Ethanolamine

CIR EXPERT PANEL MEETING
MARCH 5-6, 2012
Enclosed is the draft final amended safety assessment on ethanolamine and 12 ethanolamine salts. This is the last safety assessment generated from the split re-review of triethanolamine, diethanolamine, and monoethanolamine.

At the December 2011 meeting, the Panel issued a tentative amended safety assessment with a conclusion that ethanolamine and the 12 related ethanolamine salts are safe in the present practices of use and concentration (used in rinse-off products only) described in this safety assessment, when formulated to be non-irritating. The Panel cautioned that ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

It is expected that the Panel will issue a final amended safety assessment at this meeting.
*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

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

Original Report: In 1983, the Expert Panel determined that TEA, DEA, and MEA were safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. Ethanolamine (MEA) should be used only in rinse-off products. Triethanolamine (TEA) and diethanolamine (DEA) should not be used in products containing N-nitrosating agents.

December 2010: A formal rereview package was presented to the Panel for the report on TEA, DEA, and MEA
- the report was split into 3 separate documents – DEA, TEA, and MEA,
- appropriate new ingredients are to be added to each report

The Draft Amended Safety Assessment was presented to the Panel. The assessment was divided into two parts. The first part, entitled Ethanolamine and Related Ethanolamine-Containing Ingredients, included 21 ingredients for consideration for inclusion in the re-review of ethanolamine.

Part II, entitled Ethanolamides, was created so that if the Panel determined that the ethanolamides were not appropriate as part of the re-review of ethanolamine, the Panel could decide that it would be appropriate to re-review isostearamide, myristamide, and stearamide MEA (reviewed in 1995), and include these ethanolamides.

The Panel decided that the safety assessment should be split into two separate reports. The following ingredients were deleted from the report on Ethanolamine: All the protein salts, all the alkyl-substituted ethanolamines, and MEA-Dicetearyl Phosphate.

December 12-13, 2011: (Draft) Tentative Amended Safety Assessment
The draft Tentative Amended Report on Ethanolamine and Ethanolamine salts was presented to the Panel. No new data were received since the September meeting.

The Panel issued a Tentative Amended Safety Assessment with a conclusion of safe as used when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

March 5-6, 2012: (Draft) Final Amended Safety Assessment
Minor comments were received from the Council and addressed.
## Ethanolamine, Ethanolamine-Ingredients, and “Components” Data Profile

**– March 2012 – Writer, Monice Fiume**

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

# year the report was published
Keep Me Posted Results updates are received weekly

1. Searched all ingredients (except MEA) with CAS #s (38 substances) – **18,866 references**
   a. Refined by document type – **7091 references**
   b. Refined by removing documents in Chinese – **5701 references**

2. Searched MEA by CAS #
   a. Refined by document type – **14229 references**
   b. Refined by year 1980+ - **11440 references**

3. Combined results of SS 1 and 2 above - **18968 references**

4. Searched all ingredients without CAS #, refined by document type
   a. MEA laureth carboxylate – 1
   b. MEA steareth carboxylate – 0
   c. MEA talloweth – 0
   d. MEA hydrolyzed Silk – 0
   e. MEA hydrolyzed collagen – 1
   f. MEA distearyl phosphate – 0
   g. Butylethanolamine – 128
   h. Stearamidoethyl ethanolamine phosphate - 0
   i. Lysophosphatidylethanolamine – 1982
   j. Azelamide MEA – 0
   k. Cocamide methyl MEA – 0
   l. Deoxyphytantriyl Palmitamide MEA – 0
   m. Hydroxyethyl pantotheamide – 0
   n. Hydroxylpropyl MEA – 227
   o. Myristoyl/palmitoyl/oxostearamide/arachamide DEA – 0
   p. Oatamide MEA – 0
   q. Palm kernelamide MEA – 0
   r. Palmamide MEA – 0
   s. Panthothenamide MEA – 0
   t. Peanutamide MEA – 0
   u. PEG Cocamide MEA – 0

5. Combined SS 3 and all results of SS 4 – **18413 references**

6. Applied the following qualifiers to SS 5 above
   a. Carcinogen – **593**
   b. Mutagen – **79**
   c. Teratogen – **15**
   d. Developmental toxicity – **56**
   e. Reproductive toxicity – **8**
   f. Dermal – **46**
   g. Toxicology – **728**
   h. Ocular – **164**
   i. Irritation – **86**
   j. Sensitization – **119**
   k. Photosensitization – **59**
   l. ADME – **7**
   m. Dermal absoroption – **4**
   n. Excretion – **70**
   o. Pharmacokinetics – **116**
   p. Kidney renal – **219**
   q. Choline deficiency – **20**
   r. Nitrosation – **53**

7. Combined all of SS 6 – **2032 references**
SEARCH STRATEGY – TEA/DEA/MEA

TOXLINE  | PUBMED  | EU
---|---|---
Jan 17, 2010
**DEA**
111-42-2 & choline  | 13  | 15  
111-42-2 & carcinogen*  | 83  | 21  
choline & deficiency & human & cancer  | 38  |  
**TEA**
102-71-6 & carcinogen*  | 55  | 11  
102-71-6 & choline  | 5  | 2  
**MEA**
Jan 25, 2010
102-71-6 OR 111-42-2 (1980-current)  | 1003 (downloaded 58)  |  

**UPDATED SEARCH – May 31, 2010**

(102-71-6 OR 111-42-2 OR 141-43-5) AND (REPRODUCTI* OR TERATOGEN*) – 142 (Toxline); 41 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (DEVELOPMENT* OR FETOTOX*) – 378 (Toxline); 47 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND TOX*  

(102-71-6 OR 111-42-2 OR 141-43-5) AND (GENOTOX* OR MUTAGEN* OR CLASTOGEN*) – 286 Toxline); 7 (DART); 9 (CCRIS)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (SENSITIZA* OR SENSITIZE* OR SENSITIS* OR IRRIT*) – 306 (Toxline); 6 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (METBOLI* OR ABSORB* OR ABSORP* OR DISTRIBUT* OR EXCRET*) – 403 (Toxline); 18 (DART)

141-43-5 AND CARCINOGEN* – 193

141-43-4 AND CHOLINE - 0

Total Download (most duplicates removed): 1218

**UPDATED SEARCH – Sept 21, 2010 – last 12 mos**

102-71-8 OR 111-42-2 OR 141-43-5  128 hits/1 useful
DR. BELSITO: Ethanolamines. So this is a result of our breaking apart the MEA, DEA, TEA, and then creating
individual families around it.

And, again, I thought this was a very good job. I guess my only comments were that in the discussion, do we not need
the nitrosamine boilerplate?

And then, I just thought that in the document -- as was done for the others -- it would be nice to list in a table the
relevant acids, like benzoic acid, salicylic acid, yadda, yadda, yadda, that we had previously reviewed, and were found
to be safe. And I didn't see that in this document.

DR. ANDERSEN: On Panel Book page 29, Table 2.

DR. BELSITO: Oh -- I'm sorry. It was probably after I did the galactomannans that I was doing this. (Laughter)

DR. ANDERSEN: It was just a question of when that zinger was going to come.

DR. LIEBLER: I was curious, just for my own reference, whether sulfite had been ever reviewed, or had been a
component of ingredients that had been reviewed. Sulfite?

MS. FIUME: It's probably faster to find it by hand than me looking this way. I'm experimenting..

DR. LIEBLER: Okay.

MS. FIUME: But I do have a question for the nitrosation. With it being the monoethanolamine, is the nitrosation
boilerplate relevant in this report?

DR. BELSITO: I don't know.

MS. FIUME: I don't remember. I thought there was one that it was not relevant, and I don't remember which
ethanolamine --

DR. BERGFELD: This one.

MS. FIUME: Is it this one?

DR. SNYDER: I think, yes, Ron made a comment about the secondary (inaudible).

DR. BERGFELD: Unless it was a contaminant.

DR. BELSITO: But isn't there some DEA and MEA? I don't know, I'm not a chemist. I'm just pointing it out that it's
not there.

Dan, what is your feeling?

DR. LIEBLER: The only time it would become an issue is if there's a significant amount of a diethanolamine present.
And that would be as a contaminant of the ingredient -- and I'm looking for "Impurities."

Under "Impurities," Panel Book page 16, it simply says, "Ethanolamine contains a small amount of diethanolamine,"
and that quotes a previous safety assessment.

MS. FIUME: It was never quantified as to what that compound is.

DR. LIEBLER: Mm-hmm. So, I guess the question is: What level of contaminant would trigger the nitrosation
boilerplate? And I don't know if we have an --

DR. BERGFELD: Is it necessary to know? It just shouldn't have it.

DR. LIEBLER: Simply say, if it --

DR. BELSITO: Well, then, then we should put the boilerplate in.

DR. BERGFELD: Yes.

DR. LIEBLER: Okay.

DR. BELSITO: Rachel?

MS. WEINTRAUB: I have a broad comment about this ingredient, as well as its sister ingredient, ethanolamides.
And there seems to be a bit of a shift about how we're describing the conclusion.
For some of the previous ingredients that, I guess, we've pulled away from in this assessment, such as DEA, the reports in -- one of the older reports, it talks about the conclusion not broadly, as it does in these ingredients, in terms of "formulated to be non-irritating," but, instead, talks about not being used in leave-ons, and being formulated at specific concentrations.

So I wanted to make sure that the Panel considered that distinction and the appropriateness of such a conclusion for these. And if it's not appropriate, I wanted to have a discussion ruling that type of specific conclusion out for these ingredients.

DR. BELSITO: I guess I'm not following you, Rachel. You said, "appropriate for use in leave-ons?"

MS. WEINTRAUB: So, for example, one of the previous reports, I think it was for isostearamide DEA and MEA, the conclusion -- and this is just as an example -- the conclusion was that these are safe for rinse-off products. And then, in leave-on products, it was concluded that the ingredients are safe at certain concentrations.

DR. BELSITO: Right. That was a mode the Panel was in for a few years, where if we did not have sensitization data at the reported level of uses, we would go with -- we would limit leave-ons at that level. And I think we've evolved past that, to look at clinical experience in terms of allergic reactions to the products, et cetera.

So I think that's where you saw those concentration limits coming in -- not because we had any evidence of adverse effects above that level, but simply we had no data specifically on skin sensitization or irritation.

And I suspect, for those ingredients, it was more irritation. And then when we started getting into the lactic acids, with irritation, we realized, well, it's pH-dependent, yadda, yadda, yadda. So we really could not set all of the scenarios that will allow you to say, okay, well, your lactic acid at 10 percent is fine. Well, it may be if the pH is, you know, 8, but not if the pH is 3. So that's when we changed our language to "when formulated to be non-irritating."

So I think that's what you're seeing with those concentration limits.

MS. WEINTRAUB: Okay. That's helpful. I mean, the consequence is it clearly gives much more leeway to the formulators for determining when, in fact, it is irritating or not.

DR. BELSITO: Mm-hmm.

MS. WEINTRAUB: But I just wanted to draw this to the attention of the Panel. Because it was -- you know, in reading the past reports, and since it's based on mostly the same body of evidence, it struck me -- but this makes more sense.

And I know that recently we really haven't come to that conclusion unless there's a clear, a clear study that, you know, sort of offers a bright line in some sense.

DR. BELSITO: Yes, I think with irritation, you know, what we've all come to realize is that it's such a variable endpoint that depends upon so many other parts of the formulation, that you really can't set limits. So it's one tox endpoint where we can't do it. You know, we simply can say, "when formulated not to be irritating."

I mean, because you put benzoic acid in, but, you know, you put it in with sodium hydroxide, you end up with sodium benzoate, it's a totally different animal.

MS. WEINTRAUB: Right. Okay.

DR. SNYDER: Yes, I think this is a much better conclusion from a consumer standpoint, because I think we're putting out there that is irritating and that you need to avoid that, instead of we put a limit on it previously, and depending upon the formulation, it may or may not have been irritating, even at a concentration lower than what we had indicated.

I guess a follow-up question to that would be, Alan, on the re-reviews, are we going to -- do we need to have some kind of a red flag that we utilize that -- "when formulated to be non-irritating," when we do have those limits in the older reports?

DR. ANDERSEN: I think that, based on this conversation, we really do need to focus on that question of why did we have a concentration limit? And can we now change that to a different caveat, more appropriate to acknowledging that formulation can carry the day.

DR. BERGFELD: Alan, though, would that change the conclusion? Therefore mean we have to amend?

DR. ANDERSEN: Well, it's something we're going to have to decide. I would argue that the answer is probably, no, we don't need to change the conclusion. It's still safe with qualifications. We've just modernized the qualification.
But it's also -- I mean, the reason I don't want to make it amended is that's work that doesn't necessarily accomplish anything, other than getting it right.

I think we can convey to the readers -- since we publish all the re-reviews, we can convey to the reader what the Panel has done. So I don't think we're going to be hiding it by doing it as part of the re-review process.

But I also think, unless there's some other reason, maybe we don't amend.

DR. BELSITO: And I think, quite honestly, you know, when you're looking at irritation, the data frequently is with the material as is, in either petrolatum or water. And, in fact, our concentration limits would be lower than any formulation that would cause irritation as a result of that.

And therefore, it would really be industry saying, hey, you know, we want to use this at two times what you said was the limit. And we have at showing that it's non-irritating. So you need to take a look at this and amend your conclusion. So I think all of those restrictions that we put on irritation are extraordinary conservative.

DR. ANSELL: We agree. And, indeed, that's what's happened, is we come into an old study that has a limitation, because that was the highest concentration used, and then someone comes in and they want to use it at 12 instead of 9. And then we have to request reopening. And, when the relevant point was the non-irritating, and not the actual use concentration.

DR. ANDERSEN: Dan, back to the comment that you asked earlier: Yes, we have reviewed sulfites. The ammonium, potassium, and sodium salts, bisulfites, and safe in the present practices of use. Although I think it says 3 percent is the highest for sodium sulfite.

So it's not quite in the same league as the ethanolamines, but then again, the MEA sulfite isn't in current use.

DR. LIEBLER: Right. I just wanted to make sure that wasn't a problem for us.

DR. ANDERSEN: Yep.

DR. LIEBLER: Thank you.

DR. BELSITO: Okay.

DR. KLAASSEN: I have kind of a small point. In this review, we put the statement at least a half a dozen times, "from the final report on the safety assessment of triethanolamine, diethanolamine, and monoethanolamine." I guess, couldn't we just have that as a reference, instead of saying that whole sentence six times in here?

So, for example, if we look under "Occupational Exposure," on page 10, we have "From the final report on the safety assessment of," those three. And kind of we do that a half a dozen times in here.

Why not just reference the final report? Do you see what I'm saying?

MS. FIUME: So, example on page 10?

DR. KLAASSEN: Yes.

MS. FIUME: We've adopted the practice in all of the re-reviews, of any time the data was summarized from the previous re-review, so that it was clear where it was coming from, that in addition to the reference number, putting "From the final report."

DR. KLAASSEN: Oh, yeah?

MS. FIUME: And we've done it in all of the re-reviews, just so that it's clear. It's been a standing practice. It means --

DR. KLAASSEN: It just seemed more evident in this one, because I kept reading it and reading it and reading -- six times in two pages. But, you know, if that's the way it is, that's the way it is. I thought -- I didn't quite understand the reason for it.

DR. BELSITO: Okay. Draft discussion, so we're going "safe as used." And I apologize. Actually, my comment about the prior acids that were reviewed is that I thought they should be put into the discussion, as well, you know, stating that we've looked at them and that they were considered safe as used. And that was the only addition that I wanted to the discussion.

DR. LIEBLER: So, Don, you raised the issue of the boilerplate for the nitrosating chemistry.

DR. BELSITO: Yes.
DR. LIEBLER: And the last paragraph of the discussion addresses the level of free diethanolamine.

DR. BELSITO: Mm-hmm.

DR. LIEBLER: Are you okay with that? As written?

DR. BELSITO: Well, it says that it must be limited to the present practice of use and concentration of diethanolamine itself. And then we have the nitrosation warning with diethanolamine. And I just thought that -- I'm not a chemist, I just thought --

DR. LIEBLER: So, would you simply just replace that last sentence with the boilerplate, then?

DR. BELSITO: Yes.

DR. LIEBLER: Okay. I'm good with that.

MS. FIUME: Excuse me, Dr. Liebler, you said to replace that sentence? Or add another paragraph?

DR. LIEBLER: Well, it seemed to me the most efficient thing to do would be to replace that sentence.

So the first sentence of that paragraph basically says, "concern with levels of free diethanolamine present as an impurity," and then you go on to say, "Panel stated the amount of free diethanolamine must be limited to present practices for diethanolamine itself."

Perhaps you could simply -- by replacing it, I think you raise the issue of potential nitrosamine formation --

DR. BELSITO: Right.

DR. LIEBLER: -- and that these products should be formulated to minimize, or to prevent nitrosamine, whatever our boilerplate says.

You could also add it after.

MS. FIUME: Well, the only reason I'm concerned about taking it out was because in the triethanolamine report, one of the issues was talking about the diethanolamine concentrations, was how to limit it. And so that statement purposely put in to say that it was limited to the amount that's okay in the diethanolamine report.

I'm okay taking it out here --

DR. LIEBLER: So that's the absolute limit. And then on top of that, you add the boilerplate.

MS. FIUME: That's what we had done --

DR. LIEBLER: I see.

MS. FIUME: -- for the other one.

DR. LIEBLER: I guess I got -- I'm fine with that, too.

MS. FIUME: I'm happy to do it either way. I just wanted to point out why --

DR. BELSITO: Well, I mean, I guess the only -- I would agree with Dan getting rid of it, because basically we're saying that the amount of free diethanolamine available is less than that for diethanolamine itself, which sort of contradicts the prior statement that we said small amounts of diethanolamine may be present.

And the concentrations of use of these, it's not like ethanolamine is used at 100 percent, and diethanolamine is used at 0.05 percent, which could therefore result in more DEA being present in what we used to call "MEA." I mean, they're about the same concentration of use. So I would just get rid of that last sentence.

The bottom line is, we're concerned about nitrosation. And I would just put that caveat. You know, so, "Expert Panel was concerned about the impurity DEA. Therefore, these should not be formulated under conditions," or whatever our boilerplate is for that.

DR. BERGFELD: So you're mixing -- you want to mix the two sentences and shorten them.

DR. BELSITO: No, we're going to keep the first sentence --

DR. BERGFELD: Right.

DR. BELSITO: -- saying that we're concerned about levels of free diethanolamine. "Therefore" --

DR. BERGFELD: "Therefore," right.
DR. BELSITO: -- the nitrosation issue.

DR. BERGFELD: So you're mixing the --

DR. BELSITO: Right.

DR. BERGFELD: -- content of what you just said.

DR. ANSELL: I'm not exactly sure where we finished on that.

We had a concern, in the statement about use and concentration of "diethanolamine itself," when, in fact, it really isn't used "itself." It's only there as an impurity.

But these changes kind of resolved that, clarified that.

DR. LIEBLER: It gets rid of that sentence.

DR. ANSELL: Okay.

DR. BERGFELD: It gets rid of the sentence, but you add the nitrosating statement.

DR. BELSITO: Right.

DR. BERGFELD: "Therefore," and then you're going to add something about it should not -- I forgot what that boilerplate actually says, the nitrosating statement. It must be under the next one.

DR. BELSITO: It's in the ethanolamine report.

DR. BERGFELD: Yes.

DR. BELSITO: Or the DEA report.

DR. ANDERSEN: The boilerplate language is, "Should not be used in cosmetic products in which n-nitroso compounds can be formed." And I think, arguably --

DR. BELSITO: "Can be" or "may be?"

DR. ANDERSEN: "Can be."

DR. BELSITO: Okay.

DR. ANDERSEN: Because "may be" is, who cares? If they are formed, if they "can be" formed, that's the issue. If they "may be" formed, that's theoretical. So we went to that.

I'm just -- I don't know how relevant that is to the monoethanolamine safety assessment. I guess I'm a little bit nervous about that.

The debate wasn't so much, at the last meeting, when this was discussed, over forming nitrosamines. The debate was diethanolamine itself, not wanting that to be a significant part -- and it's an impurity. No question it was being looked at as an impurity. But that impurity to ethanolamine shouldn't be any more than if it were actually being used as an ingredient. And that was the way that it was captured.

If the concern in your mind is n-nitrosation, then the nitrosamine caveat will work just fine. It's just that wasn't clear to me from the last meeting. But if that's where you're at now, then that will do it.

DR. BELSITO: I mean, I think it covers our concern better than the way it's phrased now.

DR. LIEBLER: If there was that data on the impurities that said diethanolamine is typically no more than, you know, 20 ppm, or some documented low concentration, then I don't think we would be having this discussion, because we really wouldn't be concerned about it. It's simply, it's ambiguous, this statement about the impurity diethanolamine, is just uninformative. "Small amount" doesn't tell you enough.

So, because of that, I think that's why you can't discard the concern about nitrosation.

So, unless we can have more precise information about the impurity, I think we'd need to go with the boilerplate on nitrosation.

DR. ANDERSEN: But were information to become available, that characterizes what you could really expect, that could better inform the discussion.

DR. LIEBLER: I agree.
Ethanolamine – Marks Team – Dec 12, 2011

DR. MARKS: Next is ethanolamine. And again, what we have before us is a draft tentative amended safety assessment of ethanolamine and ethanolamine salts.

We'll take a one minute break. Maybe two minute break.

DR. SLAGA: Could be longer.

DR. MARKS: Could be longer. I have safe when formulated to be nonirritating.

Draft conclusion. So we move that a tentative amended safety assessment be issued.

Do you want to stretch again?

MS. EISENMANN: I have a comment in the discussion.

DR. MARKS: Sure. Go ahead.

MS. EISENMANN: I have a problem with the word "itself." Diethanolamine itself, because in Europe diethanolamine itself is not permitted so the levels of diethanolamine in the products are really driven by addition of other ingredients. And when you -- I thought at the last meeting you discussed -- you referred to the levels as discussed in the diethanolamine report which included levels when cocamide DEA are put in products.

DR. SHANK: I don't see what the problem is.

DR. MARKS: You're talking about the last paragraph?

MS. EISENMANN: You're using the word "itself." Yes, "itself." Because diethanolamine is not added to products.

DR. MARKS: Stated in the amount of three, diethanolamine available must be limited to the present practice of use and concentration. Oh, I see what you're saying, of diethanolamine itself. You're saying that sentence implies that it's actually used as a cosmetic ingredient?

MS. EISENMANN: Very rarely because it's not permitted in Europe to be used that way but you can -- I mean, it can be in products because you're adding cocamide DEA or some other (inaudible).

DR. MARKS: How would you change that sentence?

MS. EISENMANN: At a minimum, delete "itself." But another option is just refer to the -- you would discuss -- at the last meeting I thought that you were referring to the DEA report because I provided trace and use information for that report. That was based on levels of DEA in products in which the DEA could then (inaudible).

DR. MARKS: Actually, if you get rid of "itself" it kind of answers it. Right?

MS. EISENMANN: That would be the minimum.

DR. MARKS: Okay. That's straightforward.

MS. EISENMANN: Okay.

DR. SHANK: You don't use (inaudible) normally.

DR. MARKS: Yeah. Any other changes to that sentence, Carol, that you would suggest? I'll let you and Monice kind of wordsmith that.

MS. FIUME: I'll word it like it is in the TEA report. I, for the life of me, don't know why I didn't --

MS. EISENMANN: (inaudible) has its own persona.

DR. MARKS: So Ron, Ron Hill, tomorrow I'm going to move that we issue a tentative amended safety assessment of ethanolamine and ethanolamine salts as stated on Panel Book page 27. Safe as long as formulated to be nonirritating. Okay?

DR. HILL: Yeah. Good.

DR. MARKS: Okay. Let's move on to the next one then. Unless did you have any other --

DR. SHANK: In the discussion..

DR. MARKS: Okay, good.
DR. SHANK: I think I would like to see it mentioned specifically that the safe for use in rinse-off only and that we do not include leave-on in this even though the table doesn't list, if I remember correctly, leave-ons. It's in the list here. Everything is just not reported. I think it would be better to say that we concluded that these ingredients are safe for use as used in rinse-off because that's what we had considered, I believe.

DR. MARKS: If that's the case, shouldn't it be in the conclusion?

DR. SHANK: The table lists leave-on but then this kind of ambiguous not reported -- not reported doesn't mean that it's not right. It's just another way of saying no data.

DR. MARKS: Yeah. So you're concerned about leave-ons?

DR. SHANK: Well, our review with the current uses and the current uses that are listed in the data are rinse-off. Should we say in the discussion? I don't know that you have to say it again in the conclusion. Not a big thing. Okay.

DR. MARKS: Tom. Ron Hill.

DR. HILL: Yeah, I mean --

DR. MARKS: It's clear. I see what you're saying, Ron. It's clear in the table we don't -- it's not being -- we don't have uses in leave-on.

MS. FIUME: It's stated in text in the use section but I'd be happy to reiterate it in the discussion if you want it there also.

DR. SHANK: I would just do that because it's a voluntary reporting system. In fact, what's not reported doesn't mean it's not in the leave-ons. And our review was based on rinse-off.

DR. MARKS: Okay.

DR. HILL: Yeah, and I mean, if it was just the MEA component, what bugged me about this whole report is that I'm not sure in some of these that the toxicology is necessarily driven by the MEA. And so, yeah, that helps spread that concern for me.

DR. MARKS: So Monice, you'll repeat that again in the discussion just so there's no -- do I need to bring that up tomorrow?

DR. SHANK: I don't think so.

DR. MARKS: Okay. Good.

DR. HILL: And we eliminated some on that basis but I'm not sure we got rid of everything that that might be true for.

Ethanolamine – Full Panel – Dec 13, 2011

Then moving on to the next ingredient, Dr. Marks, ethanolamines.

DR. MARKS: So, I move that we issue a tentative amended safety assessment of ethanolamine and ethanolamine salts, with a conclusion of safe formulated to being not irritating as expressed on Panel Book, page 27.

DR. BERGFELD: The motion's been made. Is there a second, or any discussion?

DR. BELSITO: Or do you want to include the nitroso compound formation in your conclusion as well?

DR. MARKS: Sure.

DR. BELSITO: We were -- you know, there will be some contamination with DEA and --

DR. MARKS: Thank you. Yes.

DR. BERGFELD: Does that mean you're seconding it --

DR. BELSITO: Yes.

DR. BERGFELD: -- with that inclusion? Any other discussion from anyone? Don?

DR. BELSITO: Yeah. There was a new draft discussion that was circulated, and the -- I think it looks fine. Did you get a copy of that, Jim, and a chance to read over it?
DR. MARKS: Yes, and it looked fine. I agree with what you've done. Several of our team members have looked at it.

DR. BELSITO: Okay.

DR. ANSELL: Could we request that the "can be" be changed to "may be" --

DR. BELSITO: Yes.

DR. ANSELL: -- as was discussed?

DR. BELSITO: I mean, I think that will be our nitroso boiler plate. We accept those changes.

DR. BERGFELD: Do we need a chance to read through the discussion here on Dr. Belsito's team? Have you read the discussion?

DR. BELSITO: And there'll be time to finesse the discussion. It'll be editorial only, I mean, at the next meeting.

DR. BERGFELD: It's another one.

DR. BELSITO: Tentative final, so --

DR. BERGFELD: It's okay?

DR. KLAASSEN: Yes, it's --

DR. BERGFELD: Okay.

DR. KLAASSEN: -- comfortable.

DR. BERGFELD: All right. So, we've had a little bit of a change of the conclusion that was presented by Dr. Marks, adding the nitroso, sort of precedent statement. And we've had a new discussion put before us, which can be tickled a little bit if necessary. And I see no other discussions, no other questions, no other additions.

I call for the vote. All those in favor of safe as stated? Unanimous. Thank you.
Draft Final Amended Safety Assessment

Ethanolamine and Ethanolamine Salts as Used in Cosmetics

March 5, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer and Bart A. Heldreth, Ph.D., Chemist.
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ABSTRACT
The CIR Expert Panel assessed the safety of ethanolamine and 12 salts of ethanolamine as used in cosmetics. Ethanolamine functions as a pH adjuster. The majority of the salts are reported to function as surfactants; the others are reported to function as pH adjusters, hair fixatives, or preservatives. The Panel reviewed available animal and clinical data, as well as information from previous CIR reports. Since data were not available for each individual ingredient, and since the salts dissociate freely in water, the Panel extrapolated from previous reports to support safety. The Panel concluded that ethanolamine and its salts are safe for use when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

INTRODUCTION
In 1983, the Cosmetic Ingredient Review (CIR) Expert Panel issued a safety assessment of the safety of triethanolamine (TEA), diethanolamine (DEA), and monoethanolamine (MEA). In that previous report, the Panel concluded that ethanolamine, an ingredient that functions in cosmetics as a pH adjuster, is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin, and ethanolamine should only be used in rinse-off products.1 Also in that report, ethanolamine was identified as a skin and eye irritant in animals, and a skin irritant in humans. The longer ethanolamine was in contact with the skin, the greater the likelihood of irritation.

In 2010, the Panel decided to reopen that safety assessment as three separate reports (one for each ingredient), including additional related ingredients in each of the new reviews. Diethanolamine and its salts and triethanolamine and TEA-containing ingredients are safe in the present practices of use and concentration, when formulated to be non-irritating, with the caveat that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.2,3

The International Nomenclature Cosmetic Ingredient (INCI) name for monoethanolamine is now ethanolamine. This assessment addresses ethanolamine and ethanolamine salts. The acid salt ingredients (as recited below) would be expected to dissociate into ethanolamine and the corresponding acid, some of which have been reviewed separately. In most cases, this means that the composition of these salts is stoichiometrically half ethanolamine (i.e. as its conjugate acid).

The following 12 salts are included in the re-review of ethanolamine:

Inorganic Acid Salts
Ethanolamine HCl
MEA-Sulfite

Organic Acid Salts
MEA-Benzoate
MEA-Salicylate
MEA-Undecylenate
MEA-Laureth-6 Carboxylate
MEA-PGG-6 Laureth-7 Carboxylate
MEA-PGG-8-Steareth-7 Carboxylate

Organic-Substituted Inorganic Acid Salts
MEA-Lauryl Sulfate
MEA-Laureth Sulfate

Ethanolamine HCl is reported to function as a pH adjuster and a buffering agent. MEA-sulfite is reported to function as a hair fixative. The majority of the ethanolamine salts are reported to function as surfactants. However, MEA-benzoate and MEA-salicylate are reported to function as preservatives, not surfactants.

MEA-salicylate also has been reviewed previously by the CIR Expert Panel. In 2003, the Panel concluded that MEA-salicylate is safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin’s sun sensitivity, or, when increased sun sensitivity would be expected; directions for use include the daily use of sun protection.4

The definitions and structures of ethanolamine and the ethanolamine-containing ingredients listed above are provided in Table 1. Since the ingredients included in this review consist of ethanolamine and one or more components, the conclusions of the components that have been reviewed previously are provided in Table 2.
As noted above, information relevant to the safety of ethanolamine was included in the 1983 CIR safety assessment of TEA, DEA, and MEA. Information from that report is provided in single spaced, indented text when available.

**CHEMISTRY**

Ethanolamine is an amino alcohol. (Figure 1). Ethanolamine is produced commercially by aminating ethylene oxide with ammonia; the replacement of one hydrogen of ammonia with an ethanol group produces ethanolamine.

![Ethanolamine](image1)

Figure 1. Ethanolamine

Ethanolamine is reactive and bifunctional, combining the properties of alcohols and amines. At temperatures of 140°-160°C, ethanolamine will react with fatty acids to form ethanolamides. Additionally, the reaction of ethanolamines and sulfuric acid produces sulfates, and, under anhydrous conditions, ethanolamine may react with carbon dioxide to form carbamates.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine

While many secondary amines are readily nitrosated to form isolatable nitrosamines, primary amines, such as ethanolamine, ultimately yield diazonium salts instead of nitrosamines.\(^5\)

**Acid Salts**

The acid salts (inorganic acid salts, organic acid salts, and sulfate salts), named above, are ion pairs which freely dissociate in water (e.g., Figure 2). Therefore, these salts are closely related to the corresponding free acids and ethanolamine. In other words, MEA-undecylenate, for example, is comprised of undecylenic acid and ethanolamine.

![MEA-Undecylenate](image2)

Figure 2. MEA-Undecylenate

Available physical and chemical properties are summarized in Table 3.

**Method of Manufacture**

Ethanolamine is produced by reacting 1 mole of ethylene oxide with 1 mole of ammonia. Typically, ethylene oxide is reacted with ammonia in a batch process to produce a crude mixture of approximately one-third each ethanolamine, diethanolamine, and triethanolamine, which is then separated, achieving varying degrees of single component purity. Ethanolamine combines with long-chain fatty acids to produce neutral carboxylates, also called alkanolamine soaps.\(^7\)

**Impurities**

Ethanolamine contains a small amount of diethanolamine.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine

Residual ethylene oxide is not expected during the manufacture of ethanolamine.\(^6\)

**USE**

**Cosmetic**

Ethanolamine and ethanolamine HCl are reported to function in cosmetics as pH adjusters; ethanolamine HCl is also reported to function as a buffering agent.\(^8\) MEA-sulfite is reported to function as a hair fixative. The majority of the ethanolamine salts are reported to function as surfactants. However, MEA-benzoate and MEA-salicylate are reported to function as preservatives, not surfactants.

Amines, such as ethanolamine, can be useful in pH adjustment because they can both donate a proton in an alkaline environment and accept a proton in an acidic environment. For ethanolamine HCl, a proton has already been accepted from HCl, but ethanolamine HCl can certainly function as a proton donor.

Voluntary Cosmetic Registration Program (VCRP) data obtained in 2011 report that ethanolamine is used in 788 formulations.\(^9\) All of the uses are in rinse-off products (Don Havery, personal communication), and 772 uses are in hair coloring formulations.\(^10\) A few of the other ethanolamine-containing ingredients are in use, but all of those are reported to be used in less than 15 rinse-off formulations.

According to data submitted by industry in response to a recent survey conducted by the Personal Care Products Council (Council), ethanolamine is used in rinse-off products (only) at up to 18%.\(^11\) MEA-lauryl sulfate has the highest
reported concentration of use, with a concentration of 35% reported in hair dye formulations. Use data for ethanolamine and all other in-use ethanolamine-containing ingredients are provided in Table 4a. Ethanolamine ingredients not reported to be in use, according to VCRP data and the Council survey, are listed in Table 4b.

Ethanolamine, used in a hair color aerosol spray at a maximum concentration of 3%, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm. Therefore, most droplet 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. However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions may cause toxic effects depending on their chemical and other properties.

Monoalkylamines, monoalkanolamines, and their salts are listed by the European Commission (EC) in Annex III Part 1: the list of substances which cosmetic products must not contain, except subject to the restrictions and conditions laid down. These restrictions for these ingredients include an allowed maximum secondary amine content of 0.5% in finished product; do not use with nitrosating agents; minimum purity of 99%; maximum secondary amine content of 0.5% for raw materials; maximum nitrosamine content of 50 μg/kg; and must be kept in nitrite-free containers. MEA-benzoate is listed by the EC in Annex V, a list of preservatives allowed in cosmetics; as a preservative, MEA-benzoate is allowed a maximum concentration in ready-for-use preparations of 0.5% as benzoic acid. MEA-salicylate is also listed in Annex V; as a preservative, MEA-salicylate is allowed a maximum concentration in ready-for-use preparations of 0.5% as salicylic acid, and it is not to be used in products for children under 3 years of age, except shampoos. The ingredients named in this report that have EC restrictions are listed in Table 4c.

Information provided by Health Canada indicates that ethanolamine is used primarily in hair coloring products, with concentrations of use of ≤30% (Health Canada, personal communication). Ethanolamine is also reported to be used in Canada at concentrations of ≤30% in non-coloring hair preparations and rinse-off formulations, and at ≤10% in leave-on formulations; this includes reported use at 0.3-3% in baby products and 3-10% in lipsticks.

Non-Cosmetic
Ethanolamine is used in the manufacture of emulsifiers and dispersing agents for textile specialties, agricultural chemicals, waxes, mineral and vegetable oils, paraffin, polishes, cutting oils, petroleum demulsifiers, and cement additives. It is an intermediate for resins, plasticizers, and rubber chemicals. It is also used as a lubricant in the textile industry, as a humectant and softening agent for hides, as an alkalinizing agent and surfactant in pharmaceuticals, as an absorbent for acid gases, and in organic syntheses.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine. Ethanolamine has uses as an indirect food additive; according to 21 CFR 175.105 ethanolamine is allowed for use as a component of adhesives. Ethanolamine is also used as a rust inhibitor in water-based metalworking fluids.

TOXICOKINETICS
Ethanolamine is the only naturally occurring ethanolamine in mammals, and it is excreted in the urine. Ethanolamine was converted to phosphatidylethanolamine (PE) in the liver, blood, and brain of female rats that were dosed intraperitoneally (i.p.) with radiolabeled ethanolamine. The step-wise methylation of PE that converts it to phosphatidylcholine (PC) did not occur in the brain. Labeled respiratory carbon dioxide has been found in rats after i.p. administration of labeled ethanolamine.

A coenzyme-B₁₂-dependent ethanolamine deaminase-mediated conversion of ethanolamine to acetaldehyle and ammonia was demonstrated. Intraperitoneal administration of ethanolamine to rats increased blood urea and blood glutamine, and the researchers suggested that ethanolamine was an ammonia source. Additional researchers, upon detection of labeled acetate in the urine of rats fed labeled ethanolamine, suggested that ethanolamine is phosphorylated by ATP in vivo, converted to acetaldehyde, ammonia, and inorganic phosphate, and the acetaldehyde is oxidized to acetate. The researchers further hypothesized that the removal of phosphorylated ethanolamine by its conversion to acetate may exert a regulatory effect on PE biosynthesis.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Ethanolamine.

Ethanolamine occurs naturally in phospholipids known as phosphatides. Ethanolamine is a structural component of the phospholipids as part of the headgroups in phospholipid bilayers. In man and other animals, the alcohol group of ethanolamine is phosphorylated, and phosphorylated ethanolamine is transferred to cytidine monophosphate to form cytidine-5’-diphosphoethanolamine and phospholipids via diacylglycerol.

In-Vitro
Ethanolamine

Three full thickness skin preparations from CD rats, CD-1 mice, and New Zealand White rabbits and 6 samples from female mammoplasty patients were used to compare the dermal penetration of ethanolamine through skin of different species. [14C]Ethanolamine (98.8% purity; specific activity [sp. act.] 15.0 mCi/mmol) was applied to the skin sample undiluted or as an aq. solution at a dose of 4 mg/cm². Dose volumes of 7 μl undiluted [14C]ethanolamine or 32 μl of the aq. solution (22% w/w) were applied to the exposed surface of the skin (1.77 cm²) for 6 h. With undiluted ethanolamine, the
cumulative dose absorbed (found in the effluent) was 5.98, 16.92, 8.66, and 0.61% through rat, mouse, rabbit, and human skin, respectively. With aq. ethanolamine, 1.32, 24.79, 1.87, and 1.11%, of the cumulative dose absorbed through rat, mouse, rabbit, and human skin, respectively. In vitro absorption of undiluted and aq. ethanolamine was much greater through mouse skin than human skin, and human skin was the least permeable of all the skin samples. With human skin samples, the cumulative dose absorbed was greater with aq. ethanolamine as compared to undiluted ethanolamine. The researchers hypothesized that enhanced penetration of aq. ethanolamine may be attributable to elevated skin hydration.

**Ethanolamine HCl**

The dermal penetration of [1,2-14C]ethanolamine HCl was evaluated in vitro using split-thickness skin from weanling Yorkshire pigs. An ethanolic solution was prepared so that a 5 µl application to 0.8 cm² of skin gave a chemical dose of 4 µg/cm² and a radioactive dose of approximately 0.05 µCi. After 50 h, 11% of the dose was lost to evaporation, 5% penetrated percutaneously, and 62% was recovered in the skin residue. Seven to nine times more radioactivity was recovered in the upper 100 µm layer compared to recovery from the remaining dermis.

**Dermal**

**Non-Human**

The distribution and metabolism of ethanolamine was determined using groups of 5 male athymic nude mice with human skin grafts and ungrafted athymic nude mice. [1,2-14C]Ethanolamine HCl in ethanol was applied at a dose of 4.0 µg (3.6 µCi) to a 1.45 cm² area of grafted or non-grafted skin. Penetration appeared similar for both groups. Radioactivity in expired carbon dioxide (CO₂) appeared 30 min after dosing, and the amount recovered at 30 min was 0.76% for grafted skin and 0.83% of the dose for ungrafted skin. After 24 h, 18.5-19% of the dose was recovered in expired CO₂. Distribution was also similar for both groups. At 24 h after dosing, 24.3-25.8% of the dose was recovered in the liver and 2.24-2.53% in the kidneys. At the application site, 18.4% of the radioactivity was recovered in the grafted skin, and 12.1% was recovered in the ungrafted skin. The amount of radioactivity recovered in the urine was 4.6 and 5.2% for grafted and ungrafted nude mice, respectively. Unchanged ethanolamine comprised 10.2% of the urinary radioactivity. The major urinary metabolites were urea and glycine, comprising 39.9 and 20.4% of the urinary radioactivity. Minor urinary metabolites were serine, uric acid, choline, and unidentified ninhydrin-positive compounds.

The radioactivity in proteins and amino acids isolated from the liver, human skin grafts, and mouse skin was determined as an evaluation of the metabolism of ethanolamine. The researchers stated that the appearance of ¹⁴C in skin and hepatic amino acids and proteins, and the incorporation of ethanolamine into phospholipids, was evidence of extensive metabolism of the absorbed ethanolamine. The liver was the most active site of ethanolamine metabolism.

**Oral**

**Non-Human**

In a dietary two-generation reproductive toxicity study (described later in the ‘Reproductive and Developmental Toxicity’ section), blood samples were taken from groups of 10 male and 10 female F₀ and F₁ Wistar rats that were fed 0, 100, 300, or 1000 mg/kg ethanolamine HCl in feed for 10 wks. Plasma levels of ethanolamine, calculated as ethanolamine HCl, increased in a dose-dependent manner. The plasma concentration of ethanolamine was <3 mg/kg for control male and female F₀ and F₁ animals. In the low dose group, the plasma concentration values of ethanolamine were <4 mg/kg, in the mid-dose animals, the levels were 8-11 mg/kg, and in the high dose animals, the plasma ethanolamine levels ranged from 60-81 mg/kg.

**Other**

**Non-Human**

Five male athymic nude mice were dosed intraperitoneally (i.p.) with 4.0 µg (3.6 µCi) of [1,2-14C]ethanolamine HCl in ethanol, and the distribution and metabolism were examined following dosing. Radioactivity was detected in expired CO₂, increasing gradually over time. After 24 h, 18% of the radioactivity was detected in expired air.

**TOXICOLOGICAL STUDIES**

**Acute (Single) Dose Toxicity**

**Dermal**

Female C3H mice were used to determine the in vivo and in vitro morphological response of mouse skin exposed to a single application of 1, 5, or 10% ethanolamine in acetone. In vivo, ethanolamine was applied to an area of skin 1 inch in diameter, the animals were killed the next day, and the treated skin was removed and processed. In vitro, ethanolamine was applied to a 1-inch diameter mouse skin disc for 1 min, and the skin discs were then cultured for 20 h. No lesions were observed in vivo or in vitro at any concentration tested. Lactate dehydrogenase activity in the in vitro samples was statistically significantly elevated with 5 and 10% ethanolamine, suggesting that ethanolamine was mildly toxic to the skin at these concentrations.

The dermal LD₅₀ in rabbits is reported as 1.0-2.5 g/kg ethanolamine. In a study determining the acute dermal toxicity of a mixture containing ethanolamine (as well as hydroxylamine, diglycolamine, propylene glycol, catechol, and water; percentages not specified), 2g/kg of the mixture were applied to the shaved backs of 5 male and 5 female rabbits. The dermal LD₅₀ of the mixture was greater than the 2 g/kg dose. In a similar study with a formulation containing ethanolamine (and
hydroxylamine, diglycolamine, gallic acid, and water; percentages not specified), the LD$_{50}$ of the mixture in rabbits was 1.24 g/kg bw.\textsuperscript{24}

**Oral**

The acute oral toxicity of ethanolamine, concentration not specified, ranged from 1.72-2.75 g/kg for rats. Using 90-120 rats, 20\% aq. ethanolamine had an LD$_{50}$ of 2.14-2.74 g/kg, based on results of studies performed over a 10 yr time period. With groups of 10 rats, a hair preparation containing 5.9\% ethanolamine had an LD$_{50}$ of 14.1 g/kg when diluted and 12.9 ml/kg when undiluted. In a study using guinea pigs, all in the group of 2 or 3 guinea pigs survived oral dosing with 0.6 g/kg ethanolamine, while none survived dosing with 7.0 g/kg.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.\textsuperscript{1}

In oral studies, the LD$_{50}$ of ethanolamine is reported as 0.7-15.0 g/kg in mice and 1.0-2.9 g/kg in rabbits.\textsuperscript{7} In a study determining the acute oral toxicity of a mixture containing ethanolamine (as well as hydroxylamine, diglycolamine, propylene glycol, catechol, glycolic acid and water; percentages not specified), groups of 5 male and 5 female rats were used.\textsuperscript{25} The oral LD$_{50}$ of the mixture was 0.95 g/kg. In a similar study with a formulation containing ethanolamine (and hydroxylamine, diglycolamine, gallic acid, and water; percent in formulation not specified), the oral LD$_{50}$ of the mixture was 0.815 g/kg bw.

**Inhalation**

The acute inhalation toxicity of a mixture containing ethanolamine (as well as hydroxylamine, 1-amino-propano-2-ol, catechol, and water; percent of each not specified) was determined using groups of 5 male and 5 female rats. The animals were exposed to 1.11, 1.61, 2.13, or 2.84 mg/l for 4 h. All animals exposed to 2.84 mg/l died. All animals in the other test groups survived. The inhalation LC$_{50}$ of the mixture was estimated to be 2.48 mg/l.\textsuperscript{25}

**Other**

The intraperitoneal LD$_{50}$ of ethanolamine was 1.05 g/kg for mice.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.\textsuperscript{1}

**Repeated Dose Toxicity**

**Dermal**

Percutaneous application of 4 mg/kg/day ethanolamine to rats resulted in nonspecific histological changes in the heart and lung, fatty degeneration of the liver parenchyma, and subsequent focal liver necrosis. The duration of dosing was not specified.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.\textsuperscript{1}

**Oral**

Groups of 10 rats were fed 0-2.67 g/kg/day ethanolamine for 90 days. Heavy livers and kidneys were observed at ≥0.64 g/kg/day, and deaths and “major pathology” occurred with ≥1.25 g/kg/day. In a 2-yr dietary study in which groups of 12 Beagle dogs were fed 0-0.0975 g/kg/day of a hair dye composite that contained 22\% ethanolamine, no toxic effects were observed. Despite maternal effects in the 225 mg/kg dose group, no effects on reproductive parameters were observed at any dose, and there were no treatment-related increases in the visceral or skeletal malformations. In rats, the no-observed effect level (NOEL) was 75 mg/kg/day for maternal toxicity and 225 mg/kg/day for embryonal/fetal toxicity.

In rabbits, 0, 10, 25, and 75 mg/kg bw/day ethanolamine was applied to the back (2 ml/kg) on days 6-18 of gestation. Dogs and rodents exposed to 66-102 ppm ethanolamine vapor had behavioral changes, pulmonary and hepatic inflammation, hepatic and renal damage, and hematological changes.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.\textsuperscript{1}

**Inhalation**

The dominant effects of “continuous exposure” of dogs, guinea pigs, and rats to 5-6 ppm ethanolamine vapor were skin irritation and lethargy. No dogs or rodents exposed to 12-26 ppm ethanolamine vapor for 90 days died, but mortality was reported in dogs exposed to 102 ppm ethanolamine vapor for 2 days and rodents exposed to 66-75 ppm ethanolamine vapor for 24-28 days. Dogs and rodents exposed to 66-102 ppm ethanolamine vapor had behavioral changes, pulmonary and hepatic inflammation, hepatic and renal damage, and hematological changes.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.\textsuperscript{1}

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

**Dermal**

The developmental toxicity of dermally-applied aq. ethanolamine was evaluated using groups of 30-45 gravid Sprague-Dawley rats and 15 gravid New Zealand White rabbits.\textsuperscript{26} Ethanolamine was applied at doses of 0, 10, 25, 75, and 225 mg/kg bw/day to the backs of rats on days 6-15 of gestation, with a dose volume of 1 ml/kg. Significant skin irritation, consisting of erythema followed by necrosis, scabs, and scar formation, occurred with 225 mg/kg ethanolamine, but not at the other dose levels. No effects on kidney or liver weights were reported. Despite maternal effects in the 225 mg/kg dose group, no effects on reproductive parameters were observed at any dose, and there were no treatment-related increases in the visceral or skeletal malformations. In rats, the no-observed effect level (NOEL) was 75 mg/kg/day for maternal toxicity and 225 mg/kg/day for embryonal/fetal toxicity.

In rabbits, 0, 10, 25, and 75 mg/kg bw/day ethanolamine was applied to the back (2 ml/kg) on days 6-18 of gestation. Severe skin irritation at the application site, consisting of necrosis, exfoliation, and crusting, was observed in the 75 mg/kg group, and crusting, transient erythema, and edema were observed in a few rabbits of the 25 mg/kg dose group. No effects on kidney or liver weights were reported. As with the rats, no effects on reproductive parameters were observed at any dose, and there were no treatment-related increases in the visceral or skeletal malformations. In rabbits, the NOEL was 10 mg/kg bw/day for maternal toxicity. No effect on embryonal/fetal toxicity was observed at the highest dose level of 75 mg/kg bw/day.
**Oral**

**Ethanolamine**

No reproductive or developmental effects were observed in groups of gravid rats given a hair dye and base containing 22% ethanolamine in the diet at concentrations ≤7800 ppm on days 6-15 of gestation. No differences in reproductive or developmental parameters were observed when male rats were fed treated diet for 8 weeks prior to and during mating with undosed females or when female rats were fed treated feed for 8 weeks prior to dosing until day 21 of lactation. These females were mated with undosed males. Additionally, no teratologic effects were induced by dosing gravid rabbits with ≤19.5 mg/kg/day of the hair dye and base by gavage on days 6-18 of gestation.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Ethanolamine.1

The teratogenic potential of ethanolamine was evaluated in a Chernoff-Kavlock postnatal mouse screening assay.27 Gravid CD-1 mice were dosed orally with 850 mg/kg/day ethanolamine on days 6-15 of gestation, resulting in 16% mortality of maternal mice and reduced numbers of viable litters. Litter size, percentage survival of pups, birth weight, and pup weight gains were not affected.

A preliminary study was performed in which gravid Wistar rats were dosed orally with 0-500 mg/kg/day aq. ethanolamine; details not provided.28 Maternal effects were observed in the high dose animals, but no embryonal/fetal effects were observed at any dose. Based on these results, groups of 40 Wistar rats were dosed by gavage with 0, 40, 120, or 450 mg/kg bw/day aq. ethanolamine on days 6-15 of gestation. On day 20 of gestation, 25 dams/group were killed and necropsied, while the remaining 15 were allowed to litter and then killed on day 21 of lactation. Despite evidence of maternal toxicity in the 450 mg/kg group, as indicated by statistically significant decreases in maternal body weights and feed consumption, no effects on reproductive parameters, incidences of visceral or skeletal malformations, or postnatal growth were observed at any dose. The NOEL for maternal toxicity was 120 mg/kg/day. No effect on developmental toxicity was observed at the highest dose level of 450 mg/kg/day.

Groups of 10 gravid Long-Evans rats were dosed by gavage with 50, 300, or 500 mg/kg aq. ethanolamine on days 6-15 of gestation, and a negative control group of 34 gravid rats was dosed with water only.29 The animals were killed and examined on day 20 of gestation. Significant maternal toxicity was not noted. Embryolethality was significantly increased in the 500 mg/kg group, and male pups were affected more than female pups. Male pups were also more severely affected than female pups at all dose levels in regards to intrauterine growth retardation and increased gross structural anomalies that were considered indicative of depressed fetal growth. However, pups of either sex who were contiguous to male siblings were more adversely affected that those contiguous to one or more female siblings. Male pups contiguous to male siblings (mMm) were, apparently, resorbed (mRM). The number of malformed pups per dam was significantly increased in animals dosed with 300 mg/kg ethanolamine. The number of malformed pups, when evaluated as a percent of the litter affected, was significantly increased for all 3 dose groups.

**Ethanolamine HCl**

Groups of 25 male and 25 female Wistar rats (F₀ parental generation) were fed 0, 100, 300, or 1000 mg/kg bw/d ethanolamine HCl for at least 75 days prior to mating.30 Twenty-five male and 25 female F₁ pups/group were continued on the test diets of their parents, and then mated, becoming the F₂ parental generation. The study was terminated after the weaning of the F₂ pups. No test substance-related adverse reproductive, developmental, or toxic effects were observed in any of the pups or parental animals of the 100 or 300 mg/kg bw/d groups. In the 1000 mg/kg group, adverse effects on fertility and reproduction were evidenced by statistically significant decreases in absolute and relative weights of the epididymides and cauda epididymidis in male F₀ and F₁ parents and statistically significant decreased number of implantation sites, increased post-implantation loss, and smaller litters in female F₀ and F₁ parents. Sperm head count in the cauda epididymidis and absolute and relative liver weights were also statistically significantly decreased in male F₀ parents. Body weight gains of both the F₀ and F₁ parental animals were statistically significantly decreased during gestation when compared to controls, as was feed consumption during lactation. There were no test-related signs of developmental toxicity observed in F₁ and F₂ pups of this dose group. The NOAEL was 300 mg/kg bw/day for systemic toxicity and for reproductive effects. No effect on developmental toxicity was observed at the highest dose level of 1000 mg/kg/day.

**GENOTOXICITY**

**In Vitro**

Ethanolamine, with and without metabolic activation using liver preparations from rats induced with a polychlorinated biphenyl mixture, was not mutagenic to Salmonella typhimurium TA100 or TA1535.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

Ethanolamine was negative in most Ames tests at concentrations ≤2000 µg/plate;30,31 however “weak mutagenic effects” were reported in one study.32 Ethanolamine, 25-500 µg/ml, was negative in a cell transformation assay using hamster embryo cells.33 Ethanolamine was clearly cytotoxic at 500 µg/ml. Ethanolamine did not produce chromosomal aberrations in rat liver cells,30 but a “weak positive” response was reported in human lymphocytes.32 (Concentrations tested were not provided.)
Published carcinogenicity data were not found on ethanolamine or ethanolamine salts.

**IRRITATION AND SENSITIZATION**

**Dermal Irritation**

**Non-Human**

Ethanolamine was corrosive to rabbit skin with single semi-occlusive patches of 30, 85 and 100% on intact and abraded skin. When applied to rabbit ears using non-occlusive applications and to shaved skin of the abdomen under semi-occlusive patches, ≥10% was corrosive, >1% was extremely irritating, and 1% was irritating.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

**Human**

In a study in which a formulation containing 5.9% ethanolamine was applied to the backs of 12 female subjects for 23 h/day for 21 days, the formulation was considered an experimental cumulative irritant. Results observed during the induction phase of a patch test of 165 subjects using a formulation containing 11.47% ethanolamine were interpreted by the Expert Panel as irritation.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

**Sensitization**

**Non-Human**

A local lymph node assay was performed to evaluate the sensitization potential of ethanolamine (as the hydrochloride salt).18,34 Groups of 6 female CBA/Ca mice were treated on the ear with 10, 40, or 70% w/w aq. ethanolamine HCl. Ethanolamine HCl did not have a skin sensitizing effect.

In a maximization study using 15 Dunkin-Hartley guinea pigs, intradermal and epicutaneous inductions with 0.6% and 10.3% aq. ethanolamine, respectively, were performed after 10% sodium lauryl sulfate pre-treatment.18 (Ethanolamine contained less than 0.1% diethanolamine and triethanolamine.) At challenge with 0.41, 2.05, or 4.1% ethanolamine, 3, 2, and 3 animals, respectively, reacted positively after 3 days. Two of the 15 test animals reacted to the vehicle, but none of the control animals reacted to ethanolamine or the vehicle. Possible cross-reactions to 5% triethanolamine occurred in 3 animals, and to 7% diethanolamine in 2 animals. In a second test using the same protocol, no animals reacted to 0.41% ethanolamine, 2 reacted to 2.05% ethanolamine, and 1 reacted to 4.1% ethanolamine. Additionally, 1 animal reacted to 10% triethanolamine and 2 reacted to 7% diethanolamine. The control animals did not react to any of the ethanolamines.

**Human**

A formulation containing 5.9% ethanolamine, tested undiluted in a 48-h occlusive patch test with a 10-day non-treatment period prior to challenge, and one containing 11.47% ethanolamine, tested at 5% in 25% alcohol in a repeated insult patch test using semi-occlusive patches, were not sensitizing in clinical studies.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

**Provocative Testing**

Metalworkers that were dermatitis patients were patch tested with 2% ethanolamine in petrolatum (pet.).35 The patches were applied for 1-2 days. On day 3, 3 of 155 patients (1.9%) had positive reactions.

Patch testing was performed with 2% ethanolamine in pet. in 199 patients with suspected metalworking fluid contact dermatitis.36 (All patients were metalworkers.) Patches were applied for 1 or 2 days. On day 3, 40 patients had positive reactions, i.e., 16 (?), 19 (+), 4 (++), and 1 (+++). The % positive reactions was 11.6%.

A patch test using 2% ethanolamine in pet. was performed on 370 patients with suspected dermatitis to ethanolamine-containing metal-working fluids and on 452 control subjects.37 A 10-fold higher reaction was seen in the patient group, with 12.2% of the patients having positive reactions, as compared to 1.3% in the control group.

Over a 3-yr period, 11/595 hairdresser clients (1.9%) and 7/401 female hairdressers (1.8%) reacted positively to 2% ethanolamine in pet. In 22 patients with suspected intolerance to oxidative hair dye components, 4 had a positive reaction to 2% ethanolamine in pet. Over a 15-yr period, provocative patch testing using ethanolamine was performed on 9602 subjects. There were 363 positive reactions (3.8%) to ethanolamine, and most of the reactions (277; 2.9%) were weak positives. There were 55 irritant reactions (0.6%) reported. Cosensitization was reported; 38% of the patients that reacted to ethanolamine also tested positive with diethanolamine. Occupational sensitization was reported; of 5884 male patients evaluated, 2.9% that did not work in the metal industry had positive reactions to ethanolamine, as opposed to 7.0% of those working in the metal industry and 15.2% of those exposed to water-based metalworking fluids.

**Ocular Irritation**

**In Vitro**

**Ethanolamine**

The ocular irritation potential of ethanolamine was evaluated in vitro in the rabbit corneal epithelium model.38 At concentrations of 0.05, 0.5, and 1%; ethanolamine was classified as a moderate ocular irritant in this assay.
Non-Human

Using 6 rabbits, 30% aq. ethanolamine was moderately irritating to rabbit eyes. Undiluted ethanolamine, instilled as a volume of 0.005 ml, produced severe injury to rabbit eyes. A hair preparation containing 5.96% ethanolamine had a maximum avg. irritation score of 0.7/110 for rinsed and unrisned eyes.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

OCCUPATIONAL EXPOSURE

Ethanolamine inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma and clinical symptoms of acute liver damage and chronic hepatitis.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

A case of occupational asthma in an industrial worker exposed to a detergent containing 8% ethanolamine was reported.39 Since the detergent was used in hot water, release of ethanolamine vapor was greater than if the water temperature was lower. Exposure to vapors from ethanolamine in cleaning solutions can irritate the nose, throat, and lungs.40

Occupational Exposure Limits

The Occupational Safety and Health Administration permissible exposure level for ethanolamine is 3 ppm (6 mg/m³) as an 8-hr time-weighted average concentration.41 The National Institute for Occupational Health and Safety has a recommended exposure limit of 3 ppm (8 mg/m³) for a 10 h workday and 40 h work week; the short-term exposure limit is 6 ppm (15 mg/m³), for periods not to exceed 15 min.42

MISCELLANEOUS STUDIES

Effect on Hepatic Choline

The effects of ethanolamine HCl on hepatic choline was determined in the F₀ and F₁ parental rats from the two-generation feeding study described earlier in this report.43 Liver weights were determined for all parental rats at necropsy, and the livers of control and high-dose animals (1000 mg/kg bw/day) were examined microscopically. Feeding ethanolamine HCl to rats did not affect liver weights of any of the animals. No adverse microscopic affects in the livers of high-dose rats were reported. Liver samples of F₁ female rats of the test and control groups were analyzed for choline, phosphocholine, glycerophosphocholine, and phosphatidylcholine. A statistically significant increase in phosphocholine and phosphatidylcholine metabolism in the rat.

Researchers concluded that “based on the combined hepatic observations, ethanolamine hydrochloride does not affect hepatic choline metabolism in the rat.”

Effect on Bronchoconstriction

The effect of ethanolamine on bronchoconstriction was investigated using a group of 4 anesthetized male Hartley guinea pigs.44 When an aerosol of 0.1 ml/kg of 3.3% ethanolamine solution was inhaled through a tracheal cannula, bronchoconstriction was observed. The results were compared to those obtained using an aerosol of potassium hydroxide. Bronchoconstriction induced by ethanolamine was greater than that induced by potassium hydroxide. Additional testing suggested that ethanolamine-induced bronchoconstriction may not result from induction of acetylcholine or histamine release, but that it may result partly from an agonistic effect of ethanolamine at the histamine-H₁ receptor and the muscarinic receptor.

SUMMARY

This report assesses the safety of ethanolamine and its salts as used in cosmetics. The ethanolamine salts are expected to dissociate into ethanolamine and the corresponding acid. Ethanolamine typically contains a small amount of diethanolamine as an impurity. (Diethanolamine has been found to be safe in the present practices of use and concentration when formulated to be non-irritating; it should not be used in cosmetic products in which N-nitroso compounds can be formed). Ethanolamine and ethanolamine HCl function in cosmetic formulations as a pH adjuster. The organic salts and the organic-substituted inorganic salts mostly function as surfactants, with the exception of MEA-benzoate and MEA-salicylate, which are preservatives. MEA-sulfite is reported to function as a hair fixative.

In 2011, ethanolamine was reported to be used in 788 formulations, 772 of which are hair coloring formulations. Of the ethanolamine-containing ingredients that are in use, none have more than 15 uses. Reported maximum use concentrations of ethanolamine are 0.0002-18%. MEA-lauryl sulfate has the highest reported maximum use concentration at 35% in rinse-off formulations. In Europe, monoalkylamines, monoalkanolamines, and their salts are on the list of substances which must not form part of the composition of cosmetic products, except subject to restrictions and conditions laid down. These restrictions include a maximum secondary amines contaminant content of 0.5% in finished products, a maximum secondary amines content of 0.5% in raw materials, and a maximum nitrosamine content of 50 µg/kg. MEA-benzoate and MEA-salicylate are on the list of preservatives in Europe and both, as preservatives, are allowed a maximum concentration in ready-for-use preparations of 0.5% of the acid.

Ethanolamine is the only naturally occurring ethanolamine in mammals; it occurs in phospholipids known as phosphatides. In an in vitro study, absorption of undiluted and aq. ethanolamine was much greater through mouse skin than it was...
through human, rat, or rabbit skin; human skin was the least permeable. The cumulative dose absorbed through mouse and human skin (found in the effluent) was greater with aq. ethanolamine compared to undiluted ethanolamine; 16.92% of the undiluted and 24.79% of the aq. ethanolamine absorbed through mouse skin while 0.61% undiluted and 1.11% aq. ethanolamine absorbed through human skin. In split-thickness pig skin, 5% of the dose of ethanolamine HCl in ethanol penetrated percutaneously. In a metabolism and distribution study, ethanolamine HCl was applied dermally to human skin-grafted and ungrafted athymic nude mice. Radioactivity was recovered in the skin (18.4% recovered in grafted skin; 12.1% in ungrafted skin), liver (24.26%), and kidneys (0%). Approximately 5% of the radioactivity was recovered in the urine; 10% of the radioactivity recovered in the urine was unchanged ethanolamine, and the major urinary metabolites were urea and glycine. In an oral study in which Wistar rats were fed a diet containing 100-1000 mg/kg ethanolamine HCl for 10 wks, plasma ethanolamine concentrations increased in a dose-dependent manner from <3 mg/kg in control animals and <4 mg/kg in low dose animals to 60-81 mg/kg in high-dose animals.

Single applications of 5 and 10% ethanolamine were mildly toxic to mouse skin. The dermal LD50 in rabbits was 1.0-2.5 g/kg ethanolamine. Oral LD50 values were 0.7-15.0 g/kg in mice and 1.0-2.9 g/kg in rabbits. The 4 h inhalation LC50 of a mixture containing ethanolamine, hydroxyamine, 1-aminopropanol-2-ol, catechol, and water was estimated as 2.48 mg/l. Percutaneous application of 4 mg/kg/day ethanolamine to rats for an unspecified length of time resulted in nonspecific histological changes in the heart and lung, fatty degeneration of the liver parenchyma, and subsequent focal liver necrosis. In a dietary study in which rats were dosed with 0-2.67 g/kg/day ethanolamine for 90 days, heavy livers and kidneys were observed at ≥0.64 g/kg/day, and deaths and “major pathology” occurred with ≥1.25 g/kg/day. In a 2-yr dietary study in which Beagle dogs were fed 0-0.0975 g/kg/day of a hair dye composite that contained 22% ethanolamine, no toxic effects were observed. In repeated-dose inhalation studies, the dominant effects of “continuous exposure” of dogs, guinea pigs, and rats to 5-6 ppm ethanolamine vapor were skin irritation and lethargy; mortality was observed in dogs exposed to 102 ppm ethanolamine vapor for 2 days and in some rodents exposed to 67.5 ppm ethanolamine vapor for 24-28 days. Dogs and rodents exposed to 66-102 ppm ethanolamine vapor had pulmonary and hepatic inflammation, hepatic and renal damage, and hematomatological changes.

Dermal developmental toxicity studies were performed using rats and rabbits. In a study in which gravid rats were dosed with 10-225 mg/kg bw/day ethanolamine on days 6-15 of gestation, the no-observed effect level (NOEL) was 75 mg/kg/day for maternal toxicity and 225 mg/kg/day for embryonal/fetal toxicity. In rabbits that were dosed dermally with 10-75 mg/kg bw/day ethanolamine on days 6-18 of gestation, the NOEL was 10 mg/kg bw/day for maternal toxicity and 75 mg/kg bw/day for embryonal/fetal toxicity. Significant skin irritation was observed in the high dose groups for both rats and rabbits. In a Chernoff-Kavlock post-natal mouse screening assay, oral dosing with 850 mg/kg/day ethanolamine on days 6-15 of gestation resulted in 16% mortality of maternal mice and a reduced number of viable litters. In a study in which Wistar rats were gavaged with 40-450 mg/kg bw/day aq. ethanolamine on days 6-15 of gestation, the NOEL was 120 mg/kg/day for maternal toxicity and 450 mg/kg/day for developmental toxicity. In an oral study in which Long-Evans rats were dosed with 50-500 mg/kg aq. ethanolamine on days 6-15 of gestation, there was no significant maternal toxicity, but embryolethality was increased in the 500 mg/kg group and more reproductive and developmental effects were observed involving male pups compared to female pups. There was an increase in malformed pups in all dose groups. In a dietary two-generation study in rats with 100-1000 mg/kg bw/day ethanolamine HCl, the NOAEL was 300 mg/kg bw/day for systemic toxicity and for reproductive effects, and the NOAEL was 1000 mg/kg bw/day for developmental toxicity. The effect of ethanolamine HCl on hepatic choline was investigated in the F0 and F1 parental rats, and it was concluded that ethanolamine HCl did not affect the hepatic choline metabolism in the rat.

Ethanolamine was mostly negative in Ames tests (≤2000 μg/plate). Ethanolamine (≤500 μg/ml) was negative in a cell transformation assay. Ethanolamine did not produce chromosomal aberrations in rat liver cells, but did produce a “weak positive” response in human lymphocytes. Carcinogenicity data were not found in the published literature.

Semi-occlusive application of 30-100% ethanolamine was corrosive to rabbit skin. Irritation responses ranging from irritating to corrosive were observed with 1-10% ethanolamine, respectively, applied non-occlusively to rabbit ears and under semi-occlusive patches to rabbit skin. The degree of irritation increased with the concentration applied. In human studies, a formulation containing 5.9% ethanolamine was a cumulative irritant in a 21-day study, and an irritant response was reported during the induction phase of a patch test of a formulation containing 11.47% ethanolamine. Ethanolamine HCl ≤70%, did not have a sensitzing effect in a local lymph node assay. In a maximization study in guinea pigs with intradermal and epicutaneous inductions of 0.6 and 10.3% aq. ethanolamine, respectively, positive reactions were observed at challenge with 0.41, 2.05, and 4.1% ethanolamine. Possible cross-reactions to 5% triethanolamine and 7% diethanolamine were reported. In provocative testing of metalworkers with dermatitis, a higher reaction to ethanolamine was observed for the patients as compared to control subjects. In a study of hairdressers and clients, cosensitization to diethanolamine was reported for 38% of the patients that reacted to ethanolamine. In ocular irritation studies in rabbits, 30% aq. ethanolamine was moderately irritating to rabbit eyes, and undiluted ethanolamine produced severe injury. A hair preparation containing 5.96% ethanolamine had a maximum average irritation score of 0.7/110 in rinsed and unrinsed eyes. Ethanolamine, tested at 0.05, 0.5, and 1%, was classified as a moderate irritant in the in vitro rabbit corneal epithelial model evaluating ocular irritation potential.
One-tenth ml/kg of a 3.3% ethanolamine aerosol solution induced bronchoconstriction in guinea pigs. Ethanolamine-induced bronchoconstriction may result partly from an agonistic effect of ethanolamine at the histamine-H₁ receptor and the muscarinic receptor.

**DISCUSSION**

This amended safety assessment originated as a re-review of ethanolamine, and was expanded to include ethanolamine salts, the safety of which were supported by the data available in the original safety assessment and by other published and unpublished studies. These ingredients are reported to be used only in rinse-off products; therefore the CIR Expert Panel addressed the safety as used in rinse-off products only.

While the Panel noted gaps in the available safety data for the ethanolamine salts included in this group, the Panel relied on the information available for ethanolamine in conjunction with previous safety assessments of the components of ingredients. Those data could be extrapolated to support the safety of these ingredients. For example, coconut acid has been found safe as used, and the Panel was able to extrapolate these data to support the safety of MEA-cocoate (i.e., the ethanolamine salt of coconut acid).

The Panel noted that small amounts of diethanolamine could be present in ethanolamine and was concerned with levels of free diethanolamine that could be present as an impurity. Therefore, ethanolamine and ethanolamine-containing ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

Also, because diethanolamine might be present as an impurity in ethanolamine, the Panel re-iterated its discussion regarding the positive findings reported in a dermal carcinogenicity study of diethanolamine. The hepatocarcinogenicity that was reported in mice was considered to have little relevance to the safety of diethanolamine in personal care products. Additionally, renal lesions reported in mice could have been the result of diethanolamine-induced choline deficiency, a mechanism that has little relevance in humans. If diethanolamine-induced choline deficiency was not the cause of the renal lesions, it was thought there was still no carcinogenic risk to humans because diethanolamine does not appear to penetrate human skin to any significant extent at concentrations relevant to human exposures from the use of personal care products.

Ethanolamine is used in a hair color aerosol spray at a maximum concentration of 3%. Because ethanolamine is used in products that are sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel considered other pertinent data that were available, including data characterizing the potential of ethanolamine to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

Finally, the potential exists for dermal irritation with the use of products formulated using ethanolamine or ethanolamine salts. The Panel specified that products containing these ingredients must be formulated to be non-irritating.

**CONCLUSION**

The CIR Expert Panel concluded that ethanolamine and the 12 related ethanolamine salts, listed below, are safe in the present practices of use and concentration described in this safety assessment (rinse-off products only) when formulated to be non-irritating. The Panel cautioned that ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

- Ethanolamine
- Ethanolamine HCl*
- MEA-Benzate*
- MEA Cocoate
- MEA-Laureth-6 Carboxylate*
- MEA-Laureth Sulfate
- MEA-Lauryl Sulfate
- MEA-PPG Laureth-6 Carboxylate*
- MEA-PPG-8 Steareth-7 Carboxylate*
- MEA-Salicylate*
- MEA-Sulfite*
- MEA-Tallowate
- MEA-Undecylenate*

Were the ingredients not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.
**Table 1.** Definition and structures of ethanolamine and ethanolamine-containing ingredients

<table>
<thead>
<tr>
<th>Ingredient/ CAS No.</th>
<th>Definition</th>
<th>Reported Function</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanolamine 141-43-5</td>
<td>a primary amine with one ethanol functional group.</td>
<td>pH adjuster</td>
<td><img src="structure_image1" alt="Ethanolamine Structure" /></td>
</tr>
<tr>
<td>Ethanolamine HCl 2002-24-6</td>
<td>the ethanolamine salt of hydrochloric acid.</td>
<td>pH adjuster; buffering agent</td>
<td><img src="structure_image2" alt="Ethanolamine HCl Structure" /></td>
</tr>
<tr>
<td>MEA-Sulfite 13427-63-9</td>
<td>the ethanolamine salt of hydrogen sulfite.</td>
<td>hair fixative</td>
<td><img src="structure_image3" alt="MEA-Sulfite Structure" /></td>
</tr>
<tr>
<td><strong>Organic Acid Salts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA-Benzoate 4337-66-0 33545-23-2</td>
<td>the ethanolamine salt of benzoic acid.</td>
<td>preservative</td>
<td><img src="structure_image4" alt="MEA-Benzoate Structure" /></td>
</tr>
<tr>
<td>MEA-Saliclylate 59866-70-5</td>
<td>the ethanolamine salt of salicylic acid.</td>
<td>preservative</td>
<td><img src="structure_image5" alt="MEA-Saliclylate Structure" /></td>
</tr>
<tr>
<td>MEA-Cocoate 66071-80-5</td>
<td>the ethanolamine salt of coconut acid.</td>
<td>surfactant – cleansing agent; surfactant – foam booster</td>
<td><img src="structure_image6" alt="MEA-Cocoate Structure" /></td>
</tr>
<tr>
<td>MEA-Tallowate</td>
<td>the ethanolamine salt of tallow acid.</td>
<td>IN VCRP; not in INCI Dictionary</td>
<td><img src="structure_image7" alt="MEA-Tallowate Structure" /></td>
</tr>
<tr>
<td>MEA-Undecylenate 56532-40-2</td>
<td>ethanolamine salt of undecylenic acid</td>
<td>surfactant – cleansing agent</td>
<td><img src="structure_image8" alt="MEA-Undecylenate Structure" /></td>
</tr>
<tr>
<td>MEA-Laureth-6 Carboxylate</td>
<td>the ethanolamine salt of laureth-6 carboxylic acid (wherein “-6” represents the number ethylene glycol units, including the carboxylate).</td>
<td>surfactant – cleansing agent</td>
<td><img src="structure_image9" alt="MEA-Laureth-6 Carboxylate Structure" /></td>
</tr>
<tr>
<td>MEA PPG-6 Laureth-7 Carboxylate</td>
<td>the ethanolamine salt of PPG-6 laureth-7 carboxylic acid (wherein “-7” represents the number ethylene glycol units, including the carboxylate).</td>
<td>surfactant – cleansing agent</td>
<td><img src="structure_image10" alt="MEA PPG-6 Laureth-7 Carboxylate Structure" /></td>
</tr>
</tbody>
</table>
Table 1. Definition and structures of ethanolamine and ethanolamine-containing ingredients

<table>
<thead>
<tr>
<th>Ingredient/ CAS No.</th>
<th>Definition</th>
<th>Reported Function</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEA-PPG-8-Steareth-7 Carboxylate</td>
<td>the ethanolamine salt of PPG-8 steareth-7 carboxylic acid (wherein “-7” represents the number ethylene glycol units, including the carboxylate).</td>
<td>surfactant – cleansing agent</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

**Organic-Substituted Inorganic Salts**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Definition</th>
<th>Reported Function</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEA-Lauryl Sulfate 4722-98-9</td>
<td>is the ethanolamine salt of sulfated lauryl alcohol.</td>
<td>surfactant – cleansing agent</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>MEA-Laureth Sulfate 68184-04-3</td>
<td>the ethanolamine salt of sulfated, ethoxylated lauryl alcohol (wherein the number of ethylene glycol units ranges from 1 to 4).</td>
<td>surfactant – cleansing agent</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

Table 2. Conclusions of previously reviewed ingredients and components

**PREVIOUSLY REVIEWED INGREDIENTS**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanolamine</td>
<td>is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin, and MEA should only be used in rinse-off products (1983)(^1)</td>
</tr>
<tr>
<td>MEA-Salicylate</td>
<td>safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin’s sun sensitivity, or, when increased sun sensitivity would be expected; directions for use include the daily use of sun protection (2003)(^4)</td>
</tr>
</tbody>
</table>

**COMPONENTS**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium Lauryl Sulfate</td>
<td>safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin; in products intended for prolonged contact with skin, concentrations should not exceed 1% (1983)(^3)</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>safe as used (2011)(^6)</td>
</tr>
<tr>
<td>Benzoic Acid</td>
<td>safe as used (2008)(^7)</td>
</tr>
<tr>
<td>Coconut Acid</td>
<td>safe as used when formulated to be non-irritating (2010)(^8)</td>
</tr>
<tr>
<td>Laureths</td>
<td>safe as used when formulated to be non-irritating (2010)(^9)</td>
</tr>
<tr>
<td>PPG</td>
<td>safe as used when formulated to be non-irritating (2010)(^10)</td>
</tr>
<tr>
<td>Sodium Laureth Sulfate and related salts of ethoxylated alcohols</td>
<td>safe as used when formulated to be non-irritating (2010)(^11)</td>
</tr>
<tr>
<td>Steareths</td>
<td>safe as used when formulated to be non-irritating (2010)(^12)</td>
</tr>
</tbody>
</table>
Table 3. Physical and chemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanolamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Form</td>
<td>clear viscous liquid</td>
<td>1</td>
</tr>
<tr>
<td>Color</td>
<td>colorless</td>
<td>1</td>
</tr>
<tr>
<td>Odor</td>
<td>ammonia-like</td>
<td>1</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>61.08</td>
<td>1</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.0117 (25°C)</td>
<td>1</td>
</tr>
<tr>
<td>Viscosity</td>
<td>18.95 (25°C)</td>
<td>1</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>1.4542 (20°C)</td>
<td>7</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>0.48 mm Hg (20°C)</td>
<td>1</td>
</tr>
<tr>
<td>pK&lt;sub&gt;a&lt;/sub&gt;</td>
<td>9.5 (25°C)</td>
<td>7</td>
</tr>
<tr>
<td>Melting Point</td>
<td>10.3-10.5°C</td>
<td>1</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>171°C</td>
<td>1</td>
</tr>
<tr>
<td>Water Solubility</td>
<td>miscible with water</td>
<td>26</td>
</tr>
<tr>
<td>Other Solubility</td>
<td>miscible with methanol and acetone</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>soluble in alcohol, ethanol, chloroform, glycerol, logroin</td>
<td>7</td>
</tr>
<tr>
<td>log P&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>-1.31</td>
<td>51</td>
</tr>
<tr>
<td>MEA Benzoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>165.19 (calculated)</td>
<td>52</td>
</tr>
<tr>
<td>pK&lt;sub&gt;a&lt;/sub&gt;</td>
<td>8.0 g/cm³ (most basic; 25°C) (calculated)</td>
<td>52</td>
</tr>
<tr>
<td>Density</td>
<td>1.119 g/cm³ (20°C) (calculated)</td>
<td>52</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>271.8°C (calculated)</td>
<td>52</td>
</tr>
<tr>
<td>log P</td>
<td>1.336 (25°C) (calculated)</td>
<td>52</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th># of Uses&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Max. Conc. of Use (%)&lt;sup&gt;11&lt;/sup&gt;</th>
<th># of Uses&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Max. Conc. of Use (%)&lt;sup&gt;11&lt;/sup&gt;</th>
<th># of Uses&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Max. Conc. of Use (%)&lt;sup&gt;11&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethanolamine</td>
<td>MEA Cocoate</td>
<td>MEA-Laureth Sulfate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals*</td>
<td>788</td>
<td>0.0002-18</td>
<td>4</td>
<td>NR</td>
<td>13</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Duration of Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leave-On</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rinse-Off</td>
<td>788</td>
<td>0.0002-18</td>
<td>4</td>
<td>NR</td>
<td>13</td>
<td>NR</td>
</tr>
<tr>
<td>Diluted for (Bath) Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exposure Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Area</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Inhalation-Spray</td>
<td></td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Inhalation-Powder</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>3</td>
<td>0.0002-11</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>13</td>
<td>0.05-6</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>772</td>
<td>3-18</td>
<td>NR</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nail</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>2</td>
<td>0.02-0.05</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Baby Products</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Table 4a. Frequency and concentration of use according to duration and type of exposure

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th>MEA-Lauryl Sulfate</th>
<th>MEA-Tallowate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Uses</td>
<td>Max. Conc. of Use (%)</td>
</tr>
<tr>
<td>Leave-On</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rinse Off</td>
<td>5</td>
<td>5-35</td>
</tr>
<tr>
<td>Diluted for (Bath) Use</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Exposure Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Area</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Inhalation-Spray</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental Inhalation-Powder</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>NR</td>
<td>35</td>
</tr>
<tr>
<td>Nail</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Baby Products</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>5</td>
<td>5-35</td>
</tr>
</tbody>
</table>

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.
NR – no reported uses

### Table 4b. Ingredients not reported to be in use

- Ethanolamine HCl
- MEA-Benzoate
- MEA-Laureth-6 –Carboxylate
- MEA-PPG-6 Laureth-7 Carboxylate
- MEA-Salicylate
- MEA-Sulfite
- MEA Undecylenate

### Table 4c. Status for use in Europe according to the EC CosIng Database for ethanolamine ingredients

**Fatty Acid Monoalkylamines, monoalkanolamines, and their salts – listed in Annex III – restrictions**

- (maximum secondary amine content of 0.5% in the finished product; do not use with nitrosating systems; minimum purity – 99%; maximum secondary amine content of 0.5% for raw materials; maximum nitrosamine content of 50 µg/kg; keep in nitrite free containers)

- Ethanolamine
- Ethanolamine HCl
- MEA PPG-6 Laureth-7 Carboxylate
- MEA-Benzoate
- MEA-Cocoate
- MEA-Laureth Sulfate
- MEA-Laureth-6 Carboxylate
- MEA-Laurate-7 Carboxylate
- MEA-P PPG-8-Steareth-7 Carboxylate
- MEA-Salicylate
- MEA-Sulfite
- MEA –Undecylenate

**List of Preservatives Allowed in Cosmetics – Annex V**

- MEA-Benzoate (maximum concentration in ready-for-use preparations of 0.5% benzoic acid)
- MEA-Salicylate (maximum concentration in ready-for-use preparations of 0.5% salicylic acid; not to be used in products for children under 3 years of age, except shampoos)
REFERENCES


23. Anonymous. Letter to the Environmental Protection Agency reporting an acute dermal toxicity study of a formulation containing DEA. 6-7-2010. 8EHQ-10-17970.


25. Anonymous. Letter to the Environmental Protection Agency reporting an acute inhalation toxicity studies of a formulation containing DEA. 6-8-2010. 8EHQ-0610-17981A.


52. ACD/Labs. Advanced Chemistry Development (ACD/Labs) Software. 2011. (9.02):
Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine

Triethanolamine (TEA), Diethanolamine (DEA), and Monoethanolamine (MEA) are amino alcohols used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals.

In single-dose oral toxicity for rats, TEA was practically nontoxic to slightly toxic, and DEA and MEA were slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a > 10% concentration in 10 open applications over a period of 14 days.

The ethanolamines were nonmutagenic in the Ames test and TEA is also nonmutagenic to Bacillus subtilis. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test. TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months.

Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity or photosensitization reactions with products containing up to 20.04% TEA. A formulation containing 11.47% MEA and a formulation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

The Panel concludes that TEA, DEA, and MEA are safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.
CHEMICAL AND PHYSICAL PROPERTIES

Structure

Triethanolamine (CAS No. 102-71-6) (TEA), Diethanolamine (CAS No. 111-42-2) (DEA), and Monoethanolamine (CAS No. 141-43-5) (MEA) are amino alcohols. They are produced by aminating ethylene oxide with ammonia. The replacement with ethanol groups of three, two, or one hydrogen of ammonia results in TEA, DEA, or MEA, respectively. The chemical formulas of the ethanolamines are as follows:

![Chemical formulas of ethanolamines]

Properties

TEA, DEA, and MEA are clear, colorless, viscous liquids with ammoniacal odors. They are hygroscopic and are strong bases. The ethanolamines are soluble in water, alcohol, and chloroform, and are insoluble in benzene, ether, and petroleum distillates. Chemical and physical properties of TEA, DEA, and MEA are presented in Table 1. A sampling of the variety of values available in the literature is given for several chemical and physical properties. This variation may reflect the use of different grades of chemicals.

Reactivity

TEA, DEA, and MEA are reactive and are bifunctional, combining the properties of alcohols and amines. The ethanolamines will react at room temperature with fatty acids to form ethanolamine soaps, and DEA and MEA will react at temperatures between 140° and 160°C with fatty acids to form ethanolamides. The reaction of ethanolamine and sulfuric acid produces sulfates, and DEA and MEA may react, under anhydrous conditions, with carbon dioxide to form carbamates.

The ethanolamines can act as antioxidants in the autoxidation of fats of both animal and vegetable origin. TEA and DEA have stronger antioxidant effects than MEA. TEA is an antioxidant as measured by the Tetrahymena photodynamic assay.

TEA and DEA can react with nitrite or oxides of nitrogen to form N-nitrosodiethanolamine (NDELA). As yet, MEA has not been found to form a stable nitrosamine. MEA can react with an aldehyde to form DEA, and then can be

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TABLE 1. Chemical and Physical Properties.

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nitrosated to form NDELA. The optimum pH for nitrosamine formation is variously reported to be between 1 and 6, and the reaction rate decreases as the pH increases. Neutral solutions require 100,000 times as much nitrite as strong acid solutions in order to form the same amount of nitrosamine. However, in the presence of catalysts such as chloral or an aldehyde, nitrosation reactions may occur up to a pH of 11. The rate of NDELA formation in the pH range 4–9 is four to six times greater in the presence of formaldehyde than in its absence. Higher temperatures and longer reactions times increase the yield of
Nitrosamine. Nitrosation reactions and salt formation reactions compete in aqueous solutions. The nitrosation by nitrites of DEA in an oil-in-water emulsion to NDELA can be inhibited by ascorbic acid or sodium bisulfite or much less effectively inhibited by potassium sorbate incorporated into the aqueous phase or can be inhibited by ascorbyl palmitate incorporated into the oil phase.

**Methods of Manufacture and Impurities**

The ethanolamines are commercially produced by aminating ethylene oxide with ammonia. The reaction temperature can be adjusted to produce mostly TEA or MEA. The product is purified by distillation. A "low freeze grade" product can be prepared by adding up to 15% water.

TEA contains small amounts of DEA and MEA, and DEA contains small amounts of TEA and MEA. MEA contains a small amount of DEA. TEA used in cosmetics may contain a maximum of 0.5% water, 0.05% sulfated ash, and 15 ppm iron.

**Analytical Methods**

Qualitative and quantitative determinations of the ethanolamines are made by colorimetric procedures, titrimetric methods, thin-layer chromatography, gas chromatography, gravimetric analysis, thermogravimetric analysis, the Kjeldahl method, and the Van Slyke procedure. Positive identification of the ethanolamines can be made by comparison with published infrared spectra. UV absorbance spectra are available for TEA and MEA.

Jones et al. used gas chromatography to determine the amount of TEA in a simulated vanishing cream and shampoo. They did a preliminary separation into classes of compounds and were then able to recover between 96% and 101% of the TEA added to the cosmetic formulations.

**USE**

**Purpose in Cosmetics**

Ethanolamine soaps, formed from the reaction at room temperature of TEA, DEA, or MEA and fatty acids, and ethanolamides, formed from the reaction at elevated temperatures of DEA and MEA and fatty acids, are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents.

**Scope and Extent of Use in Cosmetics**

Product types and the number of product formulations containing TEA, DEA, or MEA reported voluntarily to the Food and Drug Administration (FDA) in 1981 are presented in Table 2. Table 2 does not include products containing TEA-lauryl sulfate or TEA-coco-hydrolyzed animal protein. These two ingredients have been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in
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<tr>
<td>Hair dyes and colors (all types requiring caution statement and patch test)</td>
<td>811</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair shampoos (coloring)</td>
<td>16</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hair bleaches</td>
<td>111</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Other personal cleanliness products</td>
<td>227</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Shaving cream (aerosol, brushless, and lather)</td>
<td>114</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moisturizing skin care preparations</td>
<td>747</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1981 TOTALS</td>
<td></td>
<td>51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data from Ref. 48.
other documents.\(^{(46,47)}\) Voluntary filing of product formulation data by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations (21 CFR, Part 720.4). Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the actual concentration of the finished product; the concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. The majority of these products contained TEA, DEA, or MEA in a concentration of less than or equal to 5%.\(^{(48)}\)

**Surfaces to Which Commonly Applied**

Cosmetic products containing ethanolamines may be applied to or come in contact with skin, eyes, hair, nails, mucous membranes, and respiratory epithelium. Small amounts may be ingested from lipstick (Table 2).\(^{(48)}\)

**Frequency and Duration of Application**

Product formulations containing ethanolamines may be applied as many as several times a day and may remain in contact with the skin for variable periods of time following each application. Daily or occasional use may extend over many years (Table 2).\(^{(48)}\)

**Potential Interactions with Other Cosmetic Ingredients**

N-nitrosating agents, present as intentional ingredients or as contaminants of cosmetics, may react with the ethanolamines to form N-nitrosodiethanolamine (NDELA). NDELA has been found in cosmetic raw materials. Ninety-nine samples of 17 materials were evaluated and NDELA was detected in concentrations of greater than 1000 ppb, 501–1000 ppb, 101–500 ppb, and 50–100 ppb in 6, 3, 6, and 6 samples, respectively. NDELA was found in trace levels in nine samples and was not detected in 69 samples.\(^{(13,49)}\) NDELA has also been detected in a variety of cosmetic products.\(^{(50-60)}\) An on-going study by the FDA has provided NDELA analysis for 335 off-the-shelf cosmetic formulations. The FDA data are presented in Table 3. NDELA was detected in 110 of a total of 252 products containing TEA and in 25 of a total of 64 products not containing TEA. However, products with no TEA may have contained DEA or MEA. These findings suggest the possibility that TEA may lead to the formation of NDELA in some cosmetics.

Bronaugh et al.\(^{(61,62)}\) investigated the percutaneous absorption of NDELA through excised human skin. NDELA was dissolved in water, propylene glycol, and isopropyl myristate, and the permeability constants were $5.5 \times 10^{-6}$, $3.2 \times 10^{-5}$, and $1.1 \times 10^{-3}$ cm/h, respectively. The permeability of NDELA through ex-
cised human skin was greatly increased when applied from sufficiently lipoidal formulations. The major route of elimination after oral and topical administration of NDELA to rats was the urine.\(^{63}\) NDELA was applied to the skin of monkeys and pigs and, afterwards, was detected in their urine.\(^{64}\) NDELA was detected in rat urine following epicutaneous and intratracheal administration of NDELA and following percutaneous administration of DEA and oral administration of nitrite in drinking water.\(^{65}\) After application of an NDELA-contaminated cosmetic. NDELA was detected in human urine.\(^{66}\)

NDELA, in concentrations of 5–15 mg/plate, was mutagenic to Salmonella typhimurium strains TA1535 and TA100 in the presence of hamster liver S-9 but not in the presence of rat liver S-9.\(^{67}\) NDELA is carcinogenic to rats after oral administration\(^{68,70}\) and to hamsters after subcutaneous injections, skin painting, and oral cavity swabbing.\(^{71,72}\) Although no epidemiological data were available, the International Agency for Research on Cancer\(^{73}\) has suggested that “NDELA should be regarded for all practical purposes as if it were carcinogenic to humans.”

Nitrites have been found in cosmetic raw materials.\(^{13,49,74}\) TEA and DEA can be nitrosated to NDELA with 2-bromo-2-nitropropane-1,3-diol (BNPD), an antimicrobial agent used in cosmetics.\(^{75-77}\) A report on the safety assessment of BNPD recommended against its usage in cosmetics where its actions with amines or amides could result in the formation of nitrosamines or nitrosamides.\(^{75}\) Ong et al.\(^{78}\) discovered that NDELA could be formed from the peroxidation and subsequent nitrosation of DEA. They found that peroxides could result from the autoxidation of compounds such as polysorbate 20 and that the addition of antioxidants prevented this. Under the same experimental conditions, TEA and MEA did not yield NDELA.

### Noncosmetic Uses

The ethanolamines are used in the manufacture of emulsifiers and dispersing agents for textile specialties, agricultural chemicals, waxes, mineral and vegetable oils, paraffin, polishes, cutting oils, petroleum demulsifiers, and cement additives. They are intermediates for resins, plasticizers, and rubber chemicals. They are used as lubricants in the textile industry, as humectants and

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**Table 3.** Association of NDELA with TEA in Cosmetics

<table>
<thead>
<tr>
<th>Cosmetic product samples</th>
<th>NDELA detected</th>
<th>No NDELA detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA</td>
<td>110</td>
<td>142</td>
</tr>
<tr>
<td>No TEA</td>
<td>25</td>
<td>39</td>
</tr>
<tr>
<td>Incomplete or no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingredient information</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>(Total)</td>
<td>140</td>
<td>195</td>
</tr>
</tbody>
</table>

Data from Refs. 51–55.
softening agents for hides, as alkalizing agents and surfactants in pharmaceuticals, as absorbents for acid gases, and in organic syntheses.\(^{(5,6)}\)

TEA, at a concentration not exceeding 2 ppm, and MEA, at a concentration not exceeding 0.3 ppm, may be used in flume water for washing sugar beets prior to slicing (21 CFR 173.315). TEA, DEA, and MEA, at no specific concentration limits, may be components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food\(^{(79)}\) except that TEA and DEA may not exceed 5% by weight of rubber articles intended for repeated use.\(^{(80)}\) TEA and DEA may be used as adjuvants for pesticide chemicals and are exempt from the requirement of tolerances\(^{(81)}\) except that DEA maleic hydrazide may not be sold in the United States.\(^{(82)}\)

**GENERAL BIOLOGY**

**Antimicrobial Effects**

TEA, DEA, and MEA inhibit the growth of a wide variety of microorganisms. The concentration of ethanolamine required to inhibit growth varies with genus and species.\(^{(83,87)}\) DEA and MEA have some antimycotic activity when applied on the skin of guinea pigs.\(^{(88,90)}\)

**Effects on Chick Embryo**

The incubation of chicken eggs with 0.03% MEA for 18 h increases the number of eggs with visible blastodisks, increases the synthesis of proteins, fats, and carbohydrates, and increases the number of hatching chicks.\(^{(91)}\)

**Effects on Enzymatic Activity**

**Effects on Enzymes Involved in Lipid Biosynthesis**

TEA, DEA, and MEA affect the biosynthesis of lipids. Reactions of particular interest in mammals are those involved in the synthesis of the phosphoglycerides, phosphatidylethanolamine (PE), phosphatidylcholine (lecithin) (PC), and phosphatidylycerine (PS):\(^{(92)}\)

\[
\text{ethanolamine kinase} \\
\text{Ethanolamine + ATP} \xrightarrow{\text{ethanolamine kinase}} \text{phosphoethanolamine + ADP} \\
\text{phosphoethanolamine cytidylyltransferase} \\
\text{CTP + phosphoethanolamine} \xrightarrow{\text{phosphoethanolamine cytidylyltransferase}} \text{CDP-ethanolamine + PP}_i \\
\text{phosphoethanolamine transferase} \\
\text{CDP-ethanolamine + diacylglycerol} \xrightarrow{\text{phosphoethanolamine transferase}}
\]
The administration of MEA at a dose of 60 mg/kg/day for 30 consecutive days to albino rats with experimentally-induced coarction of the aorta resulted in elevated levels of PE, PS, and PC in the rat myocardium. Metabolic changes produced by MEA action may have inhibited the development of cardiac insufficiency in these animals. Hale et al. grew chicken embryo fibroblasts in standard media with 40 mg/ml of choline in delipidated media without choline, and in delipidated media without choline and with 40 mg/ml of MEA. The PE content of the cells was increased in both delipidated media and hexose transport was slowed in the MEA supplemented medium. The authors suggested that some property of MEA other than its accompanying increase in PE must be responsible for the drop in hexose transport in these cells. Upreti injected intraperitoneally approximately 168 mg/kg of MEA into male albino mice every day for four days. Mice were sacrificed at 6, 12, 24, 48, and 96 h. At all times from 12 to 96 h, the liver ethanol kinase levels of the treated mice were significantly higher than control mouse liver levels.

Barbee and Hartung investigated the effect of the administration of DEA on the in vivo incorporation of MEA and choline into rat liver and kidney. They found that the administration of 250 mg/kg of labeled DEA in a single injection to male albino rats did not change the amount of injected labelled MEA and choline incorporated into liver or kidney. However, when labelled DEA was administered to male albino rats at a dose of 320 mg/kg/day in drinking water for up to three weeks, the results were different. Rats were sacrificed at 0, 1, 2, and 3 weeks, and the amounts of injected labeled MEA and choline incorporated in the liver and in the kidney were lower at 1, 2, and 3 weeks than at time 0. MEA and choline phospholipid derivatives were synthesized faster and in greater amounts, and were catabolized faster than DEA phospholipid derivatives. This may favor accumulation of DEA-containing phospholipids during chronic exposure. These researchers also investigated the effects of DEA on mitochondrial function in the male albino rat. Administration of neutralized DEA at doses of 490 mg/kg/day for three days or of 160 mg/kg/day for one week in drinking water produced alterations of hepatic mitochondrial function. Barbee and Hartung hypothesize...
that DEA phospholipids are formed and incorporated into mitochondrial membranes with subsequent disruption of mitochondrial metabolism.

The activity of glucosyltransferase, isolated from Streptococcus mutans culture supernatant solutions, was stimulated by TEA at a concentration of 50 mM and a pH of 6.5. Glucosyltransferase catalyzes the formation of glucocerebroside, a sphingolipid, from ceramide and UDP-D-glucose.

**Effects on Other Enzymes**

MEA inhibits the action of purified acetylcholinesterase from bovine erythrocytes. Acetylcholinesterase catalyzes the reaction of acetylcholine and water to acetic acid and choline. This enzyme functions in the activity of the nervous system.

DEA administered intraperitoneally or orally may affect directly or indirectly the serum enzyme levels, isozyme patterns, and concentrations of some amino acids and urea in the male rat liver and kidney. These changes were observed concomitant with or just after organ damage was histologically detectable. Subchronic DEA administration in drinking water increased male rat hepatic mitochondrial ATPase and altered mitochondrial structure and function.

MEA stimulates the activity of purified aspartate transaminase from porcine heart and intraperitoneal or intravenous administration of MEA decreases aspartate transaminase activity in rabbit kidney and heart. The reversible reaction of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate is catalyzed by aspartate transaminase. Kotogyan et al. found that the intravenous administration of MEA to rabbits for seven days increased the level of aspartate and glutamate in the kidneys and decreased the levels in the brain.

The intraperitoneal or intravenous administration of MEA to rabbits decreased the activity of alanine transaminase in the kidney and the heart. Alanine transaminase is the enzyme involved in the reversible reaction that converts L-alanine and α-ketoglutarate to pyruvate and L-glutamate.

MEA can inactivate and partially dissociate β-galactosidase from Escherichia coli. Beta-galactosidase catalyzes the formation of D-glucose and D-galactose from lactose and water.

**Effects on Hormones**

MEA can affect the metabolism of catechol amines. The conversion of interest is as follows:

L-tyrosine → dihydroxyphenylalanine (DOPA) → dopamine → norepinephrine → epinephrine
Epinephrine and norepinephrine are hormones secreted by the adrenal medulla. They act in the regulation of heart rate and blood pressure. Epinephrine also activates glycogen breakdown to glucose in the liver and in muscle through its stimulation of adenylate cyclase.\(^{(92)}\) Intraperitoneal injection of MEA into rats at 10 mg/kg increased norepinephrine and decreased epinephrine in the heart. A 25 mg/kg injection of MEA had the opposite effect. At the higher MEA dose, after three days the heart norepinephrine concentration remained altered and the DOPA concentration increased.\(^{(107)}\) A 25 mg/kg intraperitoneal injection of MEA increased mouse heart muscle content of epinephrine and DOPA and decreased the content of norepinephrine.\(^{(108)}\) Goncharenko et al.\(^{(109)}\) found increased dopamine concentrations in rats following injection of MEA. DOPA decreased or remained unchanged.

Okano\(^{(110)}\) reported that the in vitro conversion of proparathyroid hormone formed in the parathyroid gland to parathyroid hormone was strongly inhibited by the action of MEA. Parathyroid hormone is involved in the metabolism of calcium and phosphorus by the body.

**Effects on Protein, Nucleic Acids, and Other Cellular Substances**

Subchronic oral administration of MEA to castrated rams increased serum albumin concentrations and total protein concentrations.\(^{(111)}\)

The administration of MEA to rabbits, either intraperitoneally or intravenously, increased RNA concentrations in the kidney, heart, and brain, decreased DNA concentrations in the heart and brain, and had no effect on total nitrogen or protein in any of the three tissues.\(^{(103)}\)

Intraperitoneal administration of MEA to rats increased glycogen, ATP, and ascorbic acid concentrations in the liver, kidney, brain, and heart.\(^{(112)}\)

**Effects on Liver Structure**

Grice et al.\(^{(100)}\) assessed morphological damage to rat liver and kidney four and 24 h after intraperitoneal injection of DEA at 100 and 500 mg/kg. At both times, after both doses and in both organs, cytoplasmic vacuolization was observed. In addition, mitochondria of the hepatocytes were swollen and less dense than in the control animals, and after 24 h, liver nuclei were more deeply basophilic than normal. At both times at the high dose of DEA, there was some renal tubular degeneration and some cells were necrotic. Barbee and Hartung\(^{(97)}\) found that the mitochondria from rats treated with 3 mg/kg/day of DEA for two weeks in their drinking water were consistently spherical and also appeared larger than mitochondria from control animals. Korsud et al.\(^{(101)}\) administered 100 to 6400 mg/kg of DEA orally to rats. They discovered that liver and kidney weights and damage to the liver and kidney increased as dose increased. They confirmed the observations of Grice et al.\(^{(100)}\) except that they found no morphological differences in mitochondria from control and treated rats.

**Effects on the Heart**

MEA, administered to rats with experimentally-induced coarctation of the aorta, at doses from 5 to 50 mg/kg enhanced myocardial contractility. Thirty-day
administration of MEA in a dose of 10 mg/kg stimulated and 60 mg/kg of MEA inhibited the development of myocardial hypertrophy. Increasing doses of MEA from $9.6 \times 10^{-7} \, M$ to $1.2 \times 10^{-5} \, M$ increased the atrial rate and force of contraction in the isolated rabbit atria.

**Effects on the Bovine Rhodopsin Chromophore**

MEA bleached the visual pigment, rhodopsin, from water-washed bovine retinal rod chromophores, which are responsible for vision in dim light.

**ABSORPTION, METABOLISM, STORAGE, AND EXCRETION**

MEA is the only naturally occurring ethanolamine in mammals and is excreted in the urine. Much of the available scientific literature on the metabolism of the ethanolamines is concerned with the effect on phospholipid biosynthesis of the intraperitoneal and intracerebral or in vitro administration of MEA to intact mammals or mammalian tissue, respectively. Ansell and Spanner have performed a representative experiment. Labeled MEA was administered intraperitoneally to adult female rats, the rats were sacrificed, and incorporation of MEA into phospholipids was traced in the liver, the blood, and the brain. They discovered that MEA was converted to phosphatidylethanolamine (PE) in all the tissues. However, the step-wise methylation of PE that converts it to phosphatidylcholine (PC), which occurs rapidly in the liver and less rapidly in extrahepatic tissues, did not occur at all in the brain. Morin found that labelled MEA was incorporated into PE and also into PC in isolated human peripheral arteries. This suggests that the enzyme system for transmethylation of PE to PC may be active in human arteries. Researchers have found labeled respiratory carbon dioxide after intraperitoneal administration of labeled MEA to rats. Further sources are available that corroborate these findings on the effect of MEA on lipid biosynthesis in mammals.

In vitro administration of MEA had no effect on the incorporation of labeled phosphate into phospholipids in swine coronary and pulmonary arteries or in rabbit or human endometria. However, in both cases TEA did inhibit the incorporation of labeled phosphate into phospholipids.

Babior labeled purified MEA from an unspecified source and demonstrated a coenzyme-B$_{12}$-dependent ethanolamine deaminase mediated conversion of MEA to acetaldehyde and ammonia. Ostrovskii and Bankovskii administered MEA intraperitoneally to rats and observed an increase in blood urea and brain glutamine. They suggested that ethanolamine was an ammonia source. Sprinson and Weliky labeled MEA and administered it in feed to rats. They detected labeled acetate in the urine of the rats. They suggested that MEA is phosphorylated by ATP in vivo, converted to acetaldehyde, ammonia, and inorganic phosphate and then the acetaldehyde is oxidized to acetate. These researchers hypothesize that the removal of phosphorylated MEA by its conversion to acetate may exert a regulatory effect on PE biosynthesis.

Labeled MEA was administered to dogs. The route of administration was unspecified. After 24 h, the total blood radioactivity as a percentage of dose was
1.69%. There was a persistence of low levels of radioactivity in dog whole blood samples; the half-life was 19 days. Excretion in urine of radioactivity as a percentage of dose was 11%.

**ANIMAL TOXICOLOGY**

**Oral Studies**

**Acute Toxicity**

The acute oral toxicity of TEA, DEA, MEA, and a hair preparation containing DEA and MEA has been studied in guinea pigs and in rats. The animals were administered the material by gavage, and then were observed for 14 days. Table 4 presents data from the experiments. The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. The LD50 values for DEA and MEA are quite similar and are lower than the LD50 values for TEA. In the Hodge and Sterner classification of single-dose oral toxicity for rats, TEA, DEA, and MEA would be classified as practically nontoxic to slightly toxic, slightly toxic, and slightly toxic, respectively.

**Oral Corrosivity**

A study was conducted on rabbits to determine the oral tissue corrosivity potential of a hair preparation containing 1.6% DEA, 5.9% MEA, and 3.2% sodium borate. The undiluted test material at a dose of 0.229 g/kg (0.210 ml/kg) was placed on the posterior tongue surface of four rabbits and they were allowed to swallow. Two rabbits were sacrificed at 24 h and two at 96 h. Gross and microscopic examinations of the tongue, adjacent pharyngeal structures, larynx, esophagus extending to the cardiac incisure, and stomach revealed no observable abnormalities. The hair preparation was not an irritant and was not corrosive in these tests.

**Subchronic and Chronic Toxicity**

Long-term oral toxicity of TEA, DEA, MEA or a composite of hair dyes and bases has been studied in guinea pigs, in rats and in dogs. Table 5 presents data from the experiments. Considerably less data are available for DEA and MEA than for TEA. However, it does appear that DEA is the most toxic ethanolamine. Workers at the Mellon Institute have suggested that this may be because MEA has a normal function in the lipid metabolism of the body and DEA is structurally similar enough to MEA to act in competition with it and interfere in lipid metabolism. TEA may be so sufficiently unlike MEA that it does not act in competition and therefore is less toxic than DEA.

**Dermal Studies**

**Acute Toxicity**

Undiluted TEAs, 91.8% and 88.1% active and both containing slightly more than 6% of DEA, were each applied to the intact skin of three rabbits and to the
<table>
<thead>
<tr>
<th>Material tested</th>
<th>Conc. of material tested (%) and vehicle</th>
<th>Dose of ethanolaminea</th>
<th>No. and species of animal</th>
<th>LD50 Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA, 99 + Percent</td>
<td>20 in water; 100</td>
<td>4.0; 5.0, 6.3 g/kg</td>
<td>2 rats at each dose level</td>
<td>0/2, 1/2, 2/2 deaths, moderate liver and kidney damage at all dose levels.</td>
<td>150</td>
</tr>
<tr>
<td>TEA, 99 + Percent</td>
<td>In gum arabic solution</td>
<td>0.6–7.0 g/kg</td>
<td>2–3 (unspecified) guinea pigs at each dose level</td>
<td>All survived 0.6 and 1.4 g/kg; None survived 7.0 g/kg.</td>
<td>146</td>
</tr>
<tr>
<td>TEA, 78.6% (DEA, 8.6%; MEA, 1.7%)</td>
<td>25 in water</td>
<td>2.6–7.4 ml/kg TFA</td>
<td>10 rats at each of 4 dose levels</td>
<td>No unusual observations.</td>
<td>151</td>
</tr>
<tr>
<td>TEA, 91.8% (DEA, 6.5%)</td>
<td>100</td>
<td>3.64–14.00 ml/kg</td>
<td>10 rats at each of 5 dose levels</td>
<td>Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.</td>
<td>152</td>
</tr>
<tr>
<td>TEA, 80.1% (DEA, 6.1%)</td>
<td>100</td>
<td>3.64–10.00 ml/kg</td>
<td>10 rats at each of 4 dose levels</td>
<td>Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.</td>
<td>152</td>
</tr>
<tr>
<td>TEA, Commercial or high purity grade</td>
<td>100</td>
<td>1.0 26.0 g/kg</td>
<td>10 guinea pigs at LD50 and at 1 g &lt; LD50 estimated from single feedings</td>
<td>Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals. Some were paralyzed in their hind quarters.</td>
<td>149</td>
</tr>
<tr>
<td>TEA, Commercial grade</td>
<td>100</td>
<td>1.0–12.0 g/kg</td>
<td>10 rats at LD50 and at 1 g &lt; LD50 estimated from single feedings</td>
<td>Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.</td>
<td>149</td>
</tr>
<tr>
<td>Material tested</td>
<td>Conc. of material tested (%) and vehicle</td>
<td>Dose of ethanolamine$^a$</td>
<td>No. and species of animal</td>
<td>LD50</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>TEA, high purity grade</td>
<td>100</td>
<td>1.0–12.0 g/kg</td>
<td>10 rats at LD50 and at 1 g &lt; LD50 estimated from single feedings</td>
<td>9 g/kg</td>
<td>Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.</td>
</tr>
<tr>
<td>TEA in water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, 99+ Percent</td>
<td>in gum arabic solution</td>
<td>0.6–5.0 g/kg</td>
<td>2–3 (unspecified) guinea pigs at each dose level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA in water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, produced from 1939–1949</td>
<td>20 in water/100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA produced from 1939–1949</td>
<td>20 in water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, produced from 1939–1949</td>
<td>20 in water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance</td>
<td>Form</td>
<td>Concentration Range</td>
<td>Description</td>
<td>Number Survived</td>
<td>Note</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>MEA, 99+ Percent</td>
<td>In gum arabic solution</td>
<td>0.64–1.4 g/kg</td>
<td>2.3 (unspecified) guinea pigs at each dose level</td>
<td>All survived 0.6 g/kg; None survived 7.0 g/kg.</td>
<td>148</td>
</tr>
<tr>
<td>MEA</td>
<td>In water</td>
<td></td>
<td>6 male rats at each dose level</td>
<td>2.74 g/kg</td>
<td>156</td>
</tr>
<tr>
<td>MEA</td>
<td></td>
<td></td>
<td>Male rats</td>
<td>1.97 g/kg</td>
<td>159</td>
</tr>
<tr>
<td>MEA</td>
<td></td>
<td></td>
<td>Female rats</td>
<td>1.72 g/kg</td>
<td>159</td>
</tr>
<tr>
<td>MEA, produced from 1939–1949</td>
<td>In water</td>
<td>2.14–2.74 g/kg</td>
<td>90–120 (unspecified) rats</td>
<td>2.14–2.74 g/kg</td>
<td>154</td>
</tr>
<tr>
<td>Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)</td>
<td>100</td>
<td>8.72–17.4 g/kg (8.00–16.0 ml/kg)</td>
<td>Animals receiving ≥ 13.8 g/kg of product had signs of melanuria, diarrhea, polyuria, and discoloration of stomach, intestinal mucosa, and gastrointestinal contents.</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 rats at each of 4 dose levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.1 g/kg (12.9 ml/kg)</td>
<td>for undiluted preparation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for concentration tested and material activity, when known.
### TABLE 5. Subchronic and Chronic Toxicity.

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Dose and vehicle</th>
<th>Length of study</th>
<th>No. and species of animals</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA</td>
<td>0-2.61 g/kg/day</td>
<td>90 days</td>
<td>10 rats at each dose level</td>
<td>No effects observed at ( \leq 0.08 ) g/kg/day. Decreased weight gain at 1.27 g/kg/day. Heavy livers and kidneys produced when dose was ( \geq 0.17 ) g/kg/day. Major pathology of small intestine, kidney, liver, or lung rare at ( \leq 0.73 ) g/kg/day. Most major pathology observed was fatty degeneration of the liver. Some deaths at ( \geq 0.73 ) g/kg/day.</td>
<td>154,156</td>
</tr>
<tr>
<td>TEA, 88.5%</td>
<td>0-1.0 g/kg/day</td>
<td>91 days</td>
<td>20 rats of each sex at each of 4 dose levels</td>
<td>Increased weight gain in female rats receiving 0.25 g/kg/day. Increased feed consumption in female rats receiving 0.5 g/kg/day. No significant differences noted in organ to body weight ratios. No gross or histopathologic indications of a treatment related effect. No significant hematologic effects.</td>
<td>163</td>
</tr>
<tr>
<td>(DEA, 6%)</td>
<td>in food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEA, commercial or high purity grade</td>
<td>0.2-1.8 g/kg/day</td>
<td>60, 120 days</td>
<td>8 rats of each dose level for each time</td>
<td>Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver changes were observed at ( \geq 0.4 ) g/kg/day for 60 or 120 days. Kidney changes were observed at 0.2 to 0.225 g/kg/day for 120 days and at 0.4-0.45 g/kg/day for 60 or 120 days. Kidney damage was observed at ( \geq 0.8 ) g/kg/day for 60 or 120 days. No kidney damage was severe enough to interfere with organ function.</td>
<td>149</td>
</tr>
<tr>
<td>TEA, commercial or high purity grade</td>
<td>0.2-1.8 g/kg/day in food</td>
<td>120 days and then, ~3 months without TEA</td>
<td>8 rats at each dose level</td>
<td>Kidney regeneration was observed after organ damage.</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>TEA, commercial or high purity grade</td>
<td>0.2-1.6 g/kg/day by pipette</td>
<td>60, 120 doses</td>
<td>8 guinea pigs at each dose level for each number of doses</td>
<td>Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver and kidney damage was observed at ≥0.8 g/kg/day. No kidney or liver damage was severe enough to interfere with organ function.</td>
<td></td>
</tr>
<tr>
<td>TEA, commercial or high purity grade</td>
<td>0.2-1.6 g/kg/day by pipette</td>
<td>120 doses and then, ~3 months without TEA</td>
<td>8 guinea pigs at each dose level</td>
<td>Liver and kidney regeneration was observed after organ damage.</td>
<td></td>
</tr>
<tr>
<td>TEA, 99%</td>
<td>1.4 mg/l in drinking water; TEA in drinking water and 6.5% TEA solution applied to skin caudally for 1 h 5 days/week; TEA in drinking water and 13% TEA solution applied to skin caudally for 1 h</td>
<td>6 months</td>
<td>10 rats in each group</td>
<td>No toxic effect observed from 6.5 percent topical TEA and 1.4 mg/l TEA in drinking water. Changes observed after 1 month in the functions of the liver and central nervous system in animals receiving 13% topical TEA and 1.4 mg/l TEA in drinking water. Increase seen in number of segmented neutrophils after 3 months and increase seen in number of lymphocytes after 4 months.</td>
<td></td>
</tr>
<tr>
<td>Material tested</td>
<td>Dose and vehicle</td>
<td>Length of study</td>
<td>No. and species of animals</td>
<td>Results</td>
<td>Ref.</td>
</tr>
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</tr>
<tr>
<td>DEA, neutralized salt (labeled)</td>
<td>1.0, 2.0, 3.0 m M/kg/day orally</td>
<td>11 days (5th–15th day after birth)</td>
<td>Neonatal rats</td>
<td>No changes observed in heart or brain. Moderate cloudy swelling seen in kidney proximal tubule. Periportal cloudy swelling and vacuolization seen in liver. Swollen hepatic mitochondria observed.</td>
<td>162</td>
</tr>
<tr>
<td>DEA, neutralized</td>
<td>4 mg/ml in drinking water</td>
<td>7 weeks</td>
<td>Male rats</td>
<td>Many deaths observed. There was liver and kidney damage and a pronounced normocytic anemia without bone marrow depletion or obvious increase in number or reticulocytes.</td>
<td>164</td>
</tr>
<tr>
<td>DEA</td>
<td>0–0.66 g/kg/day in food</td>
<td>90 days</td>
<td>10 rats at each dose level</td>
<td>No effects observed at ≤0.020 g/kg/day. Heavy livers and kidneys produced at ≥0.090 g/kg/day. Major pathology of small intestine, kidney, liver, or lung observed at ≥0.17 g/kg/day. Major pathology included cloudy swelling and degeneration of kidney tubules and liver fatty degeneration. Some animals died at 0.17 and 0.35 g/kg/day and all died at levels greater than that.</td>
<td>154,156</td>
</tr>
<tr>
<td>MA</td>
<td>0–2.67 g/kg/day in food</td>
<td>90 days</td>
<td>10 rats at each dose level</td>
<td>No effects observed at ≤0.32 g/kg/day. Heavy livers and kidneys produced at ≥0.64 g/kg/day. Some deaths and major pathology at ≥1.28 g/kg/day.</td>
<td>154,156</td>
</tr>
<tr>
<td>Composite hair dyes and bases (MEA, 22 percent)</td>
<td>0–0.0975 g/kg/day of composite in food</td>
<td>2 years</td>
<td>12 beagle dogs at each of 3 dose levels</td>
<td>No toxic effects observed.</td>
<td>166</td>
</tr>
</tbody>
</table>
ABRASION: TEA, DEA, AND MEA

The test was a 24 h closed patch test and the TEAs were applied to yield a rabbit exposure of 2 g/kg of actual TEA. The 88.1% TEA elicited mild erythema and no edema at 24 h and the skin returned to normal by Day 6. The 91.8% TEA produced moderate erythema and no edema at 24 h and the treated sites were normal by Day 10. The animals were observed for 14 days. All rabbits gained weight and none died. (168)

Subchronic and Chronic Toxicity

Kindsvatter (149) applied commercial and high purity grades of TEA each to the shaved skin of 10 guinea pigs. The test was a closed patch continuous exposure test in which 8 g/kg was applied daily for five days a week to guinea pigs. Deaths occurred at from 2 to 17 applications. No guinea pigs survived 17 applications. Adrenal, pulmonary, hepatic, and renal damage was observed.

Kostrodymova et al. (165) applied TEA caudally to rats for 1 h, five days per week, for six months. No toxic effects were observed with a 6.5% solution of TEA. A 13% solution of TEA did effect changes in the liver and central nervous system function. The toxic effect of TEA was not increased when rats were given 1.4 mg/l of TEA in their drinking water in addition to the dermal application of the 13% solution of TEA.

The percutaneous application of MEA to rats at a dose of 4 mg/kg/day resulted in nonspecific histological changes in the heart and lung. Hepatotoxic manifestations included fatty degeneration of the liver parenchyma and subsequent focal necrosis. (169)

Groups of 16 rabbits had a cosmetic formulation containing 14% TEA stearate and 1% methycellulose, applied to one of two clipped sites on their backs that were alternated weekly, at doses of 1 and 3 ml/kg five times per week for 13 weeks. Mild to moderate skin irritation which cleared within 72 h was observed and this was followed by moderate to heavy skin scaling. No toxic effects were seen in any rabbits. The control rabbits received 3 mg/ml of 1% methycellulose in water. The low dose group had significantly lower kidney weights and the high dose group gained less weight and had significantly greater kidney weights than the control rabbits. (153)

Burnett et al. (170) applied three hair dyes containing 0.10%-0.15% TEA, 1.500% TEA, or 2.0% DEA to the backs of groups of 12 rabbits for 13 weeks. The doses were 1 mg/kg twice weekly and two clipped sites were alternated. The skin of half the rabbits was abraded. The dye was placed on the skin, the rabbits were restrained for 1 h, then shampooed, rinsed and dried. Control rabbits were treated identically except that no dye was applied to their skin. No systemic toxicity was observed and there was no histomorphologic evidence of toxicity in the treated rabbits after 13 weeks.

Primary Skin Irritation

Rabbits were used in primary skin irritation studies for TEA, (171,172) DEA, (173,174) and MEA. (175-177) Data from these experiments are presented in Table 6. These data suggest that MEA is irritating to rabbit skin, and that TEA and DEA are much less irritating to rabbit skin than MEA.
### TABLE 6. Primary Skin Irritation.

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration (%)</th>
<th>Method</th>
<th>Number of rabbits</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA, 99+ percent</td>
<td>100</td>
<td>10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the intact shaved abdomen.</td>
<td>Unspecified</td>
<td>Slight hyperemia after 7 applications. “Slight to moderately irritating, prolonged or repeated exposure may be irritating.”</td>
<td>171</td>
</tr>
<tr>
<td>TEA, 99+ percent</td>
<td>100</td>
<td>3 24-hour semioccluded patch applications to the abraded shaved abdomen.</td>
<td>Unspecified</td>
<td>Moderate hyperemia, edema, and necrosis. “Slight to moderately irritating, prolonged or repeated exposure may be irritating.”</td>
<td>171</td>
</tr>
<tr>
<td>TEA</td>
<td>100</td>
<td>1 24-hour occluded patch application to clipped back. Erythema (0 to 4), edema (0 to 4), and necrosis (0 to 15) evaluations are made at 24 and 72 hours and are added and divided by 2 to yield a primary irritation score (scale = 0 to 24). Total possible score for 22 laboratories was 400.</td>
<td>8 male/each laboratory</td>
<td>Primary irritation scores ranged from 0 to 5.5 for 22 laboratories. Total score for all 22 laboratories was 27.3.</td>
<td>172</td>
</tr>
<tr>
<td>Chemical</td>
<td>Concentration</td>
<td>Application Method</td>
<td>Reaction Description</td>
<td>Result</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>DEA, 99+</td>
<td>100</td>
<td>0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.</td>
<td>Unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, 99+</td>
<td>10 in water</td>
<td>6</td>
<td>Essentially no irritation of the skin. Erythema and edema reactions are evaluated at 24 and 72 h and values are averaged to yield a primary irritation score (scale = 0 to 8).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, 99+</td>
<td>50</td>
<td>Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 h.</td>
<td>No irritation observed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEA, 99+</td>
<td>30</td>
<td>6</td>
<td>Essentially no irritation of the skin. Erythema and edema reactions are evaluated at 24 and 72 h and values are averaged to yield a primary irritation score (scale = 0 to 8).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFA, 99+</td>
<td>85, 100</td>
<td>Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 h.</td>
<td>1 Visible destructive alteration of the tissue at the site of application. “Corrosive.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA, 99+</td>
<td>30</td>
<td>Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 and 24 h.</td>
<td>6 Visible destructive alteration of the tissue at the site of application at 4 h. Necrosis observed at 24 h. “Corrosive to skin.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA, 99+</td>
<td>1-100</td>
<td>10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.</td>
<td>Unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA, 99+</td>
<td>100</td>
<td></td>
<td>10 percent or higher was corrosive to the skin. &gt;1% was extremely irritating to the skin and 1% was irritating to the skin. “Extremely corrosive to skin.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phototoxicity

The phototoxicity of a suntan lotion containing 1% TEA was evaluated by applying the lotion to the stripped ears of six guinea pigs. A known photosensitizer was used as a positive control in four other guinea pigs. Each animal was then exposed to ultraviolet (UVA) from two GE F8T5-BL lamps at a distance of 4–6 cm for 2 h. No erythema or edema was observed in any of the guinea pigs treated with suntan lotion. Results of the positive controls are unavailable.\(^{(178)}\)

Skin Sensitization

Pairs of guinea pigs were treated dermally with 5%–100% TEA in water for 6 h with occlusion, and the treated sites were scored for erythema at 24 and 48 h. Since use of undiluted TEA resulted in only one erythemic reaction at 24 h, 100% TEA was used in both induction and challenge procedures in the subsequent sensitization test. Twenty guinea pigs received dermal applications of undiluted TEA once per week for three weeks. A challenge patch was applied after 14 days and again seven days later. One erythemic reaction occurred in each of three animals during the induction procedure, in two other animals during the first challenge, and in one other animal during the second challenge. All the guinea pigs remained healthy and made normal weight gains during the test. There was no evidence of any skin sensitizing activity of undiluted TEA for guinea pigs.\(^{(179)}\)

TEA from four different suppliers was evaluated in guinea pig skin sensitization tests.\(^{(180-183)}\) The tests were conducted with 10 control and 20 treated guinea pigs. The induction patches were applied once a week for up to six hours for three weeks. Two weeks later challenge patches were applied to both control and treated guinea pigs. One test was conducted with undiluted TEA at induction and 90% TEA at challenge\(^{(181)}\) and all the other tests were conducted with 50% TEA at induction and 90% TEA at challenge.\(^{(180,182,183)}\) None of the animals showed clinical symptoms during or after the treatment period and no guinea pigs showed signs of primary irritation of the skin. Challenge reactions were measured with a reflectometer and average readings between control and experimental animals were compared. TEA was not a guinea pig skin sensitizer in these studies.

Patches containing a 25% active TEA solution and 10% and 5% TEA in aqueous solution were applied to the backs of four clipped guinea pigs. No irritation was observed in this preliminary study. Induction patches containing the 25% TEA solution were applied to the backs of 20 clipped guinea pigs for 6 h once per week for three weeks. One week later, a challenge patch containing 25% TEA was applied for 6 h to the clipped backs of the 20 treated and 10 control guinea pigs. Challenge reactions were read at 24 h and at 48 h. No irritation was observed. No positive primary irritation or sensitization responses were observed under the test conditions with the 25 percent active TEA solution.\(^{(184)}\)

Eye Irritation

The eye irritation potential of TEA, DEA, MEA, or cosmetic products containing the ethanolamines has been studied in rabbits\(^{(171,172,174,177,185-187)}\) and in rhesus monkeys.\(^{(186)}\) Data from these experiments are presented in Table 7. In high concentrations and with long contact time, TEA, and DEA may be irritating to the rabbit eye and MEA is irritating to the rabbit eye.
<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration (%)</th>
<th>Method</th>
<th>No. and species of animals</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA, 99+ percent</td>
<td>100</td>
<td>0.1 ml of test material instilled into conjunctival sac of both rabbit eyes. Left eye unwashed. After 30 sec exposure, right eye washed for 2 min with tap water.</td>
<td>Rabbits</td>
<td>Moderate pain and swelling in unwashed eye. Slight conjunctival irritation which subsided in 48 h. No irritation observed in the washed eye. ‘Slight to moderately irritating, no corneal damage likely.’</td>
<td>171</td>
</tr>
<tr>
<td>TEA, 99+ percent</td>
<td>10 in water</td>
<td>0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18-24 h.</td>
<td>Rabbits</td>
<td>0.005 ml yielded a score of ≤5.0. 0.02 ml yielded a score of &gt;5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75% of the surface of the cornea.</td>
<td>185</td>
</tr>
<tr>
<td>TEA</td>
<td>100</td>
<td>0.01, 0.03, 0.10 ml of test material applied directly to cornea and eyelids released immediately. Eyes scored at days 1, 3, 7, 14 and 21 by the method of Draize, et al.193. (scale = 0 to 110).</td>
<td>6 rabbits at each dose level</td>
<td>0.01 ml gave a 0 score on all days eyes were examined. 0.03 ml gave a score of 1 on Day 1 and 0 thereafter. 0.10 ml yielded a score of 4 on Day 1, 2 on Days 3 and 7, and 0 on Days 14 and 21. The median number of days for eyes to return to normal was 1 for 0.01 and 0.03 ml and 3 for 0.10 ml.</td>
<td>187</td>
</tr>
<tr>
<td>TEA</td>
<td>100</td>
<td>0.1 ml of test material was placed inside the lower eyelid. Lids were held together for a few seconds. Eyes were examined at 1, 24, and 72 hours and 7 days after application. Scoring was according to the scale of Draize et al.193 (scale = 0 to 110).</td>
<td>6 male rabbits</td>
<td>Eye irritation scores ranged from 0-10 for 24 laboratories.</td>
<td>172</td>
</tr>
<tr>
<td>Material tested</td>
<td>Concentration (%)</td>
<td>Method</td>
<td>No. and species of animals</td>
<td>Results</td>
<td>Ref.</td>
</tr>
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</tr>
<tr>
<td>DEA, 99+ percent</td>
<td>30 in water</td>
<td>~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.</td>
<td>6 rabbits</td>
<td>The material was essentially nonirritating to the eye. &quot;Noncorrosive to eye&quot;.</td>
<td>174</td>
</tr>
<tr>
<td>DEA, 99+ percent</td>
<td>50 in water</td>
<td>~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.</td>
<td>6 rabbits</td>
<td>Moderate to severe conjunctival irritation and corneal injury with slight reddening of the iris was observed. The eye essentially healed in 7 days. &quot;Severe irritant&quot;.</td>
<td>174</td>
</tr>
<tr>
<td>DEA</td>
<td>100</td>
<td>0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 hours.</td>
<td>Rabbits</td>
<td>0.005 ml yielded a score of ≤5.0; 0.02 ml yielded a score of &gt;5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.</td>
<td>185</td>
</tr>
<tr>
<td>MFA, 99+ percent</td>
<td>30 in water</td>
<td>~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.</td>
<td>6 rabbits</td>
<td>Slight discomfort, slight conjunctival irritation, and slight corneal clouding which healed in 48 hours was observed. &quot;Moderately irritating.&quot;</td>
<td>177</td>
</tr>
<tr>
<td>MEA</td>
<td>1,5,100</td>
<td>0.005 ml of undiluted or diluted test material applied to corneal center while lids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 hours.</td>
<td>Rabbits</td>
<td>1% solution yielded a score ≤5.0; 5 and 100% solutions yielded scores &gt;5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.</td>
<td>185</td>
</tr>
<tr>
<td>Shampoo (TEA, 12.6%)</td>
<td>100 of the shampoo</td>
<td>0.1 ml of the shampoo was instilled into the conjunctival sac of the left eye. Held closed for 1 sec. After 15 sec, rinsed with 50 ml tap water. Eyes were examined at 24, 48, and 72 hours and at 4 and 7 days post-instillation.</td>
<td>6 rhesus monkeys</td>
<td>Slit lamp examinations at 24 h revealed edematous cornea and slight sloughing of the corneal epithelium in the treated eyes of 2 animals. At 72 h, a slight positive fluorescein staining was observed in the eye of one monkey and at Day 7, a faint, diffuse positive staining was noted in one monkey.</td>
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<td></td>
</tr>
<tr>
<td>Hair preparation</td>
<td>100 of the hair preparation</td>
<td>0.1 ml of the hair preparation was placed into the conjunctival sac of one eye. The lids were held together for 1 sec. After 30 sec, the eyes of 3 animals were washed with 20 ml of deionized water. The eyes were examined at 24, 48, and 72 hours and at 4 and 7 days and were scored according to the method of Draize et al. (scale = 0 to 110).</td>
<td>9 rabbits</td>
<td>Maximum average irritation scores for both washed and unwashed eyes was 0.7.</td>
<td></td>
</tr>
</tbody>
</table>
Vaginal Mucosa Irritation

A spermicidal preparation containing 1.92% TEA was tested for vaginal mucosa irritation using six female rats in the same stage of estrus. A 0.5 ml volume of the ointment was placed inside the vaginas of the rats at a depth of 0.6–0.8 cm daily for three days. On the fourth day, the vaginas were exposed and examined for erythema, exudate, and edema. The researchers classified the spermicidal preparation as a nonirritant to rat vaginal mucosa.\(^{(189)}\)

Inhalation Studies

Respiratory difficulties and some deaths in male rats resulted from the short-term inhalation of 200 ppm DEA vapor or 1400 ppm DEA aerosols. Inhalation of 25 ppm DEA for 216 continuous hours resulted in increased liver and kidney weights. A workday schedule inhalation of 6 ppm DEA for 13 weeks resulted in growth rate depression, increased lung and kidney weights, and some deaths in male rats.\(^{(164)}\)

Weeks et al.\(^{(190)}\) reported that the dominant effects of continuous exposure of dogs, guinea pigs, and rats to 5–6 ppm MEA vapor were skin irritation and lethargy. The inhalation of MEA vapor at concentrations of 12–26 ppm for 90 days did not result in any mortality in dogs or rodents. Some deaths did occur after 25 days in dogs exposed to 102 ppm MEA vapor, and after 24–28 days in rodents exposed to 66–75 ppm MEA vapor. Exposure to 66–102 ppm MEA vapor caused behavioral changes and produced pulmonary and hepatic inflammation, hepatic and renal damage, and hematologic changes in dogs and rodents.

Parenteral Studies

The mouse acute intraperitoneal LD50s of TEA and MEA have been reported to be 1.450 and 1.050 g/kg, respectively.\(^{(191)}\) Blum et al.\(^{(192)}\) determined that the mouse acute intraperitoneal LD50 of DEA was 2.3 g/kg. This level of DEA produced hepatic steatosis, cellular degeneration and swollen hepatic mitochondria in the 24 h following the injection. After 24 h, survivors were apparently normal. The livers of mice that survived over 48 h appeared to have returned to normal. Other information can be found in the literature on the intraperitoneal administration of the ethanolamines to mice and rats.\(^{(164,195,196)}\)

SPECIAL STUDIES

Mutagenesis

The Ames assay has been used to investigate the mutagenic potential of the ethanolamines.\(^{(197)}\) TEA, 99+ percent, with or without metabolic activation, was not mutagenic at concentrations of 0.001 to 100 mg/plate to Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538.\(^{(198)}\) The National Toxicology Program (NTP) tested 0–3.333 mg/plate of TEA and DEA in their preincubated Salmonella mutagenicity assay in strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation and reported both
chemicals to be negative. Hedenstedt tested DEA and MEA with and without metabolic activation by liver preparations from rats induced with a polychlorinated biphenyl mixture in S. typhimurium strains TA100 and TA1535. There was no observed increase in the number of mutants per plate with either DEA or MEA.

The mutagenicity of TEA, sodium nitrite, and a mixture of the two, with and without metabolic activation by liver S-9, was tested with Bacillus subtilis. Only the mixture of TEA and sodium nitrite was mutagenic to the bacteria. N-nitro-sodiethanolamine (NDELA) was found in this mixture, but NDELA does not induce mutations in B. subtilis without metabolic activation. Some other reaction mixture product must be mutagenic and this product loses its mutagenic activity in the presence of liver enzymes.

Fresh primary rat hepatocyte cultures were treated simultaneously with TEA and ³H-thymidine in an unscheduled DNA synthesis test. DNA repair was quantitated by microautoradiographic evaluation of the incorporation of ³H-thymidine into nuclear DNA. The concentrations of TEA tested ranged from $10^{-8}$ to $10^{-1}$ M and three cultures were tested per concentration. The authors reported that TEA did not appear to cause DNA-damage inducible repair.

Carcinogenesis

Kostrodymova et al. used a total of 560 male mice, strain CBA × C57Bl6, in a series of three experiments to study the possible carcinogenic and cocarcinogenic effects of pure TEA, 99+ percent, and industrial TEA, 80+ percent, and the combined effect of TEA and syntanol DC-10, applied cutaneously. The experiments ran for 14–18 months, and they found no evidence of TEA carcinogenicity or cocarcinogenicity.

Hoshino and Tanooka fed a diet containing 0.01%, 0.03%, or 0.3% TEA to groups of 40 ICR-JCL male and 40 ICR-JCL female mice throughout the life-span of the animals. The malignant tumor incidence in females was 2.8%, 27%, and 36%, and in males was 2.9%, 9.1%, and 3.6% for the mice fed diets containing 0.0%, 0.03%, and 0.3% TEA, respectively. Treated females showed a much higher incidence of thymic and nonthymic tumors in lymphoid tissues than treated males. The mice fed TEA in their diet survived as long as the control mice.

DEA is currently being tested in an NTP carcinogenesis bioassay program. It is being administered in drinking water to rats and mice.

Teratogenesis and Reproduction Studies

Hair dyes containing 0.10%–0.15% TEA, 1.5% TEA, or 2.0% DEA were topically applied to the shaved skin of groups of 20 pregnant rats on Days 1, 4, 7, 10, 13, 16, and 19 of gestation. On Day 20, the rats were sacrificed and comparisons were made with control rats. No significant soft tissue or skeletal changes were noted in the fetuses. The mean number of corpora lutea, implantation sites, live fetuses, resorptions per pregnancy, and number of litters with resorptions were not significantly different in the dye-treated and control rats.

A composite hair dye and base containing 22% MEA was given to 60 female rats at concentrations of 0 to 7800 ppm in the diet from Day 6 to 15 of gestation.
The rats were sacrificed at Day 19 and there was no evidence of any adverse effects on the rats or their pups. No differences were observed in the average number of implantation sites, live pups, early or late resorptions per litter, or females with one or more resorption sites. Thirty male rats were fed diets containing 0–7800 ppm composite for eight weeks prior to mating and during mating to 60 female rats on a basal diet. Sixty female rats were fed 0–7800 composite-containing diets eight weeks prior to mating through Day 21 of lactation. They were mated with 30 male rats on the basal diet. In both experimental designs, there were no dose-related significant differences in male and female fertility, length of gestation, number of females with resorption sites, live pups per litter, pup body weights, and pup survival. The composite hair dye and base was also administered at a dose of 0–19.5 mg/kg/day by gavage to 48 artificially inseminated female rabbits from Day 6 to 18 of gestation. The rabbits were sacrificed at Day 30. There was no evidence of any teratologic effects. Fetal survival was not adversely affected and no grossly abnormal fetuses or soft tissue defects were seen. \(^1\)

**CLINICAL ASSESSMENT OF SAFETY**

**Dermal Studies**

Patch tests can be used to measure skin irritation and sensitization by a chemical substance in human subjects. However, caution should be exercised in the interpretation of patch tests. Patches will elicit positive reactions in cases where the test material is a primary irritant or when the human subject has been sensitized by previous contact with the chemical, either in a past patch or in the course of his daily life. \(^0\) In addition, patch tests may elicit positive responses because the threshold irritating concentration of a chemical has decreased after repeated exposure of the skin to irritants; this would be a fatigue response. The population from which the subjects are drawn is also important. Certain skin types may be predisposed to react more intensely to chemical insult. \(^2\)

Triethanolamine is the only ethanolamine for which human skin irritation and sensitization data are presented. The results of six patch test experiments with triethanolamine and details of those experiments are presented in Table 8. TEA produced minimal irritation in 1143 “normal” subjects and was more irritating to subjects chosen because they were “hyper reactors” to skin irritants or because they were suffering from eczema.

The cosmetic industry has conducted studies on the skin irritation, sensitization, and photosensitization of a variety of products containing the ethanolamines. Data from these unpublished experiments are presented in Table 9. There was some evidence of irritation by some products.

**Inhalation Studies**

MEA inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma \(^3\) and clinical symptoms of acute liver damage and chronic hepatitis. \(^4\)
### TABLE 8. Skin Irritation and Sensitization by Triethanolamine.

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration and dose</th>
<th>Method</th>
<th>Number of subjects</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA, 88.6% (DEA, 6%)</td>
<td>0.5 ml of 1% active TEA</td>
<td>24 h semicocclusive induction patches were applied on the dorsal surface of the upper arm 3 times per week for 3 weeks. 14 days later, challenge patches were applied to the same site and the other arm and these were graded at 48 and 96 h on a scale of 0-6.</td>
<td>64</td>
<td>No irritation (0) in 451 inductions. Mild irritation (1) in 420 and moderate irritation (2) in 3 inductions (includes residual reactions). 188 and 68 scores of 0 and 1 at challenge, respectively. “No sensitization.”*</td>
<td>214</td>
</tr>
<tr>
<td>TEA 5%</td>
<td></td>
<td>Patch test, 1979 1980</td>
<td>479</td>
<td>9 (2%) positive reactions for contact dermatitis observed. (Sensitizing)</td>
<td>215</td>
</tr>
<tr>
<td>TEA 2% in water</td>
<td></td>
<td>Patch tests, 1974-1976, Marseille, France</td>
<td>500</td>
<td>23 (4.6%) positive reactions for contact dermatitis observed. (Sensitizing)</td>
<td>216</td>
</tr>
<tr>
<td>TEA 5% in petrolatum</td>
<td></td>
<td>Patch tests</td>
<td>100</td>
<td>2 positive reactions for allergic contact dermatitis were observed. (Sensitizing)</td>
<td>217</td>
</tr>
<tr>
<td>TEA 100%; 10 and 5% in ethanol</td>
<td></td>
<td>Test material applied in an aluminum chamber containing a cotton disk once daily for 3 days. After light scarification of the forearm site with a needle. Readings on a scale of 0-4 at 72 h 30 min after chamber removal.</td>
<td>5-10 (unspecified)</td>
<td>100% TEA was required to produce an irritant reaction on nonscarified skin. 10% TEA was a marked irritant (2.5-4.0) and pustules were observed and 5% TEA was a slight irritant (0.5-1.4) on scarified skin.</td>
<td>218</td>
</tr>
<tr>
<td>TEA 5%, 1% in eucerin with water</td>
<td></td>
<td>24 h patch tests. Readings after 24 and 48 h.</td>
<td>22 subjects suffering from different types of eczemas</td>
<td>4 and 3 positive reactions to 5% and 1% TEA, respectively. (Irritating)</td>
<td>219</td>
</tr>
</tbody>
</table>

*Conclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.
### TABLE 9. Skin Irritation, Sensitization, Phototoxicity, and Photosensitization by Products Containing the Ethanolamines.

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration and dose</th>
<th>Method</th>
<th>Number of subjects</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaving preparation (TEA, 4.2%)</td>
<td>100%</td>
<td>2 24-hour patches applied 10 to 14 days apart on the same site. Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +. Additionally, there was UV exposure of the second patch.</td>
<td>508</td>
<td>46 weak (nonvesicular) (+) reactions to the first closed patch, 42 + and 7 strong (edematous or vesicular) (+ +) reactions to the second closed patch. 67 + reactions after UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 in for 1 min) exposure of the second patch. “Nonirritating.” (Irritating. Either mildly phototoxic or UV enhancement of an irritation response).</td>
<td>222</td>
</tr>
<tr>
<td>Shaving preparation (TEA, 4.2%)</td>
<td>100%</td>
<td>10 24-hour induction patches with 24-hour recuperative periods in between. After 2 to 3 weeks rest, a 48-hour challenge patch (modification of Ref. 221). Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +. Additionally, there was UV exposure of induction patches 1, 4, 7, and 10, and the challenge patch.</td>
<td>260</td>
<td>Between 31 and 64 + reactions were observed to closed induction patches 1 through 10. 1, 3, 3, 4, and 4 strong + + reactions to closed induction 60 + and 2 + + reactions to the closed challenge patch. Following UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 inches for 1 min.) exposure, 7, 6, 1, 4, and 8 + reactions were observed at induction patches 1, 4, 7, and 10, and the challenge patch, respectively. “Nonsensitizing and nonphotosensitizing.” (Irritating)</td>
<td>222</td>
</tr>
<tr>
<td>Shaving preparation (TEA, 4.2%)</td>
<td>Normal use</td>
<td>Used on the face for 4 weeks and scored each week.</td>
<td>52 male</td>
<td>No reactions were observed. “Nonirritating.”</td>
<td>223</td>
</tr>
<tr>
<td>Sun cream (TEA, 3.75%)</td>
<td>100%, - 0.1 ml</td>
<td>24-hour occlusive induction patches applied to the upper back 3 times a week for 3 weeks. After 2 weeks rest, a 24-hour occlusive challenge patch was applied to a previously unpatched site. Reactions were scored 24 and 48 hours after patch removal on a scale of 0 to 4.</td>
<td>48</td>
<td>1 barely perceptible (±) reaction; minimal faint (light pink) uniform or spotty erythema at induction patch 2. “No potential for inducing allergic sensitization.”</td>
<td>186</td>
</tr>
</tbody>
</table>
12-hour occlusive induction patches applied to the medial surface of the upper arm 4 times a week for 2 weeks and scored at patch removal on a scale of 0 to 4. After 2 weeks rest, a 24-hour occlusive challenge patch was applied. Reactions were scored at 24, 48, and 72 hours.

23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 4.

48-hour occluded patch was applied to the arm or back; 24-hour aqueous sodium lauryl sulfate occluded patch on arm or back, then 5 alternate day 48-hour occluded patches of the test material. After a 10 day rest, 3 10 percent sodium lauryl sulfate was applied to another test site for 1 hour and followed by a 48-hour occluded patch of the test material. Reactions were observed at patch removal and 24 hours later.

5, 16, and 14 very slight erythema (+), slight erythema (1), and well defined erythema (2) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions increased with each induction. No reactions to the challenge patch. (Irritating)

104, 36, 5, and 2 slight erythema (1), moderate erythema (2), severe erythema (3), and edema with or without erythema (4) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions generally increased with each induction. 6 1 + and 1 2 + reactions were observed on challenge at 24 hours. At 48 hours, 4 1 + and 1 2 + reactions were observed, and at 72 hours, 2 1 + reactions were observed. (Irritating)

27 slight erythema (1) and 1 moderate erythema (2) reactions were observed to the 8 induction patches. 1 1 + reaction was observed on challenge at 24 hours. (Mildly Irritating)

7, 42, 2, and 3 questionable erythema (+), erythema (1), erythema and papules (2), and erythema, papules, vesicles, and possibly edema (3) reactions, respectively, to the 21 patches. (Irritating)

5, 54, and 6 *, 1, and 2 reactions, respectively, to the 21 patches. (Irritating)

No reactions observed to challenge. "No sensitization."

No reactions observed to challenge. "No sensitization."
TABLE 9. (Continued.)

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration and dose</th>
<th>Method</th>
<th>Number of subjects</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suntan lotion (TEA, 1.0%)</td>
<td>100%</td>
<td>48-hour occlusive induction patches were applied 3 times a week for a total of 10 times. Patches 1, 5, 6, and 7 were on the left shoulder, the others on the right. The sites were scored 24 to 48 hours after patch removal. After 8 days rest, a challenge patch was applied to a virgin back site and scored 24 hours after patch removal. The skin sites where patches 1, 4, 7, and 10 and the challenge patch had been were exposed to UV light (Hanovia Tanette Mark I Lamp) at a distance of 12 inches for 1 min and scored 48 hours later.</td>
<td>26 female</td>
<td>No reactions observed. “Not a phototoxicant.”</td>
<td>230</td>
</tr>
<tr>
<td>Mascara (TEA, 20.04%)</td>
<td>100%, ~0.1 ml/cm²</td>
<td>2 times/week for 3 weeks, duplicate 24-hour occlusive induction patches applied to the back. Then, one site and a control site (no test product) irradiated with 3 times the individual’s “minimal erythema dose” (MED) using a Xenon arc solar simulator (290-400 nm). 48 hours later, both sites were read. There was a 10-day rest and then, duplicate challenge patches were applied at fresh sites. 24 hours later one site and a control site exposed to 3 min. of irradiation from the solar simulator (Schott W345 filter). Sites graded at 15, 24, 48, and 72 hours after light exposure.</td>
<td>26 female</td>
<td>2 slight reactions upon challenge to test product alone. One doubtful and one erythema reaction before irradiation. “No sensitization.” (Irritation)</td>
<td>231</td>
</tr>
<tr>
<td>Mascara (TEA, 2.8%)</td>
<td>100%, ~0.1 ml/cm²</td>
<td></td>
<td>23</td>
<td>No reactions observed. “Not phototoxic or photoallergenic.”</td>
<td>232</td>
</tr>
<tr>
<td>Skin lotion</td>
<td>100%,</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TEA, 0.83%)</td>
<td>~0.2 ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites on both forearms were tape-stripped several times. Duplicate 24-hour occlusive patches applied to each forearm. Then, one site irradiated with UV light for 15 min. at a distance of ~10 cm (~4,400 μW/cm² UVA). Sites scored after patch removal, after irradiation, and 24 and 48 hours after irradiation. Examined for tanning after 1 week. Scored on a scale of 0-4.</td>
<td></td>
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</tr>
</tbody>
</table>

24-hour occlusive induction patches were applied 3 times a week to both forearms for a total of 10 times. At the end of 24 hours the sites were scored and 1 site was irradiated with nonerythrogenic UV radiation for 15 min. at a distance of 10 cm (~4,400 μW/cm² UVA) and then scored again. After 10 to 14 days rest, challenge patches were applied to virgin adjacent sites. 24 hours later, the sites were scored, 1 site was irradiated and scored. The challenge sites were also read 48 and 72 hours later. Scored on a scale of 0-4.

One subject had minimal erythema (±) at both sites at all readings except for the irradiated site at the 24-hour before and after irradiation readings. Another subject had minimal erythema (±) at the irradiated site at the 72-hour reading. No tanning was observed. "Not phototoxic." (Irritating)

One subject had minimal erythema (±) at both sites at all readings. Another subject had minimal erythema (±) at the irradiated site at the 48- and 72-hour readings. No tanning was observed. "Not phototoxic." (Irritating)

Among 300 induction readings for the nonirradiated sites, there were 13 minimal erythema (±) and 2 erythema (1) readings. There was 1 minimal erythema (±) challenge reading at 48 hours. Among 600 induction readings for the irradiated sites, there were 8 and 9 minimal erythema (±) readings before and after irradiation, respectively, and 4 erythema (1) readings after irradiation. There was 1 minimal erythema (±) reading after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)

Among 300 induction readings for the nonirradiated sites, there were 15 minimal erythema (±) and 3 erythema (1) readings. There were 2 minimal erythema (±) challenge readings, one at 24 and one at 48 hours. Among 600 inductions for the irradiated sites, there were 7 and 10 minimal erythema (±) readings before and after irradiation, respectively, and 5 erythema (1) readings after irradiation. There was one erythema reading (1) after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)
<table>
<thead>
<tr>
<th>Material tested</th>
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<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaving cream</td>
<td>100%</td>
<td>10 48- to 72-hour occlusive induction patch applications to the same site, readings before the application of the succeeding patch, followed by a rest period of about 3 weeks and then a final challenge patch on a fresh site. Modified Draize test.</td>
<td>104</td>
<td>Among 1040 induction readings, there were 172 readings, 11 (1) readings and one (3) reading. There were 16 (?) challenge readings. (Irritating)</td>
<td>237</td>
</tr>
<tr>
<td>(TEA, 2.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaving cream</td>
<td>100%</td>
<td>9 8-hour &quot;semi-open&quot; induction applications, scored 48 to 72 hours later just before application of the next patch, a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to the original and to virgin sites. Reactions were scored on a scale of 0-6.</td>
<td>76</td>
<td>Among 684 induction readings there were 231, 83, and 1 reaction of (1) (slight erythema), (2) (marked erythema) and (3) (erythema and papules), respectively. There were 28 (1), 4 (2), and 3 (E) (erythema and possibly also edema) reactions upon challenge at the original site and 23 (1) reactions at the virgin site among 304 challenge readings. &quot;Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization.&quot; (Sensitizing)</td>
<td>238</td>
</tr>
<tr>
<td>(TEA, 2.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaving cream</td>
<td>100%</td>
<td></td>
<td>76</td>
<td>Among 684 induction readings there were 222 and 101 reactions of (1) and (2), respectively. Among 304 challenge readings there were 33, 13, and 2 reactions of (1), (2), and (E), respectively, at the original site and 20, 7, and 1 reactions of (1), (2) and (E), respectively, at the virgin site. &quot;Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization.&quot; (Sensitizing)</td>
<td>238</td>
</tr>
<tr>
<td>(TEA, 2.1%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Shaving cream (TEA, 2.1%) 100% 0.5 ml

9 24-hour “semi-open” patch induction applications scored 48 to 72 hours later just before application of the next patch a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to original and virgin sites. Reactions were scored on a scale of 0–6.

Among 567 induction readings, there were 106, 4, 2, and 4 reactions of 1, 2, 3 and 4 (erythema, edema, and papules), respectively. Among 252 challenge readings there were 28, 6, 1, 9, and 1 reactions of 1, 2, 3, 4, and 6 (strong reaction spreading beyond test site), respectively, at the original site and 9, 4, and 2 reactions of 1, 2, and 3, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. “ Probably skin fatigue.”
<table>
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<tr>
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<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaving cream (TEA, 2.1%)</td>
<td>100% 0.5 ml</td>
<td>Every other day for a total of 20 days (10 open-patch applications) a 1 in. square of gauze was dipped in sample and applied to the subjects' arm (the same site was used each time), 24 hours after application the sites were scored. Reactions were scored on a scale of 1 to 4.</td>
<td>63</td>
<td>Among 567 induction readings, there were 131, 23, 2, and 14 reactions of 1, 2, 3, and 4, respectively. Among 252 challenge readings, there were 34, 16, 6, 18, and 1 reactions of 1, 2, 3, 4, and 6 respectively, and 19, 5, 1, and 1 reactions of 1, 2, 3, and 4, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. &quot;Probably skin fatigue.&quot;</td>
<td>239</td>
</tr>
<tr>
<td>Shaving cream (TEA, 2.1%)</td>
<td>100%</td>
<td>60</td>
<td>Among 600 induction and 170 challenge readings, there were no reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
<td>60</td>
<td>Among 600 induction readings there were 5 (1+) (mild erythema) reactions. There were no challenge reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
</tr>
<tr>
<td>Shaving cream (TEA, 2.6%)</td>
<td>100%</td>
<td>60</td>
<td>Among 600 induction readings there were 5 (1+) reactions. There were no challenge reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
<td>60</td>
<td>Among 600 induction readings there were 3 (1+) reactions. There were no challenge reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
</tr>
<tr>
<td>Shaving cream (TEA, 2.1%)</td>
<td>100%</td>
<td>60</td>
<td>Among 600 induction readings, there was 1 (1+) reaction. There were no challenge reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
<td>60</td>
<td>Among 600 induction readings, there was 1 (1+) reaction. There were no challenge reactions. &quot;Short-lived acute irritation, no sensitization.&quot;</td>
</tr>
</tbody>
</table>

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Shaving cream (TEA, 2.3%)

100%  

10 24-hour occlusive patch applications with 24- to 48-hour rest periods in between. Sites scored just prior to next patch application. An 11- to 15-day rest followed by a 24-hour challenge patch on a virgin site. Sites scored at 24 and 48 hours after application. Scored on a scale of 0-4.

Sunscreen product (TEA, 0.45%)

100%, -0.2 g  

10 24-hour occlusive patch applications to both arms, patches removed, sites scored, and one site subjected to 15 minutes of UV light (~4,400 µW/cm² UVA) at a distance of 10 cm and rescored. Additional readings were made 48 and 96 hours after application. Scored on a scale of 0-4.

10 Forearms were tape-stripped to remove cornified epithelium. 24-hour occlusive patch applications to both arms, patches removed, sites scored, and one site subjected to 15 minutes of UV light (~4,400 µW/cm² UVA) at a distance of 10 cm and rescored. Additional readings were made 48 and 96 hours after application. Scored on a scale of 0-4.

Sunscreen product (TEA, 0.45%)

100%, -0.2 g  

10 24-hour occlusive patch applications to both arms with 24- to 48-hour rest periods in between. Sites scored at patch removal and then irradiated for 15 min at a distance of 10 cm (~4,400 µW/cm² UVA) and re-scored. An 11- to 15-day rest period, 24-hour challenges to virgin sites, patches removed and sites scored, irradiated, scored again and scored 24 and 48 hours later. Scored on a scale of 0-4.

100 Among 600 induction readings there were 2 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."

52 Among 520 induction readings, there were 7 ± (minimal erythema) scores. Among 104 challenge readings, there were 2 ± scores. "No irritation or sensitization."

10 24-hour occlusive patch applications to both arms with 24- to 48-hour rest periods in between. Sites scored just prior to next patch application. An 11- to 15-day rest followed by a 24-hour challenge patch on a virgin site. Sites scored at 24 and 48 hours after application. Scored on a scale of 0-4.

60 There was 1 ± reaction at 24 hours and 1 + reaction at another site after irradiation at 24 hours. "No phototoxic response."

10 Among 260 induction readings of the non-irradiated site, there were 5 ± scores. Among 70 challenge readings, there were 3 ± scores. Among 520 induction readings of the irradiated site there were 5 ± scores before and 5 ± scores after irradiation. Among 104 challenge readings, there were 2 ± scores. "No photoallergic response."

100 Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. "No irritation or sensitization."

242 Among 1100 induction readings and 200 challenge readings, there were no reactions. "No irritation or sensitization."
<table>
<thead>
<tr>
<th>Material tested</th>
<th>Concentration and dose</th>
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<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyeless Base Formulation (DEA, 2%), non-commercial product</td>
<td>0.3 ml, 10% in distilled water</td>
<td>24-hour semiocclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.</td>
<td>165</td>
<td>No reactions observed. &quot;No contact sensitization.&quot;</td>
<td>243</td>
</tr>
<tr>
<td>Shave gel (DEA, 2.7%)</td>
<td>100%, ~0.1 ml/cm³</td>
<td>10 48- to 72-hour nonocclusive induction patch applications. Sites scored at patch removal. 10th patch also scored 24 hours later, 11-day rest period, followed by a 48-hour challenge patch to a virgin site. Challenge site scored at patch removal and 24 hours later.</td>
<td>100</td>
<td>Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. &quot;No irritation or sensitization.&quot;</td>
<td>242</td>
</tr>
<tr>
<td>Dyeless Base Formulation (MEA, 11.47%), non-commercial product</td>
<td>0.3 ml, 5% in 25% alcohol</td>
<td>24-hour semiocclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.</td>
<td>165</td>
<td>19, 1, 1, and 1 scores of mild erythema (1), definite papular response (2), definite edema (3), and definite edema and papules (4), respectively, during induction. No reactions observed at challenge. &quot;No contact sensitization.&quot; (Irritating)</td>
<td>243</td>
</tr>
<tr>
<td>Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)</td>
<td>~0.2 ml, 100%</td>
<td>23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 7.</td>
<td>12 female</td>
<td>4, 3, and 225 scores of minimal erythema, barely perceptible (1), definite erythema, readily visible (2), erythema and papules (3). &quot;Experimental cumulative irritant.&quot;</td>
<td>244</td>
</tr>
<tr>
<td>Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)</td>
<td>0.3 ml, 100%</td>
<td>48-hour occluded patch on the forearm; 5 48-hour occluded induction patches, a 10-day rest, then a 48-hour occluded challenge patch. Reactions scored at patch removal and 24 hours later on a scale of 0 to 3.</td>
<td>25</td>
<td>Test material was irritating during a pre-test. No reactions observed during the induction and challenge procedures. &quot;No contact sensitization.&quot;</td>
<td>245</td>
</tr>
</tbody>
</table>

*aConclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.*
An eight-year-old female developed a nasal allergic reaction to a detergent containing TEA. The prick test was positive for 10⁻⁷–10⁻⁴ M TEA and not for any of the other ingredients in the product. Sneezing was relieved after removal of the detergent from the clothes by extensive washing and recurred upon re-exposure. 💡 Potential hazards from inhalation of TEA and DEA are probably minimized by their low vapor pressures. 🧪

**Occupational Exposure**

Information on vascular, neurologic, and hepatic disorders and respiratory and skin allergies of people who come in contact with the ethanolamines in their work environment can be found in the literature. 📚

**SUMMARY**

TEA, DEA, and MEA are amino alcohols and as such, are chemically bifunctional, combining the properties of alcohols and amines. The pHs of 0.1 N aqueous solutions of TEA, DEA, and MEA are 10.5, 11.0, and 12.05, respectively. Ethanolamine soaps and ethanolamides are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. Most products contained TEA, DEA, and MEA in concentrations less than or equal to 5%. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals. Traces of NDELA (below 5 ppm) have been found in a variety of cosmetic products.

The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. In single-dose oral toxicity for rats, TEA is practically nontoxic to slightly toxic, and DEA and MEA are slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a greater than 10% concentration in 10 open applications over a period of 14 days. A lotion containing 1% TEA was not phototoxic to guinea pigs, and TEA was not a guinea pig skin sensitizer. With long contact time TEA, DEA, and MEA are irritating to the rabbit eye at concentrations of 100%, 50%, and 5%, respectively.

The ethanolamines have been shown to be nonmutagenic in the Ames test and TEA is also nonmutagenic to *Bacillus subtilis*. 1EA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test.

TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months. There was a higher incidence of malignant lymphoid tumors in female mice fed diets containing TEA for their whole lifespan than in male mice on the same diet or in control mice.
Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity and photosensitization reactions with products containing up to 20.04% TEA. A dyeless base formulation containing 11.47% MEA and a hair preparation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

COMMENTS

In the presence of N-nitrosating agents, TEA and DEA may give rise to N-nitrosodiethanolamine, a known animal carcinogen.

TEA and DEA are mild skin and eye irritants and irritation increases with increasing ingredient concentration.

Animal studies with MEA indicate that it is both a skin and eye irritant and clinical studies with formulations containing MEA indicate that it is a human skin irritant. The longer MEA stays in contact with the skin the greater the likelihood of irritation. MEA is primarily used in rinse-off hair products.

CONCLUSION

The Panel concludes that TEA, DEA, and MEA are safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.

ACKNOWLEDGMENT

Ms. Karen Brandt, Scientific Analyst and writer, prepared the literature review and technical analysis used by the Expert Panel in developing this report.

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ASSESSMENT: TEA, DEA, AND MEA


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<th>Category</th>
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<td>05C - Hair Straighteners</td>
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<td>05D - Permanent Waves</td>
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<td>05F - Shampoos (non-coloring)</td>
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<td>05H - Wave Sets*</td>
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<td>06B - Hair Tints</td>
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<td>10A - Bath Soaps and Detergents</td>
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*It is known that this formulation is rinse-off.

**MEA-COCOATE** 4 10E - Other Personal Cleanliness Products

**MEA-LAURETH SULFATE** 1 06F - Shampoos (non-coloring)
**MEA-LAURETH SULFATE** 11 06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)
**MEA-LAURETH SULFATE** 1 06H - Other Hair Coloring Preparation

**MEA-LAURYL SULFATE** 1 01A - Baby Shampoos
**MEA-LAURYL SULFATE** 3 05F - Shampoos (non-coloring)
**MEA-LAURYL SULFATE** 1 10A - Bath Soaps and Detergents

**MEA-TALLOWATE** 6 10E - Other Personal Cleanliness Products
Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 11, 2012

SUBJECT: Comments on the Tentative Report on Ethanolamine and Ethanolamine Salts as Used in Cosmetics

p.3 - Please include the concentration of Ethanolamine reported to be used in color aerosol sprays.

p.9 - In the summary of the Irritation and Sensitization section, please also include the challenge concentration for the guinea pig maximization study.

p.13 - Because the species are stated in the descriptions of the studies, the second last paragraph of the Discussion does not need to start with “In non-human studies…”.

p.14 - In the second line on this page, “hepatogenicity” should be “hepatocarcinogenicity”.

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 6, 2011


Key issue

In the draft Discussion, it states that the amount of free Diethanolamine is limited to “the present practices of use and concentration of diethanolamine itself.” As DEA “itself” is not permitted for use in Europe, and much of the DEA in products comes from the addition of DEA condensates to products, please change this sentence to: ”The Panel stated that the amount of free diethanolamine available is limited to levels described in the CIR report on DEA.”

Additional comments

p.1 - The last paragraph on this page should be deleted as this information is also presented in the Cosmetic Use section.

p.2 - It is not necessary to present the method of manufacture and impurities of Ethanolamine twice on this page (once under the Chemistry heading, a second time under the Impurities heading)

p.3, 11 - Please indicate that the highest use concentration of MEA-Lauryl Sulfate is 35% in hair dyes and colors. Stating that this concentration is in rinse-off formulations suggests it was reported to be used at 35% in several rinse-off product categories.

p.3 - In the discussion of European regulations, it would also be helpful to add the Annex VI (preservatives) status of MEA-Benzoate and MEA-Saliclylate.

p.4, 11 - In the discussion of the in vitro penetration study, it is not clear what is meant by “penetrated the skin” (amount in skin + amount in receptor fluid?) used to describe the results of undiluted Ethanolamine, and “penetrated through the skin” (amount in receptor fluid?) used to describe the results of aqueous Ethanolamine. If the techniques used to measure Ethanolamine were the same in the two parts of this study, the language describing the results should be the same. In the Summary, does “penetrated through” skin mean just the material found in the receptor fluid?
p. 5 - The current summary under the heading Toxicological Studies just describes acute studies. Either this summary should be moved under the Acute heading, or highlights of the repeat dose studies should be added to the summary.

p.5, 12 - Please include the low dose used in the 90 day oral study in rats and the 2 year dog study (from the original report). Was a NOAEL or NOEL identified in the 90 day study?

p.7, 12 - The word “gavage” is not a verb.

p.9 - In the summary of the Irritation and Sensitization section, “studying” should be “study in”

p.9 - Please indicate if the “clinical studies” examining sensitization potential of formulations containing Ethanolamine (from the old report) were HRIPTs.

p.10 - Please change “detergent temperature” to “water temperature”

p.17, Table 4c - This table should also include the Annex VI status (preservative list) for MEA-Benzoate and MEA-Salicylate.