personal Care Products Council.

9. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

10. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.

11. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.

12. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 8-28-2011;205(2):97-104.

13. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/consumers/cosmetics/cosing/. Date Accessed 1-14-0015.

14. Jones, DC, Carr, CM, Cooke, WD, and Lewis, DM. Investigating the photo-oxidation of wool using FT-Raman and FT-IR spectroscopies. *Textile Research Journal*. 1998;68(10):739-748.

15. BASF. 2010. Product specification Tinogard ® HS Sodium Benzotriazolyl Butylphenol Sulfonate. Unpublished data submitted by Personal Care Products Council.

16. The Good Scents Company. EPI Summary. http://www.thegoodscentscompany.com/episys/ep1064231.html. Date Accessed 3-28-2014.

Personal Care Products Council
Committed to Safety, Quality & Innovation

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: January 9, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Sodium Benzotriazolyl Butylphenol Sulfonate as Used in Cosmetics

Key Issue

In the Discussion, please delete the following sentence: "Additionally, there were no reported uses of products containing sodium benzotriazolyl butylphenol sulfonate that are specified for used around the eyes." Although Sodium Benzotriazolyl Butylphenol Sulfonate was not reported to be used in eye area products, it was reported to be used in face products which may be used near the eyes. In addition, this sentence implies that the CIR Expert Panel thought that at the use concentrations reported, Sodium Benzotriazolyl Butylphenol Sulfonate should not be used in products near the eyes. Based on the low maximum use concentrations (up to 0.64%) compared to the concentrations tested in eye irritation studies (30%), the CIR Expert Panel was not concerned with the potential for eye irritation.

The Discussion still needs to address Rachel Weintraub's concern about the lack of carcinogenicity data (based on low use concentrations, limited absorption, lack of systemic toxicity and negative *in vivo* genotoxicity data, the CIR Expert Panel did not think a carcinogenicity study was necessary).

Additional Comments

Introduction - Please explain what is meant by the function light stabilizer the first time it is mentioned. The Dictionary says that light stabilizers "protect the product from chemical or physical deterioration induced by light".

Physical and Chemical Properties - Chemical and physical properties are presented in Table 1, not Table 2 as currently stated in the text.

Cosmetic Use - Please revise: "311 products are exposed to mucus membranes". It is not known for sure if all of the products include mucous membrane exposure. There may be hand wash products included among the FDA product categories in this exposure category. It

would be better to state: “311 products are in product categories with the potential for mucus membrane exposure.”

As there is only one ingredient in this report, please revise: “These ingredients are reportedly used at concentrations up to 0.1%.”

Absorption, Distribution, Metabolism and Excretion, Overview - Please delete “is likely” after “excreted in both urine and bile” in the second last sentence of this section.

Dermal/Percutaneous - Please correct “penetration of cadaver skin” to “penetration into cadaver skin”

Single Dose Exposure, Oral-Non-Human - What is meant by “dark red focus”? (focus should probably be foci)

Summary - Please indicate that the *in vitro* dermal penetration studies were done in human skin.

Discussion - Please be more specific when describing the completed studies. “Multiple studies” suggests many studies were completed. There are only 3 repeat dose studies described in this report.

As there is only one ingredient in this report “these ingredients” and “the ingredients are” need to be revised.

Droplet size of spray products is determined by the packaging. Therefore, the statement that “particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate...” does not make sense.

The last paragraph should note that Sodium Benzotriazolyl Butylphenol Sulfonate did not penetrate cadaver skin. Please delete “is not a small molecule”. The molecular weight is about 369 which is not a molecular weight that prevents penetration through membranes. In this case, charge and solubility appear to be more important in preventing this ingredient from penetrating membranes.

Table 2 - The source of the two 0.035% values in the Incidental inhalation-spray row is not clear. Use information from the Council included a 0.035% concentration in bath soaps and detergents, body and hand products - not spray and indoor tanning preparations. Only the value for indoor tanning preparations is appropriate for this row. It appears that the top 0.035-0.1% values should be 0.05-0.1% which was the range of concentrations reported for perfume.

There was no 0.5% use concentration included in the concentration of Use table from the Council. Therefore, the 0.033-0.5% concentration in the Incidental inhalation - powders row is not correct.