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Benzyl Alcohol, Benzoic Acid, and its Salts and Ester

CIR EXPERT PANEL MEETING

SEPTEMBER 26-27, 2011

Cosmetic Ingredient Review
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September 1, 2011

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Manager/Lead Specialist

Subject: Draft Amended Final Report on Benzyl Alcohol, Benzoic Acid, and its Salts and Benzyl Benzoate

At the June 27-28, 2011 Expert Panel meeting, the Panel issued a tentative amended final report with a conclusion stating that benzyl alcohol, benzoic acid and its salts, and benzyl benzoate are safe in the present practices of use and concentration. Comments were received during the 60-day comment period following announcement of this report, and the report was revised to include pertinent comments.

A copy of the draft amended final report on these ingredients is included along with the following: CIR report history, Minutes from the June 2011 Panel meeting, Literature search strategy, Data profile, and the Council's technical comments on the tentative amended final report (pdf file).

We are seeking Panel input on the suggestion that the abstract should mention dermal irritation and sensitization data, e.g., current use concentrations of these ingredients are below concentrations that may result in dermal irritation or sensitization. We have been keeping abstracts with a safe as used conclusion to a bare minimum, so this would be a departure.

Also, the Council has suggested that the discussion should note that, as stated in the Toxicokinetics section, these ingredients are metabolized and excreted via a common pathway. Therefore, the data on Benzyl Alcohol are directly relevant to Benzoic Acid and its salts. It should also be noted that additional data are summarized in the original report.

If the Panel agrees, these would be editorial changes. After reviewing the draft amended final report to make certain that the discussion reflects the Panel's rationale, the Panel needs to issue an amended final report at this meeting.

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Benzyl Alcohol

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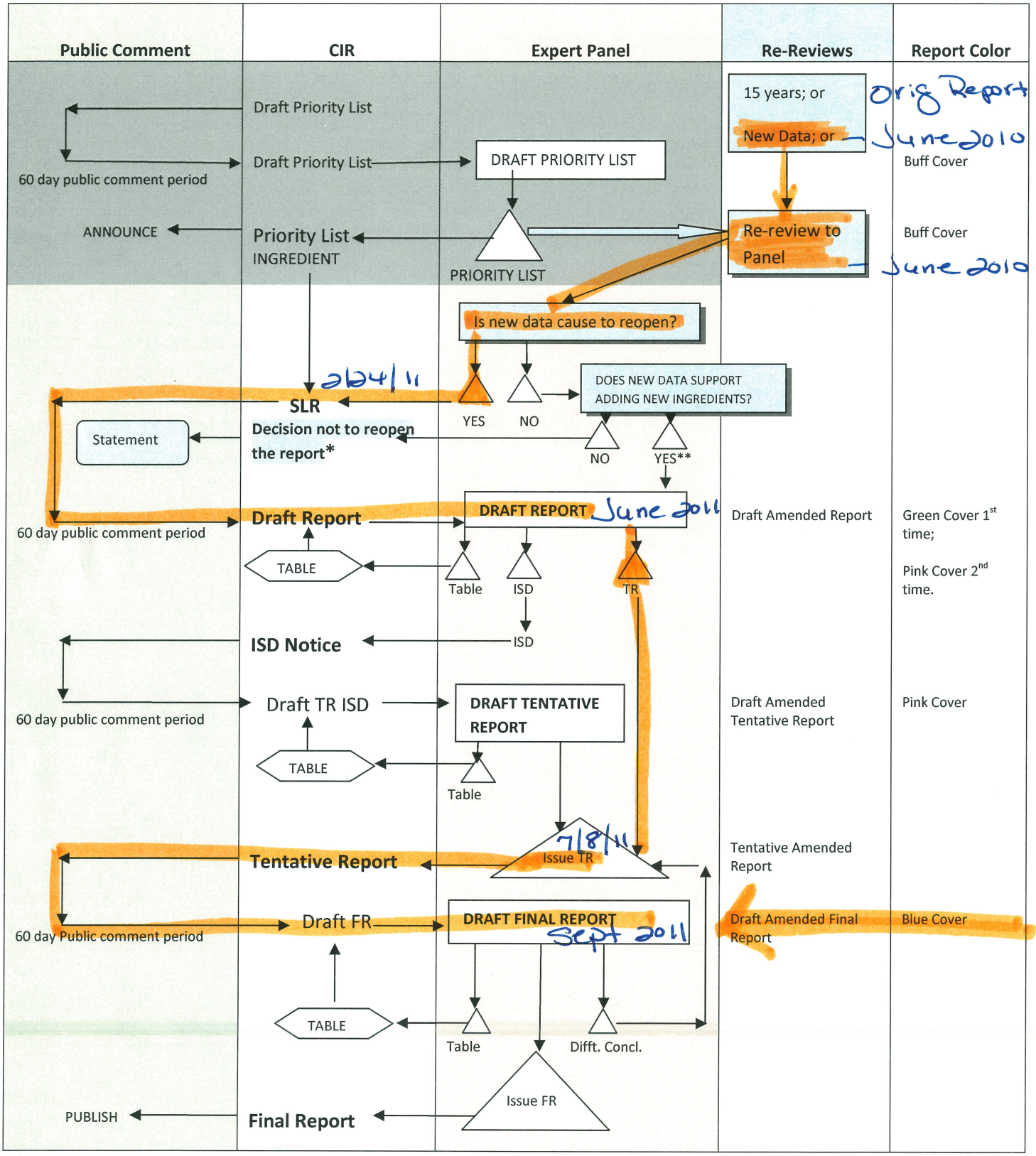
Sept 2011

SAFETY ASSESSMENT FLOW CHART



*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.

Expert Panel Decision

Document for Panel Review

Option for Re-review

CIR History of:

Benzyl Alcohol, Benzoic Acid, and its Salts and Benzyl Benzoate

In 1998, the CIR Expert Panel issued a final safety assessment of Benzyl Alcohol, Benzoic Acid and Sodium Benzoate, concluding that they are safe for use in cosmetics up to 5%, but that the data are insufficient to support the safety of these ingredients in which the primary route of exposure is inhalation. The report was published in 2001.

In June, 2010, the Expert panel reviewed new data provided by the Council on the safety of benzyl alcohol and benzoic acid for inhalation use. The Panel decided to reopen its review of this report to consider the new data.

New Data Review, Belsito and Marks Teams/Panel: June 28-29, 2010

The Council provided data in response to the insufficient data determination on the inhalation use of benzyl alcohol, benzoic acid and sodium benzoate. The Personal Care Products Council provided a 4-week inhalation toxicity study (rats) of aerosolized benzyl alcohol and benzoic acid. After reviewing this study, the Expert Panel determined that the final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate should be reopened to amend the original conclusion. Furthermore, the Panel determined that data available in the original safety assessment, with the addition of the new inhalation toxicity data, were likely sufficient to support the safety of other simple salts of benzoic acid (calcium, magnesium, and potassium benzoate) and the benzyl benzoate ester. Thus, it was agreed that the safety of these ingredients and those reviewed in the original final report would be reviewed in the SLR that will be developed.

SLR in February, 2011

The availability of a scientific literature review (SLR) on this group of ingredients was announced on February 24, 2011. Technical comments and use concentration data from the Council were received during the 60-day comment period.

Draft Report, Belsito and Marks Teams/Panel: June 27-28, 2011

Technical comments on the SLR and use concentration data, received from the Council during the 60-day comment period have been added to the draft report. The draft report also contains an inhalation toxicity study on benzyl alcohol and benzoic acid and studies from a RIFM synopsis of data on benzyl benzoate that were received in 2010.

The Expert Panel concluded that the newly available inhalation toxicity data and the safety test data already available support the safety of benzyl alcohol, benzoic acid, calcium benzoate, magnesium benzoate, potassium benzoate, sodium benzoate, and benzyl benzoate, and agreed that a tentative amended safety assessment with the conclusion that these 7 ingredients are safe in the present practices of use and concentration should be issued.

The Expert Panel discussed the finding of adenomas of the adrenal cortex of B6C3F1 mice receiving a high dose of benzyl alcohol in an oral carcinogenicity study. Such tumors were considered benign and benzyl alcohol was not considered carcinogenic. In earlier safety assessments, a 5% concentration limit for benzyl alcohol, benzoic acid, and sodium benzoate and a 10% concentration limit for benzyl alcohol in hair dyes were established. Currently available information demonstrates that the present practices of use and concentration of these ingredients are below those levels and that the limits are no longer needed. The Expert Panel did note the presence of benzene as an impurity due to photo-degradation of benzoic acid, but at current use concentrations, the levels of benzene in cosmetic products would be negligible.

Draft Amended Final Report, Belsito and Marks Teams/Panel: September 26-27, 2011

Technical comments on the tentative amended final report, from the Personal Care Products Council, were received during the 60-day comment period. The document was revised to include pertinent comments.

Literature Search on Benzyl Alcohol and Related Ingredients*

Ingre-dients	Toxline &PubMed	ChemIDplus	Multidatabase (See legend*)	DART	Household Products	Beilstein	Registry	Kosmet	Napralert	RTECS	CAplus
BZA	1098 (1997 to 2011)	1	5	44 (1997 to 2011)	1	1	1	5	341	674	1534
BA	1610 (1997 to 2011)	1	6	293 (1997 to 2011)	1	4	1	19	1263	3830	3648
SB	226 1997 to 2011)	1	4	21	1	2	1	0	5	13	643
CB	6	1	0	0	0	1	1	0	0	1	26
MB	0	1	0	0	0	1	1	0	0	1	12
PB	23	1	1	0	0	1	1	0	1	0	58
BB	331	1	1	11 (1997 to 2011)	1	1	1	1	117	31	227

*Data in Table: Total no. publications in search; Multidatabase = HSDB, CCRIS, ITER, IRIS, Gene-Tox, and LacMed;

Searches Performed on 7/9 and 12/2010, and 3/2011 (1 chemical name and 1 CAS No.; Toxline added additional chemical names to search term); Any limitations on years searched indicated. Website list also searched. Searches updated on 8/3/2011 using PubMed and Toxline.

Ingredients

(BZA) Benzyl Alcohol OR 100-51-6

(BA) Benzoic Acid OR 65-85-0

(SB) Sodium Benzoate OR 532-32-1

(CB) Calcium Benzoate OR 2090-05-3

(MB) Magnesium Benzoate OR 553-70-8

(PB) Potassium Benzoate OR 582-25-2

(BB) Benzyl Benzoate OR 120-51-4

Benzyl Alcohol OR 100-51-6 OR Benzoic Acid OR 65-85-0 OR Sodium Benzoate OR 532-32-1 OR Calcium Benzoate OR 2090-05-3 OR Magnesium Benzoate OR 553-70-8 OR Potassium Benzoate OR 582-25-2 OR Benzyl Benzoate OR 120-51-4

Benzyl Alcohol Group Check List for September, 2011. Writer – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Benzyl alcohol	X		X	X		X	X	X			X	X	X	X	X	X	X	X	X	
Benzoic acid	X		X	X		X	X	X			X	X	X	X	X	X	X	X	X	
Sodium benzoate			X	X		X		X				X	X		X	X	X	X	X	
Calcium benzoate																				
Magnesium benzoate																				
Potassium benzoate			X	X		X		X				X					X	X		
Benzyl benzoate	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X		X

Transcripts

Day of the June 27-28, 2011 CIR Expert Panel Meeting – Dr. Belsito's Team

Benzyl Alcohol, Benzoic Acid, and its Salts and Ester

Dr. Belsito: Benzoic acid. So we agreed to reopen the report because we had data on inhalation. And2 then we included in addition to the original three, calcium, benzoic, magnesium, potassium, and sodium benzoate to the list. My comment here was that there seem to be new data or data that I didn't see before about if you package it in such a way that there is UV exposure to the product that then benzene is formulated or is formed in the product itself. And so the question I have is it's okay, but do we need to specify UV packaging for the products or is the concentration of these ingredients and the potential -- therefore potential formation of benzene so low that it really doesn't matter? Regardless of how we approach this I think we need to say something in1 the discussion about that since it's part of the document.
DR. LIEBLER: I agree. I just don't know -- I don't have a suggestion on how to do that. I guess you put in the discussion?
DR. BERGFELD: That's a good place.
DR. LIEBLER: That's what I would suggest.
DR. BELSITO: Then how do
DR. BERGFELD: There is no discussion
here, so you'd have to add that.
DR. LIEBLER: Right.
DR. BELSITO: Right.
DR. LIEBLER: In other words, as the
discussion is formulated that can be referred to there. I'm looking for the -- this is under the
chemistry section. Yeah, this would be Panel page 8, 9, and 10.
SPEAKER: (inaudible) and benzoic acid.
DR. LIEBLER: Yeah, I mean, the benzene production from benzoic acid in the presence of a hydroxyl radical generating system has been demonstrated. True and unrelated, in my opinion.
I mean, I don't think that's relevant to the circumstances that these compounds would be in. And you're basically adding, you know, a metal catalyzed hydroxyl radical generating system. Of course you can get some detectable benzene out of that, but that's not going to be the circumstance that you'd be dealing with in a product formulation that contains benzoic acid.
DR. BELSITO: So you think that there is no potential for a -- that a cosmetic product would be formulated such that this would be an issue?
DR. LIEBLER: Not based on that reference. Not based on that scenario. The other scenario is the issue of UV stabilized and non-UV stabilized packaging. This is a more realistic scenario, I think, where you do have the ingredient, it may be exposed to light. And then the question is benzene can be detected, does that pose a hazard or a risk? And I would say probably not based on the levels that would be produced; they're very low. That could be -- this study, which is the top of page -- I've got the Panel Book -- 10, top of Panel Book 10 -- top of page 10 in the Panel Book, that could be referenced in the discussion.
DR. SNYDER: Well, under Impurities we did -- it's mentioned that it's always less than one part per billion, so.
DR. LIEBLER: Right.
DR. BELSITO: Okay. So, again, but I think it bears --
DR. LIEBLER: Just mentioning, yeah.
DR. BELSITO: -- mentioning, okay.
DR. LIEBLER: Not really a safety issue.
MR. JOHNSON: Excuse me, Dr. Liebler,
specifically what do you want mentioned regarding that first paragraph.
DR. BELSITO: Just that photodegradation of benzoic acid has been reported to result under whatever circumstances in the release of benzene. However, as used in cosmetic products this would be highly unlikely. In addition, the levels of benzoic acid that are being used in cosmetic products are such that the amount of benzene that could potentially be liberated is negligible. Is that pretty much what you're saying?
DR. LIEBLER: Yeah, basically, right.
DR. BELSITO: But just there needs to be something in the discussion to note -- that indicates that we noted this issue of potential photodegradation, we dealt with it, and we felt that it was a non-issue for cosmetics. DR. LIEBLER: Wilbur, it's the stuff that's referred to under Reference 18. And on the top of page 10 it refers to, you know, UV -- intense UV light increasing benzene levels by as much as 53 percent in model solutions. Now that

sounds big, but actually 53 percent increase in a very small number is still a very small number. So, you know, there's not enough information here to, I think, raise any real concern. And down at the bottom of the paragraph you do say about another survey that the levels were (inaudible) formulated beverage tested were shown to contain less than 1. nanogram per gram. That's very low. If you do cite the Reference 18 where the model system is used and it showed benzene levels going up by 53 percent it'd be good to just mention what the absolute amount was in that study, so that we could see that that -- it was indeed a low number.

DR. BELSITO: Any other issues on the generation of benzene? Does the Cosmetic Ingredient Dictionary really state that these ingredients may function as pesticides in cosmetics?

DR. EISENMANN: Probably (inaudible).

DR. BELSITO: Okay. I mean, I just -- I've never seen that.

DR. EISENMANN: It's an international --

DR. SNYDER: (inaudible) microbial.

DR. BELSITO: What?

DR. EISENMANN: It's an international dictionary, so sometimes things get in from other jurisdictions that seem strange to us.

DR. BELSITO: Okay. And then this is, I guess, a generic question in a sense. The Personal Care Product Council may have provided us with a copy of the inhalation toxicity data, but that was actually performed by RIFM. So in your first -- or third paragraph you say, "In response to the need for inhalation toxicity data the Personal Care Product Council provided a four-week inhalation toxicity study."

DR. EISENMANN: Actually it was joint study from -- we helped pay for it, but RIFM monitored the study and placed it.

DR. BELSITO: Okay, fine.

DR. EISENMANN: But it was a joint study.

DR. BELSITO: Okay. I didn't realize that. And then you go on in that sentence, "and the results of the study were discussed at this panel meeting." I don't think that needs to be part of the report. There's a lot of editorial stuff here that I did, but then in that report there was a large number of references to studies -- patch test studies, provocative use, RIPT studies -- that were referenced by the people who did them. And in your summary, Wilbur, you referenced the report that Carol or PCPC provided you. I don't think that's the appropriate way to reference all of those patch test studies. It's a secondary reference. Quite honestly, I think you need to go back and reference the actual studies that were referenced in that report of which there 2 are a large number. Because it made it very 2 difficult for me when I was reviewing Table 5, I know you like to quote the -- what they said, but if you go to page 25 of the report, CIR Panel Book page 32, just a couple of issues. 4 One, the benzyl benzoate in a maximization test was not a provocative test treatment. That was -- that actually is under the wrong label. That's a maximization test as a predictive test, so it needs to be moved under Predictive Tests. But throughout all the provocative test treatments you keep saying, "sensitization rate of." As a dermatologist who does this what that means to me is that in the course of patch testing these people you sensitized.3 percent of them, and that's not what these studies are reporting. They're reporting positive reactions in.3. So I stopped changing it, but under all of the provocative test treatments instead of using the word "sensitization" it gets boring, but ".3 percent of patients tested positive" or "had responses that 2 were determined to be allergic" or however you 2 want to phrase it. But when you use the term "sensitization" it typically means you have induced an allergy that didn't exist before, and that's not the case with a provocative test. Okay. And again, you use a lot of the Reference 18 or whatever that RIFM study was rather than the actual true references, so you're going to have to go in and expand, I think, that reference list.

MR. JOHNSON: Dr. Belsito, I know in some cases the primary references are unpublished data. So in the event that it's not, you know, a typical (inaudible) --

DR. BELSITO: Where it's unpublished, you know, for instance, I mean, RIFM has a lot of HRIPT data that has not been published and it would be appropriate to put it under 58. But when I started checking some of the references actually they were studies that had been done in Japan, they were studies that had been done in -- by Walt Larson and other people that were referenced to 2 the conjoint RIFM-PCPC report when actually they were studies that had been done that were included in that report. I mean, if you go back to the report, which is in the back of a page here someplace you'll see what I'm talking about.

DR. EISENMANN: Dr. Belsito, to clarify,

I mistook the synopsis of data of benzyl benzoate. That is RIFM. The inhalation study was joint.

DR. BELSITO: Okay.

DR. EISENMANN: Okay.

DR. BELSITO: Okay. So then the synopsis on benzyl benzoate, I mean, there's -- I don't know where it is in the data here, I think it was towards the end of the book, but you'll see that there are -- it's Cosmetic Ingredient Review. Okay. Yeah, so under the benzyl benzoate that was from RIFM?
DR. EISENMANN: Yes, it was (inaudible).
DR. BELSITO: Okay. So you'll see that there are a whole slew of references that just seem to -- you just reference the RIFM report 2 rather than referencing the primary authors of 2 those studies.
MR. JOHNSON: That's just for Table 5?
DR. BELSITO: Yeah, Table 5 for the dermal irritation. So basically the RIFM Reference 58, what you need to do, Wilbur, is everything that you referenced as 58, which has got Research Institute for Fragrance Material, you need to go back and actually find what reference they used to quote that rather than the 58.
MR. JOHNSON: Sure, okay.
DR. BELSITO: Paul, you had some comments?
DR. SNYDER: A few editorial ones, but the one was on page 6 under benzyl alcohol and benzyl benzoate, octanol-water partition coefficient.
1 MR. JOHNSON: Which page?
DR. SNYDER: Page 6 of the report, Panel Book page 13, under benzyl alcohol, benzyl benzoate, you've got an octanol-water partition coefficient there of 9,333. The last sentence of 2 that first paragraph, the 7.4 and 9,333.
DR. LIEBLER: Take the log.
DR. BELSITO: And then, Wilbur, on page 1 --
MR. JOHNSON: Panel Book 11.
DR. BELSITO: Panel Book 18, page 11, under the synopsis of irritation and sensitization.
MR. JOHNSON: Yes.
DR. BELSITO: You say fourth line down, "was classified as a non-sensitizer at 5 percent and a weak sensitizer at percent." I think you mean 10 percent.
MR. JOHNSON: Okay.
DR. BELSITO: And then the next header under Benzyl Alcohol Benzoic Acid, the third line towards the end it says, "In the same report benzoic did not induce." Is that benzoic acid or benzoic alcohol?
MR. JOHNSON: Are you in the same paragraph?
DR. BELSITO: Under -- no, no, no, under-- no. Your first paragraph below the italicized Benzyl Alcohol Benzoic Acid, that one.
MR. JOHNSON: Yes, uh-huh.
DR. BELSITO: Okay. Third line.
MR. JOHNSON: Okay.
DR. BELSITO: Go to the end, fourth word in from the end, "benzoic." Acid or alcohol? You see what I'm talking about?
MR. JOHNSON: Okay, yeah, "In the same report benzoic," okay.
DR. BELSITO: Right.
MR. JOHNSON: I'll check that.
DR. BELSITO: Paul, I'm sorry, I cut you off. You had some other comments?
DR. SNYDER: No. He'll pick them up in the report.
DR. LIEBLER: One comment from me, the title. Why not just replace "ester" with "benzyl benzoate" since there's only one ester we're considering?
DR. BRONAUGH: I had a comment, Paul, that octanol-water partition coefficient of 9,000and something, that's what we calculated. It's not the log. That's the actual octanol-water partition coefficient. The log would be like 10 to the 3 or something like that.
DR. SNYDER: Okay. It just kind of struck me (inaudible).
DR. BRONAUGH: Yeah. We did that a long time ago and we just didn't -- it just seemed like the way to go then, but now we do the logarithm.
DR. SNYDER: Okay. Thanks for clarifying that.
MR. JOHNSON: So I probably should indicate that that isn't the logarithm, but it's the actual --
DR. BRONAUGH: It's the actual partition coefficient.
MR. JOHNSON: Partition coefficient, right.
DR. LIEBLER: Could take the log of it and just report that if people are more familiar with seeing that --
SPEAKER: That's what we typically report.
DR. LIEBLER: -- I would do that.

DR. BRONAUGH: Yeah, that would be good.
DR. KLAASSEN: Bob did that before logs were invented.
(Laughter)
DR. BELSITO: Ouch. Table 5 again, Wilbur, Panel Book 30, page 23 of the report, benzyl benzoate. So the third time you talk about benzyl benzoate going down that column sort of towards the end of the middle, 40 percent? Your conclusion was non-sensitizer at 5 and 10 percent benzyl benzoate, mild sensitizer at 40 percent, 4 of 10 animals. Do you see what I'm talking about?
1 MR. JOHNSON: I'm trying to find it now. You're on page 33?
DR. BELSITO: No, page 23 of the report, page 30 of the Panel Book.
MR. JOHNSON: Okay.
DR. BELSITO: Okay. Scan down the list and when you get to benzyl benzoate it's the third mention of benzyl benzoate.
MR. JOHNSON: Okay.
DR. BELSITO: Okay. And your conclusion there was non-sensitizer at 5 and 10 percent, mild sensitizer at 40 percent. Do you see what I'm talking about?
MR. JOHNSON: Yes, mm-hmm.
DR. BELSITO: Okay. But the induction
was only done at 10 percent, so the sensitization would have been induced at 10 percent, but wasn't elicited unless you put 40 percent on the skin. So I'm not sure that that statement is correct unless the synopsis of what you said is not correct. So if they did induction at 10 and 40 percent, and then they were able to elicit only in the group that was induced at 40 percent, that is what you're saying in your summary. But under your test methods the induction was 10 percent, so it was inducing some -- DR. SNYDER: I think he's referring to a sensitization rate of 40 percent, 4 of 10 animals, afterwards.
DR. BELSITO: No. Mild sensitization at -- see, if you read it, the challenge concentrations were done up to 40 percent. So they sensitized with 10 percent and then they did various concentrations to try and elicit the sensitization. But if they elicited it at 40 percent, then the animals were sensitized. Some animals had low levels of sensitivity at 10 percent, I would think. I don't know. Next time you come around to doing that I'd like to see that study. Again, it's a 58 study and I got tired of trying to go through the RIFM report to figure out whether it was a RIFM study or whether it was published in the literature, but if we could try and get the details of that study. Because I think the next thing that we need to grapple with in this report is, I think, we probably -- I don't know, we haven't said that yet -- but we probably will remove the "insufficient for aerosol use," but we previously had put levels, restricted levels, on these compounds and leave-ons and wash-offs and are those levels still valid. So we gave a 5 2 percent limit for cosmetic formulations for all 2 ingredients and a 10 percent limit for benzyl alcohol in hair dyes. And that was based upon sensitization and irritation data that I think still holds, but.
DR. BERGFELD: I'm confused. So your conclusion is moving it to safe, taking the restricted concentrations off?
DR. BELSITO: No, I don't want to take the restricted concentrations off, but I want to make sure that, you know, we have everything -- you know, there is data that suggests, I think it's in the guinea pig, that 10 percent, at least in some animals, can sensitize and 5 percent was fine. So this is a little misleading in the sense that it would suggest in this study for benzyl benzoate -- I mean, there's only 10 animals -- that 10 percent was fine and 40 percent wasn't. Just trying to get all the facts straight, so.
DR. SNYDER: So essentially 10 percent for that one and 5 percent for all the rest.
DR. BELSITO: Yeah, I've got to go back 2 and look at how it's used. I don't think that -- 2 I mean, if -- we could also go "safe as used," depending upon what the concentrations are. Okay. So benzoic acid we have leave- ons to 1, wash-offs to 5. For benzyl alcohol we have leave-ons to 3, wash-offs to 10. For sodium benzoate it's 1 percent. For calcium benzoate it's negligible. For potassium benzoate -- for benzyl benzoate we have leave-ons to 4; we have wash-offs to 2. And for the others they're either negligible or not reported.
So quite honestly, "as used" is below our prior restrictions, so we could either keep the restrictions or go "safe as used," since none of the reported uses are exceeding the restrictions we had previously set for this group.
DR. LIEBLER: Safe as used.
DR. BELSITO: I mean, that would actually imply a lower restriction than we had given before. Curt? Paul?
DR. BERGFELD: Politically it looks better.
DR. BELSITO: To go safe as used?
DR. SNYDER: I agree.
DR. BELSITO: Okay. So then the document needs to be cleaned up a little bit and we're going to go as "safe as used," get rid of the prior use concentrations, and the discussion obviously probably needs to focus on why we now think the respiratory use is okay based upon the study that was provided to us.

DR. BERGFELD: Anything about the benzoate?
DR. BELSITO: Yes, we've already discussed that.
DR. BERGFELD: Okay.
DR. BELSITO: That needs to go in the discussion, the photodegradation and why we felt that was a non-issue. And maybe, Dan, you could craft some kind of language between now and tomorrow morning?
DR. LIEBLER: Okay.
DR. BELSITO: In terms of not the right circumstances in a cosmetic and even if it were, 2 it'd be negligible.
DR. LIEBLER: Right. I can.
MR. JOHNSON: Dr. Belsito, given the panel's published conclusion with limitations, should there be any explanation as to why those limitations are no longer valid?
DR. BELSITO: Sure. I mean, in a brief sentence the current use is below the level of restriction that we had previously given.

Day of the June 27-28, 201 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: Mm-hmm. Okay. Next is Green Book, benzoic acid, alcohol, salts, and esters. And these are in 88. Let me take a look at the notes in here. So June of last year -- so about a year ago -- the Panel reopened the safety assessment to expand the group. Those are listed, and I'll refer to page 37 with the chemical structures. So it's the alcohol, the acid, the benzoate, sodium benzoate, and then there are four more. We have a new document, and there was concern in the past about inhalation. Has that been resolved at this point? I'll ask you, Ron.
DR. HILL: Yes.
DR. MARKS: And is it okay to expand to
those four add-ons? So inhalation okay, Ron?
1 DR. HILL: It seems to be. The study was done at up to gram per cubic meter inhalation, and that was okay. It's used at 4 percent, and I don't know how to convert that to consumer using any of the ingredients. But it has to be in the close enough area, so I don't think inhalation is an issue. There was one other issue. EPA 2 considered benzyl alcohol as equivocal. Well, 2 they looked at adrenal cortex adenomas. I think this was in mice, and I think those are benign too this. But the EPA said this was equivocal evidence of carcinogenic activity, and NTP said no. I would go with the NTP interpretation that these are not in evidence for carcinogenic activity. That should be in the discussion. DR. MARKS: So the discussion will be the inhalation that is okay now.
DR. HILL: Yes.
DR. MARKS: Inhalation is okay. Obviously we need to address that since that was insufficient in a previous conclusion. NTP carcinogenicity addressed --
DR. HILL: Well, there was an NTP study, and the high-dose mice had adenomas of the adrenal cortex, which are benign tumors, are not cancers. EPA used that evidence as equivocal evidence for carcinogenicity and NTP said it is not.
DR. MARKS: Okay. So we addressed thatin the discussion.
DR. HILL: Just in the discussion.
DR. MARKS: Adenoma carcinoma. Okay.
DR. SLAGA: No. Not carcinoma, adenoma.
DR. MARKS: No. But the issue of course of carcinogenicity.
DR. SLAGA: No. Okay.
DR. MARKS: So I would say consider safe as used. And then the other then when you look at the original conclusion on these three, lead the alcohol, the acid, and the benzoate, sodium benzoate.
DR. HILL: Mm-hmm.
DR. MARKS: There were limits of concentration, and I wonder if this is similar to what you talked about, Tom, historically for the 5 percent and in the benzyl alcohol and hair dyes up to 10 percent. And when you look at there's this combination of contact urticaria and sensitization. When I look at the present uses of concentration in products, it meets those. It's 5 2 percent, 10 percent. So I would be okay with just 2 saying safe as used, and in discussion just refer back to that one.
DR. SLAGA: Right. I agree.
DR. MARKS: Okay. So the third portion of the discussion that should deal with this, the sensitization, contact urticaria, and the 5 and 10 percent limit. Any other things about the discussion?
DR. SHANK: Not for me.
DR. HILL: I have a couple questions for the toxicologist. We don't have any inhalation toxicology on benzyl benzoate, at least per the table. Does that concern anybody? It doesn't really concern me. I just thought I'd raise it

for people to think about. And also, there are some repro toxicity findings for benzyl benzoate, although it was unclear because we -- both places it's written it describes dermal doses up to 1 percent in diet. I'm not sure what to make of that.
DR. MARKS: What page?
DR. HILL: Well, if you look on PanelBook page 20, it appears -- yeah, that's the summary section.
DR. MARKS: I didn't look that closely.
On benzyl benzoate none of those are addressed in the RIFM paper because that's a large document. MR. JOHNSON: That was a mistake. That should have been daily doses greater than 0.5 grams per kilogram per day.
DR. MARKS: All right.
MR. JOHNSON: Instead of up to 1 percent.
DR. HILL: Okay.
MR. JOHNSON: That's what that --
DR. HILL: Also there are these findings that a whopping huge dose compared to art of use that's -- because of that I wasn't able to make that correlation. Benzyl benzoate up to 4 percent possible dermal contact, according to the use survey.
DR. MARKS: Okay. So I'll move that a tentative amended report be issued with the said ingredients, three of the original and four add-on safe as used.
Okay. Any other?
MR. JOHNSON: Just one question.
DR. MARKS: Sure.
MR. JOHNSON: Per the discussion, Dr. Marks, you mentioned, I guess, addressing sensitization and contact urticaria potential in the 5 and 10 percent limits that were established in the published file report.
DR. MARKS: Yeah.
MR. JOHNSON: Specifically, what do you want to say there?
DR. MARKS: I think what we should do is point out that these are the present use concentrations and products. So we're not contradicting that by saying "safe as used." And I would -- there is obviously a lot of thought and effort reaching when we read the discussion and the data coming up with the 5 percent was, I think, a compromise in terms of what percentage.
MR. JOHNSON: Okay.
DR. MARKS: Yeah. That's all I – to point out that this previous document did set limits. We're just saying present use of concentration.
MR. JOHNSON: But you're not saying anything specifically about sensitization or contact urticaria?
DR. MARKS: No.
MR. JOHNSON: Okay.
DR. MARKS: No. I don't think so. You would just refer back. You can just mention that that was considered.
MR. JOHNSON: Okay.
DR. MARKS: Okay. Anything else with the benzyl alcohol, acids, salts, and esters? If not, we'll move onto methylene glycol, which is the cosmetic ingredient, and the formaldehyde, which is not.

Day 2 of the June 27-28, 2011 CIR Expert Panel Meeting

Benzyl Alcohol, Benzoic Acid, and its Salts and Ester

DR. MARKS: So, in 1998, the CIR Expert Panel issued a final safety assessment on the alcohol, acid, and sodium benzoate with concerns about inhalation and labeled it as an insufficient for safety in inhalation as the primary root of exposure of these three ingredients. In June of last year, this was reopened considering new data about inhalation and then also we considered adding more ingredients. And so for this draft report we have the benzyl alcohol, benzyl acid, sodium benzoate, which were in the 1998 report, plus we have the salts, calcium, magnesium, potassium, benzoate, and also benzyl -- benzoate the ester. And so we felt that review of this now that the concerns about inhalation were met and we felt that we could have these seven ingredients all in one report with a 2 -- a tentative amended report with a conclusion 2 safe as used.
DR. BERGFELD: And that's a motion?
DR. MARKS: Yes.
DR. BERGFELD: Is there a second?
DR. BELSITO: Second.

DR. BERGFELD: Second. Further discussion?

DR. MARKS: Yes, I think in the discussion section we went through several points. One, obviously, is dealing with the inhalation insufficiency had to be addressed in the discussion from the original report. Then, Tom and Ron, was it the NTP that an adenoma was found in some of the experimental animals, but the EPA did not feel that it was carcinogenic? So we can --

1 DR. SLAGA: It's a benign tumor.

DR. MARKS: Yeah, it's a benign tumor and so we can address that in the discussion. And then the other -- when you look at the original report there were limits set, 5 percent and 10 2 percent, and when you look at the concentration of 2 use in products now as we -- safe as used will actually address those concerns from the original report. So, that should be in the discussion.

DR. BERGFELD: Don.

DR. BELSITO: We would agree with that. The other thing we added to the discussion was their mention in the report that photodegradation can result in release of free benzene in these products and we felt that at the current level of use that really would not be of any toxicologic consequence. The other issue that we raised is in the list of provocative studies that were done -- there were two issues on benzyl benzoate, that was provided by the Research Institute for Fragrance Material, and they were all referenced to that article, but that article referenced primary articles regarding that data and they should be referenced rather than as secondary review article. And the second issue that I think we 2 need to be very cognizant of is that in the 2 provocative testing they use words like "three patients sensitized." The implication of that is that three patients were sensitized during the process of patch testing and that's -- to any dermatologist who does that -- and that's not the case. Three patients were positive, so I think that word "sensitized" throughout that provocative table has to be removed and put "positive." Otherwise, you get the implication that at that concentration you're sensitizing individuals during the course of patch testing and that's not the case regardless of how the authors might have phrased it.

DR. BERGFELD: Any other discussion or comment? If not, I'm moving the question then, all those in favor of a safe conclusion?

Report

Final Amended Report

Benzyl Alcohol, Benzoic Acid, and its Salts and Benzyl Benzoate

September 26, 2011

The 2011 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 F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Scientific Analyst/Writer.

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ABSTRACT: Benzyl alcohol, benzoic acid, and its salts and benzyl benzoate function mostly as fragrance ingredients/preservatives in cosmetic products. The Expert Panel noted that benzoic acid, benzyl alcohol, and benzyl benzoate are dermally absorbed, and it is likely that the same is true for benzoic acid salts. The Panel concluded that negative oral carcinogenicity data on benzyl alcohol and negative inhalation toxicity data on benzoic acid and benzyl alcohol support the safety of all of the ingredients that are being reviewed. Thus, it was concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This report assesses the safety of benzyl alcohol, and benzoic acid and its salts and benzyl ester as used in cosmetics. In cosmetics, these ingredients are reported to function as fragrance ingredients, pesticides, pH adjusters, preservatives, solvents, and/or viscosity decreasing agents in cosmetic products.

In 2001, the Cosmetic Ingredient Review (CIR) published a final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate with the conclusion that benzyl alcohol, benzoic acid, and sodium benzoate are safe for use in cosmetic formulations at concentrations up to 5%.[1] Benzyl alcohol was safe for use in hair dyes at concentrations up to 10%. The available data were insufficient, however, to support the safety of these ingredients in cosmetic products in which a primary route of exposure is inhalation. The Expert Panel stated that inhalation toxicity data were needed.

The Personal Care Products Council provided a 4-week inhalation toxicity study (rats) of aerosolized benzyl alcohol and benzoic acid. After reviewing this study, the Expert Panel determined that the final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate should be reopened to amend the original conclusion. Furthermore, the Panel determined that data available in the original safety assessment, with the addition of the new inhalation toxicity data, were sufficient to support the safety of other simple salts of benzoic acid (calcium, magnesium, and potassium benzoate) and the benzyl ester.

Additional new data reviewed included an Organization for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS) for high volume chemicals initial assessment report on benzoic acid, sodium benzoate, potassium benzoate, and benzyl alcohol published by the United Nations Environmental Program Chemicals Branch (UNEP chemicals) in 2001,[2] the same year that the CIR Final Safety Assessment on benzyl alcohol, benzoic acid, and sodium benzoate was published. In addition to the SIDS data summaries included in this CIR safety assessment, the 2001 SIDS report may be consulted for further details. Further, the European Commissions' International Uniform Chemical Information Database (IUCLID) on benzyl alcohol, benzoic acid, sodium benzoate, and benzyl benzoate was created in the year 2000.[3] Data from the OECD SIDS assessment and IUCLID data sets are summarized in the Toxicology section. In the process of selecting new data for inclusion in the current report, efforts were made to eliminate redundancy between OECD SIDS, IUCLID, or other data found in the published literature and data included in the original final report.

CHEMISTRY

Definition and Structure

Definitions, other chemical names, and cosmetic ingredient functions for ingredients reviewed in this safety assessment are included in Table 1. Structural formulas are included in Figure 1.

Chemical and Physical Properties

Chemical and physical properties of benzyl alcohol, benzoic acid and its salts, and the benzyl benzoate ester are included in Table 2.

The photodegradation of benzoic acid aqueous solution in the presence of UV light has been reported. Benzoic Acid absorbs UV light below 300 nm, and its concentration in solution was monitored using reverse-phase high-performance liquid chromatography (HPLC). The mercury lamp used emitted polychromatic radiation between 240 and 540 nm. The photon

flow absorbed by the reaction system varied with the concentration of benzoic acid and with the presence of the products of degradation. When the temperature was increased from 25ºC to 50ºC, photodegradation was increased by 20%. Photodegradation products were not mentioned.[4]

The conversion of benzyl alcohol to benzaldehyde and benzoic acid in aqueous solution has been demonstrated using liquid chromatography/spectrophotometry.[5] When benzyl benzoate (in ethanol) was exposed to sunlight for 11 days (at 25ºC), 35 products were isolated from exposed samples and identified using gas chromatography/mass spectrometry. Benzyl alcohol and benzoic acid were among the products identified.[6]

Method of Manufacture

Benzyl Alcohol

Large scale production of benzyl alcohol is achieved by the action of sodium or potassium carbonate on benzyl chloride.[1]

Benzoic Acid

Benzoic acid is produced via the decarboxylation of phthalic anhydride in the presence of catalysts. Another production method involves the chlorination of toluene to yield benzotrichloride, which is hydrolyzed to benzoic acid.[7]

Sodium Benzoate

Sodium benzoate is produced by the neutralization of benzoic acid with sodium bicarbonate, sodium carbonate, or sodium hydroxide.[8]

Potassium Benzoate

Potassium benzoate can be prepared by reacting methyl benzoate with potassium thioacetate.[9]

Benzyl Benzoate

Benzyl benzoate results from the condensation of benzoic acid and benzyl alcohol. It can also be generated from benzaldehyde via the Tishchenko reaction.[10]

UV Absorption

The following UV absorption maxima have been reported for salts and an ester of benzoic acid: 228.6 nm (magnesium benzoate), 226.8 nm (potassium benzoate), and 256 nm (benzyl benzoate).[11,12]

Analytical Methods

Benzoic acid has been analyzed using mass spectrometry,[13] and potassium benzoate has been analyzed using IR spectroscopy.[14] Benzyl benzoate has been analyzed using IR and NMR spectroscopy.[15,16]

Impurities

Benzoic acid can react with ascorbic acid in beverages via metal-catalyzed reduction (cans) or on exposure to solar UV (bottles) to form benzene, but the yield of benzene is < 1 ppb. Limits for heavy metal impurities in food-grade sodium benzoate (as Pb, ≤ 2 mg/kg) and pharmaceutical-grade potassium benzoate (heavy metals, ≤ 0.001%) have been established.

Benzoic Acid and Sodium Benzoate

The effects of UVA exposure on benzene formation have been determined. Benzene formation was examined for samples contained in UV stabilized and non-UV stabilized packaging.[17] Some of the samples selected for UVA testing included model solutions prepared with 0.04% benzoate and 0.025% ascorbic acid in unbuffered water. The results of 24-h irradiation studies indicated that, under intense UV light, benzene levels increased by as much as 53% (to 315 ng/g benzene, compared to model solutions exposed to visible light [206 ng/g benzene]) in model solutions stored in non-UV stabilized bottles.

However, the use of UV stabilized polyethylene terephthalate bottles reduced benzene formation by ~ 13%, relative to the non-UV stabilized bottles. Similar trends were observed following irradiation for 7 days. According to the Food and Drug Administration (FDA), the U.S. beverage industry voluntarily reformulated beverages that were found to contain benzene levels at or above the 5 ng/g maximum contaminant level (mcl) for drinking water established by the U.S. Environmental Protection Agency (EPA).[17] An mcl of 0.005 mg/L (5 ppb) is the EPA's official limit for benzene in drinking water.[18]anorectal Furthermore, in a 2008 survey conducted by FDA, all of the reformulated beverages tested were shown to contain ≤ 1.1 ng/g benzene. Most of the beverages were reformulated by removing or reducing either benzoate or ascorbic acid, or by adding EDTA.[19]

Benzyl Benzoate, Potassium Benzoate, and Sodium Benzoate

According to the *United States Pharmacopoeia*, benzyl benzoate contains less than 99% and not more than 100.5% $C_{14}H_{12}O_2$ and potassium benzoate contains not less than 100.5% and not more than 99% $C_7H_5KO_2$. Limits for water and heavy metals in potassium benzoate are stated as ≤ 1.5% and ≤ 0.001%, respectively.[20]

The Food Chemicals Codex specification for sodium benzoate includes the following limitations: heavy metals, as Pb (≤ 2 mg/kg), alkalinity, as NaOH (≤ 0.04%), and water (≤ 1.5%).[21]

USE

Cosmetic

As stated in the *International Cosmetic Ingredient Dictionary and Handbook*, benzoic acid, benzyl alcohol, sodium benzoate, calcium benzoate, magnesium benzoate, potassium benzoate, and benzyl benzoate may function as fragrance ingredients, pesticides, pH adjusters, preservatives, solvents, viscosity decreasing agents, and pH adjusters in cosmetic products (See Table 1).[22]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2010, the following ingredients were being used in personal care products: benzoic acid, benzyl alcohol, sodium benzoate, potassium benzoate, and benzyl benzoate.[23] Uses of calcium benzoate and magnesium benzoate were not reported to the VCRP. These data are summarized in Table 3.

Independent of the VCRP data, a survey of ingredient use concentrations was conducted by the Personal Care Products Council in 2010. The results of this survey indicated that the following ingredients were being used in cosmetic products: benzoic acid (0.000002 to 5%), benzyl alcohol (0.000006 to 10%), sodium benzoate (0.000001 to 1%), calcium benzoate (0.002 to 0.004%), potassium benzoate (0.002 to 0.003%), and benzyl benzoate (0.000005 to 4%). [24] No uses of magnesium benzoate were reported in the Council survey.

Personal care products containing the ingredients reported as being used may be applied to the skin, nails, or hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin, nails, or hair for variable periods following application. Daily or occasional use may extend over many years.

In the European Union, the maximum authorized concentrations for benzoic acid and sodium benzoate as preservatives in cosmetic products are: rinse-off products, except oral care products (2.5%, as acid), oral care products (1.7%, as acid), and leave-on products (0.5%, as acid). For salts of benzoic acid other than sodium benzoate, the maximum authorized concentration is 0.5% (as acid).[25]

The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) was asked to review the data submitted to support the safety of benzoic acid and its salts and esters, when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC as preservatives, for other specific non-preservative purposes apparent from the presentation of the products and to answer the following question: Can benzoic acid and it salts and esters be used safely for non-preservative purposes in cosmetic rinse-off products at a maximum concentration of 2.5% and in cosmetic oral-care products at a maximum concentration of 1.7%. Data were provided to the SCCNFP in support of the use of benzoic

acid as a non-preservative. The SCCNFP did not find the submission appropriate for a safety evaluation of benzoic acid and sodium benzoate for the applied "other uses" in cosmetic products.[26] Subsequently, a second data set was provided, and these data were considered adequate for arriving at a conclusion on the safety of benzoic acid and sodium benzoate, but not the other salts or esters. Based on these data, the Scientific Committee on Consumer Products (SCCP) issued the following opinion: The SCCP is of the opinion that benzoic acid and sodium benzoate are safe for use for preservative and non-preservative purposes in cosmetic rinse-off products at a maximum concentration of 2.5 % and in cosmetic oral-care products at a maximum concentration of 1.7%, and in leave-on products up to 0.5%.[27]

Noncosmetic

According to FDA's Select Committee on Generally Recognized as Safe (GRAS) substances, benzoic acid (21 CFR [Code of Federal Regulations] 184.1021)[28] and sodium benzoate (21 CFR 184.1733)[29] are classified as GRAS food substances. Sodium benzoate has also been approved by FDA for use as an antimycotic when migrating from food-packaging material (21 CFR 181.23).[30] Other CFR citations relating to FDA-approved direct/indirect food additive ingredient uses include: benzyl alcohol (21 CFR 172.515, 175.105, 175.300, and 177.1210)[31,32,33,34] ; benzoic acid (21 CFR 150.141, 150.161, 166.110, 175.300, and 177.1390)[35,36,37,33,38] ; sodium benzoate (21 CFR 150.141, 150.161, and 166.110)[35,36,37] ; calcium benzoate (21 CFR 166.110 and 178.2010)[37,39] ; potassium benzoate (21 CFR 166.110 and 177.1210)[37,34] ; and benzyl benzoate (21 CFR 172.515 and 175.105).[31,32]

Benzyl alcohol is an FDA-approved diluent in color additive mixtures for external drug use.[40] In 2009, the FDA approved benzyl alcohol lotion, 5%, as a prescription medication for the treatment of head lice (*Pediculosis capitis*) infestation in patients 6 months of age and older.[41] The results of clinical trials supporting benzyl alcohol lotion 5% (UlesfiaTM) as a safe and effective topical treatment for head lice are included in the section on Skin Irritation and Sensitization later in the report text.[42] Benzyl benzoate (10%) has been used in the treatment of scabies in developing countries.[43]

Benzyl alcohol has been classified by FDA regarding its use in the following types of over-the-counter (OTC) drug products (Category I: generally recognized as safe (S) and effective (E) for the claimed therapeutic indication; Category II: not generally recognized as safe and effective or unacceptable indications; Category III: insufficient data available to permit final classification):[44]

- anorectal (final monograph: 1 to 4% use concentration range established; Category I)
- external analgesic (both Category I and final monograph pending)
- external analgesic (final monograph: Category III)
- oral health care (Category I pending)
- oral discomfort care (Category II pending)
- oral discomfort care (Category IIISE pending)
- pediculicide (final monograph: Category III)
- skin protectant (final monograph: Category III)

Similarly, benzoic acid has been classified by FDA regarding its use in the following types of OTC drug products:[44]

- acne (final monograph: Category III)
- antifungal (final monograph: Category III)
- oral health care - (Category IIIE pending)
- skin protectant - (final monograph: Category III)

Sodium benzoate has been classified by FDA regarding its use in menstrual/diuretic OTC drug products (final monograph: Category III), and benzyl benzoate has been approved for use in OTC pedulicides (final monograph: Category II).[44]

Calcium benzoate, magnesium benzoate, and potassium benzoate are inert non-food ingredients that, under the Federal Insecticide, Fungicide, and Rodenticide Act, are permitted by the Environmental Protection Agency (EPA) for use in non-food use pesticide products.[45] Pesticide products containing benzoic acid as the active ingredient have been registered with EPA for use in the extermination of dust mites.[46]

Benzyl alcohol has been listed as a chemical in photographic developing systems,[47] and, at concentrations of 0.9 to 2%, is commonly used as an antibacterial agent in a variety of pharmaceutical formulations intended for intravenous administration.[48] Additionally, benzyl alcohol has been used in parenteral medications commonly administered to critically ill neonates.[49]

TOXICOKINETICS

Oral Studies

Benzyl alcohol and benzoic acid and its salts are rapidly metabolized and excreted via a common pathway within 24 h. Benzyl alcohol is metabolized to benzoic acid via simple oxidation. Benzoic acid and sodium benzoate are rapidly absorbed from the gastrointestinal tract of mammals, conjugated with glycine in the liver, and then excreted as hippuric acid. The urinary excretion of benzyl benzoate as glycuronide conjugates and hippuric acid in mammals has also been reported.

Benzyl Alcohol, Benzoic Acid, Sodium Benzoate, and Potassium Benzoate

Benzyl alcohol is metabolized to benzoic acid. Both benzoic acid and sodium benzoate are rapidly absorbed from the gastrointestinal tract of mammals and conjugated with glycine in the liver; the resulting hippuric acid is rapidly excreted in the urine.[1] Benzyl alcohol and benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, because they are all rapidly metabolized and excreted via a common pathway within 24 h.[2]

Benzyl Benzoate

Following oral administration (gavage, 0.5, 1, and 2 ml/kg) of benzyl benzoate to fasted female dogs, urine was collected for 5 to 6 days. All 3 doses resulted in creatinuria and urinary excretion of glycuronate conjugates.[50]

Following the administration of unspecified oral doses of benzyl benzoate to cats and dogs (number and breed not stated), small amounts of hippuric acid were detected in the 24 h urine. The metabolism of benzyl benzoate to benzoic acid *in vivo* has also been reported. Additional details for these 2 studies were not provided. [3]

In a human subject, urinary excretion of hippuric acid was measured after oral dosing (single dose, 2.02 g) with benzyl benzoate. Urine was collected for 6 h. Approximately 90% of the dose administered was excreted as hippuric acid in the urine. After oral dosing with 1 g, approximately 80% of the administered dose was excreted as hippuric acid. In a second subject, 71% of the administered dose was excreted as hippuric acid during the first 6 h and an additional 14% of the dose was excreted as such during the second 6 h after dosing.[51]

Dermal Studies

In in vitro studies, the percutaneous absorption of benzoic acid through guinea pig skin and the percutaneous absorption of benzyl alcohol and benzyl benzoate through human skin was reported. The percutaneous absorption and urinary excretion of benzyl alcohol and benzyl benzoate was observed following dermal application to rhesus monkeys.

Benzoic Acid

The penetration of benzoic acid through excised dorsal skin (full-thickness and with stratum corneum removed) from guinea pigs was examined. Skin preparations were mounted in a two-chamber diffusion cell. A suspension of excess amount of benzoic acid in saline was added to donor compartments. In full-thickness skin, permeation proceeded with a short lag time. Solubility (C_d, unit = mM) and permeability (K_p, unit = x 10^{-2} cm · h^{-1}) coefficients for benzoic acid were 32.7 ± 1.6 and 9.01 ± 1.51, respectively. Removal of the stratum corneum by tape stripping and its delipidation using an organic solvent mixture enhanced the skin penetration of benzoic acid.[52]

Benzyl Alcohol and Benzyl Benzoate

The percutaneous absorption of [7-^{14}C]benzyl alcohol and [7-^{14}C]benzyl benzoate *in vivo* was evaluated using 4 female Rhesus monkeys (10 to 19 years old). Each chemical was applied (4 µg/cm^2, without or with occlusion [glass chamber - G or plastic wrap - P]) to a clipped 1 cm^2 area of abdominal skin; the vehicle was acetone (10 to 20 µl/cm^2). The animals remained in metabolism chairs/metabolism cages for 5 days. The amount of absorbed compound in the urine was determined by liquid scintillation counting. Mean values (± SEM, 4 animals) for urinary excretion of the administered dose were: 77.4 ± 4.3% (benzyl alcohol) and 65.3 ± 13.4% (benzyl benzoate). Percutaneous absorption values (absorption, as % of applied dose) were as follows: benzyl alcohol (31.6 ± 4.2% [unoccluded]; 56.3 ± 14.5% [P]; 79.9 ± 7.4% [G]) and benzyl benzoate (57.0 ± 10.4% [unoccluded]; 71.2 ± 4.4% [P]; 64.7 ± 10.2% [G]). Over a 5-day period, the urinary excretion of radioactivity was 65.3 ± 13.4% following dermal application of benzyl benzoate and 56.5 ± 7.7% following dermal application of benzyl alcohol. When the acetone vehicle was replaced with a lotion (10 mg/cm^2), percutaneous absorption was increased. The increase was significant for benzyl benzoate ($P < 0.05$), but not benzyl alcohol. There was no apparent correlation between the skin penetration of benzyl alcohol and benzyl benzoate and their octanol-water partition coefficients of 7.4 and 3.97, respectively.[53]

The percutaneous absorption of benzyl benzoate *in vitro* was evaluated using human epidermis (from abdominal skin) placed in a glass diffusion chamber. Saline (5 ml) was added to the chamber and was in contact with the bottom of the epidermis. Benzyl benzoate (0.2 ml) was applied to the top of the epidermis. Six experiments were performed and the mean value for skin penetration of benzyl benzoate was 0.018± 0.002%.[54]

The penetration of benzyl alcohol through split-thickness cadaver skin was evaluated using nonoccluded Franz diffusion cells. Benzyl alcohol (spiked with ^{14}C radiolabel) in ethanol was applied to the skin at doses ranging from 0.9 to 10,600 µg/cm^2. After 24 h, the percentage of radioactivity that penetrated the skin increased gradually with dose, ranging from 19.8 ± 2.9% (lowest dose) to 29.2 ± 3.0% (highest dose). Also, less than 4% of the administered radioactivity was retained in the tissues at 24 h, and evaporation accounted for the remaining percentage. Data from this study were also analyzed in relation to a finite dose diffusion/evaporation model. The results of this analysis indicated that the increase in benzyl alcohol absorption with dose was consistent with a 3-fold increase in diffusivity in the stratum corneum, as the concentration of benzyl alcohol increased from tracer levels to saturation.[55]

In Vitro Study

The rate of hydrolysis of benzyl benzoate (in acetonitrile) by 80% human plasma *in vitro* was studied. The t ½ for the *in vitro* hydrolysis of benzyl benzoate to benzoic acid in human plasma was 19 minutes.[56]

TOXICOLOGICAL STUDIES

An Organization for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS) for high volume chemicals initial assessment report on benzoic acid, sodium benzoate, potassium benzoate, and benzyl alcohol was published by the United Nations Environmental Program, Chemicals Branch (UNEP chemicals) in 2001, with the following recommendation relating to human safety: "Taking into account the rapid metabolism and excretion, the non-bioaccumulation, the low toxicity after acute and repeated exposures, the non-reproductive toxicity, the non-genotoxicity and the non-carcinogenicity, the low irritating and non- to very low sensitizing properties of these substances, as well as the ontrolled (industrial settings) and /or regulated (pharma, cosmetics and /or food) uses, these substances will pose a minimal risk to humans (workers and consumers)." Because the database for this safety assessment is similar to that for the 2001 CIR Final Report on Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate, the available data in the OECD SIDS assessment are summarized with minimal details in sections that follow.

Acute and Repeated Dose Inhalation Toxicity

Neither acute nor repeated inhalation exposures to benzyl alcohol or benzoic acid caused death in rats. The results of a repeated dose inhalation toxicity study indicated no test substance-related macroscopic or microscopic findings for either

test substance, and the no-observed-effect-level (NOEL) and no-observed-adverse-effect level (NOAEL) were considered to be 1,072 mg/m^3 for benzyl alcohol and 12.6 mg/m^3 for benzoic acid.

Benzyl Alcohol and Benzoic Acid

According to the OECD SIDS initial assessment report on Benzoates, 4 h of inhalation exposure to benzyl alcohol or benzoic acid at 4 and 12 mg/L aerosol/dust, respectively, did not cause death in rats. Thus, low acute toxicity was associated with these compounds.[2]

A 4-week inhalation toxicity study of aerosolized benzyl alcohol and benzoic acid was performed using groups of Crl:CD(SD) rats.[57] Four groups of rats (10/sex/group) were exposed (nose-only) to aerosolized benzyl alcohol 5 days per week (6 h/day) for 4 weeks. Each animal received a minimum of 20 exposures of benzyl alcohol, and target exposure concentrations were 30, 100, 300, and 1,000 mg/m^3 for the four groups. Two additional groups of rats were exposed to aerosolized benzoic acid (2.5 and 12.5 mg/m^3) according to the same procedure. The group designated for exposure to benzyl alcohol (30 mg/m^3 target) was actually exposed to a mean atmosphere concentration that was 136% of the target concentration. For the remaining groups, all mean atmosphere concentrations were within 96.7% to 107.2% of the respective target concentrations. A concurrent control group was exposed to filtered air only.

There were no test-substance related deaths or effects on any of the following: body weight, food consumption, clinical pathology parameters, and organ weights. Additionally, there were no test substance-related macroscopic or microscopic findings. The (NOEL) and NOAEL were considered to be 1,072 mg/m^3 for benzyl alcohol and 12.6 mg/m^3 for benzoic acid.[57]

Acute Oral Toxicity

Some of the oral LD50 values that have been reported for various species include > 10,000 mg/kg for potassium benzoate in rats, mice, and guinea pigs, and the following values for benzyl benzoate: > 2,000 mg/kg (rats), 1400 mg/kg (mice), 1,122 mg/kg (guinea pigs), 1,680 mg/kg (rabbits), 2,240 mg/kg (cats), and 2,244 mg/kg (dogs).

Acute oral toxicity data are summarized in Table 4.

Benzyl Alcohol, Benzoic Acid, Sodium Benzoate, and Potassium Benzoate

According to the OECD SIDS initial assessment report on Benzoates, low acute oral toxicity is associated with benzoic acid and its sodium and potassium salts. The LD50 values were > 2000 mg/kg body weight, except for benzyl alcohol (LD50 = 1610 mg/kg [rats]), which needs to be considered harmful via the oral route.[2]

Acute Intraperitoneal Toxicity

Benzyl Benzoate

Mice were dosed i.p. with benzyl benzoate (test procedure/number of mice not stated), and an LD50 of > 500 mg/kg body weight was reported.[3]

Acute Dermal Toxicity

An acute dermal LD50 of 2,000 mg/kg for benzyl alcohol in rabbits and acute dermal LD50s of 4,000 mg/kg (rats) and 4,448 mg/kg (rabbits) for benzyl benzoate have been reported. Death of cats has been observed, following single dermal applications of a benzyl benzoate solution.

Benzyl Alcohol, Benzoic Acid, Sodium Benzoate, and Potassium Benzoate

According to the OECD SIDS initial assessment report on Benzoates, low acute dermal toxicity is associated with benzyl alcohol and benzoic acid and its sodium and potassium salts.[2]

Benzyl Alcohol and Benzyl Benzoate

The acute dermal toxicity of benzyl benzoate was evaluated using rats (number not stated), and an LD50 of 4,000 mg/kg body weight was reported. Study details were not included. In a study involving rabbits, the acute dermal toxicity of undiluted benzyl benzoate was evaluated according to the Draize procedure (no GLP; number of animals not stated), and an LD50 of 4,448 mg/kg body weight was reported.[3] In another study involving rabbits, acute dermal LD50s of 2,000 mg/kg and 4,000 mg/kg have been reported for benzyl alcohol and benzyl benzoate, respectively.[58]

Single dermal applications of 25% benzyl benzoate (20 ml in isopropanol/water) to the backs of cats resulted in death. Additional study details were not provided.[3]

Acute Subcutaneous Toxicity

Benzyl Benzoate

Groups of adult C57BL/6J mice (5 per group) were injected s.c. with 0.1 ml benzyl benzoate (~111 mg) daily for 4 weeks. An untreated group of sham injected animals served as the untreated concurrent control group. The adrenal glands were prepared for light and electron microscopic examination. The animals died within 3 h of initial injection. Additional study details were not provided.[3]

Guinea pigs (number not stated) received single s.c. injections of benzyl benzoate, and mortality rates at the administered doses were as follows: 0 (0.5 g/kg), 30% (1 g/kg), 80% (5 g/kg), 100% (10 g/kg), and 100% (20 g/kg).[59]

Acute Intramuscular Toxicity

Benzyl Benzoate

Following benzyl benzoate intramuscular injection into cats (number not stated) i.m., doses of 2 and 10 g/kg were described as lethal.[59]

Repeated Dose Toxicity – Oral Studies

Benzoic acid and its salts and benzyl alcohol have caused a low degree of toxicity in repeated dose oral toxicity studies. NOAEL values of 800 mg/kg/day and > 1,000 mg/kg/day have been reported for benzoic acid and its salts, respectively. An NOAEL of > 400 mg/kg/day has been reported for benzyl alcohol. Toxic effects were not associated with repeated oral doses of benzyl benzoate, and an NOEL of 800 mg/kg was reported.

Benzyl Alcohol, Benzoic Acid, Sodium Benzoate, and Potassium Benzoate

According to the OECD SIDS initial assessment report on Benzoates, repeated dose oral toxicity studies yielded an NOAEL of 800 mg/kg/day for benzoic acid and > 1000 mg/kg/day for the salts. At greater doses, increased mortality, reduced weight gain, and liver and kidney effects were observed. Systemic toxic effects of a similar nature (e.g. liver, kidney) were observed after dosing with benzyl alcohol, benzoic acid, sodium benzoate, and potassium benzoate. However, these effects were observed at higher doses of benzoic acid and its salts when compared to dosing with benzyl alcohol. Long-term studies on benzyl alcohol yielded an NOAEL of > 400 mg/kg body weight per day for rats and > 200 mg/kg body weight per day for mice. At higher doses, effects on body weight and lesions in the brain, thymus, skeletal muscle, and kidneys were observed. It was noted that one should take into account that oral administration was by gavage in these studies, whereby saturation of metabolic pathways is likely to occur. It was concluded that benzoic acid and its salts exhibited very low repeated dose toxicity and that benzyl alcohol exhibited low repeated dose toxicity.[2]

Benzyl Benzoate

No effects were observed in a 7-month toxicity study in which mice (no. and strain not stated) were dosed orally with benzyl benzoate (800 mg/kg).[60]

Repeated Dose Toxicity – Dermal Studies

Systemic/dermal effects induced by benzyl benzoate were observed in rats receiving repeated dermal doses up to 2.0 g/kg and in rabbits receiving 2.2 g/kg doses. Benzyl benzoate was lethal at doses of ~ 2.0 g/kg (rabbits) and higher (cats).

Benzyl Benzoate

The following effects were observed in groups of rats (3 males/3 females/group; strain not stated) that received dermal applications of 0.188, 0.488, 0.781, 1.25, or 2.0 g/kg for 30 days: hyperplasia of squamous epithelium, degeneration of hair follicles and sebaceous glands, subcutaneous fibrosis, and hyperplasia of the thyroid gland. Seven areas of the shaved back were dosed in rotation. Dosing with 2.0 g/kg also caused 4 deaths, decreased white blood cell numbers, and other blood effects. Body weight changes, decreased white blood cell numbers, and other blood effects were also observed following dosing with 1.25 g/kg. Additional study details were not provided.[61]

In a study involving rabbits, (non-GLP; number and strain not stated) dermal doses of benzyl benzoate were applied daily for 90 days.[3] The range of doses tested was not stated. Deaths occurred at doses of 2.2 g/kg body weight/day and greater. Testicular atrophy was noted at high doses, and, possibly, there was also an increased incidence of focal nephritis and encephalitis. Very mild skin irritation was also observed. Additional details relating to this study were not provided. Benzyl benzoate was also applied topically to rabbits at doses of 0.5 ml/kg/day daily for 90 days. Slight dermatitis and inanition were observed, and, at higher doses, slight to moderate testicular atrophy was apparent. Increased leucocyte counts were reported and results were also suggestive of kidney damage. Benzyl benzoate also caused death, but the number of mortalities and corresponding toxic doses were not reported. Repeated dermal applications of benzyl benzoate (doses not stated) did not cause toxic symptoms in the following species: dogs, horses, cows (young females), sheep, or pigs. Additional study details were not provided.[3]

In another study, rabbits (no. and strain not stated) received dermal applications of benzyl benzoate at doses of 0.5, 1.0, 2.0, and 4.0 ml/kg daily for 90 days.[62] Lethality and effects on the following were reported after dosing: blood effects (at 2.0 ml/kg), kidneys, skin (slight dermatitis and other effects), reproduction, leukocyte (increased 2.5 x normal), testicular damage, and kidney damage. Animal deaths were not preceded by the usual pattern of systemic effects prior to death. Additional details were not included.

Five applications of benzyl benzoate (undiluted) were made to the backs of the following domestic animals: 1 sheep (250 ml dose), 1 pig (200 ml), 1 young cow (500 ml), and 1 horse (1000 ml). The animals were observed for 2 weeks. None of the animals died. In another study, 6 applications of undiluted benzyl benzoate were made to the backs (clipped skin, 4 " x 6" area) of 3 dogs as follows: 1 dog (200 ml volume) and 2 dogs (100 ml). The animals were observed for 2 weeks. No test substance-related effects were observed.[63]

Benzyl benzoate was rubbed onto cutaneous lesions on the shaved upper thighs of cats (no. not stated). Three applications per animal were made. Within 24 to 36 h, the test substance was lethal at doses of 8.7 to 12.8 g/kg.[59]

Repeated Dose Toxicity – Parenteral Studies

Subcutaneous dosing with benzyl benzoate resulted in death of mice (111 mg doses) and rabbits (2.5 ml/kg doses).

Benzyl Benzoate

Rabbits (1 or 2 animals) were injected s.c. once with benzyl benzoate in olive oil (doses of 1 to 2.5 ml/kg) or received 4 daily 0.25 mg/kg s.c. injections. Effects on leukocyte counts were monitored over an 11-day period and the animals were also examined for mortalities and clinical signs. The 2.5 ml/kg dose was lethal and clinical signs were observed. No effects were associated with the 0.25, 1, or 1.5 ml/kg doses.[64]

Ocular Irritation/Toxicity

Benzyl alcohol (4% aqueous), benzoic acid (undiluted), and its sodium salt (concentration not stated) were irritating to the eyes of rabbits, and it was expected that potassium benzoate would be irritating as well. A vehicle containing benzyl alcohol as a preservative for injected triamcinolone acetonide (TA) was toxic when injected intravitreally into the eyes of rabbits. However, it has been noted that retinal toxicity is not observed following injection of 0.1 ml preserved TA in clinical practice. Benzyl benzoate (undiluted) was irritating to the eyes of rabbits and humans.

Benzyl Alcohol

The ocular toxicity of benzyl alcohol was evaluated using 9 New Zealand rabbits. The following test concentrations of benzyl alcohol (in stock solution of carboxymethylcellulose and polysorbate 80) were injected intravitreally, each into 3 eyes (15 eyes total injected): 0.0073%, 0.022%, 0.073%, 0.222%, and 0.733%. Control eyes (2) were injected intravitreally with 0.9% normal saline. Ocular toxicity was not observed at the lowest concentration; transient clinical changes (retinal hemorrhage and whitening), but no remarkable pathological changes, were noted in 1 of 3 eyes tested with 0.022% benzyl alcohol. Ocular toxicity was observed at the remaining concentrations; changes in the outer retina included loss and shortening of outer segments and receptors.[65]

Triamcinolone acetonide (TA) has been increasingly applied intravitreally in therapy for retinal diseases, and the vehicles of TA injections usually contain benzyl alcohol as a preservative. The ocular toxicity of 2 commercial vehicles (A and B) for drugs was evaluated using 3 groups of 12 New Zealand white rabbits (vehicle A, vehicle B, and balanced saline solution [BSS, negative control] groups). The 2 vehicles were similar in that each also contained benzyl alcohol (9.9 mg/ml), sodium carboxymethylcellulose (CBC, 7.5 mg/ml), and polysorbate 80 (0.4 mg/ml). Each group of 12 was divided into 2 groups, each receiving a different intravitreal dose (0.1 or 0.2 ml). Ocular examination (using ophthalmoscope) results were normal for group A and the negative control group; retinal damage was obvious in group B. However, at microscopic examination, retinal toxicity was observed in groups A and B. Vehicle B induced extensive retinal necrosis and atrophy, while vehicle B induced localized retinal changes.[66]

In a published comment on the preceding publication, the association of the benzyl alcohol preservative with retinal toxicity was acknowledged. However , it was noted that retinal toxicity is not observed at concentrations achieved following injection of 0.1 ml preserved TA in clinical practice.[67]

In a similar study, 4 groups of Chinchilla rabbits (pigmented) were injected intravitreally with the following 4 materials, respectively: 0.1 ml BSS, 0.1 ml TA (1.3 mg/ml), 0.1 ml vehicle (0.99% BA and other excipient) alone, and 0.1 ml TA + vehicle. Given the materials tested, it should be noted that commercially prepared TA was described as a suspension containing 40 mg TA plus vehicle containing 0.99% BA, 0.75% excipient sodium carboxymethylcellulose, and 0.04% polysorbate. At microscopic examination, morphologic changes in the ciliary body, lens, and retina were observed only in 2 groups (TA + vehicle and vehicle alone). Thus, it was concluded that benzyl alcohol was toxic to these tissues when injected intravitreally.[68]

Benzoic Acid, Benzyl Alcohol, Sodium Benzoate, and Potassium Benzoate

According to the OECD SIDS initial assessment report on Benzoates, benzyl alcohol (4% aqueous) and benzoic acid (undiluted) were irritating to the eyes of rabbits and sodium benzoate (concentration not stated) was only slightly irritating. Data on potassium benzoate were not available; however, it was expected that this chemical would induce slight ocular irritation.[2]

Benzyl Benzoate

Undiluted benzyl benzoate was instilled (0.1 ml) into the eyes of 6 rabbits (3 males, 3 females), and reactions were scored up to 72 h post-instillation. Ocular irritation was observed in 3 rabbits (only reactions reported) at 1 h post-instillation.[69]

In an ocular irritation study involving human subjects (test procedure/number of subjects not stated), undiluted benzyl benzoate was classified as an ocular irritant.[3]

Skin Irritation and Sensitization

Undiluted benzyl alcohol and benzoic acid were slightly irritating and an unspecified concentration of sodium benzoate was non-irritating to the skin of rabbits. In studies involving guinea pigs, benzyl benzoate was non-irritating over the range of test concentrations, 2.5% to 50%. For the lower concentrations evaluated for sensitization in guinea pigs, benzyl benzoate was classified as a non-sensitizer at 5% and a weak sensitizer at 1%. At a concentration of 10%, results were consistent with classifications ranging from non-sensitizer to moderate sensitizer. Benzyl benzoate was classified as a mild sensitizer in guinea pigs when tested at a concentration of. In rabbits, undiluted and 25% benzyl benzoate were classified as non-irritants. Results for healthy human subjects indicate that benzyl benzoate was classified as a non-irritant undiluted and at concentrations down to 2%, except for its classification as a minimal irritant at 50% in a very small percentage of subjects in one of the studies. Benzyl benzoate was classified as non-sensitizer when tested at a concentration of 30% in healthy human subjects. Most of the skin sensitization studies on benzyl benzoate involved groups of patients, and mixed results regarding sensitization potential were reported.

Skin irritation and sensitization data (human and non-human) are included in Table 5**.**

Benzyl Alcohol, Benzoic Acid, Sodium Benzoate, and Potassium Benzoate

According to the OECD SIDS initial assessment report on Benzoates, benzoic acid and benzyl alcohol were slightly irritating to the skin, whereas, sodium benzoate was non-irritating. Skin irritation data on potassium benzoate were not available; however, it is not expected that this compound would be irritating to the skin.[2] In the same report, benzoic acid did not induce sensitization in animal studies; however, a low incidence of positive reactions was observed in dermatologic patients patch tested. Similar results were reported for sodium benzoate, and it has been suggested that the positive reactions observed were actually non-immunologic contact urticaria. Both positive and negative results were reported for benzyl alcohol in animal skin sensitization studies. A maximum skin sensitization incidence of 1% was reported for benzyl alcohol in human patch tests. Occupational exposure to benzyl alcohol, benzoic acid, or sodium benzoate has not resulted in skin sensitization over a period of decades.[2]

Case Reports

Case reports included positive patch test reactions to benzoic acid, negative patch test reactions to benzyl benzoate, and positive or negative patch or intradermal/prick test reactions to benzyl alcohol and sodium benzoate.

Case reports involving patch, intradermal, or prick testing of benzyl alcohol, benzoic acid, sodium benzoate, or benzyl benzoate are included in Table 6.

Cytotoxicity

Sodium Benzoate

The potential for sodium benzoate and other preservatives to induce lipid peroxidation in normal and α-linolenic acid -loaded cultured hepatocytes from male Wistar rats was evaluated. Cell injury was measured by the release of lactic acid dehydrogenase into the culture medium after 10 h of incubation. At concentrations up to 10 mM, sodium benzoate was not cytotoxic to either group of hepatocytes. Also, lipid peroxidation was not detected in either group of hepatocytes incubated with sodium benzoate.[70]

Benzyl Benzoate

In an *in vitro* assay**,** benzyl benzoate was toxic to ascites sarcoma BP8 cell cultures. Additional details were not provided.[3]

Phototoxicity

A slightly positive reaction was observed in a phototoxicity study involving hairless mice tested with an unspecified concentration of benzyl benzoate (4, 24 h exposures). Photo-irritation was not observed in guinea pigs tested with benzyl benzoate at concentrations up to 30%.

Benzyl Benzoate

The phototoxicity of benzyl benzoate was evaluated using hairless mice (number and strain not stated). Details relating to the test protocol were not included. Following test substance application, test sites were irradiated for a total of 3 or 4, 24 h exposures. No reactions were observed after 3 exposures; however, a slightly positive reaction was observed after 4 exposures.[3]

The phototoxicity of benzyl benzoate was evaluated, using 5 female Hartley guinea pigs, at concentrations of 10%, 30%, and 50% in acetone. At 4 h after depilation, the test substance was applied to a circular area (diameter = 1.5 cm) on both sides of the back. Two applications (left and right side) of each concentration were made to the back of each animal. One side of each animal was covered with aluminum foil and the other was irradiated with 5 Toshiba model FL-40 BLB lamps (320 to 400 nm) at a distance of 10 cm for 70 min. Photo-irritation was not observed at any of the 3 test concentrations.[71]

Photohemolysis

Neither benzyl alcohol (10^{-3} mol/l or 0.1%) nor sodium benzoate (10^{-3} mol/l) induced significant photohemolysis of human erythrocytes exposed to UVA/UVB light in vitro. However, in another assay, moderate photohemolysis of human erythrocytes was induced by benzyl alcohol (10^{-4} mol/l) only in the presence of UVA light, and benzyl benzoate did not induce photohemolysis in the presence of UVA or UVB light.

Benzyl Alcohol, Sodium Benzoate, and Benzyl Benzoate

The photohemolytic activity of benzyl alcohol and sodium benzoate *in vitro* was evaluated in a test involving human erythrocyte suspensions, incubated with either chemical (10^{-3} mol/l) for 1 h and exposed to UVA or UVB radiation. The UVA rich light source was a UVASUN 5000 lamp (320 to 460 nm; 42 mW/cm^2) and the UVB rich light source was a lamp with TL 20 W/12 light bulbs (between 275 and 365 nm; 1 mW/cm2 [UVB] and 0.4 mW/cm2 [UVA]) Cultures without either chemical served as negative controls. Neither benzyl alcohol nor sodium benzoate induced significant hemolysis.[72]

A similar *in vitro* photohemolysis test (human erythrocyte suspensions) was used to evaluate the phototoxicity of benzyl alcohol and benzyl benzoate. The radiation sources described in the preceding study were used. Moderate hemolysis (~6%) was induced by benzyl alcohol (at 10^{-4} mol/l) only in the presence of UVA, classifying it as a weakly phototoxic compound. Benzyl benzoate (test concentration not stated) was not phototoxic in the presence of UVA or UVB light.[73]

The photohemolytic activity of benzyl benzoate (0.1%) *in vitro* was evaluated using human red blood cells. Cultures were exposed to UVA or UVB radiation for up to 3 h and then centrifuged. Release of hemoglobin in the supernatant was determined as cyanomethaemoglobin. No photohemolytic activity was noted for 0.1% benzyl benzoate.[74]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In an OECD SIDS assessment report, benzoic acid (up to 750 mg/kg/day, maternal LOAEL)was not a reproductive toxicant in rats in a four-generation reproductive toxicity study, and repeated doses of sodium benzoate (0.01g in diet) did not induce reproductive effect in rats. Developmental effects were observed in the presence of marked maternal toxicity in rats fed sodium benzoate in the diet (≥ 2800 mg/kg/day; NOAEL = 1400 mg/kg/day) in another study; maternal toxicity was not observed in hamsters (doses up to 300 mg/kg/day, also the NOEL), rabbits (doses up to250 mg/kg/day, also the NOEL) ,or CD-1 mice (doses up to 175 mg/kg/day, also the NOEL). Benzyl alcohol was not a developmental toxicant in CD-1 mice (doses up to 750 mg/kg/day, maternal LOAEL) or in mice of an unspecified strain (doses up to550 mg/kg/day, also the NOAEL) dosed by gavage. Benzyl benzoate (up to 1% in the diet) was not found to be teratogenic in rats. However,

testicular atrophy was observed in rabbits that received repeated dermal doses of benzyl benzoate (> 0.5 g/kg/day). There was no evidence of adverse effects on pregnancy outcome in a study on the safety of topical application of benzyl benzoate (25%) lotion in pregnant women. Benzoic acid (up to 1,000 µg/kg, s.c. injection) did not induce any reproducible evidence of estrogenic activity in uterotrophic assays involving immature female Alpk:AP$_f$SD rats and female Alpk:AP$_f$CD-1 mice. Benzyl benzoate induced weak estrogenic responses in certain tests using cultured human breast cancer cells in vitro, but not in others.

Benzoic Acid, Sodium Benzoate, Potassium Benzoate, and Benzyl Alcohol

According to the OECD SIDS initial assessment report on benzyl alcohol, benzoic acid, and its sodium and potassium salts, benzoic acid did not induce reproductive effects in a four-generation reproductive toxicity study (NOAEL > 750 mg/kg).[2] Groups of rats (20 rats/sex/group) received benzoic acid doses of 375 or 750 mg/kg/day in the diet continuously. Animals of the third generation were killed after 16 weeks. Also, test substance-related effects on reproductive organs (based on gross and microscopic examination) were not observed in subchronic studies (rats and mice) on benzyl alcohol and sodium benzoate.

In groups of rats fed sodium benzoate (doses up to 5600 mg/kg/day) during each day of gestation, developmental effects were observed only in the presence of marked maternal toxicity (reduced food intake and decreased body weight; NOAEL = 1400 mg/kg/day). All developmental effects were observed at doses ≥ 2800 mg/kg/day. On days 6 through 10, 15, or 18 of gestation, dosing with sodium benzoate by gavage in hamsters (NOEL = 300 mg/kg body weight), rabbits (NOEL = 250 mg/kg), and CD-1 mice (NOEL = 175 mg/kg), did not result in maternal toxicity; doses > NOEL were not tested. In mice of an unspecified strain dosed with benzyl alcohol by gavage, an NOAEL of 550 mg/kg (only dose) body weight for developmental toxicity was reported. An LOAEL of 750 mg/kg/day (only dose) for developmental toxicity was reported for CD-1 mice dosed orally (gavage) with benzyl alcohol. In this study, maternal toxicity (increased mortality, decreased body weight, and clinical toxicity) was observed.[2]

Sodium Benzoate and Benzyl Benzoate

The effect of sodium benzoate on biochemical aspects of pregnant female albino rats and survival of their offspring was evaluated using groups of 10 Sprague-Dawley rats.[75] Two groups of weanling female rats were fed (*ad libitum*) sodium benzoate at doses of 0.01 g and 0.0125 g in the diet, respectively, daily for 12 weeks. Standard diet was fed to the control group. After mating, the animals were fed *ad libitum* during pregnancy. When compared to the control group, both doses of sodium benzoate induced a decrease in serum bilirubin and an increase in serum urea.

Both doses of sodium benzoate also induced an increase in serum uric acid ($p < 0.01$ and $p < 0.05$, respectively). Serum alanine aminotransferase (ALT) activity was significantly greater ($p < 0.01$) in the high dose group, but not in the lower dose group. The high dose did not induce a significant increase in serum creatinine. Statistically significant ($p < 0.01$) decreases in food intake, hemoglobin, and hematocrit were also reported. Pregnant rats that received high doses of sodium benzoate sustained a 13.6% decrease (statistically significant, $p < 0.05$) in mean weight of their pups, when compared to mean pup weight in the corresponding control group.[75]

The teratogenicity of benzyl benzoate was evaluated using 21 rats (strains not stated) per dose; doses administered in the diet were defined as 0.04 or 1.0% (≈ 24 or 595 mg/kg body weight/day).[3] The test substance was administered daily from day 0 of gestation to day 21 post-parturition. The results of examinations for external, skeletal, or visceral anomalies indicated that benzyl benzoate did not induce harmful effects in fetuses.

In a reproductive and developmental toxicity study, pregnant rats (no. and strain not stated) were fed diets supplemented with 0.04 or 1.0% benzyl benzoate from day 0 of gestation to day 21 post-parturition.[76]

76Another group of rats was fed a control diet. There were no effects on reproductive or developmental toxicity parameters; no external, skeletal, or visceral anomalies were observed in fetuses from either treatment group. Minor variations were observed. A significantly decreased number of fetuses with incomplete sternebrae was noted in the 1% benzyl benzoate treatment group.

Testicular atrophy was observed in 2 repeated dose dermal toxicity studies (90 days) on benzyl benzoate involving rabbits.[3] The exact doses at which this finding occurred were not stated. However, testicular atrophy was observed at daily doses > 0.5 g/kg/day. These studies are summarized in the Repeated Dose Toxicity – Dermal Studies section earlier in the report text.

Pregnant NMRI mice (34 animals) were injected s.c. with an unspecified dose of benzyl benzoate in castor oil on days 1 and 11 of gestation.[77] The animals were killed on gestation day 17. Untreated mice served as controls. Fetal observations relating to the following were made: counts, sex, weight, and malformations. There was no evidence of test substance-related effects on fetuses. Additional details were not included.

A developmental toxicity study was performed using *Drosophila melanogaster*.[78] One group of males and females was raised on food medium with 4% benzyl benzoate in ethanol and the other group was raised on control feed medium. Virgin Canton-S males and females were collected daily for 4 days and then mated. The percentage of eggs hatched was 6.5 times greater in flies on feed containing benzyl benzoate, compared to those on control feed.

The safety of benzyl benzoate lotion (25% benzyl benzoate) as a topical treatment for scabies during pregnancy was assessed using a population of 444 pregnant women and their matched controls (1,776 pregnant women).[79] The study population consisted of refugee and migrant women attending antenatal clinics on the Thai-Burmese border between August of 1993 and April of 2006. Most first treatments took place during the second and third trimesters, and the overall median gestation exposure was 24.5 weeks. Treated women (444) received 559 applications of butyl benzoate lotion (79.5%, 15.5%, 4.5%, and 0.l5% receiving 1, 2, 3, and 4 treatments, respectively).

Conditional Poisson regression was used to estimate risk ratios for outcomes of pregnancy (proportion of abortions, congenital abnormalities, neonatal deaths, stillbirths, and premature babies), mean birth weight, and estimated median gestational age for scabies and scabies-free women. Regarding pregnancy outcomes, there were no statistically significant differences between women treated with the lotion and their matched controls. Thus, there was no evidence of adverse effects on pregnancy outcome due to topical application of benzyl benzoate (25%) lotion.[79]

Benzoic Acid, Benzyl benzoate - Estrogenic effects

The estrogenic activity of benzoic acid was evaluated in the recombinant yeast human estrogen (ER_α) receptor assay *in vitro* and in uterotrophic assays involving immature female Alpk:AP_fSD rats (21 to 22 days old) and immature female Alpk:AP_fCD-1 mice.[80] Immature mouse uterotrophic assays involved 3 daily s.c. injections of benzoic acid in corn oil (100 and 1,000 µg/kg doses; 5 ml/kg = dose volume), ending on day 4. The same protocol was used for the rat assays, with the exception that benzoic acid in arachis oil was injected (doses of 10, 100, and 1,000 µg/kg).

Benzoic acid (10^{-7} to 10^{-3} M) was negative in the recombinant yeast human estrogen (ER_α) receptor assay *in vitro*. Overall (rat and mouse assays), benzoic acid produced one statistically significant and 3 statistically nonsignificant increases in average uterine weight and one significant and 6 nonsignificant decreases in average uterine weight. Therefore, in all uterotrophic assays, benzoic acid did not produce any reproducible evidence of estrogenic activity. Results for vehicle controls were negative and the positive control, estradiol, was uterotrophic.[80]

The estrogenic activity of benzyl benzoate (concentration range: 10^{-9} to 10^{-4} M) *in vitro* was evaluated in the E-screen test using MCF-7 breast cancer cells. Untreated cultures served as controls. In this test, MCF-7 cells proliferate in the presence of estrogen. Cell numbers were assessed by measurement of the total protein content, using the sulforhodamine B assay. Compared to control cultures, benzyl benzoate did not increase the proliferation of MCF-7 cells ($p > 0.05$) over the range of concentrations tested.[81]

The estrogenic activity of benzyl benzoate, benzyl salicylate, and butylphenylmethylpropional (Lilial) in the estrogen-responsive MCF7 human breast cancer cell line was evaluated using the following assays: competitive binding assay to estrogen receptor (ER) of MCF7 cytosol, competitive binding assay to recombinant ERα and ERβ, and the assay of stably transfected ERE-CAT reporter gene in MCF7 cells.[82] In the latter assay, The ERE-CAT vector consisted of the estrogen response element (ERE) of the vitellogenin A2 gene from -331 to -295 bp cloned into the pBLCAT2 vector upstream of the thymidine kinase (tk) promoter. Cell proliferation experiments were also performed.

The following results indicate that all 3 chemicals produced estrogenic responses in cultured human breast cancer cells *in vitro*. [82] At 3,000,000-fold molar excess, each chemical was able to partially displace [^{3}H]estradiol from recombinant human estrogen receptors ERα and ERβ, and from cytosolic ER of MCF7 cells.

At concentrations in the 5 x 10^{-5} to 5 x 10^{-4} M range, benzyl benzoate and the other 2 chemicals were able to increase the expression of a stably integrated estrogen-responsive reporter gene (ERE-CAT) and of the endogenous estrogen-responsive pS2 gene in MCF7 cells; however, these effects were at a lesser extent when compared to 10^{-8} M 17β-estradiol (5,000 to 50,000 molar excess of benzyl benzoate).

In cell proliferation experiments, each chemical increased the proliferation of estrogen-dependent cells over a 7-day period. Cell proliferation was inhibited by fulvestrant (antiestrogen), suggesting an ER-mediated mechanism. However, over a 35-day period, the extent of proliferation in the presence of 10^{-4} M benzyl benzoate, benzyl salicylate, or butylphenylmethylpropional increased to the same magnitude as that observed in the presence of 10^{-8} M 17β-estradiol over a 14-day period (10,000 molar excess of benzyl benzoate).[82]

GENOTOXICITY

According to the OECD SIDS initial assessment report on benzyl alcohol, benzoic acid, and its sodium and potassium salt, the weight of evidence of the in vitro and in vivo genotoxicity data indicates that these chemicals are not mutagenic or clastogenic. Mixed/equivocal results were apparent in in vitro assays, but negative results were reported in in vivo genotoxicity assays. Other test results appear to be consistent with these findings. Benzoic acid was non-genotoxic in the micronucleus test, but results were positive for sodium benzoate and potassium benzoate in the spore rec-assay to assess DNA damaging activity. Also, sodium benzoate caused a significant increase in sister chromatid exchanges when compared to control cultures. Benzyl benzoate was not mutagenic in the Ames test, but results were positive for benzyl alcohol and benzoic acid in the in vitro comet assay for evaluating DNA-damaging potential.

Benzoic Acid, Sodium Benzoate, Potassium Benzoate, and Benzyl Alcohol

According to the OECD SIDS initial assessment report on benzyl alcohol, benzoic acid, and its sodium and potassium salt, each chemical was not mutagenic in *in vitro* Ames tests. Various results (negative and positive [chromosomal/chromatid responses]) for sodium benzoate, potassium benzoate, and benzyl alcohol were obtained in other *in vitro* genotoxicity assays. However, while some mixed and/or equivocal *in vitro* chromosomal/chromatid responses have been observed, sodium benzoate and benzyl alcohol were not genotoxic in the *in vivo* cytogenetic assay, the micronucleus test, or in other *in vivo* assays. The weight of evidence of the *in vitro* and *in vivo* genotoxicity data indicates that these chemicals are not mutagenic or clastogenic.[2]

In the *in vitro* comet assay, the DNA-damaging potential of benzoic acid and benzyl alcohol was evaluated using human blood cells (lymphocytes).[83] This assay is able to detect single and double strand breaks in DNA. Benzoic acid was evaluated at concentrations ranging from 0.05 to 5 mM and, benzyl alcohol, at concentrations ranging from 1 to 50 mM. Benzoic acid was tested at lower concentrations (≤ 5 mM) because this chemical has apoptotic effects at higher concentrations. The tail moment and % tail DNA in chemicals evaluated were compared to results for the solvent control (distilled water). Significantly increased tail moment and % tail DNA were noted only with 5 mM benzoic acid and with 25 and 50 M benzyl alcohol, indicating genotoxicity. A dose response was not observed.

Benzoic acid (in DMSO) was evaluated in the micronucleus test at concentrations ranging from 250 to 1,000 µg/ml (with and without metabolic activation) using L5178Y TK+/- clone 3.7.2C mouse lymphoma cells. Cultures without benzoic acid served as negative controls and mitomycin C served as the positive control. Benzoic acid was non-genotoxic over the range of concentrations tested, both with and without metabolic activation. The positive control was genotoxic.[84]

The genotoxicity of sodium benzoate was evaluated in the sister chromatid exchanges assay (SCE assay) using human blood lymphocyte cultures incubated for 72 h. Preparations were scored blindly for cells in their first mitosis, second mitosis, and third and subsequent divisions. Forty SCEs second division cells from each culture were scored for SCEs. Compared to

negative control cultures, sodium benzoate (0.02, 0.2, 2, 4, and 8 mM) caused statistically significant delays in cell division ($p < 0.01$), indicative of weak cytostatic activity, but did not induce cytotoxicity. Also, when compared to negative control cultures, 8 mM sodium benzoate induced a statistically significant increase ($p < 0.01$) in SCEs/cell. Sodium benzoate (2 mM) induced a statistically significant decrease ($p < 0.05$) in SCEs/cell when compared to the 8 mM sodium benzoate culture.[85]

The DNA-damaging activity of sodium benzoate and potassium benzoate was evaluated in the spore rec-assay using *Bacillus subtilis* M45 (rec^-) and H17 (rec^+) strains with and without metabolic activation. Sodium benzoate (in water) was tested at doses of 16 and 20 mg/disk and potassium benzoate (in mixed solution of water and ethanol [1:1]) was tested at doses of 15 and 20 mg/disk. Results for both chemicals were judged positive in this assay.[86]

Benzyl Benzoate

In the Ames test, benzyl benzoate was not mutagenic to *Salmonella typhimurium* strains TA98 or TA 100 at doses up to 5,000 µg/plate (plate incorporation assay) or 5,000 mg/plate (pre-incubation assay). Benzyl Benzoate also was not mutagenic to the following strains at doses up to 3 µmol/plate (pre-incubation assay) with or without metabolic activation: TA98, TA100, TA1525, and TA 1537. In the recombination assay, benzyl benzoate was not mutagenic to *Bacillus subtilis* strains H17 or M45 at a concentration of 10 mg/disk.[3]

In another Ames test, the mutagenicity of benzyl benzoate (in ethanol) was evaluated using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. Benzyl benzoate was tested at a concentration of 3 µmol/plate with and without metabolic activation and was not found to be mutagenic.[87]

Photogenotoxicity

The photogenotoxicity of benzoic acid (0.5%) and sodium benzoate (0.5%) has been demonstrated in vitro using bacterial cell suspensions.

Benzoic Acid and Sodium Benzoate

The photogenotoxicity of benzoic acid (0.5%) and sodium benzoate (0.5%) and other food additives was evaluated using *Escherichia coli* cell suspensions.[88] Initially, the cytotoxic and genotoxic potential of each in the absence of sunlight (200 to 3,000 nm; mean intensity = 5.8×10^2 Wm^{-2}) was evaluated by allowing the cells to remain in contact with the additive for 80 min in the dark. Neither benzoic acid nor sodium benzoate affected cell viability (i.e., not cytotoxic) or the number of spontaneous mutations in the absence of sunlight. The number of spontaneous mutations was 2.09 mutations per 10^8 cells. Also, these chemicals did not induce mutations in the absence of sunlight.

Plates containing the cellular suspension (5 ml) and a food additive (0.5% concentration) were exposed to sunlight for periods ranging from 0 min to 60 min. Exposure to sunlight resulted in cell death in the presence or absence of benzoic acid or sodium benzoate. When cells were exposed to direct sunlight in the absence of benzoic acid or sodium benzoate, the number of induced mutations increased with duration of exposure (5.1×10^2 mutations per 10^8 cells after 60 min). In the presence of benzoic acid or sodium benzoate, the number of induced mutations increased with the duration of exposure to sunlight. This increase was almost additive over that observed with sunlight exposure alone. After 60 min, there were approximately 1×10^3 mutations per 10^8 cells.[88]

Effect on DNA Synthesis

Sodium benzoate caused a significant increase in the DNA content of protozoan nuclei, suggestive of stimulation of mitosis.

Sodium Benzoate

Aqueous sodium benzoate, at a concentration of 7.20 mg/ml, was added to *Tetrahymena pyriformis* in an experimental series consisting of six 100 ml cultures. Another experimental series, without sodium benzoate, served as the control. The quantitative analysis of DNA content of the protozoan nuclei was performed using an image analysis system. Sodium

benzoate caused a statistically significant increase ($p < 0.01$) in DNA content, suggestive of stimulation of mitosis. The authors speculated that this observation might represent a direct cytotoxic effect due to increased DNA content of nuclei. [89]

CARCINOGENICITY

Benzyl alcohol was not carcinogenic when tested dermally on mice at 2.00% in a nonoxidative hair dye. The National Toxicology Program (NTP) considered benzyl alcohol negative for carcinogenicity following 2 years of oral dosing in rats(doses up to 400 mg/kg) and mice (doses up to 200 mg/kg), but the EPA considered the 3 of 48 incidence of adrenal cortex adenoma (male mice) to be equivocal evidence of carcinogenic activity rather than negative. Following dermal application to mice, a nonoxidative hair dye containing 2.0% benzyl alcohol and 0.016% benzoic acid was negative for carcinogenicity. Sodium benzoate was negative for carcinogenicity when administered orally at up to 2% to rats (in feed for up to 2 years) or mice (in a life-time drinking water study).

The following carcinogenicity study summaries are included in the CIR final report on benzyl alcohol, benzoic acid, and sodium benzoate that was published in 2001.[1]

Benzyl Alcohol and Benzoic Acid

Groups of 100 F344/N rats 50 each sex) were dosed orally with 200 or 400 mg/kg benzyl alcohol in corn oil, 5 days per week for 103 weeks. Groups of 100 $B6C3F_1$ mice were dosed with 100 or 200 mg/kg benzyl alcohol following the same schedule. During week 80, mice were mistakenly dosed for four days with 375 (low-dose group) and 750 mg/kg (high-dose group) of α-methylbenzyl alcohol. Dose-related negative trends were noted in the incidences of anterior pituitary gland neoplasms in female rats (vehicle control, 29/50; low dose, 17/47; high dose, 9/49) and of Harderian gland adenomas in male mice (8/50; 3/50; 2/50). Epithelial hyperplasia of the nonglandular stomach was noted in 4 of 50 high-dose male rats; it was not found in controls or low-dose male rats. An increased incidence of adenomas of the adrenal cortex noted in high-dose male mice (0/48; 0/44; 3/48) was within historical range and not considered compound-related. The NTP investigators considered the study negative for benzyl alcohol-induced carcinogenicity. However, reviewing the study, the EPA considered the 3 of 48 incidence of adrenal cortex adenoma to be "equivocal evidence of carcinogenic activity rather than negative."

From the Final Report on benzyl alcohol, benzoic acid, and sodium benzoate[1]

A skin painting study was performed using groups of 120 Eppley Swiss mice (60 per sex). A non-oxidative hair dye containing 2.0% benzyl alcohol and 0.016% benzoic acid was painted onto the skin at a dose of 0.05 ml/application, three times weekly for 20 months. Sites were shaved of hair 24 h before each application and a new bottle of dye was used each week. Two groups of control animals were shaved but not treated. Nine months into the study, 10 mice/sex/group were killed. Body weights and survival differed little between treatment and control groups. Varying degrees of chronic dermal inflammation were noted in all groups, including the controls. A significant ($p < .01$) increase in malignant lymphomas was noted in treated females (23/60). However, the researchers noted that one concurrent control group had a very low incidence (7/60 or 12%) of that tumor type. The rate was 22% for the other control group and had averaged 33% for three control groups in previous studies. Thus, the findings were not considered treatment-related. The incidence of pulmonary adenomas and hepatic hemangiomas, which are common in this mouse strain, were similar between treated and control groups. No unusual neoplasms were observed.

From the Final Report on benzyl alcohol, benzoic acid, and sodium benzoate[1]

Sodium Benzoate

For 18 to 24 months, groups of Fischer 344 rats (50 males and 52 females per group) received feed containing 2% or 1% sodium benzoate. The doses corresponded to the maximum tolerated dose (MTD) and ½MTD as determined in 6-week toxicity studies. A control group of 25 male and 43 female rats received untreated feed. Average daily sodium benzoate intake was 280 and 202 mg, respectively, for male and female rats of the 2% group, and 141 and 102 mg, respectively, for male and female rats of the 1% group. No clinical signs of toxicity or differences in average body weight or mortality

rates were noted in treated rats when compared with controls. Neoplasms that were present in treated rats were similar in type and number to those in controls. No evidence of sodium benzoate-related carcinogenicity was observed.

From the Final Report on benzyl alcohol, benzoic acid, and sodium benzoate[1]

In a life-time drinking water study, 100 Albino Swiss mice (50 of each sex) were supplied with water containing 2% sodium benzoate. A control group of 200 mice was supplied with untreated water. Average daily intake of sodium benzoate was 124.0 and 119.2 mg for males and females, respectively. Sodium benzoate treatment did not affect survival. No carcinogenic effect attributable to treatment was noted at necropsy.

From the Final Report on benzyl alcohol, benzoic acid, and sodium benzoate[1]

SUMMARY

The safety of the following ingredients in cosmetics is reviewed in this safety assessment: Benzyl alcohol, benzoic acid, sodium benzoate, calcium benzoate, magnesium benzoate, potassium benzoate, and benzyl benzoate. Most of these ingredients function as fragrance ingredients/preservatives in cosmetic products. Together, data reported to the Food and Drug Administration's Voluntary Cosmetic Registration Program in 2010 and the results of a 2010 Personal Care Products industry survey indicated use of the following ingredients in cosmetics: benzyl alcohol, benzoic acid, sodium benzoate, calcium benzoate, potassium benzoate, and benzyl benzoate. According to this industry survey, ingredient use concentrations have ranged from 0.000001% (sodium benzoate) to 10% (benzyl alcohol).

Among the methods of manufacture identified are the production of benzyl alcohol via the action of sodium or potassium carbonate on benzyl chloride and the production of benzoic acid via the decarboxylation of phthalic anhydride. Hydroxyl radical generated by the metal-catalyzed reduction of O_2 and H_2O_2 by ascorbic acid can attack benzoic acid to produce benzene under conditions that are prevalent in beverages. Additionally, exposure to UV light and elevated temperature over the shelf life of beverages may result in benzene formation in products containing benzoic and ascorbic acids. The U.S. beverage industry voluntarily reformulated beverages that were found to contain benzene levels at or above the maximum contaminant level for drinking water established by the U.S. Environmental Protection Agency. Limits for heavy metal impurities in food-grade sodium benzoate (as Pb, $\leq$ 2 mg/kg) and pharmaceutical-grade potassium benzoate (heavy metals, $\leq$ 0.001%) have been established.

Benzyl alcohol is metabolized to benzoic acid via simple oxidation. Benzoic acid and sodium benzoate are rapidly absorbed from the gastrointestinal tract of mammals, conjugated with glycine in the liver, and then excreted as hippuric acid. In *in vitro* studies, the percutaneous absorption of benzoic acid through guinea pig skin and the percutaneous absorption of benzyl alcohol and benzyl benzoate through human skin was reported. The percutaneous absorption and urinary excretion of benzyl alcohol and benzyl benzoate was observed following dermal application to rhesus monkeys.

Benzoic acid (up to 1,000 µg/kg, s.c. injection) did not induce any reproducible evidence of estrogenic activity in uterotrophic assays involving immature female Alpk:AP$_f$SD rats and female Alpk:AP$_f$CD-1 mice. However, benzyl benzoate induced estrogenic responses in cultured human breast cancer cells *in vitro*. At 3,000,000-fold molar excess, benzyl benzoate was able to partially displace [^{3}H]estradiol from recombinant human estrogen receptors ERα and ERβ, and from cytosolic ER of MCF7 cells. The antiparasitic activity of benzyl benzoate has been demonstrated *in vitro*.

Neither acute (up to 12 mg/L aerosol/dust) nor repeated inhalation (up to 1,000 mg/m^3) exposures to benzyl alcohol or benzoic acid caused death in rats. Results of the repeated dose inhalation toxicity study also indicated no test substance-related macroscopic or microscopic findings for either test substance. Overall, the results of acute oral and dermal toxicity studies indicated a low level of toxicity for benzyl alcohol, benzoic acid, and benzyl benzoate. The same was true for repeated dose oral toxicity studies on benzoic acid and its salts and benzyl alcohol. Systemic/dermal effects induced by benzyl benzoate were observed in rats receiving repeated dermal doses up to 2.0 g/kg and in rabbits receiving repeated dermal doses up to 4.0 ml/kg. However, test substance-related toxic signs were not observed in other species that received repeated doses of benzyl benzoate.

Benzyl alcohol (4% aqueous), benzoic acid (undiluted), and its sodium salt (concentration not stated) were irritating to the eyes of rabbits, and it was expected that potassium benzoate would be irritating as well. Benzyl benzoate (undiluted) was irritating to the eyes of rabbits and humans. Undiluted benzyl alcohol and benzoic acid were slightly irritating and benzyl benzoate was non-irritating to the skin at concentrations up to 50% in animal studies. Undiluted benzyl benzoate was a non-irritant in human subjects. In animal studies, benzyl benzoate induced sensitization reactions ranging from none to moderate. Moderate sensitization was observed at a concentration of 10% benzyl benzoate, but not at lower concentrations, and there was one report of mild sensitization at a concentration of 40%. Benzyl benzoate was classified as non-sensitizer when tested at a concentration of 30% in healthy human subjects. Most of the skin sensitization studies on benzyl benzoate involved groups of patients, and mixed results regarding sensitization potential were reported.

A slightly positive reaction was observed in a phototoxicity study involving hairless mice tested with an unspecified concentration of benzyl benzoate (4, 24 h exposures). Photo-irritation was not observed in guinea pigs tested with benzyl benzoate at concentrations up to 30%. Moderate photohemolytic activity in human erythrocytes was observed in the presence of benzyl benzoate, but significant photohemolytic activity was not associated with sodium benzoate or benzyl alcohol in these cells

Developmental effects only were observed in the presence of marked maternal toxicity in rats fed sodium benzoate in the diet ($\geq$ 2800 mg/kg/day; NOAEL = 1400 mg/kg/day). Testicular atrophy was observed in rabbits that received repeated dermal doses of benzyl benzoate (> 0.5 g/kg/day). However, overall, benzyl alcohol, benzoic acid, and sodium benzoate were not classified as reproductive/developmental toxicants in oral and dermal animal studies. There was no evidence of adverse effects on pregnancy outcome due to topical application of benzyl benzoate (25%) lotion in pregnant women.

Mixed/equivocal results were apparent in *in vitro assays*, but negative results were reported in *in vivo* genotoxicity assays on benzyl alcohol, benzyl benzoate, benzoic acid, and its sodium and potassium salt. The photogenotoxicity of benzoic acid (0.5%) and sodium benzoate (0.5%) has been demonstrated in vitro using bacterial cell suspensions. Benzyl alcohol was negative for carcinogenicity when dermally tested on mice at 2.00% in a nonoxidative hair dye. NTP considered it negative for carcinogenicity following 2 years of oral dosing in rats (up to 400 mg/kg) and mice (up to 200 mg/kg), but the EPA considered the 3 of 48 incidence of adrenal cortex adenoma (male mice) to be equivocal evidence of carcinogenic activity rather than negative. Following dermal application to mice, a nonoxidative hair dye containing 2.0% benzyl alcohol and 0.016% benzoic acid was negative for carcinogenicity. Sodium benzoate was negative for carcinogenicity when administered orally at up to 2% to rats (in feed for up to 2 years) or mice (in a life-time drinking water study).

DISCUSSION

The Expert Panel noted gaps in the available safety data for some of the ingredients in this safety assessment. The available data on many of the ingredients are sufficient, however, and similarity between structures and structure activity relationships suggest that the available data can be extrapolated to support the safety of the entire group.

The negative inhalation toxicity data provided satisfied the CIR Expert Panel's request for data and support the safe use of these ingredients in cosmetic products in which inhalation is a primary route of exposure.

The Panel did note the formation of adenomas in the adrenal cortex of $B6C3F_1$ mice receiving a high dose of benzyl alcohol in an oral carcinogenicity study. These adenomas were considered benign by the NTP, and the Panel concurs. The Panel acknowledged that EPA reviewed the results of this study and concluded that the results suggest equivocal evidence of carcinogenicity, but it was the Panel's view that there was no evidence of carcinomas in the animals.

Data from model studies, pertaining to the beverage industry, reviewed by the Expert Panel raised the possibility that benzene could be formed from benzoic acid and benzoates in cosmetics. The yields of benzene, however, that could be generated by photodegradation are sufficiently low that they do not constitute a relevant hazard.

In its previous safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate, the Panel established a 5% safe concentration limit for benzyl alcohol, benzoic acid, and sodium benzoate and a 10% safe concentration limit for benzyl

alcohol in hair dyes. On review of the current practices of use and concentration, it was clear that industry has adhered to those limits. Accordingly, reference to present practices of use and concentration is sufficient to assure safety.

CONCLUSION

CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- benzyl alcohol
- benzoic acid
- sodium benzoate
- calcium benzoate
- magnesium benzoate*
- potassium benzoate
- benzyl benzoate

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

Table 1. Benzyl Alcohol and Benzoic Acid and its Salts and Ester[22]

Chemical Names/CAS Nos.	Definitions*	Functions in Cosmetics
Benzyl Alcohol Alcohol benzylicus; benzenemethanol; benzylic alcohol; phenylcarbinol; phenylmethanol; phenylmethyl alcohol; and α-toluenol; CAS No. 100-51-6	An aromatic alcohol	External analgesics; fragrance ingredients; oral health care drugs; preservatives; solvents; and viscosity decreasing agents
Benzoic Acid Acidum benzoicum; benzenecarboxylic acid; benzeneformic acid; benzenemethanoic acid; carboxybenzene; dracyclic acid; phenylcarboxylic acid; and phenylformic acid; CAS No. 65-85-0	An aromatic acid	Fragrance ingredients; preservatives; and pH adjusters
Sodium Benzoate Benzoic acid, sodium salt and natrii benzoas (EP); CAS No. 532-32-1	The sodium salt of benzoic acid	Corrosion inhibitors; fragrance ingredients; and preservatives
Calcium Benzoate Benzoic Acid, Calcium Salt and Calcium Dibenzoate; CAS No. 2090-05-3	The calcium salt of benzoic acid	Preservatives
Magnesium Benzoate Benzoic Acid, magnesium salt and magnesium dibenzoate; CAS No. 553-70-8	The magnesium salt of benzoic acid	Preservatives
Potassium Benzoate Benzoic Acid, Potassium Salt; CAS No. 582-25-2	The potassium salt of benzoic acid	Preservatives
Benzyl Benzoate Benylate; benzoic acid, benzyl ester; benzoic acid, phenylmethyl ester; benzylis benzoas (EP); and phenylmethyl benzoate; CAS No. 120-51-4	The ester of benzyl alcohol and benzoic	Fragrance ingredients; pesticides; and solvents

***See Figure 1 for structures, completing the definition of each chemical.**

Table 2. Properties of Benzyl Alcohol and Benzoic Acid and its Salts and Ester[90]

Properties	Benzyl Alcohol	Benzoic Acid	Sodium Benzoate	Calcium Benzoate	Magnesium Benzoate	Potassium Benzoate	Benzyl Benzoate
Form	Liquid	Monoclinic plates	White granules		White powder	White solid[2]	Leaflets/oily liquid
Molecular weight	108.14	122.12	144.1	121.12[91]	266.53	160.21	212.24
Density	1.045	1.321					1.118
Melting point	-15.19°C	122.4°C	330.6°C[2]		200°	330.6°C[2]	21°C
Boiling point	204.7°C	249.2°C	464.9°C[2]			464.9°C[2]	323-324°C
Water Solubility	dissolves (1g) in ~ 25 ml water	2.9 g/l	1 g dissolves in 1.8 ml water		Soluble in 20 parts water	556 g/l[2]	Practically insoluble in water
logP	1.1[2]	1.8[2]	-2.269[2]		1.53[92]	-2.269[2]	3.68[93]
UV absorption max.					228.6 nm[91]	226.8 nm[91]	256 nm[91]

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011[23,24]

	Benzoic Acid		**Benzyl Alcohol**		**Sodium Benzoate**		**Calcium Benzoate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type								
Eye Area	23	0.00005 to 0.2	109	0.000008 to 0.8	58	0.00001 to 0.4	NR	NR
Incidental Ingestion	64	0.003 to 2	23	0.000006 to 0.9	33	0.001 to 0.6	NR	NR
Incidental Inhalation-sprays	16	0.000003 to 0.5	496	0.0002 to 3	43	0.001 to 0.5	NR	0.004
Incidental Inhalation-powders	4	0.000002 to 0.001	28	0.0001 to 0.3	4	0.3	NR	0.002
Dermal Contact	503	0.000002 to 5	1673	0.000008 to 3	1075	0.000001 to 1	NR	0.002 to 0.004
Deodorant (underarm)	1	0.03 to 0.5	38	0.03 to 0.5	2	0.5		
Hair - Non-Coloring	97	0.00002 to 1	361	0.0002 to 3	431	0.000005 to 1	NR	NR
Hair-Coloring	22	0.004 to 0.03	56	0.00007 to 10	18	0.008 to 0.5	NR	NR
Nail	7	0.0005 to 0.2	3	0.00002 to 0.5	7	0.00001 to 0.001	NR	NR
Mucous Membrane	201	0.000003 to 2	269	0.000006 to 1	407	0.0004 to 1	NR	NR
Baby Products	3	0.000002 to 0.08	25	0.004 to 0.9	26	0.3 to 1	NR	NR
Duration of Use								
Leave-On	378	0.000002 to 5	1491	0.000008 to 3	619	0.000001 to 1	NR	0.002 to 0.004
Rinse off	295	0.000003 to 5	651	0.000006 to 10	936	0.000001 to 1	NR	NR
Diluted for (bath) use	23	0.000003 to 0.08	20	0.001 to 0.9	15	0.004 to 1	NR	NR
Totals/Conc. Range	696	0.000002 to 5	2162	0.000006 to 10	1570	0.000001 to 1	NR	0.002 to 0.004

	Potassium Benzoate		**Benzyl Benzoate**		**Magnesium Benzoate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	NR	NR	5	0.0006 to 0.002	NR	NR
Incidental Ingestion	NR	NR	82	0.000005 to 0.2	NR	NR
Incidental Inhalation-sprays	NR	NR	583	0.002 to 4	NR	NR
Incidental Inhalation-powders	NR	NR	30	0.001 to 0.3	NR	NR
Dermal Contact	NR	0.002	1321	0.0001 to 4	NR	NR
Deodorant (underarm)	NR	NR	47	NR	NR	NR
Hair - Non-Coloring	1	NR	259	0.006 to 4	NR	NR
Hair-Coloring	NR	NR	21	0.07 to 2	NR	NR
Nail	1	0.0003	26	0.2 to 0.8	NR	NR
Mucous Membrane	NR	0.0002	227	0.000005 to 2	NR	NR
Baby products	NR	NR	3	NR		
Duration of Use						
Leave-On	2	0.0003	1396	0.000005 to 4	NR	NR
Rinse off	NR	0.0002	282	0.0001 to 2	NR	NR
Diluted for (bath) use			31	0.0005 to 2	NR	NR
Totals/Conc. Range	2	0.0002 to 0.0003	1709	0.000005 to 4	NR	NR

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

Table 4. Acute Oral Toxicity Studies on Potassium and Benzyl Benzoate

Material	Animals	Test Procedure	Results
Potassium Benzoate	Rats, mice, and guinea pigs	Not stated	LD50 > 10,000 mg/kg[2]
Benzyl Benzoate (undiluted)	10 rats/dose	Oral dosing followed by 6-day observation period; no GLP*	LD50 = 1891 mg/kg[3]
Benzyl Benzoate	20 rats	Single dose by gavage; 14-day observation period; no GLP	LD50 = 2800 mg/kg[3]
Benzyl Benzoate	Rats (no. not stated)	Not stated	LD50 = 500 mg/kg[3]
Benzyl Benzoate (in arachis oil)	Rats (no. not stated)	OECD guideline 401; 100 to 2000 mg/kg oral doses; GLP study	LD50 > 2000 mg/kg[3]
Benzyl Benzoate (in arachis oil)	10 Sprague-Dawley albino rats	Single 5.0 ml/kg dose; 14-day observation period	LD50 > 2000 mg/kg[94]
Benzyl Benzoate	Rats (no. not stated)	Not stated	LD50 = 1700 mg/kg[95]
Benzyl Benzoate (1% in gum tragacanth suspension)	5 groups of 10 Sprague-Dawley rats	Doses up to 4000 mg/kg total (i.e., four 250 mg/kg doses at 40 ml/kg dose volume/dose); 14-day observation period	LD50 = 1.16 g/kg[96]
Benzyl Benzoate (in Tween 80 + gum tragacanth vehicle)	6 groups of 10 Sprague-Dawley rats 5 males, 5 females/group)	6 different dose levels (dose volume = 40 ml/kg)	LD50 = 1160 mg/kg[97]
Benzyl Benzoate (in tween 80 solution + methylcellulose vehicle)	Rats (25 males, 25 females)	Not stated	LD50 = 1550 mg/kg[98]
Benzyl Benzoate (in tween 80 solution + gum tragacanth vehicle)	Sprague-Dawley rats (5 males, 5 females)	10 mg/kg total dose (i.e., four 2500 mg/kg doses); 14-day observation period	LD50 > 10 g/kg[99]
Benzyl Benzoate	10 rats/dose	Dosing followed by 6-day observation period	LD50 = 1.7 ml/kg[100]
Benzyl Benzoate	20 rats	Dosing followed by 2-week observation period	LD50 = 2.8 g/kg[63]
Benzyl Benzoate (undiluted)	10 mice/dose	Dosing followed by 6-day observation period; no GLP	LD50 = 1557 mg/kg[3]
Benzyl Benzoate	10 mice/dose	Dosing followed by 6-day observation period	LD50 = 1.4 ml/kg[100]
Benzyl Benzoate	Mice (no. not stated)	Not stated	LD50 = 1400 mg/kg[3]
Benzyl Benzoate (undiluted)	10 rabbits/dose	Dosing followed by 6-day observation period; no GLP	LD50 = 2002 mg/kg[3]
Benzyl Benzoate	10 rabbits/dose	Dosing followed by 6-day observation period	LD50 = 1.8 ml/kg[100]
Benzyl Benzoate	9 rabbits	Single dose by gavage; 14-day observation period; no GLP	LD50 = 1680 mg/kg[3]
Benzyl Benzoate	12 rabbits	Dosing followed by 2-week observation period	LD50 = 1.68 g/kg[63]
Benzyl Benzoate	11 cats	Single dose by gavage; 14-day observation period; no GLP	LD50 = 2240 mg/kg[3]
Benzyl Benzoate	4 dogs	Single dose by gavage; 14-day observation period; no GLP	LD50 > 2244 mg/kg[3]
Benzyl Benzoate (undiluted)	10 guinea pigs/dose	Oral dosing followed by 6-day observation period ; no GLP	LD50 = 1112 mg/kg[3]
Benzyl Benzoate	Guinea pigs (no. not stated)	Not stated	LD50 = 1000 mg/kg[3]
Benzyl Benzoate	10 guinea pigs/dose	Dosing followed by 6-day observation period	LD50 = 1 mg/kg[100]

*GLP = good laboratory practice

Table 5. Skin Irritation and Sensitization Studies

Test Substance	Animals/Subjects	Doses/Concentrations Tested	Procedure	Results
		Animal Studies		
Benzyl alcohol (purity not stated)	Rabbits (no. not stated)	undiluted benzyl alcohol (10 mg)	dose applied for 24 h	Slightly irritating[2]
Benzoic Acid (purity not stated)	3 albino rabbits	undiluted benzoic acid (0.5 g/kg)	dose applied to flank under semi-occlusive dressing for 4 h	Slightly irritating[2]
Sodium Benzoate	Rabbits (no. not stated)	undiluted benzyl alcohol (10 mg)	dose applied for 24 h	Slightly irritating[2]
Sodium Benzoate	Rabbits (no. not stated)	Concentration not stated	OECD Guide - line 404 protocol	Non-irritating[2]
Benzyl Benzoate	Guinea pigs (no. not stated)	undiluted benzyl benzoate (15 g/kg)	Dose applied to intact abdominal skin (duration not stated)	Non-irritating[59]
Benzyl Benzoate (50%)	Guinea pigs (no. not stated)	up to 50%	Not stated	Non-irritant[71]
Benzyl Benzoate (40%)	10 female Hartley albino guinea pigs	10% induction concentration; challenge concentrations up to 40%	10% w/v in complete adjuvant (intradermal induction); 10% w/v in Freund's complete adjuvant + saline (topical induction); topical challenge concentrations up to 40% benzyl benzoate in propylene glycol + acetone	No reactions at challenge concentrations of 5% and 10% benzyl benzoate; mild reactions at 40% challenge concentration (4 of 10 animals)
Benzyl Benzoate (25% in acetone/PEG vehicle)	4 male guinea pigs	up to 25%	24-h occlusive patch test	Non-irritant[101]
Benzyl Benzoate (10%)	Guinea pigs (no. not stated)	10%	Maximization test	Moderate sensitization[102]
Benzyl Benzoate (10% in ethanol)	4 female guinea pigs	up to 10%	24-h occlusive patch test; up to 10% during induction and challenge with 2.5%	Non-irritating at 5 and 10% concentrations. Barely perceptible erythema (at 24 and 48 h) at 2.5% concentration[103]
Benzyl Benzoate (10% in acetone)	10 guinea pigs	10%	Modified Fruend's complete adjuvant test	Weak sensitization[104]
Benzyl Benzoate (1 and 10%)	Guinea pigs (no. not stated)	1% and 10% (15 or 30 mg)	Modified Freund's complete adjuvant test: Challenge with 1% and 10% benzyl benzoate (in acetone)	Weak sensitization at both concentrations[105]
Benzyl Benzoate	Guinea pigs (no. not stated)	Not stated	Maximization test (no GLP)	Non-sensitizer[3]
Benzyl Benzoate	Guinea pigs (6 to 8 per group)	Not stated	Open epicutaneous test (24 h application)	Non-sensitizer[3]
Benzyl Benzoate	4 female New Zealand albino rabbits	Undiluted benzyl benzoate (0.5 ml/2.5 cm^2)	4 h semiocclusive patch test	Non-irritant[106]
Benzyl Benzoate	Rabbits (no. not stated)	Not stated	3-week subacute skin toxicity test	Very mild gross skin irritation[100]
		Predictive Tests		
Benzyl Alcohol	31 healthy subjects	0.2 ml benzyl alcohol	Hill Top chamber with Webril pad applied to upper arm for up to 4 h	Skin irritation in 1 subject[107]
Benzyl Alcohol lotion 5% (Ulesfia TM)	485 subjects	Lotion tested as supplied	Topical treatment of head lice program	Low frequency of application site irritation (2.3% incidence)[42]

Table 5. Skin Irritation and Sensitization Studies

Test Substance	Animals/Subjects	Doses/Concentrations Tested	Procedure	Results
Benzoic Acid	86 healthy subjects (mean age = 37.3 years)	1 M in petrolatum	Finn chambers applied to volar arm for 20 min	Caused contact urticaria[108]
Benzoic Acid	58 healthy subjects (mean age = 39 years)	1 M in petrolatum (50 µl volume)	Finn chambers applied to volar arm for 20 min	Caused contact urticaria[109]
Benzyl Benzoate	18 subjects (18+ years)	5 to 10 drops of undiluted benzyl benzoate	Closed patch containing benzyl benzoate applied to healthy and locally inflammed skin for up to 48 h	No skin irritation[59]
Benzyl Benzoate	Male and female subjects (no. not stated; 18+ years)	undiluted benzyl benzoate (1cm-diameter area)	24-h closed patch test	No skin irritation[110]
Benzyl Benzoate (50% in diethyl phthalate/ethanol)	21 subjects (24 to 70 years old)	50% (0.3 ml)	24-h occlusive patch test	Minimal erythema in 3 subjects; negligible irritation potential[111]
Benzyl Benzoate (50% in ethanol/diethyl phthalate)	129 subjects (46 males, 83 females)	50% (0.3 ml)	RIPT (24-h applications)	No effects[112]
Benzyl Benzoate (30% in petrolatum	Patients (no. not stated)	30%	Maximization test	No positive reaction[3]
Benzyl Benzoate (30% in petrolatum)	20 healthy males	30%	Occlusive patch test; 5 48 h applications to evaluate sensitization potential	No positive reaction[113]
Benzyl Benzoate (20% in vaselinum aldum or unguentum hydrophilicum vehicle)	34 healthy male and female subjects	20%	48-h closed patch test	No skin irritation[114]
Benzyl Benzoate (4% in petrolatum)	25 healthy male and female subjects	4%	48-h closed patch test	No skin irritation[115]
Benzyl Benzoate (2% in unguentum simplex or unguentum hydrophilicum vehicle)	30 healthy male and female subjects (18 + years)	2%	24- to 72-h closed patch test	No skin irritation[114]
		Provocative Tests/Treatment		
Benzyl Alcohol (1% in petrolatum)	11,373 dermatitis patients (males and females)	1%	24 h or 48 h patch test (Finn chambers)	Questionable/irritant reactions (62 patients); sensitization reactions (46 patients)[116]
Benzyl Alcohol (5% in petrolatum)	102 patients	5%	24 h patch tests (Finn chambers)	8 subjects with positive reactions[117]
Benzyl Alcohol (1%)	2,166 dermatitis patients	1%	24 or 48 h patch tests	0.3% with positive reactions[118]
Benzoic Acid (5% in physiological saline)	7 patients (males and females) with birch pollen allergy	5%	45 min epicutaneous application (AL-tests on Scanpor)	Erythema at application sites of all patients (contact urticaria)[119]
Benzoic Acid (5% in petrolatum)	102 patients	5%	24 h patch tests (Finn chambers)	20 subjects with positive reactions[117]
Benzoic Acid	1,252 patients with oral mucosal disease	Concentration not stated	Contact urticaria test; Delayed hypersensitivity test	366 patients positive (urticaria test); 124 patients positive (hypersensitivity test)[120]

Table 5. Skin Irritation and Sensitization Studies

Test Substance	Animals/Subjects	Doses/Concentrations Tested	Procedure	Results
Benzoic Acid	417 patients	Concentration not stated	48 h occlusive patch tests (Finn chambers; 10 mm diameter)	5% of patients with questionable/irritant reactions; 4.3% with allergic reactions[121]
Benzoic Acid	465 patients	Concentration not stated	Not stated	Positive reactions (allergenicity) in 2.1% of patients[122]
Sodium Benzoate	465 patients	Concentration not stated	Not stated	Positive reactions (allergenicity) in 1.9% of patients[122]
Benzyl Benzoate (20% emulsion)	1,000 scabies patients	20%	Treatment for scabies	No dermatitis after treatment[123]
Benzyl Benzoate (0.1, 2, and 20% in vaseline ointment or cream base)	175 patients with and without dermatoses	0.1, 2, and 20%	Closed patch test (no GLP) to evaluate sensitization potential	No positive reactions[3]
Benzyl Benzoate (10% in water)	73 dermatitis patients	10%	Patch test (no GLP) to evaluate sensitization potential	No positive reactions[3]
Benzyl Benzoate (5%)	11 male and female patients (18+ years)	5%	24 h application	Positive reaction in 3 of 8 patients[104]
Benzyl Benzoate (5% in petrolatum)	20 male and female patients (18+ years)	5%	48-h patch test (aluminum-backed strips)	Positive reaction in 1 of 20 patients[124]
Benzyl Benzoate (5% in petrolatum)	45 dermatitis patients (18+ years)	5%	48-h closed patch test	No reaction[125]
Benzyl Benzoate (5% in petrolatum)	73 eczematous dermatitis patients	5%	Patch test (no GLP)	1 positive reaction[3]
Benzyl Benzoate (5% in petrolatum)	Eczema patients (no. not stated)	5%	Patch test (no GLP)	No positive reactions[3]
Benzyl Benzoate (5% in petrolatum)	8 dermatitis patients	5%	Patch test (no GLP)	1 positive reaction[3]
Benzyl Benzoate (5% in petrolatum)	19 dermatitis patients	5%	Patch test (no GLP)	No positive reactions[3]
Benzyl Benzoate (5% in yellow soft paraffin)	241 patients	5%	Patch test (no GLP)	No positive reactions[3]
Benzyl Benzoate (5% in vaseline)	103 patients	5%	Patch test (no GLP)	12 positive reactions[3]
Benzyl Benzoate (5% in vaseline)	115 patients	5%	Patch test (no GLP)	14 positive reactions[3]
Benzyl Benzoate (5% in vaseline)	465 dermatitis patients	5%	Patch test (no GLP)	7 positive reactions[3]
Benzyl Benzoate	443 patients (383 tested and 60 controls)	5%	Patch test (no GLP)	2 positive reactions (1 cosmetic dermatitis patient; 1 non-cosmetic dermatitis patient) [3]
Benzyl Benzoate (5%)	271 patients (225 tested and 46 controls)	5%	Patch test (no GLP)	2 positive reactions (1 cosmetic dermatitis patient; 1 non-cosmetic dermatitis patient)[3]
Benzyl Benzoate (5% in petrolatum)	73 patients (18+ years)	5%	Not stated	Positive reaction in 1 patient[3]

Table 5. Skin Irritation and Sensitization Studies

Test Substance	Animals/Subjects	Doses/Concentrations Tested	Procedure	Results
Benzyl Benzoate (5% in petrolatum)	5 male and female urticaria patients (18+ years)	5%	30 min closed patch test	No reaction[126]
Benzyl Benzoate (5% in petrolatum)	12 patients (18+ years)	5%	Patch test to evaluate sensitization potential	No positive reactions[127]
Benzyl Benzoate (5% in petrolatum)	3 female allergic dermatitis patients	5%	Patch tests (Finn chambers) to evaluate sensitization potential	No positive reactions[128]
Benzyl Benzoate (5%; vehicle not reported)	50 dermatitis patients	5%	Patch tests to evaluate sensitization potential	Positive reaction in 1 patient[123]
Benzyl Benzoate (5%	70 dermatitis patients; 19 eyelid dermatitis patients	5%	48 h patch tests (Finn chambers) to evaluate sensitization potential	2.9% with positive reactions (70 patients); no positive reactions (19 patients)[129]
Benzyl Benzoate (5% in petrolatum, vaseline, or alcohol)	115 patients with positive reactions to Balsam of Peru	5%	48 h closed patch tests to evaluate sensitization potential	Positive reactions in 14 patients[130]
Benzyl Benzoate (5%; vehicle not stated)	225 patients (18+ years)	5%	Patch test to evaluate sensitization potential	Positive reactions in 2 patients[131]
Benzyl Benzoate (5%; vehicle not stated)	658 male and female patients	5%	48 h patch tests (Finn chambers) to evaluate sensitization potential	Positive reaction in 1 patient[132]
Benzyl Benzoate (5% in white petrolatum)	102 contact dermatitis patients (18+ years)	5%	24 h patch tests (Finn chambers) to evaluate sensitization potential	Positive reactions in 4 patients[117]
Benzyl Benzoate (5% in petrolatum)	317 eczema patients (18 + years)	5%	Patch test to evaluate sensitization potential	No positive reactions[133]
Benzyl Benzoate (5% in petrolatum)	73 patients with eczematous dermatitis	5%	Patch test to evaluate sensitization potential	1 positive reaction (allergic contact dermatitis)[123]
Benzyl Benzoate (5% in petrolatum)	102 patients	5%	24 h patch tests (Finn chambers)	4 subjects with positive reactions[117]
Benzyl Benzoate (2 or 5% in vaseline)	144 patients (14 controls included) per test concentration	2 or 5%	Closed patch test (no GLP) to evaluate sensitization potential	1 positive reaction in cosmetic dermatitis patient)[3]
Benzyl Benzoate (2 or 5% in petrolatum)	64 dermatitis patients (18+ years)	2 or 5%	Closed patch test to evaluate sensitization potential	Positive reaction in 1 patient (5% concentration); no positive reactions (2%)[134]
Benzyl Benzoate (2%)	Patients (no. not stated)	2%	Patch test (no GLP)	Negative reaction in contact dermatitis patient[3]
Benzyl Benzoate (2%)	198 patients	2%	Patch test (no GLP)	No positive reactions[3]
Benzyl Benzoate (2% in petrolatum)	335 patients	2%	Patch test (no GLP)	No positive reactions[3]

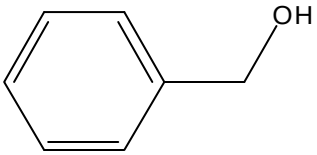
Table 5. Skin Irritation and Sensitization Studies

Test Substance	Animals/Subjects	Doses/Concentrations Tested	Procedure	Results
Benzyl Benzoate (2% in yellow paraffin)	539 patients (18+ years; 50 with photosensitivity dermatitis, 32 with polymorphic light eruption (PLE) and 457 with contact dermatitis)	2%	48 h closed patch test to evaluate sensitization potential	Positive reaction in 1 PLE patient[74]
Benzyl Benzoate (2% in petrolatum)	284 patients (18+ years)	2%	Patch test to evaluate sensitization potential	1% with positive reactions[135]
Benzyl Benzoate (2% in petrolatum)	335 patients (18+ years)	2%	Patch test to evaluate sensitization potential	No positive reactions[135]
Benzyl Benzoate (2% in petrolatum)	198 patients (18+ years)	2%	Patch test to evaluate sensitization potential	No positive reactions[136]
Benzyl Benzoate (2% in yellow soft paraffin)	241 patients (18+ years)	2%	Finn chamber technique to evaluate sensitization potential	Positive reaction in 1 male patient[137]
Benzyl Benzoate (2% in white petrolatum)	284 contact dermatitis patients (30 to 67 years)	2%	Patch test to evaluate sensitization potential	No positive reactions[138]
Benzyl Benzoate (1% in yellow petrolatum)	28 patients allergic to perfumes (18+ years)	1%	Sensitization test (procedure not stated)	No positive reactions[139]
Benzyl Benzoate (1%)	2,003 dermatitis patients	1%	24 or 48 h patch tests to evaluate sensitization potential	No positive reactions[118]
Benzyl Benzoate (0.1% in ethanol or non-irritative cream base)	111 male and female dermatitis patients (18+ years)	0.1%	24-h to 48-h closed patch test to evaluate sensitization potential	No positive reactions[114]
Benzyl Benzoate	Cosmetic dermatitis patients (no. not stated)	Concentration not stated	Patch test (no GLP) to evaluate sensitization potential	1 positive reaction[3]
Benzyl Benzoate	15 patients	Concentration not stated	Patch test (no GLP)	delayed in reaction in 1 patient sensitized to Peru balsam[3]
Benzyl Benzoate	111 patients	Concentration not stated	Patch test (no GLP)	No positive reactions[3]
Benzyl Benzoate	142 patients	Concentration not stated	Patch test (no GLP) to evaluate sensitization potential	10 positive reactions in patients sensitive to balsam of Peru[3]
Benzyl Benzoate	155 scabies patients	Concentration not stated	Treatment with benzyl benzoate (concentration not stated)	Dermatitis in 17 patients[3]
Benzyl Benzoate	460 patients	Concentration not stated	Patch test (no GLP) to evaluate sensitization potential	3 positive reactions in patients sensitive to cosmetics[3]
Benzyl Benzoate	25 patients	Concentration not stated	Maximization test (no GLP)	No positive reactions[3]
Benzyl Benzoate	465 patients	Concentration not stated	Not stated	Positive reactions (allergenicity) in 1.5% of patients[122]

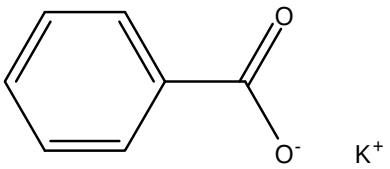
Table 6. Case Reports

Test Substance	Subjects	Procedure/Results
Benzyl Alcohol	30-year-old facial dermatitis patient	Patch testing (no test concentration) produced macular erythema[140]
Benzyl Alcohol	38-year old eczema patient	1% aqueous benzyl alcohol: negative prick test results and positive (++) intradermal injection test results. Negative injection test results in 10 healthy controls[141]
Benzyl Alcohol	39-year-old female with pruritic erythema of foot	5% benzyl alcohol in petrolatum: weak (+) reaction in patch test and strong positive reaction in repeated open application test[142]
Benzyl Alcohol	67-year-old male with leg dermatitis	1% benzyl alcohol in petrolatum: 2+ occlusive patch test reaction. 0.9% benzyl alcohol in saline: negative prick test reaction at 0.5 h reading, but marked induration and proximal spread over arm at days 3 to 8[143]
Benzyl Alcohol	53-year-old with stasis dermatitis	1% benzyl alcohol in petrolatum: redness and swelling at 1 h after patch application, wheal 1 day later, and mild urticaria at day 5[144]
Benzyl Alcohol	16-year-old female with possible anaphylactic reactions after i.m. injection with B12 preparation containing 0.9% benzyl alcohol	Benzyl alcohol preparation: negative in prick tests, but positive in intradermal tests[145]
Benzyl Alcohol	57-year-old female with pruritic dermatitis	Allergic contact dermatitis (+, ++, or +++ reaction) after patch testing with benzyl alcohol[146]
Benzyl Alcohol	40-year-old female with dermatitis	Positive patch test reaction (+++, allergic contact dermatitis) to 9.5% benzyl alcohol in petrolatum[147]
Benzyl Alcohol	65-year-old female with eyelid dermatitis	Macular erythema after patch testing with benzyl alcohol (concentration not stated)[148]
Benzyl Alcohol	30-year-old female with eyelid dermatitis	Positive (1+) patch test reaction to benzyl alcohol (concentration not stated)[140]
Benzoic Acid	30-year-old facial dermatitis patient	Patch testing (no test concentration) produced 1+ reaction[140]
Benzoic Acid	46-year-old female with history of erythema and itching	5% benzoic acid in petrolatum: positive reaction[149]
Sodium Benzoate	64-year-old female with erythema and edema of finger	Positive patch test reaction to 5% sodium benzoate on days 2 and 4; negative patch test results at interdigital area at 2 months[150]
Sodium Benzoate	52-year-old female with hand dermatitis	Negative patch test reaction to sodium benzoate (concentration not stated)[151]
Sodium Benzoate	75-year-old female with history of pruritus	Relapse of pruritus after 100 mg oral dose of sodium benzoate[152]
Benzyl Benzoate	25-year-old male with acute bullous eruption after application of 30% benzyl benzoate preparation	Negative patch test reaction to 1% benzyl benzoate in petrolatum[153]
Benzyl Benzoate (unspecified concentration or 25% emulsion in aqueous solution of triethanolamine stearate)	4 scabies patients (ages not stated)	Severe skin irritation; pruritic dermatitis within 12 to 20 h after treatment (unspecified concentration or 25% emulsion)[154]
Benzyl Benzoate	Scabies patients (no. not included)	Treatment with benzyl benzoate solution (concentration not stated) did not cause dermatitis[3]
Benzyl Benzoate	4 scabies patients	Treatment with benzyl benzoate solution caused dermatitis[3]
Benzyl Benzoate (5% in petrolatum	1 patient (18 + years)	Reaction read at 48 h and 96 h. No sensitization[155]
Benzyl Benzoate 2% in petrolatum)	23-year old male patient	Negative patch test results; no sensitization[156]

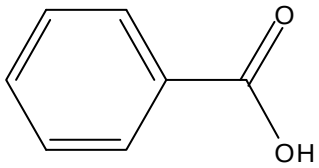
Figure 1. Chemical Structures



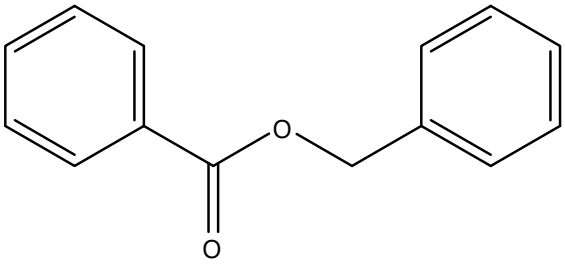
benzyl alcohol



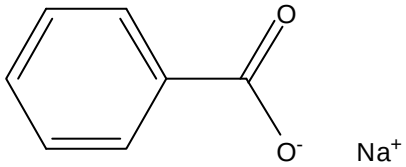
potassium benzoate



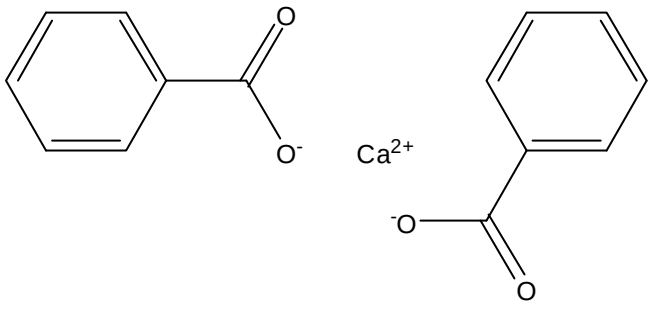
benzoic acid



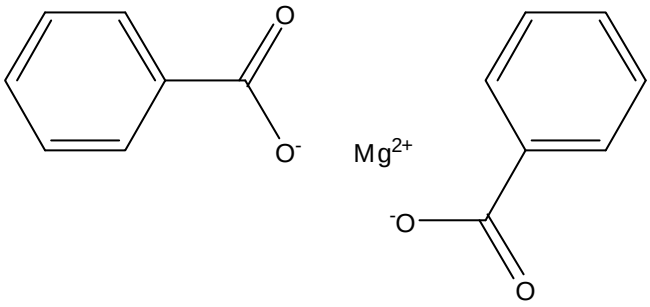
benzyl benzoate



sodium benzoate



calcium benzoate



magnesium benzoate

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Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. 7-14-11
Industry Liaison to the CIR Expert Panel

DATE: July 14, 2011

SUBJECT: Comments on the Tentative Amended Safety Assessment on Benzyl Alcohol, Benzoic Acid and its Salts and Benzyl Ester

Although the disclaimer ("Tentative reports are distributed for comment only -- do not cite") on the CIR website is helpful, it should also be included on every page of a tentative report.

Abstract - It would be helpful to mention dermal irritation and sensitization data in the abstract, e.g., current use concentrations of these ingredients are below concentrations that may result in dermal irritation or sensitization.

p.1 - In the Introduction, in the paragraph concerning the 2001 report, it would be helpful to indicate that all the details of studies in the 2001 report are not included in current report. For a complete review of all the data identified, both reports are needed.

p.1 - It would also be helpful to mention the RIFM synopsis on Benzyl Benzoate in the introduction, as it appears to be the primary source of information for this ingredient.

p.2 - The first sentence under Benzoic Acid and Sodium Benzoate in the Impurities section states: "The effects of UVA exposure on benzene formation were determined in another study." As this is the first study described, it is not clear what is meant by "in another study".

p.3 - The EPA maximum contaminant level (MCL) for drinking water should be cited directly to the EPA (one source http://water.epa.gov/drink/contaminants/basicinformation/benzene.cfm). It would also be helpful to explain how MCLs are derived. An MCL is not strictly health based - MCLs "are set as close to the health goals as possible, considering cost, benefits and the ability of public water systems to detect and remove contaminants using suitable treatment technologies."

p.4 - The final monograph for anorectal drugs (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm078704.pdf) states: "Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC anorectal drug products are generally recognized as safe and effective and not misbranded." Benzyl alcohol is included as a local anesthetic. Therefore,"category not stated" needs to be changed to Category I.

p.7 - In the summary of the Acute Oral Exposure section, please add the word "oral" before LD50.

p.9 - In the third paragraph on this page, "does" should be "doses"

p.10 - In the third paragraph under Benzyl Alcohol, it should read: "the association of the benzyl alcohol preservative..." (not vehicle as currently stated).

p.12 - At what concentration was Benzyl Benzoate not phototoxic in the presence of UVA or UVB light?

p.13 - It is not clear what is meant by "the acceptable dose".

p.14, first line - As there is now a Dermal Repeated Dose section, please change: "Parenteral Studies section" to "Dermal Studies section".

p.16 - Is the dose "5,000 mg/plate" really correct for the Ames test (pre-incubation assay) of Benzyl Benzoate?

p.16 - In the last paragraph, units of mg/ml should be called a concentration rather than dose.

p.17, 19 - In the summary of the Carcinogenicity section and the Summary of the report, it is misleading to present the single study on the non-oxidative hair dye as two separate sentences. It would be more appropriate to state: "A non-oxidative hair dye containing 2% Benzyl Alcohol and 0.016% Benzoic acid tested negative for carcinogenicity following dermal application to mice."

p.18 - As no studies on the formation of benzene in foods containing Benzoic Acid are presented earlier in the report, "foods" should be deleted from the second paragraph of the Summary.

p.19 - The Discussion should note that as stated in the Toxicokinetics section, these ingredients are metabolized and excreted via a common pathway. Therefore, the data on Benzyl Alcohol are directly relevant to Benzoic Acid and its salts. It should also be noted that additional data are summarized in the original report.

p.19 - The Discussion should note that the studies on benzene formation were in beverages, not cosmetic products.

p.21, Table 1 - The spelling of Benzyl Alcohol needs to be corrected in the first line of the table.

p.22, Table 3 - NS can be deleted from the footnotes of this table as all the ingredients were included in a Council concentration of use survey.

p.24, Table 5 - As the induction concentration was 10%, the results should say that no reactions were observed at a challenge concentrations of 5% and 10%, while mild reactions were observed at challenge concentrations of 40%. The induction concentration(s) used in reference 84 are not clear.

p.25, Table 5 - It is not clear what is meant by "24-h RIPT" in the Procedure column of reference 92.

p.32 reference 49, p.33 reference 55 - Reference 49 and reference 55 are the same reference, RIFM's synopsis of information on Benzyl Bezoate.