

BLUE

Alkyl Benzoates

CIR EXPERT PANEL MEETING

MARCH 3-4, 2011

Cosmetic Ingredient Review

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February 3, 2011

MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Subject: Draft Final Report for C12-15 Alkyl Benzoate and related Alkyl Benzoates

Attached is the draft Final Report for C12-15 alkyl benzoate and related benzoates. The tentative report was made available for public comment. Comments from industry were addressed.

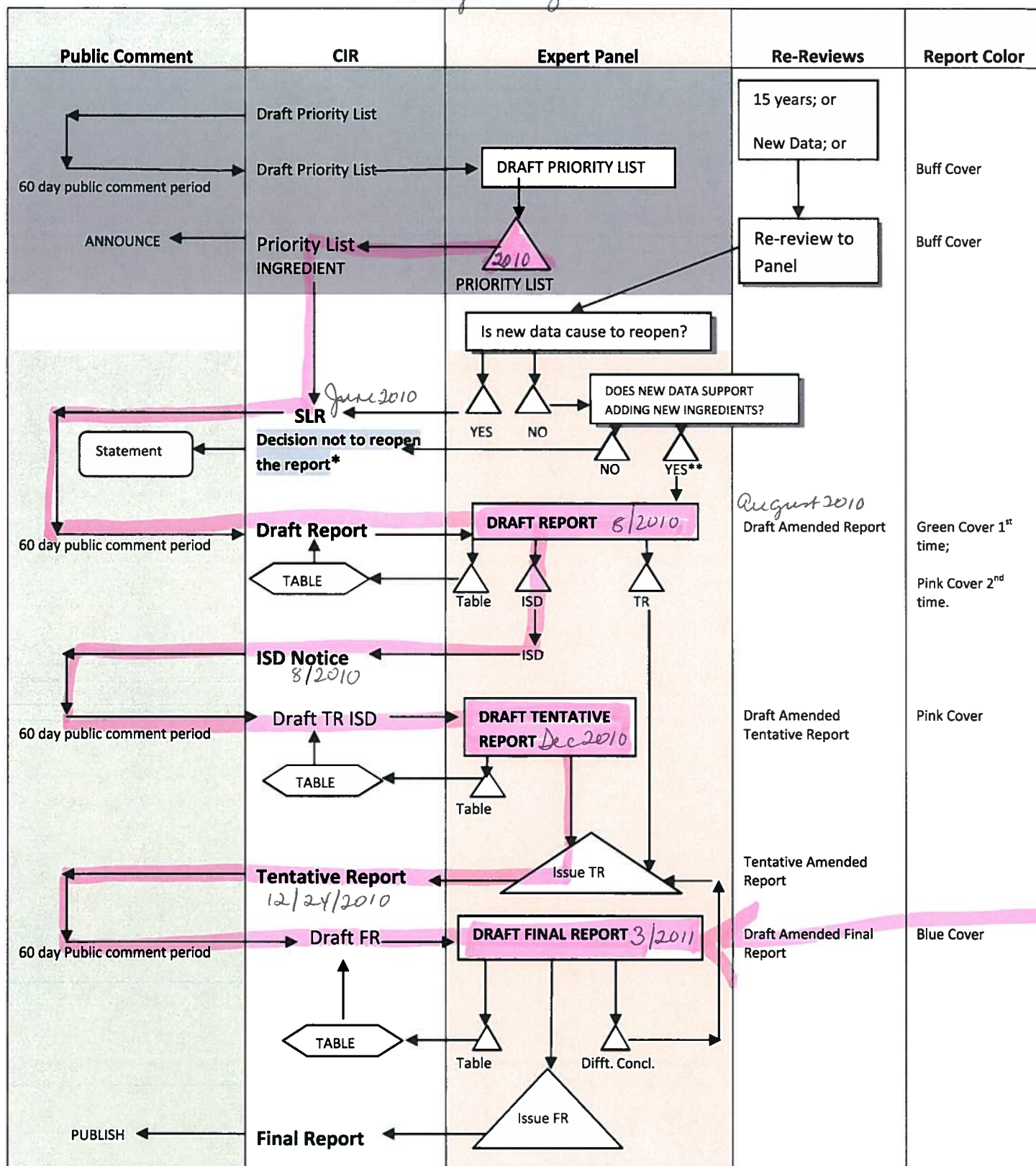
The Personal Care Products Council also submitted information on a related branched alkyl benzoate, Isononyl benzoate. That data has been included in the report.

The Panel should review the Draft Final Report and decide if the conclusion is valid. If so, then the Panel should 1) review the discussion and confirm that it reflects the Panel's thinking and 2) issue a final report.

SAFETY ASSESSMENT FLOW CHART

Allyl Benzotates

March 2011



*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 rDraft 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

History of Alkyl Benzoates

2010 Priority List

June, 2010 – SLR issued.

August, 2010 – The Panel reviewed the Draft Report and issued an Insufficient Data Announcement. The data needs are: 1) dermal penetration data, especially on ingredients smaller than C12-C15 alkyl benzoates; if there is possible dermal penetration then 2) reproduction and developmental toxicity; 3) carcinogenicity; and 4) irritation and sensitization data on ingredients smaller than C12-C15 alkyl benzoates.

There is a REACH submission being prepared that is going to be shared with CIR. It was expected before the December meeting. It has been delayed and is not in the December report. Some of the data have been submitted through PCPC and is included in the report.

The Panel decided to issue an Insufficient Data Announcement instead of tabling the report to wait for the REACH data to move the report along the process and to officially identify data needs.

December, 2010 – The Panel reviewed a Draft Tentative Report and found that the needs of the IDA had been met. The data that was to be submitted for REACH was made available to the Panel. The Panel issued a Tentative Report (12/24/2010) with a safe as used conclusion.

March, 2011 – The Panel will review a draft Final Report.

Search Strategy for Benzoates

EXPLORATORY SEARCH:

March, 2010

PUBMED: "alkyl benzoate" – 7 hits, 1 useful; CAS No. – 0 hits.

Internet (Dogpile) – "alkyl benzoate" - 1 MSDS

FULL SEARCH:

PUBMED: "lauryl alcohol" – 53 hits, 6 ordered.

"tridecyl alcohol" – 0 hits. CAS No. – 0 and 19 hits. 1 useful.

"Amyl benzoate" -0 hits. CAS no – no hits.

"benhyl benzoate" – 0 hits. CAS no – no hits.

"Butyl Benzoate" – 9 hits, 1 useful. CAS no. – no hits.

"Butyloctyl Benzoate" – 0 hits. No CAS no.

"Ethyl Benzoate" – 44 hits, 4 useful.

"Ethylhexyl Benzoate" – no hits.

"Hexyldecyl Benzoate" – no hits.

"Isobutyl Benzoate" – not hits. CAS no. – no hits.

"939-48-0" OR "34364-24-4" OR "Lauryl/Myristyl Benzoate" OR "112-53-8" OR "Octyldodecyl Benzoate" OR "2315-68-6" OR "10578-34-4" – 224 hits, 19 useful

TOXNET: 68411-27-8 – 0 hits; 112-53-8 – 253 hits, 47 useful; 112-70-9 – 33 hits, 2 useful; 26248-42-0 - 10 hits, 4 useful; 629-76-5 – 15 hits, 1 useful (already have); 2049-96-9 – 6 hits, 0 useful; "amyl alcohol" - 798 hits, 86 + 64 hits so far; 103403-38-9 – no hits; 136-60-7 - Butyloctyl Benzoate – no hits; butyloctyl alcohol – no hits; C16-17 Alkyl Benzoate – no hits; palmyl alcohol – no hits; heptadecyl alcohol – no hits; 93-89-0 – 56 hits, 64-17-5 alcohol – 50000 hits, did not explore yet; Hexyldecyl Benzoate – no hits; Hexyldecyl Benzoate – No hits; 120-50-3 – 3 hits, 0 useful; 939-48-0 – 2 hits, 0 useful; 34364-24-4 – no hits, Isopropyl Benzoate – No hits; Isostearyl Benzoate – no hits; Lauryl/Myristyl Benzoate - no hits; 112-53-8 [print toxnet] – 248 hits, 112-53-8 – 248 hits, 61 useful; 93-58-3 – 135 hits, 14 useful; Octyldodecyl Benzoate – no hits; Octyldodecyl Alcohol – no hits; 2315-68-6 – 7 hits, 2 useful; 10578-34-4 – no hits.

June, 2010

EPA – HPV – One relevant report that included methyl benzoate. Data added to report under original citations.

January, 2011

Ran PubMed search again. No new hits.

Alkyl Benzoate Data Profile for March, 2011. Writer - Lillian Becker

	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K _{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
methyl benzoate	X	X	X	X	X					X	X		X	X		X		X
ethyl benzoate	X	X	X	X	X					X	X	X	X	X		X		
propyl benzoate	X	X									X							
butyl benzoate	X	X			X	X				X	X	X						
amyl benzoate		X		X									X					
lauryl/myristyl benzoate		x																
C12-15 alkyl benzoate	X	X	X		X	X				X	X	X	X	X		X		
C16-17 alkyl benzoate			X															
stearyl benzoate		X	X															
behenyl benzoate		X																
isopropyl benzoate		X		X	X	X				X	X							
isobutyl benzoate		X	X		x						X	X	X	X				
isostearyl benzoate		X	X							X				X				
ethylhexyl benzoate		X	X							H		X						X
butyloctyl benzoate		X																
hexyldecyl benzoate		X																
octyldodecyl benzoate		x	x											x				
Isononyl benzoate*															X	X		
Benzoic acid/sodium benzoate	x			x			x					x		x	x	x	x	H
Methyl alcohol		X		X	X					X	X				X	X	X	
Ethyl alcohol.																		
Propyl alcohol												X			X			
Butyl alcohol																		
Amyl alcohol				X	X	X	X			X	X						X	
Lauryl Myristoyl alcohol											X	X					X	
C 12 - 17					X					X		X		X				x
Stearyl alcohol																		
Behenyl alcohol																		
Isopropyl alcohol									x	X				X	X		X	
Isobutyl alcohol									x									
Isostearyl alcohol												X		X				
Ethylhexyl alcohol		x		X		X	x	x	x	X	X	X		X	X	x	x	
Butyloctyl alcohol																		
Hexadecyl benzoate					x	x				x	X							
Octyldodecyl alcohol																		
Related alcohol				X	x				X									

H - human

1 which have concentrations of use at 7 percent and
2 6 percent and the data is up to 5 percent. Is
3 this of any concern at all?

4 DR. MARKS: Are you talking about
5 irritation?

6 MS. WEINTRAUB: Yes.

7 DR. MARKS: I think particularly when it
8 captures to be nonirritating I'm not concerned
9 about sensitivity with these compounds so that I
10 think we've covered that. Are there any other
11 comments?

12 If not we'll move on to the alkyl
13 benzoates group. It's the Pink Book. In August
14 the panel issued an insufficient data announcement
15 for these 17 alkyl benzoates asking for one
16 irritation and sensitization of the low-
17 molecular-weight ingredients especially
18 methylbenzoate. My review of what we received
19 addressed this and I thought it was satisfactory.
20 Two, genotox, and I don't think we received
21 anything on genotox. Do you want to comment on
22 that, Tom? Was there on the Wave 2 data that I

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1 may have missed?

2 DR. SLAGA: I don't think there was any
3 genotox.

4 DR. MARKS: No genotox. Dermal
5 penetration data was another insufficient data
6 need and my notes are that the alcohols do
7 penetrate. Is the penetration data that we have
8 okay? I have no penetration the alcohols may.
9 Are there comments on that?

10 DR. SLAGA: Correction. There is plenty
11 of genotox data.

12 DR. ANSELL: We did provide
13 micronucleus, but it was negative so that I
14 thought that's what you meant.

15 DR. MARKS: No. I want to be sure. So
16 that the genotox data is okay? How about the
17 dermal penetration? Is that okay? If there is
18 significant dermal penetration, then reproductive
19 developmental toxicity. Rons?

20 DR. SHANK: I had all the insufficient
21 data needs that we stated before have been met so
22 that are no outstanding data needs at this time.

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1 DR. SLAGA: Even though all of the data
2 needs have been met, we talked very heavily the
3 last time about this REACH data. Do we still want
4 to wait? From my understanding, that will be
5 ready in January and then this would be a complete
6 document.

7 DR. ANSELL: The REACH data has been
8 submitted in Wave 2. It did not come from the
9 consortium, it came from the individual members
10 due to REACH-specific issues in terms of ownership
11 of data, but all of the data which would have been
12 included in the aggregated report were provided
13 individually by the companies directly.

14 DR. MARKS: If I interpret what you
15 said, Jay, there is no reason to wait for the
16 REACH data.

17 DR. ANSELL: That's right.

18 DR. HILL: Lillian, could you go with me
19 to wherever that table is where you have all the
20 alkyl benzoate data profile for December 2010? I
21 assume this does not have because we got it before
22 the second wave that it would not have the second

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1 wave data in this table.

2 MS. BECKER: Correct. That's everything
3 that was as this mailing and not anything that got
4 posted on Wave 2.

5 DR. HILL: I did this in part. Have you
6 gone back through what we have in the second wave
7 and anything that might have come in after that
8 and checked-in boxes? On the repeat of dose
9 toxicity there is nothing in the one here. I
10 haven't gone myself through.

11 MS. BECKER: No, I have not updated the
12 chart. I can if you like.

13 DR. HILL: Can you give me the capsule
14 summary off the top of your head based on what's
15 sitting there? I assume you have gone through the
16 second wave data thoroughly. Do we have anything
17 on repeated dose toxicity buried in all this
18 sufficient to put in some of these checked boxes,
19 particularly dermal?

20 MS. BECKER: No.

21 DR. HILL: One of the unanswered
22 questions I had after looking at what was there,

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1 and by the way, genotox is only on isononyl esters
 2 so that we're going to extrapolate either way from
 3 that if that's the case. At least that's the way
 4 I see it. Did anybody see anything else? In all
 5 of the dermal penetration studies it appears to me
 6 that the measurements were done of benzoic acids
 7 coming out the other side and no measurement
 8 whatsoever of we have a benzoic acid ester and it
 9 might be hydrolyzed in the skin, I wish Dr.
 10 Bronaugh were in here, and we have alcohol coming
 11 out into the receptor but since the scientists
 12 weren't using radio label on the alcohol portion
 13 and looks as if as far as I can tell that nobody
 14 was doing LCMS to measure potential for alcohol
 15 coming out the other side, we really don't know in
 16 terms of anything that might be coming from the
 17 alcohols that are generated what might be coming
 18 through and into the systemic circulation because
 19 there are esterases, lipases and carboxyl
 20 esterases that can take more lipophilic carboxyl
 21 esters and cleave them.

22 DR. MARKS: In my notes I have also

1 similar alcohols may penetrate or do penetrate.
 2 If that would occur is the tox data here
 3 sufficient to come to a conclusion with safe?

4 DR. HILL: I was really looking for a
 5 table similar to this that dealt with all of the
 6 alcohols because I did have some question marks
 7 here in terms of the question you just asked. I
 8 felt like there were some serious question marks
 9 that weren't nailed down in my mind.

10 MS. WEINTRAUB: I have one question and
 11 that is about cytotoxicity because the data
 12 brought forth up there was cytotoxicity with
 13 methylbenzoate and ethyl as well as
 14 propylbenzoate. What's the position of the panel
 15 on cytotoxicity?

16 DR. MARKS: Which page are you on,
 17 Rachel?

18 MS. WEINTRAUB: Right now I'm looking at
 19 the summary on page 18.

20 DR. ANDERSEN: The data are on page 4.

21 MS. WEINTRAUB: Yes. Pages 4 and 5.

22 DR. MARKS: So you're saying that methyl

1 benzoate was cytotoxic to HeLa cells. Is there
 2 any concern as far as humans?

3 DR. SLAGA: There is no doubt that the
 4 smaller ones, methylbenzoate and ethyl are
 5 irritating at 100- percent concentration, but we
 6 can deal with that later.

7 MS. BECKER: I didn't hear the last
 8 part.

9 DR. SLAGA: I said we can deal with this
 10 as treatment at nonirritating doses.

11 DR. MARKS: Do we want to proceed on
 12 issuing a tentative report?

13 DR. HILL: Before you get to that
 14 question, remember the specific question I had was
 15 I focused particularly on ethylhexyl alcohol and
 16 at a level I wasn't worried even though there is
 17 this peroxizome proliferator activity because
 18 supposedly that's rodent-specific and doesn't
 19 apply to humans. But I had asked the question
 20 because I wondered if there were any data to know
 21 if we have tox data that's oral on these alcohols
 22 and we perhaps have some dermal penetration data

1 on the alcohols but we really don't know the
 2 answer to the question of how much alcohol might I
 3 be delivering if instead of delivering the alcohol
 4 dermally I'm delivering the alcohol benzoate ester
 5 dermally and then it's cleaved to the alcohol in
 6 the skin, we could end up with a different dose of
 7 alcohol, actually, a greater dose of alcohol, than
 8 either delivering benzoic acid ester orally or
 9 delivering the alcohol dermally and not know it.

10 DR. ANSELL: There is an ADME discussion
 11 on alcohol-specific.

12 DR. HILL: But the point is if you do an
 13 oral study on the alcohol, you probably aren't
 14 getting the right answer because again as I
 15 mentioned, rats and rodents in general are
 16 aggressive in taking orally delivered alcohols and
 17 glucuronidating and sulfating them and I don't
 18 know how high you'd have to go on dose before you
 19 saturate the liver's capacity in a rodent to do
 20 that so that I'm not sure you can rely on oral tox
 21 data. Then the question is if you rely on dermal
 22 tox data as opposed to IP, and this is the

1 question I'm really asking, how much IP tox data
 2 do we have on those alcohols, do we have a clear
 3 dose dependency and do we know where the NOAELs
 4 are if we do an IP tox study on the alcohols so
 5 that we had some since that if by chance the
 6 benzoic acid ester was delivering more of the
 7 alcohol than could be delivered by oral gavage or
 8 by dermal penetration the alcohol itself, do we
 9 have a good sense of where we still might be
 10 getting based on how fast it could dermally
 11 penetrate. Do we have solid dermal penetration
 12 data all the way across the map on all of these
 13 with enough of a range of esters that we can
 14 confidently say we know this one, this one, we've
 15 got a parabolic relationship, we know this one and
 16 I don't have that data summarized for myself in a
 17 way that I can answer that question yet. Maybe
 18 that's a dog-ate-my-homework issue.

19 DR. ANDERSEN: In the Repeated Dose
 20 Toxicity section there are data for ethylhexyl
 21 alcohol and dermal exposures. Under Dermal
 22 Irritation there are all dermal studies from

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1 methyl to ethylhexyl to hexyl, hexyldecyl, dermal
 2 sensitization and nothing on alcohol. So the
 3 alcohol data were broken out but you really have
 4 to look carefully to segregate oral from dermal.

5 DR. HILL: The question I have in
 6 relation to the long-term dermal exposure for
 7 sensitization, would they have already in these
 8 older studies looked for other end points besides
 9 sensitization. In other words, will they pick up
 10 if there are some histopathological changes in
 11 liver, for example? Would that have been picked
 12 up?

13 DR. ANDERSEN: I think the answer is
 14 it's unlikely in that methodology.

15 DR. ANSELL: I would point out at least
 16 in terms of the metabolism, it's multiple alcohols
 17 by multiple routes, inhalation, topical exposure,
 18 dermal exposure and whole-body exposure. The
 19 ethylhexyl was up to 1,000 milligrams per
 20 kilogram. It's unlikely that through the
 21 metabolism you could end up with alcohol
 22 concentrations in excess of what was studied

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1 directly. We're talking about things like
 2 isopropynol.

3 DR. HILL: I agree. We have that data
 4 for ethylhexyl. There are some other alcohols
 5 where we don't have that data. Nothing. That's
 6 all I'm saying.

7 DR. MARKS: I want to go back to Rachel
 8 when she pointed out the cytotoxicity and Ron said
 9 we can handle that as being nonirritating. I
 10 hadn't seen an alert either with irritation or
 11 dermal sensitization and when you look at the
 12 concentrations used for the compounds, they're
 13 safe. The concentration of methylbenzoate is
 14 reported up to .3 which would be nonirritating and
 15 the concentrations of the alkyl benzoate C12 to 15
 16 report up to 59 and when you look at HIRPTs it's
 17 up to those concentrations used here so that I'm
 18 not concerned about that, Rachel.

19 DR. ANDERSEN: Before you go on, I'd add
 20 or at least ask Tom and Ron whether they agree to
 21 add a sentence or an implication at least that for
 22 cytotoxicity another direction you would take that

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1 concern is to look at the genotox data. If it's
 2 cytotoxic, so you look at the genotox data and for
 3 all of the metabolites and for the representative
 4 parent compound they're not genotoxic. So when
 5 you couple those two the concern disappears.

6 DR. MARKS: Thank you, Alan, and Lillian
 7 you can capture that then in the text.

8 DR. HILL: That doesn't take into
 9 account however effects like tumor promotion.

10 DR. MARKS: Tom?

11 DR. SLAGA: I didn't hear that. I was
 12 reading. What was that?

13 DR. MARKS: Ron Hill said that Alan's
 14 comment doesn't take into effect of tumor
 15 promotion.

16 DR. SLAGA: Tumor promotion, we tried to
 17 handle that by, number one, restricting compounds
 18 to be nonirritating which would lead to
 19 self-proliferating which is an important criteria
 20 in tumor promotion and all of these that are
 21 irritating and would have effect and even be
 22 cytotoxic in culture are at high doses so that any

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1 of these that are used if they're at nonirritating
2 doses, as it was pointed out that the use of these
3 are not very high in concentration of the smaller
4 ones that are smaller ones that are extremely
5 irritating.

6 DR. MARKS: Are there any other
7 comments? Does the team feel first of all
8 comfortable moving for issuing a tentative report
9 on these alkyl benzoates?

10 DR. SLAGA: Yes.

11 DR. MARKS: Does the team feel
12 comfortable issuing a safe as used?

13 DR. HILL: Safe as used.

14 DR. ANDERSEN: Given the emphasis on
15 irritation, safe when formulated to be
16 nonirritating?

17 DR. SLAGA: That's what I originally
18 stated, but the concentration of us is so below
19 what the irritating level is and the only problem
20 is when you have multiple members of a group you
21 may miss one and that's sometimes it's better to
22 put in the nonirritating just in case.

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1 DR. MARKS: I can go either way to tell
2 you the truth. If you want to cover the gap and
3 say when formulated to be nonirritating would be
4 fine to over the gap. As I had mentioned earlier,
5 both the irritation studies and the sensitization
6 studies reassured me with a concentration of use
7 and being used now is fine.

8 DR. BAILEY: I would agree. I think
9 under current conditions of use clearly captures
10 low levels and I think, Alan, in your summary
11 tables you actually state those levels so that
12 people can easily get to that information.

13 DR. MARKS: We now in the conclusion say
14 if one is not being used would be used in a
15 similar concentration and similar products and
16 such so that we'll move forward with safe as
17 issued and issue a tentative report. I wanted to
18 get Tom and the two Rons' comments in the change
19 of format of this presentation of the section with
20 acute toxicity and in the second section is
21 repeated dose toxicity. Did you like the way that
22 was done? That's a change.

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1 DR. SLAGA: I actually like it.
2 Repeated dose tells you more than chronic.
3 Chronic could be one dose.

4 DR. MARKS: Ron and Ron, do you like
5 that change?

6 DR. SHANK: I'm not sure what the change
7 is. What are you talking about?

8 MS. BECKER: An acute dose and then
9 repeated dose instead of short-term chronic,
10 subchronic and chronic and the last three are
11 combined into one section and then we put in
12 hopefully the length of time that's being used
13 within that section.

14 DR. SHANK: Frankly, I didn't even
15 notice that. I could read it either way.

16 DR. MARKS: Obviously for you it wasn't
17 a significant change.

18 DR. SHANK: No, it wasn't. Sorry.

19 DR. MARKS: No, not at all, Ron. That's
20 perfectly fine. Probably that's the greatest
21 endorsement in that the change was made and it had
22 no impact on the way you reviewed the data. Ron

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1 Hill, I wanted to do that to give Alan, you and
2 Lillian feedback. And I assume, Ron Hill, it was
3 fine with you too.

4 DR. HILL: I liked it better.

5 DR. MARKS: So that it's an overwhelming
6 endorsement of presenting it this way. Tomorrow
7 we will hopefully second a motion on a tentative
8 report with safe as used.

9 DR. BAILEY: Could I add one comment?
10 On page 3 under General Biology Absorption
11 Distribution, the second-to-last full paragraph
12 contains a number of errors that should be
13 corrected and we've provided comments to that
14 effect to make sure it's accurate.

15 DR. MARKS: Thank you, John. John, now
16 that you've said that it contains a number of
17 errors, do you think that would have any impact on
18 our safety assessment?

19 DR. BAILEY: No, not at all.

20 DR. MARKS: Thank you. Next we have
21 triclosan. It's in the Blue Book. In August we
22 issued a tentative report with the conclusion that

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1 choline chloride to the other ingredients in this
 2 report. The lack of dermal penetration combined
 3 with the negative results of the bacterial and
 4 mammalian assays on choline chloride support the
 5 absence of any genotoxic risk.

6 MR. SNYDER: Good. (Pause)

7 MS. BECKER: Okay.

8 DR. BELSITO: Anything else.

9 MR. LIEBLER: No.

10 DR. BELSITO: Dan?

11 MR. LIEBLER: Looks good.

12 DR. BELSITO: Paul, are you done?

13 MR. SNYDER: Yes.

14 DR. BELSITO: Okay. Okie-doke. And so
 15 then in the conclusion, following our format for
 16 the day, the ingredients will be broken out into a
 17 list form rather than in the conclusion. And
 18 those that are not in current use will be
 19 asterisked. And the -- and referred to in the
 20 conclusion with that asterisk.

21 Okay. Another one bites the dust.

22 Alkyl benzoates. There's a lot of information on

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1 this one. Okay.

2 So, back in August we went with
 3 insufficient announcement for the 17 alkyl
 4 benzoates in the group. And we asked for
 5 irritation and sensitization of the low molecular
 6 weight ingredients, especially methyl benzoate.
 7 And we got that.

8 We asked for genotoxicity and we got
 9 that. We asked for dermal penetration, and we got
 10 that, although I need an explanation of what the
 11 log P's meant, because usually they tell me it
 12 goes into receptor fluid or not, and that's all my
 13 simple mind can deal with. But it looked like
 14 there was, to me, no significant penetration.
 15 Perhaps I'm wrong. So then, we don't need the
 16 reproductive and developmental toxicity data.

17 And do we need the explanation for
 18 carcinogenicity? But did we just get that this
 19 morning? Was there an explanation -- no, we
 20 didn't. So we still don't have a reasonable
 21 explanation as to why methyl benzoate has the
 22 carcinogenic effect. But if it's not getting

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1 absorbed, then do we need to know?

2 MR. SNYDER: Well we have it on the
 3 benzoic acid and the alcohol.

4 DR. BELSITO: Right. So, are we ready
 5 to go safe as used?

6 DR. EISENMANN: In wave 2 there was a
 7 developmental study on a related compound,
 8 isononyl benzoate and --

9 DR. BELSITO: Yeah, I had a question as
 10 to how that related since it's not in a cosmetic
 11 ingredient.

12 DR. EISENMANN: Well, the company that
 13 provided it --

14 DR. BELSITO: Thinks it is?

15 DR. EISENMANN: No. They said it is
 16 possible that a small component of C12 (inaudible)
 17 -- that a little bit of it may be less than 12.
 18 Very small amount, but.

19 DR. ANDERSEN: But it is arguably a
 20 related chemical structure?

21 DR. BELSITO: Right.

22 DR. ANDERSEN: So it could make a

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1 judgment -- it tells you something about the
 2 ingredients that are in there.

3 MR. LIEBLER: So, just want to clarify
 4 this. If a compound is not a cosmetic ingredient
 5 but it has been studied and it does have a
 6 reasonably appropriate relationship, analogy,
 7 structure, properties to a cosmetic ingredient
 8 that we can certainly consider, and we will
 9 incorporate that information into the report.

10 DR. ANDERSEN: Yes.

11 MS. BECKER: Yes, especially if we don't
 12 have enough of the actual ingredient.

13 MR. LIEBLER: Right. So I think this is
 14 a good example of that.

15 DR. ANDERSEN: We won't put that
 16 chemical in the title, because it's not --

17 MR. LIEBLER: Right.

18 DR. ANDERSEN: -- a cosmetic ingredient.
 19 But we'll use the data. Okay, good.

20 DR. BELSITO: In looking at it, other
 21 than some typos I didn't have any comments. I was
 22 comfortable with safe as used, assuming that your

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1 interpretation of the penetration data was the
2 same as mine, that there was very little absorbed.

3 MR. LIEBLER: In my note here -- I'll
4 scroll up and look at the dermal penetration one
5 more time. My note here on these is significant
6 dermal penetration even for the C12 to C15 esters.
7 However, the compounds appear to be largely
8 non-toxic. The alcohols are toxic at high
9 concentrations but these high concentrations will
10 not be generated by metabolism of the esters in
11 the skin. Still no repro in the esters and no
12 carcinogenicity, although I would be surprised if
13 either were observed. And now with wave 2 data we
14 have the repro on the analogous compound, and
15 that's negative.

16 So, the issue of dermal penetration,
17 Don, I'll scroll up and take a look while somebody
18 else says something.

19 DR. BELSITO: Well, it says the new
20 information we got where the permeability
21 coefficients KP for methyl benzoate 20.3, ethyl
22 benzoate 34.08, and propyl benzoate 62.7, and amyl

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1 benzoate 79.9.

2 And that says, permeability was
3 increased by removal of the stratum corneum, but
4 that's not relevant to -- and then using a
5 penetration cell, C12 -- the C12, C13, C14, C15
6 alkyl benzoates. It says that -- let's see. Less
7 than .5 percent in the horny layer epidermis,
8 dermis receptor (inaudible). So, .05 in the
9 receptor fluid and .05 in the dermis. So -- and
10 93.5 percent of it was up in the stratum corneum
11 and never got absorbed.

12 So the larger molecular weights are not
13 just -- not used to dealing with KPs and what does
14 that mean?

15 MR. BRONAUGH: It's the permeability
16 constant, which is --

17 DR. BELSITO: Right.

18 MR. BRONAUGH: -- doesn't -- the KP is a
19 permeability constant, which is the steady state
20 rate of absorption provided by the concentration
21 applied to the skin.

22 For -- water, the KP value is like 10 to

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1 the minus 3. So when you have these values for
2 methanol, .3 and then -- .3, 12, 3, and even 2.5
3 times 10 to the minus 3 are a fairly rapid
4 penetration. And methanol, you would expect to
5 penetrate the skin fairly readily.

6 So if you look down below like 10 to the
7 minus 3, then you start getting into the area
8 where the penetration is slow.

9 MR. LIEBLER: So a KP of 20?

10 MR. BRONAUGH: That's fast.

11 MR. LIEBLER: That's fast. And so the
12 way I read through this, it's 20 times 10 to the
13 minus 2.

14 MR. BRONAUGH: Okay, so that's fast.

15 MR. LIEBLER: Okay. 20 times 10 to the
16 minus 2. Okay, yeah. But I reasoned that methyl
17 benzoate must be penetrating the skin.

18 MR. BRONAUGH: Yes.

19 MR. LIEBLER: And therefore the very
20 similar numbers for ethyl and propyl and butyl
21 suggested to me that those all also would be
22 penetrating the skin.

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1 And then the numbers -- the
2 corresponding numbers, I believe, if the term
3 partition coefficient -- the next paragraph. So
4 I'm on page 3. The paragraph under alkyl
5 benzoates. The second paragraph says, using a
6 penetration cell, the partition coefficient of C12
7 alkyl benzoate -- C13, C14, so forth -- were 8.0,
8 8.6, 9.1, and 9.6, respectively. Are these
9 numbers the same types of numbers as the
10 permeability coefficients KP in the previous
11 paragraph?

12 DR. EISENMANN: No.

13 MR. BRONAUGH: Partition coefficient is
14 the optimum water partition coefficient. So it's
15 not the same as a permeability.

16 DR. BELSITO: So it's (inaudible) --

17 MR. BRONAUGH: Yes.

18 MR. LIEBLER: So my point here is that
19 the text is not clear enough. As the reader goes
20 from one set of numbers to another set of numbers,
21 and the next paragraph, they're talking about
22 different types of parameters.

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1 MR. BRONAUGH: Right. Assuming --

2 MR. LIEBLER: And -- but it's misleading

3 because the numbers all appear to be so similar.

4 So I wasn't sure about that.

5 MR. BRONAUGH: Right.

6 MR. LIEBLER: So it looks like the short

7 chain alkyl benzoate esters go into the skin. The

8 longer chain alkyl benzoate esters with these high

9 KOWs, looks like they do not go in.

10 And then the second part of that

11 paragraph talked about the baby micropigment

12 cream. The amount recovered test substance was

13 91.5 percent in the horny layer, 8.6 in the

14 epidermis, less than .07 percent in the dermis, and

15 less than .07 percent in the receptor fluid.

16 Sounds like mostly on the --

17 MR. BRONAUGH: Non-penetrating --

18 MR. LIEBLER: -- mostly non-penetrating

19 --

20 MR. BRONAUGH: Yeah. I would say if you

21 have 8.6 percent in the epidermis, I would say --

22 MR. LIEBLER: The epidermis.

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1 MR. BRONAUGH: Yeah.

2 MR. LIEBLER: Okay.

3 MR. BRONAUGH: I'd say it's going to

4 penetrate.

5 MR. LIEBLER: And that's C12 to C15.

6 DR. BELSITO: Okay. Then -- right.

7 MR. LIEBLER: Then we are on the same

8 page. So --

9 MR. BRONAUGH: But because the partition

10 -- the high partition coefficient should arrive --

11 for those -- in the second paragraph indicates a

12 lack of penetration. Wouldn't expect that the

13 partition coefficient of 8 --

14 DR. BELSITO: So the C12 alkyls aren't

15 going to get in.

16 MR. BRONAUGH: Right.

17 DR. BELSITO: Okay. Then, Lillian, on

18 page 18 of the report in the summary under the

19 alkyl benzoates, benzoic acids. So the benzoic

20 section, the third paragraph of -- the second

21 paragraph underneath that, the third line? It

22 says, methyl benzoate, ethyl benzoate, propyl

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1 benzoate, butyl benzoate, and C12 15 are not

2 expected to penetrate skin. That's incorrect,

3 then?

4 MS. BECKER: Okay. So, the C12 15 are

5 not?

6 DR. BELSITO: Well, but the others are.

7 The sentence implies that all of them are not.

8 MR. LIEBLER: So I'd just like to --

9 DR. BELSITO: This would be incorrect.

10 MR. LIEBLER: -- clarify what Bob and I

11 were just talking about here. If I understood you

12 correctly, Bob, you said that with the KOW of 8

13 for the C12 --

14 MR. BRONAUGH: Right.

15 MR. LIEBLER: That that would not be

16 expected to penetrate.

17 MR. BRONAUGH: That's right.

18 MR. LIEBLER: Yet the next sentence --

19 or as the data summary from the C12 tests, and it

20 shows 6.5 percent in the epidermis and then with

21 the baby micropigment cream 8.6 percent in

22 epidermis. And then with the protection spray 7.5

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1 percent in the epidermis. So, the prediction is

2 that it wouldn't go in, the data says it went in

3 to the epidermis about 5 to 10 percent.

4 So where are we on interpreting the KOW?

5 DR. EISENMANN: But you don't know if

6 it's really -- if it's just going to go and stay?

7 I mean -- stay in the epidermis and --

8 MR. BRONAUGH: You don't know whether

9 it's going to go further --

10 DR. EISENMANN: Right.

11 MR. BRONAUGH: I think my feeling is

12 that if you have a partition coefficient of 8,

13 that material -- some of it (inaudible) or it's

14 probably not going to penetrate. So if you do a

15 penetration study and you see 13 percent -- I

16 mean, I'm sorry. 6 percent in the epidermis, this

17 material may not penetrate further. In fact --

18 MR. LIEBLER: Is it possible -- so, you

19 have much more experience in interpreting data

20 like this than probably all of us put together.

21 And I'm wondering if you do an experiment with

22 this system and you attempt to measure what's in

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1 the epidermis, don't you somehow have to separate
 2 the horny layer from the epidermis to measure
 3 what's in the epidermis? And it could be error in
 4 the separating the horny layer from the epidermis
 5 give you enough carryover into what appears to be
 6 epidermis to give you a number like 5 or 10
 7 percent?

8 MR. BRONAUGH: I don't think so.
 9 Because it's pretty clear cut. When you're
 10 stripping off the stratum corneum with cellophane
 11 tape, you just go -- you know, like 10, 20 strips.
 12 And I don't think you can miss the material and
 13 the epidermis.

14 MR. LIEBLER: So you would have
 15 confidence in those numbers, 8 percent, 7 percent,
 16 5 percent, being --

17 MR. BRONAUGH: You know, not knowing
 18 who's done the study and all of that sort of thing
 19 it's hard to say how much confidence you have.
 20 But I know that we could never miss something like
 21 that.

22 So I really think there is -- sounds

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1 like there's material in the epidermis. But then
 2 they went on, they didn't see any in the dermis.
 3 So, that combined with the very high partition
 4 coefficients would make me think that there's not
 5 penetration.

6 MR. LIEBLER: You said earlier in our
 7 discussion on one of the other ingredients this
 8 morning that the epidermis is vascularized. And,
 9 so the compounds that could reach the epidermis
 10 don't have to go to the dermis to get to the --

11 MR. BRONAUGH: The epidermis is not
 12 vascular --

13 MR. LIEBLER: No. Oh, it's not.

14 DR. BELSITO: The vessels are right
 15 below.

16 MR. BRONAUGH: It's the upper dermis --
 17 the papillary dermis, right below the epidermis is
 18 where the blood vessels --

19 DR. BELSITO: They have to get through
 20 the base of the membrane --

21 MR. LIEBLER: If you can get -- if
 22 you're a chemical, you can get as far as the

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1 epidermis. You're still not in home free, you're
 2 not in it yet --

3 MR. BRONAUGH: That's not dermal
 4 penetration --

5 DR. BELSITO: Right.

6 MR. LIEBLER: Okay.

7 DR. BELSITO: (Inaudible) --

8 MR. LIEBLER: All right. So, okay. So
 9 the high KOW, 8 or 9, suggests that it will not be
 10 absorbed dermally.

11 DR. BELSITO: Right.

12 MR. LIEBLER: Absorbed through the skin.

13 MR. BRONAUGH: This is a little bit
 14 confusing because it also suggests that it won't
 15 get into the epidermis. Because -- it suggests
 16 that it's very lipophilic, and it would get into
 17 the stratum corneum but not go into the aqueous
 18 epidermal and dermal layers. So this is not
 19 completely consistent, this data.

20 MR. LIEBLER: Well, I guess that's my
 21 point is that it seemed to me to be inconsistent
 22 of trying to get some idea how to interpret it,

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1 because it's a pretty important point for these
 2 chemicals.

3 MR. BRONAUGH: Right.

4 MS. BECKER: Would the confounding
 5 factor be that these are all formulations and not
 6 true chemical?

7 MR. BRONAUGH: I'm sorry, I couldn't
 8 quite hear.

9 MS. BECKER: I'm sorry. Could the
 10 confounding factor be that these are formulations
 11 and not the pure chemical and something is
 12 facilitating some penetration or --

13 DR. BELSITO: Or in the case of the sun
 14 lotion, it was applied to gently shaved skin. So
 15 we don't know the state of the skin in the others.
 16 But a sun lotion where you've got 6.5 percent of
 17 the epidermis was shaved, meaning that the stratum
 18 corneum had been disrupted.

19 DR. EISENMANN: I think all three were
 20 done -- I mean, it was pig skin, I think.
 21 Probably all three were treated the same way.

22 DR. BELSITO: So all shaved?

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1 DR. EISENMANN: So it could get in --
 2 I'll look again, probably.
 3 MR. LIEBLER: If this is all three
 4 experiments within the same report?
 5 DR. EISENMANN: Correct.
 6 MR. LIEBLER: Is that what you're
 7 suggesting? Okay.
 8 DR. BELSITO: Yeah. So it's probably
 9 all gently shaved skin.
 10 MR. LIEBLER: So maybe what I take from
 11 this is that we could say that the high KOW values
 12 of 8, 8.69. and 9.6 suggest little or no
 13 penetration would be expected.
 14 In the experiments described, female pig
 15 skin, measured amounts were as follows. And
 16 that's not really inconsistent with the KOW.
 17 MR. BRONAUGH: No. I think it is
 18 consistent, actually. In fact, that you get 6
 19 percent in the epidermis --
 20 DR. BELSITO: Which is surprising --
 21 MR. BRONAUGH: If it was extremely
 22 lipophilic, you wouldn't expect it to get out of

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1 the stratum corneum.
 2 DR. BELSITO: Right.
 3 MS. BECKER: So you'd expect 0 or .001 --
 4 DR. BELSITO: Right. But it would be
 5 consistent with skin that had been shaved where
 6 the stratum corneum had been disrupted?
 7 MR. BRONAUGH: Yes. If you disrupt the
 8 stratum corneum, then that would --
 9 DR. BELSITO: So I mean, we could say --
 10 if Carol can check if all of them were done in the
 11 same way, which is likely -- the skin was shaved
 12 in all of the animals. And, you know, we could
 13 point out in -- I don't even know if we need to
 14 point it out in the discussion.
 15 MR. BRONAUGH: You know, if they did
 16 replicates, I guess we don't have the replicate
 17 data.
 18 DR. BELSITO: Right.
 19 MR. BRONAUGH: But, you could nick one
 20 animal or one piece of skin but you wouldn't nick
 21 in the same way all the way through.
 22 DR. BELSITO: Okay. So --

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1 DR. EISENMANN: The replicates are in
 2 here --
 3 DR. BERGFELD: I'm not sure what we've
 4 decided here.
 5 DR. BELSITO: Well, let's just go back.
 6 We have the irritation and the sensitization data
 7 on the low molecular weights. We have
 8 genotoxicity, and now the question is the dermal
 9 absorption. So it appears that the low molecular
 10 weights will absorb, the methyl benzoates, the
 11 propyl benzoates of the world. And under those
 12 circumstances -- so that for the lower molecular
 13 weights we want to repro and developmental
 14 toxicity, which we have not for a chemical that's
 15 used as a cosmetic but for a similar chemical.
 16 And that's clean.
 17 So, I guess the first question is, is
 18 everyone happy with that study as a surrogate for
 19 methyl benzoate et al?
 20 MR. BRONAUGH: Another issue in my mind
 21 -- I just noticed that these partition
 22 coefficients were done at pH 3. But if you're

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1 putting it on in a formulation you're putting it
 2 on at pH7 (inaudible) 6. I don't know what the
 3 partition coefficients of an alkyl benzoate would
 4 have been for the neutral of it.
 5 MR. LIEBLER: You know, it shouldn't
 6 matter. These are esters. An aqueous solution pH
 7 3 is not going to be enough to hydrolyze the
 8 ester, at least in a relatively quick experiment.
 9 And -- but I don't think since there's nothing
 10 else to be protonated or deprotonated in these
 11 molecules, I don't think pH 3 versus pH 7 should
 12 affect the KOW. Do you?
 13 MR. BRONAUGH: I just wonder why it did
 14 appear --
 15 MR. LIEBLER: Oh, yeah. No, that's --
 16 MR. BRONAUGH: Maybe -- but you're
 17 probably right.
 18 DR. BELSITO: Okay. Duly noted. So,
 19 Curt, Dan, Paul, Wilma? Happy, not happy with the
 20 repro developmental stuff we've been given on the
 21 non-cosmetic chemicals similar to (inaudible)?
 22 MR. SNYDER: Well, we certainly have,

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1 Curt, lots of information on benzoic acid and the
2 alcohols. We have the one benzoic acid isosonyl
3 (sic) ester.

4 MR. LIEBLER: Isononyl.

5 MR. SNYDER: Isononyl ester. So -- and
6 if that had a really high no adverse effect level
7 at 1,000 milligrams. So, I don't see an issue
8 unless that issue is out of my scope of chemistry,
9 is whether that's -- is that a lipophillic,
10 lipid-soluble ingredient? Because I know that
11 sometimes the others are -- focuses on that,
12 whether it's lipophillic or not and it's going to
13 have greater penetration, et cetera. So.

14 MR. KLAASSEN: Which chemical do you
15 have reference to?

16 DR. BELSITO: The one they did the repro
17 study on, the isononyl --

18 DR. EISENMANN: It's in the way of blue
19 one -- it's not in the book.

20 DR. ANDERSEN: It wasn't flagged as an
21 issue.

22 MR. LIEBLER: So there is significant

1 dermal penetration for the short chain esters? I
2 think we are in agreement on that.

3 DR. BELSITO: Right.

4 MR. LIEBLER: And then for the -- yes?

5 MS. BECKER: In the unpublished data
6 stuff at the back? The original reports are
7 there, if you want to look at it.

8 MR. LIEBLER: Oh.

9 MS. BECKER: (Inaudible) second
10 paragraph.

11 DR. BELSITO: What is there?

12 MS. BECKER: The original source
13 material for the penetration cell partition
14 coefficient.

15 DR. BELSITO: Oh.

16 MS. BECKER: That you have in front of
17 you, if somebody wants to look at it.

18 MR. LIEBLER: What's the --

19 MS. BECKER: It's --

20 MR. LIEBLER: -- number -- page number
21 from the book?

22 MS. BECKER: There's not -- this one --

1 you can get a page number for the book. It's this
2 -- it's right at the very front of the data, just
3 past the amounts of updated concentration in use.
4 It's the next section.

5 If you find the page that the data
6 starts, there's concentration in use. And then
7 the very next section is these two studies. So
8 it's the studies.

9 MR. SNYDER: What page were you
10 referring to?

11 DR. BELSITO: We don't have a page.

12 MS. BECKER: They didn't put a pat-down
13 number on it. So if you get concentration of use,
14 which is pretty easy to spot --

15 DR. BELSITO: Dermal absorption,
16 penetration, there it is.

17 MR. SNYDER: So the only thing I would
18 want to know is, did -- for all of these compounds
19 that they prepared the skin in the same way? And
20 if they did --

21 DR. BELSITO: Gentle scraping with a
22 spatula.

1 MR. SNYDER: Okay. Now, are these the
2 data that we're talking about where they --

3 DR. BELSITO: Tape strip, 16 strips.

4 MR. SNYDER: That's to analyze the horny
5 layer?

6 DR. BELSITO: (Inaudible)

7 MR. SNYDER: Yeah, so that's their
8 analytical workup.

9 So, that's the data -- these data you're
10 referring to, Lillian, are the data on the short
11 chain esters, correct? Methyl, ethyl, and propyl,
12 and butyl?

13 MS. BECKER: These are on C12 through
14 15.

15 MR. SNYDER: Oh, it's the C12, okay.

16 Those are the data we're concerned about. And, in
17 the text you described it as gently shaved skin.

18 So if these were all prepared, all --
19 the skin for all 3 (sic) of these compounds --
20 C12, C13, C14, C15 -- "is all prepared in the same
21 way, gently shaved", then it's possible we could
22 point out that the skin had been gently shaved and

1 this could affect the penetration of these
2 compounds because the measured levels in the
3 epidermis seem at odds with the prediction from
4 the KOW.

5 I think the thing we're hung up on here
6 is the apparent discrepancy between what showed up
7 in the epidermis and what the KOW would predict.
8 That's why I wanted to really get Bob Bronaugh's
9 opinion on this, because I wasn't sure if this
10 would be consistent or inconsistent. What you're
11 telling us is this seems really inconsistent.

12 MR. BRONAUGH: To me it does.

13 MR. LIEBLER: Because for us it's the
14 difference between saying whether these things are
15 significantly absorbed or not. And if the only
16 data we have are the data from this experiment,
17 and then we have what would be predicted from KOW,
18 it's very hard for me to weigh those two things.
19 I take your opinion very seriously, but then I
20 wonder why they got the measure of result in the
21 experiment that they report.

22 So, that's the only indigestible bit of

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1 this for me.

2 DR. BELSITO: Yeah, they were all
3 shaved. I don't see where Lillian got the gently
4 shaved, but if you look at the --

5 MS. BECKER: Page 4 of 14. Skin just
6 gently shaved, surface thickness 3 to 4
7 millimeters, diameter 5 centimeters, reduced.

8 DR. BELSITO: Where were you?

9 MS. BECKER: Page 4 of 14. It says --

10 DR. BELSITO: 4 of 14 --

11 MS. BECKER: I guess it's the
12 (inaudible) of 4 on 14. At the very top.

13 MR. LIEBLER: Lillian, which compound
14 are you looking at?

15 MS. BECKER: This is (inaudible) -- this
16 is the sun lotion and the baby micropigmented
17 cream and the spray.

18 DR. BELSITO: What section is
19 (inaudible)?

20 DR. ANDERSEN: C12.

21 MS. BECKER: C12 through 15.

22 DR. ANDERSEN: Alkyl benzoate.

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1 MS. BECKER: At the very top they get --
2 the first report has 7 of 7, and then the other
3 one is 14 pages.

4 DR. BELSITO: Yeah. The one that's 14
5 pages?

6 MS. BECKER: Right, go to page 4.

7 DR. BELSITO: Okay. Yeah. Gently dry
8 skin -- dry shaved surfaces.

9 MR. LIEBLER: Okay, now the description
10 of the analytical samples in which they measured
11 the compound. Skin surface with general scraping
12 with a spatula. Horny layer was Tessa tape, 16
13 strips, and then the epidermis was heating the
14 skin discs, epidermal side, for 45 seconds on an
15 80 degree hot plate. Separation of the epidermis
16 from the dermis with forceps.

17 So, is that type of sample prep clean
18 enough to give you epidermis but not have any
19 horny layer still there? If the tape stripping
20 didn't work -- do they have to tape strip first
21 and then do this heating and separation?

22 MR. BRONAUGH: Yeah.

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1 DR. BELSITO: Yeah.

2 MR. LIEBLER: And if you have 100
3 percent of the materials in the horny layer and
4 then you do this sample workup, is it possible to
5 get 5 percent carryover just by artifact of the
6 sample prep?

7 MR. BRONAUGH: It would be possible.

8 MR. LIEBLER: That's what I've been
9 wondering all along here. And that's -- I've been
10 -- by phrasing it that way. That's what I'm
11 concerned about. Is this a real -- does this
12 really reflect 5 to 7 percent of the compound in
13 the epidermis for sure? Or, is that the
14 uncertainty in this type of sample workup?

15 MR. BRONAUGH: A lot depends on how hard
16 you press the tape on the skin. Somebody presses
17 really hard they get more per strip, so if
18 somebody's not pressing the tape hard you could
19 maybe miss -- not get all of it off.

20 MS. BECKER: They're saying 80 grams per
21 centimeter squared.

22 MR. BRONAUGH: That's the pressure?

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1 MS. BECKER: That's the pressure. 80
2 grams per centimeter squared.

3 MR. BRONAUGH: Sounds like they're
4 pretty thorough. Most people don't put the
5 pressure they use.

6 DR. BELSITO: Okay. Well, I mean, we
7 have explanations that would go along with the low
8 levels in the epidermis and this gently shaved --

9 MR. LIEBLER: So they should calibrate
10 this system with one of these polyquaterniums that
11 doesn't go in and see how much they pick up in the
12 epidermis.

13 MR. BRONAUGH: And it would also be
14 interesting to see the replicates that they do.

15 MR. LIEBLER: Yeah.

16 MR. BRONAUGH: If you damage the skin,
17 you're not going to damage it the same way in each
18 replicate.

19 MR. LIEBLER: Yeah, okay. But I think
20 there's potentially a basis for pointing out that
21 the -- okay. So the amount in the epidermis is
22 relatively small, 7 percent or so.

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1 DR. BELSITO: And there's reason to
2 explain why that could occur, because they were
3 shaved. And given the log KOWs, sitting in the
4 epidermis -- we don't think that it's going to
5 sneak past the basement membranes and get
6 absorbed. I think we have that.

7 The biggest issue still left that we
8 said was insufficient is that methyl benzoate
9 clearly gets through and we don't have an
10 explanation for the carcinogenicity data.

11 DR. EISENMANN: What carcinogenicity
12 data are you talking about? Page 14?

13 DR. BELSITO: There was from -- it was
14 in the last report, which is why it got raised.
15 So let's look here.

16 DR. EISENMANN: We have benzoic acid.

17 MS. BECKER: I have benzoic acid and
18 alcohol carcinogenicity data.

19 MR. LIEBLER: I don't think we have
20 methyl benzoate carcinogenicity.

21 DR. BELSITO: All right. So why was
22 that in our data request?

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1 DR. ANDERSEN: I think it was just the
2 plain absence of information, Don.

3 DR. BELSITO: No, it says here that
4 existing criteria --

5 DR. ANDERSEN: Mode of action --

6 DR. BELSITO: -- existing
7 carcinogenicity data that appeared to show
8 increased tumor growth in rats given oral doses of
9 methyl benzoate. So maybe it's under chronic oil
10 tox?

11 MR. BRONAUGH: Well, a KP value of 20.3
12 shows that it goes through the skin.

13 DR. EISENMANN: (Inaudible) --
14 carcinogenicity. But methyl -- but if I remember
15 correctly, methyl benzoate is a normal -- I mean,
16 it's a normal constituency of plants. And it's
17 got a JACFA review. Orally, though, it's okay.

18 DR. BELSITO: Well, we put it in there.
19 I mean, it's clearly there as a data need and I
20 believe it came from the other team.

21 MS. BECKER: It's not under if there's
22 penetration?

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1 MR. SNYDER: Well, the long-term study
2 -- carcinogenicity study, dermal study (inaudible)
3 --

4 DR. BELSITO: With --

5 MR. SNYDER: Benzyl oils and --
6 non-oxidated GERDA containing benzoic acid. 016
7 percent benzyl alcohol. Between that study --
8 that tumor growth, I think that has to do they
9 were just treated orally and then they were given
10 -- tumors transplanted.

11 MS. BECKER: Which page is that?

12 MR. SNYDER: Page 14.

13 MS. BECKER: Okay, for the alcohol of
14 benzoic acid --

15 MR. SNYDER: So you don't have that
16 reference there.

17 MR. LIEBLER: So can we pull -- we need
18 to look at that (inaudible) --

19 DR. BELSITO: Okay, we'll here's the
20 transcripts. We need more information on the
21 carcinogenicity study that's in this document and
22 any additional carcinogenicity studies that are

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1 out there. So there had to be in the document we
2 saw last time carcinogenicity study with methyl
3 benzoate.

4 MS. BECKER: Which page is that in the
5 transcripts?

6 DR. BELSITO: The pages aren't listed.

7 MS. BECKER: Oh.

8 DR. BELSITO: But it's the next to the
9 last transcript page before the report. And it's
10 my recap of what's being asked. I haven't gotten
11 back to who first raised the question.

12 MR. LIEBLER: So we can't find that in
13 our document. But also, the methyl benzoate is
14 approved by the FDA as a flavor. So, probably
15 couldn't be much of a carcinogen.

16 MR. SNYDER: I don't see a basis for
17 that.

18 DR. BELSITO: Don't see a basis for that
19 there, but there must have been a basis in
20 something we saw last time.

21 MR. SNYDER: Well, I think it was
22 related to this increased tumor growth in the

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1 transplantation study in the benzoic acid. That's
2 the only thing I can figure it alluded to.

3 MR. KLAASSEN: What page is that?

4 MR. SNYDER: Page 14. So there was a 5
5 generation study in which they administered
6 benzoic acid 40 milligrams per kilogram for 5
7 generations --

8 DR. BELSITO: But why would we say,
9 specifically, methyl benzoate? We would have said
10 benzoic acid.

11 MS. BECKER: Unless somebody misspoke.
12 I have the last panel meeting's book, and Halyna's
13 coming to go grab it and see if we can find
14 anything.

15 DR. BELSITO: Okay. Do you have the
16 last one that you can scan for methyl benzoate.

17 MR. LIEBLER: I probably can't scan it
18 because (inaudible) -- let's see what I've got.

19 MS. BECKER: Oh, that was the one that
20 was the 1970 review paper that really didn't tell
21 us anything. We decided that it was not going to
22 be useful.

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1 It was that paper -- it was a big paper
2 with lots of little bits of information and a big
3 study. And the little bit -- and only had one,
4 two sentences of carcinogenicity in it. We
5 decided that the study was not going to be much
6 help.

7 DR. BELSITO: We decided because it was
8 a hard data request. We are decided -- we decided
9 at the panel meeting, you think it would have been
10 dropped from my data request.

11 MS. BECKER: No, that particular
12 citation was not useful because it was just a
13 small part of the study. It wasn't the focus of
14 the study, it was a sentence in the write up.

15 DR. BELSITO: Right. It says, in a 1970
16 review it was reported that cross-bred white mice
17 and equal 100 orally administered methyl benzoate
18 80 milligrams per kilogram per day had increased
19 tumor growth compared to controls.

20 MS. BECKER: But they didn't explain
21 what that meant. That was all they said. So it's
22 really --

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1 DR. BELSITO: I mean, I think we need to
2 toss this out, though, for discussion.

3 MR. LIEBLER: Reference 70 in green
4 book. So we need to chase down reference 70 in
5 green book 4 from the last meeting.

6 MS. BECKER: I -- what else do you need?
7 Because that's, you know --

8 MR. LIEBLER: That's what's referred to
9 there.

10 MS. BECKER: Right. And, that's all
11 they said in the whole study was, increased tumor
12 growth. They didn't say they were bigger tumors,
13 more tumors, or --

14 MR. LIEBLER: I'm wondering. Reference
15 70 is a new --

16 DR. BELSITO: It is reference 30.

17 MR. LIEBLER: Oh, reference 30, I'm
18 sorry. Reference 30 is a review? Or was it a
19 study?

20 MS. BECKER: It was a study -- when I
21 first wrote it up, it was referred to in another
22 one and it looked like a review. But when I got

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1 it after this was printed up, it was a big study
 2 of several iterations and different --
 3 DR. BELSITO: It's toxicological
 4 evaluation of some combinations of food
 5 preservatives, that's the title. And it was
 6 published in 1970 in food cosmetic toxicology.
 7 MR. SNYDER: Well, we still reference it
 8 in this one. It's reference 70 in this book.
 9 DR. BELSITO: Well, it's not in the
 10 document anymore.
 11 MS. BECKER: That part isn't. I may
 12 have put something else in there.
 13 MR. SNYDER: But that's the reference of
 14 this -- that's what I saying. That reference goes
 15 with this study that I was referring to where they
 16 administered it for five generations. And so on
 17 the tumor --
 18 MS. BECKER: Right.
 19 MR. SNYDER: They did a follow-up tumor
 20 transplantation test --
 21 MS. BECKER: Okay --
 22 MR. SNYDER: -- but then they

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1 transplanted tumors into animals that had received
 2 benzoic acid. And they saw that they increased
 3 tumor growth --
 4 MS. BECKER: Okay --
 5 MR. SNYDER: -- not meaning that the
 6 tumors were larger or more extensive or whatever
 7 -- not really --
 8 MS. BECKER: I'm starting to remember
 9 the process now, it's a lot of stuff, yes. Yeah,
 10 this was after I --
 11 DR. BELSITO: So it's probably the same
 12 issue for methyl benzoate.
 13 MR. SNYDER: Right.
 14 DR. BELSITO: So, does that alleviate
 15 our concern, or?
 16 MR. LIEBLER: Could you state that
 17 again?
 18 DR. BELSITO: Certainly was a concern
 19 before --
 20 MR. LIEBLER: Could you state that one
 21 more time for us, Paul? What you just said?
 22 DR. BELSITO: What page are you on,

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1 Paul?
 2 MR. SNYDER: On page 14. So on
 3 reference 70, which is the same reference that you
 4 just referenced in the green book number 4 from
 5 last meeting, which was reference 30. Is the food
 6 and cosmetic toxicology 1970 reference in which
 7 they treated 100 mice orally with 40 milligrams
 8 per kilogram in a paste with benzoic acid, and
 9 they did that for 5 generations. Saw no increased
 10 instance of tumors.
 11 And then there's a sentence here that
 12 says, in a follow up tumor transplantation test,
 13 benzoic acid fed to mice for three months did not
 14 increase tumor growth. So I don't know if methyl
 15 benzoate did increase tumor growth and the benzoic
 16 acid didn't, or what.
 17 So to me, there's no -- nothing that
 18 really raises any kind of a flag. And then we
 19 have the dermal study --
 20 DR. BELSITO: That would be bizarre that
 21 methyl benzoate would and benzoic acid would not
 22 --

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1 MR. SNYDER: Exactly.
 2 MR. KLAASSEN: Well, I think we've got
 3 to get the paper --
 4 MR. SNYDER: Got to get the paper.
 5 DR. BELSITO: So are we tabling this?
 6 Because based upon our prior data request, even
 7 assuming you accept the fact that the repro is
 8 okay on the isononyl ester, we still don't have an
 9 explanation for methyl benzoate carcinogenicity.
 10 Or are we saying that it's not important, going
 11 with a final safe as used?
 12 DR. BERGFELD: Well, the staff could do
 13 that before it's released.
 14 MR. SNYDER: This (inaudible) --
 15 DR. BELSITO: Then we're going to a
 16 final.
 17 DR. BERGFELD: Yeah, I think it
 18 clarified for --
 19 DR. ANDERSEN: No, you're going to issue
 20 it as a tentative.
 21 DR. BELSITO: Tentative final, yeah.
 22 DR. ANDERSEN: For public comment,

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1 period. So there's time to resolve the question.
 2 There's also time to retrieve the paper and look
 3 at it before tomorrow morning.
 4 MR. KLAASSEN: Yeah, that's where -- see
 5 if we can get the paper before tomorrow.
 6 DR. BELSITO: If we could do that, that
 7 would be good.
 8 DR. BERGFELD: Could you clarify where
 9 you're going with the penetration?
 10 DR. BELSITO: What?
 11 DR. BERGFELD: With the penetration --
 12 methyl --
 13 DR. BELSITO: Penetration?
 14 DR. BERGFELD: Yeah, with the absorption
 15 --
 16 MR. KLAASSEN: It is the -- we think it
 17 is -- penetrates.
 18 DR. BERGFELD: And so the bottom line is
 19 the carcinogenicity.
 20 DR. BELSITO: Right. The shorter
 21 molecular weights penetrate, the longer are
 22 predicted not to. We've just rehashed the fact

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1 that there's about 5 percent of the epidermis
 2 possibly shaving, possibly artifact -- but we
 3 don't think it's going to get through epidermis
 4 and be absorbed based upon the KOW. So, all of
 5 those have been addressed.
 6 The only -- if everyone's happy with the
 7 repro study, the only thing preventing this from
 8 going final safe as used is our prior request
 9 about methyl benzoate carcinogenicity.
 10 So, we're --
 11 DR. BERGFELD: If you can prove it --
 12 DR. BELSITO: -- tentatively going
 13 final. We're going to try to get that paper, take
 14 a look, and see why benzoic acid doesn't do
 15 anything and methyl benzoate supposedly did.
 16 DR. BERGFELD: Thank you.
 17 MR. SNYDER: I don't think (inaudible)
 18 -- 1970, and old paper, methodologies are probably
 19 flawed. And descriptive -- contradictory results
 20 between benzoic acid and methyl benzoate -- it's
 21 in there. So, I don't think it's any reason to
 22 hold it up. I think we should move to the next

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1 level.
 2 DR. BELSITO: So assuming we can get
 3 that clarification tomorrow, we're going safe as
 4 used with these.
 5 MR. LIEBLER: Right.
 6 DR. BERGFELD: Are you saying it's no
 7 good (inaudible) --
 8 MR. SNYDER: Wait until we see it. I
 9 mean, we have benzoic acid in the alcohol --
 10 DR. BERGFELD: Okay, okay --
 11 MR. SNYDER: So it's not going to go
 12 through anything yet.
 13 DR. BERGFELD: Okay.
 14 MR. SNYDER: So we have other data on
 15 the two major constituents (inaudible) --
 16 DR. BERGFELD: So you (inaudible) --
 17 MR. SNYDER: Yeah.
 18 DR. BERGFELD: Okay.
 19 MR. LIEBLER: So you'll get the paper
 20 for tomorrow, we'll have it handy. Who's going to
 21 look at it? Lillian? Yeah? So copies for the
 22 table.

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1 MR. SNYDER: So none of the new data is
 2 in this report?
 3 MS. BECKER: Which new data? Everything
 4 we got before --
 5 DR. BELSITO: Everything is in, a huge
 6 amount of data is in.
 7 MS. BECKER: Yeah, everything --
 8 DR. BELSITO: The only thing that's not
 9 in or that -- the two genotox studies --
 10 MR. LIEBLER: And the repro --
 11 DR. BELSITO: Pig penetration.
 12 MR. LIEBLER: And the isononyl --
 13 DR. BELSITO: And the repro is in here,
 14 no?
 15 MR. SNYDER: No.
 16 MS. BECKER: No, this is not in there.
 17 DR. BELSITO: Okay, all right.
 18 MS. BECKER: Everything that's in here
 19 is in the paper.
 20 MR. SNYDER: Okay. That's the third
 21 wave. This morning's wave.
 22 MS. BECKER: No, this was the one that

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1 we got second wave. I didn't have a third wave.

2 DR. BELSITO: No, the second wave was

3 pig penetration -- genotox -- micronucleus, and

4 the repro.

5 MR. LIEBLER: I see.

6 DR. BELSITO: Yeah. Right, so those

7 will be included. But everything that's in the

8 back of this book has already been included.

9 MS. BECKER: Yes.

10 MR. LIEBLER: I stand corrected. Good.

11 DR. BELSITO: Okay. So the alkyl

12 benzoates and then, obviously, with a conclusion

13 will be the list with the asterisks.

14 DR. ANDERSEN: Just so we keep it

15 straight, this is not going final. This is a

16 tentative conclusion for public comment?

17 DR. BELSITO: Right.

18 DR. ANDERSEN: So.

19 DR. BELSITO: I understand. But this

20 brings up an interesting point. Perhaps it would

21 be nice for the panel when a decision is made,

22 even if it's made by all the panel at the panel

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1 meetings to delete materials, since these are

2 marked up copies. If you could just cross out,

3 you know, and do like a track change where what's

4 been deleted has been crossed out? So we can be

5 comfortable with knowing what we had previously

6 reviewed as no longer in the document.

7 DR. ANDERSEN: Yeah, I hear you. We'll

8 have to talk about how to implement that.

9 DR. BELSITO: But if you made the

10 corrections in track mode, then you're

11 automatically lined out.

12 MS. BECKER: Well, then it goes out for

13 public comments.

14 DR. BELSITO: Halyna's crossing -- well,

15 then, as you cut things out could you paste them

16 into a separate document that only the panel gets?

17 DR. BRESLAWEK: We operate in the public

18 forum.

19 DR. BELSITO: Right.

20 DR. BRESLAWEK: I think we'll look for a

21 way to document for the panel what is removed from

22 documents, how's that --

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1 MR. SNYDER: Send the writer's memo,

2 highlighted, and then we can always go back to the

3 electronic version -- the old version, and see

4 that we need to -- somebody wanted to see

5 specifically what that related to.

6 DR. BELSITO: Yeah.

7 MR. SNYDER: That might be (inaudible)

8 --

9 DR. BELSITO: I mean, that would be good

10 for me, but -- okay. Anything else on the alkyl

11 benzoates?

12 DR. BERGFELD: Can I ask a question --

13 at that -- online, at the website, do you keep all

14 the old versions? Or do you always replace it

15 with the newest?

16 DR. BRESLAWEK: We take the old ones off

17 because the -- a lot of information on the website

18 would become quickly unmanageable. We do have

19 copies in our archives.

20 DR. BERGFELD: Okay.

21 DR. BELSITO: Okay. Moving on, okay.

22 Buff book, human umbilical extract. Okay. So, we

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DR. BERGFELD: Is there a --

DR. BELSITO: Second.

DR. BERGFELD: Do we have any other

discussion? Seeing none, call the question, all

those in favor, please indicate by raising your

hands.

Abstaining? One abstaining. Thank you.

All right, thank you very much. Then moving on to

Dr. Belsito's, the Alkyl Benzoate Group.

DR. BELSITO: Yes, alkyl benzoate. So,

back in August, we issued an insufficient data

announcement for the alkyl benzoates. We asked

for irritation and sensitization of a low

molecular weight ingredient of which we got quite

a bit. We asked for dermal penetration and the

information that we got suggested, in fact, that

they would penetrate so that that brought us to

the next two points: That if there was

significant dermal penetration, a reproductive and

developmental toxicity study. And we did get a

repro study that was done on benzoic acid isononyl

ester, which while not a cosmetic compound, per

se, as structurally similar, chemically similar to the ingredients we are looking at. We had asked for genotoxicity and we did get some of that.

Lastly, we had asked for an explanation. In the original document, a notation was made that methyl benzoate had some carcinogenic activity. We actually went back and looked at that report and that is not the case at all. So, there is no need for that last data point.

So, with all of that in mind we're going as a safe as used conclusion for this group.

DR. BERGFELD: That's a motion. And second?

DR. MARKS: Second.

DR. BERGFELD: Any other discussion?

DR. MARKS: Probably the only discussion in the memo from Lillian, there was an issue raised whether we should wait for the European REACH Program results and we felt that we did not need to wait. We have enough individual data that actually will appear in that report, so we didn't need to wait for the final report to move forward

with a tentative report.

DR. BERGFELD: May I ask a question as the chair? And that is, the read-across information, is there a need to do anything in the discussion regarding it?

DR. BELSITO: I think that should go in almost all discussions because there probably is not a single ingredient family we're looking at where we're not using read-across.

DR. BERGFELD: So, to reiterate, the read-across boilerplate specifics should go into the discussion for each of our ingredients? Okay. If there's no other discussion then I'll call for the vote. All those in favor indicate by raising your hand.

Unanimous. Thank you. The next large group is by Dr. Marks, the edible oils as stated here. Now the oils.

DR. MARKS: Well, there are 244 plant-derived oils. We felt that the title of this report could be changed to plant-derived fatty acid oils and in reviewing the data we had,

Alkyl Benzoates

March 4, 2011

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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 Lillian C. Becker, Scientific Analyst/Writer.

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ABSTRACT

The functions of alkyl benzoates in cosmetics include: fragrance ingredients, skin-conditioning agents-emollient, skin-conditioning agents-miscellaneous, preservatives, solvents, and plasticizers. The Cosmetic Ingredient Review Expert Panel reviewed the relevant animal and human data and noted gaps in the available safety data for some of the alkyl benzoates. The available data on many of the alkyl benzoates were sufficient, however, due to similar structural activity relationships, biologic functions, and cosmetic product usage. For example, carcinogenicity data were not available, but available data indicated that these alkyl benzoate cosmetic ingredients are not genotoxic and are not dermal sensitizers. Also, benzoic acid and tested component alcohols were not reproductive or developmental toxicants, are not genotoxic in almost all assays, and are not carcinogenic. Therefore, the low levels at which alkyl benzoates are used could not result in significant systemic toxicity. These ingredients were determined to be safe in the present practices of use and concentration.

INTRODUCTION

This is a safety assessment of alkyl benzoate esters whose function in cosmetics includes: fragrance ingredients, skin-conditioning agent-emollient, skin-conditioning agents-miscellaneous, preservatives, solvents, and plasticizers. The ingredients included in this literature review are: methyl benzoate, ethyl benzoate, propyl benzoate, butyl benzoate, amyl benzoate, lauryl/myristyl benzoate, C12-15 alkyl benzoate, C16-17 alkyl benzoate, stearyl benzoate, behenyl benzoate, isopropyl benzoate, isobutyl benzoate, isostearyl benzoate, ethylhexyl benzoate, butyloctyl benzoate, hexyldecyl benzoate, and octyldodecyl benzoate.

The alkyl benzoate ingredients are esters of benzoic acid and a corresponding alcohol, with the shorter chain alkyl benzoates (methyl, ethyl, propyl, isopropyl, butyl, isobutyl and amyl benzoate) ranging in MW from 136 to 192 and the longer chain alkyl acetates (lauryl/myristyl, C12-15 alkyl, C16-17 alkyl, stearyl, isostearyl, behenyl, ethylhexyl, butyloctyl, hexyldecyl, and octyldodecyl benzoate) ranging in MW from 234 to 431.

The smaller alkyl benzoates in this report penetrate the skin. These compounds will be metabolized in the skin to release benzoic acid and the parent alcohol. Therefore, the safety of these metabolites must be considered when assessing the safety of alkyl benzoates.

Several of the metabolites of the alkyl benzoates in this assessment have been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (benzoic acid, sodium benzoate, and the parent alcohols: methyl alcohol, ethyl alcohol, butyl alcohol, myristyl alcohol, behenyl alcohol, isostearyl alcohol). The conclusions are listed below.

Benzyl alcohol, benzoic acid and sodium benzoate – The conclusion currently states that these ingredients are safe for use in cosmetic formulations at concentrations up to 5%.¹ This safety assessment is currently being re-evaluated to possibly remove the limit.

Methyl alcohol - safe for use as a denaturant in ethyl alcohol for cosmetic products, with qualifications. The Panel has not stated that methyl alcohol is safe or unsafe as a solvent.²

Ethyl alcohol – (as “alcohol denat.”) - safe in the present practices of use and concentration [up to 99% alcohol denat.].³ The CIR Expert Panel considered the safety of cosmetic products containing up to 99% alcohol denat. and were not concerned regarding dermal exposure to ethyl alcohol from these products. The potential for exposure to ethyl alcohol from ethyl benzoate (maximum use concentration 0.01% reported) is much lower.

Butyl alcohol - safe as a cosmetic ingredient in the present practices of use.⁴ In 2005, the panel looked at new data and the safety conclusion in the report was confirmed.

Myristyl alcohol - safe as a cosmetic ingredient in the present practices of use.⁵

Cetyl alcohol - safe as a cosmetic ingredient in the present practices of use.⁶ In 2005, the Panel reviewed new data and the conclusion in the report was confirmed.

Stearyl alcohol - safe as currently used in cosmetics.⁷ In 2006, the Panel reviewed new data and the conclusion in the report was confirmed.

Isostearyl alcohol - safe as cosmetic ingredients in the present practices of use.⁶ In 2005, the Panel reviewed new data and the conclusion in the report was confirmed.

Behenyl alcohol - safe as a cosmetic ingredient in the present practices of use.⁵ In 2005, the Panel reviewed new data and the conclusion in the current report was confirmed.

Propyl alcohol and isopropyl alcohol – safe for use in cosmetic products in the present practices of use and concentration.⁸

The probable alcohol metabolites of ethylhexyl benzoate, butyloctyl benzoate, hexyldecyl benzoate, isobutyl benzoate, amyl benzoate, pentadecyl benzoate, heptadecyl benzoate, and octyldodecyl benzoate are not current cosmetic ingredients in the dictionary, thus have not been reviewed by CIR.

Some data from the reports on benzoic acid, sodium benzoate, methyl alcohol, butyl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, isostearyl alcohol, behenyl alcohol, propyl alcohol, and isopropyl alcohol are summarized. Data on isononyl benzoate, a related branched alkyl benzoate, and the other alcohols as well as ethylhexyl alcohol (from a Research Institute for Fragrance Materials [RIFM] Expert Panel review)⁹ are included to give a sense of the safety of these possible metabolites.

CHEMISTRY

Definition and Structure

Alkyl benzoates are mostly function as skin-conditioning agents, preservatives, solvents, and plasticizers. The CAS numbers, definitions, functions, as well as technical and trade names of the ingredients under review are presented in Table 1. Structures and potential metabolic pathways of these ingredients are presented in Figures 1 and 2.

Physical and Chemical Properties

The shorter chain alkyl benzoate esters are colorless liquids. Viscosity generally increases as the molecular mass (chain length) increases.¹⁰ The physical and chemical properties of the benzoates are shown in Table 2.

At room temperature and pressure, methyl benzoate, ethyl benzoate, butyl benzoate, and isobutyl benzoate are fragrant, colorless oils, and are insoluble in water.¹¹

A UV absorption spectrum of C12-15 alkyl benzoates had peaks at ~200 and 235 nm.¹²

Manufacture and Production

In general, the alkyl benzoates can be produced industrially via esterification of benzoic acid.¹⁰ The manufacture of butyl benzoate, for example, is traditionally accomplished via an acid catalyzed (e.g., sulfuric acid) reactive distillation process between benzoic acid and butyl alcohol (Figure 3).¹³

Methanol and ethanol are normally obtained via fermentation of natural sources. However, some alcohols with chains longer than ethanol are often produced synthetically. An important process for producing C₃-C₂₂ industrial alcohols involves a process known as oxo-synthesis (a process for the production of aldehydes which occurs by the reaction of olefins (which can be natural or petroleum sourced) with carbon monoxide, hydrogen and a catalyst [typically cobalt based]), followed by hydrogenation of the aldehyde products, to form the alcohols.¹⁴ A biocatalytic process specifically for the manufacture of esters for use in the formulation of cosmetic and personal care ingredients (i.e. for producing cosmetic grade esters) was developed in 2004.¹⁵

Impurities

The manufacturing processes of the benzoic esters are typically high yielding ($\geq 90\%$) and easily purified (e.g., by distillation). Therefore, the starting materials and water, at least, may be expected to be present in preparations of these esters as the major impurities.¹⁰ For example, methyl benzoate is available with a minimum of 99.2% purity, wherein the major contaminants are water ($\leq 0.1\%$) and benzoic acid ($\leq 0.02\%$).¹⁶

Analytical Methods

The benzoic esters can be analyzed using gas chromatography/mass spectroscopy (GC/MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy and infrared (IR) spectroscopy.^{10,14,17} High performance liquid chromatography was used to detect C12-15 alkyl benzoates.¹⁸

USE

Cosmetic

According to the Voluntary Cosmetic Registration Program (VCRP) administered by the Food and Drug Administration (FDA), the total number of uses of C12-15 alkyl benzoate was 971 (858 leave-on and 113 rinse-off products).¹⁹ A survey conducted by the Personal Care Products Council (Council) found that C12-15 alkyl benzoate was used at 0.0008% - 59% (highest concentration in tonics, dressings, and other hair grooming aids) in leave-on products and 0.0008% - 50% (highest concentration in paste masks [mud packs]) in rinse-off products (Table 3).²⁰ There were 2 uses reported of C16-17 alkyl benzoates (bath soaps and detergents). Stearyl benzoate was reported to have 3 uses (including face and neck creams, lotions, and powders) and to be used at 2%. While there were no uses reported by VCRP, the Council

reported methyl benzoate use at 0.0005% – 0.3% (highest concentration in perfumes), ethyl benzoate use at 0.0008% - 0.01% (highest concentration in foot powders and sprays), isobutyl benzoate use at 0.01% (perfumes), isostearyl benzoate use at 1% (body and hand creams, lotions, and powders), and octyldodecyl benzoate at 3% - 4% (highest concentration in shaving cream). No uses or concentrations of use were reported for propyl benzoate, butyl benzoate, amyl benzoate, lauryl/myristyl benzoate, behenyl benzoate, isopropyl benzoate, ethylhexyl benzoate, butyloctyl benzoate, and hexyldecyl benzoate.

C12-15 Alkyl benzoate and other benzoates are used in hair sprays and perfumes, and effects on the lungs that may be induced by aerosolized products containing these ingredients are of concern.

The aerosol properties that determine deposition in the respiratory system are particle size and density. The parameter most closely associated with deposition is the aerodynamic diameter, d_a , defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. In humans, particles with an aerodynamic diameter of $\leq 10\mu\text{m}$ are respirable. Particles with a d_a from 0.1 - $10\mu\text{m}$ settle in the upper respiratory tract and particles with a $d_a < 0.1\mu\text{m}$ settle in the lower respiratory tract.^{21,22}

Particle diameters of 60-80 μm and $\geq 80\mu\text{m}$ have been reported for anhydrous hair sprays and pump hairsprays, respectively.²³ In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as $\sim 38\mu\text{m}$.²⁴ Therefore, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

In the EU, methyl benzoate, ethyl benzoate, propyl benzoate and butyl benzoate may be used as preservatives in cosmetics up to 0.5% (acid).²⁵

Non-Cosmetic

Alkyl benzoate esters are typically used as solvents in paints, lacquers and coatings, and as intermediates in various chemistry processes.¹⁰ Methyl benzoate is used in flavoring and perfumery, and as a solvent in resins.²⁶ Ethyl benzoate is used in flavoring and perfumery, and as a solvent in lacquers and resins.²⁶ Butyl benzoate is used as a solvent for cellulose ether, as a plasticizer, as a perfume ingredient, and for dyeing of textiles.²⁶ Isobutyl benzoate is used in flavoring and perfumery.²⁶ Methyl benzoate, ethyl benzoate, propyl benzoate, isopropyl benzoate, and isobutyl benzoate have been approved by the FDA as flavors²⁷ and have no safety concerns at when used as flavoring agents.²⁸

GENERAL BIOLOGY

Benzoate esters are metabolized into benzoic acid (and the corresponding alcohols) and further metabolized to benzyl glucuronide and benzoyl CoA. Benzoyl CoA is metabolized into hippuric acid, the principal metabolite excreted in the urine. Dermally applied benzoic acid is excreted in the urine within 24 h. Methyl benzoate, ethyl benzoate, propyl benzoate, and butyl benzoate, penetrated the skin. C12-15 alkyl benzoate did not penetrate the skin.

Methyl alcohol and ethylhexyl alcohol permeated the skin or nail plates.

Absorption, Distribution, Metabolism, and Excretion

Orally administered benzoate esters are metabolized to benzoic acid and the corresponding alcohols and the acid is further metabolized to benzyl glucuronide and benzoyl CoA,²⁹ an intermediate in the formation of hippuric acid, which is the principal metabolite excreted in the urine.

In general, esters can be hydrolyzed to the parent alcohol and acid by enzymes.^{10,29} Secondary and tertiary esters are hydrolyzed more slowly than primary esters. These enzymes are in essentially all tissues, including the respiratory tract, skin, and gastrointestinal tract, and in blood.^{30,31}

Data on benzyl alcohol show that it is converted to benzoic acid by simple oxidation.¹ Orally consumed benzoic acid is absorbed from the gastrointestinal tract and conjugated with glycine in the liver. The resulting hippuric acid is excreted in the urine (75% - 100% within 6 h). Dermally applied benzoic acid is also excreted in the urine within 24 h.

In general, alcohols can be metabolized by alcohol dehydrogenases to aldehydes or ketones. The aldehydes may be further metabolized by aldehyde dehydrogenases to the corresponding acids.

Benzoic esters are not absorbed through the skin as rapidly as alkyl esters.³² If alkyl benzoates are absorbed and metabolized, the alcohols resulting from ester hydrolysis can be oxidized via alcohol dehydrogenases to produce the corresponding aldehyde or ketone. As noted above, these aldehydes can be further oxidized via aldehyde dehydrogenases, aldehyde oxidases, or xanthine oxidases to the corresponding acids.

Alkyl Benzoates

Short chain-length: The permeation of methyl benzoate, ethyl benzoate, *n*-propyl benzoate, and *n*-butyl benzoate through excised guinea pig dorsal skin was measured using diffusion cells.³³ The permeability coefficients (K_p) were $20.3 \pm 5.8 \times 10^{-2}$ cm/h, $34.08 \pm 1.2 \times 10^{-2}$ cm/h, $62.7 \pm 13.0 \times 10^{-2}$ cm/h, and $79.9 \pm 10.1 \times 10^{-2}$ cm/h, respectively, indicating significant steady state dermal penetration. Permeability was increased by removal of the stratum corneum by tape stripping and delipidization using a chloroform-methanol mixture. Permeability was decreased by the addition of *l*-methanol plus 15% ethanol.

Long chain-length: In another study, C12-15 Alkyl Benzoate was applied neat at a dose of 4 mg/cm² to 3 samples of gently shaved skin from the same pig.³⁴ Total recovery after 24 h was 82% of the applied dose, and 29% of the dose was recovered in the skin as measured by HPLC (detection limit 1.0 µg/ml). Of the material recovered, 84%, 5%, and 11%, was in the horny layer, epidermis, dermis, respectively. None was detected in the receptor fluid.

C12-15 alkyl benzoates applied to frozen and fresh pig skin did not penetrate the skin.³⁵ None of the test material was detected in the receptor fluid, 50.76% was recovered in the skin, and 34.04% was still on the skin. There were benzoate compounds (< C12) present in the test material at 4.7%.

The octanol/water partition coefficient measures the affinity of a chemical for water versus the organic solvent, octanol.³⁶ Octanol/water partition coefficient values (at pH 3.0) of 8.0, 8.6, 9.1, and 9.6 for C12 alkyl benzoate, C13 alkyl benzoate, C14 alkyl benzoate, and C15 alkyl benzoate would suggest that these longer chain-length alkyl benzoates would stay in the stratum corneum and have little affinity beyond that skin layer.

Actual test data indicated a different picture. The *in vitro* dermal absorption and percutaneous penetration of C12-15 Alkyl Benzoate from 3 product formulations in excised pig skin after 24 hours was examined. A sun lotion (with 7.5% test compound), a baby cream 5.4% (with test compound) and a sun protection spray (with 6.6% test compound) were applied at a rate of 4 mg/test/sample/cm². Total recoveries were 90%, 88% and 95% for three formulations with 21%, 34% and 26% found in the skin. The amount in the receptor fluid and dermis for all three formulations was less than the detection limit. The amount of C12-15 alkyl benzoate from the sun lotion was 93.5% and 6.5 in the horny layer and epidermis, respectively. For the baby cream, the amount of recovered test substance was 91.5%, and 8.6%, and for the sun protection spray, the amount of recovered test substance was 92.5% and 7.5%.

Alcohols

The permeability constants (K_p) for methyl alcohol using human cadaver skin were 0.3, < 0.1, 12.0, 3.0, and 2.5×10^3 cm/h in saline, polyethylene glycol 600, isopropyl palmitate, olive oil, and mineral oil, respectively.³⁷

The permeability coefficient of methyl alcohol was $5.6 \pm 1.2 \times 10^3$ cm/h through the nail plates of cadavers.³⁸

Male Fischer F344 rats (*n* = 3) were orally administered [¹³C]-tert-amyl alcohol (250 mg/kg in corn oil) and urine was collected for 48 h.³⁹ The major metabolites were tert-amyl alcohol glucuronide and 2-methyl-2,3-butanediol and its glucuronide. Free tert-amyl alcohol, 2-hydroxy-2-methylbutric acid, and 2-hydroxy-3-methylbutyric acid were minor metabolites.

Isopropyl alcohol was absorbed in 4 groups of rabbits (*n* = 3; strain not specified) exposed to the alcohol by gavage (Group 1: 2 ml/kg; Group 2: 4 ml/kg), whole-body/inhalation combined with dermal application (Group 3: 70% isopropyl alcohol soaked towel applied to the chest), and whole-body/inhalation combined with application over a plastic barrier on the chest for 4 h.⁴⁰ Maximum isopropyl alcohol concentrations in blood after oral exposures were 147 mg/dl (2 ml/kg) and 282 mg/dl (4 ml/kg), which were correlated with inebriation and near coma; the blood concentration was 112 mg/dl 4 h after whole-body/inhalation combined with dermal application. Blood concentrations of acetone (metabolite of isopropyl alcohol) were 74 mg/dl (2 ml/kg by gavage), 73 mg/dl (4 mg/kg by gavage), 19 mg/dl (whole-body/inhalation plus dermal application), and <10 mg/dl (whole-body/inhalation plus application over a plastic barrier). The authors concluded from their results that significant toxicity would require repeated sponging or soaking with isopropyl alcohol for several hours.

In vitro absorption rates for ethylhexyl alcohol in aqueous solution through rat and human skin were 0.22 ± 0.09 and 0.38 ± 0.014 mg/cm²/h, respectively.⁴¹ The corresponding permeability constants were $2.59 \pm 1.10 \times 10^{-4}$ cm/h for rat skin and $4.54 \pm 1.66 \times 10^{-5}$ for human skin.

The absorption rate for ethylhexyl alcohol (1000 mg/kg) applied to the skin of rats for 6 hours was 0.57 mg/cm²/h; 5.2% of the dose was absorbed during exposure.⁴²

Cytotoxicity

Methyl benzoate was cytotoxic to HeLa cells at 683.30 mM, A. flavus at 2.5 mg/ml, A. parasiticus at 5.0 mg/ml, and lung fibroblasts at 25 mM. Ethyl benzoate was cytotoxic to Hep-2 cells and lung fibroblasts at 289 mg/L. Propyl benzoate and butyl benzoate were cytotoxic to Hep-2 cells at 122 mg/L and 61 mg/L, respectively.

Methyl alcohol, amyl alcohol, and dodecyl alcohol were cytoxic.

METHYL BENZOATE

In a protein count assay (measuring protein synthesis) of methyl benzoate, the EC₅₀ (50% of the concentration of maximum effect) was 1506.58 (C.I. 1349.27 - 168.22) mM, the NI₅₀ (the concentration that reduced the uptake of neutral red by 50%) was 683.30 (466.46 – 1000.91) mM in a neutral red uptake assay, and the ID₅₀ (the concentration that inhibited growth by 50%) was 987.19 (605.15-1610.43) mM in a growth inhibition assay using HeLa cells.⁴³

Methyl benzoate (2.5 and 5.0 mg/ml) inhibited mycelia growth and aflatoxin release by *Aspergillus flavus* and *A. parasiticus*.⁴⁴

Human diploid embryonic lung fibroblasts (line MRC-5), labeled with [³H]uridine, were incubated in methyl benzoate (25 mM in buffered saline) for 30 min.⁴⁵ The amount of cell wall damage was measured by the release of the label. Controls released 3% to 6% of the maximum available label. Incubation in methyl benzoate caused a release of 20% of maximum available label. The authors concluded that methyl benzoate not only caused toxic effects to the cells but also promoted membrane penetration by other substances.

ETHYL BENZOATE

Human Hep-2 cells (epithelial cell line derived from human carcinoma of the larynx) were exposed to ethyl benzoate.⁴⁶ Total inhibition of cell growth was observed at 500 mg/L. This experiment was repeated and samples were taken for protein determination. There were no effects at 289 mg/L. This experiment was repeated and the cells were stained and examined for morphology. At 289 mg/L, cells lost their typical epithelial shape and became elongated.

The above experiment on human diploid embryonic lung fibroblasts (line MRC-5), labeled with [³H]uridine, was repeated with ethyl benzoate (25 mM).⁴⁵ Incubation in ethyl benzoate caused a release of 31% of maximum of available label. The authors concluded that ethyl benzoate not only caused toxic effects to the cells but also promoted membrane penetration by other substances.

PROPYL BENZOATES

Human Hep-2 cells were exposed to propyl benzoate.⁴⁶ Total inhibition of cell growth was observed at 200 mg/L. This experiment was repeated and samples were taken for protein determination. Effects were observed at 122 mg/L and the cells seemed to recover by day 7. This experiment was repeated and the cells were stained and examined for morphology. At 122 mg/L, the monolayer of the cells was disturbed within 24 h.

BUTYL BENZOATE

Human Hep-2 cells were exposed to butyl benzoate.⁴⁶ Total inhibition of cell growth was observed at 100 mg/L. This experiment was repeated and samples were taken for protein determination. Effects were observed at 61 mg/L and the cells seemed to recover by day 7. This experiment was repeated and the cells were stained and examined for morphology. At 61 mg/L, the monolayer of the cells was disturbed within 24 h.

Human Rhino HeLa cells were incubated in butyl benzoate (in dimethylsulfoxide) for 48 h. The IC₅₀ was 0.5 mM.⁴⁷

ALCOHOLS

Methyl alcohol had a 50% production inhibition (PI₅₀) of 1614 mM for Hep G2 cells.⁴⁸

Methyl alcohol was toxic to yeast cells (strain *ade6-60/rad10-198,h⁻* of *Schizosaccharomyces pombe* P₁ strain) at 0.05% but not V79 Chinese hamster cells up to 10%.⁴⁹ Amyl alcohol was toxic to yeast cells (strain *ade6-60/rad10-198,h⁻* of *S. pombe* P₁ strain) and V79 Chinese hamster cells at 0.5%.⁴⁹

Dedecyl alcohol had 50% lysis of human erythrocytes at 15 μM.⁵⁰

TOXICOLOGY

Acute Toxicity

The oral LD₅₀ of methyl benzoate was 2170 mg/kg for rabbits, 4100 mg/kg for guinea pigs, 1350-3500 mg/kg for rats, and 3000-3330 mg/kg for mice. The oral LD₅₀ of ethyl benzoate was 2630 mg/kg for rabbits and 2100-6480 mg/kg for rats. The oral LD₅₀ of butyl benzoate was 5.14 g/kg for female rats. Orally administered C12-15 alkyl benzoate was not toxic to rats at 5.0 g/kg. The oral LD₅₀ for isopropyl benzoate was 3730 mg/kg and 3685 mg/kg for isobutyl benzoate in rats.

The dermal LD₅₀ of methyl benzoate was > 2000 mg/kg for rabbits. Dermally administered ethyl benzoate at 10% caused no effects to mice and calves; at 100% it was lethal to cats. Dermally administered butyl benzoate caused diarrhea in rabbits at 5 g/kg. C12-15 alkyl benzoate was not dermally toxic to rabbits at 100%. The dermal LD₅₀ of isopropyl benzoate was 20 mg/kg for rabbits. Isobutyl benzoate was not dermally toxic to rabbits.

The oral LD₅₀ of benzoic acid was reported to be 1996 mg/kg in mice and 2000 – 2500 mg/kg in rats. The oral LD₁₀₀ was reported to be 1520 – 2000 mg/kg for rabbits, and 2000 mg/kg for cats and dogs. The oral LD₅₀ for sodium benzoate was 2100 – 4070 mg/kg for rats and 2000 mg/kg for rabbits and dogs.

Methyl alcohol has an oral LD₅₀ of 5628 mg/kg for rats and 7300 mg/kg for mice. The oral LD₅₀ of amyl alcohol for rats was reported to be 2.69 g/kg. Dodecyl alcohol has an oral LD₅₀ of 12,800 mg/kg for rats. Tridecyl alcohol has an oral LD₅₀ of 17,200 mg/kg for rats. Tetradecyl alcohol has an oral LD₅₀ 33,000 mg/kg for rats. Oral LD₅₀s for ethylhexyl alcohol in rats range from 2049 to 7100 mg/kg and 2380 to >5000 mg/kg for rabbits. The oral LD₅₀ of hexyldecyl alcohol for rats was reported to be > 8.42 g/kg. The dermal LD₅₀ of methyl alcohol was reported to be 15,800 mg/kg in rabbits. The dermal LD₅₀ of amyl alcohol for rabbits was reported to be > 3.2 g/kg. The dermal LD₅₀ of dodecyl alcohol was reported to be 3560 mg/kg in rabbits. The dermal LD₅₀ of tridecyl alcohol was reported to be 5600 mg/kg in rabbits. The dermal LD₅₀ of hexadecyl alcohol for rabbits was reported to be > 2.6 g/kg. Aerosolized amyl alcohol at near saturation caused irritation of the eyes, nose, throat, and respiratory passages of mice and guinea pigs. Rats exposed to aerosolized ethylhexyl alcohol exhibited signs of irritation of the eyes nose, throat, and respiratory passages, including blinking, lacrimation, nasal discharge, salivation, gasping, and chewing movements. No rats died from exposure for up to 8 h. Hexyldecyl alcohol was a slight irritant with no systemic effect to mice, rats, and guinea pigs at 9.6 mg/m³.

METHYL BENZOATE

The reported oral LD₅₀ of methyl benzoate was 2170 mg/kg for rabbits, 4100 mg/kg for guinea pigs, 1350-3500 for rats, and 3000-3330 mg/kg for mice.⁵¹⁻⁵⁴

The dermal LD₅₀ of methyl benzoate was > 2000 mg/kg for New Zealand white rabbits (n = 5).⁵⁵ There was fecal staining for 3 days after treatment. Irritation was observed at the application site. There was weight loss for 1 – 7 days after treatment. There were no gross findings at necropsy. There were no mortalities.

ETHYL BENZOATE

The reported oral LD₅₀ of ethyl benzoate was 2630 mg/kg for rabbits, 2100 mg/kg for rats and 6480 mg/kg for female rats.^{51,54}

Ethyl benzoate (10% in acetone) was administered to one-third of the body surface of mice (n = 2 – 4).⁵⁶ The mice were observed for 24 h then necropsied. There were no effects at 10%. This experiment was repeated with calves (with no necropsy) except covering the entire body surface and a 15-d observation period. There were no effects at 10%. No further details were provided.

Ethyl benzoate (up to 100% in “various vehicles”; 20 ml) was administered to the clipped backs of cats (n = 2), massaged into the skin with cotton balls.⁵¹ The cats were to be observed for 2 weeks. At 100%, both cats died within 20 h.

Albino rats (n = 6) showed no adverse effects from exposure to aerosolized ethyl benzoate (“approaching saturation”) for 8 h.⁵⁴

Intramuscular administration of ethyl benzoate (100%; 0.5 or 1.0 ml) administered to guinea pigs (n not provided) caused musculo-skeletal [sic], moderate deterioration of leg function and muscle toughness at 1.25 ml/kg.⁵⁷

BUTYL BENZOATE

The reported oral LD₅₀ of butyl benzoate was 5.14 g/kg for female rats.⁵⁴

Dermally administered butyl benzoate (5 g/kg) caused no mortalities in rabbits (n = 10).⁵⁸ Diarrhea was observed during the 14 day observation period.

Intramuscular administration of butyl benzoate (100%; 0.5 or 1.0 ml) to guinea pigs (n not provided) caused musculo-skeletal [sic], moderate deterioration of leg function and muscle toughness at 3 ml/kg.⁵⁷

Albino rats (n = 6) showed no adverse effects from exposure to aerosolized butyl benzoate (“approaching saturation”) for 8 h.⁵⁴

C12-15 ALKYL BENZOATE

Albino rats orally administered C12-15 alkyl benzoate (5.0 g/kg) exhibited no signs of toxicity over a 14-day observation period.⁵⁹ At necropsy, enlarged spleens were noted.

In an acute oral study, C12-15 alkyl benzoate (up to 100%; 40 ml/kg) was administered to albino rats.⁶⁰ The rats were observed for 14 days and then killed and necropsied. There was no mortality during the observation period. There were no gross internal changes.

At 30.0 g/kg, the females were described as having slight depression up to day 7. At 24 h, loss of ventral body hair and crusty, scabby skin were noted. There were no gross internal changes. At 33.0 g/kg, hair was matted and unkempt, there was a crust-like substance on the skin, and hair loss. One female rat died on day 7. At 37.0 g/kg, 5 rats died. Pyloric and intestinal mucosa were reddened; lung tissue was enlarged and consolidated; and spherical lesions were observed in the lungs.

Female MNRI EOPS mice were orally administered 5000 mg/kg C12-15 alkyl benzoate and observed for 6 days.⁶¹ There were no mortalities and no clinical signs or behavior changes were observed. Weight gain was comparable to controls.

In a dermal toxicity study, C12-15 alkyl benzoate (100%; 2 g/kg) was applied to the intact skin of albino rabbits (n = 6; 3/sex) under occlusion.⁶⁰ The rabbits were observed for 14 days. One male rabbit died which was considered non-treatment related. The authors concluded that C12-15 alkyl benzoate was not a toxic material.

Albino Wistar rats (n = 10) were exposed to aerosolized C12-15 alkyl benzoates (200 mg/L) for 1 h and observed for 2 weeks.⁶² There were no toxic effects observed.

ISOPROPYL BENZOATE

The reported oral LD₅₀ of isopropyl benzoate was 3730 mg/kg and 3.7 mg/kg for rats.^{63,64}

The reported dermal LD₅₀ of isopropyl benzoate was 20 ml/kg for rabbits.⁶³ Dermally administered isopropyl benzoate (5 ml/kg) had no effects to rabbits (n = 2).⁶⁵

There were no observed effects in rats exposed to aerosolized isopropyl benzoate (saturated vapor) for 4 h.⁶³

ISOBUTYL BENZOATE

The reported oral LD₅₀ of isobutyl benzoate was 3685 mg/kg²⁹ and 3.7 ml/kg for rats (n = 10).⁶⁵

Isobutyl benzoate (5 ml/kg; 100%) was applied to the intact and abraded clipped skin of albino rabbits (n = 4) for 24 h. There were no mortalities or clinical signs during the 14-day observation period.⁶⁵

BENZOIC ACID AND SODIUM BENZOATE

The oral LD₅₀ of benzoic acid was reported to be 1996 mg/kg in mice and 2000 – 2500 mg/kg in rats. The oral LD₁₀₀ was reported to be 1520 – 2000 mg/kg for rabbits, and 2000 mg/kg for cats and dogs. The oral LD₅₀ for sodium benzoate was 2100 – 4070 mg/kg for rats and 2000 mg/kg for rabbits and dogs.⁶⁶

ALCOHOLS

Methyl alcohol has an oral LD₅₀ of 5628 mg/kg for rats and 7300 mg/kg for mice.⁶⁷

The dermal LD₅₀ of methyl alcohol was reported to be 15,800 mg/kg in rabbits.⁶⁸

Methyl alcohol has an i.p. LD₅₀ of 336 (CI = 299, 373) mmol/kg for mice, 237 (222,252) mmol/kg for rats, 267 (235, 304) mmol/kg for hamsters, and 111 mmol/kg for guinea pigs.⁶⁹ The i.v. LD₅₀ for mice is 147 (126, 171) mmol/kg, 66.5 (61.5, 71.2) mmol/kg for rats and 278 (185, 371) mmol/kg for rabbits.

The oral LD₅₀ of amyl alcohol for Sprague-Dawley rats was reported to be 2.69 g/kg.⁷⁰ Deaths occurred within 24 h. Necropsy revealed evidence of gastrointestinal irritation and pooling of blood.

The dermal LD₅₀ of amyl alcohol for albino rabbits was reported to be > 3.2 g/kg.⁷⁰ There were signs of central nervous system depression. Recovery occurred within 4 to 48 h.

Swiss mice, Wistar rats, and English short hair guinea pigs (n = 10) were exposed to aerosolized amyl alcohol at near saturation for 6 h observed for 14 h.⁷⁰ Preconvulsive movements were observed in mice and guinea pigs; the rats tended more toward prostration. Two rats and 7 mice died during exposure. All surviving animals recovered shortly after termination of the exposure. Some animals had irritation of the eyes, nose, throat, and respiratory passages.

Dodecyl alcohol has an oral LD₅₀ of 12,800 mg/kg for rats.⁶⁷

The dermal LD₅₀ of dodecyl alcohol was reported to be 3560 mg/kg in rabbits.⁶⁸

Tridecyl alcohol has an oral LD₅₀ of 17,200 mg/kg for rats.⁶⁷

The dermal LD₅₀ of tridecyl alcohol was reported to be 5600 mg/kg in rabbits.⁶⁸

Ssc: CF-1 mice (n = 10) were exposed to *tert*-pentadecyl alcohol (2800 – 14000 ppm), with and without tracheal cannulation, after anaesthesia for 30 min.⁷¹ Sensory irritation of the upper respiratory tract was measured by timing the pauses before exhalation compared with those of untreated controls (n = 37). Stimulation of pulmonary receptors by airborne irritants was measured by the decrease in respiratory rate caused by a pause between the end of expiration and the beginning of the following inspiration, resulting in a net decrease in respiratory rate.

The characteristic sensory irritation pattern was observed in the mice immediately after the onset of the exposure. The pattern was most evident within the first minute and was followed by rapid fading of the responses. The pattern was occasionally seen during the entire exposure period. After a decrease in respiratory rate in the first minute of exposure, the rate partly increased in the next minutes followed by a new slowly progressing decrease. A concentration-dependent recovery of the respiratory rate was seen after cessation of the exposure. In cannulated mice no sensory irritation pattern was observed. The authors stated that this was due to bypass of the trigeminal nerves. The pattern indicated that pulmonary irritation was present.

Myristyl alcohol has an oral LD₅₀ 33,000 mg/kg for rats.⁶⁷

Oral LD₅₀s for ethylhexyl alcohol in rats range from 2049 to 7100 mg/kg body weight and 2380 to >5000 mg/kg for rabbits.⁹

Rats, mice, and guinea pigs (n = 10 per species) exposed (whole body) to air bubbled through ethylhexyl alcohol for 6 h exhibited signs of irritation of the eyes nose, throat, and respiratory passages, including blinking, lacrimation, nasal discharge, salivation, gasping, and chewing movements, but none died.^{70,72}

None of the 6 rats inhaling concentrated ethylhexyl alcohol for up to 8 hours died.⁷³

The oral LD₅₀ of hexyldecyl alcohol for Sprague-Dawley rats was reported to be > 8.42 g/kg.⁷⁰

The dermal LD₅₀ of hexadecyl alcohol for albino rabbits was reported to be > 2.6 g/kg.⁷⁰ There were signs of central nervous system depression. Recovery occurred within 4 to 48 h.

Swiss mice, Wistar rats, and English short hair guinea pigs (n = 10) were exposed to aerosolized hexyldecyl alcohol (1060 ppm; 9.6 mg/m³) for 6 h and observed for 14 h.⁷⁰ The alcohol was a slight irritant and no systemic effects were observed.

Repeated Dose Toxicity

Benzoic acid and sodium benzoate were orally toxic to rats and mice in short-term feeding studies at concentrations > 1% in short-term, subchronic, and chronic studies. In Subchronic studies, benzoic acid was toxic to mice at oral doses of 80 mg/kg/d. Sodium benzoate at 880 mg/kg/d incorporated into the feed of rats for 18 – 24 months was not toxic.

Short-term oral exposure to amyl alcohol was not toxic to rats at 100%. Oral NOAELs ranged from 100 to 150 mg/kg in several studies using mice or rats exposed to ethylhexyl alcohol. Dermal exposure to ethylhexyl alcohol caused physiological changes in rats at 500 mg/kg. Inhalation of isobutyl alcohol at 770 mg/m³ caused reversible inhibition of responsiveness in rats. Adverse effects of isopropyl alcohol at the LOAEL included clinical signs in rat and mice, hematological changes in rats, and increased liver weights in mice; higher doses caused kidney and testicular effects. Aerosolized n-pentadecyl alcohol was not toxic to rats.

BENZOIC ACID AND SODIUM BENZOATE

In multiple-dose oral/feed toxicity studies on rats and mice, decreased feed consumption, depressed growth, and toxic effects were observed at concentrations > 1% benzoic acid or sodium benzoate (Table 4).¹

Cross bred white mice (n = 100) were orally administered benzoic acid at 80 mg/kg/d for 3 months.⁷⁴ The treated group had decreased weight gain. Mortality was increased (68% vs. 60 % in the control group).

Sodium benzoate (0, 1%, or 2%; 735 or 880 mg/kg/d) was incorporated into the feed of Fischer 344 rats (n = 102; 50 males, 52 females) for 18 – 24 months.⁷⁵ There were no differences in mortality between groups. Necropsies were unremarkable.

ALCOHOLS

Amyl alcohol (0, 50, 150, 100 mg/kg/d) was administered orally to ASH/CSE rats (n = 30; 15/sex) for 13 weeks.⁷⁶ The rats were killed and necropsied 24 h after the last treatment. No adverse effects were observed at any dose.

The NOAEL and LOAEL for the inhalation of isopropyl alcohol was 1230 mg/m³ and 3690 mg/m³, respectively, in Fischer 344 rats and CD-1 mice (n = 10/sex) exposed (0, 1230, 3690, or 12,300 mg/m³) 6 h/d, 5 d/week for 13 weeks.⁷⁷ Adverse effect observed at the LOAEL included narcosis in rats and mice, hematological changes in rats, and increased liver weights in mice.

A NOAEL of 1230 mg/m³ for both rats and mice was reported (based on kidney and testicular effects) in a study in which Fischer 344 rats (n = 65/sex) and CD-1 mice (n = 55/sex) were exposed by inhalation to isopropyl alcohol (0, 1230, 6150, or 12,300 mg/m³) for 6 h/d, 5 d/week for 104 weeks in rats and 78 weeks in mice.⁷⁸

All of the rats (n = 10) exposed to isobutyl alcohol (0, 770, 3100, or 7700 mg/m³) by inhalation for 6 h/d, 5 d/week for 14 weeks exhibited a slight reduction in responsiveness to external stimuli, which was reversed by terminating the exposures.⁷⁹

Male Wistar rats (n = 10) were exposed to aerosolized *n*-pentadecyl alcohol (0, 100, 300 or 600 ppm) 6 h/day, 5 d/week for 7 or 14 weeks.⁸⁰ The rats were then killed and necropsied. There were no mortalities and there was no effect on body weights. No valeraldehyde, the primary metabolite of *n*-pentanol, was found in the blood, while the *n*-pentadecyl alcohol concentration in blood was linearly correlated to the dose. The brain *n*-pentadecyl alcohol was related to the blood alcohol at 7 weeks. At 14 weeks, this relationship changed because the brain *n*-pentadecyl alcohol concentration decreased. Valeraldehyde was measured in the brain only at the high dose level.

The liver *n*-pentadecyl alcohol dehydrogenase activity did not change at all. The microsomal cytochrome P-450 contents and 7-ethoxycoumarin-*O*-deethylase activities in the liver remained unaffected while the kidney deethylase activity was enhanced in a dose-dependent manner at 7 weeks. This effect lessened after 14 weeks. The kidney *n*-pentadecyl alcohol dehydrogenase activity was slightly decreased at the mid and high doses after 7 weeks. The brain acetylcholinesterase activity was greater than the control range at all doses at 7 weeks. Similar effects were noted in the muscles at the mid and high doses. The authors suggested that moderate pentadecyl alcohol vapour exposure may cause metabolic and functional adaptation in its target organs.

Rats (n=10) dermally treated daily for 17 days with ethylhexyl alcohol (100%; ~1600 mg/kg/d) administered to shaved backs exhibited decreased thymus weights and spermatogenesis, liver granulomas, bronchiectasis, renal tubular epithelial necrosis, edema in heart and testes, and increased lipid levels in the adrenal glands.⁸¹

Fischer 344 rats (n = 20; 10/sex) were topically administered ethylhexyl alcohol (500 or 1000 mg /kg/d) for 5 days under occlusion, followed by 2 days untreated, and then 4 days treatment with S9.^{82,83} Both doses produced exfoliation (minimal severity), and the high dose caused transient erythema of the treated skin. The female rats exhibited elevated serum triglycerides at both doses and reduced peripheral blood lymphocytes and spleen weights at the high dose.

NOAELs ranged from 100 to 150 mg/kg body weight/day in several studies in which mice or rats were exposed orally for 9 to 11 days to ethylhexyl alcohol by gavage, in drinking water, or in feed.⁸²⁻⁸⁶ Doses \geq 330 mg/kg body weight/day produced CNS depression, lacrimation, and decreased food consumption and body weights.

The NOAEL was 125 mg/kg/d for male and female F344 rats and B6C3F1 mice treated daily with ethylhexyl alcohol (0, 25, 125, 250, or 500 mg/kg/d) by gavage for 13 weeks.⁸⁷

Multiple in vitro and in vivo short-term repeated dose studies showed that ethylhexyl alcohol is a peroxisome proliferator and liver-enzyme inducer in mice and rats, and that doses \geq 60 mg/kg body weight/day can cause these effects and alpha-2u-nephropathy in male rats.⁸⁸

No local or systemic effects were found in male and female Wistar rats (n = 20; 10/sex) exposed 6 h/day, 5 days/week, for 90 days to aerosolized 2-ethyl-1-hexanol (15, 40, or 120 ml/m³; purity 99.9%).⁸⁹

The oral NOAEL for non-cancer systemic toxicity endpoints was 200 and 50 mg/kg/d in mice and rats, respectively, exposed chronically to ethylhexyl alcohol.⁹⁰

Ocular/Mucosal Irritation

Methyl benzoate, ethyl benzoate, isopropyl benzoate, and butyl benzoate were grade 1 ocular irritants at 100%. C12-15 alkyl benzoate and isopropyl benzoate were rated as non- to mild ocular irritants at 100% as was isostearyl benzoate at 0.95%.

Methyl alcohol, amyl alcohol, dodecyl alcohol, isopropyl alcohol, and ethylhexyl alcohol were rated as severe ocular irritants at 100%. Hexyldecyl alcohol was a slight ocular irritant at 100%.

METHYL BENZOATE

Methyl benzoate (100%) was administered to the center of the cornea while the lids were retracted in rabbits (n = 5).⁵⁴ The eye lids were released after ~1 min. The eyes were scored after 18 – 24 h in daylight and with staining. Methyl benzoate was given a grade 1 (iritis, slight internal congestion).

ETHYL BENZOATE

The above experiment was repeated with ethyl benzoate (100%).⁵⁴ Ethyl benzoate was given a grade 1.

BUTYL BENZOATE

The above experiment was repeated butyl benzoate (100%).⁵⁴ Butyl benzoate was given a grade 1 (iritis, slight internal congestion).

C12-15 ALKYL BENZOATE

In an ocular irritation test of C12-15 alkyl benzoate (1.8% - 2.4%; 0.1 ml) using rabbits, the test material was applied to the eye and washed after 24 h.⁵⁹ The eyes were observed for 7 days. There was no ocular irritation to rabbits under these test conditions.

C12-15 alkyl benzoate (100%) administered to the eyes of albino New Zealand rabbits caused diffuse crimson coloration, slight swelling, and some discharge.⁹¹ The reactions were resolved in < 6 days.

In an EpiOcular tissue model toxicity testing system, human-derived epidermal keratinocytes were incubated in culture medium to which C12-15 alkyl benzoate (2% or 20%; 10 µl), corn oil (negative control), and (0.3%) Triton X-100 (positive control).⁹² Using the instructions of the test kit, it was extrapolated that C12-15 alkyl benzoate was non-irritating at 2% and 20%.

ISOPROPYL BENZOATE

Isopropyl benzoate (100%) was administered to the center of the cornea while the lids were retracted in rabbits (n = 5).⁶³ The eye lids were released after ~1 min. The eyes were scored after 18 – 24 h in daylight and with staining. Isopropyl benzoate was given a grade 1.

ISOSTEARYL BENZOATE

In an ocular irritation assessment of a body lotion containing isostearyl benzoate (0.95%) using neutral red release (NRR) assay, the hen's egg test on the chorio-allantoic membrane (HET-CAM) assay, and the reconstituted human epithelial culture (REC) assay, the authors rated the lotion as slightly irritating.⁹³

ALCOHOLS

In a neutral red assay using human keratinocytes and fibroblasts from natal foreskins to assess ocular irritancy, methyl alcohol was rated a mild irritant.⁹⁴

Amyl alcohol (100%, 0.1 ml) was rated as a severe ocular irritant in the Draize test and ocular cell count assay.⁹⁵ Severe swelling of conjunctival tissue interfered with accurate assessment of Draize scores and cell washes at 1 h after instillation.

Amyl alcohol (100%) was rated a severe ocular irritant when applied to rabbits.⁷⁰

Dodecyl alcohol was reported to have a maximum average score (MAS) or 24.2 in an ocular Draize test.⁹⁶

Isopropyl alcohol has been described to be a severe ocular irritant, based on tests in rabbits.⁷⁹

Several in vitro tests to investigate the eye irritation potential showed an irritating effect of ethylhexyl alcohol.⁹⁷⁻¹⁰³

Undiluted ethylhexyl alcohol was moderately to severely irritating to the eyes in rabbits.¹⁰⁴⁻¹¹⁰ Effects ranged from conjunctival redness and swelling, lacrimation, and discharge, which did not clear within 96 hours after treatment, to persistent corneal dullness and vascularization.

Hexyldecyl alcohol (100%) was rated a slight ocular irritant when applied to rabbits.⁷⁰

Dermal Irritation

Methyl benzoate, ethyl benzoate, propyl benzoate, and butyl benzoate at 100% were dermally irritating to rabbits. C12-15 alkyl benzoate was a mild dermal irritant to rabbits at 100% and was found to be irritating in an in vitro test. Methyl alcohol, amyl alcohol, lauryl alcohol, ethylhexyl alcohol, and hexydecyl alcohol were dermal irritants.

METHYL BENZOATE

Methyl benzoate (100%) was applied to both the clipped dorsum (0.5 ml) and external surface of the outer ear (0.2 ml) of male New Zealand albino rabbits (n = 14) daily for 6 days.¹¹¹ On the dorsum, there were marked cellular reactions and dermal edema beginning on day 2 followed by dermal hemorrhages, desquamated crust, and thickening of the malpighian stratum beginning on day 5. On the inner ear, there was slight hyperkeratosis at day 6.

Methyl benzoate (100%; 0.01 ml) was applied to the clipped skin of albino rabbits (n = 5) and observed within 24 h.⁵⁴ Irritation was rated as grade 3 in a 1 to 10 system (grade 1 = least visible capillary injection from the undiluted material; 6 = necrosis with the undiluted material; and 10 = necrosis from a 0.01% solution).

Methyl benzoate (100%) was administered to the clipped and depilated skin of guinea pigs (n = 3 – 4) using filter paper soaked in the test substance for up to 2 min.¹¹² Before and after treatment, the guinea pigs were administered Evans Blue dye i.v. The permeability was measured by exuded dye at the treated sites. There was a minimal response observed.

ETHYL BENZOATE

Ethyl benzoate was administered to the clipped dorsum (0.5 ml) and external surface of the outer ear (0.2 ml) to male New Zealand albino rabbits (n = 14) daily for 6 days.¹¹¹ On the dorsum, there were marked cellular changes, edema, desquamated crusts, and thickening of the malpighian stratum beginning on day 1. On the inner ear, there were slight cellular reaction, no edema or hemorrhages, no necrosis, slight to marked desquamated crusts, marked thickening of malpighian stratum, hyperkeratosis, and slight hyperplasia of sebaceous glands beginning day 1.

Ethyl benzoate (100%; 0.01 ml in water, propylene glycol, or kerosene) was administered to the clipped skin of rabbits (n = 5) and scored after 24 h.⁵⁴ Grade 4 irritation was observed.

PROPYL BENZOATE

Propyl benzoate was applied to the clipped dorsum (0.5 ml) and external surface of the outer ear (0.2 ml) to male New Zealand albino rabbits (n = 14) daily for 6 days.¹¹¹ On the dorsum, there were marked cellular reactions, necrosis, thickening of the malpighian stratum beginning on day 1 followed by dermal hemorrhages, desquamated crusts beginning on days 3 or 4. On the inner ear, there were slight cellular reactions, necrosis, and moderate thickening of the malpighian stratum beginning on day 1 or 3.

BUTYL BENZOATE

Butyl benzoate was applied to the clipped dorsum (0.5 ml) and external surface of the outer ear (0.2 ml) to male New Zealand albino rabbits (n = 14) daily for 6 days.¹¹¹ On the dorsum, there were marked cellular reaction, necrosis, and slight detachment of the dermo-epidermis beginning on day 1 followed by desquamated crusts and thickening of the malpighian stratum beginning on day 3. On the inner ear, there were slight cellular reactions, necrosis beginning on day 1, and moderate desquamated crusts and hyperplasia of the sebaceous glands on day 2 or 3.

Butyl benzoate (100%; 0.5 ml) was applied to the clipped skin of female New Zealand white rabbits (n = 4) under occlusion for 4 h.⁵⁸ Observations were made at 1, 24, 48, and 72 h. There were no effects at 1 h, well defined erythema and slight edema at 24 h, and very slight erythema and edema at 72 h.

In a Draize test, butyl benzoate (5 g/kg) had slight to no irritation effects after 24 h.⁵⁸ The treated skin was scaly at necropsy.

C12-15 ALKYL BENZOATE

In a primary dermal irritation test of C12-15 alkyl benzoate (100%; 0.5 ml), the test material was applied to the intact and abraded clipped skin of albino New Zealand rabbits (n = 6).⁵⁹ The primary irritation index was 0.08. C12-15 alkyl benzoate was not a primary irritant to rabbits.

In a repeat 14-day irritation study, C12-15 alkyl benzoate (62% and 100% in corn oil; 0.5ml) was administered to the clipped dorsal skin of New Zealand white rabbits (n = 10; 5/sex).¹¹³ Mineral oil and isopropyl myristate were used as controls. The average combined erythema and edema score/animal/day was 4.64 and 4.11 for the high and low dose of C12-15 alkyl benzoate, respectively. The scores were 2.68 and 5.40 for mineral oil and isopropyl myristate, respectively.

C12-15 alkyl benzoate (100%) administered to the skin of male albino New Zealand rabbits (n = 3) caused slight erythema and edema at 1 h which was resolved at 24 h.⁶¹

Human derived epidermal keratinocytes (NHEK) were incubated with C12-15 alkyl benzoates (10% and 100% in corn oil; 100 µl) and Triton X-100 (1%; positive control) for 3 h in an EpiDerm in vitro toxicity testing system.¹¹⁴ The test material was found to be non-irritating at both concentrations.

ISOPROPYL BENZOATE

Isopropyl benzoate (100%) administered to the skin of rabbits (n = 5) in a Draize test had an irritation score of 3 (strong capillary injection).⁵⁴

ISOBUTYL BENZOATE

In an acute toxicity test (see above), isobutyl benzoate (100%) administered under occlusion for 24 h to the intact and abraded clipped backs of rabbits (n = 4) produced no effects at 5 ml/kg.⁶⁵

Isobutyl benzoate (100%) administered to the skin of rabbits (n = 5) in a Draize test had an irritation score of 5.⁵⁴

ALCOHOLS

Methyl alcohol (10 and 35 mg in water; 35 mg in paraffin, and 10 mg in oil) was injected intracutaneously into the dorsal skin of shaved rabbits (n = 4). The sizes of the wheals at 24 h were 9, 0, 3, and 1 mm², respectively.¹¹⁵

Amyl alcohol was rated a severe irritant at 3.2 g/kg when applied to the abraded abdominal skin of albino rabbits.⁷⁰

Amyl alcohol (10 and 35 mg in water; 35 mg in paraffin, and 10 mg in oil) was injected intracutaneously into the dorsal skin of shaved rabbits (n = 4). The sizes of the wheals at 24 h were 74, 19, 53, and 40 mm², respectively.¹¹⁵

When lauryl alcohol was applied to the skin of CD(SD) hrBI hairless rats, moderate erythema was observed.¹¹⁶

Lauryl alcohol was reported to have a primary irritative index (PII) of 0.96 in a dermal Draize test.⁹⁶

A single dermal administration of ethylhexyl alcohol (5000 mg/kg) caused slight or moderate skin irritation in studies using clipped rabbits (n=10).¹¹⁷

Slight redness and scabbing was reported in rabbits (n=10) after 10 daily dermal administrations of ethylhexyl alcohol (100%; 2 ml/kg/d).⁸¹

Occlusive exposures to ethylhexyl alcohol (100%; 3.16 mg/kg/d) administered to the clipped intact skin of rabbits (n = 4) for 7 days caused moderate dermal irritation, erythema, edema, desquamation, necrosis, and eschar formation.⁷⁰

Hexydecyl alcohol was rated a slight irritant at 2.6 g/kg when applied to the abraded abdominal skin of albino rabbits.⁷⁰ One rabbit showed transient central nervous system depression and labored respiration.

Dermal Sensitization

In guinea pigs, methyl benzoate was not sensitizing up to 10%, ethyl benzoate at 8%, amyl benzoate at 6%, C12-15 alkyl benzoate at 10%, and isobutyl benzoate up to 2%.

METHYL BENZOATE

In a modified Freund's complete adjuvant test using guinea pigs (n not provided), methyl benzoate (10%; 30 mg) was not sensitizing.¹¹⁸

A guinea pig open epicutaneous test (OET; n = 6-8) of methyl benzoate (up to 4%; vehicle not provided; 0.1 ml) was performed.¹¹⁹ The test material was applied daily for 3 weeks onto shaved skin. Controls (n = 10) were untreated or treated with the vehicle. Challenge was conducted on days 21 and 35 on the opposite flank. Observations were made at 24, 48, and 72 h. Methyl benzoate at 4% was not sensitizing.

ETHYL BENZOATE

A guinea pig OET (n = 6-8) of ethyl benzoate (up to 8%; 0.1 ml; vehicle not provided) was performed.¹²⁰ Controls (n = 10) were untreated or treated with the vehicle. The test material was applied daily for 3 weeks onto clipped skin (8 cm²). Challenge was conducted on days 21 and 35 on the opposite flank to the test and control animals. Observations were made at 24, 48, and 72 h. Ethyl benzoate at 8% was not sensitizing.

AMYL BENZOATE

A guinea pig open OET (n = 6-8) of amyl benzoate (up to 6%; vehicle not provided; 0.1 ml) was performed.¹²⁰ The test material was applied daily for 3 weeks onto clipped skin. Challenge was conducted on days 21 and 35 on the opposite flank. Amyl benzoate at 6% was not sensitizing.

C12-15 ALKYL BENZOATE

In a guinea pig sensitization test, C12-15 alkyl benzoate (10%; 0.5 ml) was administered to the clipped backs and flanks of white male guinea pigs (n = 12) for 6 h/day under occlusion, 3 times/week for 3 weeks.⁶² Two challenges were performed 14 days after the last application. There were no topical or systemic reactions observed.

ISOBUTYL BENZOATE

A guinea pig OET (n = 6-8) of isobutyl benzoate (up to 2%; vehicle not provided; 0.1 ml) was conducted.¹²⁰ Water or the vehicle were administered to the controls (n = 10). The test material was applied daily for 3 weeks onto shaved skin (8 cm²). Challenge was conducted on days 21 and 35 and read at 24, 48, and 72 h; the opposite flank was treated with the minimal irritation concentration and lower concentrations (not provided). Isobutyl benzoate at 2% was not sensitizing.

Comedogenicity

Cetyl alcohol, stearyl alcohol, benzyl alcohol, and propyl alcohol had no comedogenic activity. Lauryl alcohol and myristyl alcohol had slight comedogenicity. Octyl alcohol had strong comedogenicity.

ALCOHOLS

Alcohols were tested for comedogenicity by repeated application to the inner ear of rabbits (5 days/week for 2 weeks).¹²¹ Cetyl alcohol (100%), stearyl alcohol (100%), benzyl alcohol (100%), and propyl alcohol (100%) had no comedogenic activity. Lauryl alcohol (50% in mineral oil) and myristyl alcohol (50% in mineral oil) had slight comedogenicity. Octyl alcohol (100%) had strong comedogenicity.

Reproductive and Developmental Toxicity

One oral study of the related compound isononyl benzoate resulted in a slight reduction in mean pup weight and consequently in litter weight in high dose females at birth and on day 4 post-partum. The NOAEL was 1000 mg/kg/d.

Oral studies on sodium benzoate and benzoic acid did not show reproductive or developmental toxicity. Where effects of the fetus were noted, they occurred at maternally toxic concentrations (> 4% sodium benzoate in rats).

Aerosolized methyl alcohol caused no maternal effects in Sprague-Dawley rats but caused reduced weights and increased malformations in offspring. Male mating success was reversibly reduced. The oral NOAELs for the maternal and developmental toxicity of isopropyl alcohol were 400 mg/kg in rats (maternal and developmental) and 240 mg/kg (maternal) and 480 mg/kg (developmental) in rabbits.

No data were discovered for reproductive and developmental toxicity of alkyl benzoates. There was one study submitted on the related compound isononyl benzoate. It is necessary to rely on the data on this compound, benzoic acid, sodium benzoate and the alcohol metabolites.

ISONONYL BENZOATE – RELATED COMPOUND

Isononyl benzoate (100, 300, 1000 mg/kg/d) was orally administered to male and female Sprague-Dawley rats before mating through 3 days post-partum.¹²² The males began treatment 4 weeks before mating and the females 2 weeks before mating. Body weights, body weight gains, and feed consumption were not affected by the test substance. Treatment groups did not show differences in fertility index, pre-coital interval, and copulatory index compared to controls. There

was a slight reduction in mean pup weight and consequently in litter weight in high dose females at birth and on day 4 postpartum. Histopathological examination of the ovaries, testes (including the stage in the spermatogenic cycle) did not reveal any differences between the findings observed in the treated and control animals. The authors concluded that 1000 mg/kg/d was the NOAEL.

BENZOIC ACID AND SODIUM BENZOATE

Sodium benzoate (0, 1%, 2%, 4%, or 8%; 0, 667, 1333, 1600, or 710 [sic] mg/kg/d) was administered in the feed of female Wistar rats (n = 27-30) during gestation (number of days not provided).¹²³ On day 20, 20-25 of each group were killed and necropsied. The rest were allowed to live through pregnancy and nurse for 3 or 8 weeks and then killed. Half of the pups were then killed at each of these times and necropsied. The 2 highest dose groups had an increase in the number of dead fetuses and resorbed embryos. The body weights of the viable pups were decreased and mild systemic edema was observed. The number of fetal abnormalities was increased in a dose-dependent manner. The number of pups born was decreased, the number of perinatal deaths increased to 100%, lactation rate decreased, and survival rate decreased to 0 in the 2 highest dose groups. The effects on the fetus occurred only at maternally toxic concentrations of $\geq 4\%$ sodium benzoate.

Sodium benzoate (up to 5mg/egg) was injected twice into the air sac of fertilized chicken eggs at 0 and 96 h and incubated to hatching.¹²⁴ Surviving chicks were killed and necropsied. There were no teratogenic effects reported. The LD₅₀ was 4.74 mg/egg.

Female Wistar rats (n = 20) were orally administered sodium benzoate (0, 1.75, 8.0, or 175 mg/kg/d) during days 6 – 15 of gestation.¹²⁵ On day 20 of gestation, the pups were delivered by Caesarean section. There were no differences in the types or incidences of abnormalities observed in any of the treatment groups compared to the control. The fetal and maternal NOAEL was 175 mg/kg.

The study above was repeated with mice (n = 20), hamsters (n = 21 - 22; gestation days 6 - 10), and rabbits (n = 10). Similar results were reported.

In oral teratogenicity studies, benzoic acid administered on gestation days 6 - 10 increased the number of resorptions at ≥ 30 mg/kg/d and increased the number of fetal malformations at > 600 mg/kg/d results in hamsters. Results for benzoic acid were negative in 2 oral rat studies up to 500 mg/kg/d.¹²⁶

Cross bred white mice (n = 50; 25/sex) were orally administered benzoic acid (40 mg/kg/d) for 8 months before breeding.⁷⁴ This was continued for 5 generations. The parental and F1 cohorts had increased mortality compared to controls after a 5-day 100% food restriction test. Otherwise, there were no effects on reproduction.

A neurobiological study on the effects of sodium benzoate (0.1%, 0.5%, and 1.0%) on the offspring of rats and mice was negative.¹²⁷ The dams (n = 8) were administered feed incorporated with sodium benzoate (0, 0.1%, 0.5%, or 1.0%) from gestation day 5 until weaning. Locomotor activity and brain chemistry of the pups were not affected.

ALCOHOLS

Sprague-Dawley rats were exposed to aerosolized methyl alcohol (5000, 10,000 or 20,000 ppm) for 6 h/d on days 1 – 19 of gestation.¹²⁸ There were no maternal effects observed at any concentration. The offspring had reduced weights in the mid and high-dose groups. The high-dose group also had increased incidences of external malformations, skeletal malformations, and visceral malformations compared to controls.

Mating success was not affected in male (n = 18) and female (n = 15) Sprague-Dawley rats exposed to propyl alcohol (8.61 mg/L) via inhalation 7 h/d, 7d/week for 62 days.¹²⁹ The decreased mating success of the male rats exposed to a higher dose of propyl alcohol (17.2 mg/L) in this study was reversed 15 weeks after exposure. Changes in activity measures were observed in the offspring of the 8.61 mg/L propyl alcohol maternally-exposed group, and crooked tails were found in 2-3 offspring.

The NOAELs for the maternal and developmental toxicity of isopropyl alcohol were 400 mg/kg in rats (maternal and developmental) and 240 mg/kg (maternal) and 480 mg/kg (developmental) in rabbits exposed by gavage during gestation (rats: 0, 400, 800, or 1200 mg/kg/day on gestation days 6 through 15; rabbits: 0, 120, 240, or 480 mg/kg/day on gestation day 6 through 18).¹³⁰

No effects on rat reproductive cells or organs (liver, lungs, spleen, lymph nodes, kidneys) were observed in several in vitro studies of ethylhexyl alcohol (200 μ M) for up to 48 h or in oral in vivo studies using rats (up to 500 mg/kg/d) for up to 90 days.^{87,89,131-136}

In Wistar rats administered a single dose of 1,666 mg/kg ethylhexyl alcohol by gavage on day 12 of pregnancy, 22.2% of the surviving fetuses had malformations (compared to 2% and 0% for 833 mg/kg and controls, respectively), and average fetal weight was reduced.^{131,137} No maternal toxicity or effects on implantation index or numbers of dead and resorbed fetuses were found in this study.

The embryos of pregnant Sprague-Dawley rats (n = 6) administered a single dose of ethylhexyl alcohol (1,625 mg/kg) by gavage exhibited decreased ⁶⁵Zn content, although the percentage of resorptions was not affected.^{138,139}

No treatment-related increases in the incidences of malformations or variations were found in F344 rats (n = 25) dermally exposed (clipped dorsal skin) to 2-ethyl-1-hexanol (0, 252, 420, 840, 1680 or 2520 mg/kg/d, 6 h/d, occlusive) on gestation days 6 to 15.^{42,130,140} Maternal effects at ≥ 840 mg/kg/d included persistent exfoliation, crusting and erythema at the site of application, and doses ≥ 1680 mg/kg/d were associated with decreased maternal weight gain.

Maternal and developmental NOAEL was found to be 130 mg/kg/d in Wistar rats (n = 10) orally exposed to ethylhexyl alcohol (0, 130, 650, and 1,300 mg/kg/d) on days 6 to 19 of gestation.¹⁴¹

The pups of Charles River CD-1 mice (n = 50) exposed to 2-ethyl-1-hexanol (1,525 mg/kg/d in corn oil) on days 7 to 14 of pregnancy exhibited reduced viability and body weights on day 3 of lactation.¹⁴² Maternal effects included decreased fertility and pregnancy indexes, body weights, and other signs of toxicity.

No maternal, reproductive, or developmental toxicities were found in CD-1 Swiss mice (n = 28) ingesting microencapsulated ethylhexyl alcohol (0.13, 43, and 129 mg/kg/d; >99% pure) in the diet on days 0 to 17 of pregnancy.^{143,144}

The NOAEL for maternal and developmental toxicity was 850 mg/m³ (160 ml/m³) aerosolized ethylhexyl alcohol in Sprague-Dawley rats (n = 15) exposed (whole body) 7 h/d on gestation days 0-19.¹²⁹

GENOTOXICITY

In Ames tests, methyl benzoate, ethyl benzoate, C12-15 alkyl benzoate were not genotoxic. Benzoic acid and sodium benzoate produced both positive and negative results in several genotoxic assays.

Methyl alcohol and ethylhexyl alcohol were not genotoxic in various assays (Ames test, chromosome aberration test, rec-assay).

METHYL BENZOATE

In an Ames test using *S. typhimurium* (TA97, TA98, TA100, TA1535, and TA1537), methyl benzoate (6666 µg/plate) was not mutagenic with or without metabolic activation.¹⁴⁵ Methyl benzoate (dose not reported) was not found to be mutagenic in *E. coli* (Sd-4-73).¹⁴⁶

ETHYL BENZOATE

In an Ames test using *S. typhimurium* (TA98, TA100, TA102, TA1535, and TA1537), ethyl benzoate (15 to 5000 µg/plate without metabolic activation and 5 to 5000 µg/plate with metabolic activation) was not mutagenic with or without metabolic activation.⁵⁶

C12-15 ALKYL BENZOATE

In an Ames test using *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538), C12-15 alkyl benzoate (100%; 0.1 ml) was not mutagenic to any strain tested, with or without metabolic activation.¹⁴⁷ Saline was the negative control and Dexon and 2-aminofluorene were the positive control.

ISONONYL BENZOATE – RELATED COMPOUND

In an oral in vivo micronucleus test of benzoic acid isononylester (500, 1000, 2000 mg/kg) using Sprague-Dawley SD rats (n = 5/sex), no remarkable adverse reaction was observed after treatment.¹⁴⁸ A slight depression of bone marrow erythropoietic cell division was observed at the high and intermediate dose-levels of treatment for female animals from the 24 h sampling time. A slight depression of bone marrow erythropoietic cell division was also observed at the 48 hour sampling time for both male and female animals from the high dose-group. The authors concluded that isononyl benzoate administered orally at these dose-levels to male and female rats does not induce micronuclei in the polychromatic erythrocytes.

BENZOIC ACID AND SODIUM BENZOATE

Benzoic acid and sodium benzoate had both positive and negative results in genotoxicity assays (Table 5). Sample studies are presented below.

Benzoic acid was negative in several Ames tests using *Salmonella typhimurium* (including TA98, TA100, TA1535, TA1537 and TA 1538) with and without metabolic activation.^{1,149-152}

In one Ames test using *S. typhimurium* (TA98 and TA100), benzoic acid (0.1 mg/plate) and sodium benzoate (0.1 mg/plate) were genotoxic with activation.¹⁵¹ In a reverse mutation test, benzoic acid (5 mg/disc) was positive for genotoxicity.

In a sister chromatid exchange assay using human lymphocytes, benzoic acid (0 – 2.0 mM) was not genotoxic with metabolic activation.¹⁵²

Sodium benzoate was positive without metabolic activation and negative with metabolic activation in a reverse mutation assay using *Bacillus subtilis*.¹⁴⁹ Benzoic acid (1.5 mg/ml) was positive in a chromosomal aberration test without metabolic activation.

In a sister chromatid exchange assay using hamster lung fibroblasts, sodium benzoate was not clastogenic without metabolic activation.¹⁵³

ALCOHOLS

In an Ames test, methyl alcohol (5 – 5000 µg/plate) was not mutagenic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2uvrA).¹⁵⁴

Genotoxicity tests of ethylhexyl alcohol were generally negative, including in vitro tests for chromosome aberrations,^{129,155-157} unscheduled DNA synthesis,¹⁵⁸ mutagenicity (Ames, TK⁺ mouse lymphoma, and HPRT assays),¹⁵⁹⁻¹⁶¹ and cell transformation.^{41,162,163} The exceptions include one positive result in one of two rec-assays^{164,165} and another in a test of mutagenicity in *S. typhimurium* TA-100 (mutation resistance to 8-azaguanine),¹⁶⁶ both of which were questionable.⁷²

Urine samples from Sprague-Dawley rats exposed to ethylhexyl alcohol (1000 mg /kg/d) by gavage for 15 days tested negative for mutagenicity in *S. typhimurium* with and without rat liver microsomes or beta-glucuronidase/arylsulfatase.^{167,168}

In vivo tests of ethylhexyl alcohol genotoxicity were also negative, including assays for covalent binding to liver DNA,^{169,170} dominant lethal mutations,¹⁷¹ and bone marrow micronuclei.^{172,173}

CARCINOGENICITY

No data was discovered on the carcinogenicity of alkyl benzoates.

Benzoic acid (40 mg/kg/d) orally administered to mice increased the number of tumors compared to controls.

Benzoic acid was negative for carcinogenicity when dermally applied to mice at 0.016% in a non-oxidative hair dye.

Orally administered methyl alcohol, amyl alcohol, lauryl alcohol, and dodecyl alcohol caused increases in polyploidy cells, cells with gaps, and cells with aberrations in the bone marrow of rats. Ethylhexyl alcohol was a weak liver tumor promoter in female mice. The reviewers noted that humans are less sensitive to the induction of peroxisome proliferation than rodents.

BENZOIC ACID

Cross bred white mice (n = 100) were orally administered benzoic acid (40 mg/kg/d in a paste).⁷⁴ After 8 months the mice were bred and also administered the benzoic acid paste. This was repeated for 5 generations. Eight of 100 mice in the first generation and 1 of 100 in the third generation were found to have malignant tumors. No tumors were found in the control group. In a follow up tumor transplantation test, benzoic acid fed to mice for 3 months did not increase tumor growth.

A non-oxidative hair dye containing benzoic acid (0.016%) and benzyl alcohol (2.0%) was negative for carcinogenicity when dermally applied to mice (n = 60) 3 times per week for 20 months.⁷⁵ In a feeding study of rats and mice (n = 102), feed containing sodium benzoate (1% or 2%; 102-151 or 202-280 mg/d) was not carcinogenic after 6 weeks.¹⁷⁴

ALCOHOLS

Orally administered methyl alcohol, amyl alcohol, and lauryl alcohol at one-fifth of the lethal dose, caused increases in polyploidy cells, cells with gaps, and cells with aberrations in the bone marrow of rats.¹⁷⁵

Male rats exhibited a concentration-dependent increase in the incidence of interstitial (Leydig) cell adenomas of the testes at all doses in a study in which Fischer 344 rats (n = 65/sex) and CD-1 mice (55/sex) were exposed by inhalation to isopropyl alcohol (0, 1230, 6150, or 12,300 mg/m³) for 6 h/d, 5 d/week for 104 weeks in rats and 78 weeks in mice.¹⁷⁶ No other tumors or neoplastic lesions were found in the rats or mice. International Agency for Research on Cancer (IARC)¹⁷⁷ has determined that isopropyl alcohol is not classifiable as to its carcinogenicity to humans (Group 3).

Male and female rats and mice were exposed chronically to ethylhexyl alcohol by gavage 5 times a week (rats: 0, 50, 150, 500 mg/kg/d for 24 months; mice: 0, 50, 200, 750 mg/kg/d for 18 months).⁹⁰ The results of this study suggested that ethylhexyl alcohol was a weak liver tumor promoter in female mice. Mechanistic studies suggest that tumor promotion in mice is attributable to the induction of peroxisome proliferation by ethylhexyl alcohol, which has questionable relevance for human exposures. Belsito et al.⁷² concluded that “while this mechanism cannot be completely discounted, it is reasonable to assume that humans are less sensitive than rodents.”

CLINICAL ASSESSMENT OF SAFETY

Toxicity

BENZOIC ACID

In clinical studies, toxic symptoms (including: discomfort, malaise, nausea, headache, weakness, esophageal burning, irritation, hunger, indigestion, vomiting, itching, perspiration) were observed following oral doses far exceeding the acceptable daily intake (ADI; 0 – 5 mg/kg)¹ established by JECFA.¹⁷⁸ The Registry of Toxic Effects of Chemical Substances (RTECS) cited the human low lethal oral dose of benzoic acid to be 500 mg/kg.¹⁷⁹

Ocular/Mucosal Irritation

Ethylhexyl benzoate was not an ocular irritant in a sunscreen at 3.5%.

Ethylhexyl alcohol ≥ 10 ml/m³ increased nasal and eye irritation and perceived odor intensity.

ETHYLHEXYL BENZOATE

A sunscreen liquid containing ethylhexyl benzoate (3.5%) was randomly administered to the eyes of subjects (n = 30; 10 male, 20 female) with an eye swab.¹⁸⁰ The reactions were scored at 5 min then the eyes were washed. Scoring was repeated at 15 and 60 min. The control was a baby shampoo (10%) with no ethylhexyl benzoate. The test material and the control exhibited no differences at all scoring times and all reactions were cleared at 1 h. The test material caused no tearing.

ALCOHOLS

Self-reported nasal and eye irritation and perceived odor intensity were increased in a concentration-related manner in male volunteers exposed to ethylhexyl alcohol (≥ 10 ml/m³) for 4 h in an exposure chamber.¹⁸¹

Dermal Irritation

Ethyl benzoate and butyl benzoate were not dermally irritating at 8%. C12-15 Alkyl benzoate was not irritating at 100%. Isobutyl benzoate was non irritating at 2% as was ethylhexyl benzoate at 3.5%.

Benzoic acid at 0.2% was not irritating to subjects. Benzoic acid at 0.2% caused mild, transient irritation when applied daily in a liquid foundation product at least twice/day for 45 days.

Little or no dermal irritation was observed in tests of propyl alcohol, lauryl alcohol, cetyl alcohol, isostearyl alcohol, and ethylhexyl alcohol on humans.

ETHYL BENZOATE

In a 48-h closed patch test (n = 5 males), ethyl benzoate (8% in petrolatum) produced no effects.¹⁸²

BUTYL BENZOATE

In a 48-h closed patch test (n = 5 males), butyl benzoate (8% in petrolatum) produced no effects.¹⁸²

C12-15 ALKYL BENZOATE

In an irritation study, C12-15 alkyl benzoate (0, 3%, 10%, 30, and 100% in vegetable oil) was applied to the backs of subjects (n = 21) under occlusion for 48 h.¹⁸³ No signs of irritation were observed at 48 and 72 h.

ISOBUTYL BENZOATE

Isobutyl benzoate (2%) administered in a 24 h patch test (n = 5 males) produced no effects.⁶⁵

ETHYLHEXYL BENZOATE

In a 14-day cumulative irritation test of a sunscreen liquid containing ethylhexyl benzoate (3.5%), the test material was applied to the skin of subjects (n = 28).¹⁸⁴ The positive control was SLS (0.25%) and the negative control was saline. There was a total dermal irritation score of 5.0 out of 1120. The authors concluded that there was no potential for eliciting cumulative dermal irritation.

A sunscreen lotion spray containing ethylhexyl benzoate (3.5%) was administered to the skin on the arms and legs of subjects (n = 35; male and female; 7 months to 8 years old) daily for 4 weeks.¹⁸⁵ There were no increases in erythema, edema or dryness of the arms and no increase in erythema and edema of the legs. One subject exhibited mild dryness of the legs following the four-week use period.

BENZOIC ACID

Benzoic acid (0.2%) was not irritating to subjects (n = 12) after 3 occlusive patches were applied over 1 week.¹⁸⁶ Benzoic acid (0.2%) caused mild, transient irritation when applied daily in a liquid foundation product at least twice/day for 45 days.¹⁸⁷

ALCOHOLS

Propyl alcohol produced no dermal irritation or skin sensitization in several clinical studies in which it was used as a vehicle and control.¹⁸⁸⁻¹⁹³ These studies include a cumulative irritation study (n = 20 males) in which AI-test® patches containing propyl alcohol were applied daily for 10 days to the interscapular area of each subject, each application remaining in place for 24 hours.¹⁹¹

In a patch test lauryl alcohol (C12), subjects (n = 20) had scores of ~ 0.02, 0, and 0.05 for irritation for 2, 1, and 0.5 mg in petrolatum, respectively. In a nitrocellulose-replica test, the scores were ~ 0.35, 0.2, and 0.1, respectively.¹⁹⁴

One subject of 80 males (21 to 52 years old) exposed to cetyl alcohol (11.5%) in a cream base five times daily (every 3 h) for 10 days developed erythema, folliculitis, and pustules (forearm site).^{5,191} Mild cumulative irritation (total score 418 for 21 applications) was reported in 12 female subjects (18 to 60 years old) exposed to cetyl alcohol (6.0%) using the same protocol.

No irritation was found in female subjects (n = 110) exposed to cetyl alcohol (8.4%), 10 patch application sites per subject, followed 14 days later by a challenge patch.^{5,191}

Isostearyl alcohol (25.0% in petrolatum and 25.0%, 27.0%, and 28.0% in lipstick) did not induce skin irritation in subjects (n = 19; 18 - 65 years old).^{5,191}

No skin irritation was found in 29 healthy male volunteers in an occlusive patch test with 4% ethylhexyl alcohol in petrolatum.¹⁹⁵

Dermal Sensitization

In HRIPTs, methyl benzoate at 4%, ethyl benzoate at 8%, C12-15 alkyl benzoate at 100%, stearyl benzoate at 2%, isobutyl benzoate at 2%, isostearyl benzoate at 0.95%, ethylhexyl benzoate at 3.5% and octyldodecyl benzoate at 0.4% were not sensitizing. Benzoic acid was negative for sensitization up to 2%.

Dodecyl alcohol, cetyl alcohol, isopropyl alcohol, isopropyl alcohol, isostearyl alcohol, and ethylhexyl alcohol were not sensitizing. A product containing isostearyl alcohol at 5.0% was sensitizing.

The results of several human insult patch tests (HRIPT) of products containing various benzoate esters are summarized in Table 6. None were irritating or sensitizing.

METHYL BENZOATE

Human maximization studies were conducted on methyl benzoate (0.05% – 0.5% in a perfumed base cream, a non-perfumed base cream, or 99% ethanol) in multiple studies (total n = 4737; 2341 Japanese men, 2396 Japanese women).¹⁹⁶ There were no visible reactions to the test substance observed.

A human repeated insult patch test (HRIPT ; n = 25), methyl benzoate (4% in petrolatum) was not sensitizing.¹⁹⁶

ETHYL BENZOATE

Human maximization studies were conducted on ethyl benzoate (0.05% – 0.5% in a perfumed base cream, a non-perfumed base cream, or 99% ethanol) in multiple studies (total n = 4737; 2341 Japanese men, 2396 Japanese women).⁵⁶ There were no visible reactions to the test substance observed.

In an HRIPT (n = 25), ethyl benzoate (8% in petrolatum) was not sensitizing.¹⁹⁶

C12-15 ALKYL BENZOATE

In an HRIPT (n = 101) was conducted on C12-15 alkyl benzoate (100%).¹⁹⁷ There were no visible reactions to the test substance observed.

An HRIPT (n = 48) was conducted on C12-15 alkyl benzoate (20% in corn oil).¹⁹⁸ Induction consisted of 10 applications under occlusion over 3.5 weeks. The challenge was applied ~14 days after last application on a naïve site. There were no signs of irritation or sensitization.

ISOBUTYL BENZOATE

In a human maximization test, isobutyl benzoate (in petrolatum) was applied to the volar surface of male subjects (n = 25) on 5 alternate days.⁶⁵ The test surfaces were pretreated with 5% aqueous sodium lauryl sulfate (SLS) under occlusion for 24 h. After 10 days, fresh sites were treated with 10% SLS for 1 h then isobutyl alcohol was applied. Test sites were read at removal and 24 h. There was no sensitization at 2% isobutyl alcohol.

ISOSTEARYL BENZOATE

A HRIPT (n = 107) was conducted on a body lotion product containing isostearyl benzoate (0.95%) under semi-occlusion.¹⁹⁹ Except for one subject, who also reacted to several other test substances on the shared panel, there were no visible reactions to the product containing isostearyl benzoate at 0.95%.

OCTYLDODECYL BENZOATE

An HRIPT (n = 105) was conducted on a shaving cream product containing octyldodecyl benzoate (4%) under semi-occlusion.²⁰⁰ The product was diluted to a 10% aqueous solution. There were no visible reactions to the product containing octyldodecyl benzoate at 0.4%.

BENZOIC ACID

In 4 clinical studies, tests for the sensitization of benzoic acid were negative.¹ A liquid/powder foundation containing benzoic acid (0.2%) produced no reactions at induction or challenge (n = 75).²⁰¹ Benzoic acid (2.0%) in petrolatum produced no reactions at induction or challenge (n = 25).^{202,203} Benzoic acid (5% in petrolatum) produced no reaction at induction or challenge (n = 10).²⁰⁴ In a cosmetic intolerance assay, a reaction to benzoic acid (concentration not provided) was observed in 34 of 5202 subjects; a reaction was observed in 1 of 155 subjects described as having a cosmetic allergy.²⁰⁵

ALCOHOLS

No primary sensitization was found in female subjects (n = 110) exposed to cetyl alcohol (8.4%), 10 patch application sites per subject, followed 14 days later by a challenge patch.⁵

An isopropyl alcohol (80.74%) spray concentrate did not exhibit any potential for dermal sensitization in human subjects (n = 9).²⁰⁶

An HRIPT study on test subjects (n = 9) showed that a hair dye base formulation of isopropyl alcohol (2.85%) and a isopropyl acetate (1.95%) caused no dermal sensitization in humans.²⁰⁷

No reactions were observed in healthy individuals (n = 12; 8 males, 4 females; 18 to 64 years old) exposed to isopropyl alcohol (Finn chambers, occlusive patches) on the flexor side of the right and left forearm for 24 h.²⁰⁸

Three of 12 male subjects (21 - 60 years old) exposed to isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) exhibited erythema during induction.^{5,191} However, 12 of 148 male and female subjects exhibited signs of sensitization after

exposure to a pump spray antiperspirant containing isostearyl alcohol (5.0%) using an occlusive patch applied to the upper arm for 24 h, 3 times/week for 3 weeks. Six of 10 of these subjects had reactions during the re-challenge 2 months later, and all 4 of the 6 subjects re-challenged with isostearyl alcohol (5.0%) in ethanol tested positive 6 weeks after the first re-challenge. In a second study, 5 of 60 male and female subjects had positive responses after the first challenge with the same product and test protocol; one of which was later re-challenged with isostearyl alcohol (5.0%), and again tested positive.

No skin sensitization was found in healthy male subjects (n = 29) in an occlusive patch test with ethylhexyl alcohol (4% in petrolatum).^{209,210} Like other saturated alcohols, 2-ethyl-1-hexanol has little skin sensitizing potential.⁷²

Phototoxicity

Methyl benzoate at 0.1% and ethylhexyl benzoate at 3.5% were not phototoxic in an in vitro study. Products containing benzoic acid up to 0.2% were not phototoxic. A product containing cetyl alcohol was not phototoxic.

METHYL BENZOATE

Human erythrocytes in suspension (0.4 ml) in methyl benzoate (0.1 ml) were exposed to UVA and UVB for 1 h.²¹¹ Photohemolysis was not induced.

ETHYLHEXYL BENZOATE

A sunscreen liquid containing ethylhexyl benzoate (3.5%; 0.2 ml) was administered to a 2-4 cm² area of the backs of subjects (n = 21) that had fair skin.²¹² Patches were removed and the test area cleaned 24 h later. After scoring, UVA was applied to 1 of the test sites and to a naïve site. Sites were graded at 24, 48, and 72 h. There were no signs of phototoxicity observed.

BENZOIC ACID

Phototoxicity and photosensitivity tests of benzoic acid were negative for a matte eye shadow (0.1%; n = 77) and a liquid/powder foundation (0.2%; n = 10 and 30).²¹³⁻²¹⁵

ALCOHOLS

No photosensitization reactions were found in subjects (n = 52) exposed to cetyl alcohol (40%) in a lipstick product or to cetyl alcohol (1.0%) in subjects (n = 407) tested (product and experimental procedure not stated).⁵

Case Reports

ALCOHOLS

Over 19 months, 33 cases of acute allergic contact dermatitis from epilating waxes and/or accompanying tissue were presented.²¹⁶ Patch tests of 26 of the patients resulted in 9 positive tests for lauryl alcohol (10% in petrolatum) varying from minor to severe.

Patients (n = 34) with allergic reactions to fatty alcohols had no positive reactions to lauryl alcohol (5% in petrolatum).²¹⁷

A 37-year-old man presented with severe genital swelling and inflammation that was not responding to treatment.²¹⁸ Prolonged oral prednisolone and antihistamines relieved the symptoms. Patch testing revealed a persistent 3+ reaction to octyldodecyl alcohol (13.5% in liquid paraffin) at 48 and 96 h.

A 62-year-old man had a 5-year history of eczematous eruption that he treated with a topical corticosteroids, emollients and an itch reliever.²¹⁹ Patch test revealed a + reaction to octyldodecyl alcohol (3% in petrolatum).

SUMMARY

This is a safety assessment of alkyl benzoates that are used in cosmetics. Alkyl benzoates function as skin-conditioning agents, preservatives, solvents, and plasticizers. In general, the alkyl benzoates can be produced industrially via esterification of benzoic acid. The manufacturing processes of the benzoic esters are typically high yielding ($\geq 90\%$) and easily purified (e.g., by distillation). The esters, acids and alcohols can be analyzed using gas chromatography/mass spectroscopy (GCMS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy and infrared (IR) spectroscopy.

The toxicity of the metabolites (benzoic acid and the parent alcohols) was taken into consideration in this safety assessment.

ALKYL BENZOATES

The total number of uses of C12-15 alkyl benzoate was 971 (858 leave-on and 113 rinse-off products) at concentrations up to 35% and 50% in leave-on and rinse-off products, respectively. The highest concentrations of use for C16-17 alkyl benzoates, stearyl benzoate, behenyl benzoate, ethyl benzoate, isobutyl benzoate, isostearyl benzoate, methyl benzoate, and octyldodecyl benzoate were reported to be from 0.01% to 4%. No uses or concentrations of use were reported for propyl benzoate, butyl benzoate, amyl benzoate, lauryl/myristyl benzoate, isopropyl benzoate, ethylhexyl benzoate, butyloctyl benzoate, and hexyldecyl benzoate.

Benzoate esters are metabolized into benzoic acid (and the corresponding alcohols) and further metabolized to benzoyl glucuronide and benzoyl CoA. The benzoyl CoA metabolizes into hippuric acid, the principal metabolite excreted in the urine.

Methyl benzoate, ethyl benzoate, propyl benzoate, butyl benzoate do penetrate the skin. C12-15 alkyl benzoate does not penetrate skin.

Methyl benzoate was cytotoxic to HeLa cells at 683.30 mM, *A. flavus* at 2.5 mg/ml, *A. parasiticus* at 5.0 mg/ml, and lung fibroblasts at 25 mM. Ethyl benzoate was cytotoxic to Hep-2 cells and lung fibroblasts at 289 mg/L. Propyl benzoate and butyl benzoate were cytotoxic to Hep-2 cells at 122 mg/L and 61 mg/L, respectively.

The oral LD₅₀ of methyl benzoate was 2170 mg/kg for rabbits, 4100 mg/kg for guinea pigs, 1350-3500 mg/kg for rats, and 3000-3330 mg/kg for mice. The oral LD₅₀ of ethyl benzoate was 2630 mg/kg for rabbits and 2100-6480 mg/kg for rats. The oral LD₅₀ of butyl benzoate was 5.14 g/kg for female rats. Orally administered C12-15 alkyl benzoate was not toxic to rats at 5.0 g/kg. The oral LD₅₀ for isopropyl benzoate was 3730 mg/kg and 3685 mg/kg for isobutyl benzoate in rats.

The dermal LD₅₀ of methyl benzoate was > 2000 mg/kg for rabbits. Dermally administered ethyl benzoate at 10% caused no effects to mice and calves; at 100% it was lethal to cats. Dermally administered butyl benzoate caused diarrhea in rabbits at 5 g/kg. C12-15 alkyl benzoate, at 100% or 2 mg/kg, was not dermally toxic to rabbits. The dermal LD₅₀ of isopropyl benzoate was 20 mg/kg for rabbits. Isobutyl benzoate was not dermally toxic to rabbits.

Methyl benzoate, ethyl benzoate, and butyl benzoate were grade 1 ocular irritants at 100%. C12-15 alkyl benzoate and isopropyl benzoate were rated as non- to mild ocular irritants at 100% as was isostearyl benzoate at 0.95%.

Methyl benzoate, ethyl benzoate, propyl benzoate, and butyl benzoate at 100% were dermally irritating to rabbits. C12-15 alkyl benzoate was a mild dermal irritant to rabbits at 100% and was found to be irritating in an in vitro test.

In guinea pigs, methyl benzoate was not sensitizing up to 10%, ethyl benzoate at 8%, amyl benzoate at 6%, C12-15 alkyl benzoate at 10%, and isobutyl benzoate up to 2% to guinea pigs.

One oral study of the related compound isononyl benzoate resulted in a slight reduction in mean pup weight and consequently in litter weight in high dose females at birth and on day 4 post-partum. The NOAEL was 1000 mg/kg/d.

In Ames tests, methyl benzoate, ethyl benzoate, C12-15 alkyl benzoate were not genotoxic. Isononyl benzoate administered orally at 2000 mg/kg to rats does not induce micronuclei in the polychromatic erythrocytes.

Ethylhexyl benzoate was not an ocular irritant to humans in a sunscreen at 3.5%.

Ethyl benzoate and butyl benzoate were not dermally irritating to humans at 8%. C12-15 Alkyl benzoate was not irritating at 100%. Isobutyl benzoate was non irritating at 2% as was ethylhexyl benzoate at 3.5%.

In HIRPTs and maximization studies, methyl benzoate at 4%, ethyl benzoate at 8%, C12-15 alkyl benzoate at 100%, stearyl benzoate at 2%, isobutyl benzoate at 2%, isostearyl benzoate at 0.95%, ethylhexyl benzoate at 3.5% and octyldodecyl benzoate at 0.4% were not sensitizing.

Methyl benzoate at 0.1% and ethylhexyl benzoate at 3.5% were not phototoxic to humans.

BENZOIC ACID AND SODIUM BENZOATE

Dermally applied benzoic acid is excreted in the urine within 24 h.

The oral LD₅₀ of benzoic acid was reported to be 1996 mg/kg in mice and 2000 – 2500 mg/kg in rats. The oral LD₁₀₀ was reported to be 1520 – 2000 mg/kg for rabbits, and 2000 mg/kg for cats and dogs. The oral LD₅₀ for sodium benzoate was 2100 – 4070 mg/kg for rats and 2000 mg/kg for rabbits and dogs.

Benzoic acid and sodium benzoate were orally toxic to rats and mice in short-term feeding studies at concentrations > 1% in short-term, subchronic, and chronic studies. In Subchronic studies, benzoic acid was toxic to mice at oral doses of 80 mg/kg/d. Sodium benzoate at 880 mg/kg/d incorporated into the feed of rats for 18 – 24 months was not toxic.

Studies on sodium benzoate and benzoic acid did not show reproductive or developmental toxicity in rats. Where effects of the fetus were noted, they occurred at maternally toxic concentrations (> 4% sodium benzoate in rats).

Benzoic acid and sodium benzoate produced both positive and negative results in several genotoxic assays.

Benzoic acid (40 mg/kg/d) orally administered to mice increased the number of tumors compared to controls.

Benzoic acid was negative for carcinogenicity when dermally applied to mice at 0.016% in a non-oxidative hair dye.

Benzoic acid at 0.2% was not irritating to subjects. Benzoic acid at 0.2% caused mild, transient irritation when applied daily in a liquid foundation product at least twice/day for 45 days.

Benzoic acid was negative for sensitization up to 2%.

ALCOHOLS

Methyl alcohol and ethylhexyl alcohol permeated the skin or nail plates. Aerosolized lauryl alcohol caused mild dyspnea and scattered hemorrhagic areas in the lungs of rats.

Methyl alcohol, amyl alcohol, and dodecyl alcohol were cytotoxic.

Methyl alcohol has an oral LD₅₀ of 5628 mg/kg for rats and 7300 mg/kg for mice. The oral LD₅₀ of amyl alcohol for rats was reported to be 2.69 g/kg. Dodecyl alcohol has an oral LD₅₀ of 12,800 mg/kg for rats. Tridecyl alcohol has an oral LD₅₀ of 17,200 mg/kg for rats. Tetradecyl alcohol has an oral LD₅₀ 33,000 mg/kg for rats. Oral LD₅₀s for ethylhexyl alcohol in rats range from 2049 to 7100 mg/kg and 2380 to >5000 mg/kg for rabbits. The oral LD₅₀ of hexyldecyl alcohol for rats was reported to be > 8.42 g/kg. The dermal LD₅₀ of methyl alcohol was reported to be 15,800 mg/kg in rabbits.

The dermal LD₅₀ of amyl alcohol for rabbits was reported to be > 3.2 g/kg. The dermal LD₅₀ of dodecyl alcohol was reported to be 3560 mg/kg in rabbits. The dermal LD₅₀ of tridecyl alcohol was reported to be 5600 mg/kg in rabbits. The dermal LD₅₀ of hexadecyl alcohol for rabbits was reported to be > 2.6 g/kg. Aerosolized amyl alcohol at near saturation caused irritation of the eyes, nose, throat, and respiratory passages of mice and guinea pigs. Rats exposed to aerosolized ethylhexyl alcohol exhibited signs of irritation of the eyes nose, throat, and respiratory passages, including blinking, lacrimation, nasal discharge, salivation, gasping, and chewing movements. No rats died from exposure for up to 8 h. Hexyldecyl alcohol was a slight irritant with no systemic effect to mice, rats, and guinea pigs at 9.6 mg/m³.

Short-term oral exposure to amyl alcohol was not toxic to rats at 100%. Oral NOAELs ranged from 100 to 150 mg/kg in several studies using mice or rats exposed to ethylhexyl alcohol. Dermal exposure to ethylhexyl alcohol caused physiological changes in rats at 500 mg/kg. Inhalation of isobutyl alcohol at 770 mg/m³ caused reversible inhibition of responsiveness in rats. Adverse effects of isopropyl alcohol at the LOAEL included clinical signs in rat and mice, hematological changes in rats, and increased liver weights in mice; higher doses caused kidney and testicular effects. Aerosolized n-pentadecyl alcohol was not toxic to rats.

Methyl alcohol, amyl alcohol, dodecyl alcohol, isopropyl alcohol, and ethylhexyl alcohol were rated as severe ocular irritants to rabbits at 100%. Hexyldecyl alcohol was a slight ocular irritant at 100%.

Methyl alcohol, amyl alcohol, lauryl alcohol, ethylhexyl alcohol, and hexyldecyl alcohol were dermal irritants.

Cetyl alcohol, stearyl alcohol, benzyl alcohol, and propyl alcohol had no comedogenic activity. Lauryl alcohol and myristyl alcohol had slight comedogenicity. Octyl alcohol had strong comedogenicity.

Aerosolized methyl alcohol caused no maternal effects in rats but caused reduced weights and increased malformations in offspring. Male mating success was reversibly reduced. The oral NOAELs for the maternal and developmental toxicity of isopropyl alcohol were 400 mg/kg in rats (maternal and developmental) and 240 mg/kg (maternal) and 480 mg/kg (developmental) in rabbits.

Methyl alcohol and ethylhexyl alcohol were not genotoxic in various assays.

Orally administered methyl alcohol, amyl alcohol, lauryl alcohol, and dodecyl alcohol caused increases in polyploidy cells, cells with gaps, and cells with aberrations in the bone marrow of rats. Ethylhexyl alcohol was a weak liver tumor promoter in female mice. The reviewers noted that humans are less sensitive to the induction of peroxisome proliferation than rodents.

Ethylhexyl alcohol ≥ 10 ml/m³ increased nasal and eye irritation and perceived odor intensity at ≥ 10 ml/m³.

Little or no dermal irritation was observed in tests of propyl alcohol, lauryl alcohol, cetyl alcohol, cetyl alcohol, isostearyl alcohol, and ethylhexyl alcohol on humans.

Dodecyl alcohol, cetyl alcohol, isopropyl alcohol, isopropyl alcohol, isostearyl alcohol, and ethylhexyl alcohol were not sensitizing. A product containing isostearyl alcohol at 5.0% was sensitizing.

A product containing cetyl alcohol was not phototoxic in humans.

DISCUSSION

The CIR Expert Panel noted the shorter chain-length alkyl benzoates clearly penetrated the skin and were thus available for systemic exposure. Less clear was the dermal penetration of long chain-length alkyl benzoates. C12-15 alkyl benzoate stayed in the stratum corneum, but there was some penetration to the epidermis and minimal penetration to the dermis. Octanol/water partition coefficients were not consistent with those findings --- alkyl benzoates with octanol/water partition coefficient values around 8 were not expected to leave the stratum corneum and reach the epidermis.

The Panel reasoned that the data showing presence of alkyl benzoates in the epidermis suggest the need for a conservative approach that would consider the potential for systemic exposure to long chain-length alkyl benzoates. Alkyl benzoates are largely non-toxic, but, given that these ingredients may penetrate the skin, they may be cleaved and result in systemic exposure to the component alcohol and benzoic acid. Component alcohols may be toxic at high levels, for example, so the Panel considered available data on the parent compounds, and on Benzoic Acid and component alcohols. While data were not available on reproductive/developmental toxicity of alkyl benzoates used in cosmetics, one study on a chemically similar alkyl benzoate demonstrated an absence of reproductive/developmental toxicity.

The Panel noted that carcinogenicity data were not available for alkyl benzoates, but that available data indicated that these alkyl benzoate cosmetic ingredients are not genotoxic and are not dermal sensitizers. In addition, available data demonstrate that Benzoic Acid and tested component alcohols are not reproductive or developmental toxicants, are not genotoxic in almost all assays, and are not carcinogenic. The Panel considered, therefore, that the low levels at which alkyl benzoates are used could not result in any significant systemic toxicity for cleavage products.

Several of the shorter chain-length alkyl benzoates were cytotoxic at high doses and were dermal irritants in animal tests, but were not significant irritants in clinical tests. Due to the lack of irritation by the shorter chain length alkyl benzoates when used in cosmetic formulations, alkyl benzoates are not expected to result in any cytotoxicity.

The Panel considered that certain of the alcohol components may be sourced from plant material or animal material. The extensive processing, however, to obtain the component from plant or animal material and subsequent chemical reaction to form alkyl benzoates would preclude any presence of residual heavy metals, pesticides, or infectious agents.

Certain of the alkyl benzoates are used in cosmetic products that may be inhaled during their use. In practice, however, the particle sizes produced by cosmetic aerosols are not respirable.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe in the present practices of use and concentration described in this safety assessment (ingredients not in current use identified with an *):

- methyl benzoate,
- ethyl benzoate,
- propyl benzoate*,
- butyl benzoate*,
- amyl benzoate*,
- lauryl/myristyl benzoate*,
- C12-15 alkyl benzoate,
- C16-17 alkyl benzoate,
- stearyl benzoate,
- behenyl benzoate*,
- isopropyl benzoate*,
- isobutyl benzoate*,
- isostearyl benzoate,
- ethylhexyl benzoate,
- butyloctyl benzoate*,
- hexyldecyl benzoate*, and
- octyldodecyl benzoate.

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

TABLES AND FIGURES

Table 1. Definitions, functions and structures of alkyl benzoate ingredients in this safety assessment.²²⁰

Ingredient	CAS No.	Definition	Function(s)	Technical names
Alkyl Benzoates				
Methyl Benzoate	93-58-3	Methyl benzoate is the ester of methyl alcohol and benzoic acid that conforms to the formula in Figure 1.	Fragrance ingredient, skin-conditioning agent-emollient, solvent	Benzoic Acid, Methyl Ester; Methyl Benzenecarboxylate Methyl benzoate (RIFM)
Ethyl Benzoate	93-89-0	Ethyl benzoate is the ester of ethyl alcohol and benzoic acid.	Fragrance	Benzoic Acid, Ethyl Ester; Ethyl benzoate (RIFM)
Propyl Benzoate	2315-68-6	Propyl benzoate is the ester of n-propyl alcohol and benzoic acid.	Fragrance ingredient, preservative	Benzoic Acid, n-Propyl Ester; Propyl benzoate (RIFM)
Butyl Benzoate	136-60-7	Butyl benzoate is the ester of butyl alcohol and benzoic acid.	Fragrance ingredient, preservative	Benzoic Acid, n-Butyl Ester; Butyl benzoate (RIFM)
Amyl Benzoate	2049-96-9	Amyl benzoate is the ester of amyl alcohol and benzoic acid that conforms to the formula in Figure 1.	Fragrance ingredient	Benzoic Acid, Pentyl Ester; Pentyl Benzoate Pentyl benzoate (RIFM)
Lauryl/ Myristyl Benzoate	No CAS No.	Lauryl/Myristyl benzoate is the organic compound that conforms to the formula in Figure 1.	Skin-conditioning agent-miscellaneous	-
C12-15 Alkyl Benzoate	68411-27-8	C12-15 alkyl benzoate is the mixture of esters of benzoic acid and C12-15 alcohols.	Skin-conditioning agents - emollient	Alkyl (C12-C15) Benzoate; Benzoic Acid, C12-15 Alkyl Esters; C12-15 Alcohols Benzoate
C16-17 Alkyl Benzoate	669700-05-2	C16-17 alkyl benzoate is a mixture of esters of C16-17 alcohols and benzoic acid that conforms generally to the formula in Figure 1.	Skin-conditioning agents-emollient, solvent	-
Stearyl Benzoate	10578-34-4	Stearyl benzoate is the ester of stearyl alcohol and benzoic acid that conforms to the formula in Figure 1.	Skin-conditioning agent-emollient, solvent	Benzoic Acid, Octadecyl Ester; Benzoic Acid, Stearyl Ester; Octadecyl Benzoate
Behenyl Benzoate	103403-38-9	Behenyl benzoate is the ester of behenyl alcohol and benzoic acid that conforms to the formula in Figure 1.	Skin-conditioning agent – emollient	Benzoic Acid, Docosyl Ester
Branched Alkyl Benzoates				
Isopropyl Benzoate	939-48-0	Isopropyl benzoate is the ester of isopropyl alcohol and benzoic acid.	Fragrance ingredient	Benzoic Acid, Isopropyl Ester; Benzoic Acid, 1-Methylethyl Ester; Isopropyl benzoate (RIFM); 1-Methylethyl Benzoate
Isobutyl Benzoate	120-50-3	Isobutyl benzoate is the ester of isobutyl alcohol and benzoic acid.	Fragrance ingredient, solvent	Benzoic Acid, Isobutyl Ester; Benzoic Acid, 2-Methylpropyl Ester; Isobutyl benzoate (RIFM); 2-Methylpropyl Benzoate
Isostearyl Benzoate	34364-24-4	Isostearyl benzoate is the ester of isostearyl alcohol and benzoic acid.	Skin-conditioning agent-emollient	Benzoic Acid, Isooctadecyl Ester; Benzoic Acid, Isostearyl Ester
Ethylhexyl Benzoate	5444-75-7	Ethylhexyl benzoate is the ester of 2-ethylhexanol and benzoic acid.	Skin-conditioning agent-emollient, solvent	Benzoic Acid, 2-Ethylhexyl Ester; 2-Ethylhexyl Benzoate Octyl Benzoate
Butyloctyl Benzoate	1888038-97-3	Butyloctyl benzoate is the organic compound that conforms to the formula in Figure 2.	Plasticizer; skin-conditioning agent-emollient, solvent	Benzoic Acid, 2-Butyloctyl Ester
Hexyldecyl Benzoate	163883-40-7	Hexyldecyl benzoate is the organic compound that conforms to the formula in Figure 2.	Plasticizer, skin-conditioning agent-emollient, solvent	Benzoic Acid, 2-Hexyldecyl Ester
Octyldodecyl Benzoate	108347-89-3	Octyldodecyl benzoate is the ester of octyldodecanol and benzoic acid.	Skin-conditioning agent-emollient	Benzoic Acid, 2-Octyldodecyl Ester

Table 2. Physical and Chemical properties of the alkyl benzoate ingredients.^{14,26,26,221,221}

	Methyl Benzoate	Ethyl Benzoate	Propyl Benzoate	Butyl Benzoate	Amyl Benzoate	Lauryl/Myristal Benzoate
Molecular Weight (g/mol)	136.15	150.17	164.20	178.23	192.25	290.44/318.49
Boiling Point (°C)	198.6	212.9	230.0	247.3	248	225 (Lauryl at 20 mmHg)
Density (g/cm ³)	1.09	1.04	1.04	1.00	0.95	0.93(Lauryl)
Vapor pressure (mm Hg @ 20°C)	0.38	0.267	0.136	0.01	0.009	-
Solubility (g/1000g water @ 20°C)	2.1	0.72	0.351	0.059	0.028	-
Log K _{ow}	2.12	2.64	3.01	3.84	4.16 (est.)	7.23 (est. Lauryl)
	C12-15 Alkyl Benzoate	C16-17 Alkyl Benzoate	Stearyl Benzoate	Behenyl Benzoate	Isopropyl Benzoate	Isobutyl Benzoate
Molecular Weight (g/mol)	290.44-332.52	346.55-360.57	374.60	430.71	164.20	178.23
Boiling Point (°C)	363 (est.)	-	433 (est.)	518.3	266	237
Density (g/cm ³)	-	-	-	0.908	-	1.02
Vapor pressure (mm Hg @ 20°C)	1 x 10 ⁻⁵ (est.)	-	6 x 10 ⁻⁸ (est.)	7 x 10 ⁻¹¹	0.161 (est.)	0.0417 (est.)
Solubility (g/1000g water @ 20°C)	9 x 10 ⁻⁶ (est.)	-	9 x 10 ⁻⁶ (est.)	7 x 10 ⁻⁷	0.126 (est.)	0.098 (est.)
Log K _{ow}	7.23 (est.)	-	10.18 (est.)	13.35	3.18	3.23 (est.)
	Isostearyl Benzoate	Ethylhexyl Benzoate	Butyloctyl Benzoate	Hexyldecyl Benzoate	Octyldodecyl Benzoate	
Molecular Weight (g/mol)	374.60	234.33	290.44	346.55	402.65	
Boiling Point (°C)	426 (est.)	169-170 (at 20 mmHg)	376.9	434.8	449 (est.)	
Density (g/cm ³)	-	0.91	0.939	0.923	-	
Vapor pressure (mm Hg @ 20°C)	1 x 10 ⁻⁷	5 x 10 ⁻⁴ (est.)	7 x 10 ⁻⁶	9 x 10 ⁻⁸	2 x 10 ⁻⁸ (est.)	
Solubility (g/1000g water @ 25°C)	1 x 10 ⁻⁵	1.1 x 10 ⁻³	5.8 x 10 ⁻⁴	1.5 x 10 ⁻⁵	1 x 10 ⁻⁶ (est.)	
Log K _{ow}	10.10 (est.)	5.7 (est.)	7.857	9.982	11.09 (est.)	
Not Ingredients	C12 Alkyl Benzoate	C13 Alkyl Benzoate	C14 Alkyl Benzoate	C15 Alkyl Benzoate		
Log K _{ow} ³⁴	8.0	8.6	9.1	9.6		

est.= Values were estimated using the EPI Suite, Version 4.0 program or Advanced Chemistry Development (ACD/Labs) Software V11.02.

- Not found

Table 3. Frequency of use according to duration and exposure.^{19,20}

Use type	Concentration		Concentration		Concentration		Concentration	
	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
	Methyl benzoate		Ethyl benzoate		C12-15 Alkyl benzoate		C16-17 Alkyl benzoate	
Total/range	NR	0.0005-0.3	NR	0.0008-0.01	971	0.0008-59	2	NR
<i>Duration of use</i>								
Leave-on	NR	0.005-0.3	NR	0.0008-0.01	858	0.0008-59	NR	NR
Rinse-off	NR	0.007-0.3	NR	NR	113	0.1-50	2	NR
<i>Exposure type</i>								
Eye area	NR	NR	NR	NR	69	0.0008-11	NR	NR
Possible ingestion	NR	NR	NR	NR	66	3-16	NR	NR
Inhalation	NR	NR	NR	0.003-0.01	25	0.3-12	NR	NR
Dermal	NR	0.0005-0.3	NR	0.0008-0.01	870	0.0008-59	2	NR
Deodorant (underarm)	NR	0.004	NR	NR	6	2-12	NR	NR
Hair-noncoloring	NR	NR	NR	NR	98	0.3-35	NR	NR
Hair-coloring	NR	NR	NR	NR	-	0.5-2	NR	NR
Nail	NR	NR	NR	NR	2	0.008-10	NR	NR
Mucous Membrane	NR	0.03	NR	NR	12	0.01-0.04	2	NR
Bath products	NR	0.07	NR	NR	-	0.008-10	NR	NR
Baby	NR	NR	NR	NR	9	10	NR	NR

	Stearyl benzoate		Isobutyl benzoate		Isostearyl benzoate		Ethylhexyl benzoate	
Total/range	3	2	NR	0.01	NR	1	NR	3-4
<i>Duration of use</i>								
Leave-on	3	2	NR	0.01	NR	1	NR	3-4
Rinse-off	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure type</i>								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Possible ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	0.01	NR	NR	NR	NR
Dermal	3	2	NR	0.01	NR	1	NR	3-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair – coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Bath products	NR	NR	NR	NR	NR	NR	NR	NR
Baby	2	NR	NR	NR	NR	NR	NR	NR

	Octyldodecyl benzoate	
Total/range	NR	3-4
<i>Duration of use</i>		
Leave-on	NR	NR
Rinse-off	NR	3-4
<i>Exposure type</i>		
Eye area	NR	NR
Possible ingestion	NR	NR
Inhalation	NR	NR
Dermal	NR	3-4
Deodorant (underarm)	NR	NR
Hair-noncoloring	NR	NR
Hair-coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Bath products	NR	3
Baby	NR	NR

Table 4. Repeated Dose Oral/Feed Toxicity Studies on Benzoic Acid and Sodium Benzoate*

Protocol	Results/Comments	Reference
Benzoic Acid		
Royal Wistar rats dosed with 3% for 1, 2, 3, or 5 days (~1500 mg/kg/day); basal diet followed for 19-30 days	14/35 Rats dosed for five days died; necrosis of parenchymal cells noted in brain in all 5-day treated rats and occasionally in 3-day treated rats	222
Royal Wistar rats (no. not stated) dosed with 1.1% for 7, 14, or 35 days (~550 mg/kg/day)	Significantly poor weight gain; no signs of neurotoxicity or pathological changes in the brain	222
100 Mice (50 each sex) dosed for 3 mo with 80 mg/kg/day (oral intubation)	Weight gain in treated animals was 66% (females) and 71% (females) of gain in controls, values significant; however, feed intake comparable	74
40 Sprague-Dawley rats (20 each sex) received feed containing either 0.5% or 2% for 1 yr. Some other groups also received sorbic acid	No effect noted at 0.5%; slight reduction of growth rate noted at 2%. No additive toxicity noted of Benzoic Acid plus sorbic acid	223
50 Mice (25 each sex) dosed with 40 mg/kg/day; fed as a paste for 17 mo, followed by 5 d of oral intubation	Major finding was a reduced response to physiological stress in treated animals compared to controls	74
Mice (no. not stated) dosed with 40 or 80 mg/kg/day for 3, 8, or 18 mo	Negative effects on body weight and viability; treatment-related carcinogenic effects noted (not specified); increased liver weights, enlarged spleens, ovaries and lungs	224
20 Rats (10 each sex) dosed with 40 mg/kg/day; fed as a paste for 18 mo, followed by 13 d of oral intubation	Developed increased tolerance to lethal doses of Sodium Benzoate; daily feed and water intake significantly less for treated males; limited data reported	74
Rats (no. not stated) dosed with 40 or 80 mg/kg/day for 3, 8, or 18 mo	No apparent affect on body weight or viability; no changes noted in parenchymatous organs; developed increased tolerance to lethal doses of Benzoic Acid	224
50 Wistar rats (20 female, 30 male), 20 male Wistar rats and 20 male Osborne-Mendel rats, dosed with 1.5% in feed for 18 mo	Decreased feed intake and reduced growth	225
4 Generations of Bayer-Elberfeld rats dosed with 0.5 or 1.0% in feed	No adverse effect noted; increased life-span noted in treated rats	226
Sodium Benzoate		
28 Rats dosed with 5% in feed	19/28 Died within two wks of dosing; remaining 9 died by end of wk 3	226
12 Sherman rats (6 each sex) dosed with 2% or 5% in feed for 28 days	Slight weight depression (significant in males) noted at 2%; 5% toxic to all rats.	227
Groups of 10 Sherman rats (5 each sex) dosed with 16-1090 mg/kg/day (four doses) for 30 days	No toxic effects; increased body weight, reduced appetite (compared to control), noted. Lesions of adrenal glands, upper intestine, kidneys, liver and spleen	228
Rats (no. not stated) dosed with 1947-2195 mg/kg/day for 3-6 wk	Severe reduction of growth rate	229
Wistar rats dosed with 1.5% in feed for 6 or 8 wk (after wk 4, carotene was added to diet)	No significant effect noted. Vitamin A content in liver and kidneys comparable to control	230
Groups of 10 Sherman rats (5 each sex) dosed with 1, 2, 4, 8% in feed for 90 days	No adverse effects at ≤ 4%. At 8% reduced growth rate (feed consumption comparable to control), significantly increased liver and kidneys weight with lesions noted	231
White rats (no. not stated) dosed with 1.5, 2.0, 2.5, 3.0% in feed for unknown duration	No effects noted in rats of ≤2.5% groups; distinct growth reduction noted in rats of 3.0% group though feed intake was comparable to control. One third of rats of this group died	232

*Reviewing the studies, the GRAS report (Informatics Inc., 1972) concluded, "... at a level of approximately 1% [in food], the benzoates are at maximum non-toxic level; higher than this, they result in decreased food intake, depressed growth, and toxic effects on test animals."

Table 5. Genotoxicity tests of sodium benzoate and benzoic acid.

Assay	Concentration/method	Results/comments	Reference
Bacterial cells			
Host-mediated	Mice orally dosed (either single dose or 5 doses 24 h apart) with 50, 500, 5000 mg/kg sodium benzoate, then inoculated with <i>Salmonella</i> TA 1530, G46, and <i>Saccharomyces</i> D3; after 3 h, mice were killed and the bacteria removed (by peritoneal wash) and plated	Negative (slight increase in mutation frequencies noted; non-dose dependent)	233
Ames; <i>S. typhimurium</i> (TA97A, TA102)	33 – 10,000 µg Benzoic acid/plate ± S9	Negative	234
Ames; <i>S. typhimurium</i> (TA97, TA98, TA100, TA1535, TA1537)	Benzoic acid at 100 – 6666 µg/plate or 100 – 10,000 µg/plate ± S9 (either rat or hamster liver)	Negative	235
Ames; <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) <i>E. coli</i> (WP2)	0.033 – mg Sodium benzoate/plate ± S9	Negative	236
Reverse mutation assay; <i>Bacillus subtilis</i>	Not reported; no metabolic activation	Positive	153
Ames; <i>S. typhimurium</i> (TA98, TA100)	0.1 mg/Disc; ± metabolic activation	Positive	151
Ames; <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537)	Not reported; with metabolic activation	Positive	150
Mammal cells			
SCE in CHO	1, 3, 10 mM Benzoic acid	Negative	237
SCE in CHO	1, 2, 5, 10 mM Sodium benzoate	Positive at ≥ 2 mM (considered a high dose)	238
Chromosome aberration in CHO	Maximum effective dose: 2.00 mg/ml (138.8 x 10 ⁻⁴ M) sodium benzoate	Positive: aberrations noted in 38%	239
Cytogenetics (human embryonic lung cells)	2, 20, 200 mg/kg Sodium benzoate	Negative (checked for aberrations in anaphase chromosomes)	233
Human lymphocytes	0 – 2.0 mM Benzoic acid with metabolic activation; sister chromatid assay	Negative	152
In vivo: Mammalian			
Dominant lethal (rats)	Following dosing by oral intubation (50, 500, 5000 mg/kg sodium benzoate either single dose or 5 doses 24 h apart), male rats were mated with 2 females/week for 8 weeks. Corpora lutea, early and late fetal deaths, and total implantations monitored	Negative	233
Cytogenetic (rats)	Rats dosed by gastric intubation (50, 500, 5000 mg/kg sodium benzoate either single dose or 5 doses 24 h apart, killed at various times after dosing (were given colcemid to arrest cells in metaphase)	Negative (checked for aberrations in bone marrow metaphase chromosomes)	233

CHO – Chinese hamster ovary cells. SCE – Sister chromatid exchange.

Table 6. HRIPTs of products containing benzoate esters.

Benzoate	Product type	Concentration	N	Results	Reference
Methyl benzoate	Perfume	0.028%	110	No irritation or sensitization	240
C12-15 Alkyl Benzoate	Hand cream	0.07398%	49	No irritation or sensitization	241
C12-15 Alkyl Benzoate	Concealer	4.2%	108	No irritation or sensitization	242
C12-15 Alkyl benzoate	Blush	14.15%	116	No irritation or sensitization	233,243
C12-15 Alkyl benzoate	Lipstick	16%	104	No irritation or sensitization	244
C12-15 Alkyl benzoate	Lipstick	16%	107 ^a	No irritation or sensitization	245
C12-15 Alkyl benzoate	Lipstick	16%	107 ^a	No irritation or sensitization	246
C12-15 Alkyl benzoate	Body oil	19.5%	100	No irritation or sensitization	233,247
C12-15 Alkyl benzoate	Hair serum	35%	208	No irritation or sensitization	248
Stearyl benzoate	Face lotion	2%	206	No irritation or sensitization	249
Isobutyl benzoate	Perfume	0.01%	103	No irritation or sensitization	240
Isostearyl benzoate	Body lotion	0.95	107	No irritation or sensitization	250
Ethylhexyl benzoate	Sunscreen liquid	3.5%	212	No irritation or sensitization	184,220
Octyldodecyl benzoate	Shaving cream	0.4% (diluted from 4% in water)	105	No irritation or sensitization	251
Octyldodecyl benzoate	Perfumed bar soap	2.0473%	101	No irritation or sensitization	252

^a These two studies were completed on the same panel of subjects.

Figure 1. Straight-chain alkyl benzoates: structures, esterase metabolism, and metabolites.

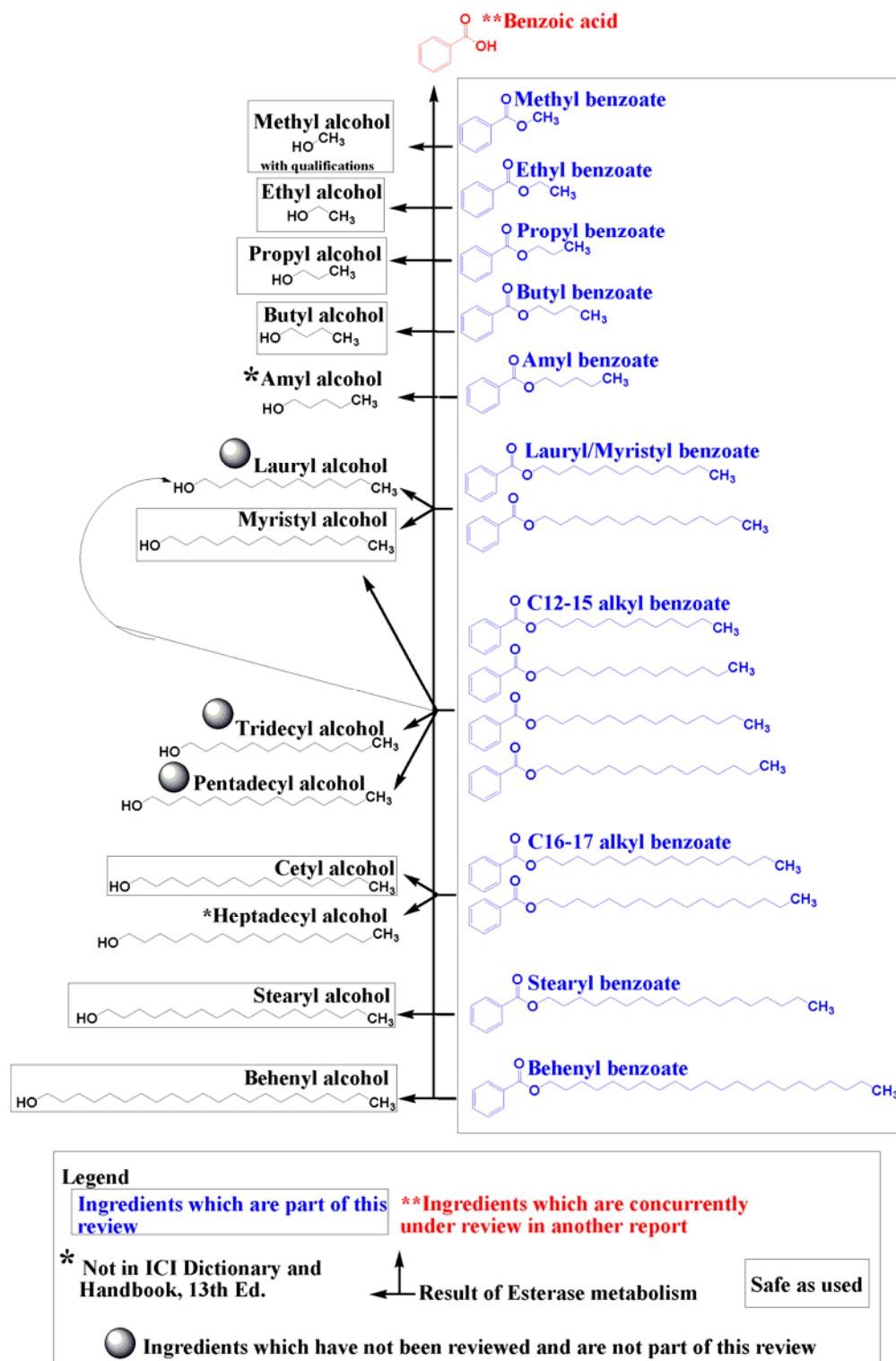


Figure 2. Branched-chain alkyl benzoates: structures, esterase metabolism, and metabolites.

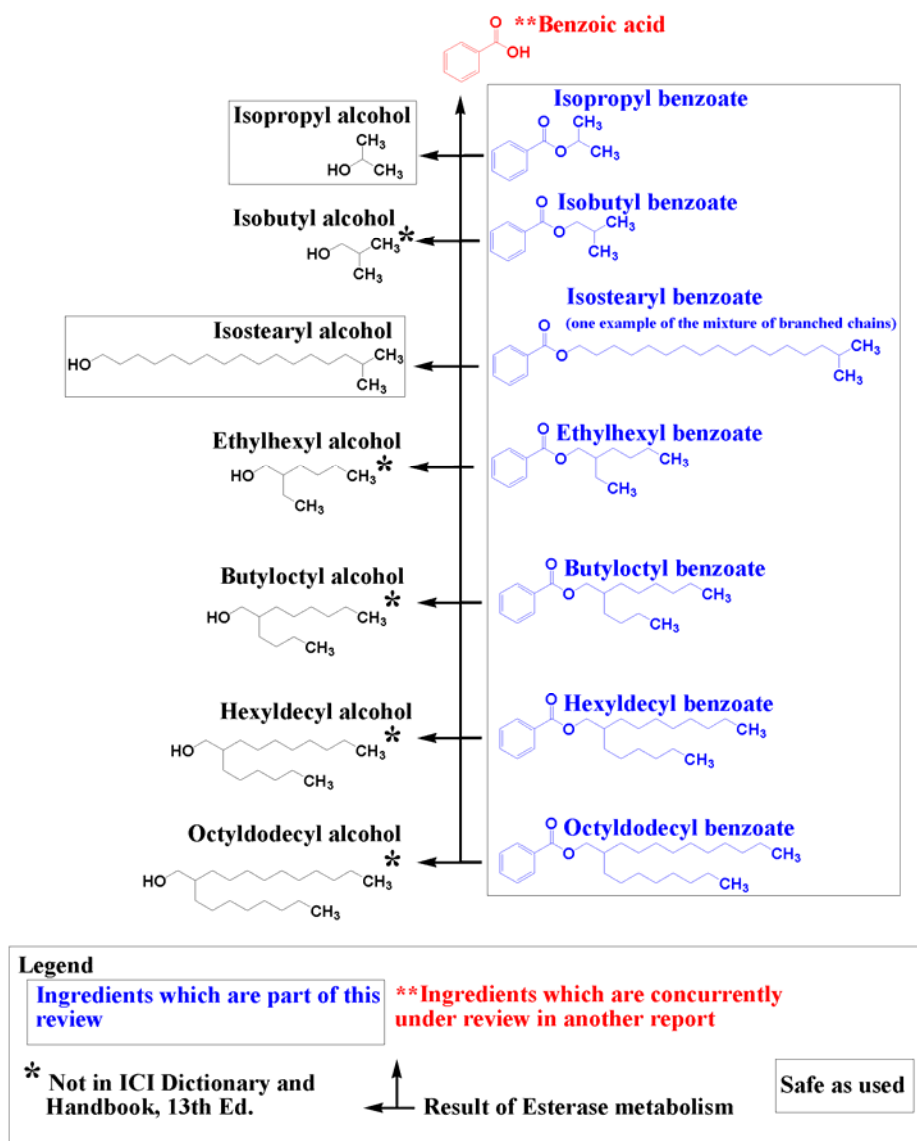


Figure 3. The synthesis of butyl benzoate.



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Memorandum

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

FROM: John Bailey, Ph.D.  1/13/2011
Industry Liaison to the CIR Expert Panel

DATE: January 13, 2011

SUBJECT: Comments on the Tentative Report on the Alkyl Benzoate Ingredients

Abstract - To give the public an opportunity to review it during the 60 day comment period, the abstract should be included in tentative reports.

- p.1 - The statement that "some data" on the report on ethyl alcohol are summarized in this report is not correct. Data on ethyl alcohol are not summarized in this report. If information on ethyl alcohol are not added to the report, the introduction should state that during the review of Alcohol Denat., the CIR Expert Panel considered the safety of cosmetic products containing up to 99% Alcohol Denat. and were not concerned regarding dermal exposure to ethyl alcohol from these products. The potential for exposure to ethyl alcohol from Ethyl Benzoate (maximum use concentration 0.01% reported) is much lower.
- p.2 - Please revise the following sentence. "Recently, a biocatalytic process developed specifically for the manufacture of esters for use in the formulation of cosmetic and personal care ingredients (i.e. for producing cosmetic grade esters) was developed in 2004." With the addition of "was developed in 2004" "Recently" and the first "developed" are no longer needed in this sentence.
- p.3 - In the second paragraph in the Absorption, Distribution, Metabolism and Excretion section, what is meant by "These enzymes"?
- p.3-4 - As penetration of C12-15 Alkyl Benzoate into the dermis was only found when this compound was studied neat, it would be helpful to present reference 35 before reference 34 (application in formulation). Please indicate how C12-15 Alkyl Benzoate was measured in these studies and provide the detection limit.
- p.4 - How long after exposure of rabbits were maximum blood isopropyl alcohol concentrations obtained?
- p.4, 19 - As all substances are cytotoxic at some concentration, please include some indication of concentrations in the summary of the Cytotoxicity section and in the Summary section.
- p.4 - The summary of the Cytotoxicity section states: "C12-15 alkyl benzoate was cytotoxic to human derived epidermal keratinocytes." Where in the body of this section is this information presented?
- p.4 - Are the concentration units (mM) correct for reference 43?

- p.5 - In the summary of the Acute Exposure section, please include the dose of dermally administered Butyl Benzoate that caused diarrhea in rabbits.
- p.5 - In the summary of the Acute Exposure section, please provide the air concentrations of the alcohols that were associated with effects (or indicate that they were near saturation levels if appropriate).
- p.6, 19 - It does not make sense to state that the “dermal LD₅₀ of methyl benzoate was ≥2000 mg/kg for New Zealand white rabbits” when there were no mortalities. If there were no mortalities, the LD₅₀ was >2000 mg/kg.
- p.6 - In reference 56, what happened to mice and calves treated with 100% Ethyl Benzoate? If no information about the 100% Ethyl Benzoate exposure of these species was provided, delete the 100% concentration for these species.
- p.6 - Please revise the following sentence. “Intramuscular administration of ethyl benzoate (100%; 0.5 or 1.0 ml) intramuscularly administered to guinea pigs (n not provided) caused musculo-skeletal [sic], moderate deterioration of leg function and muscle toughness at 1.25 ml/kg.” The route of exposure does not need to be stated twice in this sentence.
- p.6 - Studies in the Isopropyl Benzoate section are cited to reference 63 which is the RIFM summary on Isobutyl Benzoate. The RIFM summary on Isopropyl Benzoate does not appear to be in the reference section. There is no oral LD₅₀ in rats in the RIFM summary of Isopropyl Benzoate given in units of ml/kg.
- p.7 - In the description of the i.p. LD₅₀ values, the units should be placed directly after LD₅₀ (in units of mmol/kg) so they can be presented once. If the units are going to be provided for each species, they also need to be presented after the mouse value.
- p.8 - In the summary of the Repeated Dose Exposure section, please provide the concentration of isobutyl alcohol that was associated with reversible inhibition of responsiveness and the dose of isopropyl alcohol that was the LOAEL.
- p.8 - In the body of the Repeated Dose Exposure section, please describe the clinical signs observed in rats and mice exposed to isopropyl alcohol.
- p.8 - In the rat study on n-pentadecyl alcohol, it states that there was no effect on weight. Does this mean body weight or organ weights (or both)?
- p.9 - In the summary of the Ocular/Mucosal Irritation section, please provide the concentrations of the alcohols that were considered severe ocular irritants.
- p.9 - Please revise the description of the EpiOcular study. The keratinocytes were not incubated in 20% C12-15 Alkyl Benzoate. They were incubated in culture medium to which 10 µl of 2% or 20% C12-15 Alkyl Benzoate was added.
- p.10 - In the summary of the Dermal Irritation section, please revise the following “was not found to be non irritating”.
- p.11 - The bolding and italics for the Alcohols subheading has been picked up for one line of the Isobutyl Benzoate subsection. The Alcohols subheading needs to be put on a separate line.
- p.12 - In the Comedogenicity section, please revise the following: “alcohols were tested for comedogenicity of alcohols”. What concentration of octyl alcohol had strong comedogenicity?
- p.12 - In the summary of the Reproductive and Developmental Toxicity section, please provide the species used in the methyl alcohol studies.
- p.12 - Please provide the route of exposure used in the study of isononyl benzoate.

- p.12 - Did the investigators measure food intake in the rat study of sodium benzoate? A lower mg/kg dose at the highest food concentration is possible if the rats did not like the taste of the food and ate less.
- p.12 - What were the fetal abnormalities observed in the sodium benzoate study in rats (reference 122)? Was it a specific type of abnormality?
- p.12 - Please add the compound tested and the route of exposure to the following sentence. "Results were negative in 2 rat studies up to 500 mg/kg/d."
- p.12 - If the lack of information on ethyl alcohol is not mentioned in the Introduction, information on ethyl alcohol should be added to the Reproductive and Developmental Toxicity section.
- p.13 - Please add the route of exposure used in the rat study of ethylhexyl alcohol (reference 140).
- p.14 (two places), 20 - Members of the CIR Expert Panel have indicated that they do not like the use of "mixed genotoxicity". Please be more precise about the results of the assays, e.g., positive and negative results in genotoxicity assays were reported.
- p.14 - Please add the route of exposure used in the *in vivo* micronucleus assay of isononyl benzoate.
- p.15 - The information available from the mouse carcinogenicity study of benzoic acid is not sufficient to support the following statement in the summary of the Carcinogenicity section. "Benzoic acid (40 mg/kg/d) orally administered to mice increased tumor growth compared to controls." The EPA IRIS summary of this study indicates that tumor incidences were not reported for untreated mice. The information concerning this study in the Carcinogenicity section only discusses tumor numbers not the growth of tumors. The observation of 8 tumors in the first generation and 1 tumor in the third generation is insufficient information to reach a conclusion regarding the carcinogenicity potential of benzoic acid.
- p.15 - The summary of the Carcinogenicity section should also note that the liver tumor promotion activity of ethylhexyl alcohol observed in mice has questionable relevance to humans.
- p.15 - Please provide the ADI (0-5 mg/kg) for benzoic acid in this report. The ADI should be cited to JECFA (see http://www.inchem.org/documents/jecfa/jecval/jec_184.htm) not the CIR report on benzoic acid.
- p.16 - In the summary of the Ocular/Mucosal Irritation section, please provide the concentration of ethylhexyl alcohol that increased nasal and eye irritation and perceived odor intensity.
- p.16 - Please provide the number of subjects that were studied in the patch test of lauryl alcohol (reference 192).
- p.17, reference section - RIFM completed maximization studies of Methyl Benzoate and Ethyl Benzoate not HRIPTs. This has been confirmed with Dr. Anne-Marie Api at RIFM. In the Ethyl Benzoate subsection "methyl benzoate" needs to be changed to "ethyl benzoate". The information on Ethyl Benzoate needs to be cited to the RIFM summary on Ethyl Benzoate (it is currently cited to the summary on Methyl Benzoate, reference 194) which is not yet in the reference section.
- p.17 - Please revise the following: "In clinical 4 studies".
- p.18 - The following sentence is presented twice on this page (once cited to reference 5, the second time cited to references 5 and 189). "Three of 12 male subjects (21-60 years old) exposed to isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) exhibited erythema during induction, but none of the subjects exhibited evidence of sensitization when challenged 2 weeks later."

- p.19 - Other than in the Summary, where in this report is the dermal penetration enhancement information presented? The Summary section should not introduce new information. If dermal penetration enhancement information is added earlier in the report, the information on the alcohols should be presented under the Alcohols subheading.
- p.19 - Please provide the dose of dermally administered Butyl Benzoate that caused diarrhea in rabbits, and the doses (or concentration) of C12-15 Alkyl Benzoate and Isobutyl Benzoate that were not dermally toxic to rabbits.
- p.19 - Please include the concentrations of the benzoates that were either ocular irritants or non- to mild ocular irritants.
- p.19 - Please add the *in vivo* genotoxicity study of isononyl benzoate to the Summary.
- p.19 - Please provide the species tested in the ocular irritation study of a sunscreen containing 2.5% Ethylhexyl Benzoate and the dermal irritation studies of Ethyl Benzoate, Butyl Benzoate, C12-15 Alkyl Benzoate, Isobutyl Benzoate and Ethylhexyl Benzoate.
- p.19-20 - Information about the potential for “benzoates” to cause contact urticaria is not presented earlier in this report. Which benzoate ingredients are associated with this effect? If this information is left in the Summary, it should be presented earlier in the report.
- p.20 - The summary of the reproductive and developmental toxicity study of isononyl benzoate should be moved before the clinical information. Please include the species and the highest dose used in this study.
- p.20 - As some of the compounds were tested in maximization studies, please change “In HRIPTs...” to “In HRIPTs or maximization studies....”
- p.20 - Please include the species used in the phototoxicity study.
- p.20 - As a stand alone paragraph, the following sentence does not make sense. “Dermally applied benzoic acid is also excreted in the urine within 24 h.”
- p.20 - What species and doses were used in the reproductive and developmental toxicity studies of sodium benzoate and benzoic acid?
- p.20 - Please provide the concentrations of methyl alcohol, amyl alcohol and dodecyl alcohol that were cytotoxic.
- p.20 - Please provide the concentrations of aerosolized ethylhexyl alcohol and n-pentadecyl alcohol that were not toxic to rats.
- p.20 - What concentrations of the alcohols were ocular irritants?
- p.20 - What species was used in the developmental study of aerosolized methyl alcohol?
- p.21 - As only C12-15 Alkyl Benzoate was actually tested in dermal penetration studies, it is not accurate to state “Most of the applied long-chain alkyl benzoates appeared to stay in the stratum corneum..”. Perhaps the discussion should focus on the octanol/water partition coefficients and based on those values suggest which compounds should and should not penetrate the skin.
- p.21 - The available carcinogenicity data on benzoic acid are not sufficient to reach a conclusion that this compound is not carcinogenic.
- p.21 - As C12-15 Alkyl Benzoate is used in cosmetic products at concentrations up to 59%, please delete “at low levels” from the following sentence. “When used at low levels in cosmetic formulations, alkyl benzoates are not expected to result in any cytotoxicity.”
- p.21 - In both the discussion and conclusion the limitation “when formulated to be non-irritating” has been added. The CIR Expert Panel did not mention this limitation at the December 2010

meeting, and this limitation is not included in the December 2010 post-meeting announcement. The smaller alkyl benzoate ingredients may be irritating at 100%, but use concentrations of these compounds are much lower. C12-15 Alkyl Benzoate at 100% was not irritating in animal and human studies.

- p.21 - The following paragraph should be deleted. "The Panel considered that certain of the alcohol components may be sourced from plant material or animal material. The extensive processing, however, to obtain the component from plant or animal material and subsequent chemical reaction to from alkyl benzoates would preclude any presence of residual heavy metals, pesticides, or infectious agents." It is not appropriate to state that these ingredients will not contain heavy metals, pesticides or infectious agents. Highly processed substances sourced from plant or animal materials do not have a greater potential of containing residual heavy metals, pesticides or infectious agents than substances with synthetic sources.
- p.23, Table 1 - Please provide a reference for this table.
- p.25, Table 2 - As C12-, C13-, C14- and C15 Alkyl Benzoate are components of C12-15 Alkyl Benzoate, it is not appropriate to call them "Not Ingredients". Rather than presenting these values separately, please put a footnote on the Log K_{ow} of C12-15 Alkyl Benzoate and provide the Log K_{ow} values of the individual components in a footnote at the end of the table.
- p.26, Table 3 - Please change "Infant" to "Baby" to be consistent with the FDA product categories.
- p.28, Table 4 - In the footnote, please make it clear that the level of 1% benzoate is in food.
- p.28, Table 5 - Please define SCE and ABS in a footnote to this table.
- p.29, Table 6 - In the Reference column, the following needs to be revised: "Clinical Research Lab Inc. 2010 16 page 19"