IsoParaffins

CIR EXPERT PANEL MEETING

DECEMBER 13-14, 2010

ADMINISTRATIVE

Cosmetic Ingredient Review
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November 18, 2010

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Draft Final Report on Isoparaffins

A copy of the draft final report on these ingredients is included along with the following: CIR report history, Minutes from the August 2010 Panel meeting, Literature search strategy, Data profile, Comments on the tentative report from the Personal Care Products Council, a statement from the Council relating to no uses of C15-35 isoparaffin/isoalkylcycloalkanes in cosmetic products, and comments on the draft report (reviewed at August Panel meeting) from ExxonMobil.

At the August 30-31, 2010 CIR Expert Panel meeting, the Panel issued a tentative report with a conclusion stating that the isoparaffins are safe for use in cosmetics when formulated to be non-irritating. After reviewing the available safety test data, the Panel needs to determine whether a final report with this conclusion should be issued at the December 13-14, 2010 Expert Panel meeting.

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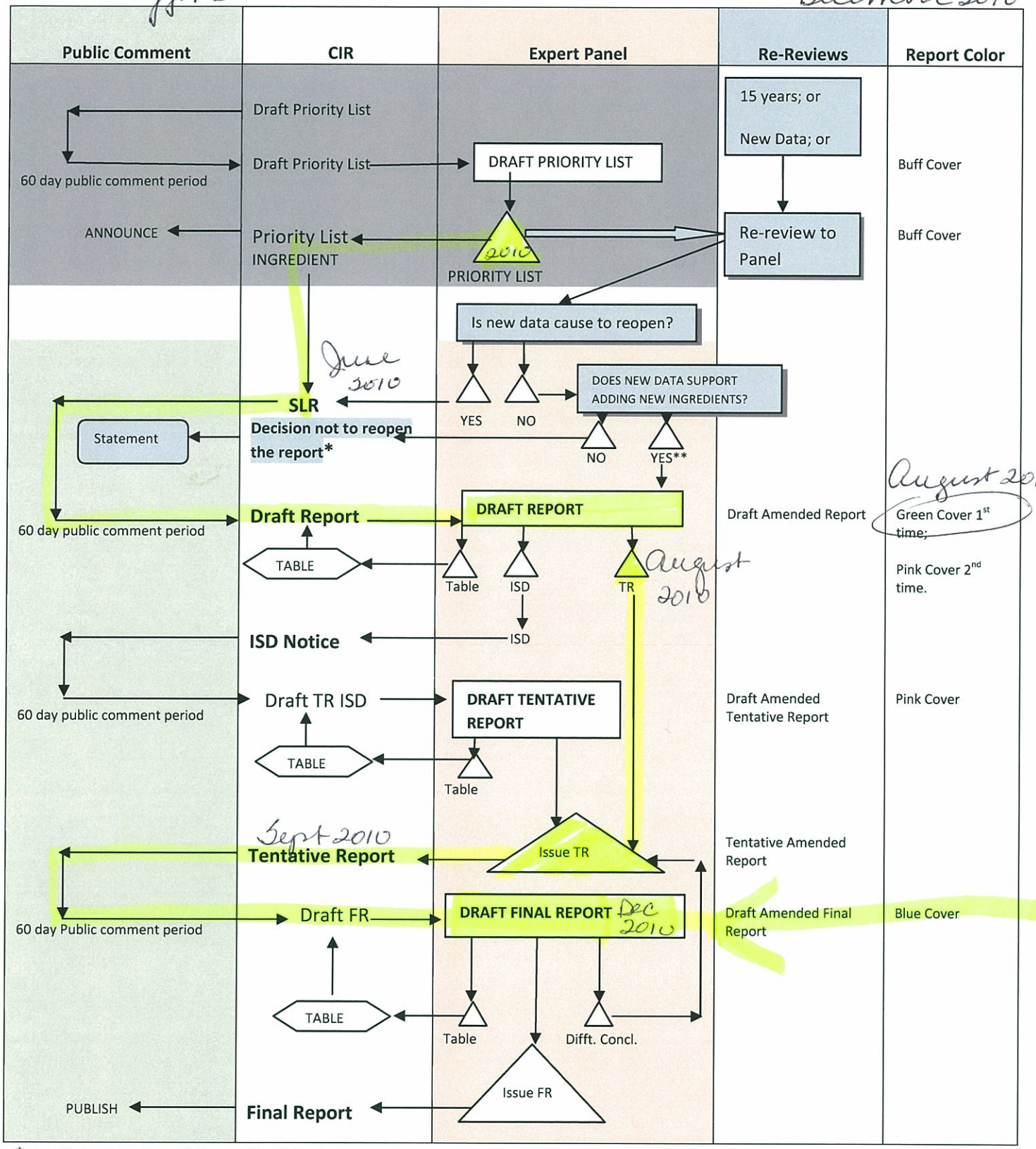
SAFETY ASSESSMENT FLOW CHART

IsoParaffins

December 2010



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

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

Expert Panel Decision

Document for Panel Review

Option for Re-review

CIR History of:

Isoparaffins

The availability of a scientific literature review (SLR) on this group of ingredients was announced on June 23, 2010. Comments and use concentration data from the Personal Care Products Council were received during the 60-day comment period.

1st Review, Belsito and Marks Teams/Panel: August 30-31, 2010

Use concentration data received from the Personal Care Products Council are included in Table 5. Skin irritation/sensitization data on products containing isododecane, isohexadecane or isoeicosane received prior to the Panel meeting will be added to the report text.

The Panel acknowledged the new skin irritation/sensitization data on products containing isododecane, isohexadecane or isoeicosane that, overall, were classified as negative, and the limited number of irritation reactions observed in 2 of the studies. The Panel also noted the potential for inhalation exposure, in that some of these ingredients are being used in hair sprays; however, it was agreed that the particle size associated with these aerosolized products would preclude any concern over exposure-related toxic effects.

All unpublished clinical data received from the Council prior to the August Panel meeting will be added to the tentative report prior to its issuance.

The Expert Panel concluded that the isoparaffins are safe for use in cosmetics when formulated to be non-irritating and issued a tentative report with this conclusion.

2nd Review, Belsito and Marks Teams/Panel: December 13-14, 2010

Prior to this meeting, comments on the tentative report and a statement indicating no reported uses of C15-35 isoparaffin/isoalkylcycloalkanes were received from the Council. Comments on the draft report (reviewed at August 30-31 Panel meeting) from Exxon-Mobil were also received.

Literature Search on Isoparaffins*

Ingre-dients	Toxline &PubMed	ChemIDplus	Multidatabase (See legend*)	DART	Household Products	Beilstein	Registry	Kosmet	Napralert	RTECS	CAplus
7-8		0	0	0	0	0	1	0	0	0	1
8-9		0	0	0	1	0	1	0	0	0	0
9-11		1	0	0	1	0	1	0	0	0	0
9-12		0	0	0	0	0	1	0	0	1	3
9-13		0	0	0	0	0	1	0	0	0	0
9-14		0	0	0	0	0	1	0	0	0	0
9-16		0	0	0	0	0	0	0	0	0	0
10-11		0	0	0	0	0	1	0	0	0	2
10-12		0	0	0	0	0	1	0	0	1	3
10-13		1	0	0	1	0	1	0	0	0	0
11-12		0	0	0	0	0	1	0	0	0	0
11-13		0	0	0	1	0	1	0	0	0	0
11-14		0	0	0	0	0	0	0	0	0	0
12-14		1	0	0	1	0	1	1	0	0	0
12-20		0	0	0	0	0	1	1	0	1	0
13-14		0	0	0	1	0	1	2	0	0	1
13-16		1	0	0	1	0	1	1	0	0	0
18-70		1	0	0	0	0	1	0	0	0	0
20-40		0	0	0	0	0	1	1	0	0	0
15-35	70 hits (all chain lengths)	0	0	0	0	0	0	0	0	0	0
Isodod	8					1	1				
Isoeic	0					0	1				
Isohex	29					1	1				
Isooc	671					1	1				

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

Searches Performed on 3/20-25/2010 and 6/8-9/10
Search updated on 10/15/2010 using PubMed and Toxline – no pertinent hits

Ingredients

7-8: C7-8 Isoparaffin OR Alkanes, C7-8-iso- OR 70024-92-9
8-9: C8-9 Isoparaffin OR Alkanes, C8-9-iso- OR 246538-71-6
9-11: C9-11 Isoparaffin OR Alkanes, C9-11-iso- OR 68551-16-6
9-12: C9-12 Isoparaffin OR Alkanes, C9-12-iso-
9-13: C9-13 Isoparaffin OR Alkanes, C9-13-iso-
9-14: C9-14 Isoparaffin OR Alkanes, C9-14-iso- OR 246538-73-8
9-16: C9-16 Isoparaffin OR Alkanes, C9-16-iso-
10-11: C10-11 Isoparaffin OR Alkanes, C10-11-iso- OR 246538-75-0
10-12: C10-12 Isoparaffin OR Alkanes, C10-12-iso-
10-13: C10-13 Isoparaffin OR Alkanes, *C10-13-iso*- OR 68551-17-7
11-12: C11-12 Isoparaffin OR Alkanes, C11-12-iso- OR 246538-76-1
11-13: C11-13 Isoparaffin OR Alkanes, C11-13-iso- OR 246538-78-3
11-14: C11-14 Isoparaffin OR Alkanes, C11-14-iso-
12-14: C12-14 Isoparaffin OR Alkanes, C12-14-iso- OR 68551-19-9
12-20: C12-20 Isoparaffin OR Alkanes, C12-20-iso-
13-14: C13-14 Isoparaffin OR Alkanes, C13-14-iso- OR 246538-79-4
13-16: C13-16 Isoparafin OR Alkanes, C13-16-iso- OR 68551-20-2
18-70: C18-70 Isoparaffin OR Alkanes, C18-70-iso- OR 246538-80-9
20-40: C20-40 Isoparaffin OR Alkanes, C20-40-iso- OR 246538-81-8
15-35: C15-35 Isoparaffin/Isoalkylcycloalkanes
Isod: Isododecane; 141-70-8 (for beilstein/registry)
Isoeic: Isoeicosane; 52845-07-5 (for beilstein/registry)
Isohex: Isohexadecane; 4390-04-9 (for beilstein/registry)

Isooc: Isooctane; 540-84-1 (for beilstein/registry)

Search Term/Strings

Isoparaffin OR Isoparaffins OR 68551-16-6 OR 68551-17-7 OR 68551-19-9 OR 68551-20-2 OR ″ Isoparaffin Isoalkylcycloalkanes″ OR Isoparaffinic

70024-92-9 OR 246538-71-6 OR 246538-73-8 OR 246538-75-0 OR 246538-76-1 OR 246538-78-3 OR 246538-79-4 OR 246538-80-9 OR 246538-81-8 – [No records found in PubMed/Toxline using these CAS Nos., not in Dictionary but found elsewhere]

Isosdodecane OR 141-70-8
Isoeicosane OR 52845-07-5
Isohexadecane OR 4390-04-9
Isooctane OR 540-84-1

Isparaffins Check List for December, 2010. Writer – Wilbur Johnson																		
				Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
C7-8 isoparaffin																		
C8-9 isoparaffin																		
C9-11 isoparaffin				X	X	X				X	X							
C9-12 isoparaffin				X	X	X					X							
C9-13 isoparaffin																		
C9-14 isoparaffin																		
C9-16 isoparaffin																		
C10-11 isoparaffin				X	X	X			X	X	X	X		X	X	X		X
C10-12 isoparaffin									X									
C10-13 isoparaffin				X	X	X			X	X	X					X		
C11-12 isoparaffin										X		X		X				
C11-13 isoparaffin				X	X	X				X	X	X	X	X		X		X
C11-14 isoparaffin																		
C12-14 isoparaffin																		
C12-20 isoparaffin																		
C13-14 isoparaffin																		
C13-16 isoparaffin																		
C18-70 isoparaffin																		
C20-40 isoparaffin																		
C15-35 isoparaffin/isoalkyl cycloalkanes																		
isododecane				X					X	X	X	X		X	X	X		
isoeicosane										X		X		X				
isohexadecane				X						X	X	X		X				
isooctane			X	X	X	X	X		X	X	X				X	X	X	

TRANSCRIPTS/MINUTES

Day 1 of the August 30-31, 2010 CIR Expert panel Meeting – Dr. Belsito's Team

DR. BELSITO: Okay. So Wilbur, are you ready to do isoparaffins?
MR. JOHNSON: I think so.
DR. BELSITO: Okay.
MR. JOHNSON: Is anyone ever ready?
DR. BELSITO: So now, it's the first time we're looking at the report. SLR was released in June, so it's the usual for a first report. My review of the data I could go comfortable going either way. Safe when formulated to be nonirritating seemed to be the major issue. Or do we need a 28-day dermal for skin since they are irritating? The thing here would be cutaneous carcinogenicity that I really don't think is an issue. And then they're used in hairspray so the cosmetic area needs the cosmetic boilerplate.
What are you dumping us with here Wilbur?
DR. KLAASSEN: (off mic)
DR. BELSITO: Okay.
DR. KLAASSEN: Revised use concentration, frequency of use table.
DR. BELSITO: Wow, okay. These that we just got would suggest that some of these compounds, even at very high concentrations, were not irritants or sensitizers. But in the original report it indicates the C-9 through C-11 and C-11 through C-13 isoparaffins were mildly irritating to the skin of rabbits or moderately -- I'm sorry, the C-9 to -11 were moderately and the C-11 to -13 were mildly irritating. And these are all on -- studies we have now are in the iso compounds. So I think we would still have to have that irritating caveat since some of these are used at very high concentrations.
But I guess the biggest question I had is because there is some benzene contamination and it says that Exxon and Texaco reported less than.1 parts per million for all of their isoparaffinic products and RICO up to.2 percent. And if we don't have a lot of good carcinogenicity data here, at least not on skin, do we need a 28-day dermal for these or not? Otherwise, I think from the cutaneous standpoint these are pretty safe as long as they're non-irritating.
DR. LIEBLER: So the highest thing we have on carcinogenicity is isooctane.
DR. BELSITO: Mm-hmm.
DR. LIEBLER: And you're wondering whether we need the higher -- bigger paraffins or a representative compound from --
DR. BELSITO: Yeah. I mean, I guess in wavering, you know, I'd probably like to hear what

Tom Slaga has to say, whether he's comfortable or anyone else who has self- professed expertise in carcinogenicity because I don't --
MR. JOHNSON: Well, just based upon the discussions on the other team earlier today, they talked about the fact that the carcinogenic effects in male rates were due to the alpha 2u-globulin, which is not present (inaudible).
DR. BELSITO: Those are the renal effects. I'm not concerned about anything internal. I don't know that we have the data that will tell us that this might not be an inductive for skin tumors.
DR. LIEBLER: Well, we just have reference 45 which is cited as the first paragraph on the carcinogenicity section that's on page -- page 14 of the report. And it simply says that it was studied in Swiss mice, male and female. And survival was good. No significant tumor incidents found.
DR. KLAASSEN: (off mic)
DR. BELSITO: That's pretty good.
DR. LIEBLER: So I mean, you know.
DR. BELSITO: So safe as used?
DR. LIEBLER: These compounds I really wouldn't think they would have any liability of genotox. Yeah, I'm safe as used.
DR. BELSITO: Safe as used when formulated not to be irritating?
DR. LIEBLER: Yeah. So let me just ask how we approach that. We're saying that we have a number of studies that say no irritating and a couple that indicate mild irritation or moderate irritation. And in that case we can say safe as used and then add the caveat, whereas at what point would we prefer to have additional data?
DR. BELSITO: Well, the problem with irritation is always that there are too many factors that determine it. You know, the pH, other components of the formulation. So, you know, the tact we've taken ever since we looked at the lactic and glycolic acids has been when formulated not to be irritating. I think the irritation really depends here upon obviously concentration and chain length and we're going over a length of carbon molecules here. So, you know, I just think that when we've gotten that kind of data in the past, you know, where there's -- these are used in potentially high concentrations, there's data showing they're moderately to mildly irritating. At least some of the shorter carbon chain lengths, you know, that's the approach we've taken.
DR. LIEBLER: Okay. I see.
DR. SNYDER: We used to put a limit, but we got away from that.

DR. BELSITO: Particularly for irritation because the limits make no sense dependent by on how you formulate it, it changes what the irritation is.
DR. ANSELL: And so even if we're entirely consistent with that, I mean, the products would simply not be put on the markets.
DR. BELSITO: And we need the respiratory boilerplate in the cosmetic section.
DR. LIEBLER: So Wilbur, on page 2, under Methods of Production, there's a paragraph on --
MR. JOHNSON: Which page? I'm sorry.
DR. LIEBLER: On page 2 of the report, under Methods and Production, the third paragraph begins, "Research for the conversion of a highly aromatic liquid product from coal conversion." It looks like that's a description of research into a method of making paraffins or isoparaffins that unless that's actually a method that's used to produce the products that we can counter, I don't think it needs to be in the report.
MR. JOHNSON: Okay.
DR. KLAASSEN: On page 12, the paragraph right before Cytotoxicity, what you have written there is true, except you need to put a little different spin on it. The reason why the Black-Reiter rats were used is because they actually don't have alpha 2u-globulins. So when you give these compounds to this graph, it doesn't cause the kidney injury. So it really supports this whole concept rather than the way it's written now it kind of sounds like it produced a different result. But it really supports the concept of the alpha 2u-globulin.
DR. BELSITO: Okay.
DR. KLAASSEN: (unintelligible) can't make the alpha 2u-globulin, thus there's no kidney injury.
DR. BELSITO: Okay. Anything else? Okie doke. Safe as used when formulated not to be irritating.
MR. JOHNSON: Dr. Belsito, just one comment. With respect to the last wave of data that were received from industry, apparently isooctane is being tested in Europe in the REACH program and a safety dossier is being developed. And a rather lengthy reference list was submitted. The panel received that. And, you know, with that in mind I was wondering whether or not the panel is interested in receiving any of the references associated with that safety dossier.
DR. BELSITO: We certainly could look at them.
MR. JOHNSON: Isooctane.
DR. ANSELL: On isooctane?

MR. JOHNSON: Mm-hmm.
DR. BELSITO: It never hurts to get a copy of them and if there are any flags that are issued we can always change the conclusion. But I think in the interest of moving this ahead we're going safe as used.
MR. JOHNSON: And a lot of these data can be used for read across.
DR. BELSITO: Okay.
MR. JOHNSON: So some, you know, may not necessarily be on isooctane, but, you know, similar chemicals.
DR. BELSITO: Great. And you were not here this morning, but one of the things we discussed, Wilbur, was since we're relying heavily on read across that there be tables constructed which were the general things we're looking for, you know, method of manufacture, impurities, dermal absorption, either the studies or octenyl water, sensitization, irritation, repro, carcinogenicity, mutagenicity. And there will be a tick box whether there's any data relevant to those general categories for each of the chemicals in the group we're looking at.
So you have the general categories across the top and down the bottom of your spreadsheet you'd have each of the chemicals in the report. And then the ideal would be, at least for me, is to have the lead chemical, which would be the one with the greatest number of uses at the top and then alphabetical after that.
DR. SNYDER: Are we moving away from the use of the term "cosmetics" and towards "personal care products?" Do you know? What's the -- (unintelligible) here in this document.
MR. BRONAUGH: Personal care products is a lot bigger improvement.
DR. SNYDER: Well, I know, but that's why I'm kind of -- because in here, in the introduction you say, "The safety of the following isoparaffins in personal care products are being reviewed."
MR. JOHNSON: Well, I know the Personal Care Product Council favors the personal care products.
DR. SNYDER: So that was purposeful?
DR. ANSELL: We favor it as it relates to the description of the entire industry, not necessarily as it reflects the CIR because we often press, you know, suggest that non-cosmetic applications be excluded. And so this really hasn't come up. But I'm going to guess that we would prefer that the CIR remain cosmetic because we certainly don't want to start getting into PC areas or non- cosmetic from a regulatory

standpoint.
DR. BELSITO: Okie doke. Anything else on the isoparaffins? So we're ready to go back to vegetable oil at this point? Okay.

Next is Green Book 5, the isoparaffins.
This is the first time we've seen this report and, as always, we need to go through a process of what data is needed at this early stage and where are we heading. One of the other things, again, when we start dealing with these reports that have a large number of ingredients, I would like the team's comment as to would it be nice to have a table at the beginning with the ingredients, and then what data we have in a check box so you could go down and say reproductive and development toxicity, we have it on this ingredient, we can focus there. Is that representative? We have genomutatox on these ingredients so you could go check. That's an idea of who one could start.
The oils even get worse in terms of the number of ingredients where we could first have a Ron Shank type table where he lists all the ingredients and the data needs and then you just go down, but that's just an idea. Does the team want to comment on that?
DR. HILL: I made a notation that it would be nice to have that in at least one of these books where there were numerous ingredients and I thought maybe I'm just asking for work to be done that I should be doing myself as I go through. A check box is one possibility and I even thought of the possibility of some kind of reference or footnotes or something that would cross-reference and maybe one fine day there may be a link you can click on in some electronic table, but not now. But some way of getting an overview because particularly when we're doing read across it would be nice to be able to see at a glance without having to go through and manually construct the table, which is fine I guess, but time-consuming, where the gaps are and what we are actually using when we make read- across conclusions. We have that in some of the documents, here are the ingredients, here are the types of studies, here is what we have, here's what we don't have where you can see there's a check in the box or there's a footnote in the box or something.
DR. MARKS: Wilbur?
MR. JOHNSON: Dr. Marks, I mentioned that I'd disturbed two handouts, the revised frequency of use concentration table and a summary of data that were received after the mail date on the isoparaffin compounds.
DR. BRESLAWEC: Could I comment on your request for what I envision is a spreadsheet of information? And if you're shocked to hear that I knew about your request while not being in the

room it's because the same request is made down the hall. We've started doing that obviously in the concentration of use and frequency of use area. That seemed to be a simple area to start. We're trying to move into that direction with all of the other information. It's just taking a little more time, but we hear you.
DR. MARKS: Thank you, Halyna. I guess one of the things when I look at this, the question that came to my mind for the team is paraffin, isobutane, isopentane were found safe in 2005. Do we chance reopening those and add these isoparaffins to it or are they so chemically different that that would not be a good idea?
DR. BRESLAWEC: If I could mention, I think that is something that was considered. Wilbur, please correct me if I'm wrong, but I think you and Bart thought about that at some point and opted not to reopen that and add the isos to the regular paraffin so that that was considered by staff.
DR. BERGFELD: The reason, Wilbur, why you and Bart decided not to include those and make it all eventually one report?
MR. JOHNSON: Bart would be able to shed more light on that perhaps tomorrow.
DR. MARKS: Then let's move on to the ingredients at hand here, these isoparaffins. What data needs do we need?
DR. SHANK: I don't have any.
DR. SLAGA: I have no needs, safe.
MS. WEINTRAUB: As I was reading the information, I had three questions. The first one is what is the significance that the EPA can't
DR. MARKS: Pardon?
MS. WEINTRAUB: What's the significance of the fact that the EPA can't establish or hasn't established an RFD for these?
The second one is kidney impacts. It seems that there were quite a number documented and I wanted to know what the panel thought about that.
The third was what's the significance for the panel that the EPA found that there was insufficient data to make a determination about carcinogenicity?
DR. SHANK: The renal toxicity and carcinogenicity was limited to the male rat and associated with a pheromone protein called alpha 2u-globulin which is produced by the male rat, but not by female rats, male mice, or humans. It is a unique problem with the male rat and there's not a relevance to human toxicity. We see this with very lipid soluble compounds. The lipid soluble compound binds to this protein in the male rat and the kidney can't processed so that the tubular

cells and there is a forced regeneration of the tubular cells, DNA mutations and you get these renal changes, necrosis, nephrosis, even tumors, but they're not relevant to humans because we don't have that protein.
DR. SLAGA: Are there any reviews on this that Ron just stated, that it has no relevance to humans?
DR. SHANK: We see this with a compound called limonene well documented which is part of the nice flavor of lemons and limes, citrus, that does the same thing. This is often seen with very lipid soluble compounds with male rat kidney toxicity only.
DR. HILL: Could any of you toxicologists with more years of experience than me comment on Panel Book page 23? There's a little section and it deals with isooctane and tumor promotion and they didn't find any statistically differences. This was an inhalation exposure of 50 PPM 5 days per week for 24, 59, or 60 weeks. It said not statistically different, but the numbers do get larger, and I wondered if anybody had any thoughts on that.
DR. SHANK: The effect is only in the male rat.
MS. WEINTRAUB: My other question about carcinogenicity is also on that same page in the first full paragraph about the lack of chronic bioassays that assess carcinogenic effects.
DR. SHANK: I'm sorry, I couldn't hear you. What was your question?
MS. WEINTRAUB: What does the panel think about the EPA determination that there is not enough data or that there isn't a chronic bioassay study that assesses carcinogenic effects? But this is for 2,2,4- trimethylpentane. I wanted to know the panel's thoughts about how narrowly or broad this impacts our view.
DR. SLAGA: First of all, in general these are not genotoxic. These have been applied to the skin in lifetime studies with no carcinogenic effect and their absorption would be limited. These would be studies that the EPA would want to do in feeding types of studies internally because of their low absorption. The fact they're not genotoxic and they've been applied to the skin for the life of the animal, those would be the relevant studies here.
DR. MARKS: Are there any other comments? Wilbur, thanks for this new information because I was going to vote for insufficient data because of lack of sensitization data on high concentrations used on the eyes and lip. And we now have HRIPT which supports up to close to 81 percent no irritation or sensitization so that I

feel comfortable from that toxicity.
DR. KATZ: I have one question.
DR. MARKS: Yes, Linda.
DR. KATZ: The question that I have is are you comfortable going up to greater than 90 percent based on the data that you have that's only to 89 percent?
DR. MARKS: When you look at that 90 percent, it was in a nail product, so I feel comfortable. That was the only one which really went over 80 other than a non- coloring hair product. Yes, I think in the present use and concentration I feel comfortable.
Are there any other comments? Rachel, are you fine with the answers?
DR. BERGFELD: I have a question about the use tables and which one we're using. We've had handed to us a new one. I believe it's for this.
DR. MARKS: I like the new one, Wilma.
DR. BERGFELD: That's the new one?
DR. BRESLAWEC: May I comment on that? This is a great example of actually having the ability to see both of the tables because when Wilbur first prepared this report, he used the old method and after issuing this draft report he went back on his own and used this data to create a new use table, so that you have in front of you the old table and the new table based on exactly the same data.
DR. MARKS: I can tell you, Wilbur, if you didn't have this new use table, I wouldn't have been able to scan the use and concentrations quick enough to correlate with the sensitivity studies that were done while Rachel's question were being answered.
Again, Rachel, are you satisfied with the answers you heard?
MS. WEINTRAUB: Yes, thank you.
DR. MARKS: I think then we should move to issue a tentative report with a conclusion that these cosmetic ingredients are safe.
DR. HILL: Wilbur, you'll see them, but I'd just like to make note that I wrote a lot of questions concerning the table of the substances so that you would take note of the notes that I've written and call me if you have any questions or contact me by e-mail.
MR. JOHNSON: Sure.
MS. WEINTRAUB: Are there any extra copies? I don't think I received it.
MR. JOHNSON: Should there be a discussion for this report? And if so, what should be the content?
DR. MARKS: I'll let the two Rons and Tom because I think the most potentially

contentious issues were the ones that Rachel brought up as in how do you reconcile the EPA cancer insufficient, the kidney issue, and then the other was the RFD. I think those would be the discussion points. Do you agree?
DR. SHANK: Yes.
DR. BERGFELD: Didn't we hear Tom say something about total body skin exposure versus oral? Shouldn't that be included?
DR. SLAGA: There is a very good study on dermal carcinogenicity for lifetime so we're basing that plus very low penetration of the amount that gets in would not affect internally what EPA was wanting.
DR. SHANK: Since we brought up the use tables for the team reviews, I like both the old-fashioned one and the new one. When you publish it, the new one is good, the condensed one, but for reviewing the safety I would like to have the old-fashioned one where there is the full detail of exactly what kinds of products rather than just dermal underarm.
MS. BURNETT: For some of the reports you received the raw data as we get it from FDA. Is that sufficient or do you want the old table created?
DR. SHANK: I would like the old table created, I'm sorry, just for our use. It's a lot of work?
MS. BURNETT: It is.
DR. BRESLAWEC: It's a huge amount of work.
MS. BURNETT: When I started doing vegetable oils I got up to 13 pages before I quit and that was only 8 ingredients.
DR. BRESLAWEC: One of the reasons that we shifted to new use tables is the inordinate amount of time it takes to create those tables based on the old format, and were hoping that providing you with the raw data information which has the same information but on tables could compensate for that. We would really very strongly rather not go back to the old tables.
DR. MARKS: I like the new format and I remember when you presented the new format in a meeting or two ago, coming up with that issue when you have dozens of ingredients creating a use and concentration table, listing individual personal care consumer products that we get a PDF potentially of not just 13 pages, it could be 100 pages of just the concentration and use. Would it be worthwhile if you had questions specifically, then you could query that?
Could you give an example, Ron, where looking at this you would want to know specifically? Because you notice when I think

Linda asked me the issue of the concentration and 90 percent, I had actually circled that before Linda had asked it, that it was in a nail product and I wasn't concerned there.
DR. SHANK: I think it's not with isoparaffins that this came up, but in two or three reports it came up that I really needed to have more use information. And rather than have you do that for every report, if I have a specific concern then I can address it to you specifically rather than every time I must have this, so that I withdraw my request for the detailed use table.
DR. BRESLAWEC: And we will be happy to provide you with any data you feel are important.
DR. BERGFELD: Linda, could I ask you a question? Since the question is reams of information coming out of the FDA, do you take a next step at the FDA in collating the uses under categories or do you just put them in a report system as they come in?
DR. KATZ: I'm not sure I understood what you're asking specifically.
DR. BERGFELD: The raw data that comes in isn't subdivided into various types?
DR. KATZ: You're talking about raw data coming in to the VCRP or are you talking about other kinds of raw data?
DR. BERGFELD: Voluntary.
DR. KATZ: For the VCRP what we do is they come in as data itself and we just go back and we look at the ingredients and tally up, so that it's really a tally listing as opposed to doing anything else with it. Is that what your question is?
DR. BERGFELD: I wondered if you could or would or are doing some of this subclassification.
DR. KATZ: We are not. We don't have the resources available to do that, nor do we have all of the rest of the information available to be able to do that.
DR. BAILEY: To add on to that, we get the use level information and then make that available, then what we can get from FDA is either a simple listing or a listing broken down by product category and frequency, but they simply don't have the information to add that to the tables. I assume that you can cut that in a database pretty much however you want to in terms of frequency by product category or just a total frequency.
DR. KATZ: We probably could, but I'm not sure that that would be very accurate because since we really only get a snapshot in time. We don't know what the actual usage is, nor do we know how much of it is being sold so that we don't

really get volumes to be able to tell what people are doing with anything beyond that. It really is just a tally up so that when we report back a number it is the tally of how many hits we have on that particular ingredient as opposed to what its actual usage is out in the marketplace.

DR. EISENMANN: I'm still preparing the concentration of use tables from the table I get by FDA product category and there is no reason why those shouldn't be provided to you in some format without the VCRP data.

DR. BRESLAWEC: In fact, they are supposed to be provided for all the reports as background information and with the exception of maybe one or two I think they are in your reports. The memos that we get from Carol exactly as she presents them are in the data part of the report.

Then going on to the next ingredient which is in a green book, isoparaffins. Dr. Belsito.
DR. BELSITO: Yes. This is the first time we're looking at this report, and in June a literature review of the ingredients was issued. And the list of ingredients -- I'm not going to read them all -- can be found on page 1 of the report. And yesterday, we also got some updated concentration of use for this family, as well as some sensitization and irritation data on isododecane, isohexadecane, promethyl, and isoeicosane promethyl, which was negative. However, there was some data on the lower molecular weight isoparaffin, suggesting there could be irritation, particularly under occlusive conditions. So we felt comfortable with the data with going with the safe as used when formulated to be non-irritating. And we would make that as a motion.
DR. BERGFELD: Second?
DR. MARKS: Second. So this would be a tentative report we would issue.
DR. BERGFELD: A tentative final is being recommended, then?
Any further discussion? Any major editorial changes? Dr. Belsito?
DR. BELSITO: Only that this has some respiratory use, inhalation potentials for hairsprays, and that boilerplate needs to be added to the cosmetic section.
DR. BERGFELD: I'd like to draw your attention to the name of the document, "C13-14 Isoparaffins." Is there any need to change that since there are some longer chains in there? Up to 35, C35?
DR. BELSITO: Well, yeah, there's also C7-8 is the lowest --
DR. BERGFELD: Yeah.
DR. BELSITO: So I'm not a chemist. If we just call it isoparaffins, does that take in the isododecane?
DR. LIEBLER: Yes.
DR. BELSITO: So I would just go with isoparaffins.
DR. MARKS: The other under -- the Panel Book, page 9, under the ingredients listed, I didn't mention it yesterday, but should C12-15 be included? Because there is a -- on page 24 of the book, there are some skin sensitization, photosensitization data on the trade name Isopor, which includes C12-15.
DR. BERGFELD: Any other comments? Then

I'll call for the vote. All those in favor of approval of this document? Thank you, unanimous. So, moving on to the first pink document, the capryly glycol group. Dr. Marks?

REPORT

Draft Final Report

IsoParaffins as used in Cosmetics

November 18, 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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur J. Johnson, Jr., Senior Scientific Analyst/Writer.

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ABSTRACT

The safety of isoparaffins in cosmetic products is reviewed in this safety assessment. These ingredients function mostly as solvents in cosmetics. No significant toxicity was identified in oral or inhalation exposure studies of the following endpoints: genotoxicity, reproductive and developmental toxicity, or carcinogenicity. However, nephrotoxicity was a concern, based on data from oral and inhalation exposure studies relating to the involvement of α_{2u}-globulin in the mechanism for isoparaffin-induced nephrotoxicity/renal tubule cell proliferation in male rats of various strains. Because humans lack this protein, the Panel agreed that findings associated with the α_{2u}-globulin protein in male rats were not relevant to humans. The CIR Expert Panel has reviewed relevant data and concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This safety assessment is on isoparaffinic hydrocarbons (isoparaffins), branched alkanes that function mostly as solvents in personal care products. The safety of the following isoparaffins in personal care products is being reviewed:

- C7-8 Isoparaffin
- C8-9 Isoparaffin
- C9-11 Isoparaffin
- C9-12 Isoparaffin
- C9-13 Isoparaffin
- C9-14 Isoparaffin
- C9-16 Isoparaffin
- C10-11 Isoparaffin
- C10-12 Isoparaffin
- C10-13 Isoparaffin
- C11-12 Isoparaffin
- C11-13 Isoparaffin
- C11-14 Isoparaffin
- C12-14 Isoparaffin
- C12-20 Isoparaffin
- C13-14 Isoparaffin
- C13-16 Isoparaffin
- C18-70 Isoparaffin
- C20-40 Isoparaffin
- C15-35 Isoparaffin/Isoalkylcycloalkanes
- Isododecane
- Isoeicosane
- Isohexadecane
- Isooctane

CIR final safety assessments on fossil and synthetic waxes, including paraffin,[1] and two other branched alkanes, isobutane and isopentane,[2] have been published. The CIR Expert Panel concluded that these ingredients are safe in the present practices of use and concentration. These two conclusions were confirmed in 2005.[3,4]

CHEMISTRY

Definition and Structure

The systematic name for the paraffins is alkanes (C_nH_{2n+2}); isoparaffins are branched alkanes. Definitions, other chemical names, and cosmetic ingredient functions for the isoparaffins reviewed in this safety assessment are included in Table 1. The naming convention for many of these ingredients, e.g., C7-8 Isoparaffin, connotes that the ingredient is a mixture of branched

chain aliphatic hydrocarbons with 7 or 8 carbons in the alkyl chain. In the case of C18-70 Isoparaffin, the mixture has a broad range of lengths.

Chemical and Physical Properties

Isooctane (colorless liquid) is practically insoluble in water, somewhat soluble in absolute alcohol, and soluble in the following chemicals: benzene, toluene, xylene, chloroform, ether, carbon disulfide, and carbon tetrachloride.[5] Additional properties of isoparaffins are included in Tables 2A and 2B.

Properties of isoparaffinic hydrocarbon tradename materials produced by various companies are included in Table 3 and Table 4. Branched aliphatic hydrocarbons that are predominantly C10-15 isoparaffinic hydrocarbons in Table 3 are colorless to water-white liquids with a faint petroleum odor.[6] Isopar C is one of the tradename materials included in Table 4. According to Exxon Company, Isopar C is approximately 85% isooctane.[7]

Stability/Reactivity

Branched aliphatic hydrocarbons are predominantly C10-15 isoparaffinic hydrocarbons. These chemicals are quite stable and relatively unreactive, such that polymerization will not occur. However, they are incompatible with strong oxidants (e.g. liquid chlorine, sodium hypochlorite, or concentrated O_2). The incomplete combustion of these compounds may produce CO and aldehydes.[6]

Isooctane, an example of this class of compounds, is considered stable under normal ambient and anticipated storage and handling conditions of temperature and pressure. It may react with oxygen and strong oxidizing agents, such as chlorates, nitrates, peroxides, etc. Hazardous decomposition products include simple hydrocarbons and carbon oxides. Hazardous polymerization is not expected to occur.[8]

Methods of Production

Alkylation is the chemical combination of 2 light hydrocarbon molecules to form a heavier one, and involves the reaction of butenes in the presence of a strong acid catalyst, such as sulfuric or hydrofluoric acid. The product is a heavier multibranched isoparaffin. Propene and various pentenes may be used to produce C_7 or C_9 isoparaffins. Additionally, isomerization is a catalytic process that converts normal paraffins to isoparaffins. The feed is usually light virgin naphtha and, the catalyst, platinum on an alumina or zeolite base.[9] According to Ineos, isoparaffin substances are produced from well-defined feedstocks and are very pure.[10]

The production of isododecane has been described as a patented process from a pre-purified isobutene (branched C4) containing feedstock, and, therefore, is totally sunthetic. The dimethyl branches (termed as germinal, or gem dimethyls) in the isobutene monomer are retained in the final product[11]

2,2,4-trimethylpentane (isooctane) is synthesized from the catalytic hydrogenation of trimethylpentene with a nickel catalyst.[12]

Composition/Impurities

Isododecane (a.k.a. hydrocarbons, C4, 1,3-butadiene-free, polymd., triisobutylene fraction, hydrogenated [CAS No. 93685-81-5]) is a mixture of highly branched C12 isoparaffins, mainly the 2,2,4,6,6-pentamethylheptane isomer (typically ~ 85%).[10] The structure of this isomer is close to a fully permethylated hydrocarbon structure, containing the maximum number of methyl groups. Isododecane also contains ~ 17% of other pentamethylheptanes that have properties that are similar to the main isomer.[11]

Isoeicosane (hydrocarbons, C4, 1,3-butadiene-free, polymd., pentaisobutylene fraction, hydrogenated [CAS No. 93685-79-1]) is a mixture of highly branched C20 isoparaffins, with not more than 10% C16 isoparaffins. Isohexadecane (hydrocarbons, C4, 1,3-butadiene-free, polymd., tetraisobutylene fraction, hydrogenated [CAS No. 93685-80-4]) is a mixture of highly branched C16 isoparaffins with a small proportion of C12 and C20 paraffins of similar structure. Isooctane (90% 2,2,4-trimethylpentane [CAS No. 540-84-1] is a mixture of C8 isoparaffins. [10]

Isododecane is virtually free of aromatics, sulfur-containing molecules, and polar compounds and Isooctane also contains virtually no aromatics or sulfur compounds.[10] The Ineos sales specification for for isododecane is as follows:[11]

- Sum of C_{12} hydrocarbons (% by weight): 98 min
- Sum of C_8 and C_{16} hydrocarbons (% by weight): 2 max
- Aromatics (mg/kg): 1 max
- Carbonyls (mg/kg): 5 max
- Bromine index (mgBr_2/100 g): 15 max
- Sulfur (mg/kg): 1 max
- Peroxides (mg/kg, calculated as H_2O_2): 1 max
- Water (mg/kg): 50 max
- Evaporation residue (mg/100 ml): 1 max
- Neutralization number (mg KOH/g): 0.01 max

Reportedly, according to the hydrocarbon solvent producers, the actual composition of Isopar G and Isopar H (tradenames for C10-11isoparaffin and C11-12 isoparaffin, respectively) may be different from batch to batch within a specific producer and may vary from producer to producer, depending upon the actual feedstock used to prepare the product. Data on average composition indicate that Isopar G contains mostly C10 (53% w/w) and that Isopar H contains mostly C12 (60% w/w). The average Isopar H branching is 3.25 (average number of branches/molecule), and estimates for the number of different branches are as follows : C (0.6), CH (2), CH2 (4.2), and CH3 (5.3). Additionally, the producers have provided information indicating that 5 to 15% w/w of the substance consists of cyclic alkanes, typically C6 with varying degrees of branching.[13]

Both Exxon and Texaco have reported benzene (< 0.1 ppm) as an impurity for all of their isoparaffinic products, and data from Ricoh Corporation in Japan established that benzene contamination was < 0.2 ppm for Isopar® G. These include, but do not appear to be limited to C9 to C15 chain lengths.[6]

As direct food additives, isoparaffinic petroleum hydrocarbons synthesized from petroleum gases consist of a mixture of liquid hydrocarbons that meet the following specifications (21 CFR 172.882).[14]

- Boiling point: 93 to 260 °C
- UV absorbance at 260-319 nm: 1.5 max.
- UV absorbance at 320-329 nm: 0.08 max.
- UV absorbance at 330 to 350 nm: 0.05 max.
- Nonvolatile residual: 0.002 g/100 ml max.

Additionally, these direct food additives may contain antioxidants authorized for use in food, in an amount not to exceed that reasonably required to accomplish the intended technical effect nor to exceed any prescribed limitations.[14] The boiling point specification for isoparaffinic petroleum hydrocarbons as indirect food additives is 63 to 260°C (21 CFR 178.3530),[15,15] and the preceding specifications relating to direct food additive use also apply.

Petroleum hydrocarbons classified as odorless and light (a mixture) is also an approved direct food additive. It is a mixture of liquid hydrocarbons derived from petroleum or synthesized from petroleum gases, and is chiefly paraffinic, isoparaffinic, or naphthenic in nature. This food additive meets the following specifications (21 CFR 172.884):[16]

- Odor is faint and not kerosenic
- Initial boiling point is 300°F min.
- Final boiling point is 650°F max.
- UV absorbance at 280-289 nm: 4.0 max.
- UV absorbance at 290-299 nm: 3.3 max.
- UV absorbance at 300-329 nm: 2.3 max.
- UV absorbance at 330-360 nm: 0.8 max.

The preceding specifications for odorless light petroleum hydrocarbons as a direct food additive is also applicable to its use as an indirect food additive (21 CFR 178.3650).[17,17]

Analytical Methods

Gas chromatography has been used to identify isoparaffins .[18] Specifically, isooctane has been identified using gas chromatography with simultaneous flame ionization detection and radioactivity detection.[7]

USE

Purpose in Cosmetics

Most of the ingredients reviewed in this safety assessment function as solvents in personal care products.[19] Additional functions are included in Table 1.

Scope and Extent of Use in Cosmetics

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2010, the following ingredients were being used in personal care products. C7-8 Isoparaffin, C8-9 Isoparaffin, C9-11 Isoparaffin, C10-11 Isoparaffin, C11-12 Isoparaffin, C11-13 Isoparaffin, C12-14 Isoparaffin, C13-14 Isoparaffin, C13-16 Isoparaffin, C18-70 Isoparaffin, Isododecane, Isoeicosane, and Isohexadecane. [20] These data are summarized in Table 5. Isooctane is not included in the VCRP database; however, Isopar C (C7-8 Isoparaffin) contains approximately 85% isooctane. Independent of these data, the results of a survey of ingredient use concentrations that was conducted by the Personal Care Products Council in 2010, also in Table 5, indicate that the following ingredients were being used: C8-9 Isoparaffin (5 to 40%), C9-11 Isoparaffin (1 to 18%), C10-13 Isoparaffin (0.08 to 0.60%), C11-12 Isoparaffin (1 to 67%), C11-13 Isoparaffin (1 to 27%), C13-14 Isoparaffin 0.0001 to 75%), C13-16 Isoparaffin (0.40 to 18%), Isododecane (0.008 to 90%), Isoeicosane (0.3 to 37%), and Isohexadecane (0.2 to 42%).[21]

No uses of the following isoparaffins were reported in the 2010 VCRP database or in the Personal Care Products Council survey conducted in 2010: C9-12 Isoparaffin, C9-13 Isoparaffin, C9-14 Isoparaffin, C9-16 Isoparaffin, C10-12 Isoparaffin, C11-14 Isoparaffin, C12-20 Isoparaffin, C 20-40 Isoparaffin, and C15-35 Isoparaffin/Isoalkylcycloalkanes. The results of a subsequent 2010 use concentration survey by the Personal Care Products Council confirmed that C15-35 Isoparaffin/Isoalkylcycloalkanes is not being used in cosmetic products.[22]

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

C11-13 Isoparaffin, C13-14 Isoparaffin, and isododecane are used in hair sprays, and effects on the lungs that may be induced by aerosolized products containing these ingredients are of concern.

The aerosol properties that determine deposition in the respiratory system are particle size and density. The parameter most closely associated with deposition is the aerodynamic diameter, d_a, defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. In humans, particles with an aerodynamic diameter of $\leq 10\mu m$ are respirable. Particles with a d_a from 0.1 - 10μm settle in the upper respiratory tract and particles with a $d_a < 0.1$ μm settle in the lower respiratory tract.[23,24]

Particle diameters of 60-80 μm and ≥ 80 μm have been reported for anhydrous hair sprays and pump hairsprays, respectively.[25] In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm.[26] Therefore, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Noncosmetic Use

ISOPAR-E™ is a mixture of predominantly C8-C9 isoparaffinic hydrocarbons that has been used as a solvent in industrial and consumer products, including, but not limited to, typewriter correction fluids.[27]

Liquid gasoline is a complex mixture of petroleum chemicals. In addition to other components, this complex mixture consists of approximately 60 to 75% alkanes (paraffins) that comprise straight-chain hydrocarbons (C_4 to C_{12}), and isoparaffins (branched-chain hydrocarbons) in approximately the same range of chain-lengths.[28] 2,2,4-Trimethylpentane

(isooctane) is used primarily in the alkylation step to derive high-octane gasoline fuels.[12] California phase-2 reformulated gasoline contains isooctane at a concentration of 32.1%. [29]

According to the United States Pharmacopoeia (USP)**,** use of ACS reagent grade isooctane is the reagent specification for prescription and over-the-counter drug products.[30]

Synthetic isoparaffinic petroleum hydrocarbons are used as direct and indirect food additives. Specifications for these classes of direct and indirect food additives are included in the earlier section on Composition/Impurities (21 CFR 172.882; 178.3530).[14,14,15]

Odorless light petroleum hydrocarbons, a mixture that is chiefly paraffinic, isoparaffinic, or naphthenic in nature, is used as a direct and indirect food additive. Specifications for these classes of direct and indirect food additive mixture are included in the earlier section on Composition/Impurities (21 CFR 172.884; 178.3650) .[16,17]

According to Ineos, isododcecane is used in the polymerization process, where it is used as either a solvent or as a dispersing agent for high reactivity organic peroxide catalysts.[10] High activity peroxide catalysts used in the production of PVC and in cross-linked unsaturated polyester are frequently dissolved in isododecane.[11] Isoeicosane has been used as a heat transfer medium for heating and cooling circuits used in chemical processes, particularly in conjunction with isohexadecane. Other applications of isoeicosame include hydraulic fluids, and as an extender in silicone-based dental impression materials. [10]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

*Following ^{14}C-isooctane inhalation in rats, elimination was almost exclusively by the kidneys, and various urinary metabolites**,** 2,4,4-trimethyl-2-pentanol included, have been identified. Following oral dosing of ^{14}C-isooctane in rats, more than half of the administered dose was recovered in the urine and feces. Accumulation in the liver and kidneys was observed, with males retaining substantially greater amounts of radioactivity in the kidneys, compared to females. 2,4,4-trimethyl-2-pentanol was the major metabolite detected in the male rat kidney, but was absent from female rat kidney. However, female rats excreted more conjugates of this metabolite, compared to males.*

Isooctane – Inhalation Exposure

Groups of 15 male F344 rats were exposed for 2 h, nose-only, to ^{14}C-labeled isooctane vapor at concentrations of ~1 and 350 ppm. Radioactivity in exhalant, urine, and feces was determined for 70 h post exposure, after which residual radioactivity in the rat carcasses was determined. Absorbed ^{14}C- isooctane equivalents were eliminated almost exclusively via the kidneys, where excretion of isooctane-introduced ^{14}C was protracted over the entire 70 hr post-exposure observation period. One to 2 % percent of the ^{14}C-isooctane equivalents inhaled at either exposure concentration (~1 or 350 ppm) remained in the carcass 70 h after inhalation exposure. [31]

Results from another inhalation study indicated that the following eight principal urinary metabolites of isooctane were found in the urine of male Fischer 344 rats: 2,2,4-trimethyl-1-pentanol, 2,4,4-trimethyl-1-pentanol, 2,4,4-trimethyl-2-pentanol, 2,2,4-trimethyl-l-pentanoic acid, 2,4,4-trimethyl-l-pentanoic acid, 2,4,4-trimethyl-2-hydroxy-1-pentanoic acid, 2,2,4-trimethyl-5-hydroxy-1-pentanoic acid, and 2,4,4-trimethyl-5-hydroxy-1-pentanoic acid.[32]

Isooctane – Oral Dosing

The metabolism of ^{14}C-isooctane was studied using 8 groups of male Fischer-344 rats (3 per group).[7] The animals were dosed by oral gavage at a dose level of ~ 1 ml/kg (2.9 x 10^7 DPM/kg). The 8 groups were held for the following time intervals between dosing and killing of the animals: 1, 2, 4, 8, 12, 24, 48, and 72 h, respectively. Expired organic vapor and carbon dioxide were trapped from expired air and urine and feces were collected while the animals were in metabolism cages.

More than half of the dose was recovered in the urine and feces after 72 h, with much of this excretion occurring between 24 h and 72 h. More than one third of the dose was detected in exhaled air after 24 h; essentially no additional lung excretion occurred between 24 h and 72 h. Approximately 2.5% of the dose remained in the tissues after 72 h. Oral dosing resulted in excretion of approximately 34% of the isooctane via the lung unmetabolized. The major route of excretion was the urine, accounting for 43% of the dose. Meaningful blood levels of isooctane were not found; however, plasma radioactivity

indicated the presence of circulating metabolites. Tissue concentrations of radioactivity indicated initial accumulation in the liver over the first 8 h, followed by a decline in liver radioactivity. A high concentration of radioactivity was detected in the kidney, surpassing the liver by 12 h. A maximum was reached at 24 h, and levels declined slowly thereafter. It was noted that tissue and plasma levels were consistent with liver formation of metabolites , followed by transport to the kidney in blood plasma and concentration or accumulations in the kidney.[7]

Sexually mature male and female Fischer 344 rats were dosed by gavage (5 ml/kg) with a single dose of ^{3}H-isooctane, in corn oil, at 4.4 mmol/kg and 230 µCi/kg. Urine was collected for 24 h after dosing. The kidneys of male rats retained more radiolabeled material than those of female rats. Subcellular fractionation of the kidneys of male rats at 24 h post-dosing showed that approximately 60% of the radiolabeled material was localized in the 116,000 g supernatant. Gas chromatography-mass spectrometry of an ethyl acetate extract of the α_{2u}-globulin-containing fractions of the 116,000 g supernatant identified 2,4,4-trimethyl-2-pentanol as the only metabolite bound to α_{2u}-globulin. [33] The role of this protein in nephrotoxicity is mentioned under that subheading later in the report text.

Adult Fischer 344 rats of both sexes were given 5 µCi of [14C-5]-isooctane (0.5 g/kg oral dose), and expired organics, expired CO_2, urine, and feces were collected for 72 h.[34] Whole body and kidney autoradiography were performed using [^{14}C-5]-isooctane (50 µ Ci/rat) at the same dose. At an oral dose of 0.5 g/kg, exhaled organics (presumably the parent compound) accounted for 45 to 50% of the dose in both males and females. There were no differences between the sexes in percentages of the administered dose excreted in the urine, feces, or as expired CO_2. A small percentage of the radioactivity was associated with exhaled CO_2, indicating that minimal terminal carbon oxidation on the isooctane molecule had occurred. Approximately 1% of the radiolabel remained in the carcasses and tissues of both male and female rats.

Relatively little radioactivity was detected in the tissues at 72 h, However, kidney levels of radioactive isooctane indicated a pronounced sex difference; male rats retained approximately 10-fold greater amounts of radioactivity than female rats. Less than 0.02% of the dose was detected in the brain, heart, spleen, fat, lung, and liver, with no apparent sex differences. Analysis of whole body autoradiography of isooctane at 72 h confirmed that the majority of the radioactivity in the male rat was localized in the kidney, with minor amounts in the peritoneal fat. Renal autoradiography results indicated that the radioactivity detected in the kidney was associated with the renal cortex. [34]

In another study, male and female Fischer 344 rats received a single oral dose of ^{14}C-isooctane (4.4 mmol/kg; 2 pCi/mmol) and radiolabeled material in the kidney, liver, and plasma was determined at 4 h, 8 h, 12 h, 24 h, and 48 h after dosing. The maximum concentration of isooctane-derived radioactivity in the kidney, liver, and plasma of male rats was found after 12 h (1252, 1000, and 403 nmol eq/g, respectively); maximum concentrations in females were found after 8 h (577, 1163, and 3 17 nmol eq/g, respectively). A selective retention of the isooctane-derived radiolabel in the kidneys of male rats was noted when peak tissue concentration was expressed as a percentage of administered dose. Kidney concentrations of isooctane-derived radiolabel increased in a nonlinear, but dose-dependent, manner. 2,4,4-Trimethyl-2-pentanol was the major metabolite detected in the male rat kidney, but was absent from the female rat kidney. However, compared to males, female rats excreted more conjugates of 2,4,4-trimethyl-2-pentanol in the urine.[35]

ANIMAL TOXICOLOGY

Acute Inhalation Toxicity

In studies on various chain length isoparaffins involving rats, the lethal concentration was greater than the highest concentration generated in each study. C10-11 isoparaffin (420 ppm) did not induce any significant effects on respiratory rate in mice. In experiments involving dogs, guinea pigs, or monkeys exposed to C10-13 isoparaffin (221 to 1806 ppm), effects ranged from retching and eye rubbing to death. In studies involving rats/mice, LC_{50}s for isooctane of up to 47.4 mg/l have been reported, and respiratory irritation was not observed at a concentration of ~ 3,000 ppm (mice). Inhalation exposure (39.63 mg/l air) to a tradename material containing 85% isooctane induced death in mice rats, and guinea pigs.

Results from acute inhalation studies on a number of isoparaffins are summarized in Table 6.

Acute Oral Toxicity

Isoparaffin mixtures of various chain length, isododecane, Permethyl 99A (isododecane), Permethyl 101A (isohexadecane), and isooctane were administered orally to rats, and most of the LD_{50}s reported were > 10 g/kg. The LD_{50} for isododecane (in 10% olive oil) was > 2 g/kg in mice. All LD50 values reported were greater than the highest doses tested.

Results from acute oral studies are summarized in Table 7.

Acute Dermal Toxicity

Isoparaffin mixtures of various chain lengths and Isooctane were administered dermally to rats, and most of the LD_{50}s reported were > 2 g/kg. After isooctane was applied to abraded skin of rabbits at doses up to 3.16 g/kg, necropsy findings included dark livers and mottled kidneys.

Results from acute dermal studies are summarized in Table 8.

Acute Intraperitoneal Toxicity

Isooctane

In an acute intraperitoneal (i.p.) toxicity study, rats (15/dose) were dosed with isooctane (in vegetable oil), followed by a 14-day observation period. An LD_{50} of 2375 mg/kg was reported.[36]

Short-Term Inhalation Toxicity

Short-term inhalation exposure to isoparaffin mixtures (C10 to C13) at a mean exposure concentration of 654 ppm did not induce mortality or remarkable gross or microscopic findings in monkeys. Results from a kidney function study involving short-term inhalation exposure to C10-11 isoparaffin at concentrations up to 900 ppm indicated mild nephrotoxic effects in male, but not female, rats.

C10-11 Isoparaffin

Groups of 50 male and 50 female Fischer 344 rats were exposed to 0 ppm, 300 ppm (1.83 g/m^3), or 900 ppm (5.48 g/m^3) C10-11 isoparaffin 5 days per week (6 h/day) for a total of 8 weeks.[37] The ability of males to concentrate urine was decreased following 4 and 8 weeks of exposure; evidence of recovery was observed 4 weeks after the cessation of exposure. Additionally, compared to controls, the urinary excretion of glucose, protein, and epithelial cells in male rats was increased following 4 and 8 weeks of exposure. Decreased creatinine clearance was observed after 8 weeks. All of these changes, considered mild, returned to normal after 4 weeks of recovery. Microscopic changes in the kidneys of exposed males (both groups) included an increased incidence of regenerative tubular epithelia and tubules dilated at the corticomedullary junction, with proteinaceous debris in the tubules; structural recovery was not complete at the end of the 4-week recovery period. Neither functional nor microscopic renal changes were observed in female rats.

In another study, 3 groups of 15 Fischer 344 rats/sex were exposed (inhalation) to the same concentrations of C10-11 isoparaffin according to a similar 8-week test procedure.[38] An increased incidence of protein droplets was found in the cytoplasm of renal tubular cells of male rats. Other renal changes (both exposures) included foci of regenerative epithelium and tubular dilatation, with intratubular protein occurring between the inner and outer stripe of the medulla. After 20 and 40 days of exposure, focal loss of the brush border, with degeneration and sloughing of necrotic cells, was evident. Reversal of the exposure-related tubular changes was noted at the end of the 4-week recovery period. Renal changes were not observed in female rats.

C 10-13 Isoparaffin (Soltrol® 130)

In a short-term study, 4 rhesus monkeys were exposed to Soltrol® 130 (mean exposure concentration = 654 ppm [4.2 mg/l]) three days per week (6 h/day) for a total of 13 exposures.[6] None of the animals died. Clinical chemistry, urinalysis, and gross and microscopic findings were unremarkable. However, slight lymphocytopenias and neutrophilia were observed in the differential leukocyte count at both the mid-point and end of the study. There were also no remarkable changes in behavioral patterns, body weight, or food consumption.

Isooctane

Wistar rats were exposed to isooctane vapor (10.3 or 24.2 mg/l; 4 h/day) for 5 days. [36] None of the animals died during the 14-day observation period (LD50 > 24.2 mg/l). Signs of toxicity included sedation and impeded breathing.

Subchronic Inhalation Toxicity

Subchronic inhalation exposure to C10-11 isoparaffin at concentrations up to 900 ppm and to C10-12 isoparaffin at concentrations up to 1444 ppm did not induce significant toxic effects, other than mild structural changes in the kidneys of male, but not female, rats. Low-grade anemia was also observed in male rats exposed to C10-12 isoparaffin. Inhalation exposure to isooctane (up to 1180 ppm) in rats for 12 weeks did not cause death; however a treatment-related increase in kidney weight was observed. The results of liver and kidney function tests were unremarkable for isooctane in rats exposed to 9.66 mg/l air for 12 weeks. Inhalation exposure to isododecane, up to 1800 ppm for 13 weeks, induced a dose-related increase in the incidence of tubular nephrosis in male rats.

C10-11 Isoparaffin (Isopar® G)

The subchronic inhalation toxicity of Isopar® G was evaluated using groups of 35 male and 35 female Sprague-Dawley rats.[39] The groups were exposed (inhalation) to 0, 300 ppm (1.91 g/m^3), or 900 ppm (5.62 g/m^3) Isopar® G 5 days per week (6 h/day) for a total of 12 weeks. Decreased body weight was noted in male rats exposed to 300 and 900 ppm. A concentration-related increase in absolute and/or relative kidney weight was observed in male rats from 300 and 900 ppm exposure groups and in female rats exposed to 900 ppm.

Kidney tubule damage (male rats only) was described as mild, but a concentration- and duration-related increase in severity was noted. Also damage to the kidneys of male rats was essentially comparable at 8 and 12 weeks. An increase in both absolute and relative liver weight was observed in male and female rats exposed to 900 ppm; however, there was no microscopic evidence of liver damage. Furthermore, this change was considered representative of a non-specific metabolic and/or physiological response to the uptake of hydrocarbon. Study results indicated that subchronic exposure to Isopar® G at doses up to 900 ppm did not induce significant toxic effects, other than mild structural changes in the kidneys of male rats.[39]

C10-12 Isoparaffin (Shell Sol TD)

In another subchronic study, male and female rats were exposed (inhalation) to Shell Sol TD at the following concentrations: 359 ppm (2.53 g/m^3), 737 ppm (5.20 g/m^3), or 1444 ppm (10.19 g/m^3).[6] A nonexposed control group was also included. Groups were exposed 5 days per week (6 h/day) for a total of 13 weeks. Neither deaths nor clinical signs occurred in both the low and intermediate dose groups. Rats in the high exposure group became slightly lethargic. Aspartate aminotransferase and alanine aminotransferase levels were decreased in females of all exposure groups, whereas, alkaline phosphatase, potassium, chloride, and albumin were increased only in males of the high exposure group. Changes in the levels of these enzymes, ions, etc. were considered minor and their toxicological significance remains unknown. A low-grade anemia, characterized by slight reductions in hemoglobin, packed cell volume, and total erythrocyte counts, was noted in males of all exposure groups.

Increased spleen weights were observed in male rats of the high exposure group. Liver weights were increased in males of the high exposure group and in males and females of the intermediate and high exposure groups. However, in the absence of histological changes, these changes in organ weight were regarded as adaptation rather than as a toxic effect. Increased kidney weights were observed in males of all exposure groups, and these weight changes were accompanied by hyaline intracytoplasmic inclusions, an increased incidence of tubular degeneration and/or dilatation in the cortical tubules. Increased kidney weights were also observed in females of the high exposure group, in the absence of any exposure-related kidney lesions. The low-grade anemia and mild renal degenerative changes were considered related to Shell Sol TD exposure and biologically significant.[6]

Isooctane

Two groups of 70 Sprague-Dawley rats were exposed, by inhalation, to Isopar C (85% isooctane) at cumulative mean exposure concentrations of 385 and 1180 ppm, respectively. [7] A third group served as the untreated control and received sham air exposures. Each group consisted of 35 males and 35 females. The animals were exposed to the test substance 5 days per week (6 h/day) for 12 weeks. No treatment-related mortalities occurred in the study. Body weights for control and test animals were comparable and unremarkable. Some of the hematocrit, hemoglobin, and red cell values were significantly depressed, compared to control values; however, all values were within biological limits. Of the clinical chemistry parameters evaluated, an elevated blood urea nitrogen level in the 385 ppm exposure group was the only finding that may have indicated a slight treatment-related response.

Compared to controls, an analysis of absolute and relative organ/body weight ratios indicated an increase in both absolute and relative mean kidney weights at 1180 ppm (males, week 8) and at both 385 and 1180 ppm (males, week 12). These

changes in organ weight were considered treatment-related. At microscopic examination, mild tubular injury at 8 and 12 weeks was observed in some of the male rats exposed to 1180 ppm. All other necropsy findings were considered unremarkable.[7]

Rats (10 males, 10 females) were exposed to isooctane vapor (9.66 mg/l, 6 h/day) 5 days per week for 12 weeks. [36] An untreated control group was also included in the study. There were no clinical signs or hematological/ macroscopic findings. Increased relative kidney weights were noted; however, the results of liver and kidney function tests were unremarkable. Decreased body weight gain was noted in male rats only.

Isododecane

In a subchronic inhalation toxicity study, groups of rats (20 males, 20 females/group) were exposed to atmospheres containing 0, 200 ppm (1.4 g/m^3 air), 600 ppm (4.2 g/m^3), or 1800 ppm (123.6 g/m^3) 5 days per week (6h/day) for 13 weeks.[40] Growth retardation and a transient reduction in red blood cell counts were noted in males and females exposed to 1800 ppm isododecane. What appeared to have been a lower degree and incidence of inflammatory reactions in the respiratory tract was associated with males exposed to 1800 ppm and females exposed to 600 and 1800 ppm. Increased plasma alkaline phosphatase activity was reported only for female rats at this level of exposure.

Relative kidney weights were increased in rats of both sexes exposed to 1800 ppm and in male rats exposed to 600 ppm. At necropsy, there appeared to have been an increased incidence of green kidneys following exposure to 1800 ppm. Microscopic examination confirmed a dose-related increase in the incidence of tubular nephrosis in male rats. Data relating to effects on the reproductive system are included in the Reproductive and Developmental Toxicity section section later in the report text. It was concluded that the no-adverse-efffect level of isododecane in rats was < 200 ppm. [40]

Chronic Oral Toxicity

The available studies provide evidence that the kidney toxicity induced by isooctane (2,2,4-trimethylpentane) in male rats is related to α_{2u}-globulin accumulation in the proximal tubules (a response that is specific to male rats), but the associated nephropathy is not used by EPA in establishing an oral reference dose.

Isooctane

According to the U.S. EPA, an oral reference dose (RfD) is an estimate of a daily oral exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime.[41]

EPA noted that a number of acute and short-term studies have been identified in the literature, but that these studies are limited, in that they were designed to only investigate endpoints specific to α_{2u}-globulin-associated nephropathy in male rats. Furthermore, it was noted that detailed studies on isooctane (2,2,4-trimethylpentane) that identify sufficient dose-response and duration information for other endpoints are lacking. The available studies provide evidence that the kidney toxicity induced by isooctane in male rats is related to α_{2u}-globulin accumulation in the proximal tubules (a response that is specific to male rats). Thus, EPA concluded that "if a chemical induces α_{2u}-globulin accumulation in male rats, the associated nephropathy is not used as an endpoint for determining noncarcinogenic hazard." No other studies were considered suitable for the derivation of an RfD, and, therefore, an oral RfD for chronic oral exposure was not derived.[41]

Chronic Inhalation Toxicity

α_{2u}-globulin-associated nephropathy has been observed in a subchronic inhalation study on isooctane (2,2,4-trimethylpentane), providing evidence that the kidney toxicity induced by this chemical is related to α_{2u}-globulin accumulation in the proximal tubules, but this endpoint was not considered useful in deriving an inhalation reference dose.

Isooctane

EPA has made an effort to derive a reference concentration for isooctane chronic inhalation exposure (RfC).[41] The RfC (mg/m^3), analogous to the RfD, takes into consideration toxic effects for both the respiratory system (portal of entry) and effects peripheral to the respiratory system (extrarespiratory effects). EPA noted that α_{2u}-globulin-associated nephropathy has been observed in a subchronic inhalation study on isooctane, providing evidence that the kidney toxicity induced by this chemical is related to α_{2u}-globulin accumulation in the proximal tubules. Thus, EPA arrived at the conclusion stated in the preceding section, and an inhalation RfC was not derived.

Nephrotoxicity

Oral dosing with isooctane (in corn oil, 0.5 mg/kg/day) in rats caused a significant decrease in the glomerular filtration rate. The results of other oral studies indicated that the kidney is the target organ for isooctane. Findings included significant increases in kidney- and liver-to-body weight ratios and stimulation of DNA turnover in the proximal tubule. Light microscopic lesions in the proximal convoluted tubule consisted of protein droplet and crystalloid body accumulation, degeneration, and necrosis. Isooctane-induced nephrotoxicity was noted at a daily dose volume of 10 ml/kg (undiluted) or daily doses of up to 500 mg/kg (in corn oil).

Isooctane

Renal function changes were evaluated in a study involving Fisher 344 rats (sex not stated).[12] Groups of 4 rats were dosed orally with isooctane (in corn oil) at a dose of 0.1 or 0.5 g/kg/day for 4 weeks (5 times/week). Groups of 3 rats served as controls (corn oil). A statistically significant decrease in the inulin clearance (marker for glomerular filtration rate [gfr]) was observed after 2 and 4 weeks of gavage with 0.5 g/kg/day. The decrease in gfr was more profound at 4 weeks than at 2 weeks. A significant increase in the urinary enzyme, N-acetyl-beta-glucosaminidase (at 2 and 4 weeks) was associated with this reduction in the gfr.

The nephrotoxicity of isooctane was evaluated using groups of 8 male Fischer-344 rats.[7] The undiluted test substance was administered by oral gavage (dose volume = 1.0 ml/kg) to the 5 test groups on consecutive days as follows: group 1 (1 day), group 2 (3 days), group 3 (7 days), group 4 (14 days), and group 5 (21 days). Similarly, control groups were dosed with distilled water on consecutive days. A 90 min pulse label (i.p.) with ^{3}H-thymidine, followed by extraction of DNA from the liver and kidney was used to determine new DNA synthesis. Compared to controls, kidney-to-body weight ratios were significantly greater in treatment groups at 3, 14, and 21 days of dosing. By day 21, kidney weight ratios were 29% greater in treatment groups. Liver-to-body weight ratios were significantly higher at 3, 7, 14 and 21 days; ratios were 61% higher by day 21. Both the liver and kidney showed an increase in relative organ weight and a concomitant decrease in DNA content, with the liver showing the greater effect. It was noted that much of the decreased DNA content could be accounted for by the relative increase in organ weight.

Daily dosing with isooctane resulted in stimulation of DNA turnover in the kidney. This effect was maximal ranging from 7 to 14 days of dosing, when ^{3}H-thymidine incorporation into DNA was 4-fold greater when compared to controls. On the other hand, the liver only showed stimulation of DNA turnover following 1 day of dosing, and subsequent dosing did not produce a significant effect. It was noted that these results are consistent with findings that the kidney is the target organ for isooctane and compounds in this class.[7]

Groups of 5 male Fischer 344 rats received oral doses of isooctane (50 to 500 mg/kg) by gavage for 21 days.[42] The animals were injected i.p. with [CH_3-^{3}H]-thymidine on day 22, and sites of renal cell proliferation induced by isooctane were localized and quantitated using histoautoradiographic analysis. Light microscopic lesions in the proximal convoluted tubule consisted of protein droplet and crystalloid body accumulation, degeneration, and necrosis. These renal lesions were not dose-related, but a finding of tubular dilation of the thin segments with granular cell debris was dose-related.

Isooctane induced a non-dose-related, 5- to 6-fold increase in the labeling index of the same proximal convoluted tubule portions (P_2 segment) that contained severe crystalloid body accumulation, degeneration, and necrosis. Less pronounced, but statistically significant ($p \leq 0.05$), increases in cell proliferation were also observed in other nephron segments, indicative of a generalized regenerative response of the kidney to isooctane. It was noted that the cytotoxic and regenerative effects of oral dosing with isooctane suggest that similar mechanisms may be involved in the induction of kidney tumors in male rats exposed (chronic inhalation) to unleaded gasoline.[42] The observed isooctane-induced increase in cell proliferation in nephron segments is also mentioned briefly in the Carcinogenicity section later in the report text.

Nephrotoxicity/Hepatotoxicity

Based on microscopic findings, oral dosing of isooctane (in corn oil, at 2 ml/kg[2252 mg/kg]) in rats appeared to have induced hepatotoxicity as well as nephrotoxicity.

Isooctane

The potential for isooctane-induced nephrotoxicity or hepatotoxicity was evaluted using groups of 6 male Wistar albino rats.[43] The test substance (in corn oil [2:1]) was administered by gavage at a single daily dose of 2 ml/kg. Control rats

received a similar volume of corn oil alone. After 2 days of treatment, all test rats had signs of toxicity and had lost a considerable amount of weight. Thus, 6 control animals and all treated animals were killed by the third day. Macroscopic examination of the kidneys revealed no visible lesions; however, white patches (slightly raised) on the liver were found in 2 rats.

Centrilobular and confluent necrosis, hydropic degeneration, and vaculolation of hepatocytes were noted at microscopic examination. Analysis of plasma alkaline phosphatase and aspartate transominase activity revealed increases that are consistent with liver damage. Microscopic examination of the kidneys revealed eosinophilic hyaline droplet accumulation in cells of the tubules and tubular dilation**.** Analysis of urinary N-acetyl-B-glucosaminidase and alkaline phosphatase activity showed increases that are consistent with renal toxicity. Based on the results of this study, the authors noted that it would appear that isooctane possess hepatotoxic as well as nephrotoxic properties.[43]

Nephrotoxicity Mode of Action in Rats

Male rat nephrotoxicity observed after exposure to isoparaffins has been attributed to reversible binding of the hydrocarbon to α_{2u}-globulin, a mechanism of action that is not relevant in humans.

Subchronic or chronic inhalation exposure to C10-12 isoparaffin at a concentration of 6.5 mg/l caused both functional and morphological renal changes in normal male Sprague-Dawley rats, but not female or castrated male rats of the same strain.[44] Male rat nephrotoxicity has been attributed to reversible binding of hydrocarbon to α_{2u}-globulin, which is not synthesized in humans. [45] Based on the measurement of several biochemical indicators of nephrotoxicity, isooctane (single oral dose, 12 or 24 mmol/kg) in corn oil was not found to impair renal proximal tubular function in male Specific Pathogen Free (SPF) rats of the Alderley park strain (Alpk/AP). There was a strong association between the presence of renal hyaline droplets and the occurrence of α_{2u}-globulin at these doses; however, the toxicological significance of increases in renal hyaline droplet formation was not established.[46] Histopathological changes in the kidney were not observed, and neither hyaline droplets nor α_{2u}-globulin were detected in a study involving NCI-Black-Reiter male rats receiving isooctane (in corn oil) at daily oral doses of 500 mg/kg. The NCI-Black-Reiter rat is the only strain of male rat that is known not to synthesize the hepatic form of the low molecular weight protein α_{2u}-globulin. In the absence of this protein, isooctane did not induce kidney injury, and these data provide further support for the role of α_{2u}-globulin in nephrotoxicity. [47]

Cytotoxicity

Isooctane did not have an effect on cell proliferation in a human cancer cell line in vitro.

HeLa cell (S3 cell line) suspensions were exposed to isooctane at concentrations ranging from 0.1% to 7.5% and examined for morphological changes associated with toxicity.[48] Cultures were incubated for 2 to 3 days at a temperature of 37°C. The overall physiologic state of the cells after exposure was quantified, in terms of the intracellular ATP concentration, using a chemiluminescence ATP assay. There was no obvious effect on cell proliferation, e.g., the absence of mitotic figures was not noted after day 1 of exposure. Additionally, there was no evidence of differences in cell shape, granularity around the nucleus, or visible damage to the cell membrane. Other results indicated that exposure to isooctane produced little change in the intracellular ATP concentration.

Ocular Irritation

*C9-11, C10-11, C10-13, and C11-13 isoparaffins (concentrations not stated) were slightly irritating and isooctane (concentration not stated), isododecane (undiluted), undiluted Permethyl 99A (isododecane) and Permethyl 101A (isohexadecane) were non-irritating to the eyes of rabbits. A mixture containing 40% isododecane and 60% trimethylsiloxysilicate was not irritating to the eyes of rabbits when tested at a concentration of 50% in olive oil (effective isododecane concentration ≈ 20%). In the in vitro MTT assay (described below, with results), an irritancy classification of no/minimal irritation was reported for a tan enhancing spray containing 42% isohexadecane. In other in vitro assays, results were negative or there was a potential for slight ocular irritation. Study summaries are included in Table 9***.***

Isohexadecane and Isododecane

The EpiOcular™ human cell construct (EOT) was used to assess the ocular irritation potential of a tan enhancing spray containing 42% isohexadecane. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide) conversion assay was used to assess cellular metabolism by EOT following product exposure. This assay measures the NAD (P)H-dependent

microsomal enzyme reduction of MTT, and, to a lesser extent, the succinate dehydrogenase reduction of MTT, to a blue formazan precipitate. The duration of exposure resulting in a 50% decrease in MTT conversion (ET_{50}) in product-treated EOTs, relative to controls, was determined. An ET50 of 698.25 min (no/minimal irritation) was reported for the tan enhancing spray containing 42% isohexadecane.[49]

In the *in vitro* hens's egg test, EXP-SR5 (contains 55.5% isohexadecane, 35% isododecane), [50] Permethyl 216C (contains 40% isohexadecane),[51]Permethyl 284C (contains 20% isododecane),[52] and Permethyl 296C (contains 50% isododecane),[53] were classified as negative for ocular irritation potential. Results for Permethyl 222C (material containing 40% isoeicosane) indicated practically no irritation to slight ocular irritation.[54] In this assay, the chorioallantoic membrane (CAM) of the chick embryo responds to injury with a complete inflammatory reaction, comparable to that induced in the rabbit eye test.

Skin Irritation

C9-12 isoparraffin was moderately irritating and C9-11 and C11-13 isoparaffins(concentrations not stated) were mildly irritating to the skin of rabbits. C10-11 isoparaffin induced reactions in rabbits ranging from none to primary skin irritation (undiluted) and C10-13 isoparaffin (concentrations not stated) induced very slight to severe skin irritation. Isooctane, isododecane (undiluted and 50% in petrolatum), and Permethyl 99A(isododecane) were slightly irritating to the skin of rabbits; Permethyl101 A (isohexadecane)was non-irritating.

Summaries of skin irritation studies are included in Table 10.

Comedogenicity

Isododecane and and isohexadecane were classified as non-comedogenic in rabbits.

Isododecane

Isododecane was applied undiluted to the ear of each of 3 New Zealand White rabbits for 3 consecutive weeks (5 days/week). The right ear served as the untreated control. At microscopic examination, hyperkeratosis was observed on the treated and control ear of one rabbit and on the treated ear of a second rabbit. There was no evidence of comedone formation on treated or control ears of rabbits, and isododecane was considered non-comedogenic.[55] Permethyl 99A (isododecane) was also classified as non-comedogenic when tested according to the same procedure.[56]

Isohexadecane

Permethyl 101A (isododecane) was classified as non-comedogenic in rabbits when evaluated according to the preceding test procedure. [57]

Skin Sensitization

Isopar® L (C11-13 Isoparaffin)

Reportedly, in a guinea pig sensitization test, Isopar® L was classified as a non-sensitizer.[6] These data were referenced as unpublished data from Exxon Company and study details were not included.

Behavioral Effects

Inhalation exposure to C8-9 Isoparaffin induced behavioral effects in mice mostly at a concentration of 6000 ppm.

C8-9 Isoparaffin (Isopar-E™)

A study was conducted to evaluate behavioral effects of ISOPAR-E™ in groups of 8 adult male CFW albino mice.[27] Static exposure chambers were used for mice tested in the functional observational battery, one of the behavioral test methods used. Vapor exposures were conducted in 29 l cylindrical jars, and all vapor exposures were 30 min in duration. Three groups of mice were exposed to concentrations of 2000, 4000, and 6000 ppm, respectively. A fourth group was exposed to air only. ISOPAR-E™ produced few effects over the range of concentrations tested, with most effects being observed at the highest test concentration (6000 ppm). Results of the functional observational battery conducted during the last 2 min of solvent

exposure indicated that ISOPAR-E™ induced decreases in CNS activity (i.e., arousal), muscle tone/equilibrium (i.e., gait, mobility, and landing foot splay), and sen=sorimotor reactivity (i.e., approach response). Exposure to a higher concentration of ISOPAR-E™ (8000 ppm) caused death due to convulsions.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

C10-11 Isoparaffin was neither fetotoxic nor teratogenic to rats following inhalation exposure at concentrations up to 900 ppm. Similarly, Isopar C (85% isooctane) was neither embryotoxic nor teratogenic at concentrations up to 1200 ppm in an inhalation study. Isopar C also did not induce reproductive effects (implantation/pregnancy rate changes) in female rats or affect reproductive organ development in male rats at the same inhalation exposure concentration. Increased relative weights of the gonads were noted in male and female rats exposed to isododecane at a concentration of 1800 ppm for 13 weeks.

Isopar® G (C10-11 Isoparaffin)

Reportedly, in a reproductive toxicity study, mated Sprague Dawley rats were exposed (inhalation, 6 h/day) to 0, 300, or 900 ppm Isopar®G on days 6 to 15 of gestation.[6] The dams were killed on day 21 of gestation, and fetuses were examined for external, visceral, and skeletal malformations. Compared to controls, there were no changes in the following parameters: resorptions, fetal size, sex distribution, and fetal alterations. Isopar® G was neither fetotoxic nor teratogenic to rats at concentrations up to 900 ppm. These data were referenced as unpublished data from Exxon Company, and the number of animals per dose group was not included.

Isooctane

The embryotoxic and/or teratogenic potential of Isopar C (85% isooctane) was evaluated using groups of 20 mated Sprague-Dawley rats.[7] Two groups were exposed to the test substance at concentrations of 400 and 1200 ppm, respectively, on days 6 to 15 of gestation. A negative control (air-exposed) group and a positive control (acetylsalicylic acid orally, 400 mg/kg/day) group were included. Female rats were killed on day 21 of gestation, and fetuses were evaluated for external, soft-tissue, and skeletal malformations.

Compared to controls, rats exposed to 400 or 1200 ppm Isopar C had a significantly higher implantation efficiency. However, this finding was not indicative of a treatment-related adverse effect. Also, in these 2 groups, there were no treatment-related effects on the following: uterine implantation data, fetal size or sex distribution data, or fetal external, soft-tissue, or skeletal examination data. The incidence of fetuses with ossification variations was significant increased in the 1200 ppm exposure group. However, the types and incidences of ossification variations were generally comparable to observations in the control group. It was concluded that Isopar C was neither embryotoxic nor teratogenic in Sprague-Dawley rats exposed at concentrations of 400 and 1200 ppm. The incidence of fetal malformations was increased in the positive control group.[7]

Isododecane

Results from a subchronic inhalation toxicity study on isododecane, summarized earlier in the report text, indicated increased relative weights of the gonads in male and female rats exposed (inhalation) to 1800 ppm isododecane for 13 weeks.[40] The test protocol and other study results are included in the Subchronic Inhalation Toxicity section.

GENOTOXICITY

C10-11isoparaffin was not genotoxic in in vitro or in vivo mutagenicity tests, including a dominant lethal test in which results showed no treatment-related reproductive effects in rats. In vitro genotoxicity test results for C10-13 and C11-13 isoparaffin, isododecane, and a mixture containing 40% isododecane and 60% trimethylsiloxysilicate were also negative. Isooctane was not genotoxic in assays involving mammalian cells, and Isopar C (85% isooctane) was not genotoxic in the dominant lethal test. Study results are summarized in Table 11.

The mutagenicity of Isopar C (85% isooctane) following inhalation exposure was evaluated in the dominant lethal test using groups of 10 male Sprague-Dawley rats, which were subsequently mated with females.[7] Two groups were exposed (inhalation) to the test substance at concentrations of 400 and 1200 ppm, respectively. Male rats were exposed 5 days per week (6 h/day) for 8 consecutive weeks. Treatment was followed by a 2-week mating period. A negative control group (air-

exposed) and a positive control group (triethylenemelamine [TEM], 0.5 mg./kg i.p.) were also included in the study. Mean body weights were comparable between negative control and test groups.

The mating of females with TEM positive control males resulted in fewer implants and lower implantation efficiency values (indictive of pre-implantation loss), compared to females mated with negative control males. There were no treatment-related effects on mortality, in-life physical observations, or necropsy observations following exposure to 400 or 1200 ppm. Pregnancy rates, implantation data, and implantation efficiency values and fetal death data for females mated to males exposed to Isopar C were comparable to data for females mated to negative control males. Microscopic evaluation of the following tissues from 5 randomly selected males did not reveal any treatment-related effects: testes, seminal vesicles, epididymides, and prostate. It was concluded that Isopar C was not mutagenic in the dominant-lethal test at doses of 400 and 1200 ppm.[7]

CARCINOGENICITY

When the tumorigenicity of 15% petrolatum (in isooctane) was evaluated in mice, there was no significant tumor incidence following lifetime skin treatment. Other study results suggest that chronic cell proliferation associated with α_{2u}-globulin nephropathy and chronic progressive nephrosis in male rats exposed to unleaded gasoline or its isoparaffinic components, such as isooctane, may be responsible for nephrocarcinogenic effects of unleaded gasoline. The EPA has determined that there is inadequate information to assess the carcinogenic potential of isooctane (2,2,4-trimethylpentane), specifically noting the absence of chronic bioassay studies that assess the carcinogenic effects of isooctane.

Isooctane

Petrolatum (15% in isooctane [concentration not stated]) was applied to the skin in groups of 30 male and 30 female Swiss mice.[58] Applications (3 drops, ~ 60 µl/application) were made to dorsal skin twice weekly during lifetime treatment. Survival of the mice was good and no significant tumor incidence was found.

Findings relating to isooctane-induced increases in cell proliferation in rat nephron segments are included in the section on Nephrotoxicity/Cell Proliferation earlier in the report text.[42]

A study was performed to better characterize the pathogenesis of α_{2u}-globulin nephropathy.[59] Groups of 3 F344 rats per sex were exposed (inhalation) to 10, 70, or 300 ppm unleaded gasoline or 50 ppm isooctane from 3 to 50 weeks (6h/day, 5 days/week). Cell proliferation was quantitated within 3 proximal tubule segments of the kidney (P_1, P_2, and P_3). Immunohistochemical staining of α_{2u}-globulin was performed on kidney sections. To determine whether accumulated α_{2u}-globulin was concentration-related, the ranking of slides based on the severity and extent of accumulation of crystalloid α_{2u}-globulin droplets and single cell necrosis of the affected P_2 tubule was performed. Results indicated significant increases in rank above age-matched controls in kidneys from male rats exposed to 300 ppm unleaded gasoline or 50 ppm TMP at each exposure interval. Mild but detectable increases in α_{2u}-globulin staining were observed in groups exposed to 10 or 70 ppm unleaded gasoline.

The largest increases in labeling indices (above controls) occurred in the P_2 segment, i.e., 6- to 11-fold increases in labeling indices at 3, 10, and 22 weeks of exposure to 300 ppm unleaded gasoline or 50 ppm isooctane. These changes were indicative of dose-related increases in cell turnover, and this proliferative response closely paralleled the extent and severity of detectable α_{2u}-globulin in the P_2 segment. Neither α_{2u}-globulin nor cytotoxicity was evident in cells of the P_1 or P_3 segment; however, in the P_3 segment, cell proliferation was increased (up to 8-fold) for up to 22 weeks of exposure. Compared to controls, increased numbers of proximal tubules affected by chronic progressive nephrosis were found in males exposed to unleaded gasoline or isooctane for 22 or 48 weeks. These lesions contained epithelial cells that were highly proliferative. Neither α_{2u}-globulin nephropathy nor increases in P_2 or P_3 cell turnover were observed in control or treated female rats. The authors noted that the results of this study suggests that chronic cell proliferation associated with α_{2u}-globulin nephropathy and chronic progressive nephrosis in male rats exposed to unleaded gasoline or its isoparaffinic components, such as isooctane, may be responsible for nephrocarcinogenic effects of unleaded gasoline in male rats.[59]

The majority of the reported studies contribute information specifically related to the histopathological sequence of α_{2u}-globulin-associated nephrotoxicity. Thus, these studies do not examine any other tissue/organ except the kidney. In comparing the tumor promoting capability between isooctane and unleaded gasoline (UG, a mixture), Short et al.[60] showed that both agents had promoting potential in male, but not female rats. However, the results were not sufficiently descriptive to ascribe the portion of the promoting potential of UG that could be attributable to isooctane. The few studies available on its genotoxic potential were negative, as isooctane does not increase mutations at the TK locus in a study by Richardson et

al.,[61] induce DNA double-strand breaks in a study by McLaren et al.,[62] or stimulate unscheduled DNA synthesis in a study by Loury et al.[63]

The U.S. EPA concluded that there are no available chronic bioassays or epidemiological studies in humans that assess the carcinogenicity of isooctane, and that this overall lack of information represented a data gap and did not allow for a quantitative assessment of the carcinogenicity of isooctane.[41,64,64]

Tumor Promotion

Isooctane

An initiation-promotion study was performed using 30 Fischer 344 rats/sex/experiment. Rats were given N-ethyl-N-hydroxyethylnitrosamine (170 ppm) in drinking water for 2 weeks, followed by a 2-week non-treatment period.[60] The rats were then exposed to isooctane via inhalation (50 ppm [~ 2.4 mg/l],6 h/day) 5 days per week for 24 or 59 to 60 weeks. Decreased kidney weights were noted in male rats only, and incidences of atypical cell foci (ACF) and renal cell tumors (RCT) were 79% and 14%, respectively, in these animals. Incidences in control rats were 35% (ACF) and 4% (RCT), and the differences between test and control rats were not found to be statistically significant. Female rats had normal kidney weights, and there were no increases in ACF or RCT.

CLINICAL ASSESSMENT OF SAFETY

Distribution/Biochemical Effects

Human brain concentrations of C8-12 isoparaffin following inhalation exposure have been calculated using mathematical modeling. There were no exposure-related changes in blood chemistry or significant changes in creatine kinase or follicle stimulating hormone.

Shell Sol TD (C8-12 Isoparaffin)

Seven subjects were exposed (inhalation) to Shell Sol TD at a concentration of 100 ppm for 5 days (6 h/day). The mean concentration in the fat was 41.1 mg/kg (measured value) , and the estimated mean half-life in fat was 7 days. At steady state, the maximum brain isoparaffin concentration was estimated to be 11 mg/kg, with an estimated maximum half-life of 18 to 19 h.[65] Following exposure of 8 subjects to Shell Sol TD at a concentration of 100 ppm (0.6 g/m^3) for 3 h, the maximum steady-state concentration was calculated (using mathematical modeling) to be 55 mg/kg for fat and 5 mg/kg for the brain.[66]

Shell Sol TS (C8-12 Isoparaffin)

None of the following symptoms associated with solvent exposure was observed in 12 human subjects, following a single, 6h inhalation exposure to 100 ppm Shell Sol TS: headache, dizziness, feeling of inebriation, visual disturbances, tremor, muscular weakness, impairment of coordination, or paresthesia. A mean blood concentration of 2.3 mg/l (14 nmol/l) was reported at the end of exposure. There were no changes in blood chemistry, and results of urinalyses indicated that exposure had no effect on the 2 urine variables albumin and β_2-microglobulin.[67]

Seven subjects were exposed (inhalation) to Shell Sol TS at a concentration of 103 ppm (0.61 g/m^3) for 5 days (6 h/day), and 5 subjects served as non-exposed controls. Compared to controls, significant differences in creatine kinase and follicle stimulating hormone were noted following exposure. It was noted that there was marked intra-individual and inter-individual variability in the serum concentrations of these parameters. There was no evidence of changes in plasma immunoglobulin or orosomucoid.[68]

Ocular Irritation

Both a mascara containing 48.28% C11-12 isoparaffin and one containing 63.7% isododecane were classified as well-tolerated, in terms of ocular irritation potential, following application to the eye lashes of female subjects.

C11-12 Isoparaffin

The ocular acceptability of a mascara containing 48.28% C11-12 isoparaffin was evaluated using 48 female subjects. The product was applied to the eyelashes twice daily (morning and early afternoon) for 4 weeks, and was considered well-tolerated. Nine subjects presented with the following subjective signs, described as being of slight intensity and of very short to long (1 day) duration: general sensation of irritation, ocular stinging, palpebral stinging, sensation of foreign body, discomfort, and sensation of dryness and tightness). One subject presented with subjective signs (ocular stinging) that were of slight intensity and very short duration. These signs were frequent and said to have been probably due to mascara.[69]

Isododecane

In another ocular acceptability study, a mascara containing 63.7% isododecane was evaluated using 10 female subjects. The product was applied to the eye lashes once daily for 5 days, and there was no evidence of ocular irritation.[70] When the test procedure was repeated in another study (same product, 50 females) over a 4-week period, an ocular irritation rate of 0.04% was reported.[71]

Skin Irritation

Though defatting of the skinand irritation have been associated with exposure to C10-11, C11-13, and C12-15 isoparaffins under closed or semi-occlusive conditions, a hair shine product containing 41.25% C11-12 isoparaffin (semi-occlusive patch application) was classified as having good skin compatibility in human subjects (skin irritation potential not stated). Mild itching/tingling reactions in subjects involved in an in-use safety test of a tan enhancing spray containing 42% isohexadecane were not classified as clinically significant.

Isopar® G (C10-11 Isoparaffin)
Isopar® L (C11-13 Isoparaffin)
Isopar® M (C12-15 Isoparaffin)

Under closed or semi-occlusive conditions where evaporation cannot freely occur, C10-11, C11-13, and C12-15 isoparaffins can produce defatting of the skin and irritation.[6]

C11-12 Isoparaffin

The skin irritation potential of a hair shine containing 41.25% C11-12 isoparaffin (as supplied) was evaluated using 20 subjects. The test substance was applied (3 repeated applications) under a semi-occlusive patch for 24 h. The application area was not stated. It was concluded that the product had very good skin compatibility. Whether or not the hair shine product caused skin irritation was not stated in the English translation (summary) of this study.[72]

Isododecane

Results were negative for isododecane (contained ~ 85% 2,2,4,6,6-pentamethylheptane) in an open patch test involving 20 subjects. However, skin irritation was observed in a study in which 20 subjects were patch tested (closed patches) with the following concentrations of isododecane (contains > 98% 2,2,4,6,6-pentamethylheptane) in petrolatum: 10% (2 subjects), 20% (3 subjects), and 50% (6 subjects). A mixture containing 40% isododecane and 60% trimethylsiloxysilicate caused skin irritation in 2 of 19 subjects patch tested (closed patches) at a concentration of 40% in petrolatum (effective isododecane concentration ≈ 16%).[73]

Isohexadecane

The in-use safety of a tan enhancing spray containing 42% isohexadecane, following 2 consecutive weeks of use (once daily), was evaluated using 30 volunteers (males and females). Safety was determined by clinically evaluating changes in dermatological data (dryness and redness) and changes in opthalmological data (e.g., eyelids and margins, conjunctivae, corneas). Product-related adverse reactions (4 subjects total) included: mild itching of forehead (1 subject), burning sensation in left eye (1 subject), mild tingling and itching of arms, chest, shoulders, and face (1 subject), and mild tingling of cheeks. The changes observed in subjects tested were reported to be not clinically significant.[74]

Predictive Skin Irritation and Sensitization

A mascara containing 48.28% C11-12 isoparaffin was classified as a non-irritant and non-sensitizer in an RIPT involving healthy subjects. The same conclusion was associated with RIPT results for cosmetic product formulations (hair, lip, or eye area products) containing isododecane at concentrations ranging from 40.16% to 90.3% and a lip balm containing 27.15%

isoeicosane applied to healthy subjects. Tradename materials containing 50% or 20% isododecane and another containing 40% isoeicosane were also classified as non-irritants and non-sensitizers in RIPTs involving healthy subjects. Similarly, cosmetic product formulations (skin, eye area, or tanning products) containing isohexadecane at concentrations ranging from 15% to 42% and tradename materials containing 40% isohexadecane or an isohexadecane (55.5%) – isododecane (35%) mixture tested at a concentration of 20%[effective test concentrations for mixture ≈ 11.1% isohexadecane and 7% isododecane] were classified as non-irritants and non-sensitizers in RIPT's involving healthy subjects.

In most of the studies summarized in this section, an RIPT procedure involving 24 h patch applications (induction and challenge phases) to the back was used. The single application procedure in the in –use safety test also involved a 24 h application period (challenge site not stated). If provided, the amount of test material applied is expressed in grams or milliliters, and, in most cases, patch dimensions (in inches or centimeters) are included.

C11-12 Isoparaffin

A mascara containing 48.28% C11-12 isoparaffin was applied (0.2 g under 2 cm x 2 cm semi-occlusive patches) to a total of 107 male and female subjects. Transient erythema and edema (slight reactions) were observed in one subject during induction, and the product was classified as a non-irritant (mean irritation index < 0.25) and non-sensitizer.[75]

Isododecane

The in-use safety of a hair oil mist spray containing 90.3% isododecane, following 6 consecutive weeks of use, was evaluated using 69 volunteers (males and females). The ability of the product to induce contact allergy was determined by conducting a challenge procedure (2 cm x 2 cm site) approximately 10 to 14 days after use of the product was discontinued. Sixty-nine subjects completed the in-use phase and 65 subjects completed the challenge phase. Safety was determined by evaluating dryness, redness, and stinging of the scalp and challenge phase data. The product was classified as having very good tolerance, i.e., no clinically meaningful changes in redness and dryness on the scalp. The skin reactivity observed during the challenge procedure was considered neither evidence of allergenicity nor clinically meaningful irritation.[76]

The skin irritation and sensitization potential of a lip primer containing 80.74% isododecane was evaluated using 108 healthy male and female subjects. The lip primer did not demonstrate a potential for eliciting skin irritation or sensitization.[77] Results for an an eye shadow containing 47.64% isododecane were also negative for skin irritation and sensitization in a study involving 104 healthy male and female subjects [78], and the same was true for an eyeliner containing 40.16% isododecane that was tested (2 cm x 2 cm patch) on 108 subjects during induction and 100 subjects from the same group during the challenge phase.[79] In another study, the skin irritation and sensitization potential of a mascara containing 63.7% isododecane was evaluated using 204 healthy subjects (males and females; 2 cm x 2 cm patches). It was concluded that the mascara was a non-irritant and non-sensitizer.[80]

Patch applications of Permethyl 296C (50% isododecane; 1″ x 1″ patches) were made to 52 healthy male and female subjects. Results were not indicative of skin irritation or sensitization potential.[81] In another study, Permethyl 284C (20% isododecane; 1″ x 1″ patches) was applied to 52 healthy male and female subjects. Two subjects had a moderate and barely perceptible reaction post-challenge. The barely perceptible reaction was considered clinically insignificant and the moderate reaction was associated with a reactive subject who should be prohibited from future patch testing. Results for Permethyl 284C were not indicative of skin irritation or sensitization potential.[82]

Isoeicosane

Patch applications of Permethyl 222C (40% isoeicosane; 1″ x 1″ patches) were made to 52 healthy male and female subjects. Results were not indicative of skin irritation or sensitization potential.[83] The same conclusion was stated in in another study in which 106 healthy male and female subjects were tested with a lip balm containing 27.15% isoeicosane.[84]

Isohexadecane

The skin irritation and sensitization potential of Permethyl 216C (40% isohexadecane; 0.1 ml on 1″ x 1″ patch) was evaluated using 52 healthy male and female subjects, and results were negative.[85] There also was no evidence skin irritation or sensitization in 100 male and female subjects tested with an an indoor tanning product containing 42% isohexadecane (0.1 ml per patch) [86] or in 102 healthy male and female subjects tested with an eye makeup remover containing 20% isohexadecane according to the same procedure.[87] In another study, a skin cleanser containing 15% isohexadecane (under 48 h patch [0.5

inch^2]) did not induce skin irritation, skin fatiguing, or allergic eczematous contact dermatitis in 600 healthy male and female subjects.[88]

Isododecane and Isohexadecane

The skin irritation and sensitization potential of 20% EXP SR5 (contains 55.5% isohexadecane and 35% isododecane; 0.2 g on 1″ x 1″ patch) in petrolatum was evaluated using 54 healthy male and female subjects. The effective concentrations tested were ~ 11.1%isohexadecane and ~ 7% isododecane. Neither skin irritation nor sensitization was observed.[89]

Provocative Skin Sensitization

Isohexadecane (undiluted) induced a low incidence of skin sensitization (2 of 26 patients), but this incidence was not significantly different ($p > 0.05$) from that of healthy controls (11 of 55). Isohexadecane (10% in petrolatum) did not induce sensitization in patients or healthy controls.

Isohexadecane

The skin sensitization potential of isohexadecane was evaluated using a classical repetitive open application patch test. Patch applications were made to the outer upper arm of subjects with dermatitis and to the anterior forearm and upper back of healthy subjects (controls).[90] Patch test reactions to isohexadecane (undiluted) were positive in 2 of 26 dermatitis patients and in 11 of 55 control subjects; however the difference between these 2 groups was not statistically significant ($p > 0.05$). Isohexadecane (10% in petrolatum) did not induce positive reactions in 19 dermatitis patients or in 56 control subjects. The authors stated that, compared to control subjects, the pattern of reactivity of isohexadecane in subjects with dermatitis suggested that it acts unspecifically as an irritant when undiluted.

Skin Sensitization/Photosensitization

C10-11, C11-13, and C12-15 isoparaffins did not induce sensitization, phototoxicity, or photosensitization in in human patch tests.

Isopar® G (C10-11 Isoparaffin)
Isopar® L (C11-13 Isoparaffin)
Isopar® M (C12-15 Isoparaffin)

Skin sensitization, phototoxicity, and photosensitization tests on Isopar® G, Isopar® L, and Isopar® M were conducted using panels consisting of more than 100 subjects. Each test material was patch-tested (semi-occlusive patches) at a concentration of 50% in petrolatum, and there was no evidence of skin sensitization, phototoxicity, or photosensitization. [6]

Case Reports

Isohexadecane

A 64-year-old female presented with a history of an eczematous rash after application of a commercially available sunscreen that contained isohexadecane. Patch test reactions to 10% isohexadecane were positive (+ reaction) at days 2 and 4. Negative results were reported for 20 control subjects patch tested with isohexadecane.[91]

Occupational Exposure

Occupational exposure to isoparaffins has produced irritation and a low incidence of sensitization in the workplace.

The use of solvent mixtures containing isoparaffins in the workplace has produced a low incidence of hypersensitization.[6]

Reportedly, C10-11 and C11-13 isoparaffins have been used by Versatec (a Xerox company) and Xerox Medical Systems, collectively, for over 16 years. Out of more than 2000 employees, there were only 2 cases of health-related incidents (skin rash and hives) following skin contact.[6]

Sixty-three of 74 male employees of a manufacturing facility developed dermatitis after exposure to the following 2 metalworking fluids : lubricant containing > 80% C9-12 isoparaffin (lubricant 1) or > 99.8% C10-14 isoparaffin (lubricant

2)[92] Irritation test (procedure not stated) results indicated that 22 of the 63 cases were due to lubricant 1 (PII = 2.1) and 32 were due to lubricant 2 (PII = 1.1); both were classified as irritants. Neither cumulative irritation nor sensitization tests were performed.

The American Conference of Governmental Industrial Hygienists (ACGIH) set the occupational exposure limit for inhaled isooctane at 300 ppm, as time-weighted average.[93]

Epidemiology

*A statistically significant elevated risk of bladder cancer in women was associated with a low level of exposure to aliphatic hydrocarbon solvents. However, a significantly elevated risk of renal cell carcinoma was not associated with these exposures***.**

Aliphatic and Other Hydrocarbons

A study was designed to provide an estimate of the occupational risk of contracting cancers of the urinary tract.[94] The 25-year incidence of bladder cancer (BC) and renal cell carcinoma (RCC) in the entire Finnish workforce was compared in relation to occupation and occupational exposure to solvents and gasoline. The study cohort consisted of 1.6 million Finns (born in years 1906 to 1945) who participated in the national population census on December 31, 1970. All cancers, diagnosed from 1971 through 1995, in individuals born in years 1906 to 1945 were extracted from the nationwide Finnish Cancer Registry and sent to Statistics Finland and compared with the 1970 census files. Cancer risk estimates were adjusted for smoking and obesity.

Overall, there appeared to be a tendency for an elevated risk of BC in women exposed to solvents, but not among men. The relative risk estimates were above 1.2 in nearly all exposure categories of all exposures studied. However, a statistically significant elevated risk of BC in women was associated with the following: a low level of aliphatic hydrocarbon solvents (1.40; 95% confidence interval (CI) = 0.85 to 2.32), a low level of chlorinated hydrocarbon solvents (1.43; 95% CI = 1.0 to 2.03), and a middle level of chlorinated hydrocarbon solvents (1.68; 95% CI = 1.15 to 2.45). The relative risks for bladder cancer in men and women occupationally exposed to gasoline (low level exposure) were: men (1.0; 95% CI = 0.89 to 1.13) and women (1.55; 95% CI = 0.50 to 4.86). There was no significantly elevated risk of RCC in any exposure category for any solvent in either gender. It was concluded that these findings suggest that occupational exposure to certain solvents may have an impact on bladder cancer risk, but the risk of renal cell carcinoma does not appear to be altered by exposure to hydrocarbon solvents or gasoline. [94]

SUMMARY

The 24 isoparaffins reviewed in this safety assessment function mostly as solvents in personal care products, and the following 15 are being used: C7-8 Isoparaffin, C8-9 Isoparaffin, C9-11 Isoparaffin, C10-11 Isoparaffin, C10-13 Isoparaffin, C11-12 Isoparaffin, C11-13 Isoparaffin, C12-14 Isoparaffin, C13-14 Isoparaffin, C13-16 Isoparaffin, C18-70 Isoparaffin, Isododecane, Isoeicosane, Isohexadecane, and Isooctane. The results of a Personal Care Products industry survey indicate that ingredient use concentrations have ranged from 0.0001% (C13-14 Isoparaffin) to 90% (Isododecane).

As a frame of reference, liquid gasoline is a complex mixture of petroleum chemicals that includes approximately 60 to 75% alkanes (paraffins) that comprise straight-chain hydrocarbons (C_4 to C_{12}), and isoparaffins (branched-chain hydrocarbons) in approximately the same range of chain-lengths. While some of the isoparaffins described as cosmetic ingredients are longer in chain length, most are in this range. 2,2,4-Trimethylpentane (isooctane) is used primarily in the alkylation step to derive high-octane gasoline fuels.

Following inhalation in rats, ^{14}C-isooctane was eliminated almost exclusively by the kidneys, and various urinary metabolites**,** 2,4,4-trimethyl-2-pentanol included, have been identified. Following oral dosing of ^{14}C-isooctane in rats, more than half of the administered dose was recovered in the urine and feces. Accumulation in the liver and kidneys was observed, with males retaining substantially greater amounts of radioactivity in the kidneys, compared to females. 2,4,4-trimethyl-2-pentanol was the major metabolite detected in the male rat kidney, but was absent from female rat kidney. However, female rats excreted more conjugates of this metabolite, compared to males. Following human inhalation exposure, the maximum steady-state concentration of isooctane in the brain and fat was calculated using mathematical modeling.

Following exposure of 8 subjects to Shell Sol TD at a concentration of 100 ppm (0.6 g/m^3) for 3 h, the maximum steady-state concentration was calculated (using mathematical modeling) to be 55 mg/kg for fat and 5 mg/kg for the brain.

A 2007 toxicological review on 2,2,4-trimethylpentane (isooctane), published by the Environmental Protection Agency (EPA) is available. The EPA has determined that there is inadequate information to assess carcinogenic potential of 2,2,4-trimethylpentane, having noted that no epidemiological studies in humans and no chronic bioassay studies are available that assess the carcinogenic effects of 2,2,4-trimethylpentane.

In many of the animals studies, involving mostly male rats, either oral or inhalation exposure to isooctane resulted in some degree of nephrotoxicity. According to some investigators, study results suggest that chronic cell proliferation associated with α_{2u}-globulin nephropathy and chronic progressive nephrosis in male rats exposed to unleaded gasoline or its isoparaffinic components, such as isooctane, may be responsible for nephrocarcinogenic effects of unleaded gasoline. α_{2u}-globulin nephropathy associated with exposure to these chemicals is not relevant to man due to the absence of this protein. The isoparaffins were not found to be genotoxic in *in vitro* or *in vivo* assays, and were neither embryotoxic/fetotoxic or teratogenic in rats. The results of an initiation-promotion study involving rats were negative for isooctane.

The isoparaffins have produced slight ocular irritation and mild to severe skin irritation, but were not comedogenic, in rabbits. Furthermore, skin sensitization was not induced in guinea pigs. Eye area cosmetic products containing isoparaffins were classified as well-tolerated, in terms of ocular irritation potential, following application to the eye lashes of female subjects. Also, these chemicals, alone or in product formulations, were not classified as irritants, sensitizers, phototoxic, or photosensitizers in human patch tests. However, it should be noted that isohexadecane (undiluted) induced a low incidence of skin irritation in patients, but this incidence was not significantly different from that of healthy controls. Isohexadecane (10% in petrolatum) did not induce any reactions in patients or healthy controls.

Occupational exposure to isoparaffins has produced irritation and a low incidence of sensitization in the workplace. In an epidemiology study (occupational exposure), a statistically significant elevated risk of bladder cancer in women was associated with a low level of exposure to aliphatic hydrocarbon solvents. However, a significantly elevated risk of renal cell carcinoma was not associated with these exposures**.**

DISCUSSION

The CIR Expert Panel noted that most of the available data related to oral or inhalation exposure to isoparaffins, but the dermal and ocular exposure data that were available suggested mild ocular irritation, mild to severe irritation, no sensitization or photosensitization, and no phototoxicity.

No significant toxicity was identified in oral or inhalation exposure studies of the following endpoints: genotoxicity, reproductive and developmental toxicity, or carcinogenicity. Nephrotoxicity, however, was a concern. The Expert Panel noted the involvement of α_{2u}-globulin in the mechanism for isoparaffin-induced nephrotoxicity/renal tubule cell proliferation in male rats of various strains in oral and inhalation exposure studies, but noted that nephrotoxic effects were not observed in one strain of rats, NCI-Black-Reiter, that does not have the α_{2u}-globulin protein. Humans also lack this protein and, thus, the Panel agreed that findings associated with the α_{2u}-globulin protein in male rats were not relevant to humans. This view was consistent with the U.S. Environmental Protection Agency (EPA) position that it was not possible for the agency to derive an oral reference dose for chronic oral exposure or a reference concentration for chronic inhalation exposure to isooctane because the available studies were limited, in that they were designed to only investigate endpoints specific to α_{2u}-globulin-associated nephropathy. EPA also concluded that there was inadequate evidence to assess the carcinogenic potential of isooctane, based on the absence of human epidemiological studies and chronic bioassays on this compound. As noted above, the CIR Expert Panel found no evidence of any concern regarding carcinogenic potential from exposure to isoparaffins as used in cosmetics.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of ≤ 10μm are respirable. After reviewing the positive acute and subchronic inhalation toxicity data considered in this safety assessment, the Expert Panel determined that C11-12 isoparaffin, C11-13 isoparaffin, C13-14 isoparaffin, isododecane, isoeicosane, and isohexadecane can be used safely in hair sprays, because the product particle size is not respirable.

CONCLUSION

The Expert Panel concluded that C7-8 isoparaffin, C8-9 isoparaffin, C9-11 isoparaffin, C9-12 isoparaffin, C9-13 isoparaffin, C9-14 isoparaffin, C9-16 isoparaffin, C10-11 isoparaffin, C10-12 isoparaffin, C10-13 isoparaffin, C11-12 isoparaffin, C11-13 isoparaffin, C11-14 isoparaffin, C12-14 isoparaffin, C12-20 isoparaffin, C13-14 isoparaffin, C13-16 isoparaffin, C18-70 isoparaffin, C20-40 isoparaffin, C15-35 isoparaffin/isoalkylcytcloalkanes, isododecane, isoeicosane, isohexadecane, and isooctane are safe as cosmetic ingredients in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Table 1. Isoparaffinic Hydrocarbons[19]

Chemical Names/CAS Nos.	Trade Names	Definitions	Functions in Cosmetics
C7-8 Isoparaffin Alkanes, C7-8-Iso-; **CAS No. 70024-92-9**	Isopar C and Soltrol 10 Isoparaffin Solvent	Mixture of branched chain aliphatic hydrocarbons with 7 or 8 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C8-9 Isoparaffin Alkanes, C8-9-Iso-; C**AS No. 246538-71-6**	Isopar E	Mixture of branched chain aliphatic hydrocarbons with 8 or 9 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C9-11 Isoparaffin Alkanes, C9-11-Iso-; **CAS No. 68551-16-6**	Soltrol 100 Isoparaffin Solvent	Mixture of branched chain aliphatic hydrocarbons with 9 to 11 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C9-12 Isoparaffin*	Isane IP 155	Mixture of branched chain aliphatic hydrocarbons with 9 to 12 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C9-13 Isoparaffin Alkanes, C9-13-Iso-; **CAS No. 246538-72-7**	Shellsol T	Mixture of branched chain aliphatic hydrocarbons with 9 to 13 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C9-14 Isoparaffin Alkanes, C9-14-Iso-; **CAS No. 246538-73-8**		Mixture of branched chain aliphatic hydrocarbons with 9 to 14 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C9-16 Isoparaffin		Mixure of branched chain aliphatic hydrocarbons with 9 to 16 carbons in the alkyl chain.	skin-conditioning agent-emollient; solvents
C10-11 Isoparaffin Alkanes, C10-11-Iso-; **CAS No. 246538-75-0**	Isopar G	Mixure of branched chain aliphatic hydrocarbons with 9 to 16 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C10-12 Isoparaffin		Mixure of branched chain aliphatic hydrocarbons with 10 to 12 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C10-13 Isoparaffin Alkanes, C10-13-Iso- ; **CAS No. 68551-17-7**	Isane IP 175 and Shellsol TD	Mixure of branched chain aliphatic hydrocarbons with 10 to 13 carbons in the alkyl chain.	solvents
C11-12 Isoparaffin Alkanes, C11-12-Iso-; **CAS No. 246538-76-1**	Isopar H and Isopar K	Mixure of branched chain aliphatic hydrocarbons with 11 to 12 carbons in the alkyl chain.	skin-conditioning agents - miscellaneous; solvents
C11-13 Isoparaffin Alkanes, C11-13-Iso-; **CAS No. 246538-78-3**	Isopar L	Mixure of branched chain aliphatic hydrocarbons with 11 to 13 carbons in the alkyl chain.	solvents
C11-14 Isoparaffin	Isane IP 185	Mixure of branched chain aliphatic hydrocarbons with 11 to 14 carbons in the alkyl chain.	solvents; viscosity decreasing agents
C12-14 Isoparaffin Alkanes, C12-14-Iso-; **CAS No. 68551-19-9**	Soltrol 170 Isoparaffin Solvent	Mixure of branched chain aliphatic hydrocarbons with 12 to 14 carbons in the alkyl chain.	solvents
C12-20 Isoparaffin	Isopar V Solvent	Mixure of branched chain aliphatic hydrocarbons with 12 to 20 carbons in the alkyl chain.	skin-conditioning agents - emollient; solvents
C13-14 Isoparaffin Alkanes, C13-14-Iso-; **CAS No. 246538-80-9**	Isopar N Fluid and Isopar M	Mixure of branched chain aliphatic hydrocarbons with 13 to 14 carbons in the alkyl chain.	solvents

Table 1. Isoparaffinic Hydrocarbons[19]

Chemical Names/CAS Nos.	Trade Names	Definitions	Functions in Cosmetics
C13-16 Isoparaffin Alkanes, C13-16-Iso-; **CAS No. 68551-20-2**	Isopar P and Soltrol 220 Isoparaffin Solvent	Mixure of branched chain aliphatic hydrocarbons with 13 to 16 carbons in the alkyl chain.	solvents
C18-70 Isoparaffin Alkanes, C18-70-Iso-; **CAS No. 246538-80-9**	PME	Mixure of branched chain aliphatic hydrocarbons with 18 to 70 carbons in the alkyl chain.	skin conditioning agents - occlusive
C20-40 Isoparaffin Alkanes, C20-40-Iso-; **CAS No. 246538-81-8**		Mixure of branched chain aliphatic hydrocarbons with 20 to 40 carbons in the alkyl chain.	skin-conditioning agents - emollient; solvents
C15-35 Isoparaffin/Isoalkylcycloalkanes		A petroleum fraction consisting chiefly of C15-35 branched chain hydrocarbons and branched chain cyclic hydrocarbons.	skin-conditioning agents - miscellaneous
Isododecane 1,1-Dineopentylethylene; Heptane, 2,2,6,6- Tetramethyl-4-Methylene-; 2,2,4,6,6-Pentamethylheptane; and 2,2,6,6-Tetramethyl-4-Methyleneheptane; **CAS Nos. 141-70-8, 13475-82-6, 31807-55-3, and 93685-81-5**		Branched chain aliphatic hydrocarbon with 12 carbons. The formula for this isoparaffin is included in Figure 1.	fragrance ingredients; solvents
Isoeicosane **CAS Nos. 52845-07-5 and 93685-79-1**		Branched chain aliphatic hydrocarbon with 20 carbons in the alkyl chain. The formula for this isoparaffin is included in Figure 1.	skin-conditioning agents - emollient; solvents
Isohexadecane 2,2,4,4,6,6,8 Heptamethylnonane and Nonane, 2,2,4,4,6,8,8-Heptamethyl-; **CAS No. 4390-04-9, 60908-77-2, and 93685-80-4**		Branched chain aliphatic hydrocarbon with 16 carbons. The formula for this isoparaffin is included in Figure 1.	skin-conditioning agents - emollient; solvents
Isooctane Isobutyltrimethylmethane and 2,2,4-Trimethylpentane; **CAS No. 540-84-1 and 26635-64-3**		Hydrocarbon that conforms to the formula in Figure 1.	solvents

*The *International Cosmetic Ingredient Dictionary and Handbook* monograph on C9-12 isoparaffin does not include the systematic name (i.e., alkanes, C9-12-iso-). Isane IP155 is the only tradename for C9-12 isoparaffin that is included in the dicitonary. However, according to another source, [13] Isopar G and Isopar H are synonyms for alkanes, C9-12-iso-, and both tradename materials are sold under the CAS number 90622-57-4.

Table 2A. Properties of Isoparaffins[95]

Chemical	Molecular Weight	logP	Specific Gravity (SG)/Density (D)	Vapor Pressure	Boiling Point	Flash Point
Isododecane	168.32	5.813 ± 0.254	0.7599 g/cm^3	7.35E-01 Torr	177.7 to 178.0 °C	56.7 ± 8.1 °C
Isohexadecane	226.44	7.976 ± 0.238	0.772 ± 0.06 g/cm^3	6.02E-02 Torr	240 ^{0}C	95.6 ^{0}C
Isooctane	114.23	4.373 ± 0.206	1.126 g/cm^3	4.52E+01 Torr	99.6 to 99.7 ^{0}C	minus 7.8 ^{0}C

Table 2B. Additional Properties of Isododecane[11]

Property	Value
Density	0.75 g/ml @ 20°C
Refractive index	1.421 to 1.422 @ 20°C
Dielectric costant	2.12 @ 20°C
Surface tension	22.6 mN/m @ 20°C
Relative vapor density	5.9 (air = 1)
Boiling range	176 to 192°C
Autoignition temperature	410°C
Freezing point	(-) 81°C

Table 3. Properties of Isoparaffinic Tradename Materials[6]

Producer	Material	Predominant Carbon Length	CAS No.	Average Molecular Weight	Boiling Range (EC)	Specific Gravity (g/ml)	Flash point (EC)
Exxon	Isopar® G	C10-11	64742489	149	155 to 176	0.748	40
	Isopar® H	C11-12	64742489	160	169 to 193	0.759	49
	Isopar® K	C11-14	64742489	164	174 to 197	0.761	49
	Isopa® L	C11-13	64742489	171	185 to 206	0.767	60
	Isopar® M	C12-15	64742478	191	205 to 254	0.783	71
Phillips Petroleum	Soltrol® 50	C8-10	68551155	116	118 to 148	0.72	10
	Soltrol® 100	C9-11	68551166	142	157 to 173	0.74	41
	Soltrol®130	C10-13	68551177	158	176 to 208	0.75	56
	Soltrol® 145	C5-16	68551188	157	171 to 299	0.77	53
	Soltrol® 170	C10-14	68551199	185	218 to 238	0.778	85
	Soltrol® 220	C13-17	64741737	206	232 to 288	0.809	106
Shell	Shell Sol 71	C9-12	64741657	158	179 to 202	0.76	52
Texaco	Texsolve® S-2	C9-10	64742887	135	156 to 157	0.778	39
	Texsolve S	C8-11	64742887	141	157 to 196	0.783	40.5
	Texsolve® S-66	C8-11	64742887	142	160 to 187	0.778	40.5
	Texsolve® S/LO	C8-11	64742887	143	161 to 190	0.7781	40.5

Table 4. Properties of Isopar™ Isoparaffinic Hydrocarbon Solvents[96]

Material*	Predominant Carbon Length	Specific Gravity	Vapor Pressure (@ 38°C)
Isopar-C™	C7-8	0.7	13.1 Torr
Isopar-E™	C8-9	0.72	6.9 Torr
Isopar-G™	C10-11	0.75	1.9 Torr
Isopar-H™	C11-12	0.76	0.8 Torr

*****All manufactured by Exxon Corporation

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2010

	C7-8 Isoparaffin		C8-9 Isoparaffin		C9-11 Isoparaffin		C10-11 Isoparaffin		C10-13 Isoparaffin	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type										
Eye Area	NR	NR	18	5 to 11	8	1 to 18	1	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	2	2	2	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	40	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR	2	2	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duration of Use										
Leave-On	1	NR	18	5 to 40	8	1 to 18	2	NR	NR	0.08 to 0.60
Rinse off	NR	NR	NR	NR	2	2	2	NR	NR	NR
Totals/Conc. Range	1	NR	18	5 to 40	10	1 to 18	4	NR	NR	0.08 to 0.60
	C11-12 Isooparaffin		**C11-13 Isoparaffin**		**C12-14 Isoparaffin**		**C13-14 Isoparaffin**		**C13-16 Isoparaffin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type										
Eye Area	90	9 to 67	5	0.3	2	NR	68	0.005 to 6	4	NR
Possible Ingestion	1	12 to 25	NR	NR	NR	NR	NR	0.2 to 1	NR	NR
Inhalation	NR	2	3	NR	NR	NR	5	52	NR	NR
Dermal Contact	90	16 to 35	23	2	9	NR	754	0.001 to 9	16	0.4 to 2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	1	NR	NR	NR
Hair - Non-Coloring	NR	1 to 2	5	1	1	NR	92	0.2 to 75	9	18
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	0.5 to 13	NR	NR
Nail	NR	35	1	27	NR	NR	2	0.02 to 0.9	1	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	3	0.06 to 0.6	NR	NR
Bath products	NR	NR	NR	NR	NR	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	5	NR	NR	NR
Duration of Use										
Leave-On	119	9 to 67	34	0.3 to 27	10	NR	818	0.001 to 65	24	0.4 to 18
Rinse off	2	20	1	NR	NR	NR	29	0.2 to 75	2	NR
Totals/Conc. Range	121	1 to 67	35	0.3 to 27	10	NR	847	0.001 to 75	26	0.4 to 18
	C18-70 Isoparaffin		**Isododecane**		**Isoeicosane**		**Isohexadecane**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type										
Eye Area	NR	NR	205	3 to 67	10	2 to 9	87	0.8 to 41		
Possible Ingestion	NR	NR	58	3 to 84	15	11 to 37	5	4 to 30		
Inhalation	NR	NR	13	4 to 33	NR	8	NR	3 to 18		
Dermal Contact	1	NR	387	0.008 to 62	66	0.5 to 5	541	0.2 to 42		
Deodorant (underarm)	NR	NR	NR	0.5	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	41	0.06 to 83	1	0.3 to 16	47	0.3 to 22		
Hair-Coloring	NR	NR	1	2	NR	NR	NR	NR		
Nail	NR	NR	NR	28 to 90	NR	NR	1	0.6		

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2010

Mucous Membrane	NR	NR	NR	0.8	NR	4	NR	0.7 to 6	
Bath Products	NR	NR	NR	6	NR	NR	NR	0.2 to 3	
Baby Products	NR	NR	NR	NR	NR	NR	1	NR	
Duration of Use									
Leave-On	1	NR	482	0.008 to 90	68	0.3 to 37	531	0.2 to 42	
Rinse off	NR	NR	36	0.06 to 83	1	5	65	0.2 to 41	
Totals/Conc. Range	1	NR	518	0.008 to 90	69	0.3 to 37	596	0.2 to 42	

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses
NOTE: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to sum total uses.

Table 6. Acute Inhalation Toxicity Studies on Isoparaffins and Isooctane

Material	Predominant Carbon Length	Animals	Procedure	Results
Isopar® E	C8-9	Mice	Not stated	Death at highest concentration (8000 ppm).[27]
Isopar® G	C10-11	Rats	Not stated	4 h LC50 > 2000 ppm (12.2 mg/l).[6]
Isopar C	85% isooctane	10 male Swiss albino mice, 10 male Wistar rats, and 10 English short-hair guinea pigs	41 min exposure to near saturated vapors	All animals died.[7]
Isopar C	85% isooctane	10 CD-1 mice, 10 Sprague-Dawley rats, and 10 Hartley guinea pigs of both sexes	4 h exposure to 39.63 mg/l air	All animals died.[7]
Isopar C	85% isooctane	6 Sprague-Dawley rats	4 h exposure to 21.0 mg/l air	Low incidences of lung discoloration and dilated renal pelves.[7]
Isopar® L	C11-13	Rats	Not stated	4 h LC50 > 715 ppm (5.01 mg/l).[6]
Soltrol® 100	C9-11	Rats	Not stated	4 h LC50 > 3684 ppm (21.4 mg/l).[6]
Soltrol®130	C10-13	Rats	Not stated	6 h LC50 > 1227 ppm (8.2 mg/l).[6]
Shell Sol 71	C9-12	Rats	Not stated	4 h LC50 > 592 ppm (3.83 mg/l).[6]
Isopar® G	C10-11	Mice	Groups exposed for 30 min to -300 ppm (1834 mg/m3) or -420 ppm (2621 mg/m3).	No significant effects on respiratory rate.[6]
Soltrol® 130	C10-13	Dogs	4 h exposure to 1308 ppm (8.4 mg/l)	Transient toxic effects, but no deaths.[6]
Soltrol® 130	C10-13	4 dogs	6 h exposure to 221 ppm (14.2 mg/l)	Death in 3 of 4 dogs.[6]
Soltrol® 130	C10-13	10 guinea pigs	4 h exposure to 1541 ppm (9.9 mg/l)	Lethargy in all 10 guinea pigs. No unusual findings at necropsy.[6]
Soltrol® 130	C10-13	4 monkeys	6 h exposure to 1806 ppm (11.6 mg/l)	Retching and eye rubbing in all 4 monkeys, but no deaths.[6]
Isooctane	C8	Rats	4 h exposure	LC50 > 14.38 mg/l .[8]
Isooctane	C8	Rats	1 h exposure	LC50 = 47.4 mg/l.[36]

Table 6. Acute Inhalation Toxicity Studies on Isoparaffins and Isooctane

Material	Predominant Carbon Length	Animals	Procedure	Results
Isooctane	C8	Rats (males and females)	4 h exposure	LC50 = 37.5 mg/l (males) and 34.7 mg/l (females).[36]
Isoctane	C8	Mice	4 h exposure	LC50 > 39.3 mg/l.[36]
Isoctane	C8	4 SPF Mice	10 min exposure to ~3000 ppm	No respiratory irritation.[6]

Table 7. Acute Oral Toxicity Studies on Isoparaffins and Isooctane

Material	Predominant Carbon Length	Animals	Results
Isopar®G	C10-11	Rats	LD50 > 10 g/kg[6]
Isopar®L	C11-13	Rats	LD50 > 10 g/kg[6]
Isopar C	85% isooctane	Groups of 5 male albino rats	LD50 > 10,000 µl/kg[7]
Soltrol® 100	C9-11	Rats	LD50 > 34.6 g/kg[6]
Soltrol®130	C10-13	Rats	LD50 > 34.6 g/kg[6]
Shell Sol 71	C9-12	Rats	LD50 > 25 g/kg[6]
Permethyl 99A	C12	Rats	LD50 > 5g/kg[97]
Isododecane (10% in olive oil)	C12	5 mice	LD50 > 2 g/kg[73]
Isohexa-decane	C16	90 rats (males and females)	LD50 > 46.4 ml/kg (> 3.57 g/kg)[98]
Isooctane	C8	Rats	LD50 > 5 g/kg[8]
Isooctane	C8	15 male rats/dose	LD50 > 2.5 g/kg[36]

Table 8. Acute Dermal Toxicity Studies on Isoparaffins and Isooctane

Material	Predominant Carbon Length	Animals	Results
Isopar® G	C10-11	Rabbits	LD50 > 3.2 g/kg[6]
Isopar® L	C11-13	Rabbits	LD50 > 3.2 g/kg[6]
Isopar C	85% isooctane	Groups of 4 albino rabbits (males and females)	LD50 >3160 µl/kg. Transient erythema/desquamation at application sites (intact abdominal skin)[7]
Soltrol® 100	C9-11	Rabbits	LD50 = 15.4 g/kg[6]
Soltrol® 130	C10-13	Rabbits	LD50 = 15.4 g/kg[6]
Shell Sol 71	C9-12	Rabbits	LD50 > 5.0 g/kg[6]
Isooctane	C8	Rabbits	LD50 > 2.0 g/kg[8]
Isooctane	C8	5 rats (males)	LD50 > 1000 µl/kg (ca. = 70 mg/kg). No deaths or signs of toxicity[36]
Isooctane	C8	Groups of 4 New Zealand white rabbits	LD50 > 3.16 g/kg. After application to abraded abdominal skin, dark livers and mottled kidneys at necropsy[7]

Table 9. Ocular Irritation Studies on Isoparaffins

Material	Predominant Carbon Length	Animals	Test Procedure	Results
Isopar®G	C10-11	Rabbits	Draize test. 0.1 ml instilled	No corneal lesions. Draize scores of 0 to 1 (max. score = 110) [6]
Isopar®L	C11-13	Rabbits	″	Slight conjunctival irritation, but no corneal lesions. Draize scores of 0 to 6[6]
Soltrol®100	C9-11	Rabbits	″	Minimal, transient conjunctival irritation[6]
Soltrol®130	C10-13	Rabbits	Not stated	Conjunctival redness and discharge (grade 1), but no corneal opacity[6]
Isododecane	C12	Rabbits	0.1 ml instilled	Non-irritant[99]
Isododecane	C12	3 rabbits	Not stated	Non-irritant[73]
Permethyl 99A	C12	6 rabbits	0.1 ml instilled	Non-irritant[100]
Mixture of isododecane (40%) and trimethylsiloxy silicate (60%) in olive oil	C12 isododecane (C12)	3 rabbits	20% isododecane tested	Non-irritant[73]
Isooctane	C8	Rabbits	0.1 ml instilled	Non-irritant[7]
Isohexadecane	C16	6 rabbits	0.1 ml instilled	Non-irritant[101]
Tan enhancing spray con-taining 42% isohexadecane	C12		MTT *in vitro* assay	No/minimal irritation[49]
EXP-SR5	C12, C16		Hen's egg test *in vitro*	Non-irritant[50]
Permethyl 216C	C16		Hen's egg test *in vitro*	Non-irritant[51]
Permethyl 222C	C20		Hen's egg test *in vitro*	Non-irritant to slight irritant[54]
Permethyl 284C	C12		Hen's egg test *in vitro*	Non-irritant[52]
Permethyl 296C	C12		Hen's egg test *in vitro*	Non-irritant[53]

Table 10. Skin Irritation Studies on Isoparaffins Using Rabbits

Material	Predominant Carbon Length	Number of Animals	Doses Tested	Procedure	Results
Isopar® G	C10-11	NA*	Not stated	24 h contact period	Slight dose-related skin irritation[6]
Isopar® G	C10-11	NA	Undiluted	Occlusive patch test	Primary irritant (grade 5) [6]
Isopar® G	C10-11	NA	"	Modified non-occlusive patch test	Non-irritant[6]
Isopar® L	C11-13	NA	Not stated	Not stated	Slight skin irritation[6]
Soltrol® 100	C9-11	NA	Not stated	Applied to intact or abraded skin	Mild skin irritation
Soltrol® 130	C10-13	NA	Not stated	Draize test	Primary irritant (grade 5.7) [6]
Soltrol® 130	C10-13	NA	Not stated	Applied to intact or abraded skin	Very slight to severe irritation[6]
Shell Sol 71	C9-12	NA	Not stated	Not stated	Moderately irritating[6]
Isododecane	C12	6 rabbits	Undiluted - 0.5ml/2.5 cm^2	24 h contact period	Mildly irritating[102]
Isododecane	C12	3 rabbits	Undiluted	Cumulative irritation test	Mild irritant[73]
Isododecane	C12	3 rabbits	50% in petrolatum	Primary irritation test	Mild irritant[73]
Permethyl 99A	C12	6 rabbits	Undiluted - 0.5ml/2.5 cm^2	24 h contact period	Mildly irritating[103]
Isohexadecane	C16	6 rabbits	0.5 ml, 2.5 x 2.5 cm patch	24 h contact period	Non-irritant[104]
Isooctane	C8	2 rabbits	Not stated	Ears painted twice daily for 5 consecutive days	Slight redness (short duration) [6]

*****NA = Not Applicable

Table 11. Genotoxicity of Isoparaffins and Isooctane

Material	Predominant Carbon Length	Strain/cell type	Assay	Dose	Results
Isopar® L	C11-13	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, TA 1537, and TA 1538	Reverse mutation assay with and without metabolic activation	Not stated	Not mutagenic.[6]
Isopar® G	C10-11	"	"	Not stated	Not mutagenic.[6]

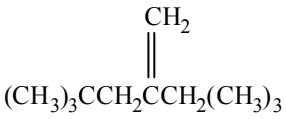
Table 11. Genotoxicity of Isoparaffins and Isooctane

Material	Predominant Carbon Length	Strain/cell type	Assay	Dose	Results
Soltrol® 130	C10-13	"	"	Doses up to 10,000 µg/plate	Not mutagenic.[6]
Isopar® G	C10-11	*Escherichia coli* strain Pol A^-	Pol A+ A^- DNA repair assay	Not stated	Not genotoxic.[6]
Isopar® G	C10-11	*Escherichia coli* strain WP2	Reverse mutation assay with and without metabolic activation	Not stated	Not mutagenic.[6]
Soltrol® 130	C10-13	L5178Y mouse lymphoma cells	Forward mutation assay with and without metabolic activation	Doses up to 1000 µg/ml	Not mutagenic.[6]
Soltrol® 130	C10-13	Chinese hamster ovary cells	*In vitro* sister chromatid exchange assay with and without metabolic activation	Doses up to those that inhibited cell growth due to toxicity	Not genotoxic.[6]
Isopar® G	C10-11	Mice (erythrocytes evaluated)	*In vivo* micronucleus assay	i.p. dosing with Isopar® G (25 ml/kg), given as 10% solution in corn oil	Not clastogenic.[6]
Isopar® G	C10-11	Sprague-Dawley rats (germ cells evaluated)	*In vivo* dominant lethal test	Inhalation exposure to concentrations up to 900 ppm	Compared to controls, no treatment-related changes in pregnancy rate, number of implantations, or numbers of early or late fetal deaths. Not mutagenic.[6]
Isopar C	85% isooctane (C8)	Sprague-Dawley rats	″	Inhalation exposure concentrations up to 1200 ppm	Negative results.[7]
Isododecane	C12	*Salmonella typhimurium* strains TA100 and TA98		Doses of 156 to 5000 µg/plate	Negative results[73]

Table 11. Genotoxicity of Isoparaffins and Isooctane

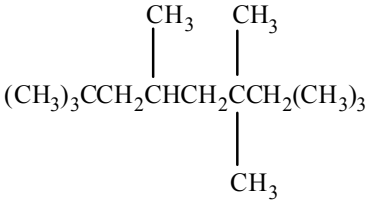
Material	Predominant Carbon Length	Strain/cell type	Assay	Dose	Results
Mixture of Isododecane (40%) and trimethylsiloxy-silictate (60%)	C12 (isododecane)	*Salmonella typhimurium* strains TA100 and TA98	Ames test	156 to 5000 µg/plate	Negative results[73]
Isooctane	C8	Rat and mouse hepatocytes	*In vivo* and *in vitro* unscheduled DNA synthesis (UDS) assays	Cells from rats and mice dosed by gavage with 500 mg/kg isooctane	No UDS.[63]
Isooctane	C8	Mouse lymphocytes	L5178Y TK+/- mouse lymphoma assay for TK locus mutations	Doses up to 0.5 µl/ml ± metabolic activation	Not mutagenic.[105]
Isooctane	C8	TK6 human lymphocytes	TK6 mutation and sister chromatid exchange assays	5% in medium (suspension 100% saturated by stirring); ± metabolic activation	Not genotoxic in both assays.[61]

Figure 1. Isoparaffin Formulas

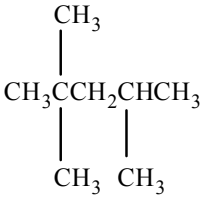


Isododecane

Isoeicosane



Isohexadecane



Isooctane

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DATA

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: John Bailey, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 13, 2010

SUBJECT: Concentration of Use - C15-35 Isoparaffin/Isoalkylcycloalkanes

C15-35 Isoparaffin/Isoalkylcycloalkanes was included in a Council concentration of use survey. No uses of this ingredient were reported.

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From: <richard.h.mckee@exxonmobil.com>
To: <CIRinfo@cir-safety.org>
Date: 11/4/2010 8:46 AM
Subject: draft report. Isoparaffins as used in cosmetics

Dear Dr. Anderson

This note is in response to the circulated draft "Isoparaffins as used in cosmetics, September 14, 2010" and on which comments were requested within 60 days. I am sorry about responding so close to the deadline, but this draft only came to my attention quite recently. Although I take no exception to the conclusions presented in this document, I would like to bring to your attention some recent information which supplements some of the points that you have made. Specifically:

(1) On page 3 it is stated that "Both Exxon and Texaco have reported benzene (< 0.1 ppm) as an impurity for all of their isoparaffinic products..." In fact this is really a statement of regulatory compliance; all solvents must contain < 0.1% benzene. However. benzene levels in isoparaffinic solvents are far below 0.1 ppm. As summarized by McKee et al. (2007), C9-C13 aliphatic solvents (< 2% aromatics) contain less than 1 ppm benzene. Note also that Texaco is no longer a corporate entity and certainly not a supplier of solvents. McKee, R. et al. (2007). Benzene levels in hydrocarbon solvents - Response to author's reply. Journal of Occupational and Environmental Hygiene 4:D60-C63.

(2) page 6, absorption, metabolism and excretion. you may wish to take note of the following...Zahlsen K, Eide I, Nilsen A, Nilsen O. Inhalation kinetics of C8 to C10 1-alkenes and iso-alkanes in the rat after repeated exposures. Pharmacol. Toxicol. 1993;73(3):163-168.

(3) page 7, section on acute dermal toxicity, the statement that "most of the LD50s reported were > 2 g/kg" is not correct. In fact ALL of the values shown in Table 8 are > 2 g/kg.

(4) pages 8 and 9 (subchronic toxicity) - A publication which contributes significantly to the toxicology literature on this group of substances is Schreiner et al. (1998). Journal of Toxicology and Environmental Health Part A. 55:277-296. In this study rats were exposed by inhalation to light alkylate naphtha, a substance described as containing > 95% isoparaffins with carbon numbers predominantly in the range of C5-C8. Animals were exposed to levels up to 6646 ppm, 6 hr/day, 5 d/week for 13 weeks. Exposure was followed by a standard toxicological and pathological examination. A neurological examination was also conducted. The only effect reported (other than alpha 2u-globulin-mediated male rat kidney effects) was increased liver weight (without pathological findings) in the high exposure group. The no observed adverse effect level was given by the authors as 2220 ppm.

(5) page 16. The sentence "The US EPA concluded that this overall lack of information represented a data gap and did not allow for a quantitative assessment of the carcinogenicity of 2,2,4-trimethylpentane." is ambigous. It would be clearer if you said that the US EPA concluded that since a carcinogenesis study of 2,2,4-trimethylpentane had not been conducted, the carcinogenic potential of 2,2,4-trimethylpentane could not be quantitatively assessed.

sincerely. R. McKee

Note also the following:

(1) page 5, last pp, isododecane and isoeicosane are misspelled.

(2) page 10, pp under chronic oral toxicity - trimethylpentane is misspelled.

(3) page 13, pp under skin irritation - isoparaffin is misspelled.

(4) page 13, last pp, sensorimotor is misspelled.

(5) page 14, pp under genotoxicity - mixture is misspelled.

(6) page 22, conclusions - isoalkylcycloalkane is misspelled

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Personal Care Products Council
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Memorandum

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

FROM: John Bailey, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 29, 2010

SUBJECT: Comments on the Tentative Report on Isoparaffins

It would be helpful to include the abstract in the tentative report so the public has the opportunity to read the abstract and provide comments.

p.4 - Were the ingredients with no uses reported to the VCRP also not reported to be used by the Council Survey?

p.4, 22 - As there are inhalation data included in this report, is the aerosol boilerplate language necessary?

p.7 - In the summary of the Acute Oral Exposure section, it would be helpful to state that the LD_{50}s were all greater than the highest doses tested.

p.12 - Male rat kidney nephropathy associated with alpha2u-globlulin is very well characterized and is not relevant to humans. Therefore, delete "reportedly" - this protein is not synthesized in humans.

p.14 - Correct "mixute" to "mixture"

p.17 - In the open patch study of Isododecane, how was the "effective isododecane concentration ≈ 0.002%" derived? Based on the information provided, the 0.002% value is not correct. It states that a 40% dilution of a mixture containing 40% Isododecane was tested. Therefore the concentration of Isododecane tested was: 0.4 x 40% = 16%.

p.18, 19 - The effective concentration of 0.001% Isohexadecane is not correct. It states that 20% of a mixture containing 55.5% Isohexadecane was tested. Therefore, the concentration of Isohexadecane tested was: 0.2 x 55.5% = 11.1%

p.18 - As there are multiple HRIPTs presented in this report, it would be helpful to state once a general protocol, e.g., generally how many induction patches are completed.

p.19, 21 - Did Elsner and Maibach (1995) (reference 91) reach a conclusion as to whether or not Isohexadecane is a sensitizer? The summary of the Provocative Skin Sensitization section seems to imply that undiluted it might be a weak sensitizer, but the section states: "the pattern of reactivity of isohexadecane in subjects with dermatitis suggested that it acts unspecifically as an irritant when diluted."

p.20 - If the ACGIH TLV-TWA is included in the report, it should be cited directly to an ACGIH reference rather than a secondary source.

p.20 - In the epidemiology study, what were the results (relative risks) for subjects exposed to gasoline?

p.21 - In the summary, please do not state that Isooctane was "detected" in human brains of subjects following voluntary exposure. Modeling was used to estimate the levels in the brain.

p.21 - In the summary, it should be made clear that the nephropathy is observed in male rats.

p.27, Table 5 - For C10-14 Isoparaffin, why do all the Exposure Types have NR when a use concentration of 0.08 to 0.6 is presented for leave-on products?

p.28, Table 5 - What does ***mean after Totals?

p.31 - What does LD50 - 15.4 g/kg mean? Should "-" be "="?

p.32 - The concentration of 0.002% for Isododecane tested as a mixture of Isododecane 40% and trimethylsiloxysilicate is not correct. The mixture was tested at 50%. Therefore, the concentration of Isododecane tested was 0.5 x 40% = 20%. Please provide the vehicle (olive oil).

p.39, reference 47 - Please change "alpha 2 micro-globulin" to "alpha 2u-globulin".