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# **Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics**

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Status: Draft Tentative Report for Panel Review  
Release Date: November 9, 2018  
Panel Meeting Date: December 3-4, 2018

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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## Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Monice M. Fiume *MNF*  
Senior Director  
Date: November 9, 2018  
Subject: Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics

Enclosed is the draft Tentative Report on the Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics. (It is identified in the pdf document as *alkfat122018rep.*) The Panel first reviewed this group of 40 ingredients at the September meeting. At that meeting, the report included 41 ingredients. However, the ingredient PEG-5 Oleamide Dioleate (a tertiary amide) was inadvertently retained in that grouping; this family of ingredients comprises secondary amides exclusively. Noting our error, we have deleted PEG-5 Oleamide Dioleate from the report.

During its review in September, the Panel found the data insufficient to determine safety for this group of ingredients. Therefore, the Panel issued an Insufficient Data Announcement (IDA) with the following data requests:

- Method of manufacture
- Impurities data
- Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide
  - If absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

Method of manufacture and impurities data for PEG-50 Hydrogenated Palmamide (*alkfat122018data\_1*) were the only data received in response to the IDA. (New information is highlighted in yellow in the report.)

Updated concentration of use data (*alkfat122018data\_2*), and studies of acute dermal toxicity in the rat, skin irritation in rabbits, and skin sensitization in guinea pigs (*alkfat122018data\_3*), for PPG-2 Hydroxyethyl Cocamide were also received. However, this information did not change what the Panel already reviewed at the September meeting. The updated concentration of use data reported a lower concentration in one category (but the overall reported maximum use concentrations did not change), and the animal studies had already been reported as summary data in a NICNAS report.

The following are also included as a part of this report package:

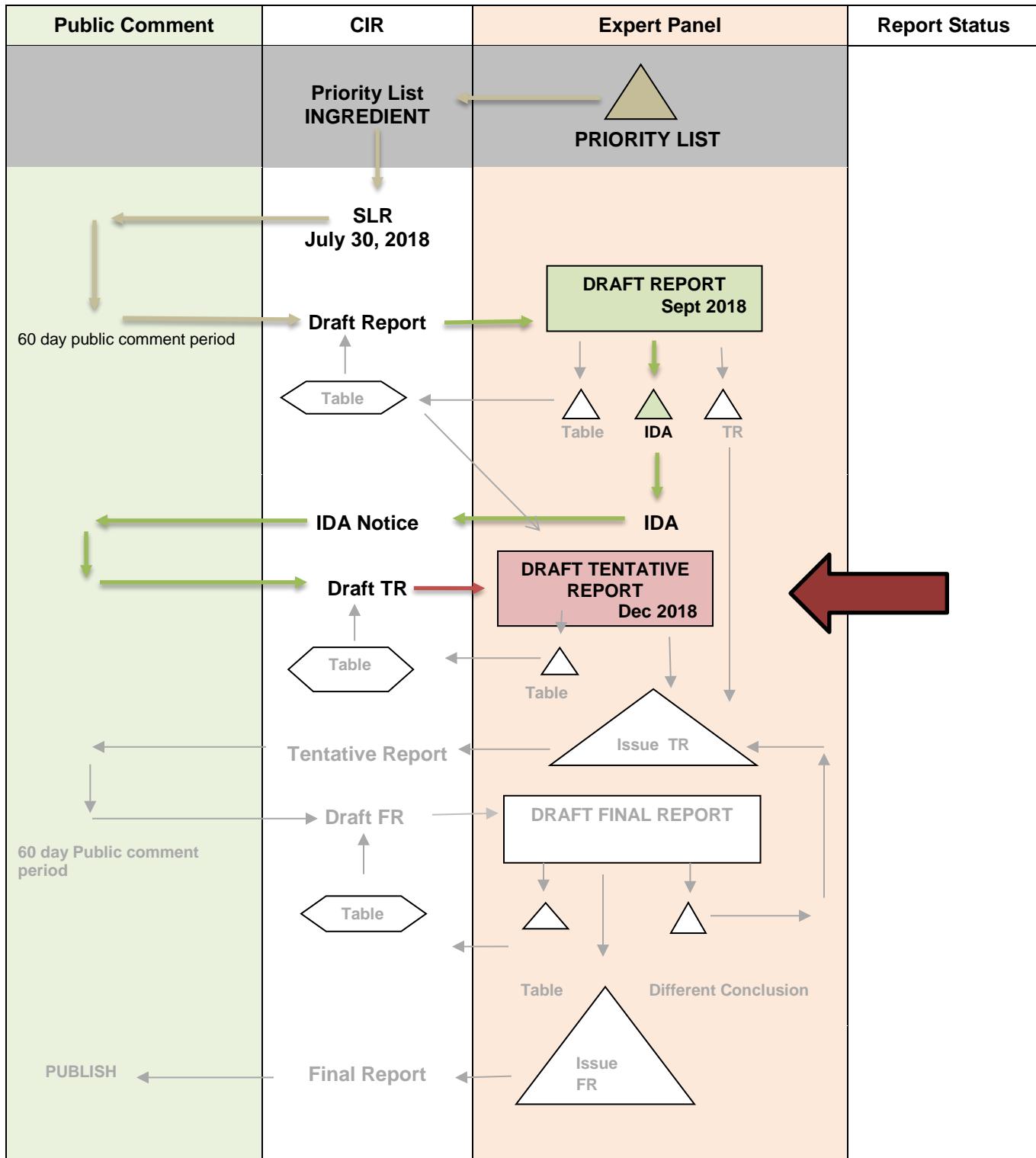
*alkfat122018flow:* report flowchart  
*alkfat122018hist:* report history  
*alkfat122018prof:* data profile  
*alkfat122018strat:* search strategy  
*alkfat122018min:* transcripts from September meeting  
*alkfat122018FDA:* 2018 VCRP data

If the Panel finds that the data are still insufficient, then a Tentative Report with an insufficient data conclusion should be issued. However, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a conclusion of safe as used or safe with qualifications. Also, please review the draft Discussion and determine whether it accurately captures the Panels deliberations, and please identify any other issues that should be addressed.

# SAFETY ASSESSMENT FLOW CHART

**INGREDIENT/FAMILY** Alkoxylated Fatty Amides

**MEETING** December 2018



**Report History – Alkoxylated Fatty Amides**

**July 30, 2018:** Scientific Literature Review announced

- Concentration of use data were incorporated into the SLR

**September 24-25, 2018:** Draft Report

- No additional unpublished data received in response to the SLR
  - o The Panel issued an IDA, requesting the following information:
    - o Method of manufacture
    - o Impurities data
    - o Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide
      - If absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

**December 3-4, 2018:** draft Tentative Report

- The ingredient, PEG-5 Oleamide Dioleate, was inadvertently retained in this grouping of ingredients (this grouping comprises secondary amides exclusively, whereas this ingredient is a tertiary amide). Noting our error, we have deleted this ingredient from the report.
- Method of manufacture and impurities data for PEG-50 Hydrogenated Palmamide were received and added to the report
- Updated concentration of use data, and studies of acute dermal toxicity in the rat, skin irritation in rabbits, and skin sensitization in guinea pigs, for PPG-2 Hydroxyethyl Cocamide were also received. However, this information did not change what the Panel already reviewed at the September meeting

Alkoxylated Fatty Amides Data Profile\* – Dec 2018 Panel meeting – Writer, Monice Fiume

## Alkoxylated Fatty Amides Data Profile\* – Dec 2018 Panel meeting – Writer, Monice Fiume

		<b>Reported Use</b>	<b>Chem/Phys Props</b>	<b>Method of Manufacture</b>	<b>Impurities</b>	<b>Dermal Penetration</b>	<b>ADME</b>	<b>Animal Tox - Acute, Dermal</b>	<b>Animal Tox - Acute, Oral</b>	<b>Animal Tox, Acute, Inhalation</b>	<b>Animal Tox - Rptd Dose, Dermal</b>	<b>Animal Tox, Rptd Dose, Oral</b>	<b>Animal Tox - Rptd Dose, Inhalation</b>	<b>DART</b>	<b>Genotoxicity - in vitro</b>	<b>Genotoxicity - in vivo</b>	<b>Carcinogenicity</b>	<b>Derm. Irr - In Vitro</b>	<b>Derm. Irr. - Animal</b>	<b>Derm. Irr. - Human</b>	<b>Sensitization - In Vitro</b>	<b>Sensitization - Animal</b>	<b>Sensitization - Human</b>	<b>Phototoxicity</b>	<b>Ocular Irritation</b>
Polyglyceryl-4-PEG-2 Cocamide																									
PPG-2 Cocamide	X																								
PPG-1 Hydroxyethyl Caprylamide																									
PPG-2 Hydroxyethyl Cocamide	X	X				X	X					X				X	X			X	X		X		X
PPG-2 Hydroxyethyl Coco/Isostearamide	X																								
PPG-3 Hydroxyethyl Soyamide																									
PPG-2 hydroxyethyl isostearamide (for read-across)						X								X											

\*“X” indicates that data were available in a category for the ingredient

### **Alkoxylated Fatty Amides**

Ingredient	CAS #	InfoB	SciFin	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
PEG-7 Oleamide	---	---	0				0												
PEG-9 Oleamide	---	---	0				0												
PEG-4 Rapeseedamide		✓	0				0					X							
PEG-4 Stearamide	----	---	0				0												
PEG-10 Stearamide	----	---	0				0												
PEG-15 Stearamide	----	---	0				0												
PEG-50 Stearamide	----	---	0				0												
PEG-5 Tallow Amide	8051-61-4	---	deltd #				0												
PEG-8 Tallow Amide	----	---					0												
PEG-50 Tallow Amide	8051-63-6	---	deltd #				0												
PEG-2 Tallowamide DEA	----	---	0				0												
Polyglyceryl-4-PEG-2 Cocamide	----	---	0				0												
PPG-2 Cocamide	----	---	0				0												
PPG-1 Hydroxyethyl Caprylamide	----	---	0				0												
PPG-2 Hydroxyethyl Cocamide	201363-52-2	✓	0				CLP					X							
PPG-2 Hydroxyethyl Coco/Isostearamide	----	✓	0				preReg					X							
PPG-3 Hydroxyethyl Soyamide	----	---	0				0												
<b>PEG-9 Cocamide MEA</b>	<i>Not INCI</i>						<i>VCRP</i>		<i>0</i>										

**Search Strategy****PubMed (8/28/17):**

(61791-08-0[EC/RN Number]) OR (68783-22-2[EC/RN Number]) OR (26635-75-6[EC/RN Number]) OR (8051-61-4[EC/RN Number]) OR (8051-63-6[EC/RN Number]) OR (201363-52-2[EC/RN Number]) – 0 hits

(alkoxylated AND amide) OR ((PEG or polyethylene glycol) AND (cocamide OR palmamide OR lanolinamide OR lauramide OR oleamide OR ricinoleamide OR rapeseedamide OR stearamide OR tallowamide OR (tallow AND amide))) OR ((PPG OR polypropylene glycol) AND (cocamide OR caprylamide OR isostearamide or soyamide)) - 14 hits/1 useful

**SciFinder (8/28/17)**

CAS #'s – see table

by name – 0 hits

structure search (per Bart ) – 6056 hits

## LINKS

### Search Engines

- Pubmed (- <http://www.ncbi.nlm.nih.gov/pubmed>)
- Toxnet (<https://toxnet.nlm.nih.gov/>); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (<https://scifinder.cas.org/scifinder>)

appropriate qualifiers are used as necessary  
search results are reviewed to identify relevant documents

### Pertinent Websites

- wINCI - <http://webdictionary.personalcarecouncil.org> - can be used as a first check for information sources/CFR citations/etc (searched 8/29/17)
- FDA databases <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>
- FDA search databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>;
- EAFUS: <http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true>
- GRAS listing: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm>
- SCOGS database: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm>
- Indirect Food Additives: <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives>
- Drug Approvals and Database: <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm>  
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf>
- FDA Orange Book: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>
- OTC ingredient list: <https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf>
- (inactive ingredients approved for drugs: <http://www.accessdata.fda.gov/scripts/cder/ig/>
- HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogon>
- NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>
- NTIS (National Technical Information Service) - <http://www.ntis.gov/>
- NTP (National Toxicology Program ) - <http://ntp.niehs.nih.gov/>
- Office of Dietary Supplements <https://ods.od.nih.gov/>
- FEMA (Flavor & Extract Manufacturers Association) - [http://www.femaflavor.org/search/apachesolr\\_search/](http://www.femaflavor.org/search/apachesolr_search/)
- EU CosIng database: <http://ec.europa.eu/growth/tools-databases/cosing/>
- ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - <http://www.ecetoc.org>
- European Medicines Agency (EMA) - <http://www.ema.europa.eu/ema/>
- IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>
- SCCS (Scientific Committee for Consumer Safety) opinions: [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/opinions/index\\_en.htm](http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm)

- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>
- International Programme on Chemical Safety <http://www.inchem.org/>
- FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>
- WHO (World Health Organization) technical reports - [http://www.who.int/biologicals/technical\\_report\\_series/en/](http://www.who.int/biologicals/technical_report_series/en/)
- [www.google.com](http://www.google.com) - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

**Botanical Websites, if applicable**

- Dr. Duke's - <https://phytochem.nal.usda.gov/phytochem/search>
- Taxonomy database - <http://www.ncbi.nlm.nih.gov/taxonomy>
- GRIN (U.S. National Plant Germplasm System) - <https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx>
- Sigma Aldrich plant profiler- <http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html>
- American Herbal Products Association Botanical Safety Handbook (database) - <http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx>
- European Medicines Agency Herbal Medicines - [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal\\_search.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp)
- National Agricultural Library NAL Catalog (AGRICOLA) <https://agricola.nal.usda.gov/>
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- [http://www.seasoningandspice.org.uk/ssa/background\\_culinary-herbs-spices.aspx](http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx)

**Fragrance Websites, if applicable**

- IFRA (International Fragrance Association) – <http://www.ifraorg.org/>
- Research Institute for Fragrance Materials (RIFM)

## **ALKOXYLATED FATTYAMIDES**

### **Full Panel – September 25, 2018**

**DR. BELSITO:** This is the first time that we're looking at the safety assessment of 41 structurally-related alkoxylated simple amides. A few of these ingredients are dye, and then alkoxy substituted amides. But most of them are fatty amides or mono.

We looked at all of the data. We also received data in Wave 2, regarding information from Council about the fact that there were a number of these ingredients for which there were no suppliers, and took that into account. And came up with a conclusion that these, at this point, were insufficient for manufacturing and impurities.

Dermal absorption, 28-day dermal, and if absorbed, other toxicity endpoints may be necessary. With a caveat that we may be able to read across from the two that are most frequently used. The PPG-2 hydroxyethyl cocamide in 342 formulations, and the PEG-4 Rapeseedamide in 280. So, basically using those as read-across and then potentially for the others, and getting information on manufacturing, impurities, dermal absorption, 28-day dermal.

**DR. BERGFELD:** So, in essence you're going insufficient. You have two lead ingredients that will read across to the others.

**DR. BELSITO:** Potentially.

**DR. BERGFELD:** Potentially. Is there a second?

**DR. MARKS:** Our team actually had a conclusion of safe for all 41 ingredients. Ron Shank, do you want to comment why, because a lot of this has to do with, obviously, toxicity, which Don listed.

**DR. SHANK:** I recommended using PEG-4 Rapeseedamide and PPG-2 hydroxyethyl cocamide for which we have a lot of data to read across to cover all the others, with the possible exception of the two dialkoxyl fatty amides. I need help from the chemist, if those could be included with the read-across or not.

The PEGs and the PPGs and the amides, individually, have already been reviewed and found to be safe. So, using the read-across for those two, the PEG-4 Rapeseedamide and the PPG-2 hydroxyethyl cocamide, to read across. So, they would be safe when formulated to be nonirritating.

**DR. BELSITO:** What about the lack of manufacturing data information?

**DR. MARKS:** Ron is smiling because we had this discussion yesterday.

**DR. SHANK:** We have reviewed a very large number of ingredients on this panel, and very seldom has the need for method of manufacture had a definitive influence on the conclusions made. So, if someone can argue as to why method of manufacture is needed, other than to fill in a blank, I would like to hear it.

**DR. BELSITO:** Because that would give us some clue as to impurities. Right now, we just know that there is some dioxane in the PEG-4 Rapeseedamide that's one-part per million maximum. And that the rapeseedamide as a raw material is reported to be 60 to 80 percent pure. What is the other 40 to 20 percent of the rapeseedamide?

**DR. SHANK:** Then ask for impurities, not method and manufacture.

**DR. BELSITO:** We asked for method and manufacture and impurities. We can always decide not to act on it.

**DR. LIEBLER:** Once in a while, when someone on our team loses their enthusiasm for box-checking, it's up to the rest of us to step forward and pick up the flag and bear the standard forward. Ron, I'm happy to do that for you. I know you'd do it for me.

But, seriously, I think that at this point there's no reason not to ask. We will probably get sufficient information to satisfy our need to have done the appropriate diligence on that issue. I don't think it's going to be limiting in the final report.

And I do agree with your suggestions on the read-across, use for the two ingredients for which we've got pretty abundant data. I think Don was essentially saying pretty much the same thing. And I have no problem with including this substituted molecule in the assessment.

**DR. BERGFELD:** Wait, Ron Hill has something.

**DR. HILL:** I agree with pretty much everything you just said. I was just making note that -- because one of our lead ingredients, the read-across ingredient, was the PEG-4 Rapeseedamide. There is a significant molecular weight, less than 600 fraction, and I was much more interested in getting information about what's in that fraction.

And in our discussion of manufacture, what we really said in this case was we're really interested in potential impurities. And what we think we know, is that the main one that we might encounter is dioxane and we would include our usual limitation on that. But, I do think having a little more idea about what potential impurities might be in these is important as part of due diligence.

**DR. MARKS:** I think, yeah, it's fine.

**DR. BERGFELD:** Ron Shank?

**DR. SHANK:** Yes.

**DR. BERGFELD:** Any other comments? Tom

**DR. SLAGA:** No.

**DR. BERGFELD:** Curt?

**DR. MARKS:** Second.

**DR. BERGFELD:** There's a second from Dr. Marks, quickly stated. Okay, you want to restate the motions since we've had some discussion?

**DR. BELSITO:** Insufficient for method of manufacturing, impurities, 28-day dermal; and depending upon that, other toxicity endpoints for the two lead ones, the PEG-4 Rapeseedamide and the PPG-2 hydroxyethyl cocamide.

**DR. BERGFELD:** All right, and it's been second. I'm going to call for the vote. All those in favor please indicate by raising your hand. Okay, unanimous.

### Belsito Team – September 24, 2018

**DR. BELSITO:** Alkoxylated Fatty Amines. So, this is the first time we're seeing the safety assessment of 41 alkoxylated fatty amines. A few of these are di-N,N-alkoxyl-substituted amides. Most of these are alkoxylated fatty amides.

**DR. LIEBLER:** They're all amides.

**DR. BELSITO:** They're all amides?

**DR. LIEBLER:** Yup. How are you with the sensitization data?

**DR. BELSITO:** I don't know, I'm getting there now.

**DR. LIEBLER:** Okay.

**DR. BELSITO:** I just ask, can we bring in data from PPG, PEG, Tallow, et cetera documents? Is that needed?

We don't have any method of manufacture. HRIPT is an only 50 for the two with the biggest use, but the guinea pig maximization tests were negative, so I'm okay with sensitization and irritation.

**DR. LIEBLER:** Okay.

**DR. BELSITO:** Dioxane impurities, respiratory boilerplate, other. And I wondered whether we're insufficient for manufacturing in 28-day dermal tox, and if absorbed, a 28-day dermal, and if absorbed, other tox endpoints. If so, could we read across from the two most frequently used, which were PEG PPG-2 hydroxyethyl cocamide and PEG-4 Rapeseedamide?

**DR. LIEBLER:** Yes, so I agree with all of those. I think that we need method of manufacture impurities, so right now we're insufficient for that. We need dermal absorption on a 28-day dermal, and if we had it for those two we would be covered. For those two that you just mentioned, which are the high use ones.

**MS. FIUME:** Dermal absorption...

**DR. LIEBLER:** And 28-day dermal tox. We have no carcinogenicity data, but the mutagenicity profile is clean. And these really don't have structural alerts. I'm not really worried about the lack of carcinogenicity. If the other team feels that we need it, I won't argue forcefully at this point; but the question is more tox than carcinogenicity here.

**MS. FIUME:** Can I ask for a point of clarification on the dermal absorption? Typically, when we have mixtures like this we say it's not feasible because they don't know what they're looking for. Is there an aspect that they would find in the dermal absorption?

**DR. LIEBLER:** Well, we use that logic for things like botanicals.

**MS. FIUME:** Okay, but not something like this?

**DR. LIEBLER:** This is a much more defined mixture with certainly very representative constituents that could be very clearly, easily measured. I think it's fair to ask for that.

**MS. FIUME:** I just searched the PEG Tallow type ingredients. We have a report on the PEG Tallow amines, but I don't have anything on just PEG Tallow that wouldn't have an amine attached.

**DR. LIEBLER:** I don't think that helps us.

**DR. BELSITO:** Let me see what Paul said. "No method of manufacture, impurities for one. The second greatest use with PEG-2 hydroxyethyl cocamide #1. No absorption. Tox data almost entirely for PEG-4 Rapeseedamide." Pretty much what we said.

**DR. LIEBLER:** I think that's really representative of the class.

**DR. BELSITO:** "Genotox, no carcinogenicity data."

**DR. LIEBLER:** Right.

**DR. BELSITO:** Yeah. So, exactly what we said. "Council comments; 23 of the ingredients have no suppliers." And then he had questions regarding the grouping to you.

**DR. LIEBLER:** The grouping?

**DR. BELSITO:** Just reading what he stated.

**DR. LIEBLER:** I think the only grouping issue is we have a few that are di-N,N-alkoxyl -- a few. And then most of them are mono-N-alkoxyl, and I think they can all be treated together.

**DR. ANSELL:** We would support dropping the di-substitute at the end in that there is no data on it, and it isn't going to inform the discussion on the other materials.

**DR. BELSITO:** Which one?

**DR. ANSELL:** The di-N,N-alkoxyl-substituted amides.

**DR. BELSITO:** Which ingredients are those?

**MS. FIUME:** I know two of them are PEG-3 cocamide DEA, and PEG-2 Tallowamide DEA.

**DR. BELSITO:** You want to drop those? Dan?

**DR. LIEBLER:** I don't object to dropping them. If you wanted them in the report to be reviewed, because they were in the dictionary then we could treat them. I mean, I don't think that we couldn't deal with them. But if there is a compelling reason, sort of administratively, to drop them, then I have no objection.

**MS. FIUME:** CIR included them in grouping. So, I know his stand on it would be to keep them; because it's actually mentioned in the introduction that they are different --

**DR. LIEBLER:** So, Jay, the reasoning for dropping them is that there are no suppliers and we are unlikely to get data?

**DR. ANSELL:** No, that the mono-substituted and the di-substituted do not inform -- the di-substituted materials do not inform the discussion about the mono-substituted materials. There is no data and it's unlikely, if there were data, that you could rely on it for the mono-substituted materials.

**DR. LIEBLER:** I don't see that as being a liability for the di-substituted. I think the mono-substituted would inform the evaluation of the di-substituted. If the di-substituted needed to be in the report because they are in the dictionary because CIR wanted them there, then we can review them, it's just going to be insufficient.

We're not counting on the di-substituted, if they are there, to inform the evaluation of the mono-substituted, I think. It would be nice if they did somehow, but we're not in that situation. I don't see it as a reason to eliminate them.

**DR. ANSELL:** If the only reason is that they are in the dictionary, but they do not help with the safety assessment, then we would argue to drop them. If you think that the di(s) can be supported with the data on the mono, then we can see where that assessment goes. I was thinking the other way around.

**DR. LIEBLER:** First of all, I don't see any reason why the di(s) should really be different in their toxicity. In our evaluation, I don't see why they should be different. They are similar enough in structure to the other materials that -- I guess the question would be, even if we have no data in uses for the di(s), would we be comfortable in reading across from the data on the mono to support the di(s)?

I would certainly be open to that possibility because of the similarities, the lack of structure alerts for toxicity, etcetera -- for carcinogenicity, and the lack of anything but maybe a little irritation for these in the skin.

**DR. ANSELL:** Well, this is the first review, so I think we're pretty flexible at this point.

**DR. LIEBLER:** That's how I feel. And let's see how the discussion with the full panel goes tomorrow. Maybe the other team might have a reason to take a position on that, and we can audible on it.

By the way, just for purposes of understanding this group, I want to just say I like the idea of including these in sort of structural, general formula groups in Table 2. That's a nice touch, I like that.

**MS. FIUME:** Thank you.

**Marks Team – September 24, 2018**

**DR. MARKS:** Okay. Next is the alkoxylated fatty amides. This is a draft report from Monice. This is the first time we've seen these ingredients; therefore, it's a first review. There are 41 ingredients. Tom, Ron and Ron, ingredients okay? And then there was an issue raised in the Wave 2 memo about the dialkyl substituted amides. Am I saying that right, Ron Hill? Amides or amides? Which his better? Or does it matter?

**DR. HILL:** It doesn't.

**DR. MARKS:** Good.

**DR. HILL:** Amides, amides, amides. All of those are heard and are acceptable as far as I understand.

**DR. MARKS:** Whether or not these should be included in the report comments. Okay. I'll open it up for discussion. First, ingredients?

**DR. SHANK:** I thought we could use two of the ingredients for read-across for all of the others, and say they're safe when formulated to be nonirritating. The two for read-across would be PEG-4, Rapeseedamides.

**DR. HILL:** PEG-4, which --

**DR. SHANK:** PEG-4, Rapeseedamides.

**DR. MARKS:** Oh, yeah. Okay, that's the one that has a lot of uses.

**DR. SHANK:** Right. And PPG-2 hydroxyethyl cocamide. We have data for those. We could use those for read across. Possible exception would be the two dialkoxy fatty amides, which are PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA. There's no toxicology data on those. And I'm not too sure -- I need help from the chemist -- can we read across from all of the others for those dialkoxy fatty amides.

The PEGs and PPGs and amides have already been reviewed by themselves and found to be safe when formulated to be non-sensitizing.

**DR. MARKS:** Yeah, based on a QRA

**DR. SHANK:** Yes. And we could add the nitrosation caveat to these compounds.

**DR. MARKS:** Ron Hill?

**DR. HILL:** Yeah, I'm looking. I'm sorry, I'm looking for one particular one that --

**DR. MARKS:** Do we have the method -- I had noted here, do we have method of manufacturing and impurities on these?

**DR. SLAGA:** I thought we did.

**DR. MARKS:** Pardon?

**DR. SLAGA:** We have that.

**DR. MARKS:** Okay.

**DR. HILL:** You do?

**DR. MARKS:** I had that as a question mark. And I didn't see any -- and it wasn't checked here in our spreadsheet. And when I looked at the report, I think it says -- let me go, which page that is?

**MS. FIUME:** PDF page 12.

**DR. MARKS:** Yeah. Method of manufacturing is not discovered, unpublished. I think -- I mean, we don't move forward -- we could aim for a safe, but I don't think we come to a conclusion of safe if we don't have the method of manufacturing. That would be an insufficient data. Impurities we have. The PEG-4 Rapeseedamide. We don't have it for the other lead ingredient that you --

**DR. HILL:** For that particular one which he proposed to use for read-across -- I'm getting a ringing, sorry because it's aiming toward the speaker. We've got molecular weight 600 indicated. I really wanted a better sense of the molecular weight distribution as focused on the low end with that one.

**DR. SHANK:** Which one are you talking about?

**DR. HILL:** Well, the PEG-4 Rapeseedamide, there's a molecular weight of less than 600 fraction that's indicated. I don't know where the percentage is, but I can find it probably in a minute. At that molecular weight range, we would have dermal absorbability, but then, presumably, surfactant character in which case it probably wouldn't get very far.

**DR. MARKS:** Sensitization data for that is okay just as Ron had mentioned earlier. Irritation sensitization for both those lead ingredients. But I actually -- again going back -- I had the method of manufacturing and impurities would have been an insufficient data announcement. Ron Hill, what more did you want?

**DR. HILL:** Well, impurities. If we had representative, method of manufacture. I doubt that most of these would vary. There were a couple places, though, where I had some question about what actually I had in terms of chemical.

**DR. MARKS:** Where do we have the method of manufacture?

**DR. HILL:** I don't.

**DR. MARKS:** No. Okay.

**DR. HILL:** I didn't flag that. I said, if we had it for a couple of representatives we could, surely, I think, use that to read across. Because I doubt they would vary much. I don't have any reason to think so. But there are a few places where I had -- so we've got this PEG-20 Cocamide MEA, which actually is an N, N-dialkyl, best I can tell.

And then the PEG-5 Oleamide Dioleate, I wanted to confirm that that's Dioleate somewhere out there. I don't know where the Dioleate can even be on that PEG-5 Oleamide. Because the only place you could attach one more would be at the very end of the PEG. So, where is the other one? That's weird.

And I would like, if we're going to use the Rapeseedamide to read across, which I think we're talking about to pull over our fatty acids distribution from our vegetable oil's report; and it would be nice if actually we could get a direct supply from the vendor -- if at all possible -- what that fatty acid distribution in that actually is. I mean, it will vary depending on the source surely; and there may be more than one vendor making it. But if we could get something typical, that would help us with the read-across to all these others.

And same with Cocamide; we already have that pretty well characterized, we just need to pull it over from another report. Because we've Cocamide it to death by this point, I think. We've got lots of information about that. We should put it in here, because that helps with how we're reading across.

And everything else, I think, I agree pretty much with Ron Shank. But we've got the cocamide MEA, which I think is an N, N-dialkyl. I don't know that any new issues are created there, honestly.

And Cocamide DEA, I was a little -- I think I wanted to be clear exactly. Because I don't think there's a structure, exactly what that is. I think I know what it is, but think I know is not really good enough.

**DR. MARKS:** Are we concerned, chemically, with these surfactants like in cocamidopropyl betaine. Is it betaine?

**DR. HILL:** I think I determined, eventually, that I had been saying that wrong; and it's betaine.

**DR. MARKS:** Betaine.

**DR. HILL:** Because of the way that name --

**DR. MARKS:** At any rate, we were concerned about DMAPA and amidoamine as contaminants. Is that also a concern as an impurity in these surfactants? Because there's a lot of coco in this.

**DR. HILL:** No. Because that was not where it was coming from.

**DR. MARKS:** Okay.

**DR. HILL:** It was coming from the other component.

**DR. MARKS:** Okay. So, that's not an issue with these?

**DR. HILL:** It is, as far as I can tell, not an issue.

**DR. MARKS:** Okay, good. What do you think about tomorrow, insufficient data announcement, method of manufacture? We got to fill something in that blank. Ron, you're not concerned?

**DR. SHANK:** Well, in the thousands of ingredients we reviewed how often has method of manufacture been a determining factor in our conclusion?

**DR. MARKS:** I'm kind of remembering back when we did one ingredient and Dan Liebler said, if there's no method of manufacture, we can't move forward. No, I agree with you, Ron. We'll be seconding it. It'll be interesting to see how the Belsito team comes. But you feel comfortable, and I agree; everything else we can just move forward with a tentative report safe. Okay.

**DR. HILL:** There was another one, too, where I'm not sure I know what it is, which is the PPG-2 Hydroxyethyl coco/Isostearamide. I'm assuming it is the Cocamide where we have the amide made from the isostearyl amine and hydroxyethyl. But these places where the structures aren't clearly defined, we should really try to get it if they're in use. And if not, we can at least retrace the steps on the dictionary work and confirm.

**DR. MARKS:** And, Ron Shank, I mean, if we aren't worried about amidoamine and DMAPA in these, then we don't even have to have a caveat, and the conclusion formulated to be non-sensitizing.

**DR. HILL:** We shouldn't need that for these.

**DR. SHANK:** Correct.

**DR. MARKS:** Okay. And then, Ron Shank, you had mentioned, I think, two ingredients you were a little bit concerned about whether they should be included. I don't want to overlook those. There wasn't much data on them, and you were wondering whether we should actually include them in the report. Is a lack of data a reason not to include it? That would be more a reason to say they're insufficient, if they're chemically similar and belong in this group.

**DR. SHANK:** We could say insufficient or use read-across to include them.

**DR. MARKS:** Right. Exactly.

**DR. SHANK:** I'd like to hear from Dr. Hill if the read-across from the two I mentioned would include the two dialkoxyl fatty amides.

**DR. MARKS:** And those two, again, Ron?

**DR. SHANK:** One is PEG-3 Cocamide DEA.

**DR. MARKS:** Hold a second. PEG-3.

**DR. SHANK:** And the other is PEG-2 Tallowamide DEA. And they're slightly different structure.

**DR. MARKS:** One is the PEG-2 Tallowamide DEA?

**DR. SHANK:** Yes.

**DR. MARKS:** Okay.

**DR. SHANK:** And the other is PEG-3 Cocamide DEA.

**DR. MARKS:** PEG-3. Why am I not -- okay. PEG-3 Cocamide DEA. Okay. I see them now on the list. Ron Hill, what do you think about those two?

**DR. HILL:** I mean, we've got quite a few others in here that are N-hydroxyethyl. From that point of view, what we really are doing is -- the DEA is just two hydroxyethyls attached to the nitrogen, nothing else. And then you start PEGylating and you make one of the two chains longer.

I mean, I'm bothered that we don't have data on PEG-3 DEA, or something, PEG-2 Cocamide, or something smaller. Because the ones that we're reading across from our -- well, I say that. PPG-2 Hydroxyethyl Cocamide might cover it. Sorry, I'm thinking out loud which is never good.

**DR. BERGFELD:** Which one was that? I'm sorry.

**DR. HILL:** He was asking about the Tallowamide DEA, but we have Cocamide DEA. Again, I mentioned coconut acids, I guess. That will translate to the kind of distribution we see in Cocamide. And I think we have that information directly, anyway, we could pull over. The comparable information about Tallow, which I know we had in vegetable oils report, one of those. And we've got soy here as well.

What do we got? We got soy, Cocamide, Tallowamide. I think that's all the ones that come -- Rapeseedamide, and here's Lanolinamide. So we know what we're doing on the read across, we need that table that has -- it looks like five. Because the rest of them, we know what they are. They're Lauramide, they're Oleamide, they're Stearamide, those.

I think things read across from the PPG to Hydroxyethyl Cocamide. Coconut oil, I think, goes down to C12 with a significant fraction. It's not huge, but it's significant.

**DR. MARKS:** Okay.

**DR. HILL:** Oh, palm. I forgot palm too.

**DR. MARKS:** It looks like -- if I interpreted that correctly -- we will move forward including those ingredients with all the others. And again, presumably I'll be seconding a proposal to issue a tentative report with safe conclusion. Any other comments?

**DR. SLAGA:** No.

**DR. MARKS:** Good discussion.

**DR. BERGFELD:** Can you repeat your final conclusion. Is it safe?

**DR. MARKS:** Safe. Yes.

**DR. BERGFELD:** And you're deleting the method of manufacturing?

**DR. MARKS:** Pardon?

**DR. BERGFELD:** You're not demanding a method of manufacturing? You're going to mention it's not there, in the discussion.

**DR. MARKS:** Well, I have a feeling it will be mentioned by the Belsito team. But if it is, then what I may do is ask Ron Shank to express why he doesn't feel the method of manufacturing is necessary. And if Dan Liebler sticks to his guns, we'll have a duel between Ron Shank and Dan Liebler.

**DR. SHANK:** That'll be fun.

**DR. MARKS:** It'll be fun is right. It'll be the meeting of the minds. Okay. Let me save this.

**MS. FIUME:** And what we can do in our post-meeting announcement is, if this does go forward with the tentative, we can mention that method of manufacture would help improve the safety assessment even though it wasn't an official IDA request.

**DR. MARKS:** Yeah. I like that, Monice, yeah.

**DR. SHANK:** That's good.

**DR. MARKS:** Yeah.

**DR. KATZ:** I have a question before you move on.

**DR. MARKS:** Sure, Linda.

**DR. KATZ:** And this is with regards to 1,4-dioxane as an impurity. Is that going to fall into your discussion at all; particularly, with PEG-4, the Rapeseedamide?

**DR. HILL:** I'm pretty sure we essentially always include dioxane in the discussion with reports that have PPG and PEG. But we've now captured that, and I think we definitely should put it there.

**DR. SLAGA:** To discuss.

**DR. HILL:** And I also, just to mention, I dropped some comments, there's some chemistry clean up that's needed in the first section on chemistry. And in particular, exactly how we say we're reading across from amides to amines, which are chemically quite disparate. It needs to be mentioned.

If we're considering them as potential metabolites, on a couple of these, then that's fine. But approving Cocamine has nothing to do with these. I think some of the ones that were mentioned, PEGs Cocamine, we aren't reading those across to the amides. That would be absurd. I just thought I'd mention that.

**MS. FIUME:** I'm sorry, Dr. Hill, where are the amines mentioned?

**DR. HILL:** I dropped a comment, it's in the introduction. There just -- the way some of these things are mentioned. And it's editorial really, but I just want to make note. Similar amines in the cosmetic ingredient review PEGs Cocamine report -- that shouldn't read across. We wouldn't use it to read across to these amides.

And I think they wouldn't be formed as metabolites in this particular case, because on the other end we don't have the coconut acids amines.

**MR. GREMILLION:** The method of manufacture doesn't inform impurities? I guess, what's the rationale behind method of manufacture in conventional sense?

**DR. HILL:** I like to see one or the other. And usually, I'm more interested in impurities that might carry over from method of manufacture than the method of manufacture itself. I mean, for me, an insufficiency is impurities. But the problem is the two ingredients that we have -- well, I don't know what the problem is. I don't know if there's a problem with impurities.

**DR. MARKS:** There wasn't, I think, in the -- we have the impurities --

**DR. HILL:** That's why I asked for more information.

**DR. MARKS:** Rapeseedamide.

**DR. HILL:** Because I was wanting more about the molecular weight, less than 600 fraction, which would include impurities that would concern us.

**DR. MARKS:** I guess I wasn't concerned with the molecular weight since we had irritation sensitization data which was okay.

**DR. HILL:** Yeah, but again, if you have something molecular weight, less than 600, at a higher percentage -- I don't know that a percentage was listed here. It could be carcinogenic, just hypothetically, to make sure that people are interested enough. Then, you know, if we get the information.

**DR. MARKS:** Yeah. Tom didn't have a concern about that. I think it gets back --

**DR. SLAGA:** I didn't. No. The impurity would take tremendous amount to be carcinogenic. I mean, you're not going to reach that level --

**DR. MARKS:** I think we're going to have that discussion tomorrow about method of manufacture impurities. And I think you bring up a point. You can see there's a bit of -- how do I want to say -- different opinions among the team members here.

**DR. HILL:** But I think you're focused on systemic carcinogenicity. I mean, the skin can get cancer, you know. I think you can't totally forget about that idea.

**DR. MARKS:** Did you want to say anything more tom?

**DR. SLAGA:** It's a concentration effect. I mean, we would never reach that.

**DR. MARKS:** Okay.

**DR. HILL:** Well, what levels are these used? If they're all in rinse off, I agree with you, if they're 90 percent; so, we need to look at that again.

**DR. MARKS:** The top percentage leave-on on the Rapeseedamide is 9.3 percent.

**DR. HILL:** Ten percent. So, if you had a one percent impurity of something that's significant, yeah it would only be -- it'd be a modest amount. But it depends on what it is.

**DR. MARKS:** Okay. I think we didn't answer your question, exactly. We will -- as you can see, when I initially started I was -- we need the method of manufacture. But I think Ron Shank, at least, and Tom agreed, and I'll defer.

And we'll see what the -- that's one of the, how do I want to say, brilliance of the way this panel is set up, is we have two different teams. Which tomorrow, without knowing what the other team has said, we'll come to a conclusion. So, we'll see. I would be surprised tomorrow they move that an insufficient data announcement is made for method of manufacture. And if that's the case, we will concur with that.

**DR. HILL:** And again, I'm much less interested in the method of manufacture, other than what might carry over versus impurities in a finished product.

**DR. MARKS:** Yeah. Versus the impurities. And then Monice has had a very diplomatic way to address it; is we'll ask for it no matter what. But it may not be hinging on whether or not a tentative report is issued.

**MR. GREMILLION:** But the response to your request seems like it may be different, depending on what conclusion you raise.

**DR. MARKS:** Oh, absolutely. No question. If we move forward with a safe conclusion, it's not a binding request. You're absolutely right.

Okay. Well, we'll see how that works tomorrow. And the other thing, which is always good about the process, is this is a tentative report. We have another look at it before it goes to final. We sometimes change our minds, going from the tentative to the final and ask for more data.

Okay. That's a robust discussion. Yes, next?

**DR. HILL:** Just because I a little bit overstated my case, there are times where method of manufacture is important. For example, if an enzyme gets used in the process, then how do you get rid of that, if the thing's used in leave-on in mucus membranes.

**DR. MARKS:** Well, the other example of that is benzene --

**DR. HILL:** Exactly. And dioxane.

**DR. MARKS:** -- and the polymers we just discussed. And that was in the conclusion of benzene. It should be. So, Ron Hill, we get that caveat. Yes, the method of manufacturing is important as is impurities. Okay, they both add important data points.

## **Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics**

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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## ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 40 alkoxylated fatty amides as used in cosmetics. These ingredients are structurally related as alkoxylated simple amides, and all but a few of these ingredients are reported to function in cosmetics as surfactants – emulsifying agents. The Panel reviewed the relevant data for these ingredients, and concluded *[to be determined]*.

## INTRODUCTION

This assessment reviews the safety of 40 alkoxylated fatty amides, listed below, as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all but a few of these ingredients are reported to function in cosmetics as a surfactant – emulsifying agent ([Table 1](#)).<sup>1</sup>

PEG-2 Cocamide	PEG-2 Lauramide	PEG-15 Stearamide
PEG-3 Cocamide	PEG-3 Lauramide	PEG-50 Stearamide
PEG-4 Cocamide	PEG-5 Lauramide	PEG-5 Tallow Amide
PEG-5 Cocamide	PEG-6 Lauramide	PEG-8 Tallow Amide
PEG-6 Cocamide	PEG-11 Lauramide	PEG-50 Tallow Amide
PEG-7 Cocamide	PEG-3 Oleamide	PEG-2 Tallowamide DEA
PEG-11 Cocamide	PEG-4 Oleamide	Polyglyceryl-4-PEG-2 Cocamide
PEG-20 Cocamide	PEG-5 Oleamide	PPG-2 Cocamide
PEG-3 Cocamide DEA	PEG-6 Oleamide	PPG-1 Hydroxyethyl Caprylamide
PEG-20 Cocamide MEA	PEG-7 Oleamide	PPG-2 Hydroxyethyl Cocamide
PEG-6 Hydrogenated Palmamide	PEG-9 Oleamide	PPG-2 Hydroxyethyl Coco/Isostearamide
PEG-50 Hydrogenated Palmamide	PEG-4 Rapeseedamide	PPG-3 Hydroxyethyl Soyamide
PEG-13 Hydrogenated Tallow Amide	PEG-10 Stearamide	
PEG-5 Lanolinamide	PEG-4 Stearamide	

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally related as *N*-alkoxylated simple amides. Although a few of the ingredients in this report (e.g., PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides (and similar to the amines in the CIR PEGs Cocamine report; ingredients reviewed in that report were found safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating<sup>2</sup>), most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. These ingredients have classic surfactant structures, with a hydrophobic, fatty alkyl tail on one end and a hydrophilic, non-ionic alkoxylated head group on the other end.

The Panel has reviewed the safety of some of the components of these ingredients. In 2010, CIR issued a final report on the safety of polyethylene glycols (PEGs); the Panel concluded that the PEGs are safe in the present practices of use and concentration.<sup>3</sup> In 2012, CIR published a report on the safety of polypropylene glycols (PPGs), with a conclusion that PPGs are safe in the present practices of use and concentration when formulated to be non-irritating.<sup>4</sup> Additionally, the safety of polyalkoxylated ethanolamides has been reviewed by CIR. In 2013, diethanolamides, including Cocamide DEA and Tallowamide DEA, were found to be safe in the present practices of use and concentration when formulated to be non-irritating, and when the levels of free DEA in the diethanolamides do not exceed the present practices of use and concentration of DEA itself.<sup>5</sup> Finally, in 2015, the Panel issued a safety assessment on the (mono-) ethanolamides, including Cocamide MEA, with the conclusion that the ethanolamides are safe in the present practices of use and concentration when formulated to be non-irritating.<sup>6</sup> Both the ethanolamides and the diethanolamides should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

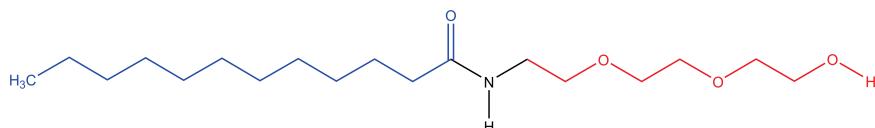
Much of the data included in this safety assessment was obtained from Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) hazard assessments.<sup>7-9</sup> These data summaries are available on the NICNAS website, and when deemed appropriate, information from the summaries has been included in this report.

## CHEMISTRY

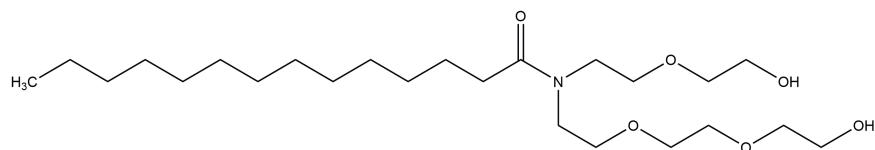
### Definition and Structure

The definitions and structures of the alkoxylated fatty amides included in this review are provided in [Table 1](#). Provided in [Table 2](#) are the total fatty acid compositions of relevant plant-derived fatty acid oils,<sup>10-12</sup> and of lanolin<sup>13</sup> and tallow.<sup>14</sup>

These ingredients are alkoxylated simple amides, and most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. However, a few of the ingredients (such as PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides. The mono-substituted ingredients reviewed in this report are classic non-ionic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic non-ionic alkoxylated head group on the other end (Figure 1). The di-substituted ingredients herein, however, comprise two alkoxylations at the head group (Figure 2).



**Figure 1.** Example of a fatty acid amide, and its mono-alkoxylated surfactant structure



**Figure 2.** Example of a fatty acid amide (lauramide), and its di-alkoxylated (PEG-3 DEA) surfactant structure (PEG-3 Cocamide DEA is a mixture of fatty acid amides, but the highest concentration constituent therein is the lauramide).

### Physical and Chemical Properties

PEG-6 Cocamide,<sup>15,16</sup> PEG-4 Rapeseedamide,<sup>17</sup> and PPG-2 Hydroxyethyl Cocamide<sup>7</sup> present as clear liquids that are generally yellow in color. Physical and chemical properties of these ingredients are listed in [Table 3](#).

### Method of Manufacture

#### PEG-50 Hydrogenated Palmamide

According to one supplier, PEG-50 Hydrogenated Palmamide is manufactured by ethoxylating a monoethanol amide with approximately 50 stoichiometric equivalents of ethylene oxide.<sup>18</sup> Vegetable and synthetic raw materials are used.

### Impurities

#### PEG-50 Hydrogenated Palmamide

Gas chromatography/mass spectrometry (GC/MS) was used to determine the potential levels of residual monoethylene glycol and diethylene glycol in PEG-50 Hydrogenated Palmamide.<sup>18</sup> Upon analysis, it was reported that PEG-50 Hydrogenated Palmamide contained less than 50 ppm of either substance.

#### PEG-4 Rapeseedamide

A supplier reports that PEG-4 Rapeseedamide is 92 - 93% “active matter;”<sup>17</sup> specifications for the presence of 1,4-dioxane are 1 ppm maximum.<sup>19</sup> According to another source, PEG-4 Rapeseedamide (as the raw material) is reported to be 60 - 80% pure.<sup>8</sup> Low levels of 1,4-dioxane, “down to 100 mg/kg or 100 mg/l,” may be present. Other possible impurities were not specified, but based on the structure, “it is not expected to contain hazardous nitrosamine impurities.”

## USE

### Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2018,<sup>20</sup> and data received in response to a Council survey of the maximum reported use concentration by category in 2015,<sup>21</sup> indicate that 11 of the 40 ingredients included in this safety assessment are used in cosmetic formulations.

According to 2018 VCRP survey data, PPG-2 Hydroxyethyl Cocamide is reported to be used in 342 formulations, and PEG-4 Rapeseedamide is reported to be used in 280 formulations ([Table 4](#)).<sup>20</sup> All other in-use ingredients are reported to be used in less than 30 formulations. The results of the concentration of use survey conducted by the Council in 2015 indicate PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors.<sup>21</sup> The ingredient with the next highest reported concentration of use is PPG-2 Hydroxyethyl Cocamide; it is used at 7.5% in “other” non-coloring hair preparations.

The alkoxylated fatty amides are primarily used in rinse-off formulations, with few uses reported in leave-on formulations. Most of the reported uses are in some type of hair or cleansing formulation. However, there are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 3% PPG-2 Hydroxyethyl Cocamide in body and hand products.<sup>21</sup>

Use concentration data were reported for PEG-6 Lauramide and PEG-50 Tallow Amide in response to the Council survey, but no uses were received in the VCRP; it should be presumed there is at least one use in every category for which a use concentration is reported. Additionally, uses were reported in the VCRP for PEG-3 Cocamide and PEG-5 Cocamide, but no concentrations of use were reported for these ingredients in the industry survey. The ingredients not in use, according to both the 2018 VCRP data and the industry survey, are listed in [Table 5](#).

The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%.<sup>21</sup> According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.<sup>22,23</sup> Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.<sup>24,25</sup>

The alkoxylated fatty amides are not restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>26</sup>

### Non-Cosmetic

PEG-4 Rapeseedamide is used in industrial dishwashing and laundry care.<sup>27</sup>

## TOXICOKINETICS

Toxicokinetics data (such as dermal penetration and absorption, distribution, metabolism, and excretion data) were not discovered in the published literature, and unpublished data were not submitted.

## TOXICOLOGICAL STUDIES

### Acute Toxicity Studies

The acute toxicity studies summarized below<sup>7-9,28</sup> are described in [Table 6](#).

The dermal LD<sub>50</sub>s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD<sub>50</sub>s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were > 2000 mg/kg. In both the dermal and the oral studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80% pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first study, but not the second study, and the LC<sub>50</sub>s were reported to be 1 - 5 mg/L/4 h and > 6 mg/L/4 h, respectively.

## Short-Term Toxicity Studies

### **Oral**

#### *PEG-4 Rapeseedamide*

Groups of 5 male and 5 female Sprague-Dawley rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg bw/day (PEG-4 Rapeseedamide 60 - 80% pure) in arachis oil for 28 days, in accord with Organisation for Economic Co-operation and Development test guideline (OECD TG) 407.<sup>8</sup> All animals survived until study termination. A statistically significant decrease in body weights was observed in females of the mid-dose group during wk 2; a non-statistically significant reduction in body weight gain and food consumption, when compared with controls, was reported for males of the high-dose group. No treatment related behavioral, functional performance, or sensory reactivity changes were observed. No toxicologically-significant changes in clinical chemistry, hematology, or urinalysis parameters were reported. A statistically significant, non-dose dependent, reduction in absolute thymus weights was observed in low- and high-dose males. Microscopic forestomach lesions (acanthosis and hyperkeratosis, occasionally with associated subepithelial inflammatory cell infiltrates) in high dose males were attributed to slight irritancy of the test material, and cortical hypertrophy of the adrenal glands observed in 3 females in the high dose group may reflect a non-specific stress response to the irritancy of the test material. The no-observable-adverse-effect-levels (NOAELs) were 15 and 150 mg/kg bw/day for male and female rats, respectively.

#### *PPG-2 Hydroxyethyl Cocamide*

Groups of 3 male and 3 female albino rats were dosed with 0, 100, 500, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide by gavage for 7 days, in accord with OECD TG 407.<sup>7</sup> The vehicle was not specified. All animals survived until study termination. Transient salivation noted with the highest doses was considered unremarkable. There were no effects on kidney, liver, or spleen weights. No gross lesions were observed at necropsy. Clinical chemistry, hematology, and microscopic studies were not conducted. No evidence of toxicity was observed.

In a 28-day study conducted in accord with OECD TG 407, groups of 5 male and 5 female albino rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide for 28 days.<sup>7</sup> The vehicle was not specified. No mortalities were reported. Transient post-dosing salivation was observed in some animals of all test groups. No treatment-related changes were reported for clinical chemistry or hematology parameters. Changes in urinary parameters included a decrease in urine volume and in urinary phosphorus and an increase in urinary pH in high-dose males, and a decrease in urinary potassium in high-dose males and high- and mid-dose females; these changes were not supported by pathological changes. Slight decreases in absolute and relative thymus weights were not considered to be toxicologically significant. Focal basophilic cortical tubules observed in three high dose male rats were not considered treatment-related. The no-observable-effect-level (NOEL) was 15 mg/kg/day, and the NOAEL was 1000 mg/kg/day.

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

#### *PEG-4 Rapeseedamide*

A reproductive/developmental toxicity screening test was performed in accord with OECD TG 421 using groups of 10 male and 10 female rats that were dosed with 0, 15, 15, or 500 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil by gavage for 55 days.<sup>8</sup> Animals were paired for mating on day 15 of dosing. Males were killed on day 43; females were allowed to litter, and were killed on 5 days post-partum. No mortalities were reported. No adverse effects on parental body weights, mating performance, fertility, or length of gestation were reported, and there were no effects on litter size, total litter weights, sex ratio, or viability of offspring. The NOAEL was 500 mg/kg bw/day.

## GENOTOXICITY STUDIES

The genotoxicity studies summarized below<sup>7-9</sup> are also described in [Table 7](#).

PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were not mutagenic in Ames tests at concentrations up to 5000 µg/plate, with or without metabolic activation. In mammalian chromosomal aberration studies, PEG-4 Rapeseedamide (60 - 80% pure) was not clastogenic at up to 5000 µg/ml, with or without metabolic activation, and PPG-2 Hydroxyethyl Cocamide was not clastogenic at concentrations up to 250 µg/ml without metabolic activation. PPG-2 Hydroxyethyl Cocamide was "not likely to be clastogenic" with metabolic activation; a statistically significant increase in the proportion of metaphase figures with chromosomal aberrations was reported at 450 and 500 µg/ml (concentrations that were cytotoxic).

In the mouse micronucleus test, PEG-4 Rapeseedamide (60 - 80% pure) dosed orally at ≤ 400 mg/kg bw in arachis oil<sup>8</sup> and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at ≤ 1000 mg/kg were not clastogenic.<sup>7</sup> Additionally, in Sprague-Dawley rats, dosing with up to 2000 mg/kg aq. PPG-2 Hydroxyethyl Cocamide by gavage did not induce DNA damage.

## **CARCINOGENICITY STUDIES**

Carcinogenicity studies were not discovered in the published literature, and unpublished data were not submitted.

## **DERMAL IRRITATION AND SENSITIZATION STUDIES**

The dermal irritation and sensitization studies summarized below<sup>7,8,29,30</sup> are also described in [Table 8](#).

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm<sup>2</sup> patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure; 2 cm<sup>2</sup> patches containing 0.2 ml test material) was not a sensitizer in a human repeated insult patch test (RIPT), and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm<sup>2</sup> patches containing 0.2 ml test material) was not an irritant. Both studies were performed using 50 subjects.

## **OCULAR IRRITATION STUDIES**

### *PEG-4 Rapeseedamide*

The ocular irritation potential of PEG-4 Rapeseedamide (60 - 80% pure) was evaluated in three New Zealand White rabbits in an acute eye irritation/corrosion test (OECD TG 405).<sup>8</sup> The undiluted test material was instilled into the conjunctival sac of one eye of each animal, and the eyes were observed for 7 days. (The volume instilled was not specified.) The test material was slightly irritating to rabbit eyes. The mean scores (calculated using the 24, 48, and 72 h scores for each animal) for the conjunctiva ranged from 1.3 - 1.7/2 for redness; 0 - 0.7/1 for chemosis; and 0.3 (all animals)/1 for discharge; irritation resolved within 7 days. Corneal opacity and iridal inflammation were not observed.

### *PPG-2 Hydroxyethyl Cocamide*

Three male New Zealand White rabbits were used to determine the ocular irritation potential of PPG-2 Hydroxyethyl Cocamide.<sup>7</sup> One-tenth (0.1) ml of the test article was instilled into the conjunctival sac of one eye of each rabbit, and the eyes were not rinsed. The contralateral eye served as an untreated control. PPG-2 Hydroxyethyl Cocamide was moderately irritating. Corneal opacification was observed in all animals at 24 h. Diffuse red coloration of the conjunctiva with eyelid swelling was reported for up to 7 days, and iridal inflammation was observed in one animal at day 14.

## **CLINICAL STUDIES**

### Case Reports

#### *PEG-4 Rapeseedamide*

A female patient developed dermatitis 1 month after exposure to massage oils while working as a masseuse, and presented with eczema on the flexor wrist and forearm of 4 mos duration.<sup>31</sup> Patch testing was conducted using a standard series and with oils from work. Two massage oils from the same manufacturer produced positive reactions. Subsequent testing with components of those oils resulted in positive reactions to 3.0% PEG-4 Rapeseedamide. Positive reactions were also reported in a dilution series with PEG-4 Rapeseedamide; “+++” reactions were observed with 0.003 - 3.0% in petrolatum and 0.03 - 3% aq., and a + reaction was observed with 0.003% aq. PEG-4 Rapeseedamide. Control subjects (n = 28) did not react to 0.3% PEG-4 Rapeseedamide in petrolatum.

## **SUMMARY**

This assessment reviews the safety of 40 alkoxylated fatty amides as used in cosmetics. These ingredients are alkoxylated simple amides, and most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. However, a few of the ingredients (such as PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides. The ingredients reviewed in this report are classic non-ionic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic, non-ionic, alkoxylated head group on the other end.

According to one supplier, PEG-50 Hydrogenated Palmamide is manufactured by ethoxylation a monoethanol amide with approximately 50 stoichiometric equivalents of ethylene oxide. Using GC/MS analysis, PEG-50 Hydrogenated Palmamide contains less than 50 ppm of residual monoethylene glycol or diethylene glycol. One supplier reports that PEG-4 Rapeseedamide is 92-92% active matter, and specifications for the presence of 1,4-dioxane are 1 ppm. According to another

source, PEG-4 Rapeseedamide is 60 – 80% pure and low levels of 1,4 dioxane (down to 100 mg/kg or 100 mg/l) may be present.

Eleven of the 40 ingredients included in this assessment are reported to be in use. PPG-2 Hydroxyethyl Cocamide has the greatest reported frequency of use (342 formulations), and PEG-4 Rapeseedamide has the second greatest reported number of uses (280). The alkoxylated fatty amides are primarily used in rinse-off formulations, and most of the reported uses are in some type of hair or cleansing formulation. PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors. PPG-2 Hydroxyethyl Cocamide has the next highest reported concentration of use is; it is used at 7.5% in “other” non-coloring hair preparations. There are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 3% PPG-2 Hydroxyethyl Cocamide in body and hand products. The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%. According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled.

The dermal LD<sub>50</sub>s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD<sub>50</sub>s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were > 2000 mg/kg. In both the dermal and the orals studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80% pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first, but not the second, study and the LC<sub>50</sub>s were reported to be 1 - 5 mg/L/4 h and > 6 mg/L/4 h, respectively.

In a 7-day oral study using groups of 6 albino rats, there was no evidence of toxicity with oral administration of ≤ 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide. In 28-day oral studies using groups of 10 Sprague-Dawley rats, NOAELs of 15 and 150 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil were reported for male and female rats, respectively, and for PPG-2 Hydroxyethyl Cocamide, the NOEL was 15 mg/kg/day and the NOAEL was 1000 mg/kg/day. The maximum dose administered in both studies was 1000 mg/kg bw/day. With PEG-4 Rapeseedamide, a statistically significant, non-dose dependent, reduction in absolute thymus weights was observed in low and high-dose males; microscopic forestomach lesions in high dose males were attributed to slight irritancy of the test material; and cortical hypertrophy of the adrenal glands, observed in 3 females in the high dose group, may reflect a non-specific stress response to the irritancy of the test material. With PPG-2 Hydroxyethyl Cocamide, slight decreases in absolute and relative thymus weights were not considered to be toxicologically significant, and focal basophilic cortical tubules observed in three high dose male rats were not considered treatment-related.

A reproductive/developmental toxicity screening test was performed with 20 rats that were dosed with up to 500 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil by gavage for 55 days. No adverse reproductive effects and no parental toxicity were reported. The NOAEL was 500 mg/kg bw/day.

PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were not mutagenic in Ames tests at concentrations up to 5000 µg/plate, with or without metabolic activation. In mammalian chromosomal aberration studies, PEG-4 Rapeseedamide (60 - 80% pure) was not clastogenic at up to 5000 µg/ml, with or without metabolic activation, and PPG-2 Hydroxyethyl Cocamide was not clastogenic at concentrations up to 250 µg/ml without metabolic activation. PPG-2 Hydroxyethyl Cocamide was “not likely to be clastogenic” with metabolic activation; a statistically significant increase in the proportion of metaphase figures with chromosomal aberrations was reported at 450 and 500 µg/ml (concentrations that were cytotoxic). In the mouse micronucleus test, PEG-4 Rapeseedamide (60 - 80% pure) dosed orally at ≤ 400 mg/kg bw in arachis oil and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at ≤ 1000 mg/kg were not clastogenic. Additionally, in Sprague-Dawley rats, dosing with up to 2000 mg/kg aq. PPG-2 Hydroxyethyl Cocamide by gavage did not induce DNA damage.

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm<sup>2</sup> patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure; 2 cm<sup>2</sup> patches containing 0.2 ml test material) was not a sensitizer in an HRIPT, and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm<sup>2</sup> patches containing 0.2 ml test material) was not an irritant. Both studies were performed using 50 subjects.

Ocular irritation studies were performed using New Zealand White rabbits. Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was slightly irritating to rabbit eyes, and undiluted PPG-2 Hydroxyethyl Cocamide was moderately irritating.

### **DRAFT DISCUSSION**

*This discussion below is in draft form and may be modified.*

This report reviews the safety of 40 cosmetic ingredients that are structurally related as alkoxylated simple amides. The Panel determined that the data were insufficient to determine safety for this group of ingredients and issued an insufficient data announcement (IDA) with the following data requests:

- Method of manufacture
- Impurities data
- Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide; if absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed.

Dermal absorption data were specifically requested on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide because these two ingredients have the highest reported frequency of use. The Panel was comfortable that information on these two ingredients could be read-across to the entire group. Additionally, the Panel determined that the di-*N,N*-alkoxyl-substituted amides are appropriate for inclusion in this report, and it was the opinion of the Panel that the information on the mono-*N*-alkoxyl-substituted ingredients informs the safety of the di-*N,N*-alkoxyl-substituted ingredients.

The Panel noted that CIR has issued reports on the component parts of these polyalkoxylated ethanolamides. Specifically, the polyalkoxyl moieties PEGs and PPGs have been found safe and safe when formulated to be non-irritating in the present practices of use and concentration, respectively. Polyalkoxylated ethanolamides (e.g. Cocamide DEA and Cocamide MEA) are safe in the present practices of use and concentration when formulated to be non-irritating, and these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. For the diethanolamides, the levels of free DEA are not to exceed the present practices of use and concentration of DEA itself.

The Panel remarked on the lack of carcinogenicity data. However, any concerns were mitigated because there were sufficient negative genotoxicity studies and there are no structural alerts for carcinogenicity.

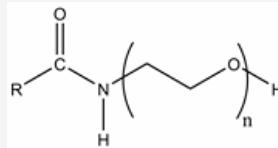
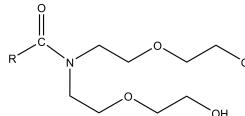
Also, the Panel discussed the issues of impurities that could be of concern with this group of ingredients. The possible presence of 1,4-dioxane as an impurity is one concern. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit this impurity in alkoxylated fatty amide ingredients before blending them into cosmetic formulations. Additionally, manufacturers should minimize primary amine impurities, and the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. The Panel acknowledged that some of the alkoxylated fatty amides may be formed from plant-derived or animal-derived constituents. The Panel thus expressed concern regarding pesticide residues and heavy metal that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in these ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the dangers risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the US FDA that tallow derivatives are not risk materials for transmission of infectious agents.

PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled. Therefore, the Panel discussed the issue of potential inhalation toxicity. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

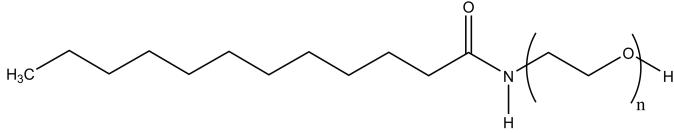
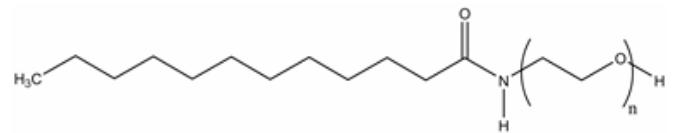
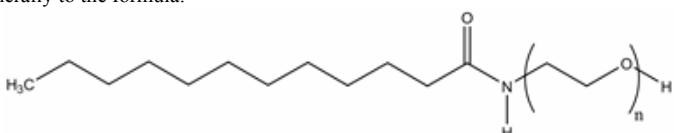
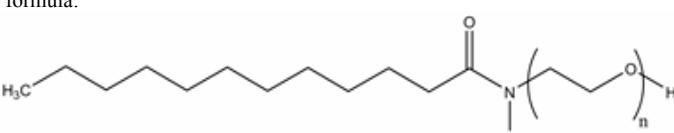
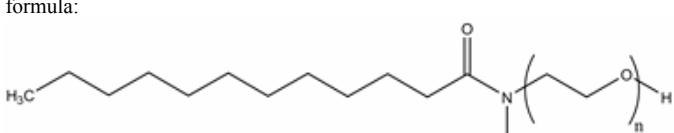
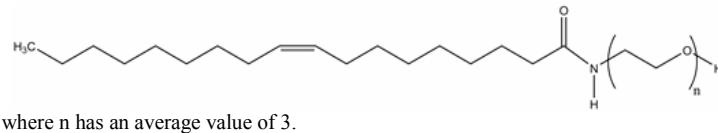
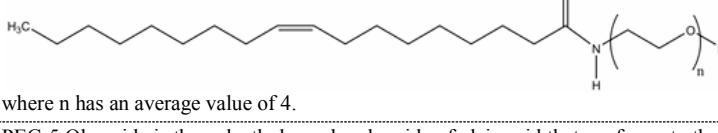
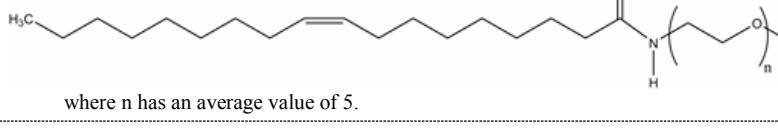
### **CONCLUSION**

To be determined.

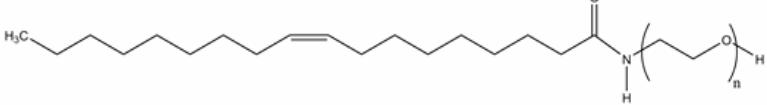
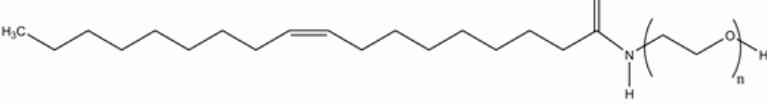
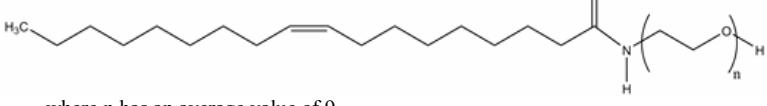
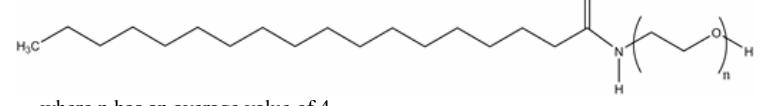
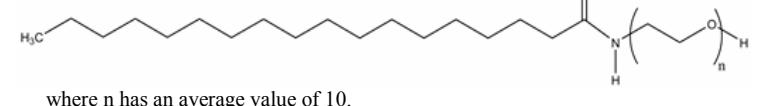
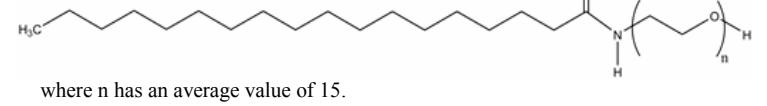
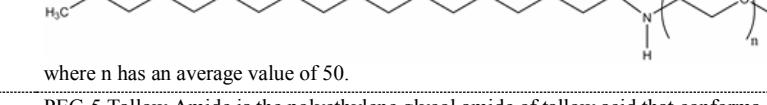
**TABLES****Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.**<sup>1, CIR Staff</sup>

Ingredient CAS No.	Definition & Structure*	Function(s)
<b>Ethoxylated</b>	<b>General formula:</b>	
		
PEG-2 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-2 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.	surfactant - emulsifying agent; surfactant - foam booster
PEG-3 Cocamide 61791-08-0 (generic)	PEG-3 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-4 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-4 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Cocamide 61791-08-0 (generic)	PEG-5 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Cocamide 61791-08-0 (generic)	PEG-6 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 6.	surfactant - emulsifying agent
PEG-7 Cocamide 61791-08-0 (generic)	PEG-7 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 7.	surfactant - emulsifying agent
PEG-11 Cocamide 61791-08-0 (generic)	PEG-11 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 11.	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-20 Cocamide 61791-08-0 (generic)	PEG-20 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 20.	surfactant - emulsifying agent
PEG-3 Cocamide DEA	PEG-3 Cocamide DEA is the polyethylene glycol derivative of Cocamide DEA with an average of 3 moles of ethylene oxide. [Cocamide DEA is a mixture of ethanolamides of coconut acid. It conforms generally to the formula: 	surfactant - emulsifying agent
PEG-20 Cocamide MEA	where RCO- represents the fatty acids derived from <i>Cocos nucifera</i> (coconut) oil.] PEG-20 Cocamide MEA is the polyethylene glycol derivative of cocamide MEA containing an average of 20 moles of ethylene oxide. [Cocamide MEA is a mixture of ethanolamides of coconut acid. It conforms generally to the above general formula, and RCO- represents the fatty acids derived from <i>Cocos nucifera</i> (coconut) oil.]	surfactant - emulsifying agent
PEG-6 Hydrogenated Palmamide	PEG-6 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated palm oil and n has an average value of 6.	emulsion stabilizer; surfactant - emulsifying agent
PEG-50 Hydrogenated Palmamide	PEG-50 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that conforms generally to the above formula, and RCO- represents the fatty acids from hydrogenated palm oil and n has an average value of 50.	cleansing agent; surfactant - solubilizing agent
PEG-13 Hydrogenated Tallow Amide 68783-22-2 (generic)	PEG-13 Hydrogenated Tallow Amide is the polyethylene glycol amide of hydrogenated tallow amide that conforms generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated tallow and n has an average value of 13.	surfactant - emulsifying agent
PEG-5 Lanolinamide	PEG-5 Lanolinamide is the polyethylene glycol amide of lanolin acid with an average of 5 [stoichiometric equivalents] of ethylene oxide. [PEG-5 Lanolinamide conforms generally to the above formula, and RCO- represents the fatty acids derived from Lanolin Acid (a mixture of organic acids obtained from the hydrolysis of Lanolin) and n has an average value of 5]	hair conditioning agent; viscosity increasing agent - nonaqueous

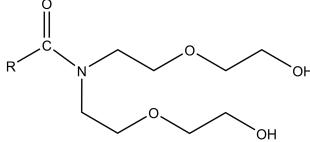
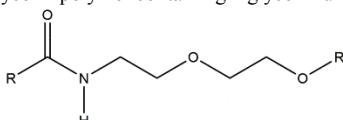
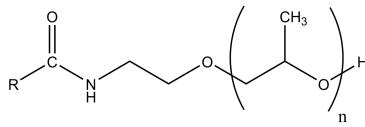
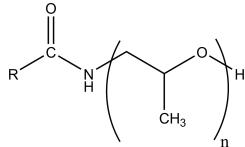
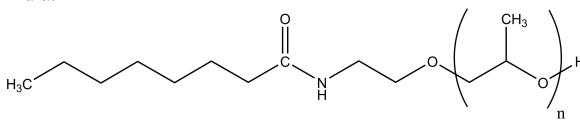
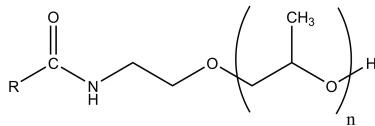
**Table 1.** Definitions, structures, and functions of the ingredients in this safety assessment.<sup>1, CIR Staff</sup>

Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-2 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-2 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:   where n has an average value of 2.	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-3 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-3 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:   where n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-5 Lauramide 26635-75-6 (generic)	PEG-5 Lauramide is the polyethylene glycol amide of lauric acid that conforms generally to the formula:   where n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Lauramide 26635-75-6 (generic)	PEG-6 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:   where n has an average value of 6.	surfactant - emulsifying agent
PEG-11 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-11 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:   where n has an average value of 11.	surfactant - emulsifying agent
PEG-3 Oleamide	PEG-3 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:   where n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-4 Oleamide	PEG-4 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:   where n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Oleamide	PEG-5 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:   where n has an average value of 5.	surfactant - emulsifying agent

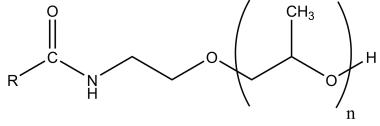
**Table 1.** Definitions, structures, and functions of the ingredients in this safety assessment.<sup>1, CIR Staff</sup>

Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-6 Oleamide	PEG-6 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:   where n has an average value of 6	surfactant - emulsifying agent
PEG-7 Oleamide	PEG-7 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:   where n has an average value of 7.	surfactant - emulsifying agent
PEG-9 Oleamide	PEG-9 Oleamide is the polyethylene glycol amide of oleic acid that conforms generally to the formula:   where n has an average value of 9.	surfactant - emulsifying agent
PEG-4 Rapeseedamide 85536-23-8	PEG-4 Rapeseedamide is the polyethylene glycol amide of the fatty acids derived from rapeseed oil with an average of 4 moles of ethylene oxide. [Rapeseed Acid is a mixture of fatty acids derived from <i>Brassica campestris</i> (rapeseed) seed oil. PEG-4 Rapeseedamide conforms generally to the above general formula, and RCO- represents the fatty acids from rapeseed oil and n has an average value of 4.]	surfactant - emulsifying agent; viscosity increasing agent - aqueous
PEG-4 Stearamide	PEG-4 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:   where n has an average value of 4.	surfactant - emulsifying agent
PEG-10 Stearamide	PEG-10 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:   where n has an average value of 10.	surfactant - emulsifying agent
PEG-15 Stearamide	PEG-15 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:   where n has an average value of 15.	surfactant - emulsifying agent
PEG-50 Stearamide	PEG-50 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:   where n has an average value of 50.	skin-conditioning agent - miscellaneous
PEG-5 Tallow Amide 8051-61-4	PEG-5 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 5.	antistatic agent; surfactant - emulsifying agent
PEG-8 Tallow Amide	PEG-8 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 8.	surfactant - emulsifying agent

**Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.**<sup>1, CIR Staff</sup>

Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-50 Tallow Amide 8051-63-6	PEG-50 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 50.	surfactant - cleansing agent; surfactant - solubilizing agent
PEG-2 Tallowamide DEA	PEG-2 Tallowamide DEA is the polyethylene glycol amine derived from tallow acid that conforms generally to the formula:   where RCO- represents tallowoyl moiety.	surfactant - cleansing agent
<b>Ethoxylated Polyglyceryl</b>		
Polyglyceryl-4-PEG-2 Cocamide	Polyglyceryl-4-PEG-2 Cocamide is an ether of PEG-2 cocamide and polyglycerin-4. [Polyglycerin-4 is a glycerin polymer containing 4 glycerin units.]   [wherein RCO- represents the fatty acids derived from coconut oil and R' represents polyglyceryl-4.]	surfactant - emulsifying agent
<b>Propoxylated</b>		
PPG-2 Hydroxyethyl Cocamide 201363-52-2	PPG-2 Hydroxyethyl Cocamide is the organic compound that conforms generally to the formula:   where RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous
PPG-2 Cocamide	PPG-2 Cocamide is the dipropylene glycol amide of coconut acid that conforms generally to the formula:   where n has an average value of 2 and RCO- represents the cocoyl moiety.	surfactant - foam booster; viscosity increasing agent - aqueous
PPG-1 Hydroxyethyl Caprylamide	PPG-1 Hydroxyethyl Caprylamide is the organic compound that conforms generally to the formula:   where n has an average value of 1.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous
PPG-2 Hydroxyethyl Coco/Isostearamide	PPG-2 Hydroxyethyl Coco/Isostearamide is the organic compound that conforms generally to the formula:   where RCO- represents a mixture of isostearic acid and coconut acid and n has an average value of 2.	surfactant - cleansing agent; surfactant - foam booster; surfactant - solubilizing agent; viscosity increasing agent - aqueous

**Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.**<sup>1, CIR Staff</sup>

Ingredient CAS No.	Definition & Structure*	Function(s)
PPG-3 Hydroxyethyl Soyamide	PPG-3 Hydroxyethyl Soyamide is the organic compound that conforms to the formula:   where RCO- represents the fatty acids derived from soybean oil and n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous

\*see Table 2 for available fatty acid composition

**Table 2. Fatty acid composition (%) of plant-derived fatty acid oils and of lanolin and tallow**

Fatty Acids	Brassica Campestris (Rapeseed) Seed Oil <sup>10</sup>	Rapeseed Acid <sup>10</sup>	Cocos Nucifera (Coconut) Oil <sup>11</sup>	Elaeis Guineensis (Palm) Oil <sup>12</sup>	Glycine Soja (Soybean) Oil <sup>10</sup>	Lanolin <sup>13</sup>	Tallow <sup>14</sup>
Caproic (C6)			0-1				
Caprylic (C8)			5-9				
Capric (C10)			6-10				
Lauric (C12)			44-52	0.2			
Myristic (C14)		≤ 0.5	13-19	1.1		3-6	
Palmitic (C16)	1.5 - 3	≤ 8	8-11	44		24-32	
Palmitoleic (C16:1)		≤ 2	0-1	0.1			
Stearic (C18)	0.7 - 1.3	≤ 3	1-3	4.5		20-25	
Oleic (C18:1)	12.1 - 57.4	54-70	5-8	39.2	11.5 - 60.0	37-43	
Linoleic (C18:2)	11.4 - 22.1	18-24	Trace-2.5	10.1		2-3	
Linolenic (C18:3)	8.3 - 12.5	5-10		0.4	2.9 - 12.1		
Arachidic (C20)		≤ 6		0.4			
Eicosenoic (C20:1)	5.6 - 3.1						
Erucic (C22:1)	1 - 58.6						
Others		< C14 = ≤ 0.5; > C18:3 = ≤ 5; > C20 = ≤ 6				7 to 41 carbons; main fatty acids are palmitic acid (C16), stearic acid (C18), and longer molecules (C20 to C 32)	

**Table 3. Physical and Chemical Properties**

Property	Value	Reference
<b>PEG-6 Cocamide</b>		
Physical Form (@ 25°C)	liquid	15
Color (@ 30°C)	clear	16
Density (g/ml @ 25 °C)	0.99	15,16
Viscosity (kg/(s x m) @ 25°C; @ 60°C)	0.217; 0.039	16
Vapor pressure (mmHg @ 20 °C)	0.01	15
Boiling Point (°C)	100	15
Hydrophilic-Lipophilic Balance (HLB)	14.6	15,16
<b>PEG-4 Rapeseedamide (60-80% purity)</b>		
Physical Form	clear liquid	17
Color	yellow	17
Molecular Weight (g/mol)	< 600	8
Density/Specific Gravity (kg/m <sup>3</sup> ; @ 20°C)	997	8
Vapor pressure (mm Hg)	0.0019	8
Melting Point (°C)	5-10	8
Boiling Point (°C)	> 262	8
Water Solubility (g/L @ 23 °C)	9.0 x 10 <sup>-4</sup>	8
Other Solubility (g/L @ 20°C)	652 – 702 in n-octanol	8
log K <sub>ow</sub>	2.6	8
HLB	~11	17
<b>PPG-2 Hydroxyethyl Cocamide</b>		
Physical Form	liquid	7
Color	yellowish	7
Specific Gravity (@ 20 °C)	0.98	7
Vapor pressure (mmHg 25 °C)	5.25 x 10 <sup>-5</sup>	7
Boiling Point (°C)	> 165 (decomposition occurs over the range 60-305)	7
Water Solubility (g/L @ 20 °C)	< 0.001	7
log K <sub>ow</sub>	0.86 to > 6.2 *	7

\* substance is a mixture containing different coconut acid amides of varying chain lengths, and a distribution of number of propyloxy groups in the PPG-2 polymer

**Table 4. Frequency and concentration of use according to duration and type of exposure**

	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>
	PEG-2 Cocamide	PEG-3 Cocamide		PEG-5 Cocamide		PEG-6 Cocamide
<b>Totals*</b>	<b>2</b>	<b>0.12-2</b>	<b>2</b>	<b>NR</b>	<b>21</b>	<b>NR</b>
<i>Duration of Use</i>						
Leave-On	NR	NR	1	NR	NR	NR
Rinse-Off	2	0.12-2	1	NR	24	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
<i>Exposure Type</i>						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1 <sup>a</sup>	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	2	0.3-2	1	NR	19	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.13	NR	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.3-2	NR	NR	19	NR
Baby Products	NR	NR	NR	NR	NR	NR
	<b>PEG-6 Cocamide</b>		<b>PEG-50 Hydrogenated Palmamide</b>		<b>PEG-6 Lauramide</b>	
<b>Totals*</b>	<b>19</b>	<b>0.75-2</b>	<b>26</b>	<b>1-3</b>	<b>NR</b>	<b>4</b>
<i>Duration of Use</i>						
Leave-On	3	NR	NR	1	NR	NR
Rinse Off	16	0.75-2	26	2-3	NR	4
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
<i>Exposure Type</i>						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1 <sup>a</sup> ; 1 <sup>b</sup>	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1 <sup>b</sup>	NR	NR	NR	NR	NR
Dermal Contact	11	2	NR	NR	NR	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	4	0.75-0.8	NR	1	NR	NR
Hair-Coloring	4	NR	26	2-3	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	NR	4
Baby Products	NR	NR	NR	NR	NR	NR

**Table 4. Frequency and concentration of use according to duration and type of exposure**

	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>	# of Uses <sup>20</sup>	Max Conc of Use (%) <sup>21</sup>
	PEG-4 Rapeseedamide		PEG-50 Tallow Amide		PPG-2 Cocamide	
<b>Totals*</b>	<b>280</b>	<b>0.93-9.3</b>	<b>NR</b>	<b>2</b>	<b>3</b>	<b>0.8-4</b>
<b>Duration of Use</b>						
Leave-On	3	NR	NR	NR	NR	0.8
Rinse-Off	274	0.93-9.3	NR	2	3	2-4
Diluted for (Bath) Use	3	2	NR	NR	NR	NR
<b>Exposure Type</b>						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1	NR	NR	NR	NR	0.8
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	52	0.93-3	NR	NR	1	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	51	2.4-2.8	NR	NR	2	0.8-2
Hair-Coloring	174	8.2-9.3	NR	2	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	54	1-3	NR	NR	NR	4
Baby Products	NR	NR	NR	NR	NR	NR
	<b>PPG-2 Hydroxyethyl Cocamide</b>		<b>PPG-2 Hydroxyethyl Coco/Isostearamide</b>			
<b>Totals</b>	<b>342</b>	<b>0.00025-7.5</b>	<b>23</b>	<b>0.5-0.6</b>		
<b>Duration of Use</b>						
Leave-On	10	0.35-7.5	NR	NR		
Rinse Off	326	0.00025-4	23	0.5-0.6		
Diluted for (Bath) Use	6	1.5-3	NR	NR		
<b>Exposure Type</b>						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	1 <sup>a</sup>	0.62 <sup>a</sup>	NR	NR		
Incidental Inhalation-Powder	NR	0.35 <sup>c</sup>	NR	NR		
Dermal Contact	309	0.008-4	12	0.5-0.6		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	33	0.00025-7.5	11	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	286	1.5-3	6	0.5-0.6		
Baby Products	2	NR	NR	NR		

\*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

<sup>a</sup> It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

<sup>b</sup> Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

<sup>c</sup> It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – no reported use

**Table 5. Ingredients not reported to be in use (according to VCRP and Council survey data)<sup>20,21</sup>**

PEG-4 Cocamide	PEG-3 Lauramide*	PEG-10 Stearamide
PEG-7 Cocamide	PEG-5 Lauramide	PEG-15 Stearamide
PEG-11 Cocamide	PEG-11 Lauramide	PEG-50 Stearamide
PEG-20 Cocamide	PEG-3 Oleamide	PEG-5 Tallow Amide
PEG-3 Cocamide DEA	PEG-4 Oleamide	PEG-8 Tallow Amide
PEG-20 Cocamide MEA*	PEG-5 Oleamide	PEG-2 Tallowamide DEA
PEG-6 Hydrogenated Palmamide	PEG-6 Oleamide	Polyglyceryl-4-PEG-2 Cocamide
PEG-13 Hydrogenated Tallow Amide	PEG-7 Oleamide	PPG-1 Hydroxyethyl Caprylamide
PEG-5 Lanolinamide	PEG-9 Oleamide	PPG-3 Hydroxyethyl Soyamide
PEG-2 Lauramide	PEG-4 Stearamide	

\*Council survey data have not yet been received for these ingredients

**Table 6. Acute toxicity studies**

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose	Protocol	LD <sub>50</sub> or LC <sub>50</sub> /Results	Reference
<b>DERMAL</b>							
PEG-4 Rapeseedamide (60 - 80% pure)	Sprague-Dawley rats	5/sex	none specified	2000 mg/kg	semi-occlusive application (OECD TG 402)	> 2000 mg/kg no dermal irritation and no signs of toxicity were observed	<sup>8</sup>
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	5/sex	none	2000 mg/kg	24-h patch; porous gauze covered with a waterproof dressing (OECD TG 402)	> 2000 mg/kg slight to well-defined erythema (7 animals) and edema (6 animals) was resolved by day 9 and 8, respectively; desquamation with scabbing was observed in 2 females	<sup>28</sup>
<b>ORAL</b>							
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	5/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg no signs of toxicity were observed	<sup>8</sup>
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	3/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg	<sup>7</sup>
PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across)	Sprague-Dawley rats	3/sex	1% (w/v) aq. methylcellulose	2000 mg/kg	by gavage (OECD TG 423)	> 2000 mg/kg	<sup>9</sup>
<b>INHALATION</b>							
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	2 males	none specified	24.34 mg/l (nominal); 4.92 mg/l (actual)	oronasal exposure (OECD TG 403) 0.5, 1, 2, or 4 h exposure period 2.14 µm particle size	1-5 mg/L/4 h labored and noisy breathing was observed 1 animal exposed for 2 h and 1 exposed for 4 h died 1 day after exposure; discolored non-collapsed lungs, mottled liver, dilatation of the kidneys and intestine were observed at necropsy	<sup>8</sup>
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	3/sex	none specified	119 mg/l (nominal); 6 mg/l (actual)	oronasal exposure (OECD TG 436) 4 h exposure period; 2.05-2.14 µm particle size	> 6 mg/L/4 h labored breathing was observed in all males and in one female (day 2); no mortality	<sup>8</sup>

Abbreviations: OECD – Organisation for Economic Co-operation and Development; TG – test guideline

**Table 7. Genotoxicity studies**

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
<b>IN VITRO</b>						
PEG-4	312.5 - 5000 µg/plate,	DMSO	<i>Salmonella typhimurium</i> TA1538, TA1535, TA1537, TA98, TA100	Ames test (OECD TG 471)	not mutagenic	8
Rapeseedamide (60 - 80% pure)	µg/plate, with and without metabolic activation					
PEG-4	39 - 5000 µg/ml, with and without metabolic activation	DMSO	human cultured peripheral lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	not clastogenic	8
Rapeseedamide (60 - 80% pure)						
PPG-2 Hydroxyethyl Cocamide	1.5 - 5000 µg/plate, with and without metabolic activation	not stated	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> CM891	Ames test (OECD TG 471)	not mutagenic	7
PPG-2 Hydroxyethyl Cocamide	<u>with activation:</u> 125 - 300 µg/ml initial study; 3 h); 300 -500 µg/ml (confirmation; 3 h); 450 and 500 µg/ml (confirmation 2; 3 h) <u>without metabolic activation:</u> 62.5 - 250 µg/ml (initial study; 3 h); 62.5 - 125 µg/ml (confirmation; 21 h)	water	human lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	“not likely to be clastogenic” with metabolic activation, statistically significant increase in proportion of metaphase figures with chromosomal aberrations at 450 and 500 µg/ml in both confirmation studies; these were cytotoxic concentrations all other results were negative	7
PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across)	5 - 5000 µg/plate, with and without metabolic activation	DMSO	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> WP2uvrA	Ames test (OECD TG 471)	not mutagenic	9
<b>IN VIVO</b>						
PEG-4	0, 100, 200, and 400 mg/kg bw (24 h)	arachis oil	albino Crl:CD-1 mice; 7/sex test animals; 14/sex negative controls; 5/sex positive controls	micronucleus test (OECD TG 474) animals were dosed by gavage cyclophosphamide served as the positive control	not clastogenic no statistically significant decreases in PCE/NCE ratios; however, marked decreases in the PCE/NCE ratio was observed in the 200 (24h) and 400 (48 h) mg/kg bw groups clinical signs were reported in the 200 and 400 mg/kg bw dose groups	8
Rapeseedamide (60-80% pure)	0 and 400 mg/kg bw (48 h)					
PPG-2 Hydroxyethyl Cocamide	0, 250, 500, and 1000 mg/kg	water	CD-1 outbred albino mice; 10 males in the control and high dose groups; 5 males in the low and mid dose groups	micronucleus test (OECD TG 474) animals were dosed intraperitoneally positive control not identified	not clastogenic	7
PPG-2 Hydroxyethyl Cocamide	0, 600, and 2000 mg/kg	water	Sprague-Dawley rats; 5 males per group	rat liver DNA repair (UDS) test (OECD TG 486) animals were dosed by gavage	did not induce DNA damage	7

Abbreviations: DMSO – dimethyl sulfoxide; NCE – normochromatic erythrocytes; OECD – Organisation for Economic Co-operation and Development; PCE – polychromatic erythrocytes; TG – test guideline; UDS – unscheduled DNA synthesis

**Table 8.** Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
<b>ANIMAL</b>					
PEG-4 Rapeseedamide (60 - 80% pure)	applied neat	3 female NZW rabbits	semi-occlusive application; animals were observed for 22 days (OECD TG 404) duration of dosing was not stated; however, according to the TG, dosing is typically 4 h in duration	irritating; no corrosive effect; no systemic toxicity mean scores (calculated using the 24, 48, and 72 h scores for each animal) ranged from 2-4/4 for erythema and 2-2.7/3 for edema irritation did not resolve by study termination	<sup>8</sup>
PEG-4 Rapeseedamide (60 - 80% pure)	intradermal induction – 0.2% topical induction – 10% topical challenge – 0.01% vehicle – sesame oil	10 (test) or 5 (control) male Dunkin Hartley guinea pigs	skin sensitization – maximization test (OECD TG 406)	not sensitizing	<sup>8</sup>
<b>HUMAN</b>					
PPG-2 Hydroxyethyl Cocamide	applied neat	3 male NZW rabbits	4 h semi-occlusive patch; 0.5 ml applied to a 2.5 cm <sup>2</sup> area using a porous gauze pad covered with elastic adhesive dressing (OECD TG 404) 1 animal also received 3 min and 1 h applications	<u>4 h exposure:</u> irritating to rabbit skin thickening of the skin, desquamation, and well-defined erythema in all 3 animals; did not resolve in 2/3 animals by day 14, with very slight erythema observed <u>3 min and 1 h exposure:</u> no irritation	<sup>29</sup>
PPG-2 Hydroxyethyl Cocamide	intradermal induction – 0.5% topical induction – 50% topical challenge – 5 and 10% vehicle – water	10 (test) or 5 (control) female Dunkin Hartley guinea pigs	Magnusson-Kligman maximization test (OECD TG 406) intradermal induction (day 0) consisted of 3 pairs of 0.1 ml injections: FCA/water 1:1; test substance only; test substance in FCA/saline 1:1 topical induction (day 7), 48 h occlusive patch (0.4 ml) challenge (day 21), 24 h occlusive patches (0.2 ml)	not sensitizing no irritation following topical applications; slight irritation at injection site after injection of test substance or sterile water (control animals)	<sup>30</sup>
PEG-4 Rapeseedamide (60 - 80% pure)	0.5% aq.	50 subjects	HRIFT <u>induction:</u> 2 cm <sup>2</sup> patches containing 0.2 ml test material were applied for 24 h (3x/wk for 3 wks), and the test sites were assessed 24 or 48 h after removal <u>challenge:</u> after a 2 wk non-treatment period, 1 test patch was applied for 24 h to a previously untreated site; the site was assessed 24, 48, and 72 h after application	not an irritant or sensitizer one instance of barely perceptible or spotty erythema for 3 subjects	<sup>8</sup>
PPG-2 Hydroxyethyl Cocamide	5% aq.	50 subjects	48 h occlusive patch; 0.2 ml applied via a 4.5 cm <sup>2</sup> gauze pad; test sites were evaluated at patch removal and after 24 h procedure was repeated using occlusive and semi-occlusive patches in subjects with positive responses	not irritating one subject had a mild and one a moderate response 24 h after patch removal; both subjects had mild responses 48 h after patch removal with follow-up testing, one subject had a positive response with the occlusive patch, but a negative response with the semi-occlusive patch	<sup>7</sup>

Abbreviations: aq. – aqueous; NZW – New Zealand White; HRIFT – human repeated insult patch test; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

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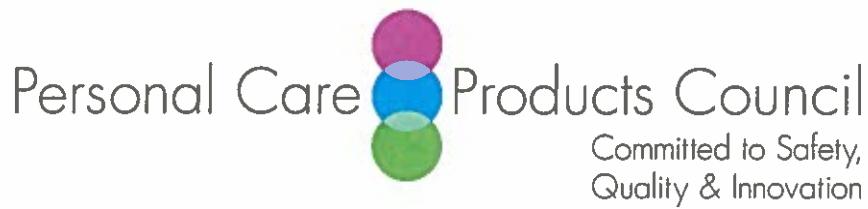
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**2018 VCRP DATA – ALKOXYLATED FATTY AMIDES**

PEG-2 COCAMIDE	10A - Bath Soaps and Detergents	2
PEG-3 COCAMIDE	12A - Cleansing	1
PEG-3 COCAMIDE	12G - Night	1
PEG-4 Cocamide – 0		
PEG-5 COCAMIDE	05F - Shampoos (non-coloring)	2
PEG-5 COCAMIDE	10A - Bath Soaps and Detergents	2
PEG-5 COCAMIDE	10E - Other Personal Cleanliness Products	17
PEG-6 COCAMIDE		
PEG-6 COCAMIDE	05F - Shampoos (non-coloring)	3
PEG-6 COCAMIDE	05I - Other Hair Preparations	1
PEG-6 COCAMIDE	06D - Hair Shampoos (coloring)	4
PEG-6 COCAMIDE	10A - Bath Soaps and Detergents	8
PEG-6 COCAMIDE	12A - Cleansing	1
PEG-6 COCAMIDE	12D - Body and Hand (exc shave)	1
PEG-6 COCAMIDE	12G - Night	1
PEG-7 Cocamide – 0		
PEG-11 Cocamide – 0		
PEG-20 Cocamide – 0		
PEG-3 Cocamide DEA – 0		
PEG-20 Cocamide MEA – 0		
PEG-6 Hydrogenated Palmamide – 0		
PEG-50 HYDROGENATED PALMAMIDE	06A - Hair Dyes and Colors	20
PEG-50 HYDROGENATED PALMAMIDE	06H - Other Hair Coloring Preparation	6
PEG-13 Hydrogenated Tallow Amide (68783-22-2 [generic]) - 0		
PEG-5 Lanolinamide - 0		
PEG-2 Lauramide - 0		
PEG-3 Lauramide (26635-75-6 [generic]) - 0		
PEG-5 Lauramide (26635-75-6 [generic]) - 0		
PEG-6 Lauramide (26635-75-6 [generic]) - 0		
PEG-11 Lauramide - 0		
PEG-3 Oleamide - 0		
PEG-4 Oleamide - 0		
PEG-5 Oleamide - 0		
PEG-6 Oleamide - 0		
PEG-7 Oleamide - 0		
PEG-9 Oleamide – 0		
PEG-5 Oleamide Dioleate - 0		

PEG-4 RAPSEEDAMIDE	02B - Bubble Baths	3
PEG-4 RAPSEEDAMIDE	05A - Hair Conditioner	3
PEG-4 RAPSEEDAMIDE	05E - Rinses (non-coloring)	1
PEG-4 RAPSEEDAMIDE	05F - Shampoos (non-coloring)	45
PEG-4 RAPSEEDAMIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
PEG-4 RAPSEEDAMIDE	05I - Other Hair Preparations	1
PEG-4 RAPSEEDAMIDE	06A - Hair Dyes and Colors	172
PEG-4 RAPSEEDAMIDE	06H - Other Hair Coloring Preparation	2
PEG-4 RAPSEEDAMIDE	10A - Bath Soaps and Detergents	34
PEG-4 RAPSEEDAMIDE	10C - Douches	3
PEG-4 RAPSEEDAMIDE	10E - Other Personal Cleanliness Products	14
PEG-4 RAPSEEDAMIDE	12J - Other Skin Care Preps	1
PEG-4 Stearamide - 0		
PEG-10 Stearamide - 0		
PEG-15 Stearamide - 0		
PEG-50 Stearamide - 0		
PEG-5 Tallow Amide (8051-61-4) - 0		
PEG-8 Tallow Amide - 0		
PEG-50 Tallow Amide (8051-63-6) - 0		
PEG-2 Tallowamide DEA - 0		
Polyglyceryl-4-PEG-2 Cocamide		
PPG-2 COCAMIDE	05F - Shampoos (non-coloring)	2
PPG-2 COCAMIDE	12A - Cleansing	1
PPG-2 HYDROXYETHYL COCAMIDE	01C - Other Baby Products	2
PPG-2 HYDROXYETHYL COCAMIDE	02B - Bubble Baths	4
PPG-2 HYDROXYETHYL COCAMIDE	02D - Other Bath Preparations	6
PPG-2 HYDROXYETHYL COCAMIDE	05F - Shampoos (non-coloring)	32
PPG-2 HYDROXYETHYL COCAMIDE	05I - Other Hair Preparations	1
PPG-2 HYDROXYETHYL COCAMIDE	10A - Bath Soaps and Detergents	34
PPG-2 HYDROXYETHYL COCAMIDE	10E - Other Personal Cleanliness Products	242
PPG-2 HYDROXYETHYL COCAMIDE	11E - Shaving Cream	2
PPG-2 HYDROXYETHYL COCAMIDE	12A - Cleansing	16
PPG-2 HYDROXYETHYL COCAMIDE	12F - Moisturizing	1
PPG-2 HYDROXYETHYL COCAMIDE	12J - Other Skin Care Preps	2
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	05F - Shampoos (non-coloring)	11
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	10A - Bath Soaps and Detergents	4
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	10E - Other Personal Cleanliness Products	2
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	12A - Cleansing	6

PPG-3 Hydroxyethyl Soyamide – 0



## Memorandum

**TO:** Bart Heldreth, Ph.D.  
Executive Director - Cosmetic Ingredient Review (CIR)

**FROM:** Carol Eisenmann, Ph.D.  
Personal Care Products Council

**DATE:** October 23, 2018

**SUBJECT:** PEG-50 Hydrogenated Palmamide

Anonymous. 2018. Method of manufacture and impurities PEG-50 Hydrogenated Palmamide.

October 2018

**Method of Manufacture and Impurities PEG-50 Hydrogenated Palmamide**

Method of manufacture: PEG-50 Hydrogenated Palmamide is manufactured by ethoxylating a monoethanol amide with approximately 50 moles of ethylene oxide. PEG-50 Hydrogenated Palmamide is based on vegetable and synthetic raw materials.

Impurities data: To determine the potential level of residual monoethylene glycol (MEG) and diethylene glycol (DEG), samples of PEG-50 Hydrogenated Palmamide were evaluated by GC/MS analysis. In summary, PEG-50 Hydrogenated Palmamide contained less than 50 ppm of either residual MEG or DEG.

**Concentration of Use by FDA Product Category – Alkoxylated Fatty Amides\***

PPG-2 Hydroxyethyl Cocamide	PEG-13 Hydrogenated Tallow Amide	PEG-10 Stearamide
PEG-2 Cocamide	PEG-5 Lanolinamide	PEG-15 Stearamide
PEG-3 Cocamide	PEG-2 Lauramide	PEG-50 Stearamide
PEG-4 Cocamide	PEG-5 Lauramide	PEG-5 Tallow Amide
PEG-5 Cocamide	PEG-6 Lauramide	PEG-8 Tallow Amide
PEG-6 Cocamide	PEG-11 Lauramide	PEG-50 Tallow Amide
PEG-7 Cocamide	PEG-3 Oleamide	Polyglyceryl-4-PEG-2
PEG-11 Cocamide	PEG-4 Oleamide	Cocamide
PEG-20 Cocamide	PEG-5 Oleamide	PPG-2 Cocamide
PEG-3 Cocamide DEA	PEG-6 Oleamide	PPG-1 Hydroxyethyl
PEG-6 Hydrogenated Palmamide	PEG-7 Oleamide	Caprylamide
PEG-50 Hydrogenated Palmamide	PEG-5 Oleamide Dioleate	PPG-2 Hydroxyethyl
	PEG-4 Rapeseedamide	Coco/Isostearamide
	PEG-4 Stearamide	PPG-3 Hydroxyethyl
		Soyamide

Ingredient	Product Category	Maximum Concentration of Use
PPG-2 Hydroxyethyl Cocamide	Bath oils, tablets and salts	1.5%
PPG-2 Hydroxyethyl Cocamide	Bubble baths	3%
PPG-2 Hydroxyethyl Cocamide	Other bath preparations	3%
PPG-2 Hydroxyethyl Cocamide	Shampoos (noncoloring)	0.00025-3%
PPG-2 Hydroxyethyl Cocamide	Tonics, dressings and other hair grooming aids	0.62%
PPG-2 Hydroxyethyl Cocamide	Other hair preparations (noncoloring)	7.5%
PPG-2 Hydroxyethyl Cocamide	Bath soaps and detergents	3%
PPG-2 Hydroxyethyl Cocamide	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.008-4%
PPG-2 Hydroxyethyl Cocamide	Face and neck products Not spray	0.35%
PEG-2 Cocamide	Shampoos (noncoloring)	0.12%
PEG-2 Cocamide	Other personal cleanliness products	0.3-2%
PEG-6 Cocamide	Hair conditioners	0.8%
PEG-6 Cocamide	Shampoos (noncoloring)	0.75%
PEG-6 Cocamide	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2%
PEG-6 Lauramide	Bath soaps and detergents	4%
PEG-50 Hydrogenated Palmamide	Other hair preparations (noncoloring)	1%
PEG-50 Hydrogenated Palmamide	Hair dyes and colors	2-3%

PEG-4 Rapeseedamide	Bath capsules	2%
PEG-4 Rapeseedamide	Hair straighteners	2.4%
PEG-4 Rapeseedamide	Shampoos (noncoloring)	2.7-2.8%
PEG-4 Rapeseedamide	Hair dyes and colors	9.3%
PEG-4 Rapeseedamide	Hair bleaches	8.2%
PEG-4 Rapeseedamide	Other personal cleanliness products	1-3%
PEG-4 Rapeseedamide	Foot products Foot soak	0.93%
PEG-4 Rapeseedamide	Other skin care preparations Rinse-off	2.5%
PEG-50 Tallow Amide	Hair dyes and colors	2%
PPG-2 Cocamide	Hair sprays Aerosol	0.8%
PPG-2 Cocamide	Shampoos (noncoloring)	2%
PPG-2 Cocamide	Bath soaps and detergents	4%
PPG-2 Hydroxyethyl Coco/Isostearamide	Bath soaps and detergents	0.5%
PPG-2 Hydroxyethyl Coco/Isostearamide	Other personal cleanliness products	0.6%
PPG-2 Hydroxyethyl Coco/Isostearamide	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3%

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

Information collected in 2015

Table prepared October 13, 2015

Updated August 14, 2018: PPG-2 Hydroxyethyl Coco/Isostearamide: added skin cleansing

Updated October 25, 2018: deleted PPG-2 Hydroxyethyl Cocamide body and hand product 3%



## Memorandum

**TO:** Bart Heldreth, Ph.D.  
Executive Director - Cosmetic Ingredient Review (CIR)

**FROM:** Carol Eisenmann, Ph.D.  
Personal Care Products Council

**DATE:** September 13, 2018

**SUBJECT:** PPG-2 Hydroxyethyl Cocamide

Huntingdon Life Sciences Limited. 1999. Acute dermal toxicity to the rat PPG-2 Hydroxyethyl Cocamide.

Huntingdon Life Sciences Limited. 1999. Acute skin irritation to the rabbit PPG-2 Hydroxyethyl Cocamide.

Huntingdon Life Sciences Limited. 1999. Skin sensitization to the guinea pig (Magnusson & Kligman method) PPG-2 Hydroxyethyl Cocamide.

MNI 002/993204/ AC

ACUTE DERMAL TOXICITY TO THE RAT

PPG-2 Hydroxyethyl Cocamide

Sponsor

Research Laboratory  
Huntingdon Life Sciences Limited  
P.O. Box 2  
Huntingdon  
Cambridgeshire  
PE18 6ES  
ENGLAND

Report issued 14 October 1999

MNI 002/993204/AC

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COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice Standards and I consider the data generated to be valid.

The UK Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.

EC Council Directive 87/18/EEC of 18 December 1986 (Official Journal No. L 15/29), and from 1 May 1999 EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).

—  
Stephen J. Mason, B.Sc. (Hons.).  
Study Director,  
Short Term Studies Group,  
Division of Toxicology,  
Huntingdon Life Sciences Ltd.

Date

MNI 002/993204/AC

## QUALITY ASSURANCE STATEMENT

The following have been inspected or audited in relation to this study.

Study Phases Inspected	Date of Inspection	Date of Reporting
Protocol Audit	26 March 1999	26 March 1999
<b>Process Based Inspections:</b>		
Husbandry	22 January 1999	25 January 1999
Housing/Environment	22 January 1999	25 January 1999
Weighing of Animals	22 January 1999	25 January 1999
Treatment Procedure	22 January 1999	25 January 1999
Scoring	22 January 1999	25 January 1999
Records Audit	22 January 1999	25 January 1999
Training Records	22 January 1999	25 January 1999
Post Mortems	22 January 1999	25 January 1999
Report Audit	12 May 1999	14 May 1999

**Protocol Audit:** An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

**Process based inspections:** At or about the time this study was in progress inspections and audits of routine and repetitive procedures employed on this type of study were carried out. These were conducted and reported to appropriate Company Management as indicated above

**Report Audit:** This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

Margaret Blows,  
Quality Assurance Group Leader,  
Department of Quality Assurance,  
Huntingdon Life Sciences Ltd.

Date

MNI 002/993204/AC

**RESPONSIBLE PERSONNEL**

Stephen J. Mason, B.Sc. (Hons.),  
Study Director,  
Short Tenn Studies Group,  
Division of Toxicology,  
Huntingdon Life Sciences Ltd.

MNI 002/993204/AC

## SUMMARY

This study was performed to assess the acute dermal toxicity of [REDACTED] to the rat. The method followed was based on that described in:

EEC Methods for the Determination of Toxicity, Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), Part B, Method B.3. "Acute toxicity (dermal)".

OECD Guideline for Testing of Chemicals No. 402 "Acute dermal toxicity". Adopted: 24 February 1987.

A group of ten rats (five males and five females) received a single topical application of the test substance, administered as supplied at a dose level of 2000 mg/kg body weight. All animals were sacrificed and examined macroscopically on Day 15, the end of the observation period. The application site was covered with porous gauze held in place with a non irritating dressing and further covered by a waterproof dressing for 24 hours. The animals were observed for signs of toxicity and behavioural changes at least twice daily (only once on Day 15) for 14 days. Body weights were recorded prior to test substance application and again on Days 8 and 15.

Clinical signs of response to treatment were confined to vocalisation and hyperactivity (excitable behaviour) in one female on Day 1 only.

Slight to well-defined dermal irritation (Grade 1 or 2 erythema with or without oedema up to Grade 2) was seen in four males and three females, resolving completely by Day 9. In addition, desquamation (characterised by dryness and sloughing of the skin) was observed in two of the three females accompanied by localised spots and/or scabbing in one female. These latter signs had resolved in all instances by Day 13. No dermal response to treatment was noted for the remaining three animals throughout the duration of the study.

All animals were considered to have achieved satisfactory body weight gains throughout the study.

No abnormalities were observed at the macroscopic examination at study termination on Day 15.

Based on findings in this study, the acute lethal dermal dose (LD<sub>50</sub>) to rats of [REDACTED] was demonstrated to be greater than 2000 mg/kg body weight.

[REDACTED] will not require labelling with the risk phase R21 "Harmful in contact with skin", in accordance with Commission Directive 93/21/EEC.

MNI 002/993204/AC

## INTRODUCTION

This study was designed to assess the toxicity of [REDACTED] following a single dermal application to the skin of rats. The rats were dosed by topical application as the test substance may come in contact with the skin during handling or use.

The study was based on that described in:

EEC Methods for the Determination of Toxicity, Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), Part B, Method B.3. "Acute toxicity (dermal)"; and

OECD Guideline for Testing of Chemicals No. 402 "Acute dermal toxicity". Adopted: 24 February 1987.

The rat was chosen as it has been shown to be a suitable model for this type of study and is one of the animals recommended in the test guidelines.

The dose level for the study was chosen in compliance with the study guidelines.

The protocol was approved by the Sponsor on 5 April 1999 and by the Study Director and Huntingdon Life Sciences Management on 8 April 1999.

The experimental phase of the study was undertaken between 9 and 23 April 1999.

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**TEST SUBSTANCE**

**Identity:**

Chemical name: Amides, coco, N-(hydroxyethyl), propoxylated

**CAS number:**

Intended use: Industrial surfactant

Appearance: Yellow liquid

Storage conditions: Room temperature

Batch number: CI# 98016

Expiry date: 14 December 2008

**Purity/Composition:**

**Source:**

Sample received: 30 December 1998

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## EXPERIMENTAL PROCEDURE

### ANIMAL MANAGEMENT

Ten animals (five males and five females) were selected for this study from a stock supply of healthy albino male and female CD rats of Sprague-Dawley origin (Hsd:Sprague-Dawley(CD)) obtained from Harlan U.K. Ltd., Bicester, Oxon, England.

Animals were in the weight range of 216 to 283 g and approximately eight to eleven weeks of age prior to dosing (Day 1). All the rats were acclimatised to the experimental environment for a period of eight days prior to the start of the study.

Rats were allocated without conscious bias to cages within the treatment group and, prior to dosing, they were housed individually in metal cages with grid floors in Building RI4 Room 6. The animals were returned to group housing on Day 11 of the study. An undertray was placed beneath each cage and was changed daily.

A standard laboratory rodent diet (Special Diet Services RMI(E) SQC expanded pellet) and drinking water were provided *ad libitum*. The batch of diet used for the study was analysed for certain nutrients, possible contaminants and micro-organisms. Results of routine physical and chemical examination of drinking water, as conducted by the supplier, are made available to Huntingdon Life Sciences Ltd. as quarterly summaries. There were no known contaminants reasonably expected to be found in the food or water at levels that would have interfered with the results of this study. Results of food and water analyses are retained in the study records and are presented in Appendices 2 and 3, respectively.

During the experimental period, the animal room temperature was in the range 19 to 23°C and relative humidity was in the range 24 - 52%. Permanent daily recordings of these parameters were made and these are archived with other Department raw data. Lighting was controlled by means of a time switch to provide 12 hours of artificial light (0700 - 1900 hours) in each 24-hour period.

Each animal was identified by cage number and ear punching. Each cage was identified by a coloured label displaying the dose level, study schedule number, animal mark and the initials of the Study Director and Home Office licensee.

### TEST SUBSTANCE PREPARATION

was administered, as supplied by the Sponsor, at a volume of 2.07 ml/kg body weight (specific gravity 0.9663).

The absorption of the test substance was not determined.

Characterisation of the homogeneity, stability and purity of the test substance was not undertaken in this study and remains the responsibility of the Sponsor.

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#### ADMINISTRATION OF TEST SUBSTANCE

A group of ten rats (five males and five females) received a single topical application of the test substance, as supplied, at a dose level of 2000 mg/kg body weight.

One day prior to treatment, hair was removed from the dorso-lumbar region of each rat with electric clippers taking care to avoid damaging the skin, exposing an area equivalent to approximately 10% of the total body surface area.

The test substance was applied by spreading it evenly over the prepared skin with a plastic syringe. The treatment area (approximately 50 mm x 50 mm) was covered with porous gauze held in place with a non irritating dressing, and further covered by a waterproof dressing encircled firmly around the trunk of the animal.

Treatment in this manner was performed on Day 1 (day of dosing) of the study only.

At the end of the 24 hours exposure period the dressings were carefully removed and the treated area of skin was washed with warm water (38°C) to remove any residual test substance. The treated area was blotted dry with absorbent paper.

#### Control animals

No control animals were included in this study.

#### OBSERVATIONS

##### Mortality

Cages of rats were checked at least twice daily for any mortalities.

##### Clinical signs

Animals were observed immediately after dosing and at frequent intervals (not less than hourly) for the remainder of Day 1. On subsequent days, animals were observed once in the morning and again at the end of the experimental day (with the exception of Day 15 - morning only). The nature and severity of the clinical signs and time were recorded at each observation.

All animals were observed for 14 days after dosing.

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**Dermal responses**

In addition to the observations undertaken on a daily basis, local dermal irritation at the treatment site was assessed daily following removal of the dressings on Day 2 using the following numerical scoring system.

**Erythema and eschar formation:**

No erythema	0
Slight erythema	1
Well defined erythema	2
Moderate erythema	3
Severe erythema (bright redness) to slight eschar formation (injuries in depth)	4

**Oedema formation:**

No oedema	0
Slight oedema	1
Well-defined oedema (edges of area well-defined by definite raising)	2
Moderate oedema (raised approximately 1 millimetre)	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure)	4

Any other lesion not covered by this scoring system was described.

**Bodyweight**

The body weight of each rat was recorded on Days 1 (prior to dosing), 8 and 15. Individual weekly body weight changes and group mean body weights were calculated.

**TERMINAL STUDIES****Termination**

All animals were sacrificed on Day 15 by carbon dioxide asphyxiation.

**Macroscopic pathology**

All animals were subjected to a macroscopic examination that consisted of opening the cranial, abdominal and thoracic cavities. The macroscopic appearance of all examined organs and tissues was recorded. No tissues or organs were retained.

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## ARCHIVES

All raw data and study related documents generated during the course of the study at Huntingdon, together with the original final report will be lodged in the Huntingdon Life Sciences Ltd. Archive, Huntingdon.

Such records will be retained for a minimum period of five years from the date of issue of the final report. At the end of the five year retention period the Sponsor will be contacted and advice sought on the future requirements. Under no circumstances will any item be discarded without the Sponsor's knowledge.

## DEVIATIONS FROM PROTOCOL

The lowest value for humidity recorded (24%) was slightly below the range of 30 - 70% stated in the protocol. This deviation from protocol did not affect the integrity or validity of the study.

There were no other deviations from the protocol.

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## RESULTS

### MORTALITY

There were no deaths following a single dermal application of the test substance to a group of ten rats (five males and five females) at a dose level of 2000 mg/kg body weight.

### CLINICAL SIGNS

Clinical signs were confined to vocalisation and hyperactivity (excitable behaviour) in one female on Day 1 only.

### DERMAL RESPONSES (Table 1)

Slight to well-defined dermal irritation (Grade 1 or 2 erythema with or without oedema up to Grade 2) was seen in four males and three females, resolving completely by Day 9. In addition, desquamation (characterised by dryness and sloughing of the skin) was observed in two of the three females accompanied by localised spots and/or scabbing in one female. These latter signs had resolved in all instances by Day 13. No dermal response to treatment was noted for the remaining three animals throughout the duration of the study.

### BODY WEIGHT (Tables 2 and 3)

All animals were considered to have achieved satisfactory body weight gains throughout the study.

### MACROSCOPIC EXAMINATION

No abnormalities were observed at the macroscopic examination at study termination on Day 15.

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#### CONCLUSION

Based on the findings in this study, the acute lethal dermal dose (LD50) to rats of was demonstrated to be greater than 2000 mg/kg body weight. will not require labelling with the risk phrase R21 "Harmful in contact with skin", in accordance with Commission Directive 93/21/EEC.

MNI 002/993204/AC

TABLE I

## Dermal responses

Dose (mg/kg)	Sex	Animal No.	E=Erthema Oe=Oedema	Days after dosing											
				2	3	4	5	6	7	8	9	10	11	12	13 to 15
2000	Male	1	E O	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		2	E O	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		3	E O	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		4	E O	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		5	E O	2 1	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		6	E O	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		7	E O	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
		8	E O	1 0	la 1	2a 2	2a 1	la 1	la 0	0 0	0 0	0 0	0 0	0 0	0 0
		9	E O	lb 1	2b 1	2a 2	2a 2	2a 2b	2a lb	lb 0	Ob 0	Ob 0	Ob 0	Ob 0	0 0
		10	E O	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

a Desquamation (characterised by dryness and sloughing of the skin)

b Spots and/or scabbing (localised response)

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**TABLE2****Individual and group mean body weights (g)**

Dose (mg/kg)	Sex	Animal Number	Body weight (g) at Day		
			1	8	15
2000	Male	1	283	322	364
		2	257	274	300
		3	258	283	303
		4	270	301	336
		5	276	317	349
	Female	Mean	269	299	330
		6	216	227	233
		7	230	239	259
		8	225	232	240
		9	218	223	232
	Mean	10	229	244	252
		Mean	224	233	243

**TABLE3****Individual body weight changes (g)**

Dose (mg/kg)	Sex	Animal Number	Body weight gains (g) at Day	
			8	15
2000	Male	1	39	42
		2	17	26
		3	25	20
		4	31	35
		5	41	32
	Female	6	11	6
		7	9	20
		8	7	8
		9	5	9
		10	15	8

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## APPENDIX I

### References

1. Commission Directive 93/21/EEC (Official Journal No. L 110 A).
2. EC Council Directive 87118/EEC of 18 December 1986 (Official Journal No. L 15/29), and from 1 May 1999 EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).
3. EEC Methods for the Determination of Toxicity. Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), Part B, Method B.3. Acute toxicity (dermal).
4. Finney, D.J. (1971) *Prob it Analysis*, 3rd ed., Cambridge University Press, Cambridge.
5. Finney, D.J. (1978) *Statistical Method in Biological Assay*, 3rd ed., Charles Griffin, London.
6. Mantel, N. (1963) *J Amer. Stat. Assoc.*, 58, 690.
7. OECD Guideline for Testing of Chemicals No. 402 "Acute Dermal Toxicity". Adopted: 24 February 1987.
8. OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.
9. The UK Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

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## APPENDIX2

## Certificate of analysis for Special Diet Services RM1(E) SQC expanded pellet Rat Diet

## Special Quality Control Certificate of Analysis

PRODUCT: RM1 (E) SQC

BATCH NO: 5411

PREMIX BATCH NO: 506

DATE OF MANUFACTURE: 18-DEC-96

Nutrient	Found Analysis	Contaminant	Found Analysis		Limit of Detection
Moisture	11.1	I	Fluoride	6	mg/kg 1.0 mg/kg
Crude Fat	4.0	X	Nitrate as NaNO <sub>3</sub>	17	mg/kg 1.0 mg/kg
Crude Protein	11.6	%	Nitrite as NaNO <sub>2</sub>	3.0	mg/kg 1.0 mg/kg
Crude Fibre	4.7	%	Lead	Non Detected	mg/kg 0.25 mg/kg
Ash	4.3	%	Arsenic	Non Detected	mg/kg 0.2 mg/kg
Calcium	0.88	%	Cadmium	0.10	mg/kg 0.05 mg/kg
Phosphorus	0.57	%	Mercury	0.03	mg/kg 0.01 mg/kg
Sodium	0.23	%	Selenium	0.12	mg/kg 0.05 mg/kg
Chloride	0.32	I			
Potassium	0.57	I			
Magnesium	0.15	I	Total Aflatoxins	Non Detected	mcg/kg 1 mcgflsg each of B1,B2,G1,G2
Iron	126	mg/kg			
Copper	9	mg/kg	Total PCB	Non Detected	mcg/kg 10.0 mcg/kg
Manganese	50	mg/kg	Total D.D.T	Non Detected	mcg/kg 10.0 mcg/kg
Zinc	45	mg/kg	Dieldrin	Non Detected	mcg/kg 10.0 mcgjk-
			Lindane	Non Detected	mcg/kg 10.0 mcgjk-
			Heptachlor	Non Detected	mcg/kg 10.0 mcgjki
			Malathion	Non Detected	mcg/kg 20.0 mcgjkkg
Vitamin A	4.7	lu/g	Total Viable Organisms x 1000	Non Detected	per grm 1000/g
Vitamin E	45	mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	Non Detected	per grm	100/g
		Salmonellae Species	Non Detected	per grm	Absent in 20 grm
		Enterobacteriaceae	Non Detected	per grm	Absent in 20 grm
		Escherichia Coli	Non Detected	per grm	Absent in 20 grm
		Fungal Units	Non Detected	per grm	Absent in 20 grm
		Antibiotic Activity	Non Detected		

Signed . ---

.....

Dated .

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## APPENDIX

## Analytical data summary sheets for water supplied by Anglian Water

## Huntingdon North Public Water Supply Zone

Population	36268	01-Jan-99	30-Jun-99	Zone	Code - FW40			
Parameter		PCV	Units	Number of samples	% samples contravening	Concentration or Value (all samples)		
Ref	Name			PCV		Minimum	Mean	Maximum
A001	Colour	20	PtCo	6	R	0	<1	<1.87
A002	Turbidity	4	FTU	14		0	0.07	<0.197
A003	Odour	3	Oil No	4	R	0	<0	<0
A03a	Odour + Nature			14		1	1	1
A03b	Odour + Intensity			34		1	1	1
A004	Taste		Oil No	4	R	0	<0	<0
A04a	Taste + Nature			34		1	1	1
A04b	Taste + Intensity			34		1	1	1
A005	Temperature	25	°C	47		0	-1.9	11.1
A006	Hydrogen ion (pH)	5.5 - 9.5	pH	34	R	0	7.74	7.86
A007	Sulphate	250	mg/l			0	134	134
A008	Magnesium	50	mg/l			0	8.05	8.05
A009	Sodium	150	mg/l			0	48.6	48.6
A00A	Sodium SO <sub>4</sub>	150	mg/l	3		0	0	65.5
A010	Potassium	12 (15)	mg/l	31	X	0	6.89	8.23
A011	ON <sup>+</sup> Residues	1500	mg/l	1		0	640	640
A012	Nitrate	50	mg/l	6		0	29.6	33
A013	Nitrite	0.1	mg/l	28		7.14	< 0.01	< 0.027
A014	Ammonium	0.5	mg/l	6		0	0.219	0.228
A016	Oxidisability	5	mg/l	1		0	1.72	1.72
A017	Total organic carbon		mg/l	1		0	3.99	3.99
A021	Aluminium	200	μg/l	7	R	0	<10	<10
A022	Iron	200	μg/l	6	RU	0	<10	<11
A023	Manganese	50	μg/l	7	R	0	<2	<3.71
A024	Copper	3000	μg/l	6	R	0	<5	<54
A025	Zinc	5000	μg/l	6	R	0	<6	<7.71
A026	Phosphorus	2200	μg/l	20		0	370	498
A027	Fluoride	1500	μg/l			0	250	250
A028	Silver	10	μg/l			0	<1	<1
B001	Arsenic	50	μg/l			0	1.49	1.49
B002	Cadmium	5	μg/l			0	<0.4	<0.4
B003	Cyanide	50	μg/l			0	<2	<2
B004	Chromium	50	μg/l			0	<1.1	<1.1
B005	Mercury	1	μg/l	1		0	<0.1	<0.1
B006	Nickel	50	μg/l	1		0	3.14	3.14
B007	Ie rd	50	μg/l	6	R	0	<1.9	<1.9
B008	Antimony	10	μg/l			0	0.49	0.49
B009	Selenium	10	μg/l			0	1.1	1.1
P014	Chlorotetra	0.1	mg/l	9		0	< 0.02	< 0.02
P032	Diume	0.1	μg/l	9		0	< 0.02	< 0.02
P048	rasoproluseon	0.1	μg/l	*		0	< 0.02	< 0.021
P051	linuron	0.1	μg/l	Y		0	< 0.02	< 0.02
P113	Monuron	0.1	μg/l	Y		0	< 0.02	< 0.02
P074	2,3,6 + TSA	0.1	μg/l	8		0	"0.02	< 0.02
P020	2,4 - O	0.1	μg/l	8		0	<0.05	<0.05
P076	2,4,5 + T	0.1	μg/l	6		0	<0.05	<0.05
P006	Sentazine	0.1	μg/l	8		0	<0.07	<0.02
P025	Oicamba	0.1	μg/l	5		0	<0.05	<0.05
P028	Oichloroprop	0.1	μg/l	8		0	"0.02	< 0.02
P054	MCPA	0.1	μg/l	8		0	< 0.02	< 0.02
POSS	M(P9	0.1	μg/l			0	<0.05	<0.05
POS3	M(PP)(Mecoprop)	0.1	μg/l			0	<0.02	<0.02
P004	Atrazine	0.1	μg/l			0	<0.02	<0.02

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## APPENDIX3 (continued)

## Analytical data summary sheets for water supplied by Anglian Water

## Huntingdon North Public Water Supply Zone

Parameter Ref Name	PCV	Units	Number of samples	% samples contravening PCV	Concentration or Value (all samples)	zone code: fW40
					Minimum	G-d Ref: TU4573S
					Mean	Maximum
P070 Prometryne	0.1	µg/l	11	0	< 0.02	<0.02
P066 Propazine	0.1	µg/l	11	0	<0.02	<0.02
P073 Simazine	0.1	µg/l	11	0	< 0.02	<0.02
P077 Terbutryne	0.1	µg/l	11	0	< 0.02	< 0.02
P132 Trietazine	0.1	µg/l	11	0	< 0.02	< 0.02
8010 Pesticides Total	0.5	µg/l	11	0	0	0.005
9011 PAH	0.2	vgn	1	R	0	0
C001 Total Coliforms	0	No/dl	50	0	0	0
C002 Faecal Coliforms	0	No/dl	50	0	0	0
COOS Colony Count 10av C 37°C		No/ml	50		0	S
CO12 Colony Count 7Day C 22°C		No/ml	50		1	76.8
C010 Chlorine Total		mg/l	50		0.1-	0.616
0011 Conductivity -M12	1500	µS/cm	34	0	807	817
002a Chloride - M12	400	mg/l		0	659	659
003a Calcium - M12	250	mg/l		0	140	140
D05a iron - M12	2000	µg/l		0	244	244
D06a Barium - M12	1000	µg/l	1	0	14.8	14.8
D07a Benzo 34 pyrene - M12	10	ng/l	1	0	5	5
D08a Tetrachloromethane - M12	3	µg/l	6	0	0.1	0.1
D09a Trichloroethene - M12	30	µg/l	6	0	0.4	0.4
D10a Tetrachloroethene - M12	10	µg/l	6	0	0.3	0.3
011r Trichloromethane - M3	100	µg/l		R	25.4	25.4
E001 Hardnessas Ca Min		mg/l			149	149
E002 Alkalinity + HCO3 - Min		mg/l			272	272

PCV = Prescribed concentration or value  
 M12 = Rolling 12 month mean  
 M3 = Rolling 3 month mean  
 Min = PCV is a minimum only where the water is softened  
 U = Undertaking  
 X = Relaxed (relaxed value in brackets under PCV column)  
 R = Reduced sampling frequency  
 - Increased sampling frequency  
 PAH = Polycyclic aromatic hydrocarbons  
 Sodium so<sup>4</sup> = the 8-th percentile of the last 3 years of sodium results

P-g\*)

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APPENDIX4

Quality control analysis

Q U A L I T Y C O N T R O L A N A L Y S I S

Date: 12/14/98

Product:

Customer Order#:

Lot# 35937

ANALYSIS

APPEARANCE:	CLEAR LIQUID
ALKALI NUMBER:	33
PH (10% Aq)	10.75
COLOR '63:	3
%MOISTURE:	0.015%

---

Quality Control

MNI 003/993156/SE

ACUTE SKIN IRRITATION TO THE RABBIT

PPG-2 Hydroxyethyl cocamide

Sponsor

Research Laboratory  
Huntingdon Life Sciences Limited  
P.O. Box 2  
Huntingdon  
Cambridgeshire  
PE18 6ES  
ENGLAND

Report issued 14 October 1999

MNI 003/993156/SE

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COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described *in* this report was conducted in compliance with the following Good Laboratory Practice Standards and I consider the data generated to be valid.

The UK Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

OECD Principles of Good Laboratory Practice (as revised in 1997),  
ENV/MC/CHEM(98)17.

EC Council Directive 87/118/EEC of 18 December 1986 (Official Journal No. L 15/29) and from  
1 May 1999, EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).

---

Stephen J. Mason, B.Sc. (Hons.),  
Study Director,  
Short Term Studies Group,  
Division of Toxicology,  
Huntingdon Life Sciences Ltd.

Date

MNI 003/993156/SE

## QUALITY ASSURANCE STATEMENT

The following have been inspected or audited in relation to this study.

Study Phases Inspected	Date of Inspection	Date of Reporting
Protocol Audit	26 March 1999	26 March 1999
<b>Process Based Inspections:</b>		
Husbandry	10 March 1999	19 March 1999
Housing(Environment	10 March 1999	19 March 1999
Test Material>		
Control	10 March 1999	19 March 1999
Treatment Procedure	2 March 1999	19 March 1999
Scoring	2 March 1999	19 March 1999
Records Audit	10 March 1999	19 March 1999
Report Audit	11 May 1999	14 May 1999

**Protocol Audit:** An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

**Process based inspections:** At or about the time this study was in progress inspections and audits of routine and repetitive procedures employed on this type of study were carried out. These were conducted and reported to appropriate Company Management as indicated above.

**Report Audit:** This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

...  
 Margaret Blows,  
 Quality Assurance Group Leader,  
 Department of Quality Assurance,  
 Huntingdon Life Sciences Ltd.

Date

MNI 003/993156/SE

**RESPONSIBLE PERSONNEL**

Stephen J. Mason, B.Sc. (Hons.),  
Study Director,  
Short Term Studies Group,  
Division of Toxicology  
Huntingdon Life Sciences Ltd.

MNI 003/993156/SE

## SUMMARY

This study was performed to assess the skin irritation potential of [REDACTED] to the rabbit. The method followed was that described in:

EEC Methods for the Determination of Toxicity, Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), Part B, Method B.4. "Acute toxicity (skin irritation)".

OECD Guideline for Testing of Chemicals No. 404 "Acute Dermal Irritation/Corrosion". Adopted 17 July 1992.

Approximately 0.5ml of the test substance, as received, was applied to an area of shaved skin on the backs of three rabbits and the application site was covered with a semi-occlusive dressing for four hours. Following exposure and removal of the dressing, skin irritation was evaluated up to 14 days. The effects of three minute, 60 minute and four hour exposures were initially investigated using a pilot animal.

A single semi-occlusive application of [REDACTED] to intact skin of the pilot rabbit for three or 60 minutes elicited no dermal irritation. A single semi-occlusive application of [REDACTED] to intact skin of all three rabbits for four hours elicited persistent, well-defined dermal irritation.

Based on the persistence of dermal responses in two rabbits at study termination on Day 14, [REDACTED] will require labelling with the risk phrase R38, "Irritating to skin", in accordance with Commission Directive 93/21/EEC.

MN! 003/993156/SE

## INTRODUCTION

This study was designed to assess skin irritation potential of following a single dermal application to rabbits. The rabbit was dosed by topical application as the test substance may come into contact with skin during handling or use.

The study was conducted in compliance with the following guidelines:

EEC Methods for the Determination of Toxicity, Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), PartB, Method B.4. "Acute toxicity (skin irritation)"; and

OECD Guideline for Testing of Chemicals No. 404 "Acute dermal irritation/corrosion". Adopted 17 July 1992.

The New Zealand White rabbit was chosen as it has been shown to be a suitable model for skin irritation studies and is the animal recommended in the test guidelines.

The amount of test substance administered was chosen in compliance with the guidelines.

The protocol was approved by the Sponsor on 5 April 1999 and by the Study Director and Huntingdon Life Sciences Management on 8 April 1999.

The experimental phase of the study was undertaken between 13 and 28 April 1999.

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**TEST SUBSTANCE**

Identity:

Chemical name: Amides, coco, N-(hydroxyethyl), propoxylated

CAS number:

Intended use: Industrial surfactant

Appearance: Yellow liquid

Storage conditions: Room temperature

Batch number: CI# 98016

Expiry date: 14 December 2008

Purity /Composition: 100%

Source:

Sample received: 30 December 1998

MNI 003/993156/SE

## EXPERIMENTAL PROCEDURE

### ANIMAL MANAGEMENT

Three male animals were selected for this study from a stock supply of healthy adult rabbits of the New Zealand White strain, obtained from Charles River UK Ltd, Margate, Kent, England.

Animals were in the weight range of 2.5 to 2.7 kg and at least 12 weeks of age, prior to treatment (Day 1). All rabbits were acclimatised to the experimental environment for a minimum period of six days prior to the start of the study.

The rabbits were selected without conscious bias for the study. They were housed individually in stainless steel cages with perforated floors in Building R14 Room 4.

A standard laboratory rabbit diet (Special Diet Services STANRAB (P) SQC pellet) and drinking water were provided *ad libitum*. The batch of diet used for the study was analysed by the supplier for nutrients, possible contaminants and micro-organisms likely to be present in the diet and which, if in excess of specified amounts, might have an undesirable effect on the test system. The animals were also fed hay on arrival and subsequently three times a week.

The water supplied to Huntingdon Life Sciences Ltd. by Anglian Water was potable water for human consumption. Anglian Water takes its guidelines on water quality from the EEC directive relating to water for human consumption (801778/EEC) and conforms to the United Kingdom Water Act 1989 and subsequent amendments. Results of routine physical and chemical examination of drinking water at Consumers' taps, as conducted by the supplier, are made available to Huntingdon Life Sciences Ltd. as quarterly summaries.

There were no known contaminants reasonably expected to be found in the food or water at levels that would have interfered with the results of this study. Results of food and water analysis are retained in the study records and are presented in Appendices 2 and 3, respectively.

During the experimental period, the animal room temperature was maintained at 17.5 to 19°C and relative humidity at 28 to 46%. These environmental parameters were recorded daily. Lighting was controlled by means of a time switch to give 12 hours of artificial light (0700 - 1900 hours) in each 24-hour period.

Each animal was identified by a numbered aluminium tag placed through the edge of one ear. This identification was unique within the Department throughout the duration of the study. Each cage was identified by a coloured label displaying the study number, animal number and initials of the Study Director and Home Office licensee.

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### TEST SUBSTANCE PREPARATION

was administered as supplied by the Sponsor. The pH of the test material was measured prior to the start of the study and was found to be pH 10.89.

The absorption of the test substance was not determined.

Characterisation of the homogeneity, stability and purity of the test substance was not undertaken as part of this study and remains the responsibility of the Sponsor.

### TREATMENT PROCEDURE

On the day prior to application of the test substance, hair was removed with electric clippers from the dorso-lumbar region of each rabbit exposing an area of skin approximately 100 mm x 100 mm. After clipping and prior to test substance application, the animals' skin was checked for any abnormalities according to the numerical system described below in the section titled "Dermal responses"

Approximately 0.5 ml of the test substance was applied to one intact skin site on each animal and covered with a 25 mm x 25 mm gauze pad.

To help clarify the irritant potential of the test substance, initially only one animal was treated (pilot animal, Table I). With this animal, the test substance was applied to three treatment sites and the exposure period was varied between treatment sites (i.e. three minutes, 60 minutes and four hours). The exposure periods were initiated in a step-wise manner with the 60-minute and four-hour exposures initiated only after consideration of results from the earlier three-minute exposure period. On the basis of initial results from this preliminary phase of the study, two further animals were exposed to the test substance for four hours.

Each treatment site was covered with "Elastoplast" elastic adhesive dressing. Only during the three-minute exposure period was the pilot animal restrained by an animal technician. For the one- and four-hour exposure, none of the animals were restrained and were returned to their cages immediately after treatment.

At the end of the exposure period(s), the semi-occlusive dressing and gauze pad were removed and the treatment sites washed with warm water (36 or 37°C) to remove any residual test substance. The treated area was blotted dry with absorbent paper.

### OBSERVATIONS

#### Clinical signs

All animals were observed daily for signs of ill health or toxicity.

#### Dermal responses

Examination of the treated skin was made on Day 1 (i.e. immediately after removal of the patches following the three-minute and 60-minute exposure and approximately 60 minutes after the four-hour exposure) and on Days 2, 3 and 4 (equivalent to 24, 48 and 72 hours after exposure). Additional observations were made for all animals on Days 5 through 12 and for two animals on Days 13 and 14. Adjacent areas of untreated skin of each animal served as controls.

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Local dermal irritation was assessed using the prescribed numerical system:

Erythema and eschar formation:

No erythema.....	0
Very slight erythema (barely perceptible).....	1
Well-defined erythema.....	2
Moderate to severe erythema.....	3
Severe erythema (beet redness) or eschar formation (injuries in depth) preventing erythema reading .....	4

Oedema formation:

No oedema.....	0
Very slight oedema (barely perceptible).....	1
Slight oedema (edges of area well-defined by definite raising).....	2
Moderate oedema (edges raised approximately 1 millimetre).....	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure).....	4

On completion of this study, the animals were killed by intravenous overdose of pentobarbitone sodium.

Any other lesion or reaction not covered by this scoring system was described.

#### ARCHIVES

All raw data and study related documents generated during the course of the study at Huntingdon together with the original final report will be lodged in the Huntingdon Life Sciences Ltd Archive, Huntingdon.

Such records will be retained for a minimum period of five years from the date of issue of the final report. At the end of the five year retention period the Sponsor will be contacted and advice sought on the future requirements. Under no circumstances will any item be discarded without the Sponsor's knowledge.

#### DEVIATIONS FROM PROTOCOL

The low value recorded for humidity (28%) was slightly outside the range specified in the study protocol. In addition, for the three-minute exposure in the pilot animal, on grounds of animal welfare the rabbit was restrained by an animal technician. These deviations had no impact on the integrity or validity of the study.

There were no other deviations from the protocol.

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## RESULTS

### CLINICAL SIGNS

There were no signs of toxicity or ill health in any rabbit during the observation period.

### DERMAL RESPONSES

The numerical values given to the dermal reactions elicited by [redacted] are shown in Table 1.

No dermal irritation was observed in the pilot animal following the three-minute or 60-minute exposure.

Well-defined erythema with or without very slight oedema was noted in all three animals following the four-hours exposure. In addition, thickening of the skin and desquamation (characterised by dryness and sloughing) were seen in these animals. Responses had resolved completely in one animal by Day 12; however very slight erythema was still evident in the remaining two animals at study termination on Day 14.

### CONCLUSION

A single semi-occlusive application of [redacted] to intact rabbit skin for four hours elicited persistent, well-defined dermal irritation. Based on the findings of this study, [redacted] will require labelling with the risk phrase R38, "Irritating to skin", in accordance with Commission Directive 93/21/EEC.

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TABLE 1  
Dermal responses

Animal No. &Sex	Exposure Time	E=Erythema O=Oedema	Day													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
2317 Male*	3 Minutes	E	0	0	0	0	0									
		O	0	0	0	0	0									
2317 Male*	1 Hour	E	0	0	0	0	0									
		O	0	0	0	0	0									
2318 Male	4 Hours	E	2	1	1	1a	2a	2a	2a	2a	1a	1b	1b	1b	1b	1b
		O	0	1	0	0	0	0	0	0	0	0	0	0	0	0
2318 Male	4 Hours	E	1	1	1a	2a	2	2	1	1b						
		O	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2319 Male	4 Hours	E	2	2	2a	2a	2a	1a	1b	1b	1b	1b	1b	1b	Ob	
		O	0	0	0	0b	0b	0b	0	0	0	0	0	0	0	

\* Pilot animal

a Thickening

b Desquamation (characterised by dryness and sloughing)

TABLE2  
Individual body weights and body weight gains (g)

Animal number & sex	Bodyweight (g) on Day 1	Bodyweight (g) at termination	Change (g)
2317 Male	2602	2744	142
2318 Male	2599	2851	252
2319 Male	2533	2613	80

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## APPENDIX I

### References

1. Commission Directive 93/21/EEC (Official Journal No. L 110 A).
2. EC Council Directive 87/18/EEC of 18 December 1986 (Official Journal No. L 15/29), and from 1 May 1999, EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).
3. EEC Methods for the Determination of Toxicity, Annex to Directive 92/69/EEC (Official Journal No. L383A, 29.12.92), Part B, Method B4. "Acute toxicity (skin irritation)".
4. OECD Guideline for Testing of Chemicals No. 404 "Acute dermal irritation/corrosion". Adopted 17 July 1992.
5. OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.
6. The UK Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

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## APPENDIX2

## Certificates of analysis for Stanrab (P) SQC Rabbit Diet

## Special Quality Control Certificate of Analysis

PRODUCT: STANRAB (P) SQC			BATCH NO: 5515		
PREMIX BATCH NO: 552			DATE OF MANUFACTURE: 27-JAN-99		
Nutrient	Found Analysis	Contaminant:	Found Analysis		Limit of Detection
Moisture	10.5 %	Fluoride	7 mg/kg	1.0 mg/kg	
Crude Fat	3.2 %	Nitrate as NaNO <sub>3</sub>	1991 mg/kg	1.0 mg/kg	
Crude Protein	17.4 %	Nitrite as NaNO <sub>2</sub>	2.9 mg/kg	1.0 mg/kg	
Crude Fibre	13.6 %	Lead	0.25 mg/kg	0.25 mg/kg	
Ash	6.5 %	Arsenic	Non Detected mg/kg	0.2 mg/kg	
Calcium	0.88 %	Cadmium	0.24 mg/kg	0.05 mg/kg	
Phosphorus	0.57 %	Mercury	Non Detected 0.07 mg/kg	mg/kg	0.01 mg/kg
			0.07 mg/kg	mg/kg	
Sodium	0.31 %	Selenium			0.05 mg/kg
Chloride	0.50 %				
Potassium	0.90 %				
Magnesium	0.23 %	Total Aflatoxins	Non Detected mcg/kg	1 mcg/kg each of B <sub>1</sub> , B <sub>2</sub> , G <sub>1</sub> , G <sub>2</sub>	
Iron	202 mg/kg				
Copper	12 mg/kg	Total P.C.B	Non Detected mcg/kg	1.00 mcg/kg	
Manganese	82 mg/kg	Total D.D.T	Non Detected mcg/kg	10.0 mcg/kg	
Zinc	81 mg/kg	Dieldrin	Non Detected mcg/kg	10.0 mcg/kg	
		Lindane	Non Detected mcg/kg	10.0 mcg/kg	
		Heptachlor	Non Detected mcg/kg	10.0 mcg/kg	
		Malathion	Non Detected mcg/kg	20.0 mcg/kg	
Vitamin A	3.8 iu/g	Total Viable Organisms x 1000	20.50 per grm	1000/g	
Vitamin E	57 mg/kg				
Vitamin C	111g/kg	Mesophilic Spores x 100	123.75 per grm	100/g	
		Salmonellae Species	Non Detected per grm	Absent in 20 grm	
		Enterobacteriaceae	Non Detected per grm	Absent in 20 grm	
		Escherichia Coli	Non Detected per grm	Absent in 20 grm	
		Fungal Units	Non Detected per grm	Absent in 20 grm	

Signed  
Dated

Antibiotic  
Activity

Non  
Detected

MNI 003/993156/SE

1

MNI 003/993156/SE

## APPENDIX 2 (continued)

## Certificates of analysis for Stanrab (P) SQC Rabbit Diet

**SDS***Special Quality Control  
Certificate of Analysis*

## PRODUCT: STANRAB (P) SQC

BATCH NO: 5310

PREMIX BATCH NO: 436

DATE OF MANUFACTURE: 12-NOV-98

Nutrient	Found Analysis	Contaminant	Found Analysis	Limit of Detection
Moisture	10.5 %	Fluoride	4 mg/kg	1.0 mg/kg
Crude Fat	2.9 %	Nitrate as NaNO <sub>3</sub>	2071 mg/kg	1.0 mg/kg
Crude Protein	17.0 %	Nitrite as NaNO <sub>2</sub>	3.0 mg/kg	1.0 mg/kg
Crude Fibre	14.1 %	Lead	0.29 mg/kg	0.25 mg/kg
Ash	8.3 %	Arsenic	Non Detected mg/kg	0.2 mg/kg
Calcium	0.72 %	Cadmium	0.05 mg/kg	0.05 mg/kg
Phosphorus	0.61 %	Mercury	Non Detected mg/kg	0.01 mg/kg
Sodium	0.29 %	Selenium	0.06 mg/kg	0.05 mg/kg
Chloride	0.44 %			
Potassium	1.00 %			
Magnesium	0.26 %	Total Aflatoxins	Non Detected mcg/kg	1 mcg/l.:g each of
Iron	217 mg/kg			B1,B2,G1,G;I
Copper	12 mg/kg	Total P.C.B	Non Detected mcg/kg	10.0 mcg/kg
Manganese	76 mg/kg	Total D.D.T	Non Detected mcg/kg	10.0 mcg/kg
Zinc	78 mg/kg	Dieldrin	Non Detected mcg/kg	10.0 mcg/kg
		Lindane	Non Detected mcg/kg	10.0 mcg/kg
		Heptachlor	Non Detected mcg/kg	10.0 mcg/kg
		Malathion	Non Detected mcg/kg	20.0 mcg/kg
Vitamin A	6.4 iu/t.,	Total Viable Organisms x 1000	8.25 per grm	1000/g
Vitamin E	55 mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	110.00 per grm	100/g
		Salmonellae Species	Non Detected per grm	Absent in 20 grm
		Enterobacteriaceae	Non Detected per grm	Absent in 20 grm
		Escherichia Coli	Non Detected per grm	Absent in 20 grm
		Fungal Units	50 per grm	Absent in 20 grm
		Antibiotic Activity	Non detected	

Dated

.....

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## APPENDIX3

## Analytical data summary sheets for water supplied by Anglian Water

## Huntingdon North Public Water Supply Zone

Parameter	PCV	Units	N-ber of samples	% samples contravening	Action	Or Value (all samples)	Zone Code - FW40	Gnd Ref - TI245735
Ref Name				PCV	Minimum	Mean	Maximum	
A001 Colour	20	PUCo	6	R	0	<1	< 1.87	3.5
A002 Turbidity	4	FTU	34		0	0.07	<0.197	0.88
A003 Odour		Oil No	4	R	0	<0	<0	<0
A03a Odour + Nature			34			1	1	1
A03b Odour - Intensity			34					
A04a Taste		Oil No	4	R	0	<0	<0	<0
A04a Taste - Nature			34			1	1	1
A04b Taste + Intensity			34			1	1	1
A005 Temperature	25	'C	47		0	19	11.1	18.2
A006 Hydrogen ion (pH)	5.5	9.5	pH	34	R	0	7.74	7.86
A007 Sulphate	250	mg/l			0	134	134	
A008 Magnesium	12 (85)	mg/l	31	X	0	8.89	8.25	5.03
A009 Sulfide residues	1500	mg/l	1		0	400	400	400
A002 Sodium ad-	150	mg/l	6		0	29.8	6.53	35.0
A013 Nitrite	0.1	mg/l	28		7.14	<0.1n	<0.027	0.207
A014 Ammonium	0.5	mg/l	6		0	0.219	0.228	0.232
A016 Oxidisability	5	mg/l			0	1.72	1.72	1.72
A017 Total organic carbon		mg/l				3.99	3.99	3.99
A021 Aluminium	200	µg/l	7	R	0	< 10	< 10	< 10
A024 Iron	200	µg/l	6	RU	0	< 10	< 11	13
A023 Manganese	50	µg/l	7	R	0	<2	<3.71	14
A024 Copper	3000	µg/l	6	R	0	<5	<54	288
A025 Zinc	5000	µg/l	6	R	0	<6	<7.71	14.1
A026 Phosphorus	2200	µg/l	20		0	170	498	620
A027 Fluoride	1500	µg/l			0	250	250	250
A028 Silver	10	µg/l			0	<1	<1	<1
B001 Arsenic	50	µg/l			0	1.49	1.49	1.49
B002 Cadmium	5	µg/l			0	<0.4	<0.4	<0.4
B003 Cyanide	50	µg/l			0	<2	<2	<2
B004 Chromium	50	µg/l			0	< 1.1	< 1.1	< 1.1
B005 Mercury	1	µg/l			0	<0.1	<0.1	<0.1
B006 Nid cl	50	µg/l			0	3.14	3.14	3.14
B007 Lead	50	µg/l	6	R	0	< 1.9	< 1.9	< 1.9
B008 Antimony	10	119/l			0	0.49	0.49	0.49
B009 Ilenium	10	µg/l			0	1.1	1.1	1.1
P014 Chlortoluron	0.1	µg/l			0	<0.02	<0.02	<0.02
P032 Diuron	0.1	pg/l	6		0	< 0.02	< 0.02	< 0.02
P048 Isoproturon	0.1	pg/l	4		0	< 0.02	< 0.021	0.03
P051 Linuron	0.1	µg/l	9		0	< 0.02	< 0.02	< 0.02
P113 Monuron	0.1	µg/l	9		0	< 0.02	< 0.02	< 0.02
P074 2,3,6-TBA	0.1	µg/l	8		0	< 0.02	< 0.02	< 0.02
P020 2,4-D	0.1	µg/l	8		0	< 0.05	< 0.05	< 0.05
P076 2,4,5-T	0.1	µg/l	8		0	< 0.05	< 0.05	< 0.05
P006 Bentazon	0.1	pg/l	8		0	< 0.02	< 0.02	< 0.02
P025 Dicamba	0.1	pg/l	8		0	< 0.05	< 0.05	< 0.05
P026 Dichloroprop	0.1	pg/l	8		0	< 0.02	< 0.02	< 0.02
P054 MCPA	0.1	µg/l	8		0	< 0.02	< 0.02	< 0.07
P055 MCPB	0.1	µg/l	6		0	< 0.05	< 0.05	< 0.05
P053 MCPP(Macoprop)	0.1	µg/l	8		0	< 0.02	< 0.02	< 0.02
P004 Atrazine	0.1	µg/l	11		4	< 0.02	< 0.02	< 0.07

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## APPENDIX 3 (continued)

Analytical data summary sheets for water supplied by Anglian Water

**Huntingdon North Public Water Supply Zone**

Population - J6288		01-Jan-99	30-Jun-99	Zone Code:- NW40 Grid Ref:- TL245735
Parameter Ref Name	PCV Units	Number of samples	% samples contravening PCV	Concen"tration or Value (all samples) Minimum Mean Maximum
P070 Prometryne	0.1 µg/l	11	0	< 0.02 < 0.02 < 0.02
P066 Propazine	0.1 µg/l	11	0	< 0.02 < 0.02 < 0.02
P071 Simazine	0.1 µg/l	11	0	< 0.02 < 0.02 < 0.02
P077 Terbutryne	0.1 µg/l	11	0	< 0.02 < 0.02 < 0.02
P132 Trietazine	0.1 µg/l	11	0	< 0.02 < 0.02 < 0.02
B010 Pesticides -Total	0.5 µg/l	11	0	0 0.005 0.03
B011 PAH	0.2 µg/l	1 R	0	0 0 0
C001 Total Coliforms	0 No/dl	50	0	0 0 0
C002 Faecal Coliforms	0 No/dl	50	0	0 0 0
C003 Colony Count 1Day @ 37°C	No/ml	50		0 0.9
C012 Colony Count 7Day @ 22°C	No/ml	50		76.8 85-
C010 Chlorine Total	mgn	50		0.15 0.616 0.94
D01a Conductivity - M12	1500 µs/cm	3-	0	807 817 832
D02a Chloride - M12	400 mg/l		0	65.9 65.9 65.5
003a Calcium - M12	250 mg/l		0	140 140 140
O005 Boron - M12	2000 µg/l		0	244 244 244
006a Barium - M12	1000 µg/l		0	14.8 14.8 14.8
D07a Benzene 34 pyrene - M12	10 ng/l	1	3	5 5 5
D08a Tetrachloromethane - M12	µg/l	6	0	0.1 0.1 0.1
D09a Trichlorethene - M12	30 µg/l	6	0	0.4 0.4 0.4
D10a Tetradichloroethene - M12	10 µg/l	6	0	0.3 0.3 0.3
011r Trihalomethanes - M3	100 µg/l	R	0	25.4 25.4 25A
E001 Hardness as Ca - Min	mg/l			149 149 149
E002 Alkalinity - KC03 - Min	mg/l			272 272 272

PCV Prescribed concentration or value  
 M12 Romm9 12monthmean  
 M3 -Rolling 3 month mean  
 Min -PCV is a minimum only where the water is softened  
 U -Undertaking  
 X -Relaxation (relaxed value in brackets under PCV column)  
 R - Reduced sampling frequency  
 I - Increased sampling frequency  
 PAH - Polycyclicaromatic hydrocarbon>  
 Sodium SO\* -the 80th percentile of the last 3 years of sodium results

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APPENDIX4  
Quality control analysis

Q U A L I T Y C O N T R O L A N A L Y S I S

Date: 12/14/98

Product:

Customer Order#:

Lot# 35937

ANALYSIS

APPEARANCE:	CLEAR LIQUID
ALK\LI NUMBER:	33
PH (10% Aq)	10.75
COLOR '63:	3
% MOISTURE:	0.015%

Quality Control (/

MNI 005/993254/SS

SKIN SENSITIZATION TO THE GUINEA PIG

(MAGNUSSON & KLIGMAN METHOD)

*pPL-2 Hydroxyethyl cocamide*

Sponsor

Research Laboratory

Huntingdon Life Sciences Limited  
P. O. Box 2  
Huntingdon  
Cambridgeshire  
PE18 6ES  
ENGLAND

Report issued 8 October 1999

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## COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice Standards and with the exception of that noted below I consider the data generated to be valid.

The United Kingdom Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

EC Council Directive 87/18/EEC of 18 December 1986 (Official Journal No L 15/29) and, from 1 May 1999, EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).

OECD Principles of Good Laboratory Practice (as revised in 1997) ENV/MC/CHEM(98) 17.

In line with normal practice in this type of short-term study, the protocol did not require chemical analysis of formulated test and control articles for determination of stability, homogeneity and concentration.

~,~  
David G. Coleman, B.Sc. (Hons.),  
Study Director,  
Short Term Studies Group,  
Division of Toxicology,  
Huntingdon Life Sciences Ltd.

Date

MNI 005/993254/SS

**QUALITY ASSURANCE STATEMENT**

The following have been inspected or audited in relation to this study.

Study Phases Inspected	Date of Inspection	Date of Reporting
Protocol Audit	29 March 1999	29 March 1999
Process Based Inspections:		
Housing/Environment	16 March 1999	31 March 1999
Husbandry	16 March 1999	31 March 1999
Treatment Procedure	16 March 1999	31 March 1999
Scoring	17 March 1999	31 March 1999
Records Audit	29 March 1999	31 March 1999
Training Records	29 March 1999	31 March 1999
Report Audit	18 May 1999	18 May 1999

**Protocol Audit:** An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

**Process based inspections:** At or about the time this study was in progress inspections and audits of routine and repetitive procedures employed on this type of study were carried out. These were conducted and reported to appropriate Company Management as indicated above.

**Report Audit:** This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

Margaret Blows,  
Quality Assurance Group Leader,  
Department of Quality Assurance,  
Huntingdon Life Sciences Ltd.

Date

MNI 005/993254/SS

**RESPONSIBLE PERSONNEL**

David G. Coleman, B.Sc. (Hons.),  
Study Director,  
Short Term Studies Group,  
Division of Toxicology,  
Huntingdon Life Sciences Ltd.

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## SUMMARY

This study was performed to assess the skin sensitization potential of [redacted] using the guinea pig. The method followed was that described in:

EEC Methods for the Determination of Toxicity, Annex to Directive 96/54/EC (Official Journal No. L248, 30.9.96). Part B, Method B.6. "Skin sensitization".

OECD Guideline for Testing of Chemicals No. 406 "Skin sensitization". Adopted 17 July 1992.

Magnusson, B. and Kligman, A.M. (1970) *Allergic Contact Dermatitis in the Guinea pig: identification of contact allergens*, Thomas, C.C., Springfield, Illinois, U.S.A.

Ten guinea pigs were dosed by intradermal injection and topical application. Based on the results of a preliminary study and in compliance with the guideline, the following dose levels were selected:

Intradermal injection: 0.5% v/v in sterile water

Topical application: 50% v/v in sterile water

Challenge application: 10 and 5% v/v in sterile water

Five control guinea pigs were treated similarly to the test animals with the exception that the test substance was omitted from the intradermal injections and topical application. An additional group of five naive control animals were induced the same way as the control group; however, at challenge they were kept naive in case of a second challenge. As a second challenge was not required, data recorded from these animals were not reported.

In this study, [redacted] did not produce evidence of skin sensitization (delayed contact hypersensitivity) in any of the ten test animals.

Based on the findings in this study, [redacted] does not require labelling with the risk phrase R43 "May cause sensitization by skin contact" in accordance with Commission Directive 93/21/EEC.

HINI 005/993254/SS

## INTRODUCTION

This study was designed to assess the skin sensitization potential of [REDACTED] using the guinea pig. The guinea pig was dosed by intradermal injection and topical application as the test substance may come into contact with skin during handling or use.

The study was conducted in compliance with:

EEC Methods for the Determination of Toxicity, Annex to Directive 96/54/EC (Official Journal No. L248, 30.9.96), Part B, Method B.6. "Skin sensitization": and

OECD Guideline for Testing of Chemicals No. 406 "Skin sensitization". Adopted 17 July 1992.

The method used was the guinea pig maximisation test described by Magnusson, B. and Kligman, A.M. (1970) *Allergic Contact Dermatitis in the Guinea pig: Identification of contact allergens*, Thomas, C.C., Springfield, Illinois, U.S.A.

Following initial exposure to the test substance (the 'induction' period comprising intradermal injections and topical application) the guinea pigs were subjected, approximately two weeks after the topical induction exposure, to a 'challenge' exposure of the test substance in order to establish if a hypersensitive state had been induced. Sensitization was determined by examining the skin reaction of test animals to the challenge exposure in comparison to skin reactions demonstrated by control animals.

On this occasion ten test and five control animals were used.

The albino guinea pig was chosen as the test species as it had been shown to be a suitable model for skin sensitization studies and is the species recommended by the test guidelines.

The dose levels for the study were chosen on the basis of a preliminary study in compliance with the guideline.

The protocol was approved by the Study Director on 19 March 1999, Huntingdon Life Sciences Management on 22 March 1999 and by the Sponsor on 11 March 1999.

The experimental phase of the study was undertaken between 5 April 1999 and 7 May 1999.

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TEST SUBSTANCE

Identity

Chemical name: Amides, coco, N-(hydroxyethyl), propoxylated

CAS number:

Intended use: Industrial surfactant

Appearance: Yellow liquid

Storage conditions: Room temperature

Batch number: CI# 98016

Expiry date: 14 December 2008

Purity/Composition: 100%

Source:

Sample received: 30 December 1998

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## EXPERIMENTAL PROCEDURE

## ANIMAL MANAGEMENT

Fifteen healthy female (nulliparous and non-pregnant) albino guinea pigs of the Dunkin/Hartley strain were obtained from D. Hall, Newchurch, Staffs, UK for use in the main study.

The guinea pigs were approximately four to seven weeks of age on arrival and were acclimatised to the experimental environment for five days prior to the start of the main study. The guinea pigs were within the weight range 323 - 402 g at the start of the study (Day 1).

An additional six guinea pigs from the same supplier were used for the preliminary investigations.

The guinea pigs on the main study were allocated without conscious bias to two groups as follows:

Group	Number of animals	Animal numbers
Control animals	5	1580 to 1584
Test animals	10	1585 to 1594

The guinea pigs were housed in groups of five in suspended metal cages with wire mesh floors in Building R17 Room 14.

A vitamin C enriched guinea pig diet (Harlan Teklad 9600 FD2 SQC) and drinking water were provided *ad libitum*. Hay was given thrice weekly. The batch of diet used for the study was analysed for nutrients, possible contaminants or micro-organisms, likely to be present in the diet, and which, if in excess, may have had an undesirable effect on the test system. The certificates of analyses were lodged in Huntingdon Life Sciences Limited Archives and are presented in the report in Appendix 5. There were no known contaminants present in the diet that were expected to be capable of interfering with the study outcome.

The water supplied to Huntingdon Life Sciences by Anglian Water was potable water for human consumption. Anglian Water takes its guidelines on water quality from the EEC directive relating to water for human consumption (80/778/EEC) and conforms to the United Kingdom Water Act 1989 and subsequent amendments. Results of routine physical and chemical examination of drinking water, as conducted by the supplier, are made available to Huntingdon Life Sciences Ltd. as quarterly summaries. These results of water analyses are lodged in Huntingdon Life Sciences Limited Archives and are presented in the report as Appendix 6. There were no known contaminants present in the water that were expected to be capable of interfering with the study outcome.

During the experimental period, the animal room temperature was maintained within the range 18 to 24°C and relative humidity within the range 29 to 63%. These environmental parameters were recorded daily. Lighting was controlled by means of a time switch to give 12 hours of artificial light (0700 - 1900 hours) in each 24-hour period.

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Each animal was identified by ear tattoo number. This number was unique within the Huntingdon Life Sciences Acute Toxicology Department throughout the duration of the study. Each cage was identified by a coloured label displaying the study schedule number, animal numbers and the initials of the Study Director and Home Office licensee.

### POSITIVE CONTROL

The sensitivity of the guinea pig strain used is checked periodically at Huntingdon Life Sciences Ltd. with known sensitisers hexyl cinnamic aldehyde (HCA) or 2-mercaptopbenzothiazole (MBT). The results of the most recent test are presented in Appendix 3.

### TEST SUBSTANCE PREPARATION

A solubility trial showed that I ; fanned an emulsion in sterile water; therefore, water was selected as the vehicle for the study.

The test substance was prepared prior to each application on the day of dosing in sterile water. The concentrations used are described in the treatment procedure.

The absorption of the test substance was not determined.

Characterisation of the homogeneity, stability and purity of the test substance were not undertaken by this laboratory and were the responsibility of the Sponsor.

### TREATMENT PROCEDURE

#### Preliminary study

The intradermal and topical irritancy of a range of dilutions of the test substance was investigated to identify where possible (a) concentrations of the test substance that would produce irritation suitable for the induction phase of the main study and (b) a maximum non-irritant concentration by the topical route of administration for the challenge phase.

The animals for the topical irritancy investigations were pre-treated with an intradermal injection of Freund's complete adjuvant, 50 : 50 with water for irrigation' (Ph.Eur.), approximately one week prior to the start of the preliminary investigations.

The procedure employed for these investigations was as follows:

<sup>1</sup> Also known as sterile water

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**Intradermal injections** - Intradermal injections (0.1 ml/site) were made into the clipped flank of two guinea pigs, using a range of concentrations (0.1 to 10% w/v) of \_\_\_\_\_ in a suitable vehicle (sterile water). The resulting dermal responses were assessed approximately 24 and 72 hours later.

**Topical application** - Patches of Whatman No. 3 paper (20 mm x 20 mm) were saturated (volume approximately 0.2 ml per patch) with a range of concentrations (10 to 75% v/v) of \_\_\_\_\_ in a suitable vehicle (sterile water) and applied to the clipped and shaved flanks of each of four guinea pigs. The patches were covered by a strip of "Blenderm" and firmly secured by "Elastoplast" wound round the trunk and covered with "Sleek" impervious plastic adhesive tape. The dressings were removed after an exposure period of approximately 24 hours and the reaction sites were assessed for erythema and oedema. Further examination of the sites was carried out approximately 24 and 48 hours after removal of the dressings.

The numerical values given to the dermal reactions observed in the preliminary tests are shown in Appendix 2.

#### Selection of concentrations of test substance for the main study

Based on the results of the preliminary investigations, the following concentrations of \_\_\_\_\_ were selected:

**Induction intradermal injection** - 0.5% v/v in sterile water

This was the highest concentration that caused slight skin irritation but did not adversely affect the animals.

**Induction topical application** - 50% v/v in sterile water

This was the highest concentration that produced mild to moderate skin irritation but did not adversely affect the animals.

**Topical challenge** - 10 and 5% v/v in sterile water

From preliminary investigations 10% v/v in sterile water was the highest concentration not giving rise to irritating effects.

#### Main study

The procedure may be considered in two parts. Induction and Challenge.

##### Induction

**Induction intradermal injections - test animals**

A 40 x 60 mm area of dorsal skin on the scapular region of the guinea pig was clipped free of hair with electric clippers. Three pairs of intradermal injections (0.1 ml/site) were made into a 20 x 40 mm area within the clipped area as shown in Figure 1.

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Injectables for the test animals were prepared as follows:

1. Freund's complete adjuvant\*\* was diluted with an equal volume of water for irrigation (Ph.Eur.).
2. , 0.5% v/v in sterile water.
3. 0.5% v/v in a 50 : 50 mixture of sterile water and Freund's complete adjuvant.

\*\* Sigma, St. Louis, Missouri, U.S.A.

#### Induction topical application - test animals

One week after the injections and one day prior to test substance application, the same 40 x 60 mm interscapular area was clipped and shaved free of hair.

A 20 x 40 mm patch of Whatman No. 3 paper was saturated with approximately 0.4 ml of , 50% v/v in sterile water. The patch was placed on the skin of the test animals and covered by a length of impermeable plastic adhesive tape (50 mm width "Blenderm"). This in turn was firmly secured by elastic adhesive bandage (50 mm width "Elastoplast") wound round the torso of the animal and fixed with "Sleek" impervious plastic adhesive tape. The dressing was left in place for 48 hours.

#### Induction - control animals

During the induction phase, the control animals were treated similarly to the test animals with the exception that the test substance was omitted from the intradermal injections and topical application.

The dermal reactions observed for test and control animals 24 hours after the intradermal injections and on removal of the bandages for the induction topical application are shown in Table I.

#### Challenge

##### Challenge - control and test animals

The control and test animals were challenged topically two weeks after the topical induction application using , 10 and 5% v/v in sterile water.

Hair was removed by clipping and then shaving from an area on the left flank of each guinea pig. A 20 x 20 mm patch of Whatman No. 3 paper was saturated with approximately 0.2 ml of , 10% v/v in sterile water and applied to an anterior site on the flank.

, 5% v/v in sterile water was applied in a similar manner to the posterior site. The patches were sealed to the flank for 24 hours under strips of "Blenderm" covered by "Elastoplast" wound round the trunk and secured with "Sleek".

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## OBSERVATIONS

### Clinical signs

All animals were observed daily for signs of ill health or toxicity.

### Body weight

The body weight of each guinea pig on the main study was recorded on Day 1 (day of intradermal injections) and after the last day observations were made of dermal responses to the challenge application.

### Dermal reactions

The dermal reactions resulting from intradermal injection and topical application on the preliminary study, and topical application at the challenge were assessed using the following numerical system:

#### Erythema and eschar formation:

No erythema	0
Slight erythema	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (bright redness) to slight eschar formation (injuries in depth)	.4

#### Oedema formation:

No oedema	0
Slight oedema	1
Well-defined oedema (edges of area well-defined by definite raising)	2
Moderate oedema (raised approximately 1 millimetre)	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure)	4

The approximate diameter (mm) of the dermal reaction at the intradermal injection sites was recorded in the preliminary study only to assist in the choice of concentrations for the main study.

Any lesion not covered by this scoring system was described.

The challenge sites were evaluated 24 and 48 hours after removal of the patches.

On completion of the study all animals were sacrificed by cervical dislocation.

## INTERPRETATION OF THE RESULTS

Dermal reactions in the test animals elicited by the challenge application were compared with the findings simultaneously obtained in the control animals.

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A test animal was considered to show positive evidence of delayed contact hypersensitivity if the observed dermal reaction at challenge was definitely more marked and/or persistent than the maximum reaction seen in animals of the control group.

If the dermal reaction seen in a test animal at challenge was slightly more marked and/or persistent than (but not clearly distinguishable from) the maximum reaction seen in control animals, the result for that test animal was classified as inconclusive.

A test animal was considered to show no evidence of delayed contact hypersensitivity if the dermal reaction resulting from the challenge application was the same as, or less marked and/or persistent than the maximum reaction seen in animals of the control group.

## ARCHIVES

All raw data and study related documents generated during the course of the study at Huntingdon Life Sciences, together with the original final report will be lodged in the Huntingdon Life Sciences Ltd. Archive, Huntingdon.

Such records will be retained for a minimum period of five years from the date of issue of the final report. At the end of the five year retention period the Client will be contacted and advice sought on the future requirements. Under no circumstances will any item be discarded without the Client's knowledge.

## DEVIATIONS FROM PROTOCOL

On occasion the temperature/humidity of the animal room was outside the range given in the protocol; however, this deviation was not considered to have had an adverse effect on the animals or to have affected the integrity or validity of the study.

The terminal body weight was recorded four days after the final observation of the challenge application. However, as all animals gained weight during the treatment period, the integrity and validity of the study was not affected.

There were no other deviations from the protocol.

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## RESULTS

### CLINICAL SIGNS

No signs of ill health or toxicity were observed.

### BODYWEIGHT

Individual body weights are shown in Appendix 1.

Body weight increases were recorded for all guinea pigs over the period of the study.

### INDUCTION

Dermal reactions seen following the induction applications are summarised in Table 1.

#### Intradermal injections

Necrosis was observed at sites receiving Freund's Complete Adjuvant in test and control animals.

Slight irritation was seen in test animals at sites receiving \_\_\_\_\_, 0.5% v/v in sterile water and slight irritation was observed in control animals receiving sterile water.

#### Topical application

No erythema was observed in test animals following topical application with \_\_\_\_\_ 50% v/v in sterile water.

No erythema was seen in the control animals.

### CHALLENGE

The numerical values given to the dermal reactions elicited by the challenge applications are shown in Table 2.

There were no dermal reactions seen in any of the test or control animals; therefore, all ten test animals gave negative responses.

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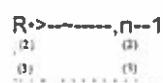
## CONCLUSION

In this study did not produce evidence of skin sensitization (delayed contact hypersensitivity) in any of the ten test animals. Based on the findings of this study, does not require labelling with the risk phrase R43 "may cause sensitisation by skin contact" in accordance with Conunission Directive 93/2 I/EEC.

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FIGURE 1

Position of intradermal injections and topical induction application



The rectangle outlines the 20 x 40 mm clipped scapular area in which injections were made and to which the topical induction application was made one week later.

Control animals:

- (1) 0.1 ml of Freunds complete adjuvant 50: 50 with water for irrigation (Ph.Eur.).
- (2) 0.1 ml of sterile water.
- (3) 0.1 ml of Freund's complete adjuvant 50 : 50 with sterile water.

Test animals:

- (1) 0.1 ml of Freunds complete adjuvant 50 : 50 with water for irrigation (Ph.Eur.).
- (2) 0.1 ml of , 0.5% v/v in sterile water.
- (3) 0.1 ml of , 0.5% v/v in a 50: 50 mixture of sterile water and Freund's complete adjuvant.

A volume of 0.1 ml was injected into both the left and right injection sites.

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TABLE I

Dermal reactions observed after each induction

Group	Guinea pig number	Intradermal injections			Topical application
		Site number	1	2	
Control	1580	N	I	N	0
	1581	N	I	N	0
	1582	N	I	N	0
	1583	N	I	N	0
	1584	N	I	N	0
Test	1585	N	I	N	0
	1586	N	I	N	0
	1587	N	I	N	0
	1588	N	I	N	0
	1589	N	I	N	0
	1590	N	I	N	0
	1591	N	I	N	0
	1592	N	I	N	0
	1593	N	I	N	0
	1594	N	I	N	0

## Intradermal injections

Control animals: See figure 1 (previous page)  
 Test animals: See figure 1 (previous page)

## Topical application

Control animals: sterile water  
 Test animals:  
 50% v/v in sterile water

- N Necrosis
- 0 No irritation
- I Slight irritation
- 2 Well-defined irritation
- 3 Moderate irritation
- 4 Severe irritation

- 0 No erythema
- I Slight erythema
- 2 Well-defined erythema
- 3 Moderate erythema
- 4 Severe erythema

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TABLE 2

Dermal reactions observed after the challenge application with  
 Freunds treated controls

Guinea pig number	E = Erythema O= Oedema	Score			
		24 Hours		48 Hours	
		A	P	A	P
1580	E	0	0	0	0
	O	0	0	0	0
1581	E	0	0	0	0
	O	0	0	0	0
1582	E	0	0	0	0
	O	0	0	0	0
1583	E	0	0	0	0
	O	0	0	0	0
1584	E	0	0	0	0
	O	0	0	0	0

A Anterior site, exposed to  
 P Posterior site, exposed to

, 10% v/v in sterile water  
 , 5% v/v in sterile water

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TABLE 2

Dermal reactions observed after the challenge application with  
(continued)

## Test animals

Guinea pig number	E = Erythema O = Oedema	Score				Results Positive (+) Negative (-) Inconclusive (±)
		24 Hours		48 Hours		
		A	P	A	P	
1585	E	0	0	0	0	-
	O	0	0	0	0	-
1586	E	0	0	0	0	-
	O	0	0	0	0	-
1587	E	0	0	0	0	-
	O	0	0	0	0	-
1588	E	0	0	0	0	-
	O	0	0	0	0	-
1589	E	0	0	0	0	-
	O	0	0	0	0	-
1590	E	0	0	0	0	-
	O	0	0	0	0	-
1591	E	0	0	0	0	-
	O	0	0	0	0	-
1592	E	0	0	0	0	-
	O	0	0	0	0	-
1593	E	0	0	0	0	-
	O	0	0	0	0	-
1594	E	0	0	0	0	-
	O	0	0	0	0	-

A Anterior site, exposed to  
P Posterior site, exposed to

, 10% v/v in sterile water  
, 5% v/v in sterile water

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## APPENDIX!

### References

EEC Methods for the Determination of Toxicity, Annex to Directive 96/54/EC (Official Journal No. L248, 30.9.96), Part B, Method B.6. "Skin sensitization".

EC Council Directive 87/18/EEC of 18 December 1986 (Official Journal No L 15/29) and, from 1 May 1999, EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No. L 77/8).

OECD Guideline for Testing of Chemicals No. 406 "Skin sensitization". Adopted 17 July 1992.

Magnusson, B. and Kligman, A.M. (1970) *Allergic Contact Dermatitis in the Guinea pig: Identification of contact allergens*, Thomas, C.C., Springfield, Illinois, U.S.A.

OECD Principles of Good Laboratory Practice (as revised in 1997) ENV/MC/CHEM(98)17.

The United Kingdom Good Laboratory Practice Regulations 1997 (Statutory Instrument No. 654).

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## APPENDIX 2

## Individual body weights (g)

Group	Guinea pig number	Day I 13 April 1999	Last observation day 11 May 1999
Control	1580	342	620
	1581	345	590
	1582	330	624
	1583	371	662
	1584	323	580
Test	1585	352	579
	1586	344	602
	1587	364	618
	1588	397	701
	1589	395	626
	1590	370	634
	1591	402	631
	1592	361	656
	1593	346	581
	1594	374	535

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## APPENDIX 3

Results of preliminary investigations with  
Intradermal injections

Vehicle: Sterile water

Guinea pig number	Concentration %v/v	Score			Guinea pig number	Concentration %v/v	Score		
		Hours	24	72			Hours	24	72
1540	10.0	D	10	10	1541	10.0	D	10	10
		E	N	N			E	N	N
		0	2	2			0	2	2
	7.5	D	10	10			D	10	10
		E	N	N			E	N	N
		0	2	2			0	2	2
	5.0	D	10	10			D	9	10
		E	N	N			E	N	N
		0	2	2			0	2	2
	2.5	D	9	10			D	9	9
		E	N	N			E	N	N
		0	2	2			0	2	2
	1.0	D	9	9			D	9	9
		E	2	SLN			E	N	N
		0	2	2			0	2	2
	0.5	D	8	9			D	9	9
		E	2	2			E	2	2
		0	2	2			0	2	2
	0.25	D	5	5			D	9	8
		E	1	1			E	2	1
		0	1	1			0	2	1
	0.1	D	5	4			D	5	4
		E	1	1			E	1	1
		0	1	1			0	1	1
Vehicle control	D	5	4		Vehicle control	D	5	4	
	E	1	1			E	1	1	
	0	1	1			0	1	1	

Key:

- D Diameter (mm)
- E Erythema (0 - 4 numerical scores)
- O Oedema (0 - 4 numerical scores)
- SLN Slight necrosis
- N Necrosis

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## APPENDIX 3

Results of preliminary investigations with  
(continued)

## Topical application

## Vehicle: sterile water

Guinea pig	Concentration	Score		
		0 Hours	24 Hours	48 Hours
number	%v/v	E	E	E
1542	75	#2	2	NP2
	50	1	0	0
	20	1	1	0
	10	0	0	0
1543	75	#2	2	NP2
	50	1	1	0
	20	1	1	0
	10	0	0	0
1544	75	#2	2	NP2
	50	1	1	0
	20	1	1	0
	10	0	0	0
1545	75	#2	2	NP2
	50	1	1	1*
	20	1	1	0
	10	0	0	0

E Erythema (0 - 4 numerical scores)

O Oedema (0 - 4 numerical scores)

# Blanching of the dose site

\* Dryness and sloughing of the epidermis

N Necrosis

NP Necrotic patch

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#### APPENDIX4

##### Summary of positive control data

###### Skin sensitization positive control study with hexyl cinnamic aldehyde (HCA) to the Magnusson & Kligman method (Sch. No. HLS/069)

This study was performed to confirm the sensitivity and reliability of the experimental technique used at Huntingdon Life Sciences to detect skin sensitization potential. The study was performed using the guinea pig and a known weak/moderate sensitizer - hexyl cinnamic aldehyde (HCA). The method followed was that described in MAGNUSSON, B. and KLIGMAN, A.M. (1970) *Allergic Contact Dermatitis in the Guinea pig: Identification of contact allergens*, Thomas, C.C., Springfield, Illinois, U.S.A.

This positive control study was conducted between 22 December 1998 and 15 January 1999 using fifteen guinea pigs of the Dunkin Hartley strain supplied by D Hall, Staffs, UK.

Based on preliminary investigations previously conducted at this laboratory, the following concentrations of HCA were administered:

Intradermal injection:	10 % v/v in Alembicol D
Topical application:	As supplied (neat)
Challenge application:	As supplied (neat) and 50% v/v in Alembicol D

#### RESULTS

##### INDUCTION

###### Intradermal injections

Necrosis was recorded at all sites receiving Freund's Complete Adjuvant.

Slight irritation was seen in test animals at sites receiving HCA, 10% v/v in Alembicol D and slight irritation was observed in control animals receiving Alembicol D.

###### Topical application

Slight to well-defined erythema was observed in test animals following topical application with HCA, as supplied. Slight to well-defined erythema was seen in the control animals receiving Alembicol D.

##### CHALLENGE

Slight to well-defined dermal reactions were observed for all ten test animals compared to no dermal reaction in the control animals. Therefore all ten test animals gave positive sensitization responses.

##### CONCLUSION

In this study HCA produced evidence of skin sensitisation (delayed contact hypersensitivity) in all of the ten animals, thus confirming the sensitivity and reliability of the experimental technique.

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## APPENDIX4

## Summary of positive control data

continued

## Individual dermal reactions after challenge application of HCA

Guinea pig number	E = Erythema 0 = Oedema	CONTROL ANIMALS				Results Positive (+) Negative (-) Inconclusive (±)	
		Score		Score			
		24 Hours		48 Hours			
		A	P	A	P		
6190	E	0	0	0	0		
	0	0	0	0	0		
6191	E	0	0	0	0		
	0	0	0	0	0		
6192	E	0	0	0	0		
	0	0	0	0	0		
6193	E	0	0	0	0		
	0	0	0	0	0		
6194	E	0	0	0	0		
	0	0	0	0	0		
TEST ANIMALS							
Guinea pig number	E = Erythema 0 = Oedema	Score		Score			
		24 Hours		48 Hours			
		A	P	A	P		
6195	E	1	1	2	1	+	
	0	1	0	20	0*		
6196	E	1	1	2	1	+	
	0	1	0	10	0*		
6197	E	1	1	2	1	+	
	0	1	0	2*	0		
6198	E	2	1	2	1	+	
	0	1	1	10	0*		
6199	E	1	1	1	1	+	
	0	0	0	1*	0*		
6200	E	1	0	1	1	+	
	0	0	0	10	0*		
6201	E	1	1	1	1	+	
	0	2	1	10	10		
6202	E	1	1	1	1	+	
	0	0	0	0	0		
6203	E	1	1	1	0	+	
	0	1	0	0*	0		
6204	E	1	1	1	1	+	
	0	0	0	0*	0*		

\* Dryness and sloughing of the epidermis

0 Thickening, dryness and sloughing of the epidermis

A Anterior site, exposed to HCA as supplied

P Posterior site, exposed to HCA 50% v/v in Alembic D

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**APPENDIX 5**  
Certificate of analysis for diet

**Harlan  
TEKIAD**

**Certificate of Analysis**

Diet. Barillo Teklad 9600FD2  
Date of Manufacture: 26.02.99

Batch Number: F041  
Certificate Number: 120965/111093

Moisture	9.5 %	12 S	0.1%	C/801
Protein (N x 6.25)	18.7 %	175	21 S	0.1% C/224
Oil (Acid Hydrolysis)	5.0 %	4	6	0.1% C/102
Crude Fibre	12.5 %	9	14	0.2% C/30[
	6.8169 %	7	9 RF VIEW	0.1% C/803
Calcium	1.08%	0.75	1.75	40mo.h C/601
Phosphorus	0.71 %	0.5	0.9	250m. n C/620
Iron	0.11 %	(1.15	0.35	Imo. < C/620
Sodium	0.36 %	0.25	0.45	Sm< " C/601
Potassium	1.15 %	0.9	1.5	20mru < C/601
Chloride	0.72 %	0.5		150mru " C/803
Zinc	76.1 mg/kg	50	90	2m. < C/611j
Manganese	110 mg/kg	80	110	4me Irc C/620
Copper	10.8 mg/kg	8	20	4ml/kg C/620
Iron	210 ppm	150	400	2ml/mg C/620
Vitamin A	19.4 IU/g	14	28	0.25mcg C/702
Vitamin E	114 IU/g	50	ISO	1.0mIU C/702
VitaminC#	3100 mMC	1500		5mU " C/710
Nitrate#	159 mg	1000	Sm!le2	C/134
Nitrite#	0.1 mg/kg	5	0.1mg/kg	(n3S
Selenium#	0.37 mg	0.5	0.02	C/610
Arsenic	0.41 mg/kg	1	0.1mg/kg	C/616
Cadmium	0.1 mg/kg	0.4	0.07mg/kg	C/604
Lead	0.66 mg/kg	3	0.05mg/kg	C/604
Macrovit	0.02 mg	0.1	0.01mg/kg	C/606
Auoridel	22.8 mg/kg	40	1*****	na
Total DDT	nd mg/kg	0.1	0.05mcg	R/1 10
Oieldrin	nd mg/kg	0.02	0.01mg/kg	R/1 10
Lindane	nd mg/kg	0.1	0.01mg/kg	R/1 10
HCOlaehlor	nd mg/kg	0.05	0.01mg/kg	R/1 10
Malathion	nd mg/kg	0.5	0.05mg/kg	R/1 10
		ns	<0.05mg/kg	R/1 10
Total PCBs#	nd mg/kg	0.25		
Total Ahaloxins	nd mg/kg	5	0.1mg/kg	C/927
Total Viable Count	39 000 cfu/g	1000000	<10cfu/g	M/312
Mycobacterium	41,000 cfu/g	000,000	<10cfu/g	M/329
Salmonella	nd mpn/g	0	mpn/g	M/351
Coliforms	nd mpn/g	5	<5cfu/g	M/3 II
E.coli	nd mpn/g	0	mpn/g	M/304
Fungi/Soil	25 IU/g	300	mpn 10g	M/315
AntibioticActiviry	...all	1	10	M/358

Data checked

Date

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## APPENDIX 5

## Certificate of analysis for diet

continued

Page 2 of 2

## Multi-Residue Screen

Certificate Number: 111093

Diet: Harlan Teklad 9600FD2

Batch Number: F041

Date of Manufacture: 26.02.99

Organophosphorus	Level (ug/kg)	LOD (ug/kg)	Organochlorine	Lcvd (ug/kg)	WD (ug/kg)	Others (cOlt.)	-LOD (ug/kg)
Aziphos	nd	\$0	Aldrin	nd	20	Carbouran	nd 50
Azinphos Methyl	nd	\$0	Dieldrin	nd	20	Qubosulphan	nd \$0
Bromophos Ethyl	nd	\$0	Chlordane	od	20	Chlobufam	nd 50
Bromophos Methyl	nd	\$0	DDT	rul	20	Chlorothalonil	nd \$0
Carbophenothion	nd	\$0	Endosulphan	nd	20	chloroxuron	nd 50
Chlorfenvinphos	nd	\$0	Eldrin	nd	20	Chlorpropham	nd 50
Chlorpyrifos	nd	\$0	Heptachlor	nd	20	Cobjenfon	nd 50
Chlorpyrifos Methyl	nd	\$0	Heptachlorobenzene (HCB)	nd	20	Dichlofluanid	nd 50
DcmdO!!-S-Methyl	nd	\$0	Heptachlorocyclohexane + a	nd	20	Dicloron	nd 50
Diazinon	nd	\$0	Heptachloroxydihexane + II	nd	20	Diofol	nd \$0
Pichloros	nd	\$0	Hexachlorocyclohexane + I	nd	20	Etiophon	nd 50
Omcloatec	nd	\$0	Hexachlorocyclohexane + O	nd	20	Ethoxyquill	nd 50
Disulfoton	nd	\$0				Etridiamle	nd \$0
Ethion	nd	\$0				Fluoxypy	nd \$0
Etrimsos	nd	\$0	Trinilles			Imazalil	nd 50
Fenchlophos	nd	\$0				Iprodione	nd 50
Fenthion	nd	\$0	Altrazine	nd	50	Melalalyl	nd 50
Fluazifop-p-Butyl	nd	\$0	Bentazon	nd	50	Methabenhaiiziron	nd 50
Fonopbos	nd	\$0	Cyanazine	Pd	50	Methomyl	nd 50
Heptochophos	nd	\$0	Prometryn	nd	50	Me thoxychlor	ad 50
Iodoso npbos	nd	\$0	Simazine	nd	50	Metc'buzin	nd 50
Malathion	nd	\$0	Terbuthylazine	nd	50	Oxadixyl	nd 50
Melhacrisos	nd	\$0	Terbutryn	nd	50	Qxamyl	nd 50
Metbamidopbos	nd	\$0				Pendimetalin	nd 50
Methidialphon	nd	\$0	Pyrebtroids			Pentachloroaniline (PCA)	nd 20
Mevinphos	nd	\$0				Pentachlorobenzene (PCB)	nd 20
Omclohole	nd	\$0	Cyfluhrin	nd	50	Pentachlorophenol (PCP)	nd \$0
Pami thio!!	nd	\$0	Cyhalothrin	nd	50	Pririmicarb	nd 50
Parathion Methyl	nd	\$0	Cypermehrin	nd	50	Procymidone	nd 50
Pborale	nd	\$0	Deltamethrin	nd	50	Propachlor	od 50
Pbosalone	nd	\$0	Fenvalcrate	ml	50	Propbam	od 50
Pbasphamidoo	nd	\$0	Permethrin	nd	50	Quinolozene	nd 20
Pirimiphos Methyl	1300	\$0				Sulfo'ep	nd \$0
Quinalphos	nd	\$0	Others			Tecnazene	nd 20
Tluometon	nd	\$0	Acephate	nd	50	Tetradifon	ad 50
Tolchnos Melby!	nd	\$0	BenJaxyl	nd	50	Tbiabelliazole	nd 50
Tri amphos	nd	\$0	Bitertianc>I	nd	50	Tolyfuanid	nd \$0
Tri-hlorfol	nd	\$0	Bupirimalc	nd	50	Triadimen->I	nd 50
'vamidothion	nd	\$0	Captan	nd	50	TriflU13lin	nd 50
			Captafol	nd	50	Vinclozolin	nd \$0
			Ca.aryl	nd	50		

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## APPENDIX 5

### Certificate of analysis for diet continued

# Harlan

16 April 1999

Dear Customer,

9600 FD2 Batch F041

The ash level in this batch of diet is marginally below the action limit. The analysis has been repeated and confirmed both values are shown in the certificate. The deviation is so small that there is not likely to be any adverse effect on the study. You will note that the individual elements are within specification.

Checking the statistics for FD2, from 52 samples the average ash value has been 7.6% with a standard deviation of 0.42. On that basis the actual action limit ( $3 \times \text{sd}$ ) should be in the region of 6.3 - 8.9%. This means that the lower action limit is probably too high. I recommend that we should consider adjusting the action limits to a range of 6.5 to 9%.

As you will appreciate, when setting up action limits before having much data, one has to make some assumptions on the likely spread of 'normal' data. In this case we have probably got the estimate slightly wrong.

I apologise for any inconvenience but if you have any further questions do not hesitate to contact me.

Yours sincerely

Technical Manager  
Harlan Teklad

MNI 005/993254/SS

## APPENDIX 6

## Water analyses results

## ANALYTICAL DATA SUMMARY SHEETS

## Huntingdon North Public Water Supply Zone

Ref	Parameter	PCV	Units	Number of Samples	No samples contravening	Concentration or Value (all samples)			Zone Code - FW40 Grd Ref - TI (45735)
						PCV		Minimum	
						Mean	Median	Minimum	
A001	Colour	20	Pt/Co	6	R	0	<1	c 1.87	3.5
I001	Turbidity	4	FTU	34		0	0.07	<0.07	0.08
A003	Odour	0.003	OBNO	4	R	0	<0	<0	<0
A03a	Odour - Nature			34			1	1	
A03b	Odour - Intensity			34			<0	<0	
A004	Taste			4	R	0	1	1	
A04a	Taste - Neutral			34			1	1	
A04b	Taste - Intensity			34			<1	<1	
A05	Temperature	25	°C						18.2
A06	Hydrogen ion (pH)	5.5 - 9.5	pH	34	R	0	4.9	11.1	8.1
A007	Sulphate	250	mg/l			0	7.74	7.86	50.5
B008	Magnesium	50	mg/l			0	134	134	+8.6
X009	Sodium	150	mg/l			0	105	8.05	0
AG1A	Sodium > 10 <sup>-3</sup>	150	mg/l			0	48.6	48.6	9.03
A010	Potassium	12 (15)	mg/l	31	X	0	0	65.5	64.0
A011	Oil Residues	1500	mg/l	1		0	6.89	8.23	35.6
A012	Nitrate	50	mg/l	6		0	640	-0	0.207
A013	Nitrite	0.1	mg/l	28		0	29.6	33	0.132
A014	Ammonium	0.5	mg/l	6		7.14	c 0.01	<0.027	1.72
A016	Oxidability	5	mg/l			0	0.219	0.228	3.99
AD17	Total organic carbon	200	mg/l			0	1.22	1.72	<10
A021	Ammonium	200	mg/l		R	0	3.99	3.99	13
A022	Iron	200	mg/l	6	RU	0	c 10	<10	
A023	Manganese	50	µg/l	7	R	0	<10	<11	14
A024	Copper	3000	µg/l	6	R	0	<2	<3.71	288
A025	Zinc	5000	µg/l	6	R	0	c 5	<54	14.1
A026	Phosphorus	2201	µg/l	20		0	<6	<7.71	620
A027	Fluoride	1500	µg/l			0	370	498	250
A028	Silicon	10	µg/l			0	250	250	<
B001	Ascorbic acid	50	mg/l			0	<1	<1	149
B002	Cadmium	5	µg/l			0	1.49	1.49	<0.4
BO01	Cyanide	50	µg/l			0	c 4	<0.4	c 1
Y001	Chromium	50	mg/l			0	<2	<2	<11
BO02	Urea	1	mg/l			0	<1.1	<1.1	<0.1
Y006	Nickel	50	µg/l			0	<0.1	<0.1	3.14
						0	3.14	3.14	<
B007	Lead	50	µg/l	6	R	0	<1.9	<1.9	1.9
B008	Antimony	10	µg/l			0	0.49	0.49	0.49
Y0Q9	Selenium	10	µg/l	1		0	1.1	1.1	1.1
P014	Chlorotoluuron	0.1	µg/l	9		0	<0.02	<0.02	c 0.01
P032	Diuron	0.1	µg/l			0	<0.02	<0.02	<0.01
P048	Isoproturon	0.1	µg/l			0	<0.02	<0.02	<0.02
P051	Unuron P113	0.1	µg/l	9		0	c 0.02	<0.02	<0.02
Monuron P074		0.1	µg/l	9		0	<0.02	<0.02	<0.02
2,3,6-TBA P020		0.1	µg/l	8		0	<0.05	<0.05	<0.05
2,4-D		0.1	µg/l	8		0	<0.03	<0.02	<0.01
P076	2,4,5-T	0.1	µg/l	8		0	<0.05	<0.05	<0.05
P096	Acetochlor	0.1	µg/l	8		0	<0.03	<0.02	<0.01
P025	Olefim	0.1	µg/l	8		0	<0.05	<0.05	c 0.0-
P028	Dichloroprop	0.1	µg/l	8		0	<0.02	<0.02	<0.02
P054	MCPA	0.1	µg/l	1		0	<0.02	<0.02	<0.02
P055	MCPB	0.1	µg/l	8		0	<0.05	<0.05	<0.05
P053	MCPB(M<sup>2+</sup>coprop)	0.1	µg/l	F		0	<0.02	<0.02	<0.02
P004	Atrazine	0.1	µg/l	17		0	<0.02	<0.02	c 0.02

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## APPENDIX6

## Water analyses results

continued

## ANALYTICAL DATA SUMMARY SHEETS

## Huntingdon North Public Water Supply Zone

Ref	Name	Population - 16288		01-Jan-99	30-Jun-99	Zone Codes - FW40		
		POI	Units	Number of samples	% samples contravening PCV	Concentration or Value (all samples)	Grid Ref	TL245735
						Minimum	Mean	Maximum
P070	Perm-tryll<	0.1	µg/l	11	0	<0.02	<0.02	<0.02
PG66	PropulitM	0.1	µg/l	11	0	<0.02	<0.02	<0.02
P013	Simaxine	0.1	µg/l	11	0	<0.02	<0.02	<0.02
P077	Tertbutyne	0.1	1µm	11	0	<0.02	<0.02	<0.02
P11	Tetra1zne	0.1	1µm	11	0	<0.02	<0.02	<0.02
R010	Peruodes Total	0.5	ppm	11	0	0	0.015	0.03
B010	PAH	0.2	ppt	11	0	0	0	0
C004	Total Coliforms	0	No/dl	10	0	0	0	0
CO01	Coliform	0	No/1l	50	0	0	0	0
co05	Colony Count 1 Day O J7T		No/ml	50		0	0.9	5
co07	Colony Count 7 Day O 22-c		No/ml	50		76.8	85.5	
ca10	Chlorine Total		mg/l	50		0.15	0.616	0.94
O014	Conductivity + M12	1500	µS/cm	24	0	807	817	832
O024	Chloride + M12	400	mg/l	24	0	65.9	65.9	65.9
O024	Chlorine - M12	250	mg/l	24	0	140	140	140
O054	Boron - M12	2000	µg/l	24	0	244	244	244
O064	Bromum + M12	1000	1µ-	24	0	14.3	14.8	14.8
O074	Benzzo34 pyrene+ M12	10	ngA	1	0	5	5	5
O084	Tetachloromethane-M12	3	µg/l	6	0	0.1	0.1	0.1
O094	Trikloro-thene + M12	30	1µg/l	6	0	0.4	0.4	0.4
O114	Tetr-chlotoethene M12	10	µg/l	6	0	0.3	0.3	0.3
O114	Trihalomethane + M3	100	µg/l	24	0	25.4	25.4	25.4
E001	Hardness a<Ca + Mn		mg/l	24	149	149	149	
E002	Al-linity + HCO <sub>3</sub> Min		mg/l	24	272	272	272	

POI = Prescribed concentration or value

M12 = Rolling 12 month mean

M1 = Rolling 1 month mean

Min = PCV is= minimum only where the water is softened

U = Undertaking

X = Relaxation level value in brackets under POI column

R = Reduced sampling frequency

I = Increased sampling frequency

PAH = Polycyclic aromatic hydrocarbon

Sodium so+ = the BOth percentile of the last 3 year of sodium results

MNI 005/993254/SS

## APPENDIX 7

### Quality Control Analysis

#### Q U A L I T Y C O N T R O L A N A L Y S I S

Date: 12/1/98

Product:

Mona Order#:

Customer Order #:

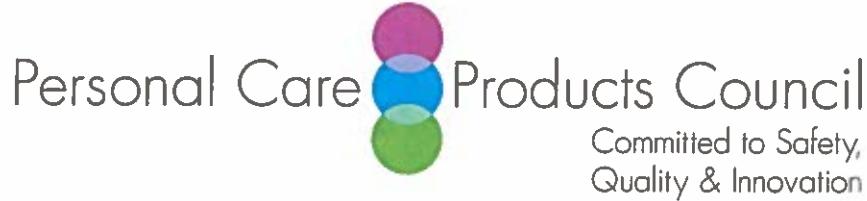
Lot# 35937

#### ANALYSIS

APPEARANCE: CLEAH LIQUID  
ALKALI NUMBER: :  
FU (10% Aq) 10.75  
COLOR( '): J

Quality Control

The ideal source for specialty chemicals



## Memorandum

**TO:** Bart Heldreth, Ph.D.  
Executive Director - Cosmetic Ingredient Review (CIR)

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** September 18, 2018

**SUBJECT:** Draft Report: Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics (draft prepared for the September 24-25, 2018 CIR Expert Panel meeting)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics.

The following comments are in addition to the comments previously provided on the SLR (many of which still need to be addressed).

Short-Term, Oral, PEG-4 Rapeseedamide - Were body weights of female rats really decreased, or was it a decrease in body weight gain? What was the adverse effect observed in male rats at the middle dose?

Table 2 - It would be helpful to include the most frequent fatty acid carbon chain lengths for the ingredients made from various plant oils.