PINK BOOK 2

Methyl Acetate

CIR EXPERT PANEL MEETING
JUNE 28-29, 2010

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Bart Heldreth Ph.D., Chemist

Date: June 28, 2010

Subject: Draft Tentative Report of Methyl Acetate, simple acetate esters and relevant metabolites as used in cosmetics.

This review includes Methyl Acetate and the following acetate esters and relevant metabolites: Propyl Acetate, Isopropyl Acetate, *t*-Butyl Acetate, Isobutyl Acetate, Butoxyethyl Acetate, Nonyl Acetate, Myristyl Acetate, Cetyl Acetate, Stearyl Acetate, Isostearyl Acetate, Acetic Acid, Sodium Acetate, Potassium Acetate, Magnesium Acetate, Calcium Acetate, Zinc Acetate, Propyl Alcohol, and Isopropyl Alcohol.

At the April 2010 meeting, the Panel agreed that the relevant metabolites (Acetic Acid, Sodium Acetate, Potassium Acetate, Magnesium Acetate, Calcium Acetate, and Zinc Acetate) which also are cosmetic ingredients in their own right, should be incorporated into this report.

Nonetheless, the Panel concluded that additional data were needed and issued an insufficient data announcement for HRIPT data for Cetyl Acetate at the highest concentration of use (lipstick). Industry identified an unpublished human insult patch study of a lipstick formulation containing 12.6% Cetyl Acetate (and commented that 12.6% was the actual highest use concentration of cetyl acetate in a lipstick, instead of 17%).

Upon reviewing the data in the report, evaluating the newly available unpublished studies and assessing the newly added ingredients, the Panel should determine the conclusion to be issued in a tentative report. If the data now are sufficient, the Panel should develop the appropriate conclusion and rationale. If the data are insufficient, the Panel should issue a tentative report with an insufficient data conclusion and describe the needed data.

The URL for this meeting's web page is http://www.cir-safety.org/jun10.shtml.

This book contains everything you need to review.

In the administrative tab - this memo, the flow chart, the review history, and search strategy.

In the transcript tab - transcript excerpt.

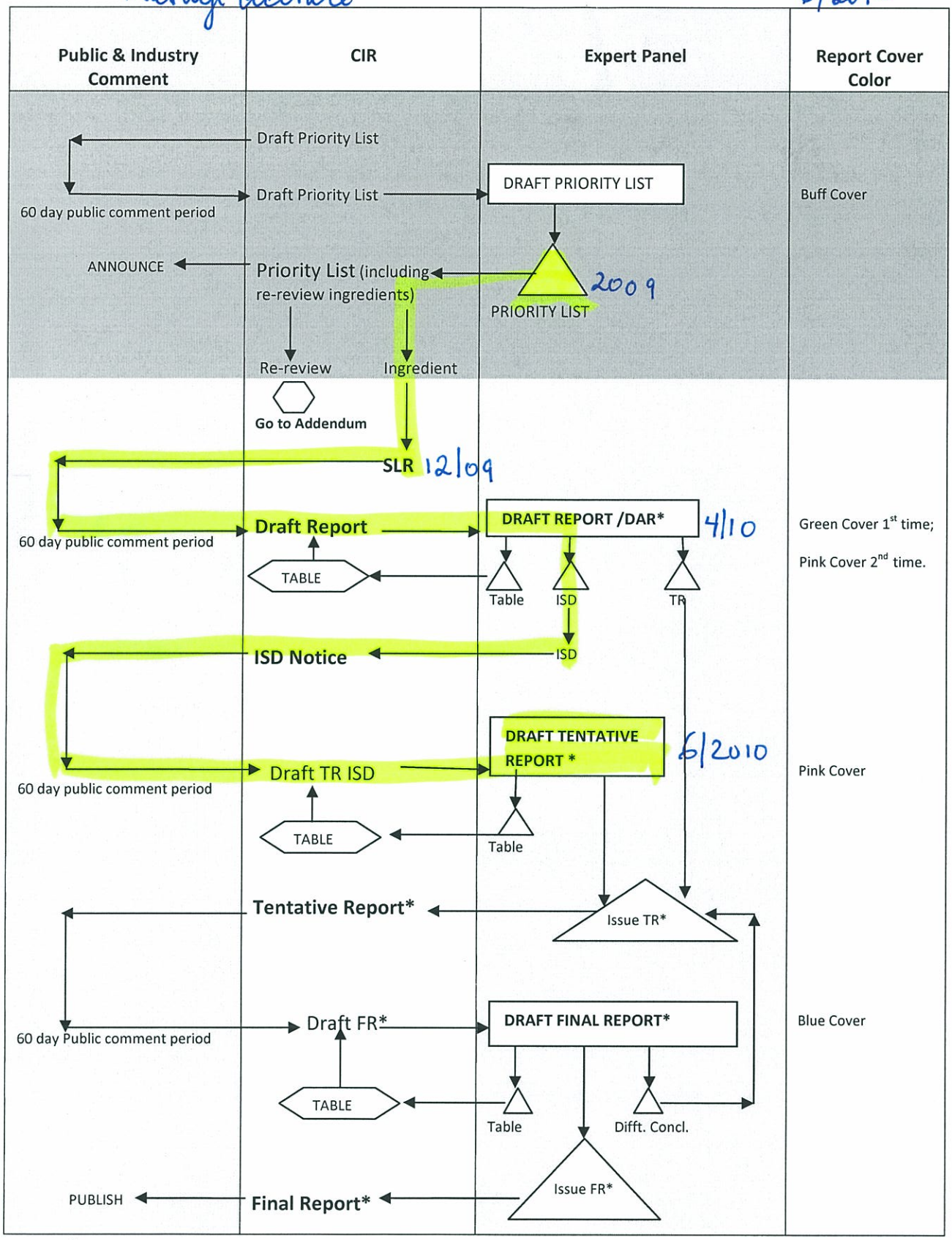
In the report tab – draft report

In the data tab - industry's newly submitted data.

All of the materil also is included as a .pdf - pink book 2 - at the url above.

SAFETY ASSESSMENT FLOW CHART

Methyl Acetate 6/2010



* For ingredient groups originating as Re-Reviews, add word "Amended" before Report; (DAR: Draft Amended Report).

△ Expert Panel Decision

▭ Document for Panel Review

CIR Expert Panel History with Methyl Acetate

2009 – Methyl Acetate was selected for review.

December 2009 - CIR issued a Scientific Literature Review.

Draft Report April 2010 - The draft report was brought before the Expert Panel, with the addition of Acetic Acid and the metal salt ingredients. The Panel decided to request a draft report. The Panel stated that additional data are needed, specifically an HRIPT of Cetyl Acetate at the highest concentration of use (reportedly 17% at the time of the panel meeting) to address the issue of sensitization.

The industry has since provided an HRIPT of Cetyl Acetate at 12.6% in a lipstick formulation, and commented that 12.6% is the actual highest use concentration in a lipstick, not 17%.

In addition, industry should confirm current practices regarding limiting the levels of propylene oxide impurities to less than detectable amounts and CIR staff should include language in the discussion section regarding the ability of these ingredients to enhance dermal penetration of other chemicals.

Ingredient Managers: Angela Howard & Bart Heldreth
Dates: 9/1/2009-2/28/2010

Ingredient Name(s):	CAS RN	Ingredient Name(s):	CAS RN	Ingredient Name(s):	CAS RN	Ingredient Name(s):	CAS RN	Ingredient Name(s):	CAS RN
Methyl Acetate	79-20-9	Isobutyl Acetate	110-19-0	Stearyl Acetate	822-23-1	Isopropyl Alcohol	67-63-0	Potassium Acetate	127-08-2
Butoxyethyl Acetate	112-07-2	Isopropyl Acetate	108-21-4	Myristyl Acetate	638-59-5			Magenesium Acetate	142-72-3
t-Butyl Acetate	540-88-5	Isostearyl Acetate	NL	Nonyl Acetate	143-13-5	Acetic Acid	64-19-7	Calcium Acetate	62-54-4
Cetyl Acetate	629-70-9	Propyl Acetate	109-60-4	Propyl Alcohol	71-23-8	Sodium Acetate	127-09-3	Zinc Acetate	557-34-6

	Checklist	Database	Search Terms	Date	Hits	Notes
	Free	PubMed	A, B	8/18/2009		
			D	11/3/2009		
			E	11/4/2009		
			F	2/5/2010		
	Free	HPDB	A			
	Free	TOXNET	A, F		100-200/chem	HSDB; Chem Idplus, Toxline, CCRIS, CPDB, DART, GENETOX, IRIS, ITER, LactMed, Multi-Database, TRI, Haz-Map, Household Products, TOXMAP
	Free	NTP	A			
	Free search/ Pay retrieval	NTIS				
	Yr license	Merck	A			
		FDA	A			Federal Register Notices
		SCCP	A, B, F			Opinions and EU Directives
		IPCS	A	11/20/2009		
	Password Required	RIFM	F			
	Pay Service	STN	A, F			RTECS, Beilstein
		OECD	A	9/3/2009		SIDS Reports
		HPVIS	A	12/17/2009		High Production Volume Iinformation System

FOIA Submitted
FOIA Results

Search Terms Key

A	CAS No(s)
B	INCI Names
C	Methanol
D	isopropyl alcohol AND toxicity
E	propyl alcohol AND toxicity
F	Acetic Acid and the metal acetate salts via name and CAS Nos. (and CAS files where available)

114th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING AND BREAKOUT SESSION

Washington, D.C.

Monday, April 5, 2010

PARTICIPANTS:

Voting Members:

WILMA F. BERGFELD, M.D., F.A.C.P.
Head of Clinical Research and Dermatopathology
The Cleveland Clinic Foundation

DONALD V. BELSITO, M.D.
Clinical Professor, Medicine (Dermatology)
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RONALD A. HILL, Ph.D.
Associate Professor of Medicinal Chemistry
College of Pharmacy
The University of Louisiana at Monroe

CURTIS D. KLAASSEN, Ph.D.
University Distinguished Professor and Chair
School of Medicine
University of Kansas Medical Center

DANIEL C. LIEBLER, Ph.D.
Director, Jim Ayers Institute for Precancer Detection
Diagnosis Professor of Biochemistry, Pharmacology, and Biomedical Informatics
Vanderbilt University School of Medicine

JAMES G. MARKS, JR., M.D.
Professor of Dermatology
Chairman, Department of Dermatology
Pennsylvania State University College of Medicine

RONALD C. SHANK, Ph.D.
Professor and Chair
Department of Community and Environmental Medicine
University of California, Irvine

THOMAS J. SLAGA, Ph.D.
Department of Pharmacology
University of Texas Health Science Center

PARTICIPANTS (CONT'D):

PAUL W. SNYDER, D.V.M., Ph.D.
School of Veterinary Medicine
Department of Veterinary Patholobiology
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Liaison Members:

JAY ANSELL, Ph.D.
Personal Care Products Council

JOHN BAILEY, Ph.D.
Personal Care Products Council

MARK SILBERGELD
Consumer Federation of America

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LILLIAN C. BECKER, Scientific Analyst

HALYNA P. BRESLAWEC, Ph.D. Deputy Director

CHRISTINA L. BURNETT, Scientific Analyst

MONICE FIUME, Scientific Analyst

KEVIN STONE FRIES, Technical Librarian/Editor

BART HELDRETH, Ph.D., Chemist

WILBUR JOHNSON, Senior Scientific Analyst

Other Attendees:

TRACY GUERRERO
Silicones Environmental, Health, and Safety
Council of North America

STEVE GUTELL
Unilever

PARTICIPANTS (CONT'D):

THOMAS RE
L'Oreal

* * * * *

DR. MARKS: Okay. So, we'll reopen. We'll add the ingredients that we discussed and then we'll see the new data that is presented to us the next time of the inquiry from industry.

Any other comments about the trimoniums? Bart, thank you for taking us through this chemical playground.

Okay. Next review is the methylacrylate group. This is the first --

DR. BERGFELD: Acetate.

DR. MARKS: -- or acetate. I'm sorry. Thank you, Wilma. The methylacetate group and this is the first time we've seen this. And, again, we have some chemistry involved in terms of the metabolism. So, it's the -- the title at least is "Methyl Acetate, Simple Acetate Esters, and Relevant Metabolites," which include acetic acid. The list is on the memo from Bart, and I think the first question, of course, is, do we want to

include all the ingredients which are listed? Including the relevant metabolite.

DR. HILL: So, I was a little bit biased here because I've had some background in butoxyethanol, which certainly colored my opinion as far as some of the add ons.

And I'll just say, philosophically, I had an issue with anchoring in the acetate at all. Because, I mean, acetate esters have probably been made of every alcohol in the chemical abstracts database could possibly be made. And so, it was for me a very odd way of even looking at this whole grouping.

But having said that, there were only a couple that I thought should be removed and then could be pushed forward.

DR. ANDERSEN: Well, the uniqueness of the group is that these are those acetate esters that are used in cosmetics.

DR. HILL: Yes.

DR. ANDERSEN: So --

DR. HILL: I get that.

DR. ANDERSEN: -- but --

DR. HILL: I get that.

DR. ANDERSEN: So which ones flagged for you?

DR. HILL: The butoxy -- the ester of butoxyethyl alcohol, which if you looked at the toxicology should have stood out anyway.

DR. ANDERSEN: But we've reviewed butoxyethanol.

DR. HILL: For cosmetic use, yes. And, yes, I agree based on what was in here that didn't seem to present any red flags, but how long ago was that review? Because --

DR. ANDERSEN: Good question. Did -- but in the way of doing reference --

DR. HILL: Actually, I know this answer, I just have to look at it.

DR. HELDRETH: '96.

DR. HILL: '96?

DR. MARKS: So, other than that one following up on Alan, that's been reviewed and found to be --

DR. HILL: It's even probably okay. It just --

DR. MARKS: Okay.

DR. HILL: I wanted to make sure that we were aware that some of these were non-trivial notes.

DR. ANDERSEN: Yes.

DR. MARKS: Any one of these other ingredients, Ron Hill, Ron Shank, Tom, raise any issues or do you like the way Bart has done this?

DR. SLAGA: No, I mean, the grouping, I thought, was pretty good.

DR. HILL: Well, and also the fact that you're ranging from very small, something like methyl acetate, ethyl acetate is a very different compound than the ester with cetyl alcohol or stearyl alcohol, especially stearyl alcohol. Then we've got isostearyl -- does "isostearyl" mean isostearyl here?

DR. ANDERSEN: Good question.

DR. MARKS: Okay. So, my sense is that the ingredients that are on the memo from Bart and

are listed on page 27 and 28 in the report, all of those are okay to include as -- in this group to review. Is that correct?

Ron Shank?

DR. SHANK: I didn't see the need to have the two alcohols.

DR. MARKS: The propyl and the isopropyl?

DR. SHANK: Right. Just the acetates.

DR. HELDRETH: The plan for the grouping -- and I have to give credit to Angela Howard who started this project -- her inclination was, you know, if we're going to look at these esters, we know that we have esterases in the skin that are going to start chopping these things up right away, we should look at the metabolites. And she suggested isopropyl alcohol and propyl alcohol as metabolites. And that sparked my interest because the -- esterase doesn't just destroy the rest of the molecule. And then I added in the acetic acid, and of course the salts because it's going to basically get chopped off as an ion here.

So, those alcohols and the sodium or potassium, magnesium, calcium, zinc acetate, or acetic acid itself were originally just added in as metabolites to better understand the potential toxicity of the acetates themselves. But if we're going to go to all the trouble of looking at these things for their toxicity, why not toss them in as ingredients? That was the idea behind it.

DR. SHANK: And then why just those two alcohols and not the others? Have we not reviewed propanol and isopropanol?

DR. HELDRETH: If we look at page 26, there's a figure that I put together. Those things that are boxed in in a rectangular fashion have been reviewed by CIR and found safe as used. Those that are put in an oval -- methyl alcohol being the case here -- actually butoxyethyl alcohol should have been in an oval, that's my mistake -- it's also safe for use with a qualification.

Those alcohols with an asterisk, specifically isobutyl alcohol and nonyl alcohol,

are not even in the dictionary, let alone have any uses that are known for them. So those ones are not brought up. The only two alcohols that were either never reviewed and are also in the dictionary and have some sort of use are propyl alcohol and isobutyl alcohol, and that's why I suggested to include those two.

DR. SHANK: Okay, thank you.

DR. HELDRETH: Right, correct.

DR. HILL: Well, but the catch to that rationale is is that if you -- if you give isobutyl acetate, you are going to generate isobutanol and you do need to know about the toxicology of isobutanol. And if it hasn't been reviewed, then that's got to be in there.

SPEAKER: (inaudible)

DR. HILL: It doesn't matter.

DR. ANDERSEN: But the exposure --

DR. HILL: If you're exposed to it, then you've got to know about it.

DR. HELDRETH: Those two alcohols, even though we're not reviewing them as ingredients,

they were searched. And there is data in here for --

DR. HILL: Right, right.

DR. HELDRETH: -- those things there. But they're not an ingredient, so they're not really in the table.

DR. HILL: In the table --

DR. HELDRETH: But they're backup info.

DR. HILL: Yeah, yeah.

DR. MARKS: Okay. So getting back now, Ron is --

DR. HILL: I get it, I'm sorry. I get it.

DR. MARKS: Ron Shank, does that -- then do you want to include the propyl and the isopropyl alcohol as listed? So, the ingredients it sounds like we've arrived at the ingredients that Bart used, and the rationale is good and -- so, we would start with those ingredients. And now we need to know, since this is the first time we've seen this, what data needs do we have as far as safety?

DR. ANDERSEN: If any, he said, hopefully.

DR. SLAGA: Based on past reviews on looking at your table here, that 20 page -- 26. And what's in here, to me we have sufficient data that we -- that are no concern.

DR. BERGFELD: I mean, I think that the skin?

DR. MARKS: Yeah, I'm looking at the sensitization. We have cetyl acetate, which had 277 uses. We have an HRIPT which it's safe, so again, that's reassuring.

If I use that as the lead and this kind of brought up, again, Lillian, the idea on page 36 where we have the product category and there are a number of products reported by the EWG. So, if we don't use the EWG for acetic acid, sodium acetate, potassium, et cetera -- actually, potassium and magnesium didn't have any uses. But we have some uses here which didn't occur from what I gather reported to the FDA. Is that correct?

DR. BRESLAWEC: We added these late in

the process. And so industry has not yet had a chance to provide us the --

DR. MARKS: Oh, okay --

DR. BRESLAWEC: -- use data.

DR. MARKS: But out of -- again, Halyna, what we discussed earlier, are we going to leave this stand as EWG or should we just table it? I can see in the future where our only source might be EWG. Will that appear in a table like this?

DR. BRESLAWEC: Can I give you some insight on how and when we use data other than VCRP data? We don't routinely go out and look at EWG data or data from Canada. When we don't have VCRP data or when there's some reason to believe that because it's a voluntary system we're not getting a full description of the actual uses, then we go to EWG, we request the data from Canada, and we use that data to further explore the uses.

So, this was such a case where we didn't have industry concentration of use or VCRP data, so we went and we looked elsewhere.

DR. BERGFELD: Halyna, but we have had to assume forever that we didn't have absolute accuracy in the volunteer reporting system to the FDA.

DR. BRESLAWEC: Oh, absolutely. I mean --

DR. BERGFELD: Okay. So, you would have to say that you'd have to do those source searches on almost everything. If that be the excuse for it.

DR. BRESLAWEC: I think what we're saying is that we're making an assumption that even though the data are voluntary -- and I think while -- I think we'd all like it to be mandatory reporting, it's not. We're -- if we feel we're getting a reasonable picture from the VCRP data, we go with it. If there are any suggestion from pretty much any source that we're not getting a complete picture, then we'll go elsewhere.

With the PMMA, we heard from EWG that it was being used as a nail cosmetic. It didn't show up on the FDA data. So, we went back to industry

and said, we're getting this suggestion it may be used in this type of a product. And they came back with data that said, yeah. And here's why it's not a problem.

So, we use it to try to get as full a picture as we can when the FDA data doesn't quite do it for us.

DR. MARKS: So, kind of go back -- I'll go back, Wilma, to what you said. My need is sensitization data. And I would use cetyl acetate as the primary one because it has so many uses. It has a high concentration in the lips, and I don't see any sensitization data on this A chart. And it was the HRIPT that I would want to see.

DR. SHANK: The -- on page 13, under Sensitization, there's just one sentence about isopropyl acetate, but, in fact, on page 26 in this map there are -- we've already reviewed several of these acetates. So, it looks like we have no information on these acetates, unless you read this report.

Under Rationale, it says we found that

these were CIR panel so that these are -- acetates are safe. But it's not in the -- that should be repeated in the report, or at least summarized under Sensitization. There's a lot more data than this one line.

DR. BRESLAWEC: Dr. Shank, that was an error on our part. The sensitization sentence on page 13 really is based on human data. So that should be summarized in the clinical section.

DR. MARKS: I'm sure there's got to be HRIPT-ing on cetyl acetate. I can't imagine (inaudible).

DR. HELDRETH: Yeah, we have submitted that.

DR. MARKS: Okay. Because I'd feel more comfortable at least having -- with that, which is a lot of use.

So, we need sensitization data. And a perspective in that portion of the report relating it to previous ingredients that we weren't -- we found to be safe from that point of view.

Any other needs?

DR. BERGFELD: I just want to ask a question, a chemical question. When you're looking at allopathic chains, and you look at the long ones and the short ones, it was my understanding the short ones were more reactive in general. Is that correct? Does the -- the one that you're asking for because of use is the longer chain.

DR. HILL: Well, if I read these boxes correctly in this diagram, in the last --

REPORTER: Microphone, sir?

DR. HILL: Yeah, sorry.

REPORTER: (inaudible), can you turn yours off?

DR. HILL: If I read the diagram properly, then we already have evaluations for ethyl acetate and butyl acetate, is that correct? So, if we have ethyl and butyl on -- data on that, which would then be captured in the report -- and then do cetyl, which I think is at the other end in terms of chain lengths -- well, isn't there stearyl? So cetyl is C-12? No. 10? Okay, it's

on here, right? Sorry.

DR. MARKS: It looks like it's 16, maybe. Is that right?

DR. HELDRETH: 16.

DR. HILL: 16. Okay, all right. Then, never mind. Stearyl is two carbons longer.

DR. MARKS: Okay, any other comments? So, in summary, all the ingredients that were proposed --

DR. BERGFELD: What happened --

DR. MARKS: I don't -- yeah, you didn't really get an answer, did you?

DR. BERGFELD: (inaudible)

DR. HILL: So what was the question again? I'm sorry. I'm fatiguing here.

DR. BERGFELD: When you have ingredients that have different chain lengths as you have here, it was my understanding that the lower chains were more -- usually more absorbable, or the absorption was greater. More reactive. Is it true in this, or is that just true of the PEGs?

DR. HILL: I think in terms of

reactivity, what kind of reactivity are you asking?

DR. BERGFELD: Absorption, basically.

DR. HILL: Absorption.

DR. BERGFELD: And possible other activity after absorption.

Because you're asking for a long chain one, which is acetyl acetate, which has -- by Jim's look, it has great use. And I wondered if you wanted to have some of the lower chain ones?

DR. MARKS: I thought the lower chain ones we had reviewed and approved.

DR. BERGFELD: We had?

DR. MARKS: And they've already had a safety assessment.

DR. BERGFELD: So you're thinking that you just, because of use, want this larger one?

DR. MARKS: That's correct. And particularly since in that paragraph as Halyna elucidated, that will become more robust in terms of the previous ingredients that were approved.

DR. HILL: I think the sense is, yes in

terms of being absorbed and going all the way into the system, the smaller ones should go more rapidly. And also their substrates for plain old pseudo-esterases or serum esterases, rather, is what I was trying to say. Whereas if you get into the long chain ones you tend to be looking more at lipases and things that will then process potentially depending on the route of entry in lymph as opposed to bloodstream and so -- there are going to be differences. But I believe those will be captured by the ones that have already been reviewed in picking up this other one. And probably interpolation in this particular case, is not likely to -- I don't feel an issue there.

DR. BERGFELD: Okay.

DR. MARKS: So what I'll do tomorrow is move that we issue an insufficient data announcement and that the needs are more robust sensitization data on these ingredients. And specifically, an HPI -- Human Repeat Insult Patch Test with a lead like cetyl acetate in the context that we have other acetates which have been safe.

DR. ANDERSEN: Okay, Jim can I back you up and Wave is going to screw us again. In the material that we sent out in that second follow up package was the data as Jay correctly flagged it from industry on HRIPT on 11.7 percent cetyl acetate.

So, we got that. Now, let's see what else I'm looking at -- what else --

DR. MARKS: The use --

DR. ANDERSEN: And isopropyl alcohol at 80 percent -- question -- keep hitting the wrong button.

DR. MARKS: So I guess the question is, is that adequate enough since it's used in a 17 percent concentration in lipstick? And we have it safe up to, you said, 11 percent.

DR. ANDERSEN: Yes. So, I think the question from my standpoint is, I'm just trying to see what else I've got here.

Those are the comments. I'm not finding any other data. Let's see, Use, four pieces of unpublished data. Let's see what those are. 1.95

percent isopropyl alcohol, acetate, RIPT.

So, so far nothing of the same magnitude of 17 percent.

DR. HILL: Dr. Bergfeld or -- let's see, I think you're the dermatologist at this table at the moment. Would --

DR. BERGFELD: Oh, no, John is, too.

DR. HILL: Yeah, okay. Sorry. Either of you. Somehow I was ignoring the chair.

SPEAKER: No, that's the chair.

DR. HILL: If there was a lot of incidence out and about of people using lipstick with that high concentration and it was causing problems, do you think that would be picked up well enough by the practice community to?

DR. MARKS: That's where it comes into the expert opinion. And I want to be on the cautious side. One definition of expert opinion is you make the same mistake over and over again with more assurety.

So, even though, you know, there hasn't been an alert out there I still, I think, would

fear -- I would -- I'd probably like to see it at 17 percent so that we could say -- and it's hard for me to believe that that lipstick hasn't had some sort of safety testing that I could say with assurety, yeah, 11 percent is fine. We had the HRIPT for that. But we don't have anything that assures us up to 17 percent.

And I think that's correct, is it not? A lipstick goes up that high?

DR. ANDERSEN: Well, I think that's what's in the use statement.

DR. HILL: Plus, it's on lips, right? So.

DR. MARKS: Somehow I stuck onto that figure. Yeah, it's on the bottom of page 34 under -- if you look at lipstick, there's actually a lot of uses, 101. And the concentration varies from 3 to 17 percent --

DR. ANDERSEN: 3 to 17 percent, yep.

DR. MARKS: So, I think I would still need sensitization data to support the safety of cetyl acetate at that concentration.

DR. ANDERSEN: So we can acknowledge we have some data, but not enough.

DR. HILL: The reason I asked was really for my edification because I'm thinking even they do that 17 percent sensitivity, they -- will they be actually doing it on lips? So, that -- no.

DR. MARKS: No.

SPEAKER: (inaudible)

DR. HILL: Yes.

REPORTER: Microphones, please.

DR. ANSELL: Typically, they would be doing it under more extreme conditions than, you know.

SPEAKER: I don't know what they call extreme.

DR. MARKS: Yeah. Any other comments?

DR. SHANK: Just one. On page 10, poor Bart, you get caught between rock and a hard place on this. Under Subchronic Toxicity, we have a chronic toxicity study.

Now there were certain group that took it out of the chronic toxicity study and said this

is subchronic. But let the toxicologists rule here by convention and definition. A rodent study six months or longer is chronic. So, it should be in the chronic. Some other group said no, but the toxicologists say it's chronic.

DR. MARKS: Any other comments? If not, then tomorrow I'll move that we issue an insufficient data announcement for the methyl acetate group and that we need more sensitization data, particularly with cetyl acetate and HRIPT to confirm the safety of the 17 percent concentration in lipstick.

114th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING

BREAKOUT SESSION

Washington, D.C.

Monday, April 5, 2010

PARTICIPANTS:

Voting Members:

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Department of Veterinary Patholobiology
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Consumer Federation of America

LINDA KATZ, M.D., Ph.D.
Food and Drug Administration

Staff Members:

LILLIAN C. BECKER, Scientific Analyst

HALYNA P. BRESLAWEC, Ph.D. Deputy Director

CHRISTINA L. BURNETT, Scientific Analyst

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MONICE FIUME, Scientific Analyst
CAROL EISENMANN, Ph.D.
KEVIN STONE FRIES, Technical Librarian/Editor
BART HELDRETH, Ph.D., Chemist
WILBUR JOHNSON, Senior Scientific Analyst

* * * * *

DR. BELSITO: Okay. So we're all back and accounted for. Okay.

So the next one is methyl acetate. This is the first time we're looking at the

report. And in 2009 we issued a SLR for the methyl acetate group which includes several other esters that I won't read. And Lillian is trying to incorporate the data industry provided.

DR. BRESLAWEC: No, this is Bart Heldreth's.

DR. BELSITO: Bart. Okay, Bart Heldreth did that. But we figured out that it's an acetate and it's an ester, so it's all going to be acetic acid. And there are a whole bunch of other acetates that we need to add to this list. So we now have -- and then some alcohols. So we now have a slightly more extended report. Again, it's a first look at so what do we need? Is it sufficient or is it insufficient? And if it's insufficient, what are we looking for?

So, again, I thought that the method of manufacturing and impurities -- that wasn't listed here. And then we were told that the metabolism and methyl acetate is the methanol. But the methyl acetate was only used in nail care products. Therefore, I don't know if we need any

restrictions or we need any discussion to talk about what the restrictions were with methanol used to -- whatever you call it for alcohol. But then sensitization and irritation, we really have for cetyl acetate and isopropyl alcohol. And just to point that out. I mean, it's rather limited. We have one acetate and one alcohol. Whether this was adequate for the group. I mean, quite honestly I'm not aware of reports in the literature of any of these chemicals causing problems in terms of sensitization and irritation. Likewise, I'm also not aware of much in terms of any publications on them either that you might be able to really get.

DR. EISENMANN: Except that in the pelargonic acid report the propyl and isopropyl alcohol is used as controls in a number of the (inaudible) studies. So they could use the control data in that.

DR. BELSITO: If you could get that out that would be nice. And I guess my other comments were to ask the other panel members their thoughts

strictly in terms of the genotoxicity and reproductive toxicity. Was it adequate? And also there were comments from the CTFA that came in that looked like they weren't incorporated into the document.

DR. EISENMANN: They were not because they came in after the report was issued.

DR. BELSITO: And I essentially agreed with CTFA's comments.

DR. LIEBLER: Well, I saw the rationale for grouping the low molecular weight and volatile esters from like propanol, isopropanol, butanol together, but I think acidic acid and the simple salts of acidic acid just don't fit here. I mean, chemically obviously they're related, but in terms of use, I actually didn't see any uses for those. In terms of their chemical properties they're actually quite different. I mean, most of these small things -- so basically two families of compounds here. They're the small things that are largely used for their solvent properties, like nail polish removers and things like that.

And then there are the larger esters, longer chain esters that are used as, you know, surfactants or related uses. And then acetic acid and sodium acetate, calcium acetate, whatever, zinc acetate, they don't have listed uses. There are just some references to EWG has some -- we just had that discussion. So I thought that it perhaps might not make sense to include acetic acid and the acetate salts in this report and just focus on the other remaining compounds.

DR. EISENMANN: Are you all right with butoxyethyl acetate in there?

DR. BELSITO: Yeah.

DR. EISENMANN: Okay.

DR. BELSITO: Yeah. That's one of the esters so I'm okay with the esters.

DR. EISENMANN: Just that there's a separate report on butoxyethanol that they've already done.

DR. BELSITO: Oh, I see. Okay.

DR. EISENMANN: I'm just a little --

DR. BELSITO: But not on the acetate

ester.

DR. EISENMANN: Right. Right.

DR. BELSITO: So that fits here, though, I think.

DR. EISENMANN: Okay. Because I thought maybe a little bit more -- if you leave it in, maybe a little bit more information from the original report needs to be put in on metabolism and the effects of that compound.

DR. BELSITO: Well, that addresses one other question about more information about that ester. I didn't catch that, that there was a second report on that.

DR. EISENMANN: But there's no uses of it so it's not terribly important. And there's a limit. That's the other thing is a 10 percent limit on that. But in your re-review there was a 50 percent nail polish remover that you said was okay. So I don't know exactly how the conclusion would be written.

DR. BELSITO: So there are no uses for it?

DR. EISENMANN: The acetate, as far as I know there's not any uses.

DR. BELSITO: Then it's a little hard to interpret because these other things that are high percentage uses, they're basically, you know, wipe offs. You know, nail polish -- I think of these like solvent uses that are not leave-ons.

DR. HELDRETH: The idea behind having the acetic acids down there was originally just a matter of trying to understand how these things break down. Originally Angela had started this report and proposed the idea of having the propyl alcohol and isopropyl alcohol included in there because they are metabolites and they may affect the toxicity of the originating acetates. With the esterase cleavage, it doesn't destroy the other half of the molecule; it just spits it back out. And so the toxicity of the metabolite components I thought might be important. Whether or not they're useful enough to include as ingredients in here, I thought that the data on those was at least something that needed to be

looked at to be understood so we could understand the potential toxicity of the acetates.

DR. LIEBLER: So I would agree if there were significant uses. It just doesn't look like there are. And then you're left with essentially issues of the biological effects of acetate (inaudible) and some of these. And that's something that certainly can be included in data in the discussion, but I don't see that as a major concern.

DR. BELSITO: Okay. So --

SPEAKER: (inaudible) don't want to include?

DR. LIEBLER: I think the only things that I would suggest taking out would be acetic acid and the simple salts of acetic acid -- sodium acetate, calcium acetate, zinc acetate.

DR. BELSITO: So starting on page 24 with acetic acid and going onto page -- well, you'd leave the propyl alcohol.

DR. LIEBLER: Correct.

DR. BELSITO: And isopropyl alcohol at

the end? Or out?

DR. LIEBLER: In.

DR. BELSITO: Okay. So then we're just deleting acetic acid and the salts of acetic acid.

DR. LIEBLER: Correct.

DR. BELSITO: And you're doing that based upon a different function.

DR. LIEBLER: Yeah. Different properties, different function.

DR. SNYDER: So then the title of the report would be -- would there be a better title than (inaudible) acetate?

DR. LIEBLER: I think the title is fine. Because it is not acetate and the esters. Methyl acetate and the esters.

DR. SNYDER: Not alkyl acetates and -- alkyl acetates and related ingredients? Or simple --

DR. LIEBLER: Well, if you wanted to simply it further then you could do that. Yeah. That's fine.

DR. BELSITO: But then we have isopropyl

alcohol and another alcohol in here.

DR. SNYDER: Well, if you look at the introduction (inaudible) prompted that was on the third paragraph where we say that alkyl ingredients -- alkyl ingredients and the corresponding alcohol.

DR. BELSITO: Right. Okay.

DR. SNYDER: So that's why I didn't know whether -- I think the methyl (inaudible) acetate is too narrow do you think? I mean, as far as what we're capturing now?

DR. BRESLAWEC: Well, methyl acetate was the lead ingredient, that's why.

DR. BELSITO: Right.

DR. SNYDER: Right.

DR. BELSITO: But I think we need to -- in this case we need something.

DR. SNYDER: To capture the other ingredient.

DR. BELSITO: To capture -- well, particularly to capture the alcohols because otherwise, I mean, you can't say alkyl acetate

esters (inaudible). Well, I guess you could.

DR. LIEBLER: You could. I mean, you could simply cut methyl acetate off the front and you could use the rest of the title.

DR. BELSITO: Yeah. But you would need to give, I think, some hint of what you're looking at. I guess the question becomes when you state related alcohols and your lead ingredient is methyl acetate, I'm going to think of methanol as being part of that report. So I think, I mean, and I'm okay still with the title, but I think quite early, like maybe in Table 1 when you're introducing them, you know, whichever acetate esters we choose make a comment as to what the parent alcohol is and whether it's been reviewed or not to indicate that we're going to bring in for review the alcohol.

DR. SNYDER: We did that on page 2, (inaudible) bring that in that we did review methyl alcohol.

DR. BELSITO: I understand, but I think --

SPEAKER: (inaudible)
DR. BELSITO: Yeah. And that's what its primary use is. But I think it would be nice to have a table that really brings that out in the document.
DR. LIEBLER: There is a reasonable attempt to do that in Figure 2, which is sort of a map that has, you know, color coding ovals and squares to represent agents that are considered in the report, agents that are already reviewed safe as used. I mean, I like the idea of Figure 2 providing sort of a family map here again. It's a nice concept, but the usage of the space might need to change a little bit. But I think that sort of does what you're saying, Don, you know, in a figure rather than in a table. You know, so you've got an oval around methyl alcohol there and then the key to the oval is safe reuse (inaudible) up to 5 percent.
DR. BRESLAWEC: And butoxyethyl alcohol should also be an oval actually.
DR. BELSITO: Then we have no comments

on the other alcohols?
DR. HELDRETH: If they do they have not been reviewed. And then the other alcohols, like ethyl alcohol and butyl alcohol are boxed in because the CIR panel has determined them safe as used.
DR. BELSITO: Okay.
DR. LIEBLER: Oh, you're looking at a black and white printout, too.
DR. BELSITO: If it's boxed then it's safe as used. If it's ovaled then --
DR. SNYDER: It's been reviewed, but there's a limitation.
DR. BELSITO: If there's nothing --
DR. SNYDER: If it's blue it's in this report. And if it's black -- there's only two that are black that are asterisked. Two alcohols that are asterisked that are not in the dictionary. And that's it.
DR. BELSITO: Okay. So basically what this box is telling us with a lot of interpretation is the only two alcohols that

haven't been reviewed are the ones that we've added to this report. I still think a table would be a hell of a lot easier to see that. You know. And with a reference as to when it was reviewed -- the alcohol was reviewed. I mean, this is nice, but it takes a lot of united -- I didn't catch that going through all this.
SPEAKER: It's (inaudible).
DR. LIEBLER: I'm easy. Table is fine.
DR. HELDRETH: How about both?
DR. BELSITO: Well, I mean, I don't have a problem with both.
DR. BRESLAWEC: You may want to look at Table 1A.
DR. BELSITO: Okay. So, yeah. That's --
DR. LIEBLER: You've got your map people and you've got your table people.
DR. SNYDER: Well, that certainly does -- for me it helps me to see where it falls in and how it's related to other things. And if there's something just kind of hanging out there.

DR. LIEBLER: Yeah. I mean, in general I like the idea of representing these families of compounds on these sort of maps. And I think we -- perhaps if we start doing this more we'll get really good at it and perhaps the interaction between the panel and the staff will help to generate a more standard representation that will end up being very useful in these documents, particularly as they become totally online postings that would be, you know, these maps would be nice to hyperlink to other information about the compounds and so forth. So I think this would be -- this is something we should pursue even if it's not the only way we represent it in this report.
DR. BELSITO: Okay.
DR. SNYDER: So we just recently did myristyl acetate, right? Myristyl alcohol. Oh, no, maybe we didn't.
DR. BELSITO: Okay. So basically we're going to take out Table 1B except for propyl and isopropyl alcohol. Okay. We're going to take out

acetic acid and its salts. Leave everything else in.

DR. HELDRETH: But as far as the background information from acetic acid and the metabolites, that should stay in here, correct?

DR. SNYDER: Right.

DR. BELSITO: Okay. And then in the body of the report we need method of manufacturing and impurities, sensitization and irritation. Again, we just have on the alcohols --

DR. SNYDER: Right. And (inaudible) 2.85 percent on the isopropyl.

DR. BELSITO: Yeah. On the other hand, we have all the other alcohols that have been reviewed that are safe as used. And then so what do we have it breaking down to? We have an alcohol. We have acetic acid. I don't know that we need anything more. What is the -- what is the highest reported concentration of use here?

DR. SNYDER: A hundred.

DR. BELSITO: Yeah, but then nail care products. I think we're probably okay.

Thirty-four percent for isobutyl acetate and then -- this is still nail. When you get off the nail the concentrations of use are quite low.

DR. SNYDER: The 9 percent in body cream.

DR. BELSITO: Makeup, blusher are 9 percent for isobutyl acetate.

SPEAKER: Lipstick, 17 on the lipstick.

DR. BELSITO: But, I mean, if you go out and you do a literature search again you're not going to find a lot for any clinical reports of sensitization for these at those concentrations so I'm less concerned about them. So other than for method of manufacturing and impurities, what else do we need?

DR. LIEBLER: I don't think so. I had a couple of other comments.

DR. BELSITO: Okay. Go ahead.

DR. LIEBLER: So on page 4 near the bottom there's the boilerplate on the aerosol particles. I'm not sure that's applicable with these because we're really talking about vapor

phase exposures. And there's a similar -- let's see. Is there another one here? On page 5 under General Biology, actually near the bottom, it says not all esterase is hydrolyzed secondary and tertiary alkyl acetates or esterase in the skin (inaudible). I think these generalizations about the esterases and the substrate specificity should probably be avoided unless there's some literature citation put in there. So I'm not sure it's all true. I mean, and the problem is there are a number of esterases and we really don't have a handle on which ones are expressed at which levels in the skin.

DR. BELSITO: So on page 5 you want that paragraph or that sentence stricken from the report or struck from the report?

DR. LIEBLER: Unless you can find some literature citation to support it. Because I think it's just an assertion. Maybe it's true. It sort of sounds reasonable, but I don't -- I don't know that it should be there.

DR. BRESLAWEC: And it's (inaudible).

DR. LIEBLER: Yeah.

DR. KLAASSEN: And I think it's in there a couple of times. I had the same kind of question.

DR. LIEBLER: Then on page 6, under acetic acid, under propyl acetates -- rat strain, sex, number of particle size, nonspecified -- there's no particle size I'm sure; it's just vapor.

SPEAKER: Right.

DR. LIEBLER: And that was it.

DR. BELSITO: Okay. Paul, anything else?

DR. SNYDER: Just on the -- when you do the little italicized summary statements at the beginning of the section, if you could include the concentrations so when you say that it was positive or negative, particularly on irritation, sometimes it's very useful to be able to have an idea of where we're at in that. So if you could just put a little bit more information; not a lot, just a little bit more.

DR. HELDRETH: Will do.
DR. BRESLAWEC: That actually is a comment that will apply to multiple reports.
DR. BELSITO: Other comments? Okay. So I think to summarize, we like method of manufacturing and impurities, but beyond that we're pretty much comfortable with safe as used?
DR. BRESLAWEC: Oh, excuse me. You found the method of manufacturing and impurities inadequate in this report or -- is that your --
DR. BELSITO: I didn't --
DR. EISENMANN: The method to produce what's used in cosmetics is not going to be different from method to produce it in general. So if you find public -- I suspect some of this information is probably on Merck Index. That will probably be sufficient information.
DR. BELSITO: Yeah, because, I mean, it basically says we don't know the method that's used and the impurities will depend upon the method that's used. So I didn't see that there was any information.

DR. EISENMANN: Well, there's now some public -- I have looked on the Eastman website. There's some information on what's in it. And I suspect there's information in the Merck Index.
DR. BELSITO: If we could at least, you know, get something and it would tell us how it was manufactured or how we assumed it was manufactured and what we assume the impurities to be, then when we say safe as used that implies that while the method of manufacturing might debate a little bit -- I mean, I think the biggest concern is what the impurities might be. So.
DR. HELDRETH: I totally get, you know, the idea that they're most likely manufactured by these other methods, but are we comfortable with the "most likely" term? Do we know that they're not manufactured in a different way?
DR. EISENMANN: They are not manufactured any differently for -- especially with Eastman. They listed a whole series of this can be used for X, Y, Z in cosmetics. So they're selling the same material for different

applications. So, yes, I think we can be comfortable that the method of -- general method of manufacturing is enough information rather than calling out to each company that's selling it to the cosmetics industry to try to find out (inaudible).
DR. BELSITO: That's fine. But I think we need something --
DR. EISENMANN: Right.
DR. BELSITO: -- a little bit more definite in the report.
DR. BRESLAWEC: (inaudible)
DR. BELSITO: Okay. Good. Okey-doke.
DR. BAILEY: So safe as used. Get us some definite information on method of manufacturing and what the expected impurities might be. Eliminate acetic acids and the salts. And that's it.
DR. BRESLAWEC: And you're comfortable issuing a tentative report?
DR. BELSITO: Mm-hmm. And in terms of incorporate the CTFA or PCPC comments.

DR. BRESLAWEC: There is one, if you will, that we will not incorporate. This also applies to a couple of others. The structures. We've been asked to provide a reference for the structures. And we've made kind of a categorical decision after some discussion not to provide structures for -- not to provide citations for structures unless there's a reason to. And a reason could be where there's a variation or difference between the structure presented in one dictionary as opposed to the CAS file or something like that. But other than that we will not be routinely providing citations for structures.

114th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING

Washington, D.C.

Tuesday, April 6, 2010

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* * * * *

DR. MARKS: This is the first time we've seen this first draft report. Scientific Literature Review has sent out for the methyl

acetate, simple acetate esters and relevant metabolites back in December. There are actually some interesting chemistry in terms of what's included in here in terms of the metabolites which include acetic acid and alcohols, propyl alcohol, isopropyl alcohol. We moved that we issue an insufficient data announcement, and really what our team was concerned with was sensitization data. If we pick cetyl acetate as a lead ingredient based on its 277 uses and we have an HRIPT indicating it's safe at 11 percent however it's used in lipstick at a concentration of 17 percent, so we would want to confirm that it's safe in that concentration and in that use. Otherwise, we felt the data was sufficient.

DR. BERGFELD: Is there a second or further discussion? Dr. Belsito?

DR. BELSITO: We thought first of all, Dan had recommended that we get rid of acetic acid and the salts because of a different function for those in cosmetic ingredients, that obviously the data for acetic acid needed to stay in the report

it was a metabolite of what we were looking at, but in terms of functional use, they were different. Otherwise we felt they were safe as used. We realized that there was a use concentration for a lipstick higher than the sensitization via HRIPT that we saw, but on the other hand there have been no significant numbers of reports in the literature of the acetates causing problems and we didn't feel that we needed to hold it up for that data.

DR. BERGFELD: Dr. Marks?

DR. MARKS: Have we eliminated ingredients because of different uses? When we have ingredients, they often times have multiple uses. I don't recall eliminating ingredients just because of their use.

DR. BERGFELD: Dr. Liebler?

DR. LIEBLER: I haven't been on the panel long enough to be familiar with the history there, but I think when I read the report, the logic for including the ingredients was largely chemical and reasonable at first glance. Then

when I actually thought about the uses of the small low molecular weight methyl esters, the low molecular weight alcohols like propyl and isopropyl and so forth, I thought that the acetic acid and the acetate salts really don't fit functionally, they're being included for chemical completeness, and then when I looked and there is very little use data on these or very little evidence that these are actually used as ingredients, I felt that the chemical logic was insufficient to keep them in the report so that that was my rationale for saying I'm suggesting that these go away.

DR. BERGFELD: Dr. Bailey?

DR. BAILEY: We could go either way on this one. I think that I would ask the question is acetic acid one of the ingredients that's been excluded from the CIR review? It's a food additive I believe; certainly it's vinegar. We looked up in the database the number of vinegars, the different types, I think there are four or five different types of vinegars that are included

in the dictionary. I can see a logic for including it and I can see a logic for not including it. I think it's probably already covered through some other authoritative review so maybe that's enough if in fact that's the status for it.

DR. BERGFELD: Dr. Hill?

DR. HILL: I'm good either way. My gut reaction was the same as Dr. Liebler's was about that. Particularly the salts don't seem to fit, but if there's reason to keep them in there.

DR. BERGFELD: Dr. Shank?

DR. SHANK: The functions may be different, but the toxicity issue I think if we have acetic acid it's logical to include the salts as well.

DR. BERGFELD: Dr. Slaga?

DR. SLAGA: I agree with Ron.

DR. BERGFELD: Dr. Klaassen?

DR. KLAASSEN: I don't feel strongly, but I think it's more appropriate not to have them in here.

DR. BERGFELD: Dr. Snyder?
DR. SNYDER: I really have nothing further to add. I think it's just kind of finding our way and as we grow these large groups to have these discussions.
DR. BERGFELD: Dr. Belsito?
DR. BELSITO: I would agree I think with Ron in that certainly when we're reviewing the toxicity of these we have to review the toxicity of acetic acid, so even though they have different functions, toxicologically they belong together so that I would be happy keeping them all together.
DR. MARKS: I would add to that, does that mean at some latter point what we delete are we going to have to generate another report to confirm the safety and toxicologic data we have now? I think including them all saves us work in the future, and if you think of it both as a chemical and toxicologic grouping then it does make sense, but Dan, I hear you in terms of uses.
DR. BERGFELD: Dr. Liebler?
DR. LIEBLER: Having heard the comments

of my colleagues, this is why the wisdom of the group prevails and I'm happy to go along with the wisdom of the group.
DR. BERGFELD: We have one other issue and that is the concentration and going out as an insufficient, there's been a motion, but not a second. Do you want to comment again on your motion?
DR. MARKS: I agree with the experience that there have not been alerts either in the literature or in my personal experience. However, I think in this case, I'm not sure you would say 6-percent differences is really that significant, but in line with the kojic acid discussion we just had, I would think industry would have an HRIPT at 17 percent and it would be nice to have that in the report. Again I guess I could go either way also. If the Belsito team doesn't feel that strongly about the sensitization potential, and we see lots of cheilitis and we don't know the reason and I'm sure we don't patch test to this all the time, some of us.

DR. BERGFELD: Dr. Bailey, will you respond?
DR. BAILEY: I'm not so sure. I'd have to check and see. I can't commit without checking. But I think that Dr. Belsito's points are well taken, if there's no reason to believe that there's a safety concern with regard to this, then why not go ahead and proceed with it? It's really up to you guys.
DR. BERGFELD: The other question is can you ask industry for the use tests or HRIPT?
DR. BAILEY: I can ask, yes. I can't guarantee it, but I can certainly ask.
DR. BERGFELD: Dr. Belsito?
DR. BELSITO: This is the first time we're seeing this. I don't have a problem going insufficient and asking for the data at this point and see what we get. Again I'm not concerned. I really felt that we could go safe as used aware of the fact that we didn't have sensitization data at the highest level reported, but I'm find going insufficient at this point.

DR. BERGFELD: So you're seconding the motion?
DR. BELSITO: I'll second it.
DR. BERGFELD: Is there any other discussion? Then I'm going to call for the vote. All those in favor of an insufficient data announcement? Unanimous. Thank you very much. I think that's a good precedent that you just set.

Draft Report

Methyl Acetate, Simple Alkyl Acetate Esters and Metabolites

June 28, 2010

The 2010 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D.

Cosmetic Ingredient Review

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INTRODUCTION

This document presents a summary of the available safety information that pertains to several alkyl acetates and corresponding esterase metabolites, and their use in personal care products/cosmetics.

The ingredients included in this safety assessment are: methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, isostearyl acetate, acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate, zinc acetate, propyl alcohol and isopropyl alcohol.

The alkyl acetate ingredients are esters of acetic acid and the corresponding alcohol, with the shorter chain alkyl acetates (methyl, propyl, isopropyl, t-butyl, isobutyl and butoxyethyl; MW range 74-160 g/mol) functioning in cosmetics as fragrance ingredients and solvents, and the longer chain alkyl acetates (nonyl, myristyl, cetyl, stearyl and isostearyl; MW range 186-312) functioning in cosmetics as skin conditioning agents. These ingredients can be metabolized via hydrolysis, by esterases present in skin, to the parent alcohol and acetic acid (or a salt). (The ability and efficiency of esterases in the skin is often species dependent and may even vary considerably between individuals of the same species.[1]) Esterases found in the skin, such as human acetyl cholinesterase (hAchE), are capable of metabolizing branched substrates, including tertiary esters.[2]

The following ingredients are metabolites of the ingredients in this safety assessment and have been previously reviewed: methanol, *t*-butyl alcohol, butoxyethyl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol and isostearyl alcohol. Citations for the completed reports are provided, however, toxicity information on these previously reviewed ingredients has not been duplicated in this safety assessment, with the exception of excerpts from the clinical sections of each prior report.

Methyl acetate, mainly a nail polish remover ingredient, is metabolized to methyl alcohol. Methyl alcohol is used as a solvent, a denaturant, and a fragrance ingredient. Concentrations of up to 5% are typically used to denature ethyl alcohol. The CIR Expert panel concluded that methyl alcohol is safe for use as a denaturant in ethyl alcohol for cosmetic products. The Panel has not stated that methyl alcohol is safe or unsafe as a solvent.[3] CIR does not review the safety of ingredients used as a fragrance. In addition to the data included in this report regarding methyl alcohol, a substantial amount of information is available in the EPA's external peer review draft toxicological report on methyl alcohol available at http://www.epa.gov/iris.

t-Butyl acetate is metabolized to *t*-butyl alcohol. *t*-Butyl alcohol is used as a solvent, a denaturant, and a fragrance ingredient. Concentrations of up to 0.5% were reported in a 1999 CTFA survey. The CIR Expert panel concluded that *t*-butyl alcohol is safe as used in cosmetic products.[4]

Butoxyethyl acetate is metabolized to butoxyethanol. Butoxyethanol is used as a solvent, a viscosity decreasing agent and a fragrance ingredient. Concentrations of up to 10% were reported in product formulation data from the FDA in the 1989 survey. The CIR Expert panel concluded that butoxyethanol is safe for use in hair and nail cosmetic products at concentrations up to 10%.[5] In a 2002 re-review, a use concentration of 50% in nail polish and enamel removers was reported wherein "it was concluded that the increased use concentration was of little concern because the nail plate is made up of dead tissue, and thus the amount of absorption through the nail would be negligible."

Myristyl acetate is metabolized to myristyl alcohol. Myristyl alcohol is used as an emulsion stabilizer, a fragrance ingredient, a skin conditioning agent, a surfactant, and a viscosity increasing agent. Concentrations up to 5% were reported in product formulation data from the FDA in 1982. The CIR expert panel concluded that myristyl alcohol is safe as a cosmetic ingredient in the present practices of use.[6] In 2005, the panel looked at new data and decided the data was not sufficient to re-open the report. The conclusion in the current report was confirmed.

Cetyl acetate is metabolized to cetyl alcohol. Cetyl alcohol is used as an emulsion stabilizer, a fragrance ingredient, an opacifying agent, a surfactant and a viscosity increasing agent. Concentrations up to 50% were reported in product formulation data from the FDA in 1982. The CIR Expert panel concluded that cetyl alcohol is safe as a cosmetic ingredient in the present practices of use.[6] In 2005, the panel looked at new data and decided the data was not sufficient to re-open the report. The conclusion in the current report was confirmed.

Stearyl acetate is metabolized to stearyl alcohol. Stearyl alcohol is used as an emulsion stabilizer, a fragrance ingredient, a surfactant and a viscosity increasing agent. Concentrations up to 50% were reported in product formulation data from the FDA in 1981. The CIR Expert panel concluded that stearyl alcohol is safe as currently used in cosmetics.[7] In 2006, the panel looked at new data and decided the data was not sufficient to re-open the report. The conclusion in the current report was confirmed.

Isostearyl acetate is metabolized to isostearyl alcohol. Isostearyl alcohol is used as a skin-conditioning agent and a viscosity increasing agent. Concentrations up to 50% were reported in product formulation data from the FDA in 1982. The CIR Expert panel concluded that isostearyl alcohol is safe as a cosmetic ingredient in the present practices of use.[6] In 2005, the panel looked at new data and decided the data was not sufficient to re-open the report. The conclusion in the current report was confirmed.

Acetic acid is a principal metabolite of all of the above alkyl acetates, and in addition to its sodium, potassium, magnesium, calcium and zinc acetate salts, is a cosmetic ingredient and has been included in this safety assessment.

Propyl alcohol and isopropyl alcohol are principal metabolites of propyl acetate and isopropyl acetate, respectively.

Isobutyl alcohol and nonyl alcohol are principal metabolites of isobutyl acetate and nonyl acetate, respectively. They are not currently listed as cosmetic ingredients in the INCI, but available data has been provided for the evaluation of the parent alkyl acetates.

The CIR Expert Panel has also reviewed Ethyl Acetate,[8] Butyl Acetate,[8] Ethyl Alcohol (as "Alcohol Denat." with methyl alcohol),[9] and Butyl Alcohol[10] and concluded that these ingredients are safe in the present practices of use and concentration.

CHEMISTRY

Definition and Structure

The registry numbers, definitions, functions and CIR review history of the ingredients under review are presented in Table 1 and the structures are presented in Figure 1. The technical names for these ingredients are listed in Table 2. A map of how the structures and metabolic pathways of these ingredients are related is presented in Figure 2.

Physical and Chemical Properties

The shorter chain aliphatic esters are colorless and highly volatile liquids. Volatility generally decreases as the molecular mass (chain length) increases.[11] The physical and chemical properties of the acetates are shown in Table 3. Experimental boiling point, density, vapor pressure, solubility, and $\log K_{ow}$ values were available for the shorter alkyl esters while only estimated $\log K_{ow}$ values were available for the longer alkyl esters. The shorter alkyl esters (methyl acetate to butoxyethyl acetate) have $\log K_{ow}$ values ranging from 0.18 – 1.78 (values for isopropyl acetate and butoxyethyl acetate were estimated using EPI Suite v. 4.0) while the longer alkyl esters (nonyl acetate to isostearyl acetate) have estimated $\log K_{ow}$ values > 4.

Acetic acid and the metal acetate salts dissociate readily in water, as expected, and therefore have negative log octanol/water partioning coefficients and high solubilities in water. Propyl alcohol and isopropyl alcohol are volatile liquids. The physical and chemical properties of acetic acid, the acetate salts and alcohols are shown in Table 4.

Manufacture and Production

In general, the alkyl acetates can be produced industrially via esterification of acetic acid.[11] The manufacture of methyl acetate, for example, is traditionally accomplished via a reactive distillation process between acetic acid and methanol.[12] Methanol and ethanol are normally obtained via fermentation of natural sources. However, some sources of

alcohols with chains longer than ethanol are often produced synthetically. An important process for producing C_3- C_{20} 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.[13] However, an industry shift began a couple of years ago towards a green, 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).[14]

Acetic acid is most commonly manufactured by metal (e.g., rhodium or iridium) catalyzed carbonylation of methanol (via addition of carbon monoxide), or oxidation of ethylene (through an acetaldehyde intermediate and in the presence of manganese acetate, cobalt acetate, or copper acetate), also known as the Wacker process.[15]

Impurities

The manufacturing processes of the alkyl esters are typically high yielding (≥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.[11] For example, methyl acetate is available with a minimum of 96% purity, wherein the major contaminants are methanol (≤2.5%) and water (≤1.5%).[16] In the case of isopropyl acetate, which is available at 99.6% purity, the major impurities are isopropanol (≤0.2%), water (≤0.05%), and acetic acid (≤0.005%). [16]

Propyl alcohol and isopropyl alcohol can be obtained as 99.8% pure. [16]

Acetic acid can be obtained as glacial acetic acid (99.85% acetic acid, 0.15% water).[16]

Analytical Methods

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.[11,13,17] No UV spectroscopy was available. However, based on the chemical structures of these ingredients, UV absorption is unlikely to be relevant.

USE

Cosmetic

The Voluntary Cosmetic Registration Program (VCRP) administered by the FDA indicates total number of uses in cosmetic formulations in 2010 for methyl acetate (7), propyl acetate (46), isopropyl acetate (6), isobutyl acetate (4), cetyl acetate (264), stearyl acetate (1), acetic acid (11), sodium acetate (88), calcium acetate (7), zinc acetate (1), propyl alcohol (1)

and isopropyl alcohol (1748) (Table 5).[18] Use information was not available for *t*-butyl acetate, nonyl acetate, or isostearyl acetate.

The main use of methyl acetate is in nail polisher removers. Concentration of use surveys conducted in 2007 and 2009 by the Personal Care Products Council reported use percent ranges for methyl acetate (10-60), propyl acetate (0.005-39), isopropyl acetate (0.5-), *t*-butyl acetate (10), isobutyl acetate (6-45), nonyl acetate (0.0004), cetyl acetate (0.01-17), stearyl acetate (0.02-0.5), isostearyl acetate (0.002-5), propyl alcohol (0.0001-0.5), and isopropyl alcohol (0.002-100).[19,20] Concentration of use survey results for acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate and zinc acetate have not yet been received. Neither use nor concentration information was available for the other ingredients in this safety assessment.

These ester and alcohol ingredients are used in aerosol/spray products, and effects on the lungs that may be induced by aerosolized products containing these ingredients may be of concern when these ingredients are vaporized.

In the EU, methanol is allowed only as a denaturant for ethanol and isopropyl alcohol at a concentration of 5%, calculated as a % ethanol or % isopropyl alcohol.[21] Additionally, the EU limits the amount of zinc acetate in cosmetics to 1% calculated as zinc.

Non-Cosmetic

The following ingredients in this report are permitted for direct addition to food for human consumption for flavoring purposes and are generally recognized as safe (GRAS) according to the USFDA: methyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, nonyl acetate, propyl alcohol, isopropyl alcohol, acetic acid, sodium acetate, potassium acetate, magnesium acetate, and calcium acetate.[22] Zinc acetate is an approved ingredient for OTC skin protectant drug products.

Additionally, esters are used as solvents in paints, lacquers and coatings, and as intermediates in various chemistry processes.[11]

Alcohols are commonly used as solvents and antiseptics.[23]

Isopropyl Alcohol (rubbing alcohol) is an approved ingredient for topical antimicrobial OTC drug products.

Acetic acid is naturally occurring as the acid in apple cider vinegar and other fruit derived products. It, and several of its salts (all in this report except zinc acetate), are commonly used as food additives (e.g., flavor or texture enhancers) and are GRAS by the USFDA.[24]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion (ADME)

Exposure to these ingredients is expected to occur mostly by inhalation and dermal routes, although some oral or ocular exposure could occur depending upon the product types that these ingredients are used in. There are not enough data to organize this section by species or route of exposure, so all data on any ADME study is included under the ingredient heading in the animal and in the human sections.

Low molecular weight esters, in general, readily penetrate the skin and mucous membranes. Acetic acid esters can be metabolized by esterases (present in the respiratory tract, skin, blood and gastrointestinal tract) to the parent alcohol and acetic acid. Acetic acid is oxidized via the citric acid cycle to carbon dioxide and water. The parent alcohols can be oxidized via alcohol dehydrogenases to produce the corresponding aldehyde or ketone. The aldehydes can then further be oxidized via aldehyde dehydrogenases to the corresponding acids.

In general, esters can be hydrolyzed to the parent alcohol and acid.[11] The rate of this reaction can be increased by raising the temperature and decreased by lowering pH. Secondary and tertiary acetates are hydrolyzed more slowly than primary acetates. Enzymatic hydrolysis occurs via enzymes called esterases. These enzymes are present in the respiratory tract, skin, blood and gastrointestinal tract.[25,26]

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.

t-Butyl alcohol is slowly metabolized by alcohol dehydrogenases and is eliminated in urine as a glucuronide conjugate and acetone. *t*-Butyl alcohol is also eliminated in exhaled air as acetone and carbon dioxide.[17,27]

Propyl alcohol is metabolized to propanal and propanoic acid, which can be further metabolized to acetaldehyde and acetic acid.[28]

Isopropyl alcohol is metabolized to acetone and then to acetate, formate and ultimately carbon dioxide.[29] However, the half-life of acetone in humans is 22.5 hours.

Bioavailability following inhalation, dermal or gavage exposure has been examined for acetic acid, propyl acetate, isopropyl acetate, *t*-butyl acetate and isopropyl alcohol in animals and methyl alcohol bioavailability has been examined in humans.

Animal

Acetic Acid

Acetic acid is absorbed from the gastrointestinal tract and through the lungs and is readily, although not completely, metabolically oxidized.[30] As noted above, acetic acid can be metabolized and eliminated as carbon dioxide and water.

Propyl Acetate

Rats (strain/sex/number not specified) were exposed via inhalation to 2,000 ppm (8360 mg/m^3) for 90 min.[31] Propyl acetate was rapidly hydrolyzed to propyl alcohol. During the 90 min exposure period, blood levels of propyl alcohol were between 2.6 and 7.7 fold greater than propyl acetate.

Isopropyl Acetate

Male Sprague-Dawley rats (n=6) were placed in a chamber charged with 2000 ppm isopropyl acetate and allowed to inhale for 90 min.[32] During this time, the concentration in the chamber decreased and the amount of test article lost to the chamber and on the surface of the animal was corrected for. Blood samples were taken at 0, 5, 10, 20, 25, 30, 40, 50, 60 and 90 min. Blood levels of isopropyl alcohol exceeded those of isopropyl acetate at 5 min into the exposure and at each time-point after that. At 90 min, 245 µM isopropyl alcohol and 24 µM isopropyl acetate were measured in the blood.

t-Butyl Acetate

Female Sprague-Dawley rats (n=5) were exposed via a tracheal cannula to 440 ppm (1900 mg/m^3) *t*-butyl acetate in air for 5 h.[33] The concentrations of both the acetate and the alcohol increased continuously in the blood over the course of the exposure. By the end of the exposure, the concentration of *t*-butyl alcohol in the blood (~340 µmol/L) was greater than that of *t*-butyl acetate (285 µmol/L). In a second experiment, female Sprague-Dawley rats (n=5) were exposed via a tracheal cannula to 900 ppm (4275 mg/m^3) *t*-butyl acetate in air for 255 min. A similar pattern was observed with concentrations in the blood at the end of the exposure of approximately 400 and 450 µmol/L blood for *t*-butyl acetate and *t*-butyl alcohol respectively.

Isopropyl Alcohol

Male rabbits (3/group; strain not specified) were treated by different routes of exposure to compare the absorption and metabolism of isopropyl alcohol.[34] Groups 1 and 2 were treated via gavage with the equivalent of 2 and 4 ml/kg absolute isopropyl alcohol, respectively, as a 35% isopropanol/water solution. Groups 3 and 4 were treated via whole-body inhalation for 4 h (towels soaked with isopropyl alcohol were place in the inhalation chamber and replenished at ½ hour intervals to maintained a saturated environment; no exact concentration given), with Group 3 animals receiving an additional dermal exposure in the form of a towel soaked with 70% isopropyl alcohol applied to the animals' chests and Group 4 animals having plastic barriers on their chests and towels prepared the same way as in Group 3 applied on top of the plastic barriers.

The alcohol on the towels was replenished at half hour intervals throughout the duration of the experiment. Blood samples were taken at 0, 1, 2, 3 and 4 h. Samples were analyzed for isopropyl alcohol and the metabolite acetone.

Following gavage exposure to 2 or 4 ml/kg, maximum blood levels of 147 and 282 mg/dl, respectively, of isopropyl alcohol were measured. Concentrations of acetone rose steadily over the 4 h period and were 74 and 73 mg/dl following exposure to 2 or 4 ml/kg, respectively. The authors stated that the maximum levels of isopropyl alcohol observed in this experiment, correlated with inebriation and near coma in the animals. Following inhalation and dermal exposure, the concentration of isopropyl alcohol in the blood continued to rise and was 112 mg/dl at 4 h while the concentration of acetone was 19 at 4 h. Inhalation exposure with a plastic barrier between the soaked towel and the chest resulted in isopropyl alcohol and acetone blood levels of <10 mg/dl.

The researchers concluded that isopropyl alcohol is absorbed by the dermal route but that prolonged dermal exposure (i.e. repeated sponging or soaking for several hours) would be required to produce significant toxicity.

Butoxyethanol

The results of eight studies on the metabolism, distribution, and excretion of Butoxyethanol were presented in the CIR expert panel review of butoxyethanol.[5] These data suggest that butoxyacetic acid is the major metabolite (and toxicant) of butoxyethanol, that the first step of metabolism is mainly by alcohol dehydrogenase in the liver, and that excretion is mainly via urine.

Human

Methanol

Methyl acetate is metabolized to methanol and therefore, data on the effects in humans following inhalation exposure are applicable to this assessment. Metabolism of methyl acetate to methanol proceeds at a rate directly proportional to the exposure level. Methanol is further metabolized to formaldehyde and then to formic acid. The CIR Expert Panel concluded that Formic Acid is safe where used in cosmetic formulations as a pH adjustor with a 64 ppm limit for the free acid.[35] The main toxicological risks in humans are severe metabolic acidosis with increased anion gap, typically following oral exposure resulting in > 100 mg/L of formate in the urine.[36] The acidosis and the formic acid metabolite are believed to play a central role in both the central nervous system toxicity and the ocular toxicity.

A study to determine the formate levels that resulted from exposure of human volunteers to 200 ppm of methanol for 4 h was conducted. Human volunteers (n=27; age 20-55 y) were exposed to 200 ppm methanol (the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit) for 4 h and to water vapor for 4 h in a double-blind, random study.[37] Urine samples were collected at 0, 4 and 8 h and blood samples were collected from the subjects before they entered

the chamber, every 15 min for the first hour, every 30 min from the first to the third hour and at 4 h. Urine and serum samples were analyzed for formate (LOD 0.5 mg/L). Twenty-six of 27 enrolled subjects completed the study (11 females and 15 males). One volunteer withdrew from the study due to blood drawing intolerance. Urine formate data were excluded for one subject due to their consumption of high levels of vitamin C which interfered with the formate assay. The researchers did not find any statistically significant differences in serum or urine formate levels between the two exposure conditions at any time point. At the end of the 4 h methanol exposure, formate concentrations of 14.28 ± 8.90 and 7.14 ± 5.17 mg/L were measured in serum and urine, respectively. Under control conditions, formate concentrations of 12.68 ± 6.43 (p=0.38; n=26) and 6.64 ± 4.26 (p=0.59; n=25) mg/L were measured in serum and urine respectively. After 8 h (4 h of no exposure) the serum concentrations were not statistically different with 12.38 ± 6.53 mg/L under methanol exposure conditions and 12.95 ± 8.01 (P=0.6; n=26) under control conditions. Urine formate concentrations after 8 h were 6.08 ± 3.49 and 5.64 ±3.70 (p=0.6; n=25) in exposed and control conditions, respectively, and were not statistically significantly different.

ANIMAL TOXICOLOGY

With the exception of acetic acid which has an oral LD_{50} of 3.31 g/kg, the oral LD_{50} values, for those ingredients with acute toxicity data, are greater than 5 g/kg. With the exception of butoxyethyl acetate which has a dermal LD_{50} of 1.5 g/kg and acetic acid which has a dermal LD_{50} of 3.36 g/kg, all of the other ingredients with acute dermal toxicity data had LD_{50} values greater than 5 g/kg. Central nervous system depression has been documented in animals exposed to acetic acid and the smaller solvent acetates, and in humans exposed to isopropyl alcohol.

Acute Toxicity

Table 6 provides a summary of the available literature on the acute toxicity and LD_{50}s for ingredients in this assessment.[38-44] An oral LD_{50} of 6.97 ml/kg (6500 mg/kg) was reported in rats for methyl acetate. No inhalation LC_{50} was reported, but exposure to 32000 ppm (96960 mg/m^3) for 4 h caused 6/6 rats to die within 14 days. Oral LD_{50}s of 9370 and 8300 mg/kg were reported in rats and mice respectively for propyl acetate. Isopropyl acetate has a reported oral LD_{50} of 6750 mg/kg while isobutyl acetate has a reported oral LD_{50} of 15.4 ml/kg (13400 mg/kg). The dermal LD_{50} values for propyl, isopropyl and isobutyl acetates are greater than 20 ml/kg (~17400 mg/kg). For butoxyethyl acetate, an oral LD_{50} of 7.46 ml/kg (7000 mg/kg) was reported in rats and a dermal LD_{50} of 1.58 ml/kg (1500 mg/kg) was reported in rabbits. Hemolysis was observed in acutely treated animals. Nonyl acetate has reported oral and dermal LD_{50} values greater than 5000 mg/kg in rats and cetyl acetate has reported oral and dermal LD_{50} values greater than 5000 mg/kg in rats and rabbits respectively.

Narcotic-like effects have been associated with the inhalation of high concentrations of volatile esters (i.e. methyl, propyl, isopropyl, isobutyl, and t-butyl acetates).[45] Skin, eye and upper respiratory irritation are also associated with exposure to the volatile esters.[45]

A cutaneous LD_{50} of greater than 3.2 ml/kg (3360 mg/kg) was reported for 28% acetic acid on guinea pigs.[46] A 5% solution of acetic acid (equivalent to vinegar) resulted in a cutaneous LD_{50} of greater than 20 ml/kg (21000mg/kg). An inhalation LC_{50} of 5620 ppm was reported in mice for acetic acid. In rats, a 4 hour exposure to 16000 ppm killed 1 of six rats. Oral LD_{50}'s of 3.15 ml/kg (3310 mg/kg) and 0.4-3.2 ml/kg (420-3400 mg/kg) were reported in rats for acetic acid.[46,47] An oral LD_{50} of 4280 mg/kg was reported in rats for calcium acetate.[24] An oral LD_{50} of 8610 mg/kg was reported in rats for magnesium acetate.[24] An oral LD_{50} of 3250 mg/kg was reported in rats for potassium acetate.[24] An oral LD_{50} of 3530 mg/kg in rats, an inhalation LC_{50} greater than 30 g/m3 in rats, and a subcutaneous LD_{50} of 3200 mg in mice were observed with sodium acetate. [24]

Additional reports were identified in reference texts that did not provide complete information.[27,30] These data have not been evaluated by CIR and are not included in the table.

SHORT-TERM TOXICITY

Butoxyethyl Acetate

Wistar rats (40 male and female rats divided into groups of 10 males or 10 females) and New Zealand rabbits (4/group) were exposed via inhalation to air-vapor mixtures of butoxyethyl acetate (approximately 400 ppm) 4 hr/day, 5 days/week for 1 month.[43] No effects were observed on body weight gain, as compared to controls. Red blood cell (RBC) counts and hemoglobin decreased slightly in 2 of 4 rabbits after 3 weeks of treatment. Hemoglobinuria and hematuria were observed in the rabbits, but were less pronounced in treated rats. Two rabbits died during the fourth week of treatment and blood filled kidneys and bladders were observed at necropsy in these two animals. No other gross pathological lesions were observed in the other animals killed at either the end of the study or after a 1-week recovery period.

Acetic Acid

Three out of five rats (sex and strain not specified) exposed via inhalation to 1300 µg/l of acetic acid showed slight red staining around the nose, with one animal showing staining around the mouth.[48] Very focal lesions in the respiratory epithelium of the dorsal meatus of level 1 of the nasal cavity in three out of five rats were observed. Acetic acid also increased spleen and kidney weights/damage at 23-31 mg/kg in rats, and induced hyperplasia at 60 mg/kg.[24]

SUBCHRONIC TOXICITY

Acetic Acid

Rats (number, sex and strain not specified) were exposed to 0.01% to 0.25% solutions, via drinking water, of acetic acid (corresponding to 0.2 ml/kg) with no toxic effects over a period of two to four months. However, 0.5% solutions (corresponding to 0.33 ml/kg) immediately affected feed consumption and growth. A maximum toleration level of 30 mM (1.8 g) daily for two weeks was established for rats.[30]

Sodium Acetate

In contrast to the maximum toleration level recited above for acetic acid, sodium acetate was reported to have a maximum toleration level of 80 mM (4.2-4.8 g).[49]

Isobutyl Acetate (-Metabolite: *Isobutyl Alcohol*)

Isobutyl alcohol, the primary metabolite of isobutyl acetate, was evaluated for potential neurotoxicity in Sprague-Dawley rats. Rats (10/sex/group) were exposed via inhalation to isobutyl alcohol vapor concentrations of approximately 0, 770, 3100, or 7700 mg/m^3, for 6 h/day, 5 days/week, for 14 weeks.[17] The functional observational battery was conducted along with endpoints of motor activity, neuropathology and scheduled-controlled operant behavior. A slight reduction in responsiveness to external stimuli was observed in all treated groups during exposure. This effect resolved upon cessation of exposure to isobutyl alcohol.

Isopropyl Alcohol

Fischer 344 rats and CD-1 mice (10/sex/group) were exposed via inhalation to 0, 100, 500, 1500, or 5000 ppm (0, 246, 1230, 3690, or 12,300 mg/m^3) isopropyl alcohol for 6 h/day, 5 days/wk for 13 weeks.[50] To evaluate the neurobehavioral effects of isopropanol exposure, an additional 15 rats/sex were exposed (via inhalation) to 0, 500, 1500, or 5000 ppm (0, 1230, 3690, or 12,300 mg/m3) for 6 h/day, 5 days/wk for 13 weeks. Clinical signs, feed and water consumption, and body weights were recorded throughout the study. At 6 weeks, hematological and clinical chemistry evaluations were performed, and at the end of the study, necropsy, and hematological and clinical chemistry evaluations were performed on 10/rats/sex/group and 10/mice/sex/group.

Ataxia, narcosis, hypoactivity and the lack of a startle reflex were observed during exposure at 5000 ppm. Hypoactivity was observed in animals exposed to 1500 ppm isopropyl alcohol. At 6 weeks, male rats had decreased platelet counts and female rats had decreased red blood cell counts at 1500 ppm. These effects were not observed at the 13-week hematological evaluation. At 13 weeks, no gross lesions were observed. Microscopic examination of control and 5000 ppm

exposed animal tissues showed hyaline droplets within the kidneys of male rats only. The size and frequency of the droplets was increased in the treated group. The authors concluded that the NOAEL for this study was 500 ppm and the LOAEL was 1500 ppm based upon clinical signs and changes in hematology at 6 weeks.

Isopropyl alcohol did not produce any changes to the parameters of the functional observations battery which was conducted at 1, 2, 4, 9 and 13 weeks. Clinical signs observed in mice, during the exposure, included ataxia, narcosis, hypoactivity and lack of a startle reflex at 5000 ppm. Narcosis, ataxia and hypoactivity were observed in animals exposed to 1500 ppm isopropyl alcohol. At 5000 ppm, increased body weight and increased rate of weight gain were observed in female mice. Water consumption was increased in male and female mice. Hemoglobin, hematocrit, and mean corpuscular volume were increased in female mice.

Clinical chemistry changes were also noted in the 5000 ppm female mice group including increased total protein, albumin, globulin, total bilirubin, direct bilirubin and inorganic phosphorus. No clinical chemistry changes were observed in male mice or in the other treated female mice groups. At 13 weeks, no gross lesions were observed and no treatment-related microscopic changes were observed. A 10% and 21% increase in relative liver weight was observed in female mice at 1500 and 5000 ppm, respectively. The authors concluded that the NOAEL for this study was 500 ppm and the LOAEL was 1500 ppm based on clinical signs and increased liver weights.

CHRONIC TOXICITY

Chronic toxicity results are described in the CARCINOGENICITY section.

DERMAL IRRITATION

Acetic acid and the alkyl acetate ingredients have been labeled minor skin irritants in animal studies. Acetic acid, at 10% concentration, has been labeled a minor skin irritant in humans. At high concentrations, acetic acid is a irritant which can cause tissue destruction.[30] Many of the adverse effects of acetic acid, however, may be contributed to its pH reducing character. Accordingly, the metal salts (e.g., sodium acetate) are likely to be less detrimental.

Propyl Acetate

Male and female rabbits (n=4; strain not specified) were tested for primary irritation on intact, abraded skin using the Draize method. Undiluted propyl acetate (0.5 ml) was applied to the skin without occlusion and produced only minor irritation with slight erythema in 1 of 4 animals. No edema was observed 72 h after application.[31]

No irritation was observed in 5 rabbits (sex/strain not specified), following a 24-h non-occluded treatment with 0.01 ml of undiluted propyl acetate (no further experimental details provided).[31]

Erythema and necrosis were observed in rabbits (sex/strain/number not specified) exposed to 20 ml/kg bw (17,756 mg/kg bw) undiluted propyl acetate.[31] Erythema and desquamation were observed in guinea pigs (sex/strain/number not specified) exposed to 10 ml/kg bw (8,880mg/kg bw), undiluted propyl acetate, for 24 h with occlusion. In the guinea pigs, the skin appeared normal after 14 days.

Butoxyethyl Acetate

New Zealand rabbits (6/group/concentration not provided) were tested for primary irritation on intact, abraded skin using the Draize method.[43] Butoxyethyl acetate produced slight erythema (Grade 1) in 4 of 6 rabbits at 24 h. At the 72-h reading, there was no perceptible irritation; the primary irritation index was reportedly 0.17.

Acetic Acid

Glacial acetic acid (equivalent to 95% acetic acid) caused complete destruction of the skin of guinea pigs on 24-hour contact. 28% acetic acid, however, resulted in only moderate irritation after 24-hours.[46] Generally at high concentrations, acetic acid is a irritant which can cause tissue destruction.[51]

Zinc Acetate

The dermal irritancy of six zinc compounds was examined in three animal models. In open patch tests involving five daily applications, aqueous zinc acetate (20%) was severely irritant in rabbit, guinea-pig and mouse tests, inducing epidermal hyperplasia and ulceration. Epidermal irritancy in these studies is related to the interaction of zinc ion with epidermal keratin. The compounds studied were not consistently bacteriostatic in the three species tested.

OCULAR IRRITATION

The metal acetate ingredients have been labeled minor eye irritants in animal studies. Acetic acid (5%) and isopropyl alcohol have been labeled severe ocular irritants in rabbit ocular irritation tests.

Propyl Acetate

Undiluted propyl acetate (0.5 ml) caused minor corneal injury described as Grade 2 on the Draize scale (0-10) in the rabbit eye (n/sex/strain not specified).[31]

Butoxyethyl Acetate

New Zealand rabbits (6/group) were tested for eye irritation using the Draize method.[43] (Standard Draize method - 0.1 ml or 0.1 g solid or semisolid was instilled in the conjunctival sac of one eye for 24 h. Both eyes were examined at 1, 24, 48 and 72 h after treatment.) Butoxyethyl acetate produced slight conjunctival redness and discharge in 2 of 6 rabbits at 24 h. At 48 and 72 h observations, no irritation was observed.

Isopropyl Alcohol

Isopropyl alcohol has been labeled a severe ocular irritant based on rabbit ocular irritation tests.[29]

Acetic Acid

Acetic acid at concentrations greater than 10% caused severe permanent eye injury in rabbits. In contrast, a 5% solution (equivalent to vinegar) caused severe, but reversible (two week recovery), eye injury.[46]

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

For t-butyl acetate, NOAELs for maternal and embryo-fetal developmental toxicity in rats were 800 and 400 mg/kg, respectively. Exposure to 3500 ppm propyl alcohol resulted in significantly different activity measurements as compared to controls. For isopropyl alcohol, NOAELs for maternal and developmental toxicity of 400 mg/kg each were reported in rats. In rabbits, the corresponding NOAEL values were 240 and 480 mg/kg, respectively.

t-Butyl Acetate

Female Sprague-Dawley rats (22/group) were exposed to 0, 400, 800, or 1600 mg/kg/day *t*-butyl acetate via gavage on gestational days (GD) 6 through 19.[52] Dams were monitored for clinical effects, feed consumption and changes in body weight, and the fetuses examined for body weight, sex and visceral and skeletal alterations at GD 20. Two dams died after treatment with 1600 mg/kg. Necropsy findings on these animals included liver hypertrophy, stomach expansion and congestion/hemorrhage of the small intestines. Clinical signs in the 1600 mg/kg group included piloerection, abnormal gait, decreased activity, loss of fur, reddish vaginal discharge, nasal hemorrhage, and coma. There were no deaths and no clinical signs in the 400 and 800 mg/kg groups. A dose-dependent decrease in gestational weight gain was observed during the treatment period, but this was not statistically significant as compared to controls. Feed consumption was significantly decreased on GD 6 and 9 in the 1600 mg/kg treatment group as compared to controls. No effects were observed on maternal reproductive health, including the number of corpora lutea, implantations, fetal deaths, litter size, and gender ratios. Male fetal body weight was significantly decreased in the 1600 mg/kg group as compared to controls. Female fetal body weight was also decreased at this exposure level, but the difference was not statistically significant. An increase in the incidence of skeletal variation and a delay in fetal ossification were observed in the 1600 and 800 mg/kg treatment groups, with the changes in the 800 mg/kg treatment group described as minimal by the authors. No evidence of teratogenicity was observed at any tested exposure level. The authors concluded that the observed developmental effects were due to maternal toxicity and determined NOAEL's for both maternal and embryo-fetal developmental toxicity in rats of 800 and 400 mg/kg, respectively.

Propyl Alcohol

The effects of propyl alcohol on fertility were investigated by exposing male Sprague-Dawley rats (18/group) to 0, 3500 or 7000 ppm (0, 8.61 or 17.2 mg/L) propyl alcohol vapor via inhalation 7 h/day, 7days/week for 62 days, prior to mating with unexposed virgin females.[53] Female Sprague-Dawley rats (15/group) were similarly exposed and mated with

unexposed males. Following parturition, litters were culled to 4/sex and the pups fostered by unexposed dams. The pups were weaned on post natal day (PND) 25 and weighed on PND's 7, 14, 21, 28 and 35. Male rats exposed to 7000 ppm exhibited a decrease in mating success with 2/16 producing a litter (1 male died as a result of a cage fight and 1 male did not mate). Mating success was not affected in 3500 ppm exposed males or in females. Six males from the 7000 ppm group were retained to determine if this effect was reversible. All 6 males successfully mated 15 weeks after exposure. The authors reported that weight gain was not affected in 7000 ppm exposed females (data not shown), but feed intake was decreased in this treatment group. Crooked tails were observed in 2-3 offspring in 2 of 15 litters from the 7000 ppm maternally exposed group. No other effects on female fertility were reported. No significant differences resulted between offspring of the 7000 ppm group and controls on several behavioral toxicology measures including the Ascent test, Rotorod test, Open Field test, activity test, running wheel activity, avoidance conditioning, and operant conditioning. Activity measures were significantly different between offspring of the 3500 ppm exposure group and controls.

Isopropyl Alcohol

Female Sprague-Dawley rats (25/group) were exposed to 0, 400, 800, or 1200 mg/kg/day isopropyl alcohol via gavage on gestational days (GD) 6 through 15.[54] Female New Zealand white rabbits (15/group) were exposed to 0, 120, 240, or 480 mg/kg/day isopropyl alcohol via gavage on GD 6 through 18. Animals were observed for body weight, clinical effects and feed consumption and the fetuses examined for body weight, sex and visceral and skeletal alterations at GD 20 for rats and GD 30 for rabbits. In rats, 2 dams died at the 1200 mg/kg dose and 1 dam died at the 800 mg/kg dose. Maternal gestational weight gain was reduced at the highest dose tested. No other effects were observed on maternal reproductive health. Fetal body weights at the two highest doses were decreased statistically. No evidence of teratogenicity was observed at any dose. In rabbits, four does died at the 480 mg/kg dose. Treatment related clinical signs of toxicity were observed at the 480 mg/kg dose and included, cyanosis, lethargy, labored respiration and diarrhea. No treatment related findings were observed at GD 30. Decreased feed consumption and maternal body weights, at 480 mg/kg, were statistically significant. No other effects were observed on maternal reproductive health. No evidence of teratogenicity was observed in the rabbits at any dose. The authors determined NOAEL's for both maternal and developmental toxicity of 400 mg/kg, each, in rats and 240 and 480 mg/kg, respectively, in rabbits.

Acetic Acid

No effects were observed on nidation or on maternal or fetal survival in mice, rats, and rabbits at doses up 1600 mg/kg bw/day of acetic acid. [24]

Sodium Acetate

No maternal of neonatal effects were observed in mice exposed to 1000 mg/kg of sodium acetate.[24] Sodium acetate was also determined to be nonteratogenic to chick embryos.

GENOTOXICITY

Those alkyl acetates that have been tested in vitro were not mutagenic. Acetic acid was also not mutagenic, when buffered to a physiological pH.

Methyl Acetate, Propyl Acetate, Isopropyl acetate, t-Butyl Acetate, Propyl Alcohol and Isopropyl Alcohol

Methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, propyl alcohol and isopropyl alcohol were not mutagenic in in vitro bacterial and mammalian cell assays.[31,55-61] Isopropyl alcohol was not genotoxic in an in vivo micronuclei assay.[62] Details of these studies are provided in Table 7.

Acetic Acid

Acetic acid was reported to be slightly mutagenic to *E. coli* and mammalian cells, but, a more recent mammalian assay suggests that acetic acid is not mutagenic and that previous results were an aberration due strictly to low pH, and not the identity of the pH reducer.[63,64]

CARCINOGENICITY

For isopropyl alcohol, an inhalation NOAEL for toxic effects of 500 ppm for both rats and mice based on kidney and testicular effects was reported. For t-butyl alcohol, all orally treated females showed nephropathy and a dose-related (up to 650 mg/kg/day) increase in kidney weight, while males also demonstrated increased kidney weights(at 420 mg/kg/day), but not at all doses.

Butoxyethyl Acetate

Wistar rats (40 male and female rats divided into groups of 10 males or 10 females) and New Zealand rabbits (2/sex/group) were exposed via inhalation to 100 ppm butoxyethyl acetate (butylglycol acetate (BGA)) 4 h/day, 5 days/week for 10 months.[43] No effects on body weight gain, as compared to controls, and no hematological changes were observed. Upon necropsy, rabbits exhibited very discrete renal lesions including a few areas of tubular nephritis. Additionally, dilation of Henle's loop and the distal convoluted tubules was observed to a greater degree than in control animals. Treated and control rats also exhibited discrete renal lesions such as tubular enlargement in males and tubular nephrosis in females.

Isopropyl Alcohol

Fischer 344 rats and CD-1 mice (65/rats/sex/group; 55/mice/sex/group) were treated via inhalation with 0, 500, 2500, or 5000 ppm (0, 1230, 6150, or 12,300 mg/m^3) isopropyl alcohol for 6 h/day, 5 days/wk for 104 weeks in rats and 78 weeks in mice.[65] An additional 10/animals/sex/species were treated with these same concentrations of isopropyl alcohol for

6 h/day, 5 days/wk for 72 weeks in rats and 54 weeks in mice and underwent an interim evaluation. Another 10 mice/sex/group were treated according to the paradigm described above for 54 weeks and then allowed to recover before being killed at 78 weeks. Animals were observed and evaluated for body and organ weights, ophthalmology, and clinical and anatomic pathology.

In rats, increased mortality due to chronic renal disease was observed at 5000 ppm (both sexes) and at 2500 ppm (males only). Hypoactivity and lack of startle reflex were observed in 2500 ppm treated rats and hypoactivity, lack of startle reflex and narcosis were observed in 5000 ppm treated rats. With the exception of the ataxia, the clinical signs were transient and ceased when the exposure ended. Increases in body weight, body weight gain, and liver weights were observed in 2500 and 5000 ppm treated rats. Chronic renal disease was exacerbated in rats treated with isopropyl alcohol. Male rats had a concentration related increase in absolute and relative testes weights. At the interim euthanasia (after 72 weeks) male rats treated with 5000 ppm had an increased frequency of testicular seminiferous tubule atrophy upon microscopic evaluation. At the terminal euthanasia (104 weeks), male rats had a concentration dependent increase in the incidence of interstitial (Leydig) cell adenomas of the testes. No other tumor types were increased in rats under these treatment conditions as compared to controls.

In mice, no differences in mortality were observed between control and treated animals. Hypoactivity, lack of a startle reflex, narcosis, ataxia, and prostration were observed in 5000 ppm treated mice. Hypoactivity, lack of startle reflex and narcosis were observed in 2500 ppm treated mice. Increases in body weight, body weight gain, and liver weights were observed in 2500 and 5000 ppm treated mice. Male mice in all treatment groups had a decrease in relative testes weights, and female mice exposed to 5000 ppm isopropyl alcohol exhibited decreases in absolute and relative brain weights. At the terminal euthanasia (78 weeks) an increased incidence of minimal to mild renal tubular proteinosis was observed in males and females in all treatment groups. Male mice exposed to 2500 and 5000 ppm exhibited an increased incidence of dilation of the seminal vesicles. No neoplastic lesions were observed in male or female mice. The authors reported a NOAEL for toxic effects of 500 ppm for both rats and mice based on kidney and testicular effects.

IARC (International Agency for Research on Cancer) has determined that isopropyl alcohol is *not classifiable as to its carcinogenicity to humans* (Group 3).[66]

t-Butyl Acetate (-Metabolite: *t-Butyl Alcohol*)

F-344 rats (n=60/group, males and females) were exposed orally, via drinking water, to *t*-butyl alcohol at various doses for 15 months to 103 weeks. At 420 mg/kg/day in males and 650 mg/kg/day in females there was decreased survival.[67] Additionally, a dose related decrease in body weight gain was observed. All treated females had nephropathy and a dose-related increase in kidney weight. Males also demonstrated kidney weight gain, but not at all doses.[67]

After 24 months of exposure, combined adenoma and carcinoma of the renal tubules was found in 8/50, 13/50, 19/50 and 13/50 of the control, low-, mid-, and high-dose males, respectively.[67]

CLINICAL ASSSESSMENT OF SAFETY

Clinical data from previous CIR reports is interspersed below, and delineated by block quotations, to supplement metabolite profiles. Complete assessments of these metabolites may be found in the cited reports.

ADME

Butoxyethyl Alcohol

> The percutaneous absorption of Butoxyethanol was evaluated using five healthy male volunteers (weights not stated) who had not been exposed to Butoxyethanol in the workplace. Each subject placed four fingers of the left hand into a polyethylene jar (21°C) filled with undiluted Butoxyethanol. Unexposed fingers served as controls. At the conclusion of the 2-h exposure, each subject washed the exposed hand with a mild soap and tap water. There was no evidence of skin irritation; however, exposed fingers appeared wrinkled and somewhat more rigid after exposure. These effects reached a maximum at 2-4 h post exposure and then gradually disappeared. The percutaneous uptake rate of Butoxyethanol into the blood varied from 127 to 1891 pmol. These values corresponded to 7-96 nmol Butoxyethanol/min/cm^2 of exposed area. During the decay phase, the half-time of Butoxyethanol ranged from 0.6 to 4.8 h (geometric mean 1.3 h). A linear regression analysis for all of the experiments suggested that, on the average, 17% of the absorbed dose of Butoxyethanol was excreted in the urine.
>
> Two adult male subjects (between 30 and 45 years old) and one female subject (24 years old) breathed 200 ppm Butoxyethanol during two 4-h periods, separated by a 30-mm lunch. Blood pressure and pulse rate were determined three times, and erythrocyte fragility tests were conducted twice during the day of exposure. Urinalyses for glucose and albumin were conducted during the morning after exposure, and butoxyacetic acid concentrations were determined in 24-h urine samples that were collected at the end of the day of exposure. One male subject and the female subject excreted considerable amounts of butoxyacetic acid, while the other male subject excreted only trace amounts. All three subjects experienced immediate irritation of the nose and throat, followed by ocular irritation and disturbed taste. The female subject, who excreted the largest amount of butoxyacetic acid, reacted most adversely to the exposure. She acquired a headache that lasted for ~24 h.

(Excerpted from CIR final report on butoxyethyl alcohol)[68]

Toxicity

Isopropyl Alcohol

An LD_{lo} of 2-4 ml/kg of isopropyl alcohol has been reported in adults and 6 ml/kg (9 ml/kg 70% isopropyl alcohol) was reported to induce coma in children.[29] Other than the study recited above (in the ADME section) to determine the formate levels that resulted from exposure of human volunteers to 200 ppm of methanol for 4 h, no published studies were identified regarding acute toxicity.

Methyl Alcohol

> Clinical data show that Methyl Alcohol can cause severe metabolic acidosis, blindness, and death: toxicity was manifested earlier and at a lower dose compared to ethyl alcohol, but the comparative fatal

dose was the same for both alcohols. All routes of exposure were toxicologically equivalent, as the alcohol distributed readily and uniformly throughout all tissues and organs. Individual susceptibilities to Methyl Alcohol varied, but typically, the ingestion of 80 to 150 ml of 80% Methyl Alcohol was fatal. Symptoms of Methyl Alcohol intoxication after ingestion were delayed for 12 to 18 hours; afterwards, the symptoms included headache, anorexia, weakness, fatigue, leg cramps, and/or pain and vertigo. Severe gastrointestinal pain, nausea, vomiting, diarrhea, mania, failed vision, and convulsions could occur. Chronic exposure to Methyl Alcohol could cause edema, granular degeneration, and necrosis of heart muscle fibers, as well as fatty degeneration of the heart muscle; sudden cardiac failure was associated with Methyl Alcohol intoxication. The liver and kidneys often had parenchymatous degeneration, and the liver had focal necrosis and fatty infiltration. Severe acidosis was necessary for the development of blindness. Similar symptoms were observed after percutaneous or inhalation exposure to Methyl Alcohol.

(Excerpted from CIR final report on methyl alcohol)[69]

Irritation and Sensitization

Cetyl Acetate

According to unpublished data, a 12.6% lipstick formulation caused no dermal sensitization in humans.[70]

Propyl Acetate

In a human maximization test pre-screen, 2% propyl acetate in petrolatum was applied to the backs of 25 healthy subjects for 48 hours under occlusion. No subject experienced any irritation.[71]

Methyl Acetate

Human maximization tests were carried out with 10% methyl acetate in petrolatum on various panels of volunteers. Application was under occlusion to the same site on the forearms or backs of all subjects for five alternate-day 48-hour periods.[72] Patch sites were pre-treated for 24 hours with 2.5% aqueous sodium lauryl sulfate (SLS) under occlusion. Following a 10 – 14 day rest period, challenge patches were applied under occlusion to fresh sites for 48 hours. Challenge applications were preceded by a 60 minute SLS treatment. Reactions were read at patch removal and again at 24 hours thereafter. The following results were obtained: No sensitization reactions were observed in any of the 25 subjects tested.

Methyl Alcohol

Methyl Alcohol caused primary irritation to the skin; prolonged and repeated contact with Methyl Alcohol resulted in defatting and dermatitis. In one occupational study, 3.2% of 274 metalworkers with dermatitis had positive results to a patch test of 30% Methyl Alcohol. Typical allergic responses observed after contact with alcohols were eczematous eruption and wheal and flare at the exposure sites. Eczema and erythema were reported after the consumption of alcoholic beverages by persons sensitized to ethyl alcohol. Five percent Methyl Alcohol caused a slight positive (+) reaction in a closed patch test for allergic contact dermatitis, and concentrations of 7% and 70% caused (+++) reactions.

(Excerpted from CIR final report on methyl alcohol)[69]

Propyl Alcohol

A cumulative irritation study was conducted involving 20 male subjects, where the relative irritancy of free fatty acids of different chain lengths was evaluated.[73] Equimolar concentrations (0.5 M and 1.0 M) of even- and odd-numbered -

straight chain saturated fatty acids were dissolved in propanol. Each Al-test® patch containing a fatty acid (0.5 M) was applied to the interscapular area of 10 subjects, and, similarly, each fatty acid was applied at a higher concentration (1.0 M) to the remaining 10 subjects. A control patch containing propanol was also applied to each subject. Patches remained in place for 24 h and reactions were scored 30 minutes after patch removal. This procedure was repeated daily for a total of 10 applications. In both groups of 10 subjects, there were no reactions to propanol.

In an irritation study, wherein 116 healthy male subjects (21 to 55 years old) were patch tested with pelargonic acid at concentrations of 5%, 10%, 20%, and 39.9% in propanol, a propanol-treated control patch was used.[74] Dose response curves were developed. Patches (Al-test® discs) were saturated with 0.04 ml of a test solution and applied to the upper back for 48 h. Reactions were scored at 48 h and 96 h post-application. There were no reactions to propanol.

In an another irritation study, wherein 16 volunteers (10 females, 6 males; median age of 29.5 years) were patch tested (closed patches, Finn chambers) with 20% pelargonic acid in propanol (pH of 4.3), propanol was one of the controls used.[75] Patches were applied to the anterolateral surface of both upper arms for 24 h. Reactions were scored at 24, 48, and 96 h post-application according to the following scale: 0 (no reaction) to 3 (strong positive reaction: marked erythema, infiltration, possibly vesicles, bullae, pustules and/or pronounced crusting). There were no reactions to propanol.

A skin irritation study was conducted using 42 healthy, non-atopic male volunteers (mean age = 34 years; skin types: II [20 subjects], III [17 subjects], and IV [5 subjects]).[76] Pelargonic acid was patch-tested (Finn chambers, volar forearm) at the following concentrations (in propanol): 40% (12 subjects), 60% (32 subjects), 70% (32 subjects), and 80% (28 subjects), and propanol was used as a control. Each subject received between 3 and 10 patch tests. The patches remained in place for 48 h, and reactions were scored 1 h later according to the following scale: - (no visible reaction) to 4+ (intense erythema with bullous formation). There were no reactions to propanol.

In an irritation study, wherein 16 healthy subjects (ages not stated) were patch tested with pelargonic acid (20% in propanol), propanol was used as a control.[77] Closed patches (Finn chambers) containing the test substance were applied to the anterolateral surface of both upper arms. The patches were removed at 24 h post-application and reactions were scored at 24 h and 96 h post-application. There were no reactions to propanol.

In study conducted to investigate a possible seasonal variation in the skin response to pelargonic acid during the winter and summer, propanol was used as a control.[78] The study was conducted using 17 healthy volunteers (10 males, 7 females; mean age = 27 years). The test substance was applied (closed patch, Finn chamber) to each arm for 24 h. Reactions were scored at 30 min post-removal. Reactions were not observed at sites treated with propanol, water, or to which an empty chamber was applied.

Isopropyl Alcohol

According to unpublished data on 109 test subjects, neither a 2.85% formulation of isopropyl alcohol nor a 1.95% formulation of isopropyl acetate caused dermal sensitization in humans.[79]

The applicability of fluorescence confocal laser scanning microscopy for in situ imaging of irritant contact dermatitis caused by pelargonic acid using 12 healthy individuals (8 males, 4 males; 18 to 64 years old) was studied.[80] Using Finn chambers (occlusive patches), the flexor side of the right and left forearm was exposed to 60 µl of 10% (w/v) pelargonic acid in isopropanol solution and isopropanol vehicle. Isopropanol was used as a control. The Finn chambers were removed at 24 h post-application and reactions were scored according to the following scale: 0 (no visible reaction) to 4+ (intense erythema with bullous formation). Reactions were not observed at sites treated with isopropanol.

t-Butyl Alcohol

> Methyl Alcohol caused primary irritation to the skin; prolonged and repeated contact with Methyl Alcohol resulted in defatting and dermatitis. In one occupational study, 3.2% of 274 metalworkers with dermatitis had positive results to a patch test of 30% Methyl Alcohol. Typical allergic responses observed after contact with alcohols were eczematous eruption and wheal and flare at the exposure sites. Eczema and erythema were reported after the consumption of alcoholic beverages by persons sensitized to ethyl alcohol. Five percent Methyl Alcohol caused a slight positive (+) reaction in a closed patch test for allergic contact dermatitis, and concentrations of 7% and 70% caused (+++) reactions.

(Excerpted from CIR final report on t-butyl alcohol)[81]

Butoxyethyl Alcohol

> The skin sensitization potential of 10.0% (vol/vol) aqueous Butoxyethanol was evaluated using 214 male and female subjects between 18 and 76 years of age. A total of 201 subjects completed the study; withdrawal from the study was not related to administration of the test substance. Challenge reactions were observed in 14 subjects. Definite erythema, with no edema, was observed in one subject at 72 h and doubtful (barely perceptible erythema, only slightly different from surrounding skin) responses were observed in 13 subjects: 6 subjects at 48 and 72 h, 6 subjects at 72 h, and 1 subject at 48 h. Eleven of the 14 subjects with challenge reactions also had reactions ranging from doubtful to definite erythema, but with no edema, during the induction phase. Additionally, a total of 52 subjects had reactions only during the induction phase; 35 subjects had doubtful reactions and 17 subjects had reactions ranging from doubtful to definite erythema, but with no edema. The authors concluded that there was no evidence of sensitization to 10.0% aqueous Butoxyethanol.

(Excerpted from CIR final report on butoxyethyl alcohol)[68]

Cetyl Alcohol

> A topical tolerance study involving an 11.5% Cetyl Alcohol cream base was conducted with 80 male subjects, ranging in age from 21 to 52 years and in weight from 120 to 220 pounds. The preparations were applied five times daily (every 3 hours) for 10 days. One subject had erythema, folliculitis, and pustule formation (forearm site).
>
> A formulation containing 6.0% Cetyl Alcohol was tested for its skin irritation potential in 20 subjects according to the protocol stated above. The product did not induce skin irritation.
>
> In another study, the skin irritation potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 12 female subjects (18-60 years old). The total irritation score (all panelists) for the 21 applications was 418, indicating mild cumulative irritation.

The skin irritation and sensitization potential of a product containing 8.4% Cetyl Alcohol was evaluated in 110 female subjects. Fourteen days after scoring of the tenth application site, a challenge patch was applied to each subject and removed after 48 h; sites were scored after patch removal. The product did not induce primary irritation or sensitization.

The sensitization potential of a cream containing 3.0% Cetearyl Alcohol was evaluated in 25 subjects (18-25 years old). Following a 10-day non-treatment period, occlusive challenge patches were applied to new sites and removed after 48 h. Sensitization reactions were not observed in any of the subjects.

(Excerpted from CIR final report on cetyl alcohol)[82]

Myristyl Alcohol

A moisturizing lotion containing 0.80% Myristyl Alcohol was applied to the face of each of 53 subjects over a period of 4 weeks. None of the subjects had signs of skin irritation.

In another study, the irritation potential of a moisturizing lotion containing 0.25% Myristyl Alcohol was evaluated in 51 subjects, used daily during a 1-month period. A burning sensation was experienced by 1 of the subjects 1 day after initial use of the product. None of the subjects had signs of skin irritation.

A moisturizing lotion containing 0.25% Myristyl Alcohol was applied to the backs of 229 male and female subjects via occlusive patches for 24 h. The product was reapplied to the same sites following a 24-h non-treatment period and repeated for a total of 10 induction applications. None of the subjects had reactions to the product. The product was considered neither an irritant nor an allergen.

(Excerpted from CIR final report on myristyl alcohol)[82]

Stearyl Alcohol

In 24-hour single insult occlusive patch tests, mild irritation was produced by 100 percent Stearyl Alcohol.

(Excerpted from CIR final report on myristyl alcohol)[83]

Isostearyl Alcohol

The skin irritation potential of lsostearyl Alcohol was evaluated in 19 male and female subjects (18-65 years old) at a concentration of 25.0% in petrolatum. The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05). In three similar studies, three different lipstick products containing 25.0, 27.0, and 28.0% Isostearyl Alcohol, respectively, were tested according to the same protocol. The three products did not induce skin irritation.

The irritation and sensitization potential of Isostearyl Alcohol (25% v/v in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21-60 years old). Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch. Three of 12 subjects had slight erythema during induction, and there was no evidence of sensitization.

The sensitization potential of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was evaluated using 148 male and female subjects. The product was applied via an occlusive patch to the upper arm for a total of nine induction applications (3 times/week for 3 weeks). Each patch remained for 24 h, and sites were scored immediately before subsequent applications. During the challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject. Reactions were scored 48 and 96 h after application. Ten of the twelve subjects with reactions suggestive of sensitization were re-challenged with the product 2 months later. Patches remained for 24 h, and sites were scored at 48 and 96 h post-application. Six subjects had reactions during the re-challenge. Four of the six subjects were then tested with 5.0% Isostearyl Alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge;

all had positive responses. Negative responses were reported when the product (without lsostearyl Alcohol) and 100.0% ethanol each were tested. In a second study, the same product was applied to 60 male and female subjects (same protocol). Five of the subjects had positive responses after the first challenge. One of the five was re-challenged with 5.0% Isostearyl Alcohol in ethanol solution, and a positive reaction was observed.

(Excerpted from CIR final report on isostearyl alcohol)[82]

Acetic Acid

Human volunteers (sex not provided) were tested for acetic acid dermal irritation via an interlaboratory 4-hour patch test.[84,85] At a concentration of 10% acetic acid, 70-94% of volunteers, depending on the laboratory, reported irritation.

Photosensitization

Cetyl Alcohol

The photosensitization potential of a lipstick product containing 4.0% Cetyl Alcohol was evaluated in 52 subjects. The experimental procedure was not stated. Photosensitization reactions were not noted in any of the subjects. In another study, a skin care preparation containing 1.0% Cetyl Alcohol did not induce photosensitization in the 407 subjects tested. The experimental procedure was not stated.

(Excerpted from CIR final report on cetyl alcohol)[82]

Myristyl Alcohol

A moisturizing lotion containing 0.10% Myristyl Alcohol was evaluated for its photosensitization potential in a study involving 52 subjects. The experimental procedure was not stated. The product did not induce photosensitization in any of the subjects.

(Excerpted from CIR final report on myristyl alcohol)[82]\

Case Reports

Butoxyethyl Alcohol

Three employees at a glass manufacturing facility were evaluated for health effects resulting from inhalation of a solvent vapor mixture containing 3-5 ppm Butoxyethanol. The only employee who was asked to complete a medical questionnaire had the following signs and/or symptoms: occasional headaches, sore throat, and soreness and bleeding of the nose. The following signs and/or symptoms were also observed in one of six employees at a label printing company exposed to a solvent vapor mixture con-taming 2 ppm Butoxyethanol: headaches, ocular irritation, dry throat, tightness of the chest, and coughing. In another study involving 14 employees of a can manufacturing plant, the following symptoms were observed after exposure to a vapor mixture containing 0.047-0.185 ppm Butoxyethanol: asthma, transient symptoms of respiratory irritation, and abnormal baseline pulmonary functions. The authors stated that the transient symptoms of respiratory irritation were consistent with the effects of an inhaled amine.

(Excerpted from CIR final report on butoxyethyl alcohol)[68]

t-Butyl Alcohol

A woman who had a positive patch test reaction to ethanol was tested with 100% t-BuOH. The alcohol was applied for 48 h and the site was scored at 3, 24, and 48 h after removal of the test material.

The woman did not react to t-BuOH. Four female patients were tested on the upper back with 1% and 10% t-BuOH in water. The patches were applied for 24 h and reactions were read 24 and 48 h after removal. None of the women had any reaction to t-BuOH.

Edwards and Edwards described a case of allergic contact dermatitis to the t-BuOH component of SD-40 alcohol in a commercial sunscreen preparation. A man who had a widespread, pruritic, red, vesicular eruption of his face, neck, arms, and chest and who had used a variety of sunscreens was patch-tested with sunscreens and with the individual components of the product to which he reacted. A 70% concentration of t-BuOH was applied to the forearms. At 72 h. erythema was observed and at 96 h, vesiculation was observed. No reactions were observed in two controls who also had applied t-BuOH to their forearms.

(Excerpted from CIR final report on t-butyl alcohol)[81]

Stearyl Alcohol

Contact sensitization to Stearyl Alcohol has been reported in 3 individuals: 2 had an urticarial-type reaction, and 1 of these reactions was thought to be due to impurities in the Stearyl Alcohol sample.

(Excerpted from CIR final report on myristyl alcohol)[83]

SUMMARY

The ingredients methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, and isostearyl acetate are alkyl esters that function in cosmetics as fragrance ingredients, solvents and skin conditioning agents. The ingredients acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate and zinc acetate are also included because they represent the acetic metabolite of the above alkyl acetates and they function as one or more of the following agents: pH adjusters, buffering agents viscosity controllers, cosmetic astringents, cosmetic biocides, skin protectants and fragrance ingredients. The ingredients propyl alcohol and isopropyl alcohol are also included because they are metabolites of propyl acetate and isopropyl acetate, respectively and they function in cosmetics as antifoaming agents, fragrance ingredients, solvents and viscosity decreasing agents.

Exposure to these ingredients is expected to occur mostly by the inhalation and dermal routes, although some oral or ocular exposure could occur depending on the types of products that they are used in. Acetic esters in general, readily penetrate the skin and mucous membranes and are metabolized via esterases to the parent alcohol and acetic acid. The alcohols are further metabolized to the corresponding aldehyde or ketone and then to the corresponding acid. The LD_{50} values, for those ingredients in this assessment with acute toxicity data, are greater than 1 g/kg.

Alkyl acetates:

Central nervous system depression and narcotic like effects have been documented in animals for the shorter alkyl chain acetates.[86] The alkyl acetate ingredients have been labeled minor skin and eye irritants in animal studies. Those alkyl acetate ingredients that have been tested have been found negative for mutagenicity, in vitro.

A formulation of 1.95% isopropyl acetate did not cause sensitization in humans in one report. NOAELs for reproductive toxicity were greater than or equal to 400 mg/kg in rats for *t*-butyl acetate.

Ethyl acetate and butyl acetate have been found safe as used by the CIR Expert Panel. In addition, the alcohol metabolites ethyl alcohol, butyl alcohol, *t*-butyl alcohol, butoxyethyl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol and isostearyl alcohol have been found safe as used by the CIR Expert Panel.

Longer chain esters, such as the myristyl, cetyl and stearyl acetate, which have high octanol/water partioning coefficients are less likely to penetrate the skin.

Acetic acid/salts:

Central nervous system depression has been documented in animals for acetic acid. Acetic acid has been labeled a minor skin irritant, at low concentrations, in animal and human studies, and a severe ocular irritant in a rabbit ocular irritation test. The sodium salt of acetic acid has a more than two-fold higher toleration level than the free acid, and acetic acid is not mutagenic when buffered to physiological pH.

The metabolite of acetic acid, formic acid, has been found to be safe as used up to a 64 ppm concentration by the CIR Expert Panel.

Alcohols:

The alcohol metabolites ethyl alcohol, butyl alcohol, *t*-butyl alcohol, butoxyethyl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol and isostearyl alcohol have been found safe as used by the CIR Expert Panel.

Isopropyl alcohol has been labeled a severe ocular irritant in a rabbit ocular irritation test. Isopropyl alcohol was negative in an in vivo micronuclei assay. A formulation of 2.85% isopropyl alcohol did not cause sensitization in humans, in one report. Central nervous system depression behavioral effects have been documented in humans for isopropyl alcohol. Reproductive toxicity NOAEL's for isopropyl alcohol were reported for maternal and developmental toxicity of 400 mg/kg each in rats and 240 and 480 mg/kg in rabbits, respectively. In an inhalation carcinogenicity study of isopropyl alcohol, rats exhibited an exacerbation of chronic renal disease and a concentration dependent increase in interstitial cell adenomas of the testes. Male mice exhibited dilation of the seminal vesicles at 2500 ppm, but no neoplastic lesions were observed.

Exposure to 3500 ppm of *n*-propyl alcohol resulted in significantly different offspring behavioral toxicology measures as compared to controls.

Inhalation exposure to isobutyl alcohol induced a slight reduction in responsiveness to external stimuli in rats.

Long term oral exposure of *t*-butyl alcohol to rats resulted in more combined adenoma and carcinoma of the renal tubules than in controls (13-19/50 versus 8/50).

Discussion

A Scientific Literature Review (SLR) for Methyl Acetate, Propyl Acetate, Isopropyl Acetate, t-Butyl Acetate, Isobutyl Acetate, Butoxyethyl Acetate, Nonyl Acetate, Myristyl Acetate, Cetyl Acetate, Stearyl Acetate, Isostearyl Acetate, Propyl Alcohol, and Isopropyl Alcohol was announced in December 2009. Asdfhqewihwjh;ewuh

Interested parties had 60 days to respond to this formal request for data. Industry identified an unpublished insult patch study of formulations containing Isopropyl Alcohol and Isopropyl Acetate which has been incorporated into this report.

The CIR Expert Panel was informed that similar relevant metabolites (Acetic Acid, Sodium Acetate, Potassium Acetate, Magnesium Acetate, Calcium Acetate, and Zinc Acetate) are also cosmetic ingredients. At the April 2010 meeting, the Panel agreed that the relevant metabolites should be incorporated into this report. The Panel requested that further information on the method of manufacture and the identity, and concentration of, impurities, be identified and incorporated. The CIR Expert Panel noted that while the unpublished data from an HRIPT on isopropyl alcohol (2.85%) and ispropyl acetate (1.95%) was helpful, an HRIPT at the highest concentration of use (17% cetyl acetate in lipstick formulation) would provide greater confidence. The Panel issued an insufficient data announcement and also requested an HRIPT for Cetyl Acetate at the highest concentration of use.

Industry identified an unpublished human insult patch study of a lipstick formulation containing 12.6% Cetyl Acetate (and commented that 12.6% was the actual highest use concentration of cetyl acetate in a lipstick, instead of 17%).

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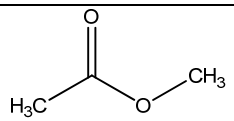
Figure 1. Structures of the ingredients in this assessment.



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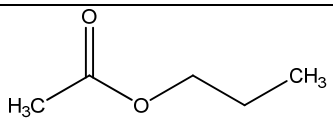

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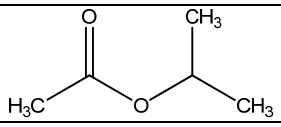
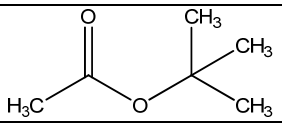


Isopropyl Acetate



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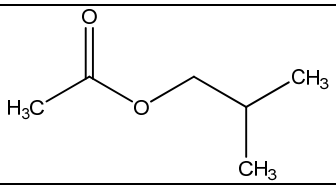

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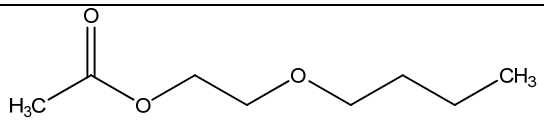

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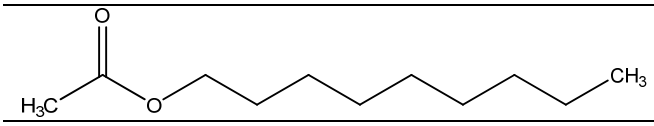

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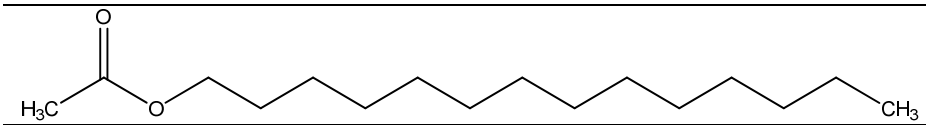

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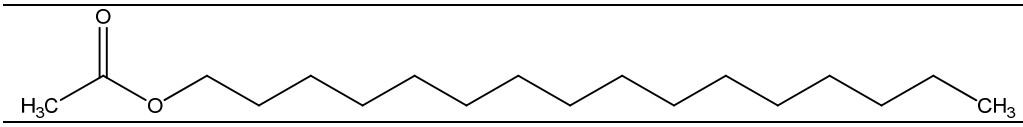

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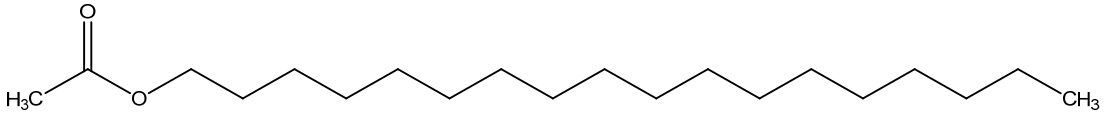

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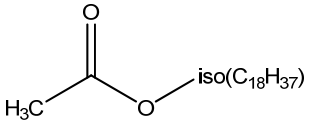


Isostearyl Acetate

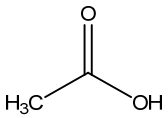
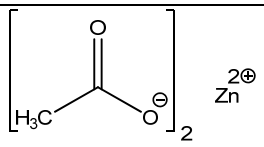
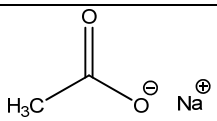
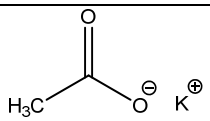
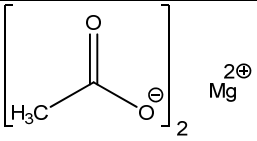
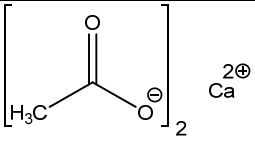
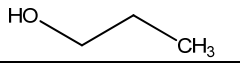
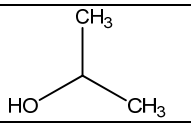
	
Acetic Acid	**Zinc Acetate**
	
Sodium Acetate	**Potassium Acetate**
	
Magnesium Acetate	**Calcium Acetate**
	
Propyl Alcohol	**Isopropyl Alcohol**

Figure 2. Map of the ingredients in this assessment, and associated esterase metabolites.

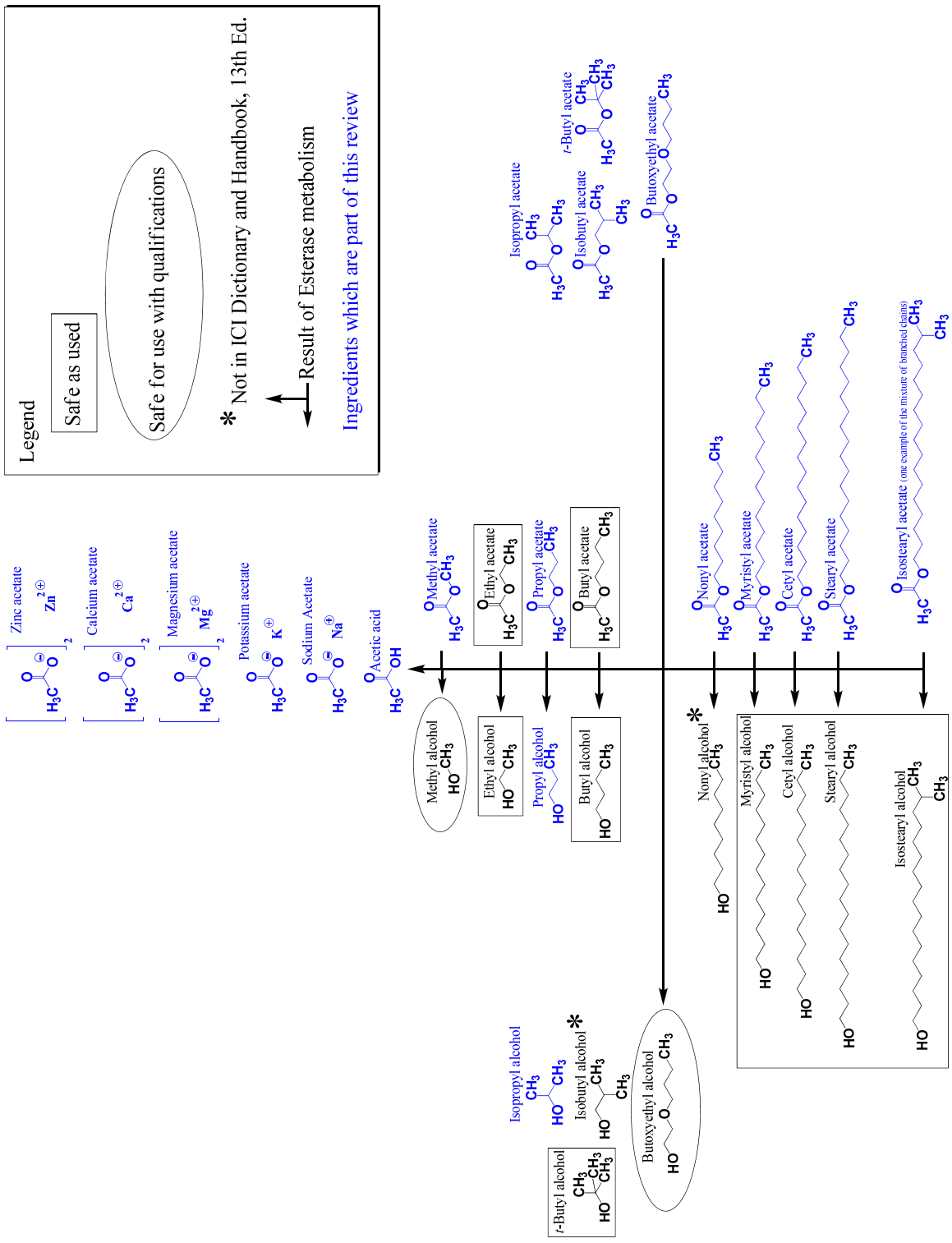


Table 1a. The name, CAS registry number, definition, function and CIR review history of metabolites of alkyl acetate ingredients in this assessment, which are also cosmetic ingredients. [87]

Ingredient	Definition	Function	CIR Review History of Alcohol Metabolite
Methyl Acetate (CAS No. 79-20-9)	The ester of methyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Methyl Alcohol IJT 20 (S1):57-85, 2001 Safe for use as a denaturant in ethyl alcohol
Propyl Acetate (CAS No. 109-60-4)	The ester of propyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Propyl Alcohol Included in this Review
Isopropyl Acetate (CAS No. 108-21-4)	The ester of isopropyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Isopropyl Alcohol Included in this Review
t-Butyl Acetate (CAS No.540-88-5)	Organic compound	Solvents	*t*-Butyl Alcohol IJT 24 (S2):1-20, 2005 Safe as used
Isobutyl Acetate (CAS No. 110-19-0)	The ester of isobutyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Isobutyl Alcohol Not listed as a cosmetic ingredient
Butoxyethyl Acetate (CAS No.112-07-2)	Organic compound	Fragrance Ingredients; Solvents	Butoxyethanol JACT 15(6):62-526, 1996 Safe for use in hair and nail products at concentrations up to 10%
Nonyl Acetate (CAS No. 143-13-5)	The ester of nonyl alcohol and acetic acid	Fragrance Ingredients; Skin-Conditioning Agents-Emollient	Nonyl Alcohol Not listed as a cosmetic ingredient
Myristyl Acetate (CAS No. 638-59-5)	Organic compound	Skin-Conditioning Agents-Emollient	Myristyl Alcohol JACT 7(3):359-413, 1988 Safe as used
Cetyl Acetate (CAS No. 629-70-9)	The ester of cetyl alcohol and acetic acid	Fragrance Ingredients; Skin-Conditioning Agents-Emollient	Cetyl Alcohol JACT 7(3):359-413, 1988 Safe as used
Stearyl Acetate (CAS No. 822-23-1)	The ester of stearyl alcohol and acetic acid	Skin-Conditioning Agents-Emollient	Stearyl Alcohol JACT 4(5):1-29, 1985 Safe as used

Ingredient	Definition	Function	CIR Review History of Alcohol Metabolite
Isostearyl Acetate (CAS No. NL)	The ester of isostearyl alcohol and acetic acid	Skin-Conditioning Agents-Emollient	Isostearyl Alcohol JACT 7(3):359-413, 1988 Safe as used

Table 1b. The name, CAS registry number, definition, function and CIR review history of acid, metal salts, and alcohol ingredients in this assessment.

Ingredient	Definition	Function	CIR Review History of Metabolite
Acetic Acid (CAS No. 64-19-7)	A carboxylic acid	Fragrance Ingredients; pH Adjusters	Formic Acid IJT 16(3) 1997 Safe where used in cosmetic formulations as a pH adjustor with a 64 ppm limit for the free acid
Sodium Acetate (CAS No. 127-09-3)	The sodium salt of acetic acid	Buffering Agents; Fragrance Ingredients	
Potassium Acetate (CAS No. 127-08-2	The potassium salt of acetic acid	Buffering Agents; Fragrance Ingredients	
Magnesium Acetate (CAS No. 142-72-3)	The magnesium salt of acetic acid	Buffering Agents	
Calcium Acetate (CAS No. 62-54-4)	The calcium salt of acetic acid	Fragrance Ingredients (Viscosity Controller – via EWG database)	
Zinc Acetate (CAS No. 557-34-6)	The zinc salt of acetic acid	Cosmetic Astringents; Cosmetic Biocides; Skin Protectants	
Propyl Alcohol (CAS No. 71-23-8)	An alkyl alcohol	Antifoaming Agents; Fragrance Ingredients; Solvents; Viscosity Decreasing Agents	
Isopropyl Alcohol (CAS No. 67-63-0)	An alkyl alcohol	Antifoaming Agents; Fragrance Ingredients; Solvents; Viscosity Decreasing Agents	

Table 2. Nomenclature for the ingredients in this safety assessment.[23,87]

Ingredient Name	Other Technical Names	IUPAC Name
Methyl Acetate	Acetic Acid, Methyl Ester	Methyl ethanoate
	Methyl Ethanoate	
Propyl Acetate	Acetic Acid, Propyl Ester	Propyl ethanoate
	n-Propyl Acetate	
	Propyl Ethanoate	
	1-acetoxypropane	
Isopropyl Acetate	Acetic Acid, Isopropyl Ester	Methylethyl ethanoate
	Acetic Acid, 1-Methylethyl Ester	
	Isopropyl Ethanoate	
	1-Methylethyl Acetate	
t-Butyl Acetate	Acetic Acid, *t*-Butyl Ester	Dimethylethyl ethanoate
	Acetic acid 1,1-dimethylethyl ester	
Isobutyl Acetate	Acetic Acid, Isobutyl Ester	2-Methylpropyl ethanoate
	Acetic Acid, 2-Methylpropyl Ester	
	2-Methylpropyl Acetate	
Butoxyethyl Acetate	2-Butoxyethyl Acetate	2-Butoxyethyl ethanoate
	Butyl Glycol Acetate	
	Ethanol, 2-butoxy-, Acetate	
	Ethylene Glycol Monobutyl Ether Acetate	
	Glycol Monobutyl Ether Acetate	
Nonyl Acetate	Acetic Acid, Nonyl Ester	Nonyl ethanoate
	1-Acetoxynonane	
	n-Nonyl Ethanoate	
	Perlargonyl Acetate	
Myristyl Acetate	Acetic Acid, Tetradecyl Ester	Tetradecyl ethanoate
	Tetradecanol Acetate	
	Tetradecyl Acetate	
Cetyl Acetate	1-Acetoxyhexadecane	Hexadecyl ethanoate
	1-Hexadecanol, Acetate	
	Hexadecyl Acetate	
	Palmityl Acetate	
Stearyl Acetate	Acetic Acid, Octadecyl Ester	Octadecyl ethanoate
Isostearyl Acetate	Acetic Acid, Isostearyl Ester	16-Methylheptadecyl ethanoate
Acetic Acid	Acidum aceticum	Ethanoic acid
	Ethanoic Acid	
	Ethylic Acid	
	Glacial Acetic Acid	
	Methanecarboxylic Acid	
Sodium Acetate	Acetic Acid, Sodium Salt	Sodium ethanoate
	Natrii acetas	

Ingredient Name	Other Technical Names	IUPAC Name
Potassium Acetate	Acetic Acid, Potassium Salt	Potassium ethanoate
	Kalii acetas	
	Potassium Ethanoate	
Magnesium Acetate	Acetic Acid, Magnesium Salt	Magnesium ethanoate
	Magnesium Diacetate	
Calcium Acetate	Acetic Acid, Calcium Salt	Calcium ethanoate
	Calcium Diacetate	
Zinc Acetate	Acetic Acid, Zinc Salt	Zinc (II) ethanoate
Propyl Alcohol	1-Propanol	Propanol
	n-Propanol	
	n-Propyl Alcohol	
	1-Hydroxypropane	
Isopropyl Alcohol	2-Propanol	Methylethanol
	Isopropanol	
	1-Methylethanol	
	2-Hydroxypropane	

Table 3. Physical and Chemical properties of the acetate ingredients.[11,27,88-90]

	Methyl Acetate	Propyl Acetate	Isopropyl Acetate	t-Butyl Acetate	Isobutyl Acetate	Butoxyethyl Acetate
Cas No.	79-20-9	109-60-4	108-21-4	540-88-5	110-19-0	112-07-2
Molecular Weight (g/mol)	74.08	102.13	102.13	116.16	116.16	160.21
Boiling Point (°C)	56.9	101.6	89	97.8	118	187.8
Density (g/cm^3)	0.933	0.887	0.872	-	0.871	0.943
Vapor pressure (mm Hg @ 20°C)	170	-	-	47(@25°C)	13.0	-
Solubility (g/100g water @ 20°C)	25	1.5 @16°C	-	-	0.8	-
Log K_{ow}	0.18	1.24	1.28 (EST)	1.76	1.78	1.57(EST)
[a]Conversion Factor	1ppm = 3.03 mg/m^3	1ppm = 4.18 mg/m^3	1ppm = 4.18 mg/m^3	1ppm = 4.75 mg/m^3	1ppm = 4.75 mg/m^3	1ppm = 6.55 mg/m^3

	Nonyl Acetate	Myristyl Acetate	Cetyl Acetate	Stearyl Acetate	Isostearyl Acetate
Cas No.	143-13-5	638-59-5	629-70-9	822-23-1	NL
Molecular Weight (g/mol)	186.29	256.43	284.48	312.54	312.54
Boiling Point (°C)	208-212	-	-	-	-
Density (g/cm^3)	-	-	-	-	-
Vapor pressure (mm Hg @ 20°C)	-	-	-	-	-
Solubility (g/100g water @ 20°C)	-	-	-	-	-
Log K_{ow}	4.3(EST)	6.76(EST)	7.74(EST)	8.72(EST)	8.65(EST)
[a]Conversion Factor	-	-	-	-	-

[a] Conversion factors were obtained from the NIOSH Online Pocket Guide to Chemical Hazards
EST- Values were estimated using the EPI Suite, Version 4.0 program.
- Not found

Table 4. Physical and Chemical properties of the acid and alcohol ingredients.[13]

	Acetic Acid	Sodium Acetate	Potassium Acetate	Magnesium Acetate	Calcium Acetate	Zinc Acetate
Cas No.	64-19-7	127-09-3	127-08-2	142-72-3	62-54-4	557-34-6
Molecular Weight (g/mol)	60.05	82.03	98.14	142.39	158.17	183.50
Boiling Point (°C)	118	(melt at 58°C)	(melt at 292°C)	(melt at 80°C)	(decomp. above 160°C)	-
Density (g/cm^3)	1.05	-	-	-	-	-
Vapor pressure (mm Hg @ 20°C)	14.8 (@25°C)	7.08E-007 (EST)	1.37E-008 (EST)	1.79E-005 (EST)	0.00548 (EST)	6.57E-006 (EST)
Solubility (g/100g water @ 25°C)	100	100 (EST)	100 (EST)	100 (EST)	100 (EST)	30.3
Log K_{ow}	-0.17	-3.72 (EST)	-3.72 (EST)	-1.38 (EST)	-1.38 (EST)	-1.28 (EST)
[a]Conversion Factor	1ppm = 2.46 mg/m^3					

	Propyl Alcohol	Isopropyl Alcohol
Cas No.	71-23-8	67-63-0
Molecular Weight (g/mol)	60.1	60.1
Boiling Point (°C)	97.2	82.4
Density (g/cm^3)	0.8035	0.7850
Vapor pressure (mm Hg @ 20°C)	14.9	33.0
Log K_{ow}	0.25	0.05
[a]Conversion Factor	1ppm = 2.46 mg/m^3	1ppm = 2.46 mg/m^3

[a] Conversion factors were obtained from the NIOSH Online Pocket Guide to Chemical Hazards

Table 5. Current cosmetic product uses and concentrations for methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, nonyl acetate, cetyl acetate, stearyl acetate, propyl alcohol and isopropyl alcohol.[18-20,91]

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Methyl Acetate		
Noncoloring hair care products		
Sprays/aerosol fixatives	1 (312)	-
Nail care products		
Creams and lotions	-(14)	11
Polish and enamel removers	-(24)	45 - 60
Other	-(138)	10
Total uses/ranges for Ingredient	**1**	**10 - 60**
Propyl Acetate		
Eye products		
Lotion	-(254)	0.005
Nail care products		
Basecoats and undercoats	2 (79)	10
Polish and enamel	26 (333)	1-39
Polish and enamel removers	-(24)	10
Other[a]	6 (138)	7
Skin care products		
Body and hand sprays	-(-)	0.8
Paste mask/mud packs	-(441)	0.042
Total uses/ranges for Propyl Acetate	**34**	**0.005-39**
Isopropyl Acetate		
Noncoloring hair care products		
Tonics, dressings, etc.	2 (1205)	-
Hair coloring products		
Dyes and colors	5 (2393)	2
Nail care products		
Polish and enamel	-(333)	2
Polish and enamel removers	1(24)	0.5
Total uses/ranges for Isopropyl Acetate	**8**	**0.5-2**
t-Butyl Acetate		
Nail care products		
Polish and enamel removers	-(24)	10
Total uses/ranges for t-Butyl Acetate	**-**	**10**
Isobutyl Acetate		
Nail care products		
Basecoats and undercoats	1 (79)	6

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Creams and lotions	-(14)	34
Polish and enamel	3 (333)	45
Polish and enamel removers	-(24)	35
Total uses/ranges for Isobutyl Acetate	**4**	**6-45**
Nonyl Acetate		
Bath products		
Bubble baths	-(169)	0.0004
Total uses/ranges for Nonyl Acetate	**-**	**0.0004**
Cetyl Acetate		
Baby products		
Lotions, oils, powders, etc.	2 (137)	0.07
Bath products		
Soaps and detergents	3 (1665)	0.8-3
Other	1 (234)	-
Eye products		
Eyebrow pencil	-(144)	0.9
Eyeliner	2 (754)	3-4
Shadow	8 (1215)	3-8
Lotion	1 (254)	--
Mascara	-(499)	0.03
Other	4 (365)	-
Fragrance products		
Colognes and toilet waters	-(1377)	0.3
Perfumes	-(666)	2
Powders	1 (221)	-
Other	1 (566)	-
Noncoloring hair care products		
Conditioners	1 (1226)	0.3-0.9
Sprays/aerosol fixatives	1 (312)	2
Tonics, dressings, etc.	6 (1205)	2-7
Other	7 (807)	-
Hair Color Preparations		
Other hair coloring preparations[b]	-(168)	0.4
Makeup		
Blushers	7 (434)	0.3-9
Face powders	9 (661)	2-8
Foundations	2 (589)	12
Lipstick	101 (1883)	3-12.6 *(Corrected from 3-17%) 70

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Makeup bases	-(117)	2
Other	3 (485)	-
Nail care products		
Basecoats and undercoats	-(79)	0.2
Polish and enamel removers	-(24)	0.2
Personal hygiene products		
Underarm deodorants	-(580)	0.9
Shaving products		
Aftershave lotions	2 (367)	-
Shaving cream	1 (122)	0.01-0.9
Shaving soap	1 (10)	-
Skin care products		
Cleansing creams, lotions, liquids, and pads	4 (1446)	0.3
Face and neck creams, lotions, etc.	7 (1583)	0.5-2
Body and hand creams, lotions, etc.	33 (1744)	0.9-9
Foot powders and sprays	3 (47)	0.9
Moisturizers	51 (2508)	2
Night creams, lotions, powder and sprays	2 (353)	0.9
Paste masks/mud packs	2 (441)	-
Fresheners	1 (259)	-
Other	5 (1308)	-
Suntan products		
Suntan gels, creams, liquids and sprays	4 (107)	-
Indoor tanning preparations	1 (240)	-
Total uses/ranges for Cetyl Acetate	**277**	**0.01-17**

Stearyl Acetate		
Bath products		
Soaps and detergents	-(1665)	0.5
Makeup		
Face powders	-(661)	0.4
Nail care products		
Basecoats and undercoats	-(79)	0.02
Shaving products		
Shaving soap	1 (10)	-
Skin care products		
Face and neck creams, lotions, etc.	1 (1583)	-
Body and hand creams, lotions, etc.	-(1744)	0.3

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Total uses/ranges for Stearyl Acetate	**2**	**0.02-0.5**
	Isostearyl Acetate	
Fragrance products		
Perfumes	-(666)	5
Noncoloring hair care products		
Shampoos	-(1361)	0.002
Total uses/ranges for Isostearyl Acetate	**-**	**0.002-5**
	Acetic Acid	
Tonics, Dressings, and Other Hair Grooming Aids	1	
Other Hair Coloring Preparation	1	
Bath Soaps and Detergents	9	
Total uses/ranges for Acetic Acid	**11**	-
	Sodium Acetate	
Total uses/ranges for Sodium Acetate	**64**	-
	Potassium Acetate	
Total uses/ranges for Potassium Acetate	**0**	-
	Magnesium Acetate	
Total uses/ranges for Potassium Acetate	**0**	-
	Calcium Acetate	
Cleansing	1	
Face and Neck (exc shave)	1	
Moisturizing	5	
Total uses/ranges for Potassium Acetate	**7**	-
	Zinc Acetate	
Mouthwashes and Breath Fresheners	1	
Total uses/ranges for Potassium Acetate	**1**	-
	Propyl Alcohol	
Bath products		
Other	-(234)	0.0001
Makeup		
Lipstick	-(1883)	0.0001

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Nail care products		
Cuticle softeners	-(27)	0.0001
Creams and lotions	-(14)	0.0001
Oral hygiene products		
Mouthwashes and breath fresheners	-(74)	0.5
Skin care products		
Body and hand creams, lotions, etc.	-(1744)	0.0001
Total uses/ranges for Propyl Alcohol	**-**	**0.0001-0.5**
Isopropyl Alcohol		
Baby products		
Lotions, oils, powders, etc.	-(137)	0.2
Bath products		
Soaps and detergents	11(1665)	0.004-0.07
Oils, tablets, and salts	3 (314)	0.8
Bubble baths	1 (169)	-
Eye products		
Eyebrow pencil	2 (144)	3
Eyeliner	1 (754)	2
Shadow	1 (1215)	0.014
Mascara	12 (499)	0.3-3
Other[c]	5 (365)	14
Fragrance products		
Colognes and toilet waters	1 (1377)	0.2-2
Perfumes	-(666)	0.2-0.7
Other	2 (566)	0.02
Noncoloring hair care products		
Conditioners	184 (1226)	0.4-2
Sprays/aerosol fixatives	7 (312)	0.05-5
Hair straighteners	- (178)	0.6
Permanent waves	2 (69)	0.8-2
Rinses	3 (33)	0.8-1
Shampoos	13 (1361)	0.2-8
Tonics, dressings, etc.	45 (1205)	0.6-41
Wave sets	1 (51)	-
Other	50 (807)	2
Hair coloring products		
Dyes and colors	758 (2393)	3-16

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Tints	15 (21)	3
Shampoos	7 (40)	-
Color sprays/aerosol	1 (7)	4
Hair lighteners with color	2 (21)	-
Hair bleaches	8 (149)	-
Other[d]	6 (168)	7
Makeup		
Blushers	1 (434)	0.05
Face powders	-(661)	0.2
Foundations	15 (589)	0.002-5
Leg and body paints	3 (29)	-
Lipstick	1 (1883)	0.009-1
Makeup bases	-(117)	0.02
Rouges	1 (102)	-
Makeup fixatives	2 (45)	-
Other	1 (485)	0.3
Manicuring preparations		
Basecoats and undercoats	71 (79)	5-25
Cuticle Softeners	1 (27)	0.04-17
Nail creams and lotions	1 (14)	5-23
Nail polish and enamel	292 (333)	6-18
Nail polish and enamel removers	4 (24)	8-35
Other[e]	40 (138)	15-100
Personal Cleanliness		
Other	3 (792)	0.3
Shaving preparations		
Aftershave lotion		1
Shaving cream	1 (122)	
Other[f]		10-76
Skin care preparations		
Cleansing creams, lotions, liquids, and pads	8 (1446)	0.3-26
Face and neck creams, lotions, etc.	6 (1583)	0.1-1
Body and hand creams, lotions, etc.	10 (1744)	1
Body and hand sprays	-(-)	0.08
Foot powders and sprays	-(47)	6
Moisturizers	25 (2508)	0.04-0.2
Paste masks/mud packs	2 (441)	0.02-4

Product Category (FDA 2009)	2009, 2010 uses (total number of products in category; FDA 2009, 2010)*	2007, 2009 concentrations (%) (PCPC 2007; 2009)
Fresheners	7 (259)	0.07-7
Other	10 (1308)	14
Suntan products		
Suntan gels, creams and liquids	- (107)	0.06
Indoor tanning preparations	1 (240)	-
Total uses/ranges for Isopropyl Alcohol	**1647**	**0.002-100**

[a] 7% in a nail mender
[b] 0.4% in a gradual hair color
[c] 14% in a eye lash tint
[d] 7% in a hair color remover
[e] 50% in a nail surface sanitizer; 100% in a nail degreaser
[f] 76% in a razor burn/ingrown hair eliminator
- Not found
* Some concentration data came in 2009 and some in 2010

Table 6. LD_{50}/LC_{50} values reported in the literature for methyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, cetyl acetate, and isopropyl alcohol for various routes of exposure and test species.

	Species/Strain	N	Route	LD_{50} or LC_{50}*	Signs of Toxicity	Reference
Methyl Acetate						
	Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	6.97 ml/kg (6500 mg/kg)		[41]
	Albino rats	6/group (Male)	Inhalation	16000 ppm (48,480 mg/m^3) for 4 h did not cause mortality within 14 days. 32000 ppm (96,960 mg/m^3) for 4 h caused 6/6 animals to die within 14 days.		[41]
Propyl Acetate						
	Osborne-Mendel Rats	5/sex/group	Oral-Gavage	9370 mg/kg 95%CI (7670-11,430)	Depression soon after treatment, rough fur, scrawny appearance	[39]
	Mice/NR	NR	Oral-Gavage	8300 mg/kg 95% CI (7280-9460)	Depression soon after treatment	[39]
	Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	9.8 ml/kg (8692.6 mg/kg)		[42]
	New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (>17,740 mg/m^3)		[42]
	Albino rats	6/group (Male)	Inhalation	8000 ppm (33,440 mg/m^3) for 4 h caused 4/6 animals to die within 14 days		[42]
Isopropyl Acetate						
	Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	6750 mg/kg		[40]
	New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (>17440 mg/kg)		[40]
	Albino rats	6/group (Male)	Inhalation	32,000 ppm (133,700 mg/m^3) for 4 h caused 5/6 animals to die within 14 days		[40]
Isobutyl Acetate						
	Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	15.4 ml/kg (13,400 mg/kg)		[41]
	New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (~17,400 mg/kg)		[41]
	Albino rats	6/group (Male)	Inhalation	8000 ppm (38,000 mg/m^3) for 4 h caused 4/6 animals to die within 14 days		[41]

	Species/Strain	N	Route	LD_{50} or LC_{50}*	Signs of Toxicity	Reference
Butoxyethyl Acetate						
	Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	7.46 ml/kg (7000 mg/kg)		[41]
	New Zealand giant albino rabbits	4/group (Male)	Dermal	1.58 ml/kg (1500 mg/kg)		[41]
	Wistar rats	10/group	Oral-Gavage	3000 mg/kg in males 2400 mg/kg in females	Kidney pathology; Hemoglobinuria and hematuria	[43]
	New Zealand rabbits	6/group	Dermal	1500 mg/kg	Kidney pathology; Hemoglobinuria and hematuria	[43]
	Wistar rats	10/group (Male and Female)	Inhalation	400 ppm (2,620 mg/m^3) for 4 h did not cause mortality.		[43]
	New Zealand rabbits	2/sex/group	Inhalation	400 ppm (2,620 mg/m^3) for 4 h did not cause mortality.	Transient hemoglobinuria and hematuria in rabbits only.	[43]
Nonyl Acetate						
	Rat/NR	NR	Oral	>5000 mg/kg		[44]
	Rat/NR	NR	Dermal	>5000 mg/kg		[44]
Cetyl Acetate						
	Rat/NR	NR	Oral-Gavage	>5000 mg/kg		[38]
	Rabbit/NR	NR	Dermal	>5000 mg/kg		[38]
Acetic Acid						
	Rat/NR	NR	Oral-Gavage	0.4-3.2 ml/kg	Kidney pathology; Hemoglobinuria and hematuria	[38]
	Rat/NR	NR	Oral-Gavage	3310 mg/kg		[47]
	Mouse/NR	NR	Oral	4960 mg/kg		[24]
	Mice/NR	NR	Inhalation	5620 ppm for a 1 h exposure		[38] / [92]
	Rat/NR	NR	Inhalation	11.4 mg/l for a 4h exposure		[24]
	Rats/NR	6/group	Inhalation	16000 ppm for a 4 hour exposure caused 1/6 animals to die.	Pharyngeal edema and chronic bronchitus	[38]
	Guinea pigs/NR	NR	Dermal	> 3.2 ml/kg of 28% acetic acid. > 20 ml/kg of a 5% acetic acid		[46]

	Species/Strain	N	Route	LD_{50} or LC_{50}*	Signs of Toxicity	Reference
	Rabbit/NR	NR	Dermal	1060 mg/kg		[93]
	Mice/NR	NR	Intravenous	525 mg/kg of 10% acetic acid (buffered with sodium hydroxide to pH 7.3)		[46]
Sodium Acetate						
	Rat/NR	NR	Oral	3530 mg/kg		[24]
	Rat/NR	NR	Inhalation	>30 g/m^3		[24]
	Mouse/NR	NR	Subcutaneous	3200 mg/kg		[24]
	Mice/NR	NR	Intravenous	380 mg/kg		[94]
Calcium Acetate						
	Rat/NR	NR	Oral	4,280 mg/kg		[24]
	Mouse/NR	NR	Intravenous	52 mg/kg		[24]
Magnesium Acetate						
	Rat/NR	NR	Oral	8610 mg/kg		[24]
	Mouse/NR	NR	Intravenous	111 mg/kg		[24]
Potassium Acetate						
	Rat/NR	NR	Oral	3250 mg/kg		[24]
Propyl Alcohol						
	Rat/NR	NR	Oral	1870 mg/kg		[95]
	Rat/NR	NR	Inhalation	2000 mg/kg for 4 hours		[95]
Isopropyl Alcohol						
	Rat/NR	NR	Oral	4420 – 5840 mg/kg	Hind leg paralysis, lack of coordination, respiratory depression, stupor	[29]
	Rabbit/NR	NR	Dermal	13,000 mg/kg		[29]

*****Values in ( ) were calculated by CIR

Table 7. Summary of the genotoxicity data available for the ingredients in this assessment.

Test substance	Type of test, test species	Dose*	Result	Reference
	In vitro tests			
Methyl Acetate	Reverse mutation, *S. typhimurium*, TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	[55]
Propyl Acetate	Reverse mutation, *S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	10 mg/plate	Negative (w/ and w/o metabolic activation)	[31]
	Mitotic aneuploidy, *S. cerevisiae, D61.M*	1.23% (v/v)	Negative (w/o metabolic activation)	[56]
Isopropyl Acetate	Reverse mutation, *S. typhimurium*, TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	[55]
***t*-Butyl Acetate**	Reverse mutation, *S. typhimurium*, TA98, TA100, TA102, TA1535, TA1537 *and E. coli* WP2uvrA/pKM101	5 mg/plate	Negative (w/ and w/o metabolic activation)	[57]
Acetic Acid	Reverse mutation, *E. coli*; B/Sd-4/1,3,4,5; B/Sd-4/3,4	0.03% (v/v)	Slight	[63]
	Sister Chromatid Exchange (SCE), Chinese hamster K1 cells	10 mM	Negative w/o metabolic activation	[64]
Propyl Alcohol	Forward mutation, *S. pombe*, *ade6-60/rad10-198,h*$^-$	10% (v/v) cytotoxic	Negative (w/ and w/o metabolic activation)	[58]
	Sister Chromatid Exchange (SCE), Chinese hamster V79 cells	100 mM (6 mg/mL)†	Negative (w/ and w/o metabolic activation)	[59]
	Sister Chromatid Exchange (SCE), Chinese Hamster Ovary (CHO) cells	0.1% (v/v)	Negative (w/o metabolic activation)	[60]
	Micronucleus Assay, Chinese hamster V79 cells	40 mg/mL	Negative (w/o metabolic activation)	[61]
Isopropyl Alcohol	Reverse mutation, *S. typhimurium*, TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	[55]
	Sister Chromatid Exchange (SCE), Chinese hamster V79 cells	100 mM (6 mg/mL)†	Negative (w/ and w/o metabolic activation)	[59]
	In vivo tests			
Isopropyl Alcohol	Micronuclei, bone marrow erythrocytes of male and female ICR mice (n=40/group)	1173 mg/kg (IP) 2500 mg/kg caused mortality	Negative	[62]

*Doses are the highest ineffective dose.
+ calculated by CIR

w/ - with
w/o - without

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: John Bailey, Ph.D. 4/8/10
Industry Liaison to the CIR Expert Panel

DATE: April 8, 2010

SUBJECT: HRIPT Lipstick Containing 12.6% Cetyl Acetate
Updated Use Information

Ivy Laboratories (KGL, Inc.). 1993. Final report on the determination of the contact-sensitization potential of four materials by means of the maximization assay (including a lipstick containing 12.6% Cetyl Acetate)

Updated concentration of use information (the maximum use concentration of Cetyl Acetate reduced from 17% to 12.6%; the maximum use concentration of Isopropyl Alcohol in face products increased to 2%)

IVY LABORATORIES (KGL, INC.)

FINAL REPORT

on

THE DETERMINATION OF THE CONTACT-SENSITIZATION POTENTIAL OF FOUR MATERIALS BY MEANS OF THE MAXIMIZATION ASSAY

Sponsor: Lipstick containing 12.6% Cetyl Acetate

Monitor: ---

Investigator: Kays Kaidbey, M.D.

Testing Facility: Ivy Laboratories (KGL, INC.)
3401 Market Street - Suite 226
Philadelphia, PA 19104-3355
(Phone: 215-387-8400)

Protocol: KGL Protocol:

Final Report Date: December 7, 1993

Kays Kaidbey, M.D.
Investigator

December 7, 1993
Date

"The names of Ivy Laboratories (KGL, INC.), any officer, employee, or collaborating scientist are not to be used for any advertising, promotional or sale purposes without the written consent of Ivy Laboratories."

FINAL REPORT

PROTOCOL:

Ivy Laboratories - KGL Protocol

SPONSOR:

SPONSOR STUDY:

Letter: October 11, 1993

TITLE:

Evaluation of the contact-sensitizing potential of a test agent.

OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

KGL Protocol:

TEST MATERIAL:

The test sample used in this study was a product labelled Lipstick supplied by the sponsor and tested neat. The lipstick contains 12.6% Cetyl Acetate

TEST DRUG/PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked against the protocol for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet signed by the receiver, the technician and the investigator (physician). All test materials were stored in an inaccessible location under the supervision of the investigator.

INVESTIGATOR:

Kays Kaidbey, M.D.

KGL TECHNICIAN:

(Ms.) Madeline Billings

STUDY LOCATION:

Ivy Laboratories (KGL, INC.)
3401 Market Street - Suite 226
Philadelphia, PA 19104

CONDUCTION DATES:

This study was conducted from October 18, 1993 through November 18, 1993.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses
2 - History of drug hypersensitivity or recurrent dermatological diseases
3 - Pregnancy or mothers who are breastfeeding
4 - Scars, moles or other blemishes over the test site which can interfere with the study
5 - Recent sunburn
6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at Ivy Laboratories (KGL, INC.). A copy of the blanket informed consent used in this study is enclosed in Appendix A. Each subject was assigned a permanent identification number and completed a Medical History Form. These forms are also on file at Ivy Laboratories.

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of three distinct phases: (1) Pre-testing phase (2) Induction phase and (3) Challenge phase.

KGL Protocol:

(1) Pre-Testing Phase:

After signing an informed consent form, the test material was pre-tested on the panelists in order to determine whether it was irritating and whether sodium lauryl sulfate (SLS) was required. Approximately 0.1gm of the test material was applied to a skin site under a 15mm disc of non-absorbing cotton cloth (Webril). The patch was sealed with occlusive tape (Blenderm) and the patch reinforced with Scanpor Tape to ensure intimate contact with the skin. The patch was left in place for 48 hours after which it was removed and the site examined for evidence of irritation. None of the subjects showed any evidence of irritation (viz. erythema, scaling, etc.) with the test sample during the pre-test phase. Induction was therefore conducted with SLS pre-treatment.

(2) Induction Phase with SLS pre-treatment:

Approximately 0.1ml of aqueous SLS (0.5%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.1gm of the test material was applied to the same site before the sites were again covered with occlusive

tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.5% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

KGL Protocol:

(3) Challenge:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Since the test material was found to be non-irritating in the pre-test phase, pre-treatment with SLS was performed prior to challenge. Approximately 0.1ml of a 10.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded one hour later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

KGL Protocol:

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

Twenty-seven healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 19 females and 8 males ranging in age

from 20 to 50 years. All 27 subjects completed this investigation as outlined in the protocol. The demographic data are shown in Table 1. No other adverse or unexpected reactions were seen in any of the panelists.

The results of the challenge are shown in the enclosed table. No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample coded (Lipstick) does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

KGL Protocol:

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
1	J.A.H.	31	M	B
2	R.B.B.	50	M	B
3	R.- W.	23	F	B
4	A.Y.S.	22	M	A
5	L.- F.	20	F	C
6	V.- G.	20	M	C
7	D.A.W.	42	F	C
8	M.R.L.	40	M	C
9	D.E.O.	41	F	C
10	J.G.P.	45	M	C
11	S.F.T.	21	F	C
12	K.A.D.	21	F	C
13	J.M.J.	20	F	C
14	W.T.E.	42	M	C
15	S.A.J.	23	F	C
16	K.L.C.	21	F	C
17	C.- W.	36	F	B
18	D.V.V.	30	F	B
19	C.E.C.	24	F	B
20	S.- R.	41	F	C
21	S.A.F.	36	F	C
22	T.M.S.	20	F	C
23	G.P.M.	43	M	C
24	L.- B.	46	F	B
25	L.J.H.	35	F	B
26	M.A.D.	39	F	C
27	J.M.G.	20	F	C

TABLE 2

MAXIMIZATION TESTING RESULTS

Lipstick -

Subject Number:	CHALLENGE READINGS 48 Hours	72 Hours
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	0	0
9	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0
27	0	0

CHALLENGE READINGS:

48 Hours - November 17, 1993
72 Hours - November 18, 1993

Concentration of Use - Methyl Acetate, Propyl Acetate, Isopropyl Acetate, t-Butyl Acetate, Isobutyl Acetate, Butoxyethyl Acetate, Nonyl Acetate, Myristyl Acetate, Cetyl Acetate, Stearyl Acetate, Isostearyl Acetate, Propyl Alcohol and Isopropyl Alcohol*

Ingredient	Product Category	Concentration of Use
Methyl Acetate	Nail creams and lotions	11%
Methyl Acetate	Nail polish and enamel removers	45-60%
Propyl Acetate	Eye lotion	0.005%
Propyl Acetate	Basecoats and undercoats (manicuring preparations)	10%
Propyl Acetate	Nail polish and enamel	1-39%
Propyl Acetate	Other manicuring preparations	7%
Propyl Acetate	Body and hand sprays	0.8%
Propyl Acetate	Paste masks (mud packs)	0.042%
Isopropyl Acetate	Hair dyes and colors (all types requiring caution statement and patch testing)	2%
Isopropyl Acetate	Nail polish and enamel	2%
Isobutyl Acetate	Nail creams and lotions	34%
Isobutyl Acetate	Nail polish and enamel	45%
Nonyl Acetate	Bubble baths	0.0004%
Cetyl Acetate	Baby lotions, oils, powders and creams	0.07%
Cetyl Acetate	Eyebrow pencil	0.9%
Cetyl Acetate	Eyeliner	3-4%
Cetyl Acetate	Eye shadow	3-8%
Cetyl Acetate	Mascara	0.03%
Cetyl Acetate	Colognes and toilet waters	0.3%
Cetyl Acetate	Perfumes	2%
Cetyl Acetate	Hair conditioners	0.3-0.9%
Cetyl Acetate	Hair sprays (aerosol fixatives)	2%
Cetyl Acetate	Tonics, dressings and other hair grooming aids	2-7%
Cetyl Acetate	Other hair coloring preparations[1]	0.4%
Cetyl Acetate	Blushers (all types)	0.3-9%

Cetyl Acetate	Face powders	2-8%
Cetyl Acetate	Foundations	12%
Cetyl Acetate	Lipstick	3-**12.6%**
Cetyl Acetate	Makeup bases	2%
Cetyl Acetate	Basecoats and undercoats (manicuring preparations)	0.2%
Cetyl Acetate	Nail polish and enamel removers	0.2%
Cetyl Acetate	Bath soaps and detergents	0.8-3%
Cetyl Acetate	Deodorants (underarm)	0.9%
Cetyl Acetate	Shaving cream (aerosol, brushless and lather)	0.01-0.9%
Cetyl Acetate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.3%
Cetyl Acetate	Face and neck creams, lotions and powders	0.5-2%
Cetyl Acetate	Body and hand creams, lotions and powders	0.9-9%
Cetyl Acetate	Foot powders and sprays	0.9%
Cetyl Acetate	Moisturizing creams, lotions and powders	2%
Cetyl Acetate	Moisturizing sprays	0.9%
Stearyl Acetate	Face powders	0.4%
Stearyl Acetate	Basecoats and undercoats (manicuring preparations)	0.02%
Stearyl Acetate	Bath soaps and detergents	0.5%
Stearyl Acetate	Body and hand creams, lotions and powders	0.3%
Isostearyl Acetate	Perfumes	5%
Isostearyl Acetate	Shampoos (noncoloring)	0.002%
Propyl Alcohol	Other bath preparations	0.0001%
Propyl Alcohol	Lipstick	0.0001%
Propyl Alcohol	Cuticle softeners	0.0001%
Propyl Alcohol	Nail creams and lotions	0.0001%
Propyl Alcohol	Mouthwashes and breath fresheners (liquids and sprays)	0.5%
Propyl Alcohol	Body and hand creams, lotions and powders	0.0001%
Isopropyl Alcohol	Baby lotions, oils, powders and creams	0.2%
Isopropyl Alcohol	Bath oils, tablets and salts	0.8%

Isopropyl Alcohol	Eyebrow pencil	3%
Isopropyl Alcohol	Eyeliner	2%
Isopropyl Alcohol	Eye shadow	0.014%
Isopropyl Alcohol	Mascara	0.3-3%
Isopropyl Alcohol	Other eye makeup preparations[5]	14%
Isopropyl Alcohol	Colognes and toilet waters	0.2-2%
Isopropyl Alcohol	Perfumes	0.2-0.7%
Isopropyl Alcohol	Other fragrance preparations	0.02%
Isopropyl Alcohol	Hair conditioners	0.4-2%
Isopropyl Alcohol	Hair sprays (aerosol fixatives)	0.05-5%
Isopropyl Alcohol	Hair straighteners	0.6%
Isopropyl Alcohol	Permanent waves	0.8-2%
Isopropyl Alcohol	Rinses (noncoloring)	0.8-1%
Isopropyl Alcohol	Shampoos (noncoloring)	0.2-8%
Isopropyl Alcohol	Tonics, dressings and other hair grooming aids	0.6-41%
Isopropyl Alcohol	Other hair preparations (noncoloring)	2%
Isopropyl Alcohol	Hair dyes and colors (all types requiring caution statement and patch test)	3-16%
Isopropyl Alcohol	Hair tints	3%
Isopropyl Alcohol	Hair color sprays (aerosol)	4%
Isopropyl Alcohol	Other hair coloring preparations[4]	7%
Isopropyl Alcohol	Blushers (all types)	0.05%
Isopropyl Alcohol	Face powders	0.2%
Isopropyl Alcohol	Foundations	0.002-5%
Isopropyl Alcohol	Lipstick	0.009-1%
Isopropyl Alcohol	Makeup bases	0.02%
Isopropyl Alcohol	Other makeup preparations	0.3%
Isopropyl Alcohol	Basecoats and undercoats (manicuring preparations)	5-25%
Isopropyl Alcohol	Cuticle softeners	0.04-17%
Isopropyl Alcohol	Nail creams and lotions	5-23%

Isopropyl Alcohol	Nail polish and enamel	6-18%
Isopropyl Alcohol	Nail polish and enamel removers	8-35%
Isopropyl Alcohol	Other manicuring preparations[2]	15-100%
Isopropyl Alcohol	Bath soaps and detergents	0.004-0.07%
Isopropyl Alcohol	Other personal cleanliness products	0.3%
Isopropyl Alcohol	Aftershave lotions	1%
Isopropyl Alcohol	Other shaving preparations[3]	10-76%
Isopropyl Alcohol	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.3-26%
Isopropyl Alcohol	Face and neck creams lotions and powders	0.1-**2%**
Isopropyl Alcohol	Body and hand creams, lotions and powders	1%
Isopropyl Alcohol	Body and hand sprays	0.08%
Isopropyl Alcohol	Foot powders and sprays	6%
Isopropyl Alcohol	Moisturizing creams, lotions and powders	0.04-0.2%
Isopropyl Alcohol	Paste masks (mud packs)	0.02-4%
Isopropyl Alcohol	Skin fresheners	0.07-7%
Isopropyl Alcohol	Other skin care preparations	14%
Isopropyl Alcohol	Suntan gels, creams and liquids	0.06%

*Ingredients in the table title but not found in the table were included in the concentration of use survey, but no uses were reported.

[1]0.4% in a gradual hair color

[2]50% in a nail surface sanitizer; 100% in a nail degreaser

[3]76% in a razor burn/ingrown hair eliminator

[4]7% in a hair color remover

[5]14% in an eye lash tint

Information collected in 2009
Table prepared December 11, 2009
Updated January 21, 2010
Updated April 7, 2010 (changes in bold)