Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

Status:	Final Amended Report for Panel Review
Release Date:	September 11, 2026
Panel Meeting Date:	October 5-6, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Thushara Diyabalanage, Ph.D., former Scientific Analyst/Writer, CIR.

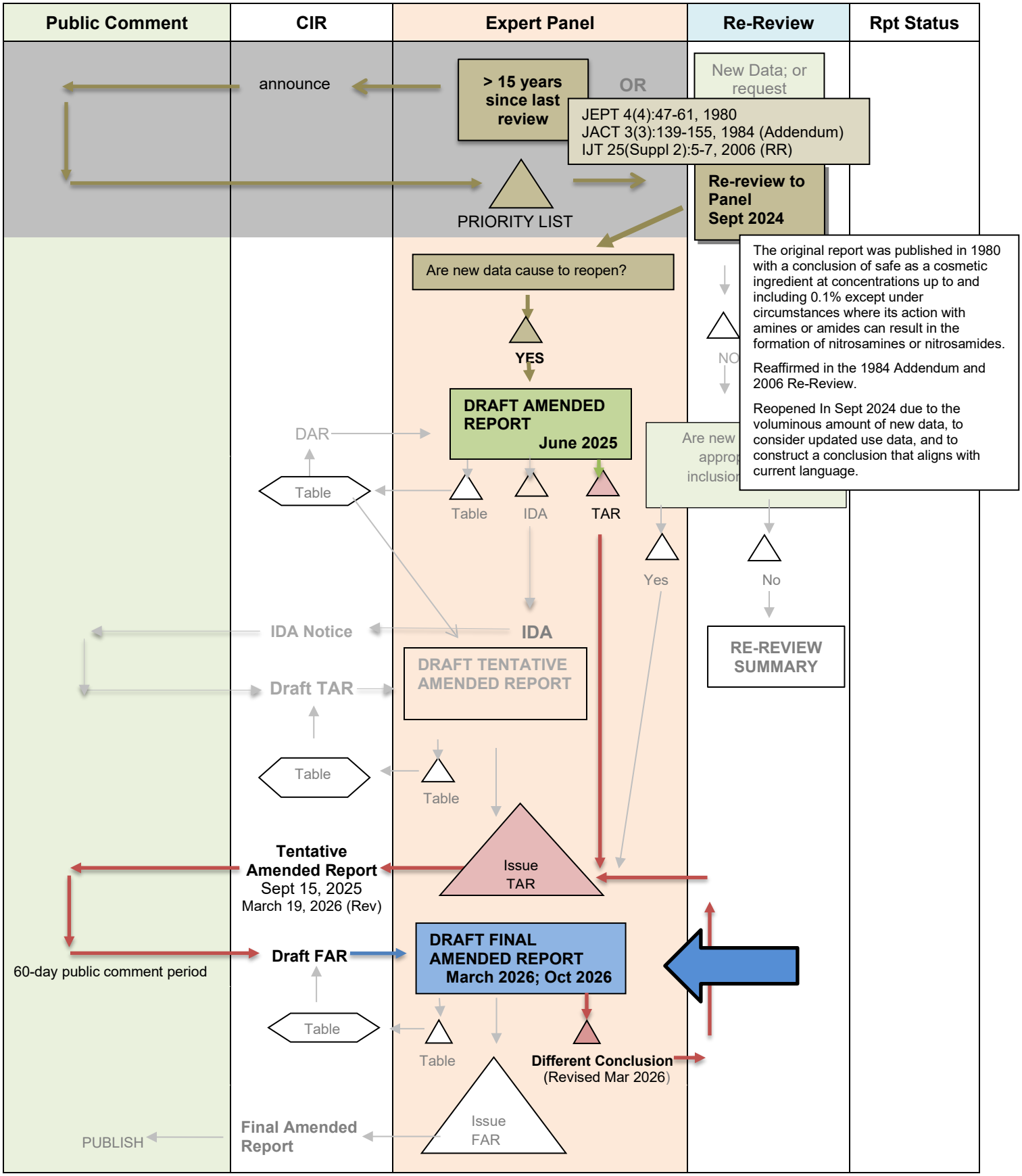
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RE-REVIEW FLOW CHART

INGREDIENT/FAMILY 2-Bromo-2-Nitropropane-1,3-Diol

MEETING October 2026



Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice Fiume, M.B.A.
Senior Director, CIR
Date: September 11, 2026
Subject: Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics. (It is identified as *report_2-Bromo-2-Nitropropane-1,3-Diol_102026* in the pdf document.) At the March 2026 meeting, the Panel issued a revised Tentative Amended Report with the conclusion that 2-Bromo-2-Nitropropane-1,3-Diol is safe in cosmetics when formulated to be non-sensitizing, which may be based on a quantitative risk assessment (QRA) or other appropriate methodology.

No new data have been received, although some updates are identified with yellow highlighting. Comments received from the Council on the on the revised Tentative Amended Report have been addressed (*PCPCcomments_2-Bromo-2-Nitropropane-1,3-Diol_102026* and *response-PCPCcomments_2-Bromo-2-Nitropropane-1,3-Diol_102026*).

The following supporting documents are also included:

- flow chart (*flow_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- history (*history_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- data profile (*dataprofile_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- search strategy (*search_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- transcripts from the discussing the current report (*transcripts_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- minutes from the past reviews (*originalminutes_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- original report (*originalreport1980_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- addendum (*addendum1984_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- original re-review summary (*rereview2006_2-Bromo-2-Nitropropane-1,3-Diol_102026*)
- RRData (*RRdata2003_2-Bromo-2-Nitropropane-1,3-Diol_102026*)

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

CIR History of:
2-Bromo-2-Nitropropane-1,3-Diol

1980

First Safety Assessment- The Panel concluded that 2-Bromo-2-Nitropropane-1,3-Diol was safe as a cosmetic ingredient up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamines.

1984

An addendum to this report was published due to the availability of new scientific literature. The Panel re affirmed the 1980 conclusion and stated that the additional data suggested the possibility that on absorption 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the formation of endogenous formation of nitrosamines in humans.

2003

Re-reviewed, the Panel decided not to re-open and re-affirmed their earlier conclusion after considering the data submitted. The rereview was published in 2006.

September 2024

Panel decided to reopen the safety assessment of this ingredient expecting to revisit safety information related to the possibilities of the formation of endogenous nitrosamines in humans due to dermal penetration.

June 2025

The Panel issued a Tentative Amended Report with a conclusion of safe in cosmetics in the present practices of use and concentration described in this safety assessment.

March 2026

The Panel issued a revised Tentative Amended Report with a conclusion of safe in cosmetics when formulated to be non-sensitizing, which may be based on a quantitative risk assessment (QRA) or other appropriate methodology

2-Bromo-2-NitroPropane-1,3-Diol* – October 2026																														
	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
2-Bromo-2-Nitropropane-1,3-Diol	X	X	X		X	X,O	O	O	O	X,O		O		O	O	X,O	O	O		X	O	O		X,O				X.O	X,O	X

* “X” indicates that new data were available in this category for the ingredient; “O” indicates that data from the original assessment were available

2-Bromo-2-Nitropropane-1,3-Diol

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
2-Bromo-2-Nitropropane-1,3-Diol	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

Following key words were searched in PubMed

2-bromo-2-niropropane-1,3-diol, (50 results 17 relevant)
bronopol, (213 results, 71 relevant)
CAS number 52-51-7(28 results, 5 relevant)

Searched following Websites

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- a general Google and Google Scholar search- www.google.com https://scholar.google.com/

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: March 30, 2026

SUBJECT: Revised Tentative Amended Report: Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics (release date: March 19, 2026)

The Personal Care Products Council respectfully submits the following comments on the revised tentative amended report, Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics.

Key Issues

In several places, the CIR report states that the report was opened to "re-investigate the possibility of endogenous formation of nitrosamines". In the Discussion, it would be helpful to state that the Expert Panel did not consider the information in the original CIR report to support endogenous formation of nitrosamines, nor was any new information to support endogenous formation of nitrosamines found.

Discussion – Is the following paragraph correct? It is not clear what is meant by "this level". It seems to be referring to the highest use concentration reported, but that is not stated until later in the paragraph.

"According to studies conducted by the US EPA on 2-Bromo-2-Nitropropane-1,3-Diol, this chemical may release a minimal amount of formaldehyde upon hydrolysis due to its long half-life. Concern for this issue was mitigated as the Panel noted that this level is less than the 0.074% formaldehyde limit established by the Panel in its final safety assessment of formaldehyde published in 2013 and is well below the threshold for toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by 2-Bromo-2-Nitropropane-1,3-Diol in formulation would be even lower, considering that this ingredient is

being used at concentrations up to 0.05%."

Additional Considerations

Acute, Inhalation – Please revise the following sentence to clarify at which concentrations 4/5 males and 3/5 females died (presumably it was at the high concentration since it says only one male rat died at the low concentration). "At low-dose level, one male rat died whereas 4/5 males and 3/5 females died during exposure."

Developmental and Reproductive Toxicity, old report summary - Please delete "respectively" from the following sentence: "In another study 2-Bromo-2-Nitropropane-1,3-Diol was administered via the drinking water of Charles River COBS CD strain rats (13 males and 26 females in a group) during premating (80-87 d), mating, gestation, and lactating periods at 0, 0.25, 7,0 and 200 mg/kg/d, respectively." [the comma in 70 also needs to be deleted] Including the word "respectively" suggests the rats were treated at 0 during premating, 0.25 mg/kg/day during mating, 70 mg/kg/day during gestation, and 200 mg/kg/day during lactation, which is not suggested by the rest of the description of this study.

Genotoxicity, In Vitro – For the study in mammalian cells cited to reference 6, please indicate whether this was a guideline study and the type of mammalian cells in which it was completed.

Summary – The Summary says: "2-Bromo-2-Nitropropyne-1,3-Diol at 1% was not a sensitizer in guinea pig assays." It is not clear where the 1% concentration is coming from. Since the Summary only includes new information, only the new guinea pig study should be included. Based on the information in the Sensitization section, the guinea pigs were induced intracutaneously with 0.2%, followed by epicutaneous induction with 1.5% and then challenged (epicutaneously) with 0.4%. All three concentrations used should be included in the Summary.

Table 3, Reference 31 – It is not clear why the information on females is not included in the first part of the results but is included in the rest of the results. If it is available, please add the information for females even if 2-Bromo-2-Nitropropane-1,3-Diol was not one of the top 20 allergens in females.

Table 3, Reference 41 – Many 7s need to be deleted in the Years column.

Table 3, Reference 52 – Please correct: "between to" (delete "to")

2-Bromo-2-Nitropropane-1,3-Diol – October 2026	
Comment Submitter: Jaap Venema, Ph.D.; Personal Care Products Council **Subject:** Revised Tentative Amended Report: Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics (release date March 19, 2026) **Date of Submission:** March 30, 2026	
Comment	**Response/Action**
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Discussion – Is the following paragraph correct? It is not clear what is meant by "this level". It seems to be referring to the highest use concentration reported, but that is not stated until later in the paragraph. "According to studies conducted by the US EPA on 2-Bromo-2-Nitropropane-1,3-Diol, this chemical may release a minimal amount of formaldehyde upon hydrolysis due to its long half-life. Concern for this issue was mitigated as the Panel noted that this level is less than the 0.074% formaldehyde limit established by the Panel in its final safety assessment of formaldehyde published in 2013 and is well below the threshold for toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by 2-Bromo-2-Nitropropane-1,3-Diol in formulation would be even lower, considering that this ingredient is being used at concentrations up to 0.05%."	Addressed.
Acute, Inhalation – Please revise the following sentence to clarify at which concentrations 4/5 males and 3/5 females died (presumably it was at the high concentration since it says only one male rat died at the low concentration). "At low-dose level, one male rat died whereas 4/5 males and 3/5 females died during exposure."	Addressed.
Developmental and Reproductive Toxicity, old report summary - Please delete "respectively" from the following sentence: "In another study 2-Bromo-2-Nitropropane-1,3-Diol was administered via the drinking water of Charles River COBS CD strain rats (13 males and 26 females in a group) during premating (80-87 d), mating, gestation, and lactating periods at 0, 0.25, 7,0 and 200 mg/kg/d, respectively." [the comma in 70 also needs to be deleted] Including the word "respectively" suggests the rats were treated at 0 during premating, 0.25 mg/kg/day during mating, 70 mg/kg/day during gestation, and 200 mg/kg/day during lactation, which is not suggested by the rest of the description of this study.	Addressed.
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Table 3, Reference 41 – Many 7s need to be deleted in the Years column.	Addressed.
Table 3, Reference 52 – Please correct: "between to" (delete "to")	Addressed.

SEPTEMBER 2024 PANEL MEETING – INITIAL REVIEW/RE-REVIEW FOR CONSIDERATION

Belsito Team – September 30, 2024

DR. BELSITO: 2-Bromo-2-Nitropropane-1,3-Diol. So, the Panel published a review on this in 1980, concluded safe as a cosmetic ingredient, concentration of 0.1 percent, except under circumstances where its action with amines or amides can result in a formation of nitrosamines or nitrosamides. An addendum was published in '84 due to the availability of new test data. We reaffirmed in a 1980 conclusion and further stated the possibility that upon absorption the material could contribute to endogenous formation of nitrosamines in humans.

And we looked at this and again in 2004, 2005 reaffirmed the conclusion. It was published in 2006. 2024, an extensive search or the world's literature was performed for studies dated 2000 onward. There was a historical review, search strategy. And so, basically, in 2022, indicated that the ingredient is used up to 17 -- no, is that right, 17.9?

DR. SNYDER: No, no, no, no.

MS. BURNETT: No.

DR. BELSITO: I got --

DR. SNYDER: No. Wrong page.

DR. BELSITO: Wrong page.

DR. SNYDER: It was at 0.1 percent in '80, and then it's gone down to 0.05 percent today.

DR. BELSITO: Right.

DR. SNYDER: But it's gone from one use to 36 uses.

DR. BELSITO: Right. Okay, thank you. What happened here. Got my pages mixed up. Okay, thank you, Paul. Yeah. So, it's gone up to 167 products.

DR. SNYDER: Well, with the new dataset. Yeah.

DR. BELSITO: With the new data. Reported use concentration is decreased to 0.05 in hand wipes, a leave-on, and eye makeup remover. And then there were --

DR. SNYDER: New data.

DR. BELSITO: New data. And there were comments the last time from the Council about the in vitro absorption of the rate of hydroxyanisole. And I have the --

DR. SNYDER: Paper.

DR. BELSITO: -- paper. I sent that to Monice.

MS. FIUME: Yes. Do you want me to distribute it to --

DR. BELSITO: Yeah, if you could.

MS. FIUME: Okay.

DR. BELSITO: So, I think that can be included in the report.

MS. FIUME: BHA into the 2-Bromo report?

DR. BELSITO: No, no, no. Oh, sorry.

MS. FIUME: That's okay.

DR. BELSITO: I'm like --

MS. FIUME: Your notes are -- sorry.

DR. BELSITO: My notes are on the wrong page.

MS. FIUME: The wrong order. Your notes are in the wrong order.

DR. BELSITO: Okay, I stapled them incorrectly. Yeah. No, no. Okay. Let me look at this here. Stop reading from my notes that I've -- okay. So, it's increased, but no increase in concentration. But there's a use in baby products that's new. And I guess my comment about -- so we always were getting baby comment -- or baby use. And if it's absorbed, this could contribute to systemic nitrosamine levels is what we heard before. And of course, we noted the body surface area versus

weight of babies is different. We previously discounted the systemic nitrosamine levels because of negative carcinogenicity data. And my comment to you: Is this a concern with baby products, or are we okay with these reported new uses?

MS. FIUME: In the baby product categories, other baby products, so we don't know what those are.

DR. BELSITO: Right.

DR. SNYDER: Or insufficient for baby products. We all know the specific product or have any data, right, on nitrosamine systemic exposure.

DR. BELSITO: Well, theoretically, baby skin, except for premature infants, the absorption across the skin is the same.

DR. SNYDER: Okay, okay.

DR. BELSITO: The permeability barrier is --

DR. SNYDER: Okay. Intact.

DR. BELSITO: -- intact.

DR. SNYDER: Okay. So, we can just put that in discussion.

DR. BELSITO: Yeah. So, we can just dig up references in that.

DR. SNYDER: Yeah.

DR. BELSITO: There are references out there.

MS. FIUME: So, we do have the baby skin reference paper, I believe, on our website that has discussed that because we had it in open discussion a couple years ago.

DR. BELSITO: Yeah.

DR. SNYDER: Just put that in for reference.

DR. BELSITO: So, we can refer to that.

MS. FIUME: Yeah.

DR. BELSITO: But then the only issue is the volume of skin versus the weight.

DR. SNYDER: Yeah.

DR. BELSITO: Or the amount of skin versus the weight. So, do we do a -- is there enough data on the absorption and the systemic nitrosamine? What page was that on? So, that was in the report from not the original 1982 report, right?

MS. FIUME: So, PDF Page 35 is the 1984 addendum that just has a small paragraph on absorption.

DR. BELSITO: But where was the report that systemic absorption can result in nitrosamines? That was the reason for doing that reevaluation supposedly.

MS. FIUME: Absorption in the original report is on PDF Page 16.

DR. BELSITO: No, but the reason we reopened it, wasn't it because of some data that suggested that the 2-Bromo-2-Nitropropane-1,3-Diol when absorbed systemically could contribute to endogenous levels of nitrosamine?

DR. SNYDER: It's on Page 3. It references the addendum 1980 conclusion. Reaffirms with more data, suggests, furthermore, the possibility that absorption of diol --

DR. BELSITO: But where is that data?

DR. SNYDER: You'd have to look in the addendum and see where it's referenced in there.

DR. BELSITO: That's where we are now, and I'm not seeing --

DR. SNYDER: Yeah, yeah, yeah.

DR. DIYABALANAGE: Check the Page 34.

DR. BELSITO: Yeah, this is ingested squid extract. But these are containing nitrosamines. Where's the absorption of 2-Bromo-2-Nitropropane-1,3-Diol causing nitrosamine?

MS. FIUME: So, Page 27 talks about nitrosation, potential interactions with other ingredients. But I don't know that's what led to the statement.

DR. RETTIE: So, are they considering that this ingredient here could substitute for, say, sodium nitrite in the formation of nitrosamine?

DR. BELSITO: The way that I read the reason that -- I mean, I wasn't on the Panel at the time. So, we issued a report, and then like two years later, we issued an addendum to the report because apparently there was data suggesting that when 2-Bromo-2-Nitropropane-1,3-Diol -- 2-Bromo -- let's call it Bronopol, which is the trade name. When Bronopol is absorbed systemically, it can be converted to endogenous nitrosamines and contribute to the level of endogenous nitrosamines. That's what stated for the reason for reopening the report.

DR. SNYDER: That's on Page 26 in the overview or summary on Page 26. It contributed endogenous formation of nitrosamines in humans.

DR. BELSITO: Right. But where's that data?

DR. KLAASSEN: Is it may or it does?

DR. BELSITO: May contribute. But that's what I'm looking for in the report. Where's the data on that? Says it's a known nitrosating agent. I mean, because wouldn't that be important if we're going to ask for a margin of exposure on baby products how this -- I mean, because that's the concern, right, that it would be -- that a greater amount would actually be absorbed by children even though the absorption across the skin isn't different. Just given the volume of skin versus their weight. But then we need to know what kind -- what are they talking about in terms of if this is absorbed what percent could be converted to a nitrosamine, right. Wouldn't that be our concern? And I don't see that data anyplace. I mean, there's all this information about measuring nitrosamines.

MS. FIUME: So, on PDF Page 30, there's a table that's showing the amounts of NDELA.

DR. BELSITO: In product.

MS. FIUME: In product, yes.

DR. BELSITO: Right. And talking about when it's combined with triethanolamine and all of that. But I just couldn't -- I mean, I didn't see the data that raised the concern for the reopening, which was the ability of 2-Bromo-2-Nitropropane-1,3-Diol to be absorbed and then on its own contribute to endogenous nitrosamines. Because if that's not the case, then I don't think we even need to worry about new baby products.

DR. SNYDER: Yeah, I read through the whole thing. I don't see it.

DR. KLAASSEN: Yeah.

DR. BELSITO: Yeah.

MS. FIUME: Yeah.

DR. RETTIE: So, is this theoretical concern.

DR. DIYABALANAGE: Yeah. So, there's not continuity study about the endogenous nitrosamine.

DR. KLAASSEN: That's what I thought. It was a it may.

DR. DIYABALANAGE: It may, yeah.

DR. KLAASSEN: Yeah, not that it does.

DR. BELSITO: So, is this just someone's speculation? I mean, it says, "New data suggest." And they never talk about the data.

DR. SNYDER: I think it's just because they're -- well, yeah.

DR. BELSITO: Because in the report then they start talking about its presence with materials that could be nitrosated and detecting nitrosamines. Big deal. We know that. Okay.

DR. SNYDER: Well, we're going to have to reopen and clarify that if that's an inaccurate statement.

MS. FIUME: Is the statement inaccurate? I mean --

DR. BELSITO: Well, is it in any of our reports? Is it in the last report?

DR. SNYDER: It's in that addendum.

DR. BELSITO: It's in that addendum.

DR. SNYDER: Yeah.

DR. BELSITO: But the last -- there's another --

DR. SNYDER: Oh, 2004-2005, I don't know.

MS. FIUME: That was a re-review summary.

DR. BELSITO: Yeah. So, actually in our conclusion to the addendum, we actually said, "An update of the scientific literature available since 1979 reaffirms the earlier concern to the Panel. Suggests, furthermore, the possibility that on absorption, Bronopol may contribute to endogenous formation of nitrosamines in humans." That's in our conclusion. From 19 -- whatever -- 80 --

DR. SNYDER: Four.

DR. BELSITO: Right. And then the next one was just when we're doing very brief reviews, right? We just published --

DR. KLAASSEN: Well, if Ron Meek would remember -- I mean Ron --

DR. SNYDER: Shank.

DR. KLAASSEN: -- Shank would remember.

DR. BELSITO: I mean, we talk about the 1980 publication and '84 reported addendum. We reaffirm the conclusion. And we don't say anything about the addition to that conclusion, which was specifically there about absorption. I mean, I just don't know what to do with this. I mean, there are new reported baby -- other baby products which weren't there before. Concentrations of use have decreased, but use has increased, which sort of find hard to believe because it's formaldehyde release. And companies have been getting rid of formaldehyde in cosmetic products. I'm shocked that it's reported to have increases.

DR. RETTIE: This is one where David reports tomorrow. That's something we wait for?

DR. BELSITO: Yeah. So, if you look at --

MS. FIUME: So, Don, it's interesting. I'm reading the conclusion. That second paragraph of the addendum, it's not something the Panel would normally include as part of the conclusion. It'd be part of the discussion. It almost seems more like a discussion item that the conclusion really should end as what it was in the 1980 report.

DR. BELSITO: But it's in the conclusion.

MS. FIUME: I know. But does it conclude anything other than give data? And I looked through the entire addendum. Besides the introduction where it says, "These data were received indicating that" --

DR. BELSITO: Yeah.

MS. FIUME: -- that reference is never cited again.

DR. SNYDER: Yeah.

DR. BELSITO: Well, the only one I can see in the reference list is this Holland, 1981, *Bronopol and nitrosamine formation*, from Cosmetic Technology Volume 3. It's Reference 14 in that report, which looks like that could be the one.

MS. FIUME: But in the introduction, the statement that's referring to the additional data is Reference 2.

DR. BELSITO: Which is Boots, submission of data.

MS. FIUME: But I don't think I ever see that reference made again throughout the document in a quick search.

DR. BELSITO: No, I don't. I mean, they don't discuss what it is. On the other hand, we have data on Bronopol gavage study, doses up to 100 milligrams per kilogram to rabbits. There was no effect on parturition, litter size, postnatal survival or development in young rats given 40 milligrams per kilogram orally on Day 15 through lactation, which means that these rats were getting it as weanlings without any effect. So, I think that -- it's a small study, but gives -- I mean, we could use if we don't want to reopen. But if that data came from Boots, right, it's going to be unpublished information from 1980s. Are we even going to be able to get it? Do you hold onto those documents?

MS. FIUME: We do. It's just if we could actually get our hands on it from the boxes. It depends on how well that file was maintained for all these years. Sometimes, we can. Sometimes, we can't.

DR. BELSITO: Well, actually, the Reference 2 says, "Additional information on nitrosamines was submitted, Reference 2." We don't know that that is the new data suggesting the possibility. But otherwise, only other one that I can see is that Reference 31, which is --

MS. FIUME: Reference 30.

DR. BELSITO: No, 14. I'm sorry.

MS. FIUME: Fourteen.

DR. BELSITO: Holland. *Bronopol and nitrosamine formulation*. But that could be with -- I tell you, these old reports sometimes amaze me. Can't believe that --

DR. SNYDER: The wording.

DR. BELSITO: Well, not only that, but Dietrich Hoffman was on this panel.

MS. FIUME: See him referenced in here a few times.

DR. BELSITO: What?

MS. FIUME: I said I see him referenced in this report a few times.

DR. BELSITO: Yeah. I mean, he was a stickler. I worked with him for several years when I first joined.

Okay. I don't know what to say. Curt, Paul, Allan? Where are we with these baby products? Do we reopen to look at this potential for endogenous formation if absorbed?

DR. SNYDER: Unless we get clarification on where they come from, what reference. Unless we can find the reference. I mean, it's asterisked, and it says contact CIR to get it.

DR. BELSITO: Well, let's move on. There were a couple of other issues here. This is PDF Page 6, the ECHA skin corrosion. What were the conditions? It says, "Bronopol showed a corrosive potential in the EpiDerm skin corrosivity under both test conditions chosen." I think we need to specify the test conditions. And the one below that, again from ECHA 2005, it says, "Bronopol did not reveal skin sensitization potential under the conditions of the study." What were the doses that were tested? On PDF Page 6, under Clinical Studies, the Wentworth, Yiannias, Keeling, et al., study of 315 patients that were studied. That wasn't irritancy; it was sensitization. Highlights reducing sensitization rates. Are you with me on these?

MS. FIUME: Yeah.

DR. BELSITO: Okay. Okay. If we don't want to reopen, we can, again, use the results of the repro teratogenicity study where they looked at weaning rats that were being fed by mothers getting 100 milligrams per kilogram per day. Again, we have that statement in the conclusion. Okay. So, who's reporting tomorrow?

MS. FIUME: David.

DR. SNYDER: David.

DR. BELSITO: What do we want to do with this? Reopen to look at the endogenous absorption -- or absorption causing endogenous nitrosamine levels given reports of use in other baby products?

DR. SNYDER: Baby use. I think so.

DR. BELSITO: Curt?

DR. KLAASSEN: Yes.

MS. FIUME: Don, on the LLNA, it looks like it was up to 10 percent as the test concentration.

DR. BELSITO: Yeah, I'm okay with sensitization.

MS. FIUME: Okay.

DR. BELSITO: My only concern here about reopening is this prior report where they claim that there's endogenous production of nitrosamine if absorbed in –- if used in babies. Okay.

Cohen Team - September 30, 2024

DR. COHEN: So, we published a review with 2-Bromo-2-Nitro-1,3-Propane-1,3-diol in 1980 and concluded safe as a cosmetic ingredient at a concentration to and including 0.1 percent except under the circumstance where its action with amines and amides can result in the formation of nitrosamines or nitrosamides. An addendum to the report was published in 1984 due to the availability of new test data; the Panel referred reaffirmed the 1980 conclusion and further stated that the additional data suggested the possibility that on absorption, bromo-nitropropane may contribute to the endogenous formation of nitrosamines in humans.

The Panel previously reconsidered reopening of the report and reaffirmed the conclusion in 2006. So, it's been 15 years. So, we have studies on chemistry, dermal absorption, toxicology, genotox, dermal irritation and sensitization. The frequency of use is 36 cosmetic formulations as opposed to one in 2003. Cosmetic Direct had 167. Maximum use has decreased to 0.05, about half of the previous report. And the question to us is reopen or not. So, this is a formaldehyde releasing preservative in cosmetics. It’s part of routine patch testing in the U.S. Susan, you want to?

DR. TILTON: Yeah. So, as you noted, the frequency of use has increased although I noted that it was likely underreported in 2003, since there were concentrations of use listed where there were no reported uses in that report. And the max concentration of use has decreased by half. The toxicity data that's been provided, there's both new and confirmatory studies on chemistry, dermal absorption, toxicology, genotoxicity, dermal irritation and sensitization, and some pharmacological effects.

I did not see any additional data that would change the prior conclusions with the restrictions that are noted, but it is being used in more or different formulations than previously reported. So, we can have a discussion about that, if that would be a reason to reopen. Otherwise, my conclusion was do not reopen.

DR. COHEN: David?

DR. ROSS: I found this one quite difficult, actually. Yeah. The concentrations had come down, uses up, fair amount of new data. I'm not convinced any of it would give us a different conclusion, as Susan had just pointed out. But you know, there are some differences in there. For example, there's some positives cropping up. So again, I am sort of on the fence, we could update the nitrosamine discussion, we could update the formaldehyde releasing discussion, we could review the new data. So yeah. David, I'm having a hard time sitting on this fence. Can you push me one way or the other?

DR. COHEN: I was going to hopefully push the panel to reopen for a few reasons. One --

DR. BERGFELD: I would agree with you.

DR. COHEN: Thank you. It's good to have the tail wind pushing me on this. Number one, it's a formaldehyde releasor, that is a hot button issue from the get out. Two, the old conclusions are uninterpretable to a person. I'm not sure -- when you say you know it's safe, but by the way, can form carcinogens under certain circumstances, it's just it's not translatable to anybody. So, if this had a more resolute, modern conclusion, I could see us not reopening it because you're quite right, Susan, I don't think it's going to change, but I don't think people can interpret this old report very well and formaldehyde releasers deservedly need a little extra modern attention.

DR. ROSS: There's one thing I forgot to add, there's now a new absorption study in there so, we could probably do some sort of MOE --

DR. COHEN: That would be really nice.

DR. ROSS: -- I haven't looked at it in detail yet, but possible -- theoretically possible at least.

DR. COHEN: I suspect it's going to be a discussion tomorrow. Yeah, I have new dermal absorption data based on vehicle, genotox, respiratory tox. I think it's enough to want to reopen that. And Wilma you might be the deciding vote. We'll see. Maybe not. Maybe we'll want to reopen.

DR. ROSS: I think we lose all three in instant votes because we're one panel member down.

DR. COHEN: Personally, it's an even fight. I'll just remind Don of that. What we're left with is inhalation, toluene and propylene carbonate. You want to do that when we get back? Is lunch served now? Yeah. Let's break. Do you want to come back at 1:00 and then we could probably finish rather quickly, yeah? It'll be a lot to organize for tomorrow, but I think we'll be okay.

Full Panel– October 1, 2024

DR. COHEN: Yes. So, the Group first published a review of the safety of Bromo-Nitro-Propane in 1980 and concluded it was safe as a cosmetic ingredient at concentrations up to and including 0.1 percent, except under the circumstance where its actions with amines and amides can result in the formation of nitrosamines or nitrosamides. An addendum to the report was published in 1984 due to the availability of new test data.

The Panel reaffirmed the 1980 conclusion and further stated that the additional data suggested the possibility that, on absorption, Bromo-Nitro-Propane may contribute to the endogenous formation of nitrosamines in humans. The Panel previously reconsidered a re-review in 2004 and reaffirmed the conclusion in its published work in 2006. It has been 15 years and the question of reopen has been raised.

We have studies on chemistry, absorption, toxicology, genotoxicology, dermal irritation and sensitization, and pharmacologic effects, and some case reports. We have frequency of use increasing, a 2023 VCRP at 36 formulations and Cosmetic Direct at 167. We have a decrease in maximum use concentration currently at 0.05 percent, half of the previous reports.

Because of the new dermal absorption data based on vehicle genotox, respiratory sensitization, voluminous new data, and what we believe is an existing conclusion that is archaic and difficult to understand or operationalize. Our motion is to reopen.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Any evidence?

DR. BELSITO: Our major reason for reopening is clarification on the absorption causing increased endogenous nitrosamine levels --

DR. COHEN: Yeah. Yeah.

DR. BELSITO: -- and the fact that there are new uses in baby products. Unfortunately, it appears that we may not be able to get that report, I believe, on the nitrosamine because it was from roots.

And it's interesting that they reopened the report two years later because of that. But there's really no information on the roots study in that report or why they discounted the endogenous nitrosamine formation.

DR. COHEN: Well, I think the point -- and, you know, if this clears, we're not going to have a conclusion like that. But we'll have discussion points about it.

DR. BELSITO: Right. I mean, I think we need to know more about the baby products and more about this endogenous nitrosamine.

DR. BERGFELD: Any other comments before I call the question to reopen? All right. I'll call the question. All those in favor of reopening. Unanimous.

JUNE 2025 PANEL MEETING – DRAFT AMENDED REPORT

Belsito Team– June 9, 2025

DR. SNYDER: 2-Bromo-2-Nitropropane-1,3-Diol.

DR. RETTIE: What an interesting molecule.

DR. BELSITO: And so, we have Wave 2, from PCPC, that I agreed to. And then Wave 2 from Women's Voice For The Earth.

DR. KLAASSEN: Formaldehyde.

DR. SNYDER: So this was a Draft Tentative Amended Report. In 1983, it was safe as used. In 2002, it was re-reviewed and affirmed the conclusion.

In June of 2024, we re-opened to re-look at sensitization and photosensitization data and added two ingredients, and came up with it as insufficient, maximum concentration of use, dermal irritation, sensitization, and UV absorption spectra. New data covers all the insufficient needs.

PCPC provided comments on Page 19 of 35. And then what was that about -- I didn't have the Women's Voices For The Earth stuff, Don. Where was that at?

DR. BELSITO: Yeah. They were going after this whole formaldehyde releaser and the Boots report.

DR. HELDRETH: It's PDF 16 in Wave 2.

DR. BELSITO: And apparently we can't get the original report. It either no longer exists or it's buried someplace in files that are not easily accessible is what we're told.

DR. SNYDER: So where are we at?

DR. BELSITO: I'm just trying to get to -- you know, when you look at -- well, first of all, she's, I think, talking about -- this is PDF Page 16. Newer data on carcinogenicity is needed for 2-Bromo-2-Nitropropane-1,3-Diol. Should be requested given that more recent tests have determined evidence of both genotoxicity and clastogenicity.

And when I looked at those studies, I thought they were cytotoxic. And I think it confused cytotoxicity with genotoxicity. And the other result was ascribe to formaldehyde which we can put in the Discussion.

The amount of formaldehyde that's released from Bronopol -- which I know is the trade name but it's easier to say -- is much less than the amount of formaldehyde that we've allowed in cosmetic products. And we could reference the margin of exposure assessment and the formaldehyde paper in the Discussion. I'm not sure that it needs to be in the full report, if we wanted to do that.

But her big issue was the formaldehyde releaser. She went after all the other formaldehyde releasers, too, DMDM Hydantoin, Diazolidinyl, Imidazolidinyl urea, Quat-15. I just didn't see that as an issue.

But going back to the original report. So, in this introduction, it says that -- and if you look at that report. So, an addendum to the report was published in 1984, due to the availability of new scientific literature. The Panel reaffirmed the 80 conclusion and further stated that the additional data suggested the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of nitrosamines in humans.

And the reference is to a Boots study, which we don't have. And there's no discussion about that information. But if you read it, it says it suggested the possibility that on absorption.

I'm not a chemist and I don't know about what would happen when this is absorbed, but how is it forming endogenous nitrosamines in humans if it's absorbed? I mean, does anyone have any thoughts on that? And again, we don't have this Boots paper. Apparently, it's not available to us anymore, and it was data that was brought in at the time of -- since then.

DR. RETTIE: So, Don, before we get to that question, I just --

DR. BELSITO: Allan, put on your mic, please.

DR. BELSITO: Oh, sorry. Before we get to that question, I had concerns about clarification on how much is absorbed. Because when you look at all the references -- at least all the ones I could get -- I varied from 0.55 percent of the dose reaching the bloodstream, all the way up to 40 percent, if you see what the Wikipedia page says.

And then the Lopez-Sanchez paper, which is as close as it gets to real data, I think, says 11 percent is absorbed in 24 hours. So there's quite a range there, 0.55 to 40 percent; maybe 11 percent is a good number.

I couldn't get the Moore and Naito references from 1974 and 1976, but I thought they might be useful to get us somewhere concrete on dermal absorption, because I thought that needed to be resolved, needed to have a better handle on that.

DR. KLAASSEN: It does have a molecular weight of 199, and an octanol/water ratio of 0.18. So, with those physical/chemical properties, one would expect it to have reasonable absorption. So, you know, I think maybe the 11 percent isn't too far off.

DR. RETTIE: Yep. I'd agree with that. I managed to compile a table of small molecular weight compounds, or ingredients, that we've looked at over the last five or six CIR meetings, and as Curt says, that's exactly where you would expect to find yourself for Bronopol with some absorption. Maybe even a bit more than 11 percent.

DR. BELSITO: Well, if it's absorbed, you have a 90-day study where rats were fed 160 milligrams per kilogram. And other than there were no deaths, respiratory distress, gastrointestinal regions in dogs, given 20 milligrams per kilogram per day. Had no toxic reaction except for some vomiting.

The DART studies are negative. The genotox studies are negative. The carcinogenicity study, applied to the skin of mice three times a week for 80 weeks, did not affect tumor incidence. And oral study in rat drinking water, as high as 116 milligram per kilograms per day for two years, didn't reveal any tumor evidence.

So, even if it's absorbed up to 11 percent, Allan, what are you concerned about?

DR. RETTIE: Well, when you put it that way and I look at all the green that I've got here on the second page, my concerns have disappeared. So, thanks for pointing that out.

DR. SNYDER: So what are we doing with this one? What are we saying?

DR. BELSITO: I think it's -- you know, I mean, the only issue I have is it can be a sensitizer, right? I mean, we know that.

DR. RETTIE: So, it was clean up to 1 percent sensitization, and we're using it at -- where is this?

DR. BELSITO: Yeah, but --

DR. SNYDER: The max concentration of use is 0.05, down from 0.1.

DR. BELSITO: Right. But it's 0.05 in wipes. And wipes is one of the categories we ran into trouble with methylisothiazolinone. And the way we handled that was we said, safe use as determined by quantitative risk assessment or other similar methodologies.

I'm just raising that red flag that just because it was okay at 1 percent on the back doesn't mean it's okay at 1 percent in a wipe that essentially ends up being leave-on on a mucosal area.

DR. SNYDER: So what do we want to say?

DR. BELSITO: Well, I mean, I'm just pointing that out. I mean, 1 percent to 0.05 percent, it would probably pass a QRA for wipes. But we don't have a -- I mean, it's being used in wipes, we -- who's reporting on this tomorrow?

DR. SNYDER: We are. We are. It's our team.

DR. BELSITO: Yeah, it's -- what's the -- max use is 0.05.

DR. SNYDER: Yeah, max concentration use is 0.05 in the wipes.

DR. BELSITO: Ocular irritation was negative.

DR. SNYDER: Yep.

DR. BELSITO: No, the contact allergy rates are pretty low. We do have the caveat it shouldn't be used in cosmetic products in which N-nitroso compounds can be formed.

The only other thing I wanted to point out is that there are more recent papers from the North American group on data on incidents, and this is in dermatitis patients, from 2019, 2020, 2021, and 2022. And I've included those references in my report for the writer to add to the report.

DR. HELDRETH: Thank you.

DR. BELSITO: I guess in the end we can reconfirm the prior conclusion that it's safe as used.

DR. SNYDER: Okay.

DR. BELSITO: I think that in PDF Page 30, the multicenter studies, I was a bit confused here because the ones that were 2013 to 2014, is repeated twice. One is in 12 centers in North America; one is in 13 centers. The number of patients differs, so I think the years are wrong here. That needs to be looked at.

So references 26 and 27 is what they're giving us. And then references 26 says 2017, 22018, with a different number of patients, so those references need to be checked and make sure that we have the right years. And then, again, as I said, I've added the 2019 through 2022 data from the North American Group.

DR. SNYDER: All right. So, we reaffirm the previous conclusion, safe as used. And we get clarification on those data in that table, Table 3. And we reaffirm that it's not to be used on cosmetic products where nitrosation can occur.

DR. BELSITO: Right.

DR. SNYDER: All right.

DR. BELSITO: And I didn't know if we wanted to put anything in the Discussion regarding this "opps" data that apparently was informally presented in the 1980's regarding endogenous nitrosamine.

There's no data in the text. But I was just wondering if it could be dismissed based on mouse skin and negative carcinogenicity, or just ignore it.

DR. SNYDER: It's your call.

DR. BELSITO: Well, bring it out for discussion of the team.

DR. SNYDER: Okay. All right. So it's discussion on the endogenous -- endogenous what now?

DR. BELSITO: One of the meetings, the second meeting, in like 1983; apparently Boots brought in this data during the meeting saying that when Bronopol is absorbed there can be endogenous nitrosamine formation. There was no data that was presented in that text, and it's very wishy-washy the way it's stated.

DR. SNYDER: We have negative mouse skin carci data, so it's not irrelevant.

DR. BELSITO: Right. And it's not a co-carcinogen. So, I don't even know if it deserves to be in the Discussion or whether we just ignore it. You know, are we putting too much emphasis on it? I just wanted to bring that out for the thought of you three gentlemen.

DR. SNYDER: Yeah, we'll bring it up for discussion, but my tendency would be not to give it attention.

DR. BELSITO: I agree.

DR. RETTIE: Couple of minor points on Table 1. Would probably change the molecular weight to 200 from 199.99, little thing. I was struck by the UV absorption at 244 in base. There was no info on phototox as per the old report. Is this enough to have us be wondering about phototox, the fact that we're mentioning it's a UV absorber? I'm kind of surprised at that. PDF 28.

DR. BELSITO: I mean, 244 is down in the UVC range.

DR. RETTIE: Yeah. So yeah, it's not 219. Are we good?

DR. BELSITO: UVC. I mean, you're looking at ranges from 290 to 400 if you're concerned about photo.

DR. RETTIE: Absolutely. And so, I guess a better way to phrase that question is do we need that line in there? Should we not just put less than 290?

DR. SNYDER: No, just put what it is. That's just what it is.

DR. RETTIE: Okay.

DR. BELSITO: Yeah.

DR. SNYDER: Just leave it the way it is. Yeah.

DR. RETTIE: Okay. That's all I had on that table.

DR. SNYDER: All right. Anything else?

DR. BELSITO: No.

DR. SNYDER: So we're going to reaffirm the previous conclusion, safe as used. We want clarification on the multicenter studies, the wrong years, number of patients. Don provided new 2019 to 2022 data to be added.

The Discussion, we're going to talk about it, but we think we should not add, or we shouldn't talk about the endogenous nitrosamine formation because we have a negative mouse carci study, and it's not a co-carcinogen. I think that's all I have. Is that right?

DR. BELSITO: Correct. And just not to be used with nitrosating agents, whatever our new boiler language is for that.

DR. SNYDER: Yep. All right. Thank you.

Cohen Team– June 9. 2025

So, 2-Bromo-2-Nitropropane-1,3-Diol was published in 1980, with the conclusion that it was safe as a cosmetic ingredient at concentrations up to and including 0.1 percent, except under circumstances where its action with amines and amides can result in the formation of nitrosamines or nitrosamides. An addendum to the report was published in 1982. Due to the availability of new literature, the Panel reaffirmed the 1980 conclusion, and further stated that the additional data suggested that the possibility of absorption may contribute to the endogenous formation of nitrosamines in humans. In 2003, the Panel reaffirmed the conclusion.

It's been 15 years, at least, since then. In September we decided to reopen the assessment due to lots of new data, and to construct a conclusion that aligns with the current language. The RLD in 2024 showed 2-Bromo-2-Nitropropane-1,3-Diol use in 167 cosmetic formulations. Highest use category was hair preparations, non-coloring.

The Council had max use of 0.05 percent in leave-on skin cleansing wipes, eye makeup removers and disposable wipes, and 0.026 percent for wash-off products. We had a second wave margin of exposure discussion in there.

I just might comment that the NACDG data is old. There's newer data. There's 2025 data there and there's some other additional contact dermatitis data that I'll put in the return. There's an April 2025 report. There's also commentary from Women's Voices For The Earth. And the response to that seems very reasonable. I'll open it up for commentary. Sam, you want to start?

DR. SAM COHEN: Yeah. Overall, I thought this is a very strange compound. And that's because in the nitrosation, just because of what we said. I know how you limit that, so it can't be used with products of DEA or TEA. And there was some very unusual findings.

One thing that it listed was in baby products it's used, but there's no use levels provided. So, I think that that's something we need. They could just as easily measure nitrosamine and nitrosamides in the products it's used, just to guarantee that they're not generating them. I don't know if that's something you can ask for or not.

Dermal absorption is very high in aqueous products and low in gels. And I found it very peculiar that the acute toxicity, the LD50, dermally, is lower than the LD50 with oral.

DR. ROSS: I would second that. I found that very strange.

DR. SAM COHEN: I just can't imagine how that could be.

DR. ROSS: No, it's very, very strange.

DR. SAM COHEN: So those studies I didn't take very seriously.

DR. ROSS: No.

DR. DAVID COHEN: Well, that's a problem. The question is, is the data correct?

DR. SAM COHEN: Yeah.

DR. DAVID COHEN: Right? I mean, it is not impossible for us to have incorrectly put the data in. We may want to recheck it. Or that the original data is not reliable.

DR. SAM COHEN: Yeah.

DR. ROSS: Yeah, the dermal LD50s were 64 to 160 mgs/kgs. The oral LD50s in different species range from 200 to 400 mg/kg.

DR. DAVID COHEN: Is it possible that the pH in the stomach may change the availability -- I don't know.

DR. SAM COHEN: I don't know. It just seemed very peculiar that -- I always just assumed that the dermal LD50 would be higher than the oral.

DR. ROSS: I don't remember seeing this before, actually.

DR. SAM COHEN: I've never seen it before. That's why I raised it.

DR. TILTON: No. And I made note of it.

DR. SAM COHEN: Yeah.

DR. ROSS: Yeah, we've all flagged it, so.

DR. SAM COHEN: The toxicity in repeat studies had very little effect. And one of the things that was a little peculiar was that in one of the drinking water studies at 12 weeks, that there was no effect up to 1000 mg/kg, which is higher than the LD50. Orally. So, there's some inconsistencies with the data.

DR. ROSS: Some of this data, Sam, is very old, though, right?

DR. SAM COHEN: Yeah. Dogs were given up to 3 mg/kg with no effects other than some vomiting. It was actually a dermal DART study that showed no effect. Genotox, again, there were plus/minuses. there was a ChromaDB study that was weakly positive, and they attributed it to the formation of the Formaldehyde. I can't imagine that that would be enough to generate a ChromaDB at those concentrations. So again, I worry about that data.

The carcinogenicity study, there was a dermal study in mice using aqueous solutions of 0.2 and 0.5 percent for 80 weeks and with no tumors. There was also an oral drinking water study, up to two years, up to 160 milligrams per kilogram, which was negative. So I think carc we don't have to worry about, and maybe the in vitro genotox gets overrated by that.

There was some dermal irritation but at relatively high concentrations, not at low concentrations. There's sensitization in guinea pigs, but it seemed to be fairly slight in humans. There is ocular irritation. There was a small percentage of people that had a positive slight reaction in the patch test.

So overall, I think the data is reassuring that it's safe. But we need a few pieces of data and clarification of some of the data.

DR. DAVID COHEN: That was a very good review. So what pieces of data -- so, are you suggesting an Insufficient Data Announcement for this?

DR. SAM COHEN: The only piece of data that I think is really needed is the baby product concentrations.

DR. BERGFELD: I thought I found it at 5 percent.

DR. SAM COHEN: Oh, it is?

DR. BERGFELD: Well, 5 percent was irritation studies.

DR. DAVID COHEN: 5 percent?

DR. BERGFELD: And the eye study was an irritant at 5.

DR. SAM COHEN: But in the actual products of --

DR. DAVID COHEN: No, the concentration of use we're talking about, right?

DR. BERGFELD: Yeah, yeah, I know, but in the ocular studies.

DR. SAM COHEN: Yeah.

DR. BERGFELD: So it would have to be under that, obviously.

DR. ROSS: There was a range of ocular studies in rabbits, and I think you went through that. But you got severe ocular damage at 10 to 20 percent. There was a study at 0.5 percent aqueous, and that was not irritating. So, I think we'd be okay at our concentration, which is 0.05 percent of maximum concentration of use.

So, I didn't see ocular as a major issue. You know, other than the strange LD50 effects, I didn't really have too many tox, DART, genotoxic carcinogenicity concerns. I thought dermal irritation was okay. I didn't think we had any human dermal sensitization. I wanted to ask you about that, David.

DR. DAVID COHEN: I noticed the same thing, except bromonytropropane has been on standard series for years, right? We know people get sensitized to it. Right? So, it's on the North American Series. It's been there probably for decades, right? We know that Formaldehyde as a patch test does not detect allergy to bromonytropropane. They don't co-react very frequently at all.

So the question is, with the current concentration of use, and a low frequency of surveillance in North America, I was okay with it because we know about it. We know it can sensitize a small number of people. But if this was a new thing coming out I would not clear it with what we have here.

It's just that we have decades of data on this specific chemical being surveyed in North America for a really long time. And overall, we have a 20-year trend of reductions in the prevalence of patch test reactivity to Formaldehyde releasers across the board. And I think it's probably because of the lower concentrations of use.

DR. SAM COHEN: I'm not concerned with the Formaldehyde release here. The amount of Formaldehyde that's being released is trivial in comparison to the endogenous levels.

DR. ROSS: Yeah, I went back into the EPA risk assessments.

DR. SAM COHEN: Oh God, don't do that.

DR. ROSS: I did. It was a mistake.

DR. SAM COHEN: Yeah.

DR. ROSS: But -- sorry, don't quote me on that, if you're interested. And, you know, the amount we have is maybe 20-fold lower than the lowest concentration that you can consume. I wasn't too perturbed about that.

DR. TILTON: I didn't have concerns about that, but I didn't know if we needed to include any additional information in the report, especially because that was a question from the WVE.

DR. ROSS: I think we -- one thing that struck me, because we've got the nitrosamines and we've got the Formaldehyde issues, on this one I would have really liked to have seen a margin of exposure calculation done on this, with a really sensitive endpoint. And we have absorption rate from that Lopez-Sanchez study, Reference 19, in the document. But we don't have, at least, a well-done NOAEL that we can use.

DR. BERGFELD: Do you remember looking at the retrospective and singular multi-centered studies, Table 3? Did that help you at all? Lots of patients were reviewed -- thousands.

DR. ROSS: Yeah, you've got to have a dose response, though. And, you know, we would need either a 90-day chronic tox or a DART endpoint to get an MOE. I mean, there are some DART NOAELs available from old studies, and Jinqiu and I did a back-of-the-envelope calculation on an MOE. I'm not volunteering that because I'm not too confident of that data. But it's possible that I would like a more modern MOE.

But I'm not quite sure we can go out there and ask for a NOAEL study. I mean, because that's an animal toxicity study. So, I'm not quite sure what we do with this, really.

DR. TILTON: Well, just related to the concern about the formation of Formaldehyde.

DR. ROSS: Mm-hmm.

DR. BERGFELD: We've handled that before on the Formaldehyde releases. We have a boilerplate for that.

DR. TILTON: Okay.

DR. ROSS: What do you think about the Personal Care Product risk assessment, where they came up with a MOE of 360,000 of all personal care products? Got any comment on that, anyone?

DR. TILTON: For Formaldehyde.

DR. DAVID COHEN: I was going to ask you to comment on that, actually.

DR. ROSS: Oh, you were? I can comment on it. I mean, I think, first of all, that is a pretty high MOE.

DR. DAVID COHEN: Yeah.

DR. ROSS: You know, what I would say is when I looked into that paper, which I have here -- which was done by a really nice technique, actually. But, you know, when I looked at what they used, they looked at Formaldehyde in three personal care -- particularly in three formaldehyde-releasing personal care products, but none of those were BNPD. It wasn't looking at BNPD itself; it was three other --

DR. DAVID COHEN: Just Formaldehyde releases.

DR. ROSS: Yeah. So yeah, it's that caveat. And one other thing I would comment on this. If you do an AI search and ask for absorption, okay, or even a Google search, and ask for absorption of this molecule, you'll get a number of around about 40 percent, okay? If you go into the Sanchez-Lopez study and do the calculation, you will actually get a value of 0.5 percent. That's quite a difference.

DR. DAVID COHEN: About 80-fold difference.

DR. ROSS: So this just shows you what we're up against here. And, so yeah, I think for your terms of the summary, David, my questions revolved around the dermal sensitization in humans, whether we needed that, and I'll defer to you on that.

How we could possibly do a margin of exposure. There were two studies that I pulled out. One was a 1979 study, which the Women's Voices For the Earth also, hopefully, discussed, which was from Boots, I believe, and it was reviewed in Bryce et al. in 1978. And that gives the NOAEL. But it looks at a value of 20 mg/kg. And they make the statement that this was well tolerated, which is not really very helpful these days. You actually really can't interpret too much from that.

But there is an old DART study which had a NOAEL of 25 mg/kg. And you could use that in a MOE calculation. But again, it was a very old study.

DR. DAVID COHEN: 25 mg/kg.

DR. ROSS: Yeah, per day. But that's a very old study. So maybe we won't get the data for that. But they were my issues. And whether or not we expanded -- this gets to Susan issues, I guess. Some of the Formaldehyde discussion is a separate discussion, but that would be incredibly difficult to write.

DR. TILTON: But you said there was a boilerplate to address Formaldehyde, Monice?

MS. FIUME: So, there is.

DR. ROSS: This came from the hair straighteners.

MS. FIUME: Yes. And it was with the Formaldehyde report.

DR. SAM COHEN: I think, looking at it, the fact of the fairly strong carc data, should we have any concern about both nitroso compound and Formaldehyde?

DR. ROSS: I think I still like the nitrosation discussion in there, which it was in previous reports.

DR. SAM COHEN: Yeah.

DR. DAVID COHEN: So, are we reiterating that complex conclusion?

DR. ROSS: Which was?

DR. DAVID COHEN: Well, the original one was safe as a cosmetic ingredient at concentrations up to and including 0.1 percent, except under circumstances where it's actually with amines and amides can result in the formation of nitrosamines or nitrosamides.

DR. DAVID COHEN: That's pretty much where we're at.

DR. ROSS: Yeah, I think that's pretty much where we're at. But, I mean, I think we're at a different concentration, right? We're at 0.5 percent, that's our max.

DR. DAVID COHEN: Apropos to our last conversation, we usually weren't concluding with a concentration unless there was extenuating circumstances. Is this an extenuating circumstance? I don't think so. It goes in the Discussion.

DR. BERGFELD: Discussion, yeah.

DR. SAM COHEN: Yeah.

DR. ROSS: Yeah. Conditions of use, I think. As long as you've got those other caveats in.

DR. DAVID COHEN: The conclusion is safe as used.

DR. ROSS: But if you're okay with the -- as you pointed out -- the sensitization.

DR. SAM COHEN: As long as that's in the Discussion.

DR. DAVID COHEN: It's in the Discussion. We'll update the epidemiology that we have from the North American group and other -- I think I have, one, two, three, four additional references to put in.

DR. ROSS: The two remaining questions were, do we need an MOE? And the other one was, what about a Formaldehyde boilerplate? So let's do the Formaldehyde boilerplate.

DR. TILTON: It requires some knowledge of how much Formaldehyde is released.

DR. DAVID COHEN: Is being formed.

DR. TILTON: Yeah.

DR. ZANG: I'm sorry, which document are you guys looking at? Is it the 2011 Formaldehyde?

MS. FIUME: Oh, they were discussing the Formaldehyde-releasing boilerplate, which comes from -- it's based on the 2013 Formaldehyde report, but you have to have calculations of the maximum level that's contained and released. So it requires some calculations. So that's just the boilerplate language that is sort of an internal document.

DR. ZANG: Oh, I see. Yeah. I was trying to search that but the only thing I could find is the 2011.

MS. FIUME: The Formaldehyde report was published in 2013, and that brought the updated Formaldehyde.

DR. ROSS: It's a difficult calculation; it would depend on the conditions. You know that Lopez-Sanchez absorption study, the one transdermal study with the pig ears. When I went through that, they got 85 percent recovery after about 24 hours. So you're missing about 15 percent max. Now, is that all Formaldehyde, you know, that's the question.

MS. FIUME: And Bart may have input on this tomorrow because I know when we talked about it, if I remember correctly, the focus wasn't on the --

DR. DIYABALANAGE: The Formaldehyde formation is really long, right?

DR. ROSS: It's very long. And then the equilibrium to methylene glycol in solution is 99.6 percent methylene glycol. So as Sam said, it's probably -- Sam, you weren't too concerned?

DR. SAM COHEN: No. The amount that you need to get carcinogenicity in rats is only about 3 to 5 parts per million over a two-year span in a lifetime. This is intermittent exposure, I assume. And it's certainly not in the ppm range by inhalation.

We have some inhalation toxicity data. There was irritation but it was at a concentration of 588 milligrams per cubic meter. So I mean, it's not irritating until extremely high levels of this compound. And Formaldehyde at the levels that produce carcinogenicity is very irritating. And the levels that are allowed in pathology laboratory, the hormone allowance are much lower than that, so.

DR. DAVID COHEN: Can you comment on the endogenous nitrosamine formation?

DR. SAM COHEN: Just put vitamin C in there and no problem.

DR. DAVID COHEN: I don't think we could conclude when formulated with ascorbic acid. That's combining reports. No, so, but that was one of the issues that we mentioned in the reopen.

Pretty much as was stated before from what I can see. Unless you wanted to add something about actually measuring nitrosamine and nitrosamide levels in products, but that seems a little extreme.

DR. ROSS: Well, you know, this paper gave the 360,000,and we have some background there with respect to endogenous Formaldehyde.

DR. DAVID COHEN: Ah, it included it.

DR. ROSS: In the abstract to that paper. You could perhaps cite that if you wanted to.

DR. SAM COHEN: That's endogenous Formaldehyde, not nitrosamine formation.

DR. ROSS: Exactly, it's endogenous Formaldehyde.

DR. DAVID COHEN: What's the difference?

DR. ROSS: The consumer exposure to Formaldehyde went 007 micrograms per kilogram per day. From using personal care products represents less than one times ten to the minus six percent of background level endogenous Formaldehyde.

DR. DAVID COHEN: But in the update in the 1984 report, there's a comment about, may contribute to the endogenous formation of nitrosamines. Any remarks on that? Instead, you're talking about Formaldehyde.

DR. TILTON: Is that cited?

DR. BERGFELD: Previous Discussion.

DR. DAVID COHEN: I think that's what Don commented on, right?

DR. SAM COHEN: They had some papers that cited that this chemical can be nitrosating under certain circumstances.

MS. FIUME: So I think that came from that Boots paper, which we're having trouble locating in our files, because everything is stored offsite and it's very old. So at least the first box that was sent did not have that Boots paper. Is that correct, Thushara?

DR. DIYABALANAGE: Yes.

DR. ROSS: But there is a Summary.

DR. SAM COHEN: Yeah.

DR. ROSS: Which you sent me, the Bryce paper.

DR. DIYABALANAGE: Yeah.

DR. ROSS: But I think you still need the nitrosating --

DR. DAVID COHEN: In the Discussion.

DR. ROSS: Yeah.

DR. DAVID COHEN: So are we going with safe as used?

DR. SAM COHEN: I think so.

DR. TILTON: So, not a complex Conclusion, but there will be information in the Discussion about the potential for formation of amines and amides.

DR. ROSS: I didn't think the Conclusion was that complex. Could you read it again, if you have it there, David?

DR. DAVID COHEN: 2-Bromo-2-Nitropropane-1,3-Diol is safe as a cosmetic ingredient at concentrations up to and including 0.1 percent except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides.

DR. BERGFELD: I don't believe we're using that one anymore.

MS. FIUME: And then it added the right --

DR. DAVID COHEN: And then contribute to endogenous nitrosamines in humans.

MS. FIUME: That's the most recent.

DR. DAVID COHEN: Yeah, that's very complicated.

DR. BERGFELD: Is that in the Discussion. Because he read it as a Conclusion.

MS. FIUME: That was the Conclusion of the addendum.

DR. ROSS: Yeah, that is complicated.

DR. BERGFELD: In what year?

DR. DAVID COHEN: '84.

DR. BERGFELD: Yeah, I think we've changed it since then.

DR. DAVID COHEN: I don't remember. We talk about nitrosamines now and again.

DR. BERGFELD: Yeah.

DR. DAVID COHEN: But we don't put it in the -- have we put it in the --

DR. BERGFELD: We always put it in the Discussion.

DR. DAVID COHEN: Right, but I don't remember the -- I can't remember if I'm just reading it from the old ones or we actually concluded that.

DR. BERGFELD: Right.

DR. DAVID COHEN: But can we not conclude that?

DR. BERGFELD: I thought we modified that.

DR. TILTON: So, it would be in the Discussion?

DR. BERGFELD: The Discussion.

DR. DAVID COHEN: I actually think the conclusion is impossible for industry and end users to work with. Right? What you're saying is don't create a product that forms nitrosamines. But what you're saying here is, don't live your life and use this product in a way where nitrosamines can form, which is impossible for an end user to understand, and it's impossible for the manufacturer to guarantee. It's impossible.

DR. SAM COHEN: Because you don't know what it's being used with.

DR. DAVID COHEN: Exactly. You don't know where the person's working. You don't know any of the environmental or occupational conditions. You don't know any of that. So we talk about it in the Discussion.

DR. SAM COHEN: Do we have any data at all on how much nitrosation this actually causes?

DR. ROSS: No.

DR. SAM COHEN: I think it would be relatively low.

MS. FIUME: For the 2-Bromo?

DR. SAM COHEN: Yeah.

MS. FIUME: Yeah. So I'm looking back at the Conclusion of the TEA report itself. And it says these ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed. It was part of the Conclusion that was published in 2013. That's for TEA. And I only looked at that because I know that that was of concern.

DR. DAVID COHEN: It said the Conclusion? And what year was that?

MS. FIUME: It was published in 2013.

DR. DAVID COHEN: And what did it say, it's safe as used?

MS. FIUME: Well, okay, so this one is a very complicated Conclusion. The CIR expert Panel concluded that TEA and the 31 related TEA-containing ingredients, listed below, are safe in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating, and when the levels of free diethanolamine do not exceed the present practices of use and concentration of diethanolamine itself. These ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed.

DR. DAVID COHEN: Oh gosh.

DR. ROSS: The last bit of that's okay. You could paraphrase just the last half sentence of that, i.e., shouldn't be used in products where N-nitrosamines can be formed.

MS. FIUME: And this was TEA. So I mean, I chose this because I knew it had the nitroso caveat in it.

DR. ROSS: Yeah, there's an easier approach. Just say when formulated to be non-toxic.

DR. DAVID COHEN: That's Ron Shank.

DR. ROSS: That's Ron Shank's line. Yep. Ron Shank was very good with that, I thought.

DR. DAVID COHEN: Help me chemistry-wise, why is this unique to form nitrosamines?

DR. SAM COHEN: The nitro group acts as a nitrosating agent.

DR. ROSS: Nitrosating agent with secondary amines.

DR. DAVID COHEN: Oh, the nitro propane. Yeah.

DR. ROSS: It's a nitro group.

DR. SAM COHEN: So it reacts to secondary amines in an acid.

DR. DAVID COHEN: Hence the endogenous ones in the stomach. Okay.

DR. ROSS: It's primarily secondary amines that you've got to worry about.

DR. DAVID COHEN: So what's our conclusion?

DR. ROSS: It's Don's presentation tomorrow.

DR. DAVID COHEN: Is it? Wait, wait, wait, no, it's mine. I think you've confused Don and I, but I'm not sure maybe I'm wrong. It's Don's. You got it. Sorry. I retract. Can we reverse to tape on that?

DR. SAM COHEN: Let them try to figure it out.

DR. DAVID COHEN: No, no, but we should --

DR. ROSS: Yeah, we should come to our conclusion.

DR. DAVID COHEN: We should always treat these as if I'm presenting them tomorrow, right? It's just some of my homework tonight is a little shorter based on that, right? But we should go out.

DR. BERGFELD: I think you should go safe, and then discuss all the problems that we've had with --

DR. DAVID COHEN: I think so, too.

DR. BERGFELD: -- nitrosating and the Formaldehyde-releasing property.

DR. ROSS: And if anybody feels that we need an MOE of this particular ingredient.

DR. DAVID COHEN: I could bring that up. I mean, that's part when Wilma pulls for a second and then we can have a conversation about it. We could talk about that. And I was going to bring up the LD50 lower for dermal exposure than for oral exposure.

DR. ROSS: That's strange.

DR. DAVID COHEN: Formaldehyde boilerplate.

DR. SAM COHEN: Formaldehyde boilerplate. Yeah, and the LD50 is lower than some of the repeat tox studies. Oral. Which doesn't make any sense at all.

DR. ROSS: (Inaudible) were very interesting.

DR. SAM COHEN: Yeah. Well, I think it means that the tox data is probably not very reliable.

DR. DAVID COHEN: Well, this is a Draft Report, right?

MS. FIUME: Draft Amended.

DR. DAVID COHEN: But Draft Amended goes to Draft Tentative?

MS. FIUME: In less than 90-days issued, yes. And so, this would come out of the meeting as a Tentative Amended Report.

DR. DAVID COHEN: Does it come back to us again?

MS. FIUME: As a Draft Final.

DR. DAVID COHEN: As a Draft Final. So, between now and then, could we go back to the original data on -- because we're not actually issuing an IDA, we're asking for corroboration and just confirmation that the data is accurate. That's not an IDA. Right? That's an internal thing. We're not going out to industry for that.

DR. BERGFELD: Can you ask the industry that sent it to you, or was this an internal find?

DR. DAVID COHEN: This is old.

MS. FIUME: This was in the 1980s.

DR. SAM COHEN: Yeah, these are old studies.

DR. ROSS: (Inaudible) 17 (Inaudible).

MS. FIUME: So, the 1984 addendum discussion has a paragraph that says perhaps -- and it's on PDF Page 27. It says, "Perhaps the greatest uncertainty exists in regards to the potential for 2-Bromo-2-Nitropropane-1,3-Diol for endogenous formation of N-nitrosamines in humans. However, a long-term mouse skin bioassay in a rat feeding study indicated that 2-Bromo is not carcinogenic in laboratory animals. Other N-nitrosating agents, nitrite and nitrogen dioxide, are involved in the endogenous formation of N-nitrosamines in laboratory animals. The ingestion of nitrite and inhalation of cigarette smoke contributes to the endogenous formation of N-nitrosoprolein in humans."

DR. DAVID COHEN: You know, the funny thing is the "perhaps" sentence has a reference of Number 1. That's the report.

DR. ROSS: It's the report.

DR. DAVID COHEN: It reports back onto the report.

DR. SAM COHEN: See, but that summary you just read --

DR. DAVID COHEN: See, that statement reports back to 1. Right? This is the original.

MS. FIUME: Oh, that's the original report.

DR. DAVID COHEN: Right, you read -- it's verbatim, right? And then you go to 1 in the original report, and the original report is the Cosmetic Ingredient Review of 1980.

MS. FIUME: So I'm wondering if that is a typo, because we don't normally have citations in a Discussion.

DR. DAVID COHEN: Was that in the Discussion?

MS. FIUME: What I read was the Discussion.

DR. DAVID COHEN: Yeah, that was the -- and that was the original Discussion too. And it's a strong statement. And then that strong statement is referencing back to the report before.

DR. SAM COHEN: That same Discussion could go into this Discussion, I think.

DR. DAVID COHEN: Right, but it's got no reference. It references itself.

DR. SAM COHEN: But I would take out a sentence about Nitrosoprolein, because that doesn't tell you anything. Nitrosoprolein is not carcinogenic for cigarette smoking. There are studies that have been published with nitrite plus secondary amines given in the diet produce tumors in the animals.

And the fact that -- I think we can take some satisfaction in the fact that the carc studies are totally negative. And the fact that they're negative tells you the amount of nitrosation here is not causing problems. Plus the genotox data is pretty clean.

DR. ROSS: The concentration of use is pretty low.

DR. BERGFELD: 0.05 to 0.1.

DR. SAM COHEN: But you have negative dermal and negative oral carc studies.

DR. ROSS: Yeah. My only concern was the sensitization.

DR. SAM COHEN: Yeah.

DR. DAVID COHEN: Yeah. When we have 20 years of sensitization data, what am I asking for? Is it sensitizing? It is. But is there an unacceptable number, or is the epidemiology concerning to me, like MI was? And the answer's no. So, no matter what I get, worst-case scenario is I find that it's sensitizing. I already knew that. Or I get HRIPT data that says it's not sensitizing, and I already know it is.

So, I don't want to ask for data that's not going to change my conclusion. Now, Don may have a different opinion about it, it's possible. But I've gotten comfortable with it because it's pretty rare that I get a Bromo Nitropropane positive patch test. I get it sometimes.

DR. BERGFELD: So are we going to see with an expanded --

DR. DAVID COHEN: With the Discussion. So did you find it?

MS. FIUME: So it was actually the report. There's about four different versions of the report. It was citing the 1980 report.

DR. DAVID COHEN: Right.

MS. FIUME: But that was a document that's in our PDF; it's a little bit later document. So it's citing back to the 1980 data from the 1980 report.

DR. DAVID COHEN: Right. That's right. But that's a little odd.

MS. FIUME: Yeah. Well, it is and it isn't. Because when we do re-reviews, we cite back to the original document.

DR. DAVID COHEN: I would agree with that except it's so specific, right? It's such specific data, you wouldn't reference back to the review article, you'd reference back to the source. Do you have in the 1980 report the source of that comment? And who on the team said this was going to go quickly?

DR. ROSS: Me.

MS. FIUME: I think -- I believe it's Boots. I believe it's that -- well, are actually Fan et al., Bryce et al. I'm not sure which one.

DR. BERGFELD: We'll be done by 5:00 maybe.

DR. DAVID COHEN: Yeah, yeah, yeah. It's several.

MS. FIUME: Yeah.

DR. DAVID COHEN: It's several. In press; FDA, Boots, 1978.

MS. FIUME: And then this was, um --

DR. DAVID COHEN: Okay.

MS. FIUME: So, can I ask one more question, then? As we prepare the Discussion, we had mentioned the Formaldehyde, but it sort of needed values. In the current document it refers to stating that not much is expected; can that be used when talking about Formaldehyde in the Discussion? On top of PDF Page 20, under degradation? Just so we know what to put in the Discussion?

DR. SAM COHEN: Yeah, I think that that would be -- in the Discussion would be fine.

MS. FIUME: Okay.

DR. DAVID COHEN: Which part, the degradation part? We just are reiterating in the Discussion?

MS. FIUME: So under it states that not a lot -- minimal risk of Formaldehyde exposure for the handlers because a lot -- about there being minimal risk due to its slow decomposition rate, rather than trying to figure out the concentration or the amounts. Because the current boilerplate requires some calculations for the Formaldehyde.

DR. DAVID COHEN: I see.

DR. ROSS: You may have to check those statements to make sure that there's no updated information.

DR. SAM COHEN: Yeah.

DR. ROSS: That's in italics that came from the old report, right?

DR. SAM COHEN: Yeah.

DR. TILTON: And then we also have the two carcinogenicity studies.

MS. FIUME: Studies that would probably make -- let those take --

DR. SAM COHEN: And dermal and oral are negative.

MS. FIUME: Okay. So focus it on that rather than trying to -- great.

DR. DAVID COHEN: All right.

DR. DIYABALANAGE: Actually, it's interesting that degradation results are not Formaldehyde. Actually, the Formaldehyde is generated as a result of hydrolysis.

DR. ROSS: Yeah.

DR. DAVID COHEN: Okay.

DR. DIYABALANAGE: So it's safe as used, right?

DR. DAVID COHEN: Safe as used.

Full Panel – June 10, 2025

DR. SNYDER: Thank you. This is a Draft Amended Report. In 1980, it was declared safe as used to 0.1 percent with no nitrosation agents. In 1984, we reaffirmed the 1980 conclusion. In 2003, it was re-reviewed and reaffirmed the conclusion.

In September of 2024, we reopened due to lots of new info. There are 167 formulations, hair preps, non-coloring, 64 uses. The maximum concentration is 0.05, down from the original 0.1 percent. Our team came to the conclusion that we could reaffirm safe is used.

DR. DAVID COHEN: Second.

DR. BERGFELD: Any further discussion regarding this ingredient? Any comments for the discussion?

DR. BELSITO: Yeah. We have to address the Women's Voices For The Earth and the formaldehyde issue. And, you know, the amount of formaldehyde released by this is less than what we had approved for formaldehyde. We did a margin of exposure for formaldehyde and we can just put that in the Discussion.

DR. BERGFELD: I think that's agreeable.

DR. DAVID COHEN: We had those exact comments. We also just discussed that the LD50 was more for dermal exposure than for oral exposure. And we just wondered why that might be; is the data accurate?

DR. SNYDER: Well, hopefully the writer can reaffirm that.

DR. DAVID COHEN: Okay.

DR. BERGFELD: All right.

DR. SAM COHEN: Also, the toxicity in the 12-weeks drinking water study was lower than the LD50, which again doesn't make sense.

DR. BERGFELD: All right. Any other comments before I call the question?

DR. BELSITO: Yeah. Then in PDF Page 30, the multicenter studies. I think the dates are wrong. We have two NACDG studies that they're both said to be in 2013/2014 with different number of patients. And also I updated references for the NACDG data from 2019 to 2022, there are two additional references that can be added there.

DR. DAVID COHEN: Yeah, Don, I have 4 references that I'm putting in my return from 2021 to 2025.

DR. BELSITO: Right. Okay. Great. Yeah.

DR. BERGFELD: Anything else to add? I'll call the question. All those in favor of going forward with this safe conclusion. Unanimous. Thank you so much.

MARCH 2026 PANEL MEETING

Belsito Team – March 12, 2026

DR. BELSITO: Okay, so we're going to move on to 2-Bromo-2-Nitropropane-1,3-Diol. And unless we can come up with that report about endogenous formation -- I could not find anything in the published literature about it. I asked Dan Liebler his thoughts whether, if it were absorbed, it could endogenously produce nitrosamines, and his answer was an affirmative no. I'd be interested in what Allan thinks about that.

DR. RETTIE: Yes, I'd go along with that.

DR. BELSITO: Okay. So, at the June 2025 meeting, we issued a Tentative Amended Report with a conclusion that 2-Bromo-2-Nitropropane-1,3-Diol is safe in cosmetics in the present practices of use and concentration described in the safety assessment. No new unpublished data were received. There were a lot of published studies that were added to the clinical use section, largely dealing with sensitization throughout the years. And we now, in this report, have an updated 2025 RLD.

We got a lot of comments from PCPC in Wave 2. There was one that says that we need Panel input. It is appropriate to use information on environmental degradation that produces formaldehyde to address concerns for the release of formaldehyde in a preservative. And I didn't think it was appropriate to use environmental degradation for what would happen on skin, but interested in your opinion. So, Curt, Paul, Allan, chime in.

DR. SNYDER: Not my area, so I'll let Curt address it.

DR. KLAASSEN: Well, sometimes what happens in the environment happens in humans, but not necessarily. I, I guess I would prefer mammalian data on that.

DR. BELSITO: Yeah, the environmental degradation are usually water studies, Curt. And what happens, does it deposit into sludge? You know, is it a permanent bioavailable, degraded, whatever?

DR. KLAASSEN: Yeah, and then if it's degraded by -- well, it can either be by organisms in the water, or it even can be by sunlight.

DR. BELSITO: Right.

DR. KLAASSEN: So, I don't put much weight on it.

DR. BELSITO: Okay. So, we're not going to use environmental. Who's doing this report?

DR. KLAASSEN: What do you think, Allan?

DR. RETTIE: I don't really have any comments beyond what you just said, Curt.

DR. KLAASSEN: Okay.

DR. SNYDER: David's doing this one.

DR. BELSITO: Yeah. But no, the writer? Is that Temima?

DR. SNYDER: Monice and LP.

MS. PAULSON: I'm LP. I'm helping out Monice today.

DR. BELSITO: Okay. So, we're not going to include the information on environmental degradation in this report. Then we have the Wave 2 comments from PCPC that although tattoos are listed in the RLD, they're not under our purview, so should we be mentioning anything about them in the report? And I thought we should delete them if, in fact, they are not under our purview. But we need a boilerplate in the Use section that we're not evaluating tattoo use since the uses appear in an RLD.

DR. EISENMANN: We want you to go even further and not even bother to put them in the report at all, so you don't have to discuss it.

DR. BELSITO: Yeah. I guess my only issue with that, Carol, is anyone who knows the RLD is going to see these tattoo uses being mentioned.

DR. EISENMANN: Well, you wouldn't mention it. That would be the whole point. So, in the future, when I do a concentration of use survey, I'm not going to include tattoos. When we summarize the data from FDA, we're not going to include tattoos in the totals. We've kind of made this decision because we don't support tattoo products.

DR. BELSITO: I understand that. But if I were a consumer and I was looking at RLD, and seeing 408 permanent tattoo uses listed as a cosmetic use for this, and I looked at your report, and it said safe as used and the FDA is reporting it as a cosmetic use in 408 tattoos, I would assume that CIR signed off on it as safe as used.

So, it's just like our airbrush thing. I think we need to mention that tattoo use is not -- in this case -- not in our purview, and our safety assessment does not address this. That's my own personal feeling. I open it up to other Panel members. I appreciate what you're saying, Carol, but also I think that if you're looking at what the FDA is reporting, it's reporting 408 cosmetic uses as a tattoo, as a permanent tattoo, right?

DR. SNYDER: I agree with you, Don. I think we need to make it clear.

DR. BELSITO: And then simply not report the tattoo uses; we've already dealt with that in our boilerplate. We're not going to say there are 400 uses, and we're not going to look at them. We're simply going to -- you know, there'll be a statement for every ingredient, whether there is a reported tattoo use or not, that the RLDs now include tattoo use under cosmetic use; however, this is not the purview of the CIR panel, and we are not ruling on the safety of these ingredients as potentially used in a permanent tattoo.

DR. EISENMANN: So, you'd remove the information from the table, though, the 408 uses?

DR. BELSITO: I would remove it from the table.

DR. EISENMANN: Okay, good. I agree with that.

DR. BELSITO: It would almost be like an airbrush, we would say it for every single ingredient. So, you wouldn't even go out and look for permanent tattooing formulations or be concerned that there might be any out there. Simply put that the RLD now lists permanent tattooing formulations as cosmetic use, and this is not a cosmetic use that's in the purview of the CIR Panel, and we're not addressing safety for that. Or something to that effect. And then, no listing of permanent tattoo inks among the products we're looking at.

DR. SNYDER: I'm fine with that.

DR. BELSITO: Curt, Allan?

DR. KLAASSEN: Yes, I think that's a very good way of addressing this.

DR. BELSITO: Okay. So, we'll have to just work on some boilerplate language, assuming the other team agrees with that. Okay, so ocular irritation, we've got good data on -- it's used at 0.05, we have data at 0.5.

There have been some reports of contact allergy with wet wipes. And I just wondered, given the whole issue of what happened with MI and that epidemic of methylisothiazolinone sensitization, where we allowed it to go out at 100 parts per million in leave-ons and rinse-offs, a lot of that was wet wipe. And given these reports of wet wipes with bronopol, and we knew it's a sensitizer, I just had a question.

For added safety, could we do a QRA2 with the wet wipe at a concentration of 0.05 and show that it would not be a sensitizer? And for the Conclusion, I thought safe as used, but would, again, be nice to have that margin of exposure for wet wipes. That was my finding. Curt, Paul?

DR. SNYDER: I think I agree with our experience with wet wipes, as you indicated. I think we should do that. With wet wipes that are known to have ingredients that are sensitizers.

DR. BELSITO: Yeah, I was particularly drawn -- when I saw it used as wet wipes. And, bronopol is something that we do see as one of the formaldehyde-releasing allergies. But, you know, this is a retrospective study; granted, it's back to 2014, but we know that that's still being used based upon our RLD data, right? And 0.9 percent of patients with a positive patch test had an allergic reaction to a wet wipe source. And the reaction to bronopol, in that 0.9 percent of patients, was 27.4 percent. So, a little more than a quarter of patients that were reacting to wet wipes were reacting to 2-Bromo-2-Nitropropane-1,3-Diol.

DR. SNYDER: I think we captured that in the report and just state it. Yeah.

DR. BELSITO: Yeah. So, maybe we could ask the scientific committee to do a margin of exposure for us, Bart -- or a QRA2 for us?

DR. HELDRETH: That's certainly one option you could do. Another option would be to alter your conclusion to add something like safe as used in wet wipes when formulated to be non-sensitizing, which could be based on a QRA 2.0 or other actual tests.

DR. BELSITO: Yeah, if we did that, will we specifically point out wet wipes, or just say, safe when used to be formulated to be non-sensitizing as based on a QRA2?

DR. HELDRETH: That totally falls in your hands. If there's a possibility of inducing sensitization in other formulations, I don't see why not to spread it out. But if you feel really confident about the other applications not inducing sensitization, you could do a split.

DR. BELSITO: Well, I mean, there is sensitization out there. We see it. I don't know if they did the clinical studies. Yeah, so the North American Group, our data, 1.3 to 4.8 percent, positive in large numbers of patients.

Yeah, I think my concern was wet wipes because that's what really set off the MI. But, like MI, we could say safe as use when formulated to be non-sensitizing as based upon a QRA2 or similar methodologies, the same type of conclusion. I'd be very happy with that.

DR. SNYDER: I'm okay with that, too, because this moves this along; because otherwise it could be drug out, so let's just move it along.

DR. BELSITO: Okay.

DR. HELDRETH: Yeah. Now that will mean, since it's more restrictive, this will have to go back out again as a Revised Draft Final Amended Report and come back to the Panel one more time. But I'm not saying that's a bad thing, I just want the Panel to be aware.

DR. BELSITO: Whereas if we did a margin of exposure for baby wipes alone, it would not? Or QRA2, rather, for baby wipes alone?

DR. HELDRETH: No, I think, either way you're making it more restrictive.

DR. BELSITO: Well, it wouldn't be more restrictive, because if the QRA2 -- baby wipes are 0.05 percent. If a QRA2, using 0.05 percent in a baby wipe, has an acceptable consumer exposure, then we would just simply say safe as used. We wouldn't restrict it. You know, if it did not have an acceptable consumer exposure level, then we would change our conclusion.

DR. HELDRETH: Either way, you know, it's not finalized today. If we're going to ask for data, we have to wait. So, whichever way the Panel thinks is the better move.

DR. BELSITO: I think the better move, all-encompassing safety, would be the safe as used when formulated to be non-sensitizing as based upon a QRA2 or similar methodologies. That's the safest for the general public.

DR. SNYDER: I agree with that, Don. I think that's what we should do. So, I'd second that.

DR. KLAASSEN: Don, you're mentioning QRA2. What's the 2?

DR. BELSITO: So, QRA2 includes aggregate exposure. So, as opposed to just looking at, say, one exposure from a face cream, it looks at exposures on the face that also occur for the user who's using a face cream, a shampoo, dadada, dadada, multiple other products. So it's aggregate exposure; it's a much more conservative approach to safety.

DR. KLAASSEN: Okay.

DR. BELSITO: Okay, anything else on this? Any additions to the Discussion?

DR. SNYDER: Nothing for me.

DR. RETTIE: All good.

DR. BELSITO: Okay, I'm just making sure -- I just think we need to add a little bit -- we sort of blow off the sensitization. And it says, a large number of subjects, the Panel concluded the contact allergy rate to 2-Bromo-2-Nitropropane-1,3-Diol has been relatively low. I guess maybe, however, we did notice among 0.9 percent of patients allergic to baby wipes, 27.4 percent were sensitized to bronopol -- I'll use the trade name -- and therefore we have concern about the potential sensitizing capability, depending upon product use. Something like that in the Discussion? It allows us to come to that conclusion about sensitization based on a QRA2, which looks at specific products.

DR. SNYDER: Yeah, let's see that wording. Let's see that in the next round. Yeah.

DR. HELDRETH: Yeah, any additional verbiage you could put in your Panel returns would be very helpful to the writer.

DR. BELSITO: Okay. Anything else?

DR. SNYDER: Nothing for me.

Cohen Team – March 12, 2026

DR. DAVID COHEN: Next is a Draft Final Amended Report on 2-Bromo-2-Nitropropane-1,3-Diol. The Panel first reviewed this ingredient in 1980, concluding that it was safe as a cosmetic ingredient at concentrations up to 0.1 percent, except under circumstances where reaction with amines or amides could lead to the formation of nitrosamines. An addendum in 1984 reaffirmed that conclusion, and the assessment was re-reviewed again in 2006, with the prior conclusion reaffirmed.

In September 2024, the Panel reopened the assessment after more than 15 years to consider the substantial body of additional data, updated use information, and to modernize the language of the safety conclusion. Following review of the available information, the Panel issued a Tentative Amended Report in June 2025, concluding that 2-Bromo-2-Nitropropane-1,3-Diol is safe in cosmetics in the present practice of concentration and use.

For this Draft Final Amended Report, the remaining issues relate primarily to wording in the Discussion, in particular, the statement regarding endogenous nitrosamine formation appears to come from the 1984 addendum as a historical hypothesis, and there's no direct data demonstrating endogenous nitrosamine formation from this ingredient. Don circulated a paper regarding the fate of bronopol in cosmetic formulations, which illustrated that kind of the nitrosamine formation can occur in formulations containing bromo nitropropane and amines under certain conditions, and that appropriate formulation practices, including use of antioxidants, can mitigate that process.

So, I guess this is a formulation chemistry thing, rather than endogenous formation of nitrosamines in humans. So, are we good with reaffirming the last report, and in the discussion talk about formulations and formation of nitrosamines?

DR. BERGFELD: I think that's a good --

DR. SAM COHEN: Endogenous formation of the nitrosamines is not going to happen because all those antioxidants are already in our bodies at sufficient levels unless you have scurvy.

DR. BERGFELD: That could be added to the Discussion as well.

DR. ROSS: But I think they're minimize -- you know, when you're putting this text there, it's to minimize the potential that these might be formed, and I'm fine with that. And I realize that we've got natural levels of antioxidants; but if you looked at that paper that Don sent around, without the antioxidants, you got significant formation of nitrosamines.

So, I thought the nitrosamine paragraph should be kept. I thought the formaldehyde paragraph had been clarified of the formaldehyde limit. I suspect that was Monice, so thank you for that. So, I thought both those paragraphs should be kept and I was fine with it, safe as used, without doing anything else to it. There was discussion of MOE, but no one else has brought it up, so I'm going to stay silent.

DR. DAVID COHEN: I didn't hear what you said on the last one.

DR. ROSS: There was some discussion of MOEs in the previous transcripts, but I'm going to stay silent on that. I mean, it could be done, but I don't think it's necessary, and I think it's good to go.

DR. SAM COHEN: I agree.

DR. TILTON: I agree. The Discussion also addresses our conversation about the disconnect between the dermal and oral LD50s, and that's addressed, so I approve.

DR. ROSS: Yeah.

DR. BERGFELD: I just wanted to ask you, were you going to put in Don's papers as references at the back? And if you were going to use those, were you going to also cite the antioxidant issue into the Discussion?

DR. DAVID COHEN: I would have hoped so. So, Wilma, can I just ask your opinion on presenting this tomorrow? I just gave a fairly long recitation about the thing. Do I just sort of do the opener that we've reviewed it, there was an addendum, we re-reviewed it, and the motion is safe as used?

DR. BERGFELD: I think a shorter presentation is better. I think, a little comment on what the issue was, and then kill it?

DR. DAVID COHEN: Okay. That's kind of my -- yeah, but I needed you to say that. All right.

DR. ROSS: And actually, if you look at Don's paper that he sent around, it was originally sent out in one of the earlier versions of this by Alex, who had forwarded that paper in one of her comments.

DR. SAM COHEN: It's a very old paper.

DR. ROSS: Yeah.

DR. DAVID COHEN: But it was a good paper.

DR. BERGFELD: Yeah. So, the max use is 0.05 percent? Is that what we're all honing in on? Not to say we're going to mention that, but that is the max use of this now?

DR. DAVID COHEN: I think that's the new max use.

DR. ROSS: Yeah, in wipes, yeah.

DR. DAVID COHEN: Yes. That's the new max use.

MS. FIUME: Can I clarify? So, under nitrosation, it does talk about the mean derivatives from cosmetics. So, do you want the 1983 paper brought in to the document as well?

DR. ROSS: I think so.

DR. DAVID COHEN: Yeah, because it discusses the value of the antioxidants in the formulations, right?

DR. BERGFELD: Yeah, I like it.

MS. FIUME: Okay. And so, since you won't see this back again, is there exact wording about the antioxidants that you would like to be used? Because since this is going on as a final, the Panel won't see it back?

DR. BERGFELD: Well, couldn't you do that in the Discussion?

DR. DAVID COHEN: Yeah, but she wants to know what we want specifically in the Discussion.

DR. BERGFELD: The use of antioxidants in the formulation reduces the nitrosating activity. Something like that.

DR. SAM COHEN: I would even put it "significantly" reduces.

DR. DAVID COHEN: What I had written here is -- I have a paragraph: "Don circulated a paper examining the fate of bronopol in cosmetic formulations, which further illustrates that nitrosamine formation can occur in formulations containing bromo nitropropane and amines under certain conditions, and that appropriate formulation practices, including the use of antioxidants, can mitigate that process."

DR. ROSS: Why don't you put it in the Nitrosation paragraph, which is just before the Use? I like your wording, by the way.

DR. DAVID COHEN: It'll be in my return, and I highlighted it in yellow.

MS. FIUME: Thank you.

Full Panel – March 13, 2026

DR. DAVID COHEN: I think we're okay. It's a Draft Final Amended Report on 2-Bromo-2-Nitropropane-1,3-Diol. At the previous review, the Panel issued a Tentative Amended Report with the conclusion that this ingredient is safe in cosmetics in the present practices of use and concentration described in this assessment. Following my motion we can have a discussion, but it is to affirm that conclusion.

DR. BERGFELD: Is there a second?

DR. BELSITO: No.

DR. BERGFELD: No second on the Belsito's side. Can we move to a discussion then?

DR. BELSITO: Yeah, I was concerned that there's that report, that retrospective study, determining the prevalence of wet wipes as a source of allergy found 0.9 percent of patients with a positive patch test had an allergic reaction to a wet wipe source. And the reaction rate for 2-Bromo-2-Nitropropane-1,3-Diol was 27.4 percent. And so, this rings a bell of what happened to us with MI, where we put one label fits all, and we got this epidemic of MI sensitization, largely driven by wet wipes.

So we went back and forth whether we wanted to ask industry to do a QRA2 on the concentrations currently used, 0.05 percent in wet wipes, to see if that would be safe. That would involve a delay in this report. Anything we do will result in a delay, but we came up with the best option being the conclusion to be when formulated to be non-sensitizing, such as with a QRA2 or other methodologies.

DR. DAVID COHEN: Don, what was the concentration in those wipes?

DR. BELSITO: 0.05 percent.

DR. DAVID COHEN: Okay, which is where we are, right?

DR. ROSS: That's our max, yeah.

DR. DAVID COHEN: Yeah. Don, did you want to have a conclusion that adds when formulated to be non-sensitizing, or do you want to create -- do you want to stop this report and send it with a new IDA?

DR. BELSITO: Well, it's going to come back to us anyway, according to Bart, because it's more restrictive. But the easiest thing, rather than waiting for someone to provide us with that QRA on wet wipes, would simply be to go ahead. When formulated to be non-sensitizing was the conclusion of my team.

DR. DAVID COHEN: I think it's very logical, Don. The question is, does it provide the safety level that we're intending it to have? If we have a 0.05 limit -- and just repeat, again, what percentage of people were positive?

DR. BELSITO: 0.9 had a reaction to a wipe. And of the ones that had a reaction to the wipe, 27.4 percent had contact allergy to 2-Bromo-2-Nitropropane,1,3-Diol.

DR. DAVID COHEN: So, the question would be that the testing on that product would need to have several hundred people to detect sensitizing level?

DR. BELSITO: No, you come up with a NESIL, and you just perform the QRA for product categories. It goes back to what I pointed out to you yesterday in Dr. MacMillan's presentation. You need to look at specific product categories because the sensitization level can change depending upon where you're placing the material. And that's what happened to us with MI, right? I mean, the vast majority of them were wet wipes and then sunscreens.

DR. DAVID COHEN: So, you believe the warning would provoke industry to do this?

DR. BELSITO: I mean, I don't think, as we discuss, we can provoke industry to do anything. It's our decision, or conclusion rather, that in order for bronopol -- so I don't have to say the whole name -- to be marketed safely in cosmetic products, the company doing that should assure that they've run some type of risk assessment, that in their specific product, the intended use of their product, it's non-sensitizing. And there are easy formulas that can be done. You have a NESIL for bronopol, and you just plug it in to a formula for a wet wipe.

DR. BERGFELD: Do you think you could do that in the Discussion and cite the differences in different areas of the body?

DR. BELSITO: But it doesn't protect from saying safe as used. Because I don't know, based upon that report, if it is safe as used in a wet wipe. I'm very concerned by when you get over a quarter of a population that has a wet wipe allergy, and there's one allergen that's popping up in the patch testing, that gives me concern, Wilma. And we had a fiasco with Methylisothiazolinone. It was a fiasco.

DR. BERGFELD: I know. I remember.

DR. BELSITO: And so, the question becomes since MI has been removed from wipes, is it being replaced by bronopol? I mean, there has to be a preservative there; so what is the preservative that's replacing MI, which was the overwhelming preservative in wet wipes?

DR. DAVID COHEN: So, Wilma, I think both has to happen. I think I'm going to revise my conclusion, and I think the Discussion needs to outline very much what Don laid out. I agree with him. Anyone on our team have any issue with that? I'll revise to a stricter conclusion.

DR. ROSS: No issues with me. I thought Don's comments were really well taken. Thanks for bringing that up.

DR. BERGFELD: So, what is your conclusion, David?

DR. TILTON: I agree, no issue.

DR. DAVID COHEN: My conclusion is now, this Bromo-Nitropropane-Diol is safe in cosmetic ingredients when formulated to be non-sensitizing.

DR. BELSITO: Second.

DR. BERGFELD: So, a second for that. Any further discussion?

DR. BELSITO: Yeah. So, there was the issue of whether when this was absorbed it would form endogenous nitrosamines. And the reason I gave you one reference for formation of nitrosamines in formulation was that I did a deep dive to see if I could find any reference related to that, and the answer was no. And then I just sort of passed it off to Dan Liebler, who is oftentimes my confidant for these matters, and he said that it's highly unlikely, that even if absorbed there would be endogenous formation of nitrosamines.

I think that that statement, which is unsupported, should be removed from the document. And, again, remove tattoo from the RLD list. And those were my only other comments.

DR. DAVID COHEN: Yeah, Don, I reviewed that paper you sent. I thought it was a really good addition, and our discussion is that the nitrosamine issue was a formulation concern more than anything, and so we came to the same conclusion.

DR. BELSITO: Right.

DR. BERGFELD: So, any other Panel members want to come in and make a statement here regarding the conclusion before we call the vote? Seeing none, I'm going to call the vote. All those opposed? Abstaining? It's approved. And will you repeat your conclusion, David?

DR. DAVID COHEN: Safe as used when formulated to be non-sensitizing.

DR. BERGFELD: And we have decided to expand the Discussion with what Don and you both agreed to put in.

DR. DAVID COHEN: Yeah.

DR. BERGFELD: Okay.

MS. FIUME: Dr. Bergfeld, can I just ask for clarification? So, in the Conclusion, do you want the mention of the QRA2 in the Conclusion?

DR. BERGFELD: I would not, but how about Don, David, do you want that in the Conclusion?

DR. BELSITO: I thought the Conclusion should run similar to the MI Conclusion, which I believe said QRA2 or other methodologies.

MS. FIUME: I believe it says that as well.

DR. DAVID COHEN: Really?

DR. BERGFELD: Could you read that for us?

MS. FIUME: Sure, let me find it.

DR. BERGFELD: It's been a while.

DR. DAVID COHEN: It's before my time, that original one; I was around for the update.

DR. SAM COHEN: But that example really points out the value of having people with long experiences on this Panel.

DR. DAVID COHEN: It does.

MS. FIUME: I'm just going to read the relevant part. "Safe in leave on cosmetic products when they are formulated to be non-sensitizing, which may be determined on a QRA or similar methodology." At that point, it was only QRA, not QRA2. We can use QRA2 here. But that was in the Methyliso Conclusion.

DR. DAVID COHEN: I have no problem with that additional provision. At that point, Don, you are creating as much a push to do that than is possible from any other conclusion we have.

DR. BERGFELD: Do you need to restate your conclusion, then?

DR. DAVID COHEN: Could we go with the conclusion that Monice just read, which is safe as used to be non-sensitizing when confirmed with a QRA2 or similar assessment?

DR. BERGFELD: All right. I think I need to have a vote on everybody who thinks this is okay. You've heard the new conclusion. This is sort of an editorial conclusion, a little bit more specific. I'm going to say anyone disagreeing please indicate right now. Abstaining?

All right, it's approved, so we have a new conclusion. And we'll consider it editorial, but it's a new conclusion. Anything else that needs to be done about this ingredient before we move on?

DR. DAVID COHEN: Wilma, when you say it's editorial --

DR. BERGFELD: It's more specific.

DR. DAVID COHEN: Right, so it'll have to go back out again because it's a tighter conclusion?

DR. SNYDER: It's more restrictive, so Bart says it has to go back out. That's why Don said we'll see it again.

DR. DAVID COHEN: Yeah, that makes sense.

DR. BERGFELD: So was the other one, the 0.05. So, yes. Okay, it's our understanding, Bart, is that correct? Will you confirm what the activity will be now?

DR. HELDRETH: That's correct. This will now be issued as a Revised Tentative-Amended Report, and it'll come back to the Panel at a future meeting as a Draft Revised Final-Amended Report.

DR. BERGFELD: Okay. And the papers that have been sort of floating around on the internet here with us, that have been sent to us, can be included?

DR. HELDRETH: Absolutely.

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MINUTES
of the
CIR EXPERT PANEL
EIGHTH MEETING

April 27-28, 1979

The Madison Hotel
15th & M Streets, N.W.
Washington, D.C.

Expert Panel Members

Karl H. Beyer, Jr., M.D., Ph.D., Chairman
Wilma F. Bergfeld, M.D.
Julius M. Coon, Ph.D., M.D.
Robert M. Fine, M.D.
Dietrich K. Hoffmann, Ph.D.
William Montagna, Ph.D.
Robert L. Roudabush, Ph.D.

Liaison Representatives

Consumers
Ms. Marcia Carroll

Industry
Dr. Jack Winstead

FDA Contact Person
Mr. Martin Greif

CIR Staff

Robert L. Elder, Sc.D., Director
Linda L. Broadwater, Administrator

Invited Guests

Mr. Sherwood Cross
ICI Americas Inc.

Mr. David Garlin
Cosmetech Laboratories, Inc.

Mr. Harold Johnson
Penick Corporation

Mr. Martin Smolin
Amerchol Corporation

Adopted July 24, 1979 (Date)

Karl H. Beyer, Jr., M.D., Ph.D.

Tentative Reports mentioned above. These comments and proposed responses will be forwarded by staff to the Panel for decision. A Final Report will then be issued.

Dr. Elder reported that he has met with the Society of Cosmetic Chemists and will be meeting within the next month with Dr. Leon Golberg, Editor of Food and Cosmetics Toxicology, to pursue possible publication of the CIR Final Reports in their journals. He and Dr. Beyer expressed the desire to have Reports available for publication in January 1980.

Dr. Elder announced that Dr. Beyer has been elected to the membership of the National Academy of Science.

Priority List.

Ms. Carroll asked if, in light of previous Panel discussions, there would be any change made in the present Priority List. Dr. Beyer and Dr. Elder said that none was anticipated at this time.

Discussion of Draft Tentative Reports.

Dr. Beyer asked that only substantive matters relating to the reports be discussed during the Panel meeting. Editorial revisions should be made directly on the copy of the report and returned to staff at the end of the meeting.

1. 2-Bromo-2-Nitropropane-1,3-Diol. Dr. Bergfeld reported that the present draft incorporates the changes suggested at the January 22-23, 1979, meeting and are acceptable to the Team. Dr. Roudabush was asked to read the following conclusion, as agreed to by the Team:

"The evidence at hand indicates 2-Bromo-2-Nitropropane-1,3-Diol to be safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides."

Subject to suggested revisions, the document was adopted as a Tentative Report of the Expert Panel. The document will be revised accordingly and issued for a 90-day public comment period.

2. Glycol Stearates Group. Dr. Bergfeld pointed out that the material reviewed thus far by the Team is lacking in information relating to clinical data of testing, marketing, or industrial experience. There is also inadequate information available on named tests such as contact irritancy, contact sensitivity, and photosensitivity. There is also an absence of information relating to metabolism, absorption and excretion of the ingredient, as well as chronic toxicity studies.

The Team stated it could not adequately assess the safety of the group at this time on the basis of the limited data available.

It was reported that the industry had provided human safety data to the CIR staff a few days before the meeting. It was agreed that the Team would review these new data and report on the status of the ingredient(s) at the July meeting.

3. Caprylic/Capric Triglyceride. Dr. Coon read the following conclusion, as recommended by the Team:

"It is the opinion of the Expert Panel, based on the evidence at hand which it believes to be relevant and accumulated in a reasonable manner, that the

Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

Status: Final Amended Report for Panel Review
Release Date: September 11, 2026
Panel Meeting Date: October 5-6, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Thushara Diyabalanage, Ph.D., former Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

ACD	allergic contact dermatitis
AD	atopic dermatitis
aq.	aqueous
BHT	butylated hydroxytoluene
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Da	Daltons
DEA	diethanolamine
Dictionary	*International Cosmetic Ingredient Dictionary*
DMSO	dimethyl sulfoxide
EBS	European baseline series
ECHA	European Chemicals Agency
EPA	US Environmental Protection Agency
ESCD	European Society of Contact Dermatitis
FCA	Freund's complete adjuvant
FDA	US Food and Drug Administration
FOU	frequency of use
GEIDAC	Grupo Español de Investigación de Dermatitis de Contacto y Alergia Cutánea
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	high-pressure liquid chromatography
ICDRG	International Contact Dermatitis Research Group
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
l.o.	leave-on
LOEL	lowest-observable-effect-level
MED	minimal erythema dose
MMAD	mass median aerodynamic diameter
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MTT	3-[4,5-dimethylthiazol-2-yl]-2, 5-diphenyl-tetrazolium bromide
NA	not applicable
NACDG	North American Contact Dermatitis Group
NDELA	*N*-nitrosodiethanolamine
NICNAS	National Industrial Chemical Notification and Assessment Scheme
NOEL	no-observable-effect-level
NR	not reported
OECD	Organisation for Economic Co-operation and Development
o/w	oil-in-water
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PR	positivity ratio
QRA	quantitative risk assessment
REIDAC	Spanish Contact Dermatitis Research Group
RI	reaction index
RLD	Registration and Listing Data
r.o.	rinse-off
SGD	scattered generalized distribution
SPIN	significance-prevalence index number
TRUE	thin-layer rapid use epicutaneous
TG	test guideline
US	United States
UV	ultraviolet
WoE	weight-of-evidence

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of 2-Bromo-2-Nitropropane-1,3-Diol, which is reported to function as a preservative in cosmetic products. The Panel reviewed all relevant data related to this ingredient. The Panel stated 2-Bromo-2-Nitropropane-1,3-Diol should not be used in cosmetic products in which *N*-nitroso compounds can be formed; antioxidant use in formulations reduces potential *N*-nitrosating activity. The Panel issued an amended report with a revised conclusion stating 2-Bromo-2-Nitropropane-1,3-Diol is safe in cosmetics when formulated to be non-sensitizing, which may be determined based on a quantitative risk assessment (QRA) or similar methodology.

INTRODUCTION

This assessment reviews the safety of 2-Bromo-2-Nitropropane-1,3-Diol (commonly known as bronopol) as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), this ingredient is reported to function in cosmetics as a preservative.[1]

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a safety assessment of 2-Bromo-2-Nitropropane-1,3-Diol in 1980.[2] The Panel concluded that 2-Bromo-2-Nitropropane-1,3-Diol was safe as cosmetic ingredient at concentration up to and including 0.1% except under the circumstance where its action with amines or amides can result in the formation of nitrosamines or nitrosamides. An addendum to the report was published in 1984 due to the availability of new scientific literature; the Panel reaffirmed its 1980 conclusion, and further stated that the additional data suggested the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of nitrosamines in humans.[3] The Panel previously considered a re-review of this report in September 2003 and reaffirmed the conclusion, as published in 2006.[4]

Because it had been at least 15 years since the previous re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel again considered a re-review of 2-Bromo-2-Nitropropane-1,3-Diol at its September 2024 meeting. At that meeting, the Panel determined that this safety assessment should be re-opened due to the voluminous amount of new data, to consider updated use data, and to construct a conclusion that aligns with current language, and to re-investigate the possibility of endogenous formation of nitrosamines.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted in May 2025 for studies published in 2001 onwards. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the previously published reports on 2-Bromo-2-Nitropropane-1,3-Diol[2,3] and the unpublished initial re-review document that was presented to the Panel at the September 2003 meeting[5] are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the Summary section).

Much of the data included in this safety assessment were found on the European Chemicals Agency (ECHA),[6] United States (US) Environmental Protection Agency (EPA)[7] and that National Industrial Chemical Notification and Assessment Scheme (NICNAS)[8] websites. Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

2-Bromo-2-Nitropropane-1,3-Diol (CAS No. 52-51-7) is a substituted aliphatic diol.[1] The general formula for this ingredient conforms with the structure displayed in Figure 1.

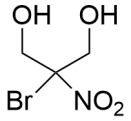


Figure 1. 2-Bromo-2-Nitropropane-1,3-Diol

Chemical Properties

2-Bromo-2-Nitropropane-1,3-Diol is a colorless-to-pale, brownish yellow, odorless crystalline solid which is soluble in water, alcohol, tetrahydrofuran and propylene glycol.[2] It is slightly soluble in mineral oil and vegetable oils.

The molecular weight of 2-Bromo-2-Nitropropane-1,3-Diol is 199.99 Da.[9] The log octanol/water partitioning coefficient (log P_{ow}) is 0.18. These and additional chemical properties can be found in Table 1.

Method of Manufacture

The following method is general to the production of 2-Bromo-2-Nitropropane-1,3-Diol, and it is unknown if it applies to cosmetic-ingredient manufacturing. Bishydroxymethylation of nitromethane using formaldehyde in the presence of a base gives the salt corresponding to 2-nitropropane-1,3-diol.[10] This salt is subsequently reacted with bromine to form 2-Bromo-2-Nitropropane-1,3-Diol.

Degradation

2-Bromo-2-Nitropropane-1,3-Diol is generally stable against hydrolysis under standard temperature and pressure, and dermal pH.[5] *However, the higher temperature and pH (in industrial applications) are known to accelerate the hydrolysis. Under the accelerated conditions the degradation can be extensive, and formaldehyde is the hydrolysate. Nevertheless, studies conducted by the US EPA have shown a minimal risk of formaldehyde exposure for the handlers of 2-Bromo-2-Nitropropane-1,3-Diol or during post-application exposure due to its slow decomposition rate. It has been shown that the half-life of 2-Bromo-2-Nitropropane-1,3-Diol, mixed with water to generate formaldehyde is 18 yr at pH 4. Only more alkaline pH values can accelerate it.*

2-Bromo-2-Nitropropane-1,3-Diol can undergo decomposition in aqueous solutions, and storage conditions have a significant impact on the rate of degradation.[11] Chemicals such as citric acid and sodium dodecylsulfate, and physical factors such as elevated temperature, sunlight, ultraviolet light (UV) , and access to air, are known to accelerate the decomposition. The degradation by-products have been identified as methanol, formic acid, tris(hydroxymethyl)methane, and 2-bromo-2-nitroethanol. High-performance liquid chromatography (HPLC) with UV detection (210 nm) is used to analyze the decomposition products and rate.[12]

Nitrosation

2-Bromo-2-Nitropropane-1,3-Diol is a known N-nitrosating agent for secondary and tertiary amines.[2,3] *It can lead to the N-nitrosation of cosmetic ingredients such as diethanolamine and triethanolamine, forming N-nitrosodiethanolamine (NDELA), and of morpholine, forming N-nitrosomorpholine. According to studies conducted by the US Food and Drug Administration (FDA), cosmetic ingredients that contain DEA, its derivatives, or contaminants may form nitrosamines if they contain nitrosating agents such as 2-Bromo-2-Nitropropane-1,3-Diol. Creams, cream lotions, hair shampoos, and cream hair conditioners are known to contain such amines and their derivatives.*[5] *The formation of nitrosamines can be avoided by proper formulation, either by not using these amines in combination with nitrosating agents or by testing the products under use conditions to make sure nitrosamines are not formed.*

Antioxidants can inhibit nitrosamine formation in formulations preserved with 2-Bromo-2-Nitropropane-1,3-Diol.[13] 2-Bromo-2-Nitropropane-1,3-Diol (0 – 0.1%) and varying amounts of the antioxidants butylated hydroxytoluene (BHT; 0.2 – 0.5%), α-tocopherol (0.1 – 0.2%), and ascorbate (0 – 0.2%) were added to 100 g samples of a shampoo formulated with 59.1% MEA-lauryl sulfate and 5.0% cocamide DEA (technical-grade); the samples were then placed in a closed box. After 2 wk, the amount of NDELA present was measured (limit of detection, 2.5 μg/kg). With ≤ 0.05% 2-Bromo-2-Nitropropane-1,3-Diol, BHT (0.2 and 0.5%), ascorbate (0.1 and 0.2%), and α-tocopherol (0.2%) reduced NDELA to below the limits of detection. NDELA was detected in all samples with 0.1% 2-Bromo-2-Nitropropane-1,3-Diol; although only 6 μg/kg was detected with the addition of 0.2% α-tocopherol, 23 – 33 μg/kg were detected with 0.1 – 0.2% ascorbate, respectively, and ≥ 174 μg/kg with 0.1% α-tocopherol and 0.2 and 0.5% ascorbate. NDELA formation was also inhibited in a commercial cream formulation containing triethanolamine, 0.01% 2-Bromo-2-Nitropropane-1,3-Diol, and the antioxidants.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of 2-Bromo-2-Nitropropane-1,3-Diol in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[14] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, 2-Bromo-2-Nitropropane-1,3-Diol is used in 572 formulations (Table 2).[15,16] A concentration of use survey using MoCRA product categories conducted by the Council in 2025 only reported use of 2-Bromo-2-Nitropropane-1,3-Diol in disposable wipes at up to 0.05%; such use might result in mucous membrane exposure;[17] in 2003, it was used at up to 0.1% in several leave-on product categories.[4] According to 2025 RLD, although 2-Bromo-2-Nitropropane-1,3-Diol is reported to be used in 143 disposable wipe formulations, it is also used in many other products, including those applied near the eye, in other product types that result in mucous membrane exposure (e.g., douches), and in baby wipes

Reported uses of 2-Bromo-2-Nitropropane-1,3-Diol in baby products are identified in the RLD; however, concentration of use data are not available for every reported category of baby product. In cases where a baby product category is reported without an associated concentration, but an analogous adult product category with reported concentration data is available, the adult product use level may be considered informative for exposure characterization. In such cases, concentrations in the corresponding baby product category are not expected to exceed those reported for the analogous adult product category. For example, 2-Bromo-2-Nitropropane-1,3-Diol has no reported concentration of use in baby wipes, but it is reported in disposable wipes at a maximum concentration of 0.05%; accordingly, concentrations in baby wipes are not expected to exceed this value. The category "other baby products" represents a miscellaneous grouping of reported uses not assigned to specific baby product subcategories. Given its broad and non-specific nature, it does not correspond to a single analogous adult product category; therefore, the adult-product concentration bridging approach is not applied to this category.

Following the passage of MoCRA, the FDA created a number of new product categories, including "(17) Other preparations (i.e., those preparations that do not fit another category)" (Category 17). CIR and the Panel utilize these product categories to inform, in part, the weight-of-evidence (WoE) in exposure and risk analyses. However, citation of Category 17, alone, as the product use category is uninformative. When a product is co-categorized with both Category 17 and one or more common product use categories (e.g., eye makeup preparations), or other information in the RLD such as the product name are indicative of use type (e.g., "lip balm" is part of the product name), then those uses are accounted for and may be considered to be part of the "the present practices of use" for those products; as such, the Panel's safety conclusion may be inclusive thereon. Conversely, for instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17 and other information in the RLD is not indicative of use type, the present practices of use for these products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

It is possible that some products containing 2-Bromo-2-Nitropropane-1,3-Diol may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for this ingredient as listed in the RLD include a designation indicating airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, the concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If this ingredient was to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

In the European Union, 2-Bromo-2-Nitropropane-1,3-Diol is included in Annex V, the List of Preservatives Allowed in Cosmetic Products.[18] The maximum concentration allowed in ready for use preparations is 0.1%, and the formation of nitrosamines is to be avoided.

Non-Cosmetic

Due to its potent antimicrobial properties, 2-Bromo-2-Nitropropane-1,3-Diol has a wide range of applications as an antimicrobial agent and a preservative.[7,8,19] It is used in pharmaceuticals, non-agricultural and agricultural pesticides, paints, coloring agents, cleaning and washing agents, solvents, perfumes and fragrances. In addition, the use of this ingredient is permitted in the production of materials used in food packaging, as adhesives (21 CFR 175.105), as a component of paper and paper board in contact with aqueous and fatty food (21 CFR 176.170), and as slimicides used in manufacture of paper or paper board that contact food (21 CFR 176. 300).[20]

TOXICOKINETIC STUDIES

Dermal Absorption

In Vitro

An in vitro skin penetration study to determine the skin permeability of 2-Bromo-2-Nitropropane-1,3-Diol was conducted following Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428 using porcine ear skin.[21] Three formulations (aqueous (aq.) solution, oil-in-water (o/w) emulsion, and a hydrogel) containing 4% (w/w) 2-Bromo-2-Nitropropane-1,3-Diol (> 98% pure) were evaluated over a 24 – 25-h period using vertical Franz-type

diffusion cells with an effective area available for diffusion of 0.79 cm^2, and a receiver compartment with a 6 ml capacity. One ml of the formulation was placed in the donor compartment, while the receptor compartment was filled with phosphate buffered saline (PBS) or 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)/saline (20/150 mM) buffer. It was evident that the transdermal absorption was dependent on the formulation, with absorption being greatest from the aq. solution and lowest with the hydrogel; transdermal flux was 11.0 and 0.8 μg/cm^2/h, respectively. However, lag time for diffusion was 6.34 h from the aqueous solution, while there was no lag time for diffusion when applied in a hydrogel or emulsion.

Because 2-Bromo-2-Nitropropane-1,3-Diol is a formaldehyde-releaser, the amount of formaldehyde in the receptor fluid was also quantified. The mass balance of 2-Bromo-2-Nitropropane-1,3-Diol at the end of the studies was less than 100%, indicating possible transformation into formaldehyde, as confirmed by formaldehyde being quantified in the receptor compartment. The concentration increase with time was linear. Transdermal fluxes of formaldehyde obtained when applying 2-Bromo-2-Nitropropane-1,3-Diol were much lower than when applying formaldehyde itself. Statistically significant differences were observed in the transdermal flux based on the type of the formulation (aq. solution > emulsion > hydrogel; 0.9, 0.24. and 0.05 μg/cm^2/h, respectively).

Animal

An aqueous solution of 2-Bromo-2-Nitropropane-1,3-Diol (4 mg/ml) was absorbed relatively slowly (approximately 11% in 24 h) when applied to the skin of rats and rabbits.[2,5] The rate of absorption "remained low" even when the material was applied using an occlusive dressing. A slightly more rapid and greater absorption was observed when 2-Bromo-2-Nitropropane-1,3-Diol was dissolved in acetone. (No further information was available.)

Absorption, Distribution, Metabolism, and Excretion

Animal

Absorption, metabolism and excretion of 2-Bromo-2-Nitropropane-1,3-Diol was studied using 2-[^{14}C]2-Bromo-2-Nitropropane-1,3-Diol administered topically and orally, and 3-[^{14}C]2-Bromo-2-Nitropropane-1,3-Diol intravenously.[2] Elimination in the urine of 60 - 80% of the dose given to rabbits intravenously occurred within 24 h. Rats excreted 80.9% of an oral dose in the urine within 24 h and 8.4% of the radiolabel was eliminated in the expired air. Plasma concentrations after oral doses peaked at 2.5 to 9.0% of the total dose in two species within about 2 h and the distribution was fairly even among body organs, with somewhat higher concentrations in the kidney and lower concentrations in fatty tissues. Metabolic breakdown includes reductive de-halogenation resulting in 2-nitropropane-1,3-diol. This in turn may be further metabolized to glycerol and eventually carbon dioxide.

In order to study metabolism of 2-Bromo-2-Nitropropane-1,3-Diol in rats, four separate studies were conducted with male and female Sprague-Dawley rats where animals were given [^{14}C]2-Bromo-2-Nitropropane-1,3-Diol by gavage.[5] In the first study animals received a single dose of 10 mg/kg, whereas a higher dose of 50 mg/kg was used in the second study. The doses higher than 50 mg/kg caused respiratory problems and death. In the third study, 14 daily doses of 10 mg/kg non-radioactive 100% 2-Bromo-2-Nitropropane-1,3-Diol were followed by one dose of [^{14}C]2-Bromo-2-Nitropropane-1,3-Diol. Irrespective of the dose, most of the administered radiolabel was excreted in urine. The feces and tissues represented minor routes. The fourth study identified the metabolites in urine, and the only metabolite found was 2-nitropropane-1,3-diol, which accounted for 45 - 50% of the radioactivity. The remaining radioactivity was not identified.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In Vitro

Inhalation

The inhalation toxicity potential of 0.02, 0.1, and 1.0% 2-Bromo-2-Nitropropane-1,3-Diol was evaluated in the airway model SoluAirway™.[22] Based on the effect on tissue viability, concentrations of 0.1 and 1.0% induced toxicity.

Animal

Dermal

The daily application of 2 or 4% 2-Bromo-2-Nitropropane-1,3-Diol in 90% acetone to the shaved skin of the mice for 1 wk produced severe (but unspecified) toxic effects (no further details available).[5] A concentration of 0.5% applied similarly for 4 wk was well tolerated. Percutaneous applications of doses of 160 mg/kg 2-Bromo-2-Nitropropane-1,3-Diol or greater caused death in rats.[2]

2-Bromo-2-Nitropropane-1,3-Diol, when applied to the skin of 2 male rats at doses 0, 64, 160, 400, and 1000 mg/kg bw, produced edema, hemorrhage, labored breathing, prostration, and lung congestion.[5] The acute dermal LD_{50} was reported to be 64 – 160 mg/kg bw.

Oral

2-Bromo-2-Nitropropane-1,3-Diol administered orally to rats (307 – 342 mg/kg) and mice (327 – 374 mg/kg) caused gastrointestinal lesions.[2] The LD_{50} values reported for mice were 374 mg/kg (male) and 307 mg/kg (female), whereas for

rats, 327 mg/kg (male) and 342 mg/kg (female).[2] In another study, the oral LD_{50} of 2-Bromo-2-Nitropropane-1,3-Diol was determined to be 180 mg/kg in rats, 270 mg/kg in mice, and 250 mg/kg in dogs. The oral toxicity of 2-Bromo-2-Nitropropane-1,3-Diol (2 samples) was tested in rats; the LD_{50} values were 292 and 320 mg/kg. The oral LD_{50} for an aqueous solution of the test material in mice and rats was reported as 350 and 400 mg/kg, respectively. The oral LD_{50} in another study in rats was 193 mg/kg; symptoms observed at 4 h included decreased motor activity and respiratory rates. Single doses of 40 or 100 mg/kg of 2-Bromo-2-Nitropropane-1,3-Diol in dogs caused transient gastric irritation.

Inhalation

In a study in which male and female rats (10/sex) were exposed to 2-Bromo-2-Nitropropane-1,3-Diol for 4 h, the LC_{50} was 18 mg/m^3 (no further details are available).[2] Survivors had severe irritation of the ears and paws and reduced body weight gain, 2 wk following exposure to ≥ 170 mg/m^3.

In an inhalation study, piloerection, hunched posture and hydronephrosis were observed in male and female rats at the 89 mg/m^3 concentration of 2-Bromo-2-Nitropropane-1,3-Diol (particle size was 1.3 - 6.7 µm).[5] At a higher concentration of 588 mg/m^3, diffused red lungs, sore eye lids, and severe dermatitis and ulceration of the head were reported. The EPA concluded that 2-Bromo-2-Nitropropane-1,3-Diol was slightly toxic, with an acute inhalation LC_{50} of > 588 mg/m^3. No deaths were reported in rats exposed to 2-Bromo-2-Nitropropane-1,3-Diol (5000 mg/m^3) for 6 h. It caused labored breathing and decreased body weight.

An acute inhalation study was conducted in which groups of 10 Sprague-Dawley rats (5/sex) were exposed (nose/head only) to 0, 38, 89, or 588 mg/m^3 of 2-Bromo-2-Nitropropane-1,3-Diol for 4 h.[6] The rats were observed hourly during the exposure and once a day over the observation period of 14 d for mortality and clinical signs of toxicity. Three deaths were reported from the high dose group, and most animals in the group showed clinical signs of toxicity. The LC_{50} of 2-Bromo-2-Nitropropane-1,3-Diol in rats was > 588 mg/m^3.

In another inhalation study, groups of 10 Fisher 344 rats (5/sex) were exposed nose-only to 2-Bromo-2-Nitropropane-1,3-Diol at concentrations of 120 and 1140 mg/m^3 for 4 h, in accord with OECD TG 403.[6] The mass median aerodynamic diameters (MMAD) were 3.29 ± 1.64 and ≤ 9.34 ± 4.67 µm for the low and high concentrations, respectively. The acute inhalation LC_{50} was determined to be > 120 mg/m^3, but < 1140 mg/m^3. An MMAD of 1 - 4 µm could not be maintained at concentrations of 2-Bromo-2-Nitropropane-1,3-Diol >1 mg/l due to agglomeration. One male low-dose male rat and 4 high-dose males and 3 high-dose females died during exposure; all the remaining high-dose animals died by day 3.

During another study, rats exposed to 0, 50, 500, or 5000 mg/m^3 of 2-Bromo-2-Nitropropane-1,3-Diol (further details not available) developed eye irritation, dyspnea, profuse mucus production and lethargy.[8] Chronic pneumonitis was also observed after the test duration. There were no mortalities; the acute inhalation LC_{50} was identified as > 5000 mg/m^3.

Short-Term Toxicity Studies

Rats given 2-Bromo-2-Nitropropane-1,3-Diol in drinking water for 6 wk had reduced water intake and slightly enlarged kidneys at 160 mg/kg/d.[2] When the dose level was 300 mg/kg/d, some deaths occurred. Male and female albino rats were fed 100 or 1000 ppm in the diet for 12 wk without apparent effect on growth, food consumption, blood, liver, and kidney weight or histopathologic changes in the major organs.

Subchronic Toxicity Studies

2-Bromo-2-Nitropropane-1,3-Diol, at an oral dose of 20 mg/kg for 90 d, was "well-tolerated" by rats; at 80 and 160 mg/kg, respiratory distress, gastrointestinal lesions, and some deaths occurred.[2] Dogs given 20 mg/kg/d by oral intubation for 90 d showed no significant toxic reaction, except for some vomiting.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In a dermal study, application of 1 ml/kg of 0.5 or 2% 2-Bromo-2-Nitropropane-1,3-Diol in 2.5% aq. methylcellulose to the dorsal skin of rats daily from day 6 - 15 of gestation produced local skin reaction at the site of application but had no other adverse effects on the dams or the fetuses.[2,3] In an oral study, male mice (20/group) were given 2-Bromo-2-Nitropropane-1,3-Diol at a maximum tolerated dose, a calculated exposure dose, and intermediate dose (actual values not reported.) daily for 5 d.[2]One other group was given vehicle, and a fifth group was untreated. Repeated matings of test animals with fresh females throughout spermatogenic cycle showed no effect from the compound. Rats given 10, 30, or 100 mg/kg daily by oral intubation during days 1 - 20 of gestation showed no embryotoxic or teratogenic effects. Doses of 1, 3.3, and 10 mg/kg 2-Bromo-2-Nitropropane-1,3-Diol administered orally to rabbits from day 8 - 16 of gestation did not induce embryotoxic or teratogenic effects. There was no effect on parturition, litter size, postnatal survival or development of the young in rats given 20 or 40 mg/kg of 2-Bromo-2-Nitropropane-1,3-Diol orally from day 15 of gestation throughout lactation. Reproductivity of male rats was not impaired by daily doses of 20 or 40 mg/kg of 2-Bromo-2-Nitropropane-1,3-Diol for 63 d before mating. Likewise, similar doses given to females from 14 d before mating to day 12 of gestation or until litters were weaned had no effect on reproduction. The males receiving 40 mg/kg daily had slightly reduced weight gain.

2-Bromo-2-Nitropropane-1,3-Diol (98% pure) was administered by gavage in acidified (pH 4) water to groups of 24 mated Sprague-Dawley rats at dose levels of 0, 10, 28 or 80 mg/kg/d from day 6 – 15 of gestation.[5] Marginal evidence of maternal toxicity was reported at the highest dose tested as indicated by decreased body weight gain. No animal was

reported as having dose-related clinical signs. The no-observable-effect-level (NOEL) for both maternal toxicity and developmental toxicity was ≥ 80 mg/kg/d. In another developmental toxicology study, groups of 18, 19, or 20 mated female New Zealand white rabbits received 2-Bromo-2-Nitropropane-1,3-Diol by gavage during gestation days 7 - 19, and were killed on day 28. Aqueous solutions of the test substance were administered daily at nominal dose levels of 0 (vehicle control), 5, 20, 40, or 80 mg/kg/d and the dose volume of 2 ml/kg. Based on the findings of these studies, the NOEL and lowest-observable-effect-level (LOEL) for developmental toxicity were 40 and 80 mg/kg/d, respectively. In another study 2-Bromo-2-Nitropropane-1,3-Diol was administered via the drinking water of Charles River COBS CD strain rats (13 males and 26 females in a group) during premating (80 - 87 d), mating, gestation, and lactating periods at 0, 0.25, 70 and 200 mg/kg/d. Reproductive toxicity was observed only in the high dose group, and the NOEL and LOEL for systemic toxicity (based on changes in organ weight and nephropathy) were 25 and 70 mg/kg/d, respectively. The NOEL and LOEL for reproductive toxicity (a decrease in the female fertility index) were 70 and 200 mg/kg/d, respectively.

GENOTOXICITY STUDIES

In Vitro

2-Bromo-2-Nitropropane-1,3-Diol was not mutagenic in the Ames assay, with and without metabolic activation, at the highest concentrations tested (62.5 and 125 µg/plate).[2,5] *In a V79 cell mutation assay conducted with Chinese hamster lung fibroblasts with and without metabolic activation at 20 - 40 µg/ml and at 1- 30 µg/ml respectively, 2-Bromo-2-Nitropropane-1,3-Diol was negative for mutagenicity.*[5]

Genotoxicity studies summarized herein are detailed in Table 3. Several gene mutation assays were performed, and results were mixed. Ames test with up to 166 µg/plate 2-Bromo-2-Nitropropane-1,3-Diol performed using *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98 and *Escherichia coli* WP2 uvrA were negative, with or without metabolic activation.[6,23] However, 2-Bromo-2-Nitropropane-1,3-Diol was genotoxic in an in vitro mammalian cell gene mutation assay **(**OECD TG 476) in which Chinese hamster lung fibroblast (V79) cells were exposed at concentrations of 3 - 27 µg/ml with and 1 – 21 µg/ml without metabolic activation; a reproducible increase of mutant frequency was induced without metabolic activation (with 6 – 15 µg/ml), while the statistically significant increase of mutant frequency observed with metabolic activation (with concentrations of 6 – 18 µg/ml) was not reproducible.[6] In studies examining the ability to induce chromosomal damage, results were negative with 2-Bromo-2-Nitropropane-1,3-Diol. With and without metabolic activation, 2-Bromo-2-Nitropropane-1,3-Diol was not genotoxic in an in vitro mammalian chromosome aberration assay (performed largely in accord with OECD TG 473) with human lymphocytes at up to 30 µg/ml, or in an in vitro mammalian cell micronucleus test (OECD TG 487) in mouse lymphoma L5178Y cells at non-specified concentrations (determined via cytotoxicity).

In Vivo

An in vivo micronucleus assay was conducted in which male and female CD1 mice that received single oral doses of 2-Bromo-2-Nitropropane-1,3-Diol (80 or 160 mg/kg bw) were killed 24, 48, and 72 h after dosing.[5] *At all sampling times, the mice treated with 2-Bromo-2-Nitropropane-1,3-Diol and the negative control (sterile double-distilled water) had similar number of micronuclei per 1000 polychromatic erythrocytes of femur bone marrow examined per animal, while the positive control cyclophosphamide (75 mg/kg) demonstrated significant increases in the micronuclei in both sexes. Based on these observations, the result of the mutagenicity test was negative.*

CARCINOGENICITY STUDIES

Application of 2-Bromo-2-Nitropropane-1,3-Diol, 0.2 and 0.5% in aqueous acetone, to the skin of mice 3x/wk for 80 wk did not affect tumor incidence.[2] *Oral administration of 2-Bromo-2-Nitropropane-1,3-Diol to rats in drinking water at doses as high as 160 mg/kg/d for 2 yr did not reveal an effect on tumor incidence.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

An in vitro study was conducted to evaluate the potential dermal irritation of 11 commonly used biocides, including 2-Bromo-2-Nitropropane-1,3-Diol (in dimethyl sulfoxide (DMSO)), using the KeraSkin™ reconstructed human epidermis model.[22] The dermal irritation was assessed by a tissue viability study employing a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) assay and histological examinations. Control tissues were treated with 1% dimethyl sulfoxide in PBS (negative) or 5% sodium dodecyl sulfate. The degree of damage was scored by 6 examiners using visual evaluation in a blinded fashion, considering parameters such as erosion, vacuolation, and necrosis. The data analysis was performed following OECD TG 439. 2-Bromo-2-Nitropropane-1,3-Diol was tested at 0.02, 0.1, and 1.0%. With 1% 2-Bromo-2-Nitropropane-1,3-Diol, tissue viability was approximately 10%; however, tissue viability was acceptable for the other 2 concentrations tested, indicating that these concentrations were non-irritating.

Animal

A 0.2 or 0.5% solution of 2-Bromo-2-Nitropropane-1,3-Diol in aq. 2.5% methylcellulose was applied to abraded clipped skin of the back of rabbits once daily in doses of 1 ml/kg for 3 wk.[2] The 0.5% solution produced moderate edema, erythema, and eschar formation, while the 0.2% solution produced local erythema. The vehicle alone produced an effect similar to that of 0.2% 2-Bromo-2-Nitropropane-1,3-Diol. 2-Bromo-2-Nitropropane-1,3-Diol (5 mg, dry) in contact with the moistened abraded and unabraded skin of rabbits for 24 h resulted in a primary irritation score of 0.75 out of a maximum possible score of 8. Erythema occurred only on abraded skin. In the Federal Hazardous Substance Act procedure, scores of less than 5 indicate that the test material is not a primary irritant. A 20% aqueous solution of 2-Bromo-2-Nitropropane-1,3-Diol applied to abraded and non-abraded skin of rabbits gave a score of 6.75/8.0, indicative of moderate to severe irritation. Emulsions and solutions containing 2-Bromo-2-Nitropropane-1,3-Diol at 0.5 and 2% tested on rabbit skin produced irritation at 2% from one application, while no irritation was produced from four daily applications of 0.5% concentrations. When 2-Bromo-2-Nitropropane-1,3-Diol was applied to non-abraded, shaved skin of rabbits in a variety of solvents, the level of irritancy depended on the vehicle. Acetone solutions were non-irritating on single occluded application at 1%, while repeated application of 0.5% was highly irritating when not occluded. 2-Bromo-2-Nitropropane-1,3-Diol at 0.5% in aqueous methylcellulose gave similar results. In PEG 300, a 5% concentration of 2-Bromo-2-Nitropropane-1,3-Diol was non-irritating as a single occluded application. A single application of a 2% emulsion caused skin irritation, but a 0.5% emulsion applied on 4 successive days did not.

Human

Ten human volunteers were tested for skin irritation with closed patches of 2-Bromo-2-Nitropropane-1,3-Diol, at 0, 0.5, 1, and 2% in soft paraffin and 0, 0.05, 0.1, and 0.25% in aqueous buffer at pH 5.5.[2] Paraffin patches with 1% test material produced slight erythema in 1 volunteer and moderate erythema in 4 volunteers at 2%. Application of the aqueous patches produced slight erythema in one volunteer at 0.25% concentration.

Sensitization

Animal

2-Bromo-2-Nitropropane-1,3-Diol was a weak sensitizer in a Magnusson and Kligman guinea pig sensitization test in which two intradermal injections of 0.02% in normal saline were given in the shoulder region.[2] This was followed by two injections of 0.02% 2-Bromo-2-Nitropropane-1,3-Diol in 50:50 Freund's complete adjuvant (FCA): normal saline and another two injections of 50:50 FCA:saline. Seven days later a booster application was given on the same site using a 48-h occlusive patch of 1.5% 2-Bromo-2-Nitropropane-1,3-Diol in water. An occluded challenge patch of 0.4% in water was applied to the flank for 24 h 14 d later. Skin reactions at the challenge sites were observed at 24 and 48 h and the challenges were repeated for a total of 4 applications followed by observations. Two of the 10 guinea pigs became sensitized after 3 challenges. It was concluded that formaldehyde, a decomposition product of 2-Bromo-2-Nitropropane-1,3-Diol which was also applied at 0.2% during the fourth challenge, was found not to be responsible for the sensitization in guinea pigs. Intradermal injections of a 0.05% aq. solution of 2-Bromo-2-Nitropropane-1,3-Diol were given to guinea pigs on alternate days for a total of 10 injections. The first dose was 0.1 ml and the others were 0.05 ml. The challenge dose, 0.05 ml of 0.05%, given 2 wk later produced no evidence of skin sensitization. In another test, a 1% solution of 2-Bromo-2-Nitropropane-1,3-Diol in acetone, failed to sensitize guinea pigs by the ear-flank method of Stevens.

2-Bromo-2-Nitropropane-1,3-Diol was tested for guinea pig sensitization in an optimization test where a group of 10 male and 10 female guinea pigs received 10 intracutaneous injection inductions over a 3-wk period (an injection every other day).[3] In the first week the injections were of a 0.1% 2-Bromo-2-Nitropropane-1,3-Diol solution and in the second and third weeks the injections were of the same concentration of 2-Bromo-2-Nitropropane-1,3-Diol in a mixture of FCA and saline. There was an intradermal challenge at week 6 with 0.1% 2-Bromo-2-Nitropropane-1,3-Diol and an epidermal challenge at week 8 with a 24-h occluded patch of 3% 2-Bromo-2-Nitropropane-1,3-Diol in petrolatum. Eighteen of the 20 guinea pigs had positive reactions to the intradermal challenge, and none had a positive reaction to the epidermal challenge.

In another study, guinea pigs received dermal application of 1% 2-Bromo-2-Nitropropane-1,3-Diol (98.8% purity) in acetone (no further information available).[5] It was determined not to be a skin sensitizer after 3 induction treatments on the outer surface of each ear, and one challenge treatment on the back and flank a week later. The positive control used in this study was dinitrochlorobenzene.

In a study with guinea pigs (male/female) to evaluate the skin sensitization potential of 2-Bromo-2-Nitropropane-1,3-Diol, two induction applications were performed, first (intracutaneous) with 0.02% test material and the second with (occlusive epicutaneous) 1.5%.[6] The third application was a 0.4% epicutaneous challenge. The test material did not reveal skin sensitization potential under the conditions of this study.

OCULAR IRRITATION STUDIES

2-Bromo-2-Nitropropane-1,3-Diol (106 mg; crystalline) in the eyes of rabbits caused immediate irritation of the conjunctiva and delayed effects on the cornea and iris.[2] These later effects noted on the fourth day, remained on the last day of observation (day 7). Scores, according to the Draize scale, on day 7 were maximum in all but 2 of 6 unwashed eyes. Washing with water did not modify the damage produced. A 0.1 ml dose of a 10 or 20% aq. solution of 2-Bromo-2-

Nitropropane-1,3-Diol placed in the conjunctival sac of a rabbit eye produced severe ocular damage. Washing 4 s after application of the 20% solution reduced the reaction. Complete clearing of the damage required 35 d in the unwashed eye and 14 d in the washed eye. When 3 mg of the solid compound was placed in the eye, damage was severe and clearing again required 35 d. Washing reduced recovery time to 14 d in one test and 21 in another. 2-Bromo-2-Nitropropane-1,3-Diol, at 2% in solution and in an emulsion, was reported to be irritating to the rabbit eye. However, 4 daily applications of 0.5% solution and emulsion were not irritating. 2-Bromo-2-Nitropropane-1,3-Diol tested as a 0.5% solution in normal saline was non-irritating in the eyes of rabbits when applied daily for 4 successive days. A solution of 5% in PEG 400 was irritating on single application, but at 2 % did not produce irritation.

Instillation of a 5% solution of 2-Bromo-2-Nitropropane-1,3-Diol in polyethylene glycol caused severe eye irritation in rabbit eyes and produced redness and swelling of the conjunctivae with moderate discharge 1 h after dosing.[8] The effects subsided in most of the animals after 7 d.

CLINICAL STUDIES

Retrospective and Single or Multicenter Studies

Patients attending a dermatitis clinic were subjected to a battery of closed patch tests for diagnosis, which included 2-Bromo-2-Nitropropane-1,3-Diol at 0.25%.[2] Three of the 149 patients showed a slight transient erythema. There was no evidence of sensitization or of cross-sensitization with formalin.

In a clinical study conducted in 7 European clinics, 8149 patients were patch tested with 2-Bromo-2-Nitropropane-1,3-Diol (0.5% in petrolatum).[5] A very low reactivity with a total of 10 (0.12%) irritation reactions and 38 allergic reactions (0.47%) was reported.

A study examining trends in patch tests results from a tertiary referral dermatitis clinic found that positive patch test outcomes were statistically significantly decreased ($p = 0.03$) with 2-Bromo-2-Nitropropane-1,3-Diol.[24] Over the 2002 – 2012 time frame, patch test positivity with 2-Bromo-2-Nitropropane-1,3-Diol was 2.5% (1400 patients), while during 2016 – 2021, positivity was 0.75% (402 patients).

Clinical studies are described in Table 4. Retrospective studies (mostly performed by the North American Contact Dermatitis Group (NACDG)) indicated that the positivity rates with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet) ranged from 1.3 – 4.8%;[25-43] the lowest rate (1.3%) was reported with NACDG analysis of testing conducted in 2015 – 2016.[38] Results for specific patient subgroups are also included,[44-46] as are several studies using pediatric test groups.[47-49] A retrospective study (2011 – 2014) determining the prevalence of wet wipes as a source of allergy found that 0.9% of patients with a positive patch test had an allergic reaction to a wet wipe source, and the reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these subjects 27.4%.[50] Co-reactivity to formaldehyde was also evaluated, with some studies showing little co-reactivity[51,52] while another found that 25% of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde.[42]

Case Reports

A 62-yr-old female presented with dermatitis of the face and neck resulting from use of baby wipes/towelettes.[53] Patch testing with 2-Bromo-2-Nitropropane-1,3-Diol produces positive results, as did testing with the wipes.

A 3-yr-old female developed a rash on her leg at the area of application of several antiseptic creams.[54] Patch testing showed ++ reactions to several substances, including 2-Bromo-2-Nitropropane-1,3-Diol. She was diagnosed as having allergic contact dermatitis (ACD) from this ingredient, but the relevance was unknown due to inadequate history details.

A 16-yr-old female with a history of childhood asthma and allergic rhinitis had eczematous eruptions of the flexor forearms.[55] Patch testing showed a ++ reaction to 2-Bromo-2-Nitropropane-1,3-Diol, an ingredient present in cat litter. In another case, a 70-yr-old male presented with a 6-wk history of an acute pruritic eruption in the axillary vaults, inguinal folds, and central lumbar area was suspected of having ACD due to the severity of symptoms.[56] The patch-testing results were positive for two known allergens and 2-Bromo-2-Nitropropane-1,3-Diol.

SUMMARY

The Panel conducted a safety assessment on 2-Bromo-2-Nitropropane-1,3-Diol in 1980 and concluded that it was safe as a cosmetic ingredient at concentration up to and including 0.1% except under the circumstance where its action with amines or amides can result in the formation of nitrosamines or nitrosamides. Due to the availability of new scientific literature, an addendum to the report was published in 1984 wherein the Panel reaffirmed their 1980 conclusion, but added a statement indicating that the additional data suggested the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of nitrosamines in humans. A re-review in 2004/2005 reaffirmed that conclusion, as published in 2006. In September 2024, since more than 15 years have passed since the last re-review, the Panel considered the updated safety information related to 2-Bromo-2-Nitropropane-1,3-Diol and decided to reopen the safety assessment due to the voluminous amount of new data, to consider updated use data, to construct a conclusion that aligns with current language, and to re-investigate the possibility of endogenous formation of nitrosamines.

2-Bromo-2-Nitropropane-1,3-Diol is a known *N*-nitrosating agent for secondary and tertiary amines. It can lead to the *N*-nitrosation of cosmetic ingredients such as diethanolamine and triethanolamine and form NDELA and of morpholine to form *N*-nitrosomorpholine.

RLD obtained from the FDA in 2025 reported that 2-Bromo-2-Nitropropane-1,3-Diol is used in 572 cosmetic formulations; 143 of these uses are in disposable wipes. The reported maximum concentration of use has decreased. According to the results of a survey conducted by the Council in 2025, the maximum reported concentration of use is 0.05% in disposable wipes; in 2003, the maximum reported concentration of use was 0.1% in leave-on products. The use of 2-Bromo-2-Nitropropane-1,3-Diol is regulated in the European Union. It is included in Annex V, the List of Preservatives Allowed in Cosmetic Products and the maximum use concentration in ready for use preparations is restricted to 0.1%, with caution to avoid formation of nitrosamines. It was evident that the transdermal absorption of 2-Bromo-2-Nitropropane-1,3-Diol was dependent on the formulation, with absorption being greatest from an aqueous solution and lowest from a hydrogel; transdermal flux was 11.0 and 0.8 $\mu g/cm^2/h$, respectively. However, lag time for diffusion was 6.34 h from the aqueous solution, while there was no lag time for diffusion when applied in a hydrogel or emulsion.

In an acute inhalation study using Sprague-Dawley rats that were exposed (nose/head) to concentrations of 0, 38, 89, and 588 mg/m^3 for 4 h, 3 deaths were reported in the high dose group, and most animals in that group showed clinical signs of toxicity. In Fischer 344 rats, the LC_{50} in rats (exposed nose-only) was > 120 mg/m^3 but < 1140 mg/m^3 2-Bromo-2-Nitropropane-1,3-Diol. During another study, rats were exposed to ≤ 5000 mg/m^3 2-Bromo-2-Nitropropane-1,3-Diol, and the clinical signs included eye irritation, dyspnea, profuse mucus production and lethargy. Chronic pneumonitis was also observed after the test duration. There were no mortalities; accordingly, the acute inhalation LC_{50} was > 5000 mg/m^3.

Several gene mutation assays were performed, and results were mixed. Ames tests with up to 166 µg/plate 2-Bromo-2-Nitropropane-1,3-Diol performed using *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98 and *Escherichia coli* WP2 uvrA were negative, with or without metabolic activation. However, 2-Bromo-2-Nitropropane-1,3-Diol was genotoxic in an in vitro mammalian cell gene mutation assay **(**OECD TG 476) in which Chinese hamster lung fibroblast (V79) cells were exposed at concentrations of 3 - 27 µg/ml with and 1 – 21 µg/ml without metabolic activation; a reproducible increase of mutant frequency was induced without metabolic activation (with 6 – 15 µg/ml), while the statistically significant increase of mutant frequency observed with metabolic activation (with concentrations of 6 – 18 µg/ml) was not reproducible. In studies examining the ability to induce chromosomal damage, results were negative with 2-Bromo-2-Nitropropane-1,3-Diol. With and without metabolic activation, 2-Bromo-2-Nitropropane-1,3-Diol was not genotoxic in an in vitro mammalian chromosome aberration assay (performed largely in accord with OECD TG 473) with human lymphocytes at up to 30 µg/ml, or in an in vitro mammalian cell micronucleus test (OECD TG 487) in mouse lymphoma L5178Y cells at non-specified concentrations (determined via cytotoxicity).

In an in vitro reconstructed human epidermis model (KeraSkin™) study, ≤ 0.1% 2-Bromo-2-Nitropropane-1,3-Diol in DMSO was not predicted to be irritating, but tissue viability was not acceptable with 1%. 2-Bromo-2-Nitropropane-1,3-Diol was not a sensitizer in a guinea pig assay in which the inductions doses were 0.02% intracutaneously and 1.5% epicutaneously, followed by epicutaneous challenge with 0.4%.

Instillation of 2-Bromo-2-Nitropropane-1,3-Diol 5% solution in polyethylene glycol caused severe eye irritation in rabbit eyes and produced redness and swelling of the conjunctiva with moderate discharge. The effects subsided in most of the animals after 7 d.

Some studies examining trends in in patch tests found that positive patch test outcomes with 2-Bromo-2-Nitropropane-1,3-Diol decreased over time. Retrospective studies indicated that the positivity rates ranged from 1.3 – 4.8% with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet); the lowest rate (1.3%) was reported with NACDG analysis of testing conducted in 2015 – 2016. A retrospective study (2011 – 2014) determining the prevalence of wet wipes as a source of allergy found that 0.9% of patients with a positive patch test had an allergic reaction to a wet wipe source, and the reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these subjects was 27.4%. Some studies analyzing co-reactivity to formaldehyde showed little co-reactivity, while another found that 25% of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde. Of note was one case report in which a patient that presented with dermatitis of the face and neck resulting from use of baby wipes/towelettes had a positive patch test to 2-Bromo-2-Nitropropane-1,3-Diol.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously issued reports approximately every 15 years. In 1980, the Panel evaluated the safety of 2-Bromo-2-Nitropropane-1,3-Diol concluded that it was safe as a cosmetic ingredient at concentration up to and including 0.1% except under the circumstance where its action with amines or amides can result in the formation of nitrosamines or nitrosamides. Due to the availability of new scientific data, an addendum to the report was published in 1984; the Panel reaffirmed its 1980 conclusion and further stated that the additional data suggested the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of nitrosamines in humans. The Panel previously considered a re-review of this report in September 2003 and reaffirmed the conclusion, as published in 2006. In June 2024, since more than 15 years have passed since the last review, the Panel considered another re-review and determined to reopen the safety assessment to re-evaluate existing endpoints, and

to reassess the possibility of the formation of endogenous nitrosamines in humans due to dermal penetration. After evaluation of previous and new data (including 2025 RLD), and in accordance with the product categories and concentrations of use identified in the Use section and Use table, the Panel issued a revised conclusion stating this ingredient is safe in cosmetics when formulated to be non-sensitizing, which may be determined based on a QRA or similar methodology.

The concern for possible sensitization stemmed from the results of an NACDG retrospective cross-sectional study determining the prevalence of wet wipes as a source of allergy during patch testing. In patients that had a positive patch, 0.9% had an allergic reaction to a wet wipe source, and the reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these patients was 27.4%. 2-Bromo-2-Nitropropane-1,3-Diol is reported to be used at a maximum concentration of 0.05% in disposable wipes.

The Panel acknowledged that the conclusion of the 1984 addendum included a statement regarding the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of *N*-nitrosamines in humans. However, upon further review and the lack of any supporting information, the Panel stated that it is highly unlikely that such endogenous formation would occur. Conversely, 2-Bromo-2-Nitropropane-1,3-Diol should not be used in cosmetic products in which *N*-nitroso compounds can be formed. Antioxidant use in formulations may reduce potential *N*-nitrosating activity *in situ*.

The Panel expressed concern about the inconsistency of some of the toxicological data, as the dermal LD_{50} value reported for 2-Bromo-2-Nitropropane-1,3-Diol was lower than the oral LD_{50} values. The observed severe acute dermal toxicity can be attributed to the corrosive effects of 2-Bromo-2-Nitropropane-1,3-Diol used in a high concentration, which may have compromised the barrier function and accelerated systemic toxicity. Also, the small sample size (2 rats per dose) also limits the reliability of this study. Thus, the observed lower dermal LD_{50} may not indicate higher systemic toxicity. The Panel also noted that this ingredient did not demonstrate developmental and reproductive toxicity. It was also observed that there was no carcinogenicity found in dermal (80-wk; mouse) or oral (2-yr; rats) studies.

Studies conducted with 2-Bromo-2-Nitropropane-1,3-Diol indicate that it can be a potential dermal and ocular irritant at high concentrations. However, the Panel noted that irritation was not observed at reported concentrations of use in cosmetics.

According to studies conducted by the EPA on 2-Bromo-2-Nitropropane-1,3-Diol, this chemical may release a minimal amount of formaldehyde upon hydrolysis due to its long half-life. Concern for this issue was mitigated by the fact that this ingredient is reported to be used at concentrations up to 0.05%, which is less than the 0.074% formaldehyde limit established by the Panel in its final safety assessment of formaldehyde that was published in 2013. Furthermore, the level is well below the threshold for toxicological concerns relating to this chemical, and as noted by the Panel, the effective formaldehyde concentration yielded by 2-Bromo-2-Nitropropane-1,3-Diol in formulation would be even lower.

Use in baby products has been reported, but concentration of use data were not available for certain baby product categories. When use in a baby product category is reported without an associated concentration, and an analogous adult product category with reported concentration data is available, the adult product concentration is considered informative for exposure characterization. Accordingly, concentrations in the corresponding baby product categories are not expected to exceed those reported for the analogous adult product categories. Thus, although no concentration of use is reported for 2-Bromo-2-Nitropropane-1,3-Diol in baby wipes, this ingredient is reported in disposable wipes at a maximum concentration of 0.05%, and concentrations in baby wipes are not expected to exceed this value. The category "other baby products" represents a miscellaneous grouping of reported uses not assigned to specific baby product subcategories; given its broad and non-specific nature, an analogous adult product category could not be identified, and the adult-product bridging is not applied.

Additionally, at least 1 use for the ingredient(s) reviewed in this assessment is reported in the RLD under Category 17, "other preparations." For instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17, and other information in the RLD is not indicative of use type, the present practices of use for such products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if this ingredient is used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that 2-Bromo-2-Nitropropane-1,3-Diol is safe in cosmetics when formulated to be non-sensitizing, which may be determined based on a QRA or similar methodology.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	Crystalline solid	[2]
Color	colorless-to-pale, brownish yellow	[2]
Odor	Odorless	[2]
Molecular Weight (Da)	200	[2]
Specific Gravity	1.9	[9]
Melting Point (ºC)	130	[9]
Flash Point (ºC)	167	[9]
Water Solubility (g/l @ 23ºC & pH)	Freely soluble	[2]
Other Solubility (g/l)	Soluble in ethanol, tetrahydrofuran and propylene glycol, slightly soluble in mineral oil and vegetable oils	[2]
log P_{ow}	0.18	[9]
UV Absorption (λ; nm; 0.1 M NaOH)	244	[5]

Table 2. Frequency and concentration of use of 2-Bromo-2-Nitropropane-1,3-Diol according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use
	RLD (2025)[15,16]	% (2025)[17]
Totals*	**572**	**0.04-0.05**
summarized by likely duration and exposure**		
Duration of Use		
Leave-On	*413*	*0.04 – 0.05*
Rinse-Off	*202*	*NR*
Diluted for (Bath) Use	*6*	*NR*
Unknown	*4*	*NR*
Exposure Type		
Baby Products	6	NR
Children's Makeup	NR	NR
Eye Area	3	NR
Incidental Ingestion	NR	NR
Mucous Membrane	282	0.04 – 0.05
Incidental Inhalation-Spray	2; 48[a]; 200[b]	NR
Incidental Inhalation-Airbrush	NR	NR
Incidental Inhalation-Powder	200[b]	NR
Dermal Contact	859	0.04 – 0.05
Deodorant (underarm)	1	NR
Hair - Non-Coloring	147	NR
Hair-Coloring	NR	NR
Nail	20	NR
Other Preparations (Unknown Exposure Type)	4	NR
as reported by product category		
Baby Products		
Baby Shampoos	1	NR
Baby Wipes	5	NR
Bath Preparations		
Bath Oils, Tablets, and Salts	3	NR
Other Bath Preparations	3	NR
Eye Makeup Preparations (other than children's eye makeup preparations)		
Eyeliner	2	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	1	NR
Hair Preparations (non-coloring)		
Hair Conditioners	4 (l.o.); 4 (r.o.)	NR
Hair Sprays (aerosol fixatives)	2	NR
Permanent Waves	3	NR
Shampoos (non-coloring)	7 (r.o.)	NR
Tonics, Dressings, and Other Hair Grooming Aids	45	NR
Wave Sets	7	NR
Other Hair Preparations	73 (l.o.); 1 (r.o.)	NR
Makeup Preparations (not eye; not children's)		
Leg and Body Paints	1 (traditional application)	NR
Manicuring Preparations		
Basecoats and Undercoats	1	NR
Cuticle Softeners	1	NR
Nail Creams and Lotions	2	NR
Nail Extenders	1	NR
Nail Polishes and Enamels	5	NR

Table 2. Frequency and concentration of use of 2-Bromo-2-Nitropropane-1,3-Diol according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use
	RLD (2025)[15,16]	% (2025)[17]
Nail Polish and Enamel Removers	1	NR
Other Manicuring Preparations	9	NR
Personal Cleanliness		
Bath Soaps and Body Washes	22	NR
Deodorants (underarm)	1	NR
Douches	4	NR
Disposable Wipes	143	0.04 - 0.05
Other Personal Cleanliness Products	20 (l.o.); 82 (r.o.)	NR
Shaving Preparations		
Beard Softeners	1	NR
Pre-shave lotions (all types)	1	NR
Shaving Creams (aerosol, brushless, and lather)	1	NR
Shaving Soaps (cakes, sticks, etc.)	1	NR
Other Shaving Preparation Products	8	NR
Skin Care Preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	27	NR
Face and Neck (excluding shaving preparations)	26 (l.o.); 7 (r.o.)	NR
Body and Hand (excluding shaving preparations)	37 (l.o.); 7 (r.o.)	NR
Moisturizing	22	NR
Paste Masks (mud packs)	7	NR
Skin Fresheners	1	NR
Other Skin Care Preparations	1 (l.o.); 2 (r.o.)	NR
Other Preparations (i.e., those preparations that do not fit another category)	4	NR

NR – not reported

l.o. – leave-on; r.o. – rinse-off

* The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.

**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

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

Table 3. Genotoxicity studies with 2-Bromo-2-Nitropropane-1,3-Diol

Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
			IN VITRO		
			Gene Mutation		
water	0 - 166 µg/plate	*S. typhimurium* TA100, TA1535, TA97, and TA98	Ames test	not mutagenic with or without metabolic activation	23
water	determined via cytotoxicity (not specified)	*S. typhimurium* TA1535, TA1537, TA98 and TA100 *E. coli* WP2 uvrA	Ames test (OECD TG 471), with and without metabolic activation; appropriate negative and positive controls were used	not mutagenic with or without metabolic activation	6
deionized water	3 - 27 µg/ml with and 1 – 21 µg/ml without metabolic activation	Chinese hamster lung fibroblast (V79) cells	in vitro mammalian cell gene mutation assay (OECD TG 476), with and without metabolic activation; appropriate negative and positive controls were used	genotoxic; induced a reproducible increase of mutant frequency without metabolic activation with 6 – 15 µg/ml, while the statistically significant increase of mutant frequency observed with metabolic activation at 6 – 18 µg/ml, was not reproducible clear cytotoxic effects were induced at ≥ 18 µg/ml with and ≥ 15 µg/ml without activation	6
			Chromosomal Damage		
distilled water	30 µg/ml (max concentration allowed by cytotoxicity)	human lymphocytes	in vitro mammalian chromosome aberration assay (largely in accord with OECD TG 473) performed with and without metabolic activation; vehicle and appropriate positive controls were used	weak but reproducible clastogenic effect was seen without, but not with, metabolic activation; researchers suggested that the observed clastogenic effect might have been due to formaldehyde liberated from the degradation of 2-Bromo-2-Nitropropane-1,3-Diol, and not from 2-Bromo-2-Nitropropane-1,3-Diol itself	6
water	determined via cytotoxicity (not specified)	mouse lymphoma L5178Y cells	in vitro mammalian cell micronucleus test (OECD TG 487) performed with and without metabolic activation; vehicle (negative control) and appropriate positive controls were used	not genotoxic with or without metabolic activation	6

Table 4. Clinical studies with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet)

Years	# patients	Study Details	Results	Reference
		Retrospective Studies		
1984-2014	54,348	Examined NACDG patch test records to analyze reaction trends over time; 13 evaluable records	positivity decreased between 1984 and 2014; - 0.6% change positive reactions, 1984 – 2.6%; positive reactions, 2014 – 2%	25
1994-2006	26,948	NACDG; PR (percentage of + (weak) reactions among the sum of all positive reactions (+, ++, +++)) and RI (number of positive reactions minus questionable and irritant reactions divided by the sum of all 3) were determined to evaluate proportion of weak, irritant, and questionable reactions	PR was considered "problematic," indicating a high proportion of weak, irritant, and questionable reactions PR – 73.5% RI – 0.45 + only reactions – 2.0%; +, ++, and +++ reactions – 2.8% allergic reactions, minus irritant or questionable reactions – 1.7%; allergic reactions, with irritant or questionable reactions – 3.8%	26
1994-2013	2111 with AD 342 without AD	Examined NACDG patch test records to compare the rates of positive patch test reactions among patients with and without AD; 2 clinics	positive reactions for patients with atopic eczema – 4.7% positive reactions for patients without atopic eczema – 2.0%	27
1994-2016	50,623	retrospective cross-sectional analysis of NACDG patch testing results	linear regression model reported decreasing trend in positive reactions (-0.33%, p = 0.024) positive reactions, 1994-2016: 2.5% second read code: 24.2% ±; 52.0% +; 17.1% ++; 5.2% +++ relevance: definite – 1.7%; probable – 35.8%; possible – 46.3%	28

Table 4. Clinical studies with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet)

Years	# patients	Study Details	Results	Reference
2001-2002	4897	NACDG; 48-h patches	positive reactions – 3.3%; irritant reactions – 0.3% relevance: definite – 0.6%; probable –13.2%; possible – 56.9%	[29]
2001 2004	see Results column	analysis of positive patch test reactions in NACDG testing associated with a cosmetic source (2-Bromo-2-Nitropropane-1,3-Diol was one of the top 20 NACDG standard screening allergens associated with cosmetic source in males, but not in females, so only data for males is included here) reactions for the category 'cosmetics, not otherwise specified' reactions for the category 'moisturizer source'	29 reactions % with allergy to cosmetic source – 4.8% (n = 611 males) % reactions associated with cosmetic source – 2.3% (n = 1286 males) (not specified for females because it is not one of the top 20 NACDG standard screening allergens associated with cosmetic source) <u>Females</u> – 41 reactions % patients – 3.8% (n = 1072) % reactions – 2.1% (n = 2003) <u>Males</u> – 28 reactions % patients – 6.0% (n = 1072) % reactions – 2.7% (n = 1025) <u>Females</u> – 18 reactions % patients – 3.4% (n = 5292) % reactions – 1.9% (n = 946) <u>Males</u> – 20 reactions % patients – 6.5% (n = 529) % reactions – 2.9% (n = 946)	[30]
2001-2004	1493	retrospective cross-sectional analysis of NACDG data, comparing patients with SGD to those without SGD.	<u>patients with SGD</u> positive reactions – 4.8% relevance: definite –0%; probable 8.3%; possible – 47.2% It was found that patients with SGD had statistically significant more relevant responses	[31]
2003-2004	5140	NACDG; 13 test centers; 48-h patches	positive reactions – 2.3%	[32]
2005-2006	4435	NACDG; 13 test centers; 48-h patches	positive reactions: 3.4%; one of the top 20 allergens in the series for the first time relevance: definite – 2.0%; probable 17.2%; possible – 47%	[33]
2006-2010	2142	Mayo Clinic; 3 clinical sites; 48-h patches	allergic reactions – 2.5% reaction grades: macular erythema – 35.6%; weak – 56.6%, strong – 5.7%, extreme – 1.9% irritant reactions – 0.8% relevance: allergic, relevant – 30.2%; allergic, not relevant - 0%; allergic, questionably relevant – 69.8%	[34]
2007-2008	5081	NACDG; 13 test centers; 48-h patches	positive reactions: 3.1% relevance: definite – 0.6%; probable – 12.5%; possible – 53.8% SPIN - 83	[35]
2011-2012	4231	NACDG; 12 test centers; 48-h patches	positive reactions: 1.6% second read code: 4.5% ±; 35.8% +; 32.8% ++; 19.4% +++ relevance: definite – 4.5%; probable – 35.8%; possible – 46.3% SPIN - 69	[36]
2013-2014	4859	NACDG; 13 test centers; 48-h patches	positive reactions: 2.1% second read code: 5.0% ±; 57.4% +; 26.7% ++; 10.9% +++ relevance: definite – 5.0%; probable – 22.8%; possible – 60.4% SPIN - 84	[37]
2015-2016	5593	NACDG; 13 test centers; 48-h patches	positive reactions: 1.3% second read code: 9.6% ±; 53.4% +; 30.1% ++; 6.8% +++ relevance: definite – 0%; probable – 13.7%; possible – 60.3% SPIN - 38	[38]

Table 4. Clinical studies with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet)

Years	# patients	Study Details	Results	Reference
2017-2018	4938	NACDG; 14 test centers; 48-h patches	positive reactions: 1.5% final reading grade: 4.1% ±; 64.0% +; 26.0% ++; 5.5% +++ relevance: definite – 1.4%; probable – 11.0%; possible – 53.4% SPIN - 39	[39]
2017-2021	2688	Mayo Clinic; 3 clinical sites; 48-h patches	allergic reactions – 4% reaction grades: weak - 3.3%, strong - 0.6%%, extreme – 0.1% irritant reactions – 0.9%	[40]
2019-2020	4117	NACDG; 13 test centers; 48-h patches	positive reactions: 2.1% final reading grade: 12.8% ±; 59.3% +; 16.3% ++; 11.6% +++ relevance: definite – 1.2%; probable – 4.7%; possible – 73.3% SPIN - 60	[41]
2019-2021	748	Clinical trial conducted to evaluate allergens for inclusion in the EBS baseline series; single center study; 48-h patch	positive reactions – 2.7% ICDRG scoring of positive reactions: 0.7% ?+; 70% +; 25% ++, 5% +++ irritant reactions – 0.1% 11.9% of patients with patch test reactivity to formaldehyde co-reacted with 2-Bromo-2-Nitropropane-1,3-Diol 25% of patients with of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde	[42]
2021-2022	3052	NACDG; 12 test centers; 48-h patches	positive reactions: 2.7% final reading grade: 4.9% ±; 64.2% +; 24.7% ++; 4.9% +++ relevance: definite – 1.2%; probable – 2.5%; possible – 40.7% SPIN - 43	[43]
Results for Specific Patient Subgroups				
1994-2014	2611; 165 were health care workers	only patients with suspected ACD were evaluated; 2 clinics	relevant positive reactions in healthcare workers – 3.0% relevant positive reactions in non- healthcare workers – 1.3%	[44]
2011-2020	148 Black patients	Mayo Clinic; 3 clinical sites; 48-h patches	positive reactions – 4.7%	[45]
2010-2022	18 solid organ transplant recipients	retrospective analysis of patch test data from adult transplant recipients; 20 tests performed Mayo Clinic; 3 clinical sites; 48-h patches were scored at 48 – 72 h and from 96 – 168 h	positive reactions – 5% (1 liver transplant patient using the immunosuppressant tacrolimus)	[46]
Pediatric Test Groups				
2012-2015	116 (ages 6 - 17 yr)	(concentration of 2-Bromo-2-Nitropropane-1,3-Diol not stated) TRUE test; multicenter study; suspected ACD 48-h patches; readings at 48, 72, and 96 h and at 1 and 3 wk	positive reactions – 17.1%	[47]
2016-2020	89 (ages 1 -18 yr)	Retrospective analysis of patch test data Mayo Clinic; 3 clinical sites; 48-h patches	positive reaction rate – 7.9% relevant positive reaction rate – 3.4%	[48]
2019-2023	13 (0 - 5 yr) 139 (6 - 16 yr)	Prospective multicenter study based on the REIDAC registry; patients were patch-tested according to ESCD guidelines with the GEIDAC baseline and extended series	positive reaction rate: 0 – 5 yr - 0% 6-16 yr - 1.44%	[49]
Studies with Wet Wipes				
2011-2014	9037 patients	NACDG retrospective cross-sectional study to determine the prevalence of wet wipes as a source of allergy during patch testing.	0.9% of patients with a positive patch test had an allergic reaction to a wet wipe source. reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these subjects - 27.4% relevance: definite – 3%; probable – 11%; possible – 6%	[50]

Table 4. Clinical studies with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet)

Years	# patients	Study Details	Results	Reference
Co-Reactivity with Formaldehyde				
2005-2009	2-Bromo-2-Nitropropane-1,3-Diol, 1192 formaldehyde, 7838	6 Spanish hospitals; examined co-reactivity between 2-Bromo-2-Nitropropane-1,3-Diol and formaldehyde	Among the 2 patients allergic to 2-Bromo-2-Nitropropane-1,3-Diol, one was also allergic to formaldehyde Among the 135 patients allergic to formaldehyde, one (0.74%) was also allergic to 2-Bromo-2-Nitropropane-1,3-Diol	[51]
2015-2018	8139	Retrospective multicenter study examining sensitization to 2-Bromo-2-Nitropropane-1,3-Diol (0.5% pet) and co-reactivity to 2% aq. formaldehyde	2-Bromo-2-Nitropropane-1,3-Diol had a sensitization prevalence of 0.49% Very little co-reactivity with formaldehyde: 96.3% of the reactions to 2-Bromo-2-Nitropropane-1,3-Diol were isolated reactions	[52]
2019-2021	748	Single-center study described above evaluating allergens for inclusion in the EBS baseline series; 48-h patch	11.9% of patients with patch test reactivity to formaldehyde co-reacted with 2-Bromo-2-Nitropropane-1,3-Diol 25% of patients with of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde	[42]

Abbreviations: ACD – allergic contact dermatitis; AD – atopic dermatitis: EBS – European baseline series; ESCD - European Society of Contact Dermatitis; GEIDAC - Grupo Español de Investigación de Dermatitis de Contacto y Alergia Cutánea; ICDRG - International Contact Dermatitis Research Group; NACDG – North American Contact Dermatitis Group; PR – positivity ratio; REIDAC - Spanish Contact Dermatitis Research Group; RI – reaction index; SGD - scattered generalized distribution; SPIN - significance-prevalence index number; TRUE - thin-layer rapid use epicutaneous

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FINAL REPORT OF THE SAFETY ASSESSMENT FOR 2-BROMO-2-NITROPROPANE-1,3-DIOL

2-Bromo-2-Nitropropane-1,3-Diol (BNPD) is used in cosmetics as an antibacterial agent. Data presented indicate that BNPD produces minimal contact allergy and/or contact irritation in both animals and humans at concentrations below 0.1%. Unformulated BNPD in concentrations of 1% or greater has been shown to be a considerable irritant. BNPD is moderately toxic orally in a variety of laboratory mammals, the LD50 varying with the test circumstances.

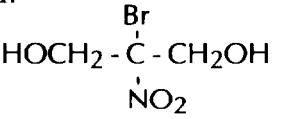
BNPD had no effect on reproduction, was not a teratogen, and had no embryotoxic effects. It was not a mutagen by the standard mouse dominant lethal test nor by the bacterial reverse mutant system.

The evidence at hand indicates that BNPD to be safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides.

CHEMICAL AND PHYSICAL PROPERTIES

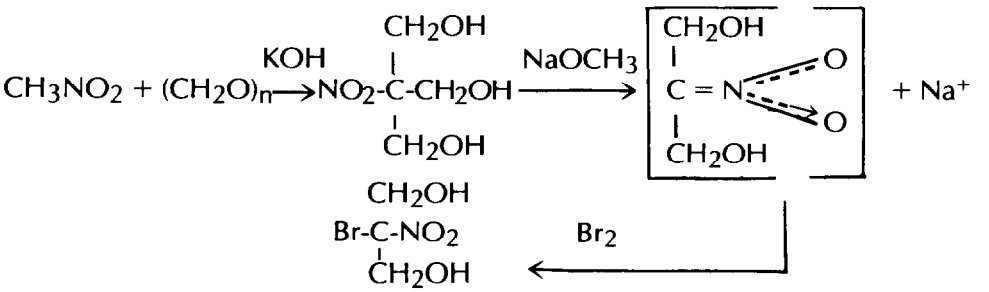
Structure

2-Bromo-2-Nitropropane-1,3-Diol (BNPD) is a substituted aliphatic diol that conforms to the formula:



BNPD is one of a family of halo-nitro compounds which have been found to inhibit the growth of bacteria, fungi, and yeasts. In a large group of aliphatic nitro compounds tested for antimicrobial properties, the most active appear to be alcohols containing a -$CBrNO_2$- group (Bowman and Stretton, 1972; Clark *et al.*, 1974; Clausen, 1973; Croshaw *et al.*, 1964).

The published method of manufacture is as follows (CTFA, 1972a):



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Physical Properties

BNPD is a colorless-to-pale, brownish yellow, odorless crystalline solid which is soluble in water, alcohol, tetrahydrofuran and propylene glycol. It is slightly soluble in mineral oil and vegetable oils. The distribution coefficient of water: chloroform is 14.7:1 at 22-29°C. Its melting point is approximately 130°C (CTFA, 1972a; Marzulli and Maibach, 1973; Fan *et al.*, 1978).

Reactivity

In solid form BNPD is stable for at least one year at temperatures up to 45°C and at relative humidities up to 90% with no observable photodecomposition. Also, BNPD does not decompose during storage at room temperature in darkness up to two years. Freshly prepared aqueous solutions of BNPD are weakly acidic (pH 5.1-5.5) and upon storage and heating become more acidic with the liberation of formaldehyde. The decomposition of BNPD is accelerated with increasing pH and with increasing temperature of the solutions. Half lives of 0.2% w/v solutions of BNPD were determined to be >5 years at pH 4, 1.5 years at pH 6, and two months at pH 8. Major decomposition products were formaldehyde, 2-hydroxymethyl-2-nitro-1,3-propanediol and bromonitroethanol (Marzulli and Maibach, 1973; Sheppard and Wilson, 1974; Bryce *et al.*, 1978).

A solution of BNPD in tetrahydrofuran with morpholine produces N-nitroso-morpholine. In aqueous solution and in the presence of diethanolamine and triethanolamine, BNPD serves as a nitrosating agent leading to formation of N-nitrosodiethanolamine. In a 5mM aqueous solution, the pH of diethanolamine plus BNPD is initially 11.5-12.0. After one hour, 0.06% of diethanolamine is N-nitrosated; after six hours, 1% has reacted; after 24 hours, 2.2% has reacted; and after 72 hours, 10.3% is N-nitrosated. During this reaction time, the pH decreases to 8.1, 6.0, and 5.2, respectively. With decreasing pH the N-nitrosating activity of BNPD decreases: in solution at pH 4, virtually no N-nitrosation of diethanolamine occurs even after 190 hours. In a solution of equimolar amounts of BNPD and triethanolamine, 0.05% of the tertiary amine is nitrosated to N-nitrosodiethanolamine (NDELA) after 24 hours (Fan *et al.*, 1978; Schmeltz and Wenger, In press).

It has been suggested that BNPD oxidizes sensitive thiol groups of enzymes (Bowman and Stretton, 1972; Clark *et al.*, 1974; Stretton and Manson, 1973).

Analytical Methods

The recent advances in analytical chemistry, which now provide sensitive and specific methods for BNPD and its decomposition products, have been reviewed elsewhere and are only briefly summarized here. BNPD, as a raw material or as extracted from a formulation, can be specifically determined by gas-liquid chromatography of trimethylsilylated or acetylated material with detection by electron capture or flame-ionization. Sensitivity is 5 ppm or more in aqueous formulations. Polarography may also be applied to aqueous

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systems containing BNPD, but calibration curves must be prepared for each system. This detects the alkyl nitro group and is thus subject to interference by degradation products. Its precision is approximately ± 2%. Thin layer chromatography is more specific but its relative errors may be as high as 15%. Microbiological assay in agar diffusion plates may be sensitive to as little as 0.005% but is non-specific (Bryce *et al.*, 1978).

Analyses of BNPD decomposition products, bromide ion, formaldehyde, and nitrate/nitrite are useful. Bromide is titrated potentiometrically in an acidic solution with silver nitrate. Formaldehyde reacts with chromotropic acid in strong sulfuric acid and the absorbance of the product may be measured at 570 nm. Nitrate and nitrite may be dtermined by reaction with 2,6-xylenol. High pressure liquid chromatography has recently been reported as having a limit of detection for BNPD of 3 μg per μl injected. The standard methods of the cosmetic industry for BNPD analysis are based on gas-liquid chromatography of the acetylated sample and titration of bromide (CTFA, 1972a; Bryce *et al.*, 1978; Schmeltz and Wenger, In press).

USE

Purpose and Extent of Use in Cosmetics

BNPD as a preservative is used in cosmetics and in pharmaceutical preparations because of its antibacterial and antifungal properties. It is effective against both gram-negative and gram-positive organisms (Bowman and Stretton, 1972; Clark *et al.*, 1974; Clausen, 1973; Croshaw *et al.*, 1964).

In the United States, BNPD is used as a preservative for a wide variety of cosmetics, especially shampoos, creams, lotions, rinses, and eye makeup. The number of product formulations containing BNPD and the concentrations of BNPD used in each of the several cosmetic categories are listed in Table 1.

Potential Interactions With Other Ingredients

It has been suggested (FDA, 1978a, b; Boots Co., 1978a, 1979; WHO: IARC, 1978) that BNPD might be a source of nitrosating agents which could react with amines or amides in cosmetics (Fan *et al.*, 1978; Bryce *et al.*, 1978; Schmeltz and Wenger, In press; FDA, 1978a; Boots Co., 1978a). An on-going study by FDA has provided initial and incomplete information on 191 off-the-shelf cosmetic formulations regarding their content of N-Nitrosodiethanolamine (NDELA), BNPD, and triethanolamine or its salts (TEA). Table 2 displays data on NDELA obtained by analyses at FDA.

These results give the following comparison details which are shown below:

1. Seventy-seven of the 191 samples analyzed contained NDELA. Of the 77 samples containing NDELA, 19 contained both BNPD and TEA, 1 contained BNPD but no TEA, 47 contained TEA but no BNPD, 5 had neither BNPD nor TEA, and 5 had incomplete or no ingredient information. Of these groups of 77 cosmetic product samples, 17 were found to contain

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TABLE 1. Product Formulation Data (FDA, 1976)

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product formulations
2-Bromo-2-Nitropropane-1, 3-Diol	Bath oils, tablets, and salts	≤ 0.1	1
	Bubble baths	≤ 0.1	4
	Other bath preparations	≤ 0.1	5
	Eyebrow pencil	≤ 0.1	14
	Eyeliner	≤ 0.1	11
	Eye shadow	≤ 0.1	3
	Mascara	≤ 0.1	6
	Other makeup preparations	≤ 0.1	2
	Other fragrance preparations	> 0.1 to 1	2
	Hair conditioners	> 0.1 to 1	2
		≤ 0.1	20
	Rinses (noncoloring)	> 0.1 to 1	3
		≤ 0.1	3
	Shampoos (noncoloring)	≤ 0.1	9
	Tonics, dressings, and other hair grooming aids	> 0.1 to 1	1
		≤ 0.1	2
	Wave sets	≤ 0.1	1
	Other hair preparations	≤ 0.1	1
	Hair dyes and colors (all types requiring caution statement and patch test)	> 0.1 to 1	3
	Hair shampoos (coloring)	≤ 0.1	6
	Blushers (all types)	≤0.1	20
	Foundations	≤ 0.1	6
	Leg and body paints	≤ 0.1	2
	Makeup bases	≤ 0.1	3
	Makeup fixatives	≤ 0.1	134
	Other makeup preparations	≤ 0.1	1
	Bath soaps and detergents	≤ 0.1	1
	Deodorants (underarm)	≤ 0.1	2
	Aftershave lotions	≤ 0.1	1
	Cleansing (cold creams, cleansing lotions, liquids, and pads)	≤ 0.1	17
	Face, body, and hand (excluding shaving preparations)	>0.1 to 1	3
	Moisturizing	≤ 0.1	9
	Night	≤ 0.1	3
	Paste masks (mud packs)	≤ 0.1	8
	Skin fresheners	≤ 0.1	3
	Other skin care preparations	≤ 0.1	6
	Suntan gels, creams, and liquids	> 0.1 to 1	2
		≤ 0.1	1
	Indoor tanning preparations	≤ 0.1	1
	Other suntan preparations	≤ 0.1	1

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NDELA at levels above 2000 ppb, 43 were found to contain NDELA at levels between 30 ppb and 2000 ppb, and 17 samples were found to contain NDELA at trace levels (10 to 30 ppb).

2. One hundred fourteen of the 191 samples analyzed contained no NDELA. Of these 114 samples, 4 contained both BNPD and TEA, 2 contained BNPD but not TEA, 81 contained TEA but not BNPD, 16 had neither BNPD nor TEA, and 11 had incomplete or no ingredient information.

FDA reported a change in sensitivity number during the analytical program between 10 ppb and 30 ppb. Values in this range are considered trace values. All negative values are below 10 ppb.

These findings suggest the possibility that the presence of BNPD and/or TEA in some cosmetics may lead to the formation of NDELA but not necessarily in all formulations. Further investigation is needed to clarify what relationship, if any, these ingredients have to the presence of NDELA in some but not all cosmetics containing them.

FDA studies have demonstrated that NDELA is absorbed through excised human skin with a permeability constant of 0.50×10^{-5} cm/hr (FDA, 1978b).

NDELA and other nitrosamines and nitrosamides are known to have varying degrees of potency as carcinogens in animals. Up to the present time, neither group of compounds has been shown to cause cancer in humans (WHO: IARC, 1978; Magee *et al.*, 1976).

TABLE 2. Association of NDELA With Certain Ingredients in Cosmetics Analyzed by FDA (1978a).

Cosmetic Product Samples Reported to Contain	NDELA	No NDELA Detected
BNPD + TEA	19	4
BNPD	1	2
TEA	47	81
Samples Containing neither BNPD or TEA	5	16
Samples with incomplete or no ingredient information	5	11
Total results reported by FDA	77	114

Surfaces To Which Commonly Applied

As implied in Table 1, BNPD is used in formulations applied to all areas of the human integument and is in contact with many, or in close proximity to all, body orifices. Some are used near sensitive and absorptive tissues (eyelids or ocular mucosa) and in proximity to mucous membranes. Formulations containing BNPD may be applied several times a day and may remain in contact with the skin for hours, e.g., in makeup (FDA, 1976).

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BIOLOGICAL PROPERTIES

General Effects

BNPD is used as a preservative in a variety of cosmetic products which are applied to the skin. It has been suggested this is due to its oxidation of sulfhydryl groups in critical enzymes of the micro-organisms. In concentrations of 1% or more it is an irritant, and human test results show that BNPD has a significant potential for sensitization (Bowman and Stretton, 1972; Clark *et al.*, 1974; Marzulli and Maibach, 1973; Stretton and Manson, 1973).

Absorption, Metabolism, and Excretion

Percutaneous absorption is generally low (11% in 24 hours) for aqueous solutions of 4 mg/ml applied to the skin of rats and rabbits. The rate of absorption remains low even when the material is applied beneath an occlusive dressing. Absorption can be enhanced by using acetone rather than water as a vehicle. Absorption appears to occur by way of hair follicles. Absorption, metabolism and excretion of the compound have been studied using BNPD 2-^{14}C administered topically and orally, and BNPD-1,3 ^{14}C intravenously. Elimination in the urine of 60-80% of the dose given to rabbits intravenously occurs within 24 hours. Rats excrete 80.9% of an oral dose in the urine within 24 hours. Approximately 8.4% of the ^{14}C is eliminated in the expired air. Plasma concentrations after oral doses peaked at 2.5 to 9.0% of the total dose in two species within about two hours (in tests using small numbers of animals) (Moore *et al.*, 1976a, b; Naito *et al.*, 1974).

Distribution (as seen by whole body autoradiography) is fairly even among body organs with somewhat higher concentrations in the kidney and lower concentrations in fatty tissues (Moore *et al.*, 1976b).

Metabolic breakdown includes reductive dehalogenation resulting in 2-nitropropane-1,3diol. This in turn, may be further metabolized to glycerol and eventually CO_2 (Moore *et al.*, 1976b).

Animal Toxicology

General Studies

Acute Toxicity

Oral BNPD administered orally to rats and mice in varying doses caused gastrointestinal lesions and indicated the following LD50 values (Bryce *et al.*, 1978):

	Mouse	Rat
Male	374 mg/kg	307 mg/kg
Female	327 mg/kg	342 mg/kg

Another study established the oral LD50 of BNPD to be 180 mg/kg in rats, 270 mg/kg in mice, and 250 mg/kg in dogs (Frear, Ed., 1969); sex of the animals was not reported.

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Administered orally as a solution containing 30 mg/ml in distilled water at five doses ranging from 150-525 mg/kg to ten rats at each dose, BNPD had an LD50 of 292 ± 31.9 mg/kg, while another sample of BNPD had an LD50 of 320 ± 26.3 mg/kg (CTFA, 1972b).

For aqueous solutions, the oral LD50 for mice was reported to be 350 mg/kg and for rats 400 mg/kg (Croshaw *et al.*, 1964).

An additional study found the oral LD50 to be 193 mg/kg in rats given oral doses of 182-205 mg/kg. Symptoms observed at four hours included decreased motor activity and respiratory rates (CTFA, ET42B).

Single doses of 40 or 100 mg/kg of BNPD in dogs caused transient gastric irritation. No methemoglobinemia occurred in cats given single oral doses of 25 mg/kg of BNPD, although 20 mg/kg acetanilide produced a marked increase in the percentage of methemoglobin present (Bryce *et al.*, 1978).

Intraperitoneal Intraperitoneal administration of BNPD in single doses allowed calculations of LD50s as follows:

	Mouse	Rat
Male	34.7 mg/kg	22.0 mg/kg
Female	32.8 mg/kg	30.2 mg/kg

Some of the injections led to peritonitis (Bryce *et al.*, 1978).

For aqueous solutions, the intraperitoneal LD50 in mice was reported to be 20 mg/kg (Croshaw *et al.*, 1964).

Subcutaneous injections of BNPD in rats produced hemorrhage at the injection sites, lesions in the stomach, edema and congestion of the lungs. The subcutaneous LD50 was approximately 200 mg/kg (Bryce *et al.*, 1978).

Skin Irritation Holding 0.5 g of dry BNPD in contact with the moistened, abraded and unabraded skin of rabbits for 24 hours resulted in a primary irritation score of 0.75 out of a maximum possible score of 8. Erythema occurred only on abraded skin. In the Federal Hazardous Substance Act procedure, scores of less than 5 indicate that the test material is not a primary irritant. A dose of 0.4 ml of a 20% aqueous solution of BNPD applied to abraded and non-abraded skin of rabbits gave a score of 6.75/8.0 and should be considered moderately to severely irritating (CTFA, 1973a; BS147B)

BNPD in 0.5 and 2% emulsions and solutions was tested on rabbit skin. At 2%, irritation was produced from one application; whereas, no irritation was produced from four daily applications of 0.5% concentrations (Croshaw *et al.*, 1964).

When applied to non-abraded, shaved skin of rabbits in a variety of solvents, BNPD's level of irritancy depended on the vehicle. Acetone solutions were nonirritating on single occluded application at 1%, while repeated application of 0.5% was highly irritating when not occluded. BNPD at 0.5% in aqueous methylcellulose gave similar results. In Polyethylene Glycol 300, a 5% concentration of BNPD was nonirritating on single occluded application. A single application of a 2% emulsion caused skin irritation but a 0.5% emulsion applied on four successive days did not (Bryce *et al.*, 1978).

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Eye Irritation BNPD in amounts of 106 mg (apparently as the crystalline material) in the eyes of rabbits caused immediate irritation of the conjuctiva and delayed effects on the cornea and iris. These later effects were noted on the fourth day and remained on the last day of observation (seventh day). Scores, according to the Draize scale, on the seventh day were maximum in all but two of six unwashed eyes. Washing with water five minutes after the compound was allowed to contact the eye for five minutes did not modify the damage produced (CTFA, 1973b).

A 0.1 ml dose of a 10 or 20% aqueous solution of BNPD placed in the conjunctival sac of a rabbit's eye produced severe ocular damage. Washing four seconds after the application of the 20% solution reduced the reaction somewhat. Complete clearing of the damage required as many as 35 days in the unwashed eye and as many as 14 in the washed eye. When 3 mg of the solid compound was placed in the eye, damage was severe and clearing again required 35 days. Washing reduced recovery time to 14 days in one test and 21 in another (CTFA, BS147B, ET26B).

Two percent BNPD in solution and in emulsion was reported to be irritating to the rabbit eye. However, four daily applications of 0.5% solution and emulsion reportedly was not irritating (Croshaw *et al.*, 1964).

BNPD was also tested as a 0.5% solution in 1N saline and was found to be nonirritating when applied daily for four successive days to the eyes of rabbits. A solution of 5% in Polyethylene Glycol 400 was irritating on single application, but 2 percent under the same conditions was not (Bryce *et al.*, 1978).

Inhalation The approximate four-hour LC50 of BNPD was 0.18 mg/1 when administered by inhalation to 10 male and 10 female rats per exposure concentration. Survivors were described as having "rather severe" irritation of the ears and paws. This could have been increased redness resulting from increased blood flow and may have been an indication of a systemic effect rather than of skin irritation of exogenous origin. Survivors showed reduced body weight gain in the two weeks following exposure to 0.17 mg/l or greater, indicating some systemic effect (CTFA, BS147B).

Percutaneous Dermal applications of an acetone solution of BNPD to rats caused death at 160 mg/kg or more (Bryce *et al.*, 1978).

Subchronic Toxicity

Oral Studies of BNPD administered by oral intubation to rats showed that daily doses of 20 mg/kg for 90 days were tolerated well. At 80 and 160 mg/kg, respiratory distress, gastrointestinal lesions, and some deaths occurred. Rats given BNPD in drinking water for six weeks had reduced water intake and slightly enlarged kidneys at 160 mg/kg/day. Some deaths occurred when the dose level was 300 mg/kg/day. Dogs given 20 mg/kg/day by oral intubation for 90 days showed no significant toxic reaction, except for some vomiting (Bryce *et al.*, 1978; Boots Co.,1978a).

Male and female albino rats, 5-6 weeks of age, were fed 100 and 1000 ppm in the diet for 12 weeks without apparent effect on growth, food consumption, blood, liver, and kidney weight or histopathologic changes in the major organs (Croshaw *et al.*, 1964).

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Skin Irritation BNPD as a 0.2 or 0.5% solution in aqueous 2.5% methylcellulose was applied to rabbits once daily in doses of 1 ml/kg for three weeks. It was applied to the intact and abraded clipped skin of the back. The abrasions penetrated the stratum corneum but did not disturb the derma. The 0.5% solution produced moderate edema, erythema, and eschar formation, while the 0.2% solution produced local erythema. The vehicle alone produced an effect similar to the 0.2% BNPD (Bryce *et al.*, 1978).

Skin Sensitization A guinea pig sensitization test was conducted using a combination of intradermal injections and topical applications following the Magnusson and Kligman procedure in which two intradermal injections of 0.02% BNPD in normal saline were given in the shoulder region. This was followed by two injections of 0.02% in 50:50 Complete Freunds Adjuvant (CFA): normal saline after which another two injections of 50:50 CFA:saline were given. Seven days later a booster application was given on the same site by an occluded patch of 1.5% BNPD in water which was left in place for 48 hours. Fourteen days later an occluded challenge patch of 0.4% in water was applied to the flank for 24 hours. Skin reactions at the challenge sites were observed at 24 and 48 hours after removal of the flank patches. The challenges and observations were repeated for a total of four applications. Two of the ten guinea pigs became sensitized after three challenges. A comment in the report stated, "In the Magnusson and Kligman test, sensitization is normally assessed after one challenge. At this stage in the present test there is no sensitization." It was concluded that BNPD was a weak sensitizer by this method of testing. Formaldehyde, a decomposition product of BNPD, which was also applied at 0.2% during the fourth challenge, was found not to be responsible for the sensitization in guinea pigs (Boots Co., 1978b).

Intradermal injections of a 0.05% aqueous solution of BNPD were given to guinea pigs on alternate days for a total of 10 injections. The first dose was 0.1 ml and the others were 0.05 ml. The challenge dose, 0.05 ml of 0.05%, given two weeks later produced no evidence of skin sensitization (Croshaw *et al.*, 1964). In another test using a 1% solution in acetone, BNPD failed to sensitize guinea pigs by the ear-flank method of Stevens (Bryce *et al.*, 1978).

Special Studies

Reproduction and Teratogenicity Studies

Rats given 10, 30, or 100 mg/kg daily by oral intubation during days 1 to 20 of pregnancy showed no embryotoxic or teratogenic effects. Some dams had a dose-related retardation in weight gain, and some died from pulmonary and gastric lesions. At the highest dose level, a slight delay in the calcification of the fetal skeleton was noted. Doses of 1, 3.3, and 10 mg/kg administered orally to rabbits from day 8 to 16 of pregnancy did not induce embryotoxic or teratogenic effects; however, the 10 mg/kg dose suppressed the weight gain of the does (Bryce *et al.*, 1978).

There was no effect on parturition, litter size, postnatal survival or development of the young in rats given 20 or 40 mg/kg of BNPD orally from day 15 of gestation throughout lactation. Reproductivity of male rats was not

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impaired by daily doses of 20 or 40 mg/kg for 63 days before mating. Likewise, similar doses given to females from 14 days before mating to day 12 of pregnancy or until litters were weaned had no effect on reproduction. The males receiving 40 mg/kg daily had slightly reduced weight gain (Bryce *et al.*, 1978).

Application of 1 ml/kg of 0.5 or 2% BNPD in 2.5% aqueous methylcellulose to the dorsal skin of rats daily from day 6 to 15 of pregnancy produced local skin reaction at the site of application, but had no other adverse effects on the dams or the fetuses (Bryce *et al.*, 1978).

Rats given oral doses in 2% gum acacia of 0.3, 3, and 8 mg/kg BNPD on days 6 through 15 of pregnancy, when compared with control rats given a 2% suspension of gum acacia, showed no teratogenic effects (CTFA, 1972c).

Mutagenesis Male mice in five groups of 20 were given BNPD at a maximum tolerated dose, a calculated exposure dose and intermediate dose. (Actual values were not reported.) Doses were given daily for five days. One other group was given vehicle and the fifth group was untreated. Results of repeated matings of test animals with fresh females each week throughout spermatogenic cycle showed no effect from the compound. Therefore, BNPD was not considered a mutagen (CTFA, ET40B).

The mutagenic potential of BNPD was tested in a reverse mutation system using auxotrophic mutants of *Salmonella typhimurium* with and without Ames S-9 rat liver microsomes for bioactivation. The following strains of *S. typhimurium* were used:

With microsomes: TA1535, TA1536, TA1537, TA1538.
Without microsomes: G46, TA1535, TA1536, TA1537, TA1538.

There was no evidence of mutagenic activity. Maximum dose levels were not stated (Bryce *et al.*, 1978; Boots Co., 1979).

Carcinogenesis BNPD in concentrations of 0.2 and 0.5% in aqueous acetone applied to the skin of mice three times a week for 80 weeks did not affect the tumor incidence (Bryce *et al.*, 1978; Boots Co.,1978a). Data on this study are displayed in Table 3.

Oral administration of BNPD to rats in drinking water at doses as high as 160 mg/kg/day for two years did not reveal an effect on tumor incidence (Bryce *et al.*, 1978; Boots Co., 1978a). Data on this study are displayed in Table 4.

The manufacturer of BNPD reports no known cases of cancer among its workers who have been exposed during production for the last 7 to 8 years. It was also pointed out, quite correctly, that the number of workers exposed and the years of their exposure are too small for any meaningful conclusion at this time.

In view of the indications discussed earlier that N-nitrosodiethanolamine (NDELA) has been found in some cosmetics, it is important to note the report of the International Agency for Research on Cancer which states that NDELA is carcinogenic in two species of animals by different routes of administration. The Agency also notes, "Although no epidemiological data were available, N-nitro-sodiethanolamine should be regarded for practical purposes as if it were carcinogenic to humans" (WHO:IARC, 1978).

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TABLE 3. Tumor Incidence in Mice Exposed Topically to BNPD (Boots Co., 1978a).

Tumor Site	Number of Mice with Tumors					
	Males			Females		
	Control	0.2[1]	0.5	Control	0.2	0.5
Lymphoreticular system	6	4	11	7	8	10
Liver	1	1	0	2	0	0
Heart	1	0	0	0	0	0
Lungs	13	13	13	10	9	11
Endocrine glands	3	3	0	3	3	1
Mesentery	0	1	0	0	0	0
Subcutaneous tissues	1	0	1	3	0	0
Cutaneous tissues	1	0	1	1	1	3
Kidney	0	0	0	1	0	0
Harderian gland	0	0	1	-	-	-
Testes	3	0	2	-	-	-
Ovary	-	-	-	1	1	0
Uterus/Vagina	-	-	-	3	0	0
Number Examined	50	50	50	51	50	49

[1]Percent BNPD

Clinical Assessment of Safety

Dermatologic Evaluation Ten volunteers were tested for skin irritation with closed patches of BNPD at 0.0, 0.5, 1.0, and 2.0% in soft paraffin and 0.0, 0.05, 0.1, and 0.25% in aqueous buffer at pH 5.5. The paraffin patches produced slight erythema in two volunteers at 1% BNPD, and moderate erythema in four volunteers at 2% BNPD. The aqueous patches produced slight erythema in one of the volunteers at 0.25% BNPD. It was concluded that BNPD is "slightly irritant to human skin at 1% in soft paraffin and at 0.25% in aqueous buffer at pH 5.5" (Bryce *et al.*, 1978).

Marzulli and Maibach (1974) and Maibach (1977) studied the potential contact sensitization to a number of biocides and concluded that BNPD at 2.5% in soft paraffin was a potential sensitizer but a nonirritant in that concentration. Their subsequent tests showed BNPD to be an irritant to human skin at concentrations greater than 1% (Marzulli and Maibach, 1973). However, Maibach later was unable to demonstrate contact sensitization in a study of 93 normal subjects on whose skin 5% BNPD in yellow paraffin was applied 10 times in three weeks followed by a two-week rest period prior to challenge with 0.25% BNPD in paraffin (Maibach, 1977).

Occupation Exposure In the industrial experience of 50 workers from 1970 to date, it was found that a documented 23 of 50 workers had reported rashes and/or superficial burns secondary to exposure to saturated aqueous solutions or powder of BNPD on at least one occasion. Of these 23, there were

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TABLE 4. Tumor Incidence in Rats Exposed Orally to BNPD (Boots Co., 1978a)

Tumor Site	Number of Rats with Tumors											
	Males (main group)				Males (satellite group)				Females			
	Control	10[1]	40	160	Control	10	40	160	Control	10	40	160
Lymphoreticular tissue	1	2	2	1	0	0	0	0	1	1	1	0
Mediastinum	1	0	0	0	0	0	0	0	0	0	0	0
Liver	1	0	0	0	1	0	0	0	0	0	0	0
Endocrine glands	21	22	12	2	3	2	1	1	30	34	33	22
Pancreas	0	1	1	0	0	0	0	0	0	0	0	0
Kidney	0	2	0	0	0	0	0	0	0	2	1	0
Stomach	0	1	0	2	0	0	0	1	0	0	0	1
Duodenum	0	1	0	0	0	0	0	0	0	0	0	0
Skin	6	6	6	5	0	0	1	0	0	0	0	0
Subcutaneous tissue	10	7	8	2	3	0	1	0	38	46	49	33
Abdominal cavity	1	1	0	0	0	0	0	0	0	0	0	0
Bone	0	0	0	0	0	1	0	0	0	1	0	0
Testes	1	0	0	0	0	0	0	0	-	-	-	-
Scrotum	0	0	1	0	0	0	0	0	-	-	-	-
Ovary	-	-	-	-	-	-	-	-	1	0	0	0
Uterus	-	-	-	-	-	-	-	-	0	0	1	5
Number Examined	43	43	42	41	6	4	6	13	52	53	49	51

[1]mg/kg/day BNPD

8 who reported a second occurence, 6 a third, and 3 a fourth. These reactions were described as apparently the result of a breakdown of protective measures and appeared to be irritant reactions rather than contact allergy (Boots, 1978a). The records indicate that no individual involved was required to terminate employment as a consequence of these injuries.

Clinical Experiences Patients attending a dermatitis clinic were subjected to a battery of closed patch tests for diagnosis which included BNPD at 0.25% in soft paraffin. Three of the 149 patients showed a slight transient erythema. There was no evidence of sensitization or of cross-sensitization with formalin (Bryce *et al.*, 1978).

Data reported for 1975-76 by the North American Contact Dermatitis Group gives the incidence of contact dermatitis among dermatology patients. The following data were presented (Rudner, 1977):

Test Material	No. of Patients	% Incidence
1% BNPD (aqueous)	190	13.2
2% Formaldehyde (aqueous)	900-2000	3.8

No information has been made available on studies of phototoxicity or photosensitization.

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SUMMARY

BNPD has been shown to possess a wide spectrum of antibacterial activity with effective activity against gram-positive and gram-negative organisms, particularly *Pseudomonas aeruginosa*. Its effectiveness is enhanced by the addition of other antibacterials or biocides such as the parabens.

BNPD is most stable under acid conditions, although it demonstrates high bacterial activity over a wide pH range. Its mode of decomposition has revealed several decomposition products including formaldehyde. Decomposition of BNPD *in vitro* produces an N-nitrosating agent. This may be expected to occur also *in vivo*.

Contact allergy and contact irritant reactions in animals and humans are reported as minimal. The spectrum of these cutaneous reactions appears to be dose dependent at 0.25% and above. Cosmetic preparations containing BNPD at levels of 0.01 to 0.1% are considered to produce minimal contact irritation. However, unformulated BNPD in concentrations of 1% or greater has been shown to be a considerable irritant.

BNPD is moderately toxic orally in a variety of laboratory mammals, the LD50 varying with the test circumstances. Intraperitoneally, it is highly toxic to rats and mice. On skin contact the dry powder produced only slight irritation, while a 20% aqueous solution caused moderately severe irritation in rabbits. Results with BNPD dissolved organic solvents and applied under occlusive dressings varied from practically nonirritating to being highly irritating for humans as well as animals.

Contact with the rabbit eye caused immediate irritation which was not relieved by irrigation. Inhalation of concentrated vapor produced an approximate 4-hour LC50 of 180 mg/1.

Repeated dosing by intubation or feeding in the diet was tolerated well while repeated skin application produced no effects different from those produced by the vehicle. It did not have a carcinogenic effect in studies of limited numbers of mice by skin painting and rats by ingestion in drinking water. In the guinea pig it appeared to be a weak sensitizer.

BNPD had no effect on reproduction, was not a teratogen, and had no embryotoxic effects. It was not a mutagen by the standard mouse dominant lethal test nor by the bacterial reverse mutant system.

CONCLUSIONS

The evidence at hand indicates 2-Bromo-2-Nitropropane-1,3-Diol to be safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides.

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JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 3, Number 3, 1984
Mary Ann Liebert, Inc., Publishers

5

Addendum to the Final Report on the Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol

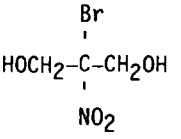
A literature review of test data that have become available since the 1979 toxicological safety report on 2-Bromo-2-Nitropropane-1,3-Diol (BNPD) is presented and discussed. The earlier conclusion that BNPD is safe as a cosmetic ingredient at concentrations up to 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides is reaffirmed. The new data suggest the possibility that when it is absorbed, this ingredient may contribute to endogenous formation of nitrosamines in humans.

INTRODUCTION

This addendum updates the Final Report of the Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol (BNPD).[1] Recent information and summaries of the original report are included in this addendum; the reader is referred to the original report for further information. During the Panel's review, additional information on nitrosamines was submitted.[2]

CHEMICAL AND PHYSICAL PROPERTIES

BNPD is a substituted aliphatic diol that conforms to the formula:



Major decomposition products of BNPD are formaldehyde and nitrite. Decomposition is accelerated by increasing pH and increasing temperature. The chemical and physical properties of BNPD have been previously reviewed.[1,3,4]

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USE IN COSMETICS

Purpose and Extent of Use

BNPD is used as a preservative because of its antibacterial and antifungal properties. It is used in a wide variety of cosmetics, especially shampoos, creams, lotions, rinses, and eye makeup.[1]

Cosmetic formulation data is submitted to the Food and Drug Administration (FDA) by companies participating in the voluntary cosmetic registration program. BNPD was reported to the FDA to be used in totals of 323, 366, 566, 474, and 546 cosmetic formulations in 1976, 1977, 1980, 1981, and 1982, respectively.[5-7]

It is the policy of the major manufacturer of BNPD to recommend concentrations of 0.01%–0.1% BNPD for cosmetic and toiletry preservation purposes. It is stated that in most cases concentrations of 0.01%–0.02% are adequate for preservation and only rarely is 0.02% exceeded.[8] In the CIR[1] safety evaluation of BNPD, it was concluded that BNPD is safe in concentrations up to and including 0.1% except when its action with amines or amides could result in the formation of nitrosamines or nitrosamides

Potential Interactions with Other Ingredients

BNPD is a known N-nitrosating agent for secondary and tertiary amines. Model assays have indicated that BNPD can lead to the N-nitrosation of cosmetic ingredients, such as diethanolamine and triethanolamine, and form the carcinogenic compound, N-nitrosodiethanolamine (NDELA), and can lead to the N-nitrosation of morpholine and form the highly carcinogenic compound, N-nitrosomorpholine.[3,4,9,10]

Ong and Rutherford[9] reported that technical grade triethanolamine (which contains more diethanolamine) yielded more NDELA than reagent grade triethanolamine under the same experimental conditions. Diethanolamine yielded the most NDELA and monoethanolamine the least. Citrate buffer catalyzed the N-nitrosation reaction and propyl gallate with disodium EDTA inhibited the reaction. Sorbitol and sorbose had very slight catalytic effects. Douglass et al.[11] state that nitrosamines are stable compounds and are difficult to destroy. Nitrosating agents are ubiquitous in the environment. Nitrosamine formation can be inhibited by substances which react preferentially with the nitrosating agent.

The FDA has provided data on the concomitant occurrence in cosmetic products of BNPD and a number of amines (Table 1).[7,12] These data are sup-

TABLE 1. Product Formulation Data Cosmetic Formulations Containing Amines and BNPD.[a]

Product category[b]	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*	
		>0.1–1	*≤0.1*
Triethanolamine and BNPD			
Other bath preparations	2	—	2
Eyeliner	2	—	2
Eye shadow	11	7	4
Sachets	2	—	2
Hair conditioners	1	—	1

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TABLE 1. (Continued.)

Product category[b]	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
		>0.1–1	≤0.1
Tonics, dressings, and other hair grooming aids	1	—	1
Blushers (all types)	7	—	7
Makeup foundations	3	—	3
Makeup bases	31	—	31
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	10	—	10
Face, body, and hand skin care preparations (excluding shaving preparations)	23	—	23
Moisturizing skin care preparations	12	—	12
Night skin care preparations	9	—	9
Skin lighteners	1	—	1
Wrinkle smoothers (removers)	1	—	1
Other skin care preparations	11	2	9
Suntan gels, creams, and liquids	5	—	5
1983 Totals Triethanolamine and BNPD	132	9	123
1981 Total number of formulations containing Triethanolamine	2720		
TEA Lauryl Sulfate and BNPD			
Bath oils, tablets, and salts	3	—	3
Hair shampoos (noncoloring)	3	—	3
Other personal cleanliness products	2	—	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	1	1	—
1983 Totals TEA Lauryl Sulfate and BNPD	9	1	8
1981 Total number of formulations containing TEA-Lauryl Sulfate	400		
TEA Coco Hydrolyzed Animal Protein and BNPD			
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	1	—	1
Other skin care preparations	1	—	1
1983 Totals TEA-Chap and BNPD	2	—	2
1981 Total number of formulations containing TEA-Chap	18		
Morpholine and BNPD			
Mascara	4	—	4
1983 Totals Morpholine and BNPD	4	—	4
1981 Total number of formulations containing Morpholine	38		

[a] Data from Refs. 7, 12.
[b] Preset product categories and concentration ranges in accordance with federal regulations (21 CFR 720.4).

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plied voluntarily and, therefore, may not be complete. The amines examined were amenable to N-nitrosation with the formation of known animal carcinogens. These amines included: Triethanolamine (TEA), Diethanolamine (DEA), TEA-Coco-Hydrolyzed Animal Protein, Morpholine, TEA-Lauryl Sulfate, Diisopropanolamine, Triisopropanolamine, Mixed Isopropanolamine and Sodium Diethylaminopropyl-Cocoaspartamide. Four of these amines occurred in cosmetic products in combination with BNPD. Total numbers of cosmetic formulations containing the above cited amines (Table 1) are for 1981, while the numbers of those containing both amines and BNPD are for 1983; the following percentage computations are estimates: 132 of 2720 products containing TEA also contained BNPD (4.85%), nine of 400 products with TEA-Lauryl Sulfate also contained BNPD (2.25%), two of 18 products with TEA-Coco-Hydrolyzed Animal Protein also contained BNPD (11.1%), and four of 38 products with morpholine also contained BNPD (10.5%).

The FDA has also provided data on the analysis of 397 cosmetic products for NDELA (Table 2).[13] No NDELA was detected in 247 (62%) of 397 cosmetic products. Traces of NDELA (10–30 ppb), from 30 ppb to 2000 ppb, and 2000 ppb and above were detected in 23 (6%), 104 (26%), and 23 (6%) of the cosmetic products, respectively. The results of nitrosamine analyses performed by FDA as of March 31, 1980 on cosmetics were as follows: two (0.9%), 62 (26.8%), and 18 (7.8%) of 231 products containing triethanolamine or a close chemical relative and not BNPD contained greater than 2000 ppb, 30–2000 ppb, and traces (10–30 ppb) of NDELA, respectively. Of 42 products containing both triethanolamine or a close chemical relative and BNPD, 16 (38.1%), 15 (35.7%), and none contained greater than 2000 ppb, 30–2000 ppb, and traces (10–30 ppb) of NDELA, respectively.[14]

The concentration of NDELA in 345 products was determined and the products were divided into categories: those that contained BNPD, NDELA precursors, both, and neither (Table 3).[13] Of 40 products containing both BNPD and NDELA precursors, 0%, 45%, and 43% contained trace (10–30 ppb), 30–2000 ppb, and 2000 ppb and above of NDELA, respectively. Of 22 products containing BNPD but no NDELA precursors, 9%, 5%, and 0% contained trace, 30–2000 ppb, and 2000 ppb and above of NDELA, respectively. Of 283 products containing NDELA precursors of, but no BNPD, 7%, 27%, and 1% contained a trace, 30–2000 ppb, and 2000 ppb and above of NDELA, respectively. Thus, cosmetic products in this FDA list which contain both BNPD and precursors for NDELA have significantly higher NDELA levels above 30 ppb (35/40) than those containing merely the precursors of NDELA (81/283).

TABLE 2. FDA Results of the Analysis of Cosmetic Products for NDELA 1978–1982.[a]

NDELA levels	*Number of samples*	*% of total*
None detected	247	62
Trace (10–30 ppb)	23	6
From 30 to 2,000 ppb	104	26
2,000 ppb and above	23	6
Total	397	100

[a] Data from Ref. 13.

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TABLE 3. FDA Results of Analysis of Cosmetic Products for NDELA and BNPD 1978–1982.[a]

		BNPD containing products that:							
	BNPD containing products analyzed	*Contained NDELA precursors*		*Did not contain NDELA precursors*		*Products that contained NDELA precursors but not BNPD*		*Products that contained no NDELA or BNPD*	
Level of NDELA	*No.*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
None detected	24	5	12	19	86	182	65	41	79
Trace (10–30 ppb)	2	0	0	2	9	20	7	1	2
30 to 2,000 ppb	19	18	45	1	5	77	27	8	15
2000 ppb and above	17	17	43	0	0	4	1	2	4
TOTALS	62	40	100	22	100	283	100	52	100

[a] Data from Ref. 13.

NDELA = N-Nitrosodiethanolamine.

BNPD = 2-Bromo-2-nitro-1,3-propanediol (a preservative).

NDELA PRECURSORS = Triethanolamine (TEA), Diethanolamine (DEA) and derivatives of TEA and DEA, as, for example: Lauramide DEA, DEA-Lauryl Sulfate, TEA-Palmitate, TEA-Laureth Sulfate, etc., (over 100 DEA and TEA derivatives are listed in the *CTFA Cosmetic Ingredient Dictionary*, 3rd Ed., 1982).

NDELA was applied undiluted, dissolved in water, and in cutting oil to the skin of rats. It was also administered in water by gavage. N-nitroso-morpholine (NMOR), in water and in ethyl acetate, was applied to the skin of rats and was also administered, in water, by gavage. Blood and urine of the rats was examined over a 24 h period. Undiluted NDELA penetrated the skin rapidly and absorption from the gut was rapid; NDELA was found in the urine. NDELA in water and in cutting oil penetrated the skin less readily. NMOR penetrated the skin to a small extent and absorption from the gut was rapid; a small amount of NMOR was found in the urine.[15]

An average density of 4 $\mu g/cm^2$ radioactive labeled NDELA (^{14}C) was applied in acetone or in a skin lotion to a 3–15 cm^2 area on the abdomens of adult rhesus monkeys or on the backs of immature Pitman–Moore white swine. Test group sizes were between three and six. The NDELA was removed after 24 h by washing with soap and water. Urine was collected for five days and analyzed for label. The percentage of applied dose penetrating the skin during the 24 h exposure was estimated by multiplying the percentage of the applied label found in the urine by a correction factor that accounted for the label that remained in the body during the five days. The percentage of applied dose that penetrated the abdominal skin for the monkeys was 34 ± 12% for NDELA in acetone and 23.4 ± 11.4% for NDELA in skin lotion. The percentage of applied dose that penetrated the skin of the backs of the swine was 11.5 ± 2.5% for NDELA in acetone and 4.0 ± 2.3% for NDELA in skin lotion.[16]

NDELA can be absorbed through excised human skin.[1] One man applied an NDELA-contaminated facial cosmetic to a 2,090 cm^2 area on his chest and back and allowed it to remain for 7.75 h. The cosmetic was removed by washing four times with soap and hot water. Urine was collected before, during, and more than 13 h after cosmetic exposure. No NDELA was detected in urine collected before or at two days or two weeks after exposure. NDELA was detected in the urine 1 h after dermal application of the cosmetic and continued to be detected for at least 13 h after its removal.[17]

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Two groups of 15 male and 15 female Syrian golden hamsters were administered NDELA in saline, in a total dose of approximately 15 g/kg, injected subcutaneously. One group received seven injections of 2260 mg/kg over a four-week period and the other group received 27 injections of 565 mg/kg over a 45-week period. Extensive local necrosis was observed. A control group of animals received injections of saline. Necropsy was performed on all moribund animals sacrificed over the 78-week experimental period and on the hamsters sacrificed at the end of the experiment. The effective number of animals was based on the number of hamsters surviving after the first tumor at any site had been observed (33 weeks). Of 27 control-group hamsters, one thyroid gland carcinoma, one splenic hemangioendothelioma, and two adrenal gland adenomas were observed. Of 55 animals in the two groups of NDELA-treated hamsters, 39 had tumors. Twelve, 15, three and three animals had tumors of the nasal cavity, trachea, liver, and injection site, respectively. In addition, a mammary gland fibroadenoma and a cholangioadenoma were observed. NDELA was carcinogenic in Syrian golden hamsters primarily to the "typical" target organs (the nasal cavity and trachea) of numerous nitrosamines in this species.[18]

NDELA is carcinogenic to rats. Sixty male and 60 female rats were divided into six groups of 10. One group was the untreated control and four other groups received from 3,900 to 31,250 ppm NDELA in drinking water for 34 weeks. A sixth group was given 62,500 ppm, but this was toxic and this treatment was discontinued and the animals destroyed. All of the treated animals developed hepatocellular carcinomas, and at the higher doses, most of the rats also had cholangiocellular carcinomas and their hepatocellular carcinomas had metastasized to the lungs and peritoneum. None of the control animals had lesions of the liver. In another experiment, mice tolerated the 62,500 ppm NDELA concentration in drinking water. No hepatic tumors were observed in the mice during the 32-week experimental period. Mice were less susceptible to the carcinogenic action of NDELA than were rats.[19]

Five groups of 36–72 male rats were administered 1.5 to 400 mg/kg/day NDELA in their drinking water five days a week. Median total dose ranged from 0.86 to 100.3 g/kg. There was a control group of 88 animals. The rats died naturally or were sacrificed when moribund; all were necropsied. Tumor induction in the liver and in the nasal cavity was significant at all doses of NDELA. Tumor induction in other organs was not related to treatment. There was a dose-response relationship between NDELA dose and tumor incidence in the liver and nasal cavity. The biological activity of NDELA was surprising to the researchers who stated that much of the NDELA administered to rats either orally or parenterally (including topical application) was excreted in the urine.[20]

Three groups of 15 male and 15 female Syrian golden hamsters were administered subcutaneously 59–500 mg/kg NDELA in saline once each week for 27 weeks. Ten male and 10 female control animals received saline subcutaneously. NDELA in acetone, in doses of 2.5 to 25 mg/kg, was administered topically three times per week for 36 weeks to three groups of 15 male and 15 female hamsters. Ten male and 10 female control animals received acetone topically. Twenty male and 20 female hamsters received 20 mg/kg of NDELA in saline by oral swabbing; the oral cavities, including lip and cheek pouches, were swabbed three times per week for 45 weeks. Saline was administered by oral swabbing to 10 male and 10 female control hamsters. Approximately the same total doses were administered subcutaneously, topically, and by oral swabbing. Animals were sacrificed when

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moribund, or at the end of 20 months, and all were necropsied. In this study, NDELA was carcinogenic to hamsters and was a carcinogen specifically for the hamster trachea, larynx, and nasal cavity whether it was administered subcutaneously, topically, or by oral swabbing. Labeled NDELA (U-^{14}C) was given by subcutaneous injection, topical application, and oral cavity swabbing each to two hamsters. Urine, feces, and expired air were collected for 16 h. In all hamsters, radioactivity was found in the urine and feces, but not in the expired air. After oral swabbing, some radioactivity remained in the oral cavity; after topical application, radioactivity remained in the skin.[21]

Pregnant rats and Syrian golden hamsters were fed diets containing 5 ppm and 50 ppm NMOR from the time of conception to parturition. The F_1 generation in both species and the F_2 generation in rats were used for long-term carcinogenicity studies with NMOR. There was one negative control group for each species. The data for the F_1 and F_2 generations of rats was combined. Of 128 rats receiving 5 ppm dietary NMOR, 55 had hepatic cell carcinomas, 15 had hepatic angiosarcomas, and 22 had metastases of hepatic cell carcinomas to the lungs. Of 94 rats receiving 50 ppm dietary NMOR, 93 had hepatic cell carcinomas, 21 had hepatic angiosarcomas, and 58 had metastases of hepatic cell carcinomas to the lungs. Other tumors were also observed although not in numbers greater than in the control rats. No tumors of the liver were observed in the control rats. NMOR was carcinogenic for rats. No tumors were observed in 35 hamsters fed 5 ppm dietary NMOR. One hepatic cell carcinoma and one hepatic angiosarcoma was observed in 18 hamsters fed 50 ppm dietary NMOR. Of 23 control hamsters, one had a hapatic cell carcinoma and four angiosarcomas were observed. Hamsters were more resistant to NMOR carcinogenesis than rats.[22]

NDELA and other nitrosamines and nitrosamides are known carcinogens for animals, with varying degrees of potency. Neither group of compounds has been reported carcinogenic in humans.[1]

Pregnant rats and Syrian golden hamsters from the time of conception, the F_1 generation, and in rats, the F_2 generation, were fed several dietary combinations of nitrite and morpholine (concentrations of 0–1,000 ppm of each in the feed) for long-term carcinogenesis studies. Hepatocellular carcinoma and sarcomas of the liver and lungs were the most common tumors observed in the rats. The tumors induced by nitrite and morpholine were morphologically similar to those induced by NMOR. High concentrations of nitrite and morpholine together were carcinogenic to rats. When the morpholine concentration was reduced and the nitrite concentration remained high, the incidence of hepatic cell carcinoma decreased with a linear dose-response relationship. With high morpholine concentration and decreasing nitrite concentrations, the number of hepatic tumors was sharply reduced. No hepatic or pulmonary tumors were observed in the control group although other tumors were seen. The high concentration of morpholine alone was either weakly carcinogenic, or nitrite from an unknown source was present; along with other tumors, two malignant gliomas, a rare finding in this study, were observed. In the rats fed the high nitrite concentration alone, there was a high incidence of tumors of the lymphoreticular system and there was a large number of animals that developed tumors other than hepatomas and angiosarcomas. The researchers suggested that morpholine itself may be a hazardous compound, and that it is likely that nitrosation occurs in the stomachs of rats. In 16 hamsters fed the high dietary concentrations of nitrite and morpholine together, five hepatic cell carcinomas and one pulmonary cystadenoma

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was observed. This regime was carcinogenic; other diets produced fewer tumors. Hamsters were more resistant to tumor induction by nitrite and morpholine than were rats.[22] These results paralleled the results with NMOR.

Pulmonary adenomas were induced in mice fed morpholine, piperazine, N-methylaniline, methylurea, and ethylurea (2–6 g/kg in the diet) and given drinking water containing sodium nitrite (1 g/l) for six months. The feeding of dimethylamine and nitrite under the same conditions did not induce tumors. When piperazine concentration was kept constant and nitrite concentrations were varied, the pulmonary adenoma yield was approximately proportional to the nitrite concentration squared. The addition of sodium ascorbate to the diets decreased tumor yields. When morpholine was fed to the mice and the drinking water contained sodium nitrite, hepatic cell tumors were produced and were attributed to the in vivo production of NMOR. The addition of sodium ascorbate decreased the production of hepatic cell tumors, but gastric papillomas and carcinomas, not seen in the morpholine and sodium nitrite without sodium ascorbate mice, were observed. It was suggested that the sodium ascorbate-treated mice did not die early of hepatic tumors and, therefore, lived long enough to develop NMOR-induced gastric tumors. The experiment was repeated and in the second trial morpholine and sodium nitrite and sodium ascorbate may have induced acathosis and hyperkeratosis of the squamous portion of the stomach.[23]

Results of inhalation studies have indicated that NMOR can be formed endogenously in animals. Groups of three to four mice were given morpholine by gavage and were then exposed to nitrogen dioxide at concentrations of 0.2–50 ppm for up to 4 h. Whole mouse bodies were powdered and NMOR concentrations were determined. NMOR yields were nitrogen dioxide concentration and time-dependent. Smaller amounts of NMOR were found when mice were exposed to nitrogen dioxide, given morpholine, and then immediately powdered. Similar smaller amounts were observed when morpholine was added to powdered mice that had been exposed to nitrogen dioxide prior to being powdered. Only very small amounts of NMOR were observed in mice given morpholine and only exposed to air. NMOR was undetectable in mice not given morpholine or exposed only to nitrogen dioxide.[24]

Mirvish[23] repeated this experiment using a method of analyzing for NMOR that prevented NMOR production after the mice had been powdered. He concluded that the NMOR found in the powdered mice in the previous experiment was an artifact. He found that a nitrosating agent was formed in vivo from nitrogen dioxide and that it produced NMOR during the analysis of the powdered mice. Mirvish dosed rats with morpholine by gavage, exposed them to nitrogen dioxide, and did not find NMOR in the rat bodies. However, rats gavaged with morpholine and sodium nitrite contained large amounts of NMOR.

In another experiment, Mirvish et al.[25] found that the nitrosating agent formed when mice were exposed to nitrogen dioxide in an inhalation chamber could be extracted with ether from the aqueous homogenate of the whole animal. This ether extract was capable of N-nitrosating morpholine. About 88% of the nitrosating agent formed on exposure of mice to nitrogen dioxide was located in the skin, one-third of which was in the hair.

Groups of male mice were exposed to nitrogen dioxide 3–6 h each day for five days or were gavaged with 1 g/kg morpholine, or were exposed to nitrogen dioxide and were also gavaged with morpholine. The researchers used the analytical method of Mirvish[23] as well as another method utilizing a different means of

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preventing artifactual NMOR production. The findings of these researchers were contrary to those of Mirvish. NMOR was found in the bodies of mice exposed to nitrogen dioxide and morpholine, but not in those exposed to either chemical alone. NMOR was found in the whole animals and in the intestinal tract (one-third of that found) but not in the heart and lungs. Coadministration of sodium ascorbate or α-tocopheryl acetate had no effect on the amount of NMOR in any tissue. The researchers concluded that there was in vivo formation of significant quantities of NMOR.[26]

Human tissues were collected from surgery and autopsy, and the metabolism of N-nitrosamines was investigated. N-nitrosamines can be metabolized by cultured human epithelial cells. There are quantitative differences in metabolism and alkylation of DNA among humans and among different organs within an individual. The major metabolites of the N-nitrosamines, carbonium ions and aldehydes, may be responsible for the effects of the N-nitrosamines.[27]

Hecht et al.[28] studied the metabolism of a cyclic N-nitrosamine, N-nitrosonornicotine, in cultures of rat esophagus and liver, hamster esophagus, mouse lung, and human esophagus, lung, and bronchus (from autopsy). While there were some metabolic pathways common to all the tissues, there were quantitative and qualitative differences in metabolism. Less N-nitrosonornicotine was converted to metabolites in human tissues than in animal tissues and the distribution of metabolites was quite different.

One man ingested a squid extract containing N-nitrosoproline, N-nitrosodimethylamine, and N-nitrosopyrrolidine. N-nitrosoproline was excreted almost quantitatively in the urine. The other two N-nitrosamines were not detected in the urine suggesting that they were completely metabolized in vivo. Similar results have been obtained in rats. N-nitrosoproline is noncarcinogenic and the other two N-nitrosamines are hepatic carcinogens in rats.[29]

N-nitrosoproline did not appear to be absorbed or metabolized in vivo and appeared to be excreted almost quantitatively into the urine in humans. The endogeneous formation of N-nitrosoproline was demonstrated by monitoring its excretion in the urine of one man who had ingested red beetroot juice, as a source of nitrate, and proline. The N-nitrosoproline excreted was proportional to the proline dose and increased exponentially with the nitrate dose. The amount of N-nitrosoproline in the urine was not increased after the ingestion of nitrate or proline alone. Simultaneous ingestion of ascorbic acid or α-tocopherol inhibited the in vivo nitrosation of proline.[29,30] Similar results were observed in rats. It was suggested that N-nitrosoproline might be used as a monitoring agent for endogenous N-nitrosamine formation.[29]

The endogenous formation of N-nitrosoproline was used to monitor the formation of N-nitrosamines in five humans, using cigarette smokers and five nonsmokers. These volunteers ate a standard diet for five days and their urine was collected and analyzed for N-nitrosoproline; under these conditions of dietary control, the endogenous concentration of N-nitrosoproline in the urine was not affected by smoking. Then the volunteers ate the standard diet with proline for five days; N-nitrosoproline formation was increased in two of the five smokers and in none of the nonsmokers. The third diet was the standard diet plus proline and ascorbic acid; the in vivo formation of N-nitrosoproline from proline added to the diet was inhibited by the simultaneous ingestion of ascorbic acid, a known inhibitor of N-nitrosation.[31] Similar experiments were conducted for 12 days and similar results were reported; the urine of smokers receiving either the stan-

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dard diet or the standard diet with proline contained significantly more N-nitrosoproline than the urine of nonsmokers.[32]

Thus far, the contribution of BNPD to endogenous N-nitrosamine formation has not been investigated.

GENERAL BIOLOGY

The gradient plate method was used to evaluate the effect of pH on the minimum inhibitory concentration (MIC) of BNPD for various microorganisms. At pHs of 4, 5.5, and 7, the MICs of BNPD for *Pseudomonas* and other gram-negatives were <20–40 ppm, <20–40 ppm, and <20–100 ppm, respectively, for yeasts the MICs were 650–1400 ppm, 150–200 ppm, and <20 ppm, respectively, and for molds the MICs were 250–700 ppm, <20–250 ppm, and <20–100 ppm, respectively. The MICs at pHs, 5.5 and 7 for cocci were <20 ppm and <20–100 ppm, respectively, and for *Bacillus sp.* the MICs were <20 ppm and <20 ppm, respectively.[33] The effects of BNPD on microorganisms may be the result of the oxidation of sulfhydryl groups in critical enzymes.[1]

ABSORPTION, METABOLISM, AND EXCRETION

BNPD is absorbed through the skin of rats and rabbits. BNPD, administered intravenously to rats and rabbits, is excreted in the urine and expired air. Distribution was fairly even among body organs. Metabolic breakdown products include 2-nitropropane-1,3-diol, which may be further metabolized to glycerol and CO_2.[1]

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

BNPD, administered orally to rats and mice, in varying doses, caused gastrointestinal lesions and when administered orally to dogs in doses of 40 mg/kg, and 100 mg/kg caused transient gastric irritation. The acute oral LD_{50}s of BNPD to rats, mice, and dogs have been reported to range from 180 to 400 mg/kg, to range from 270 to 374 mg/kg, and to be 250 mg/kg, respectively.[1]

Subchronic Toxicity

Rats tolerated oral doses (by intubation) of 20 mg/kg/day BNPD for 90 days; doses of 80 mg/kg/day and 160 mg/kg/day resulted in some deaths, respiratory distress, and gastrointestinal lesions. A dose of 160 mg/kg/day for six weeks in the drinking water caused reduced water intake by rats and slightly enlarged kidneys; some deaths occurred at a dose of 300 mg/kg/day. Rats were fed 100 and 1,000 ppm BNPD in the diet for 12 weeks and no toxic effects were observed.[1]

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Dermal Studies

Acute Toxicity

Percutaneous applications of doses of 160 mg/kg BNPD or greater caused death in rats.[1]

Skin Irritation

Dry BNPD was not a primary irritant for abraded and nonabraded rabbit skin (primary irritation score was 0.75 out of a maximum possible score of 8) and erythema occurred only on abraded skin. A 20% aqueous solution of BNPD was moderately to severely irritating to abraded and nonabraded rabbit skin (primary irritation score was 6.75/8.0). Two percent BNPD emulsions and solutions produced irritation of rabbit skin after one application; 0.5% emulsions and solutions were not irritating after four daily applications.[1]

The irritation of BNPD to nonabraded rabbit skin depended to some extent on the vehicle. Acetone solutions of 1% BNPD were nonirritating after a single occluded application, but repeated application of a 0.5% solution was highly irritating when not occluded. BNPD at a 0.5% concentration in aqueous methylcellulose gave similar results. A 5% concentration in Polyethylene Glycol 300 was nonirritating on single occluded application.[1]

BNPD in aqueous methylcellulose was applied daily for three weeks to abraded and nonabraded rabbit skin. A 0.5% solution produced moderate edema, erythema, and eschar formation, and a 0.2% solution and the vehicle produced local erythema.[1]

Skin Sensitization

A guinea pig sensitization test was conducted using the Magnusson and Kligman procedure. In this procedure, sensitization was assessed after one challenge; no sensitization was observed in 10 guinea pigs after one challenge. The challenge was repeated four times; two of the 10 guinea pigs became sensitized after three challenges. BNPD was a weak sensitizer with this test method. There was no evidence of guinea pig skin sensitization after 10 intradermal injections of aqueous BNPD followed by a challenge dose two weeks later. BNPD failed to sensitize guinea pigs with the ear-flank method.[1]

BNPD was tested for guinea pig sensitization in the optimization test. A group of 10 male and 10 female guinea pigs received 10 intracutaneous injection inductions over a three-week period (an injection every other day); in the first week the injections were of a 0.1% BNPD solution and in the second and third weeks the injections were of the same concentration of BNPD in a mixture of Freund's complete adjuvant and saline. There was an intradermal challenge at Week 6 with 0.1% BNPD (reactions were read 24 h later) and an epidermal challenge at Week 8 with a 24 h occluded patch of 3% BNPD in petrolatum (reactions were read 24 h after patch removal). Eighteen of the 20 guinea pigs had positive reactions to the intradermal challenge and none had a positive reaction to the epidermal challenge. The authors suggest that allergic skin reactions in man may occur when BNPD is in contact with diseased or otherwise more permeable skin.[34]

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Eye Irritation

Solid BNPD and 10% and 20% aqueous solutions of BNPD placed in the conjunctival sac of rabbits produced severe ocular damage; washing after application either did not reduce the reaction, or reduced it only slightly. Two percent BNPD in solution and in emulsion was irritating to the rabbit eye. However, four daily applications of a 0.5% solution and emulsion or a 0.5% solution in saline was nonirritating. A 5% BNPD in Polyethylene Glycol 400 solution was irritating to rabbit eyes; 2% was nonirritating.[1]

Intraperitoneal Studies

The acute intraperitoneal LD_{50}s of BNPD to rats and mice have been reported to range from 22.0 mg/kg to 30.2 mg/kg and to range from 20 mg/kg to 34.7 mg/kg, respectively.[1]

Subcutaneous Studies

The subcutaneous LD_{50} of BNPD for rats was approximately 200 mg/kg. Subcutaneous injections in rats produced hemorrhages at the injection sites, lesions of the stomach, edema, and congestion of the lungs.[1]

Inhalation Studies

The approximate 4 h LC_{50} of BNPD was 0.18 mg/l when administered by inhalation to rats. Survivors had reduced body weight gain during the two weeks following exposure.[1]

SPECIAL STUDIES

Reproduction and Teratogenicity

BNPD had no embryotoxic or teratogenic effects when it was administered to rats throughout pregnancy in daily oral (by intubation) doses of up to 100 mg/kg or to rabbits from Day 8 to Day 16 of pregnancy in oral doses of up to 10 mg/kg; maternal weight gain was retarded in both rats and rabbits and some rats died from pulmonary and gastric lesions. There was no effect on parturition, litter size, postnatal survival, or development of the young in rats given up to 40 mg/kg BNPD orally from Day 15 of gestation throughout lactation. Similar doses were given to male rats for 63 days prior to mating and to female rats 14 days prior to mating; BNPD had no effect on reproduction. Dermal application of up to 2% BNPD to rats from Day 6 to Day 15 of pregnancy had no adverse effects other than local skin reactions. Up to 8 mg/kg BNPD in gum acacia given orally to rats on Days 6–15 of pregnancy had no teratogenic effects.[1]

Mutagenesis

BNPD (dose unspecified) was given to male mice daily for five days and the mice were continually mated with fresh females throughout the spermatogenic cycle. No adverse effects were reported; BNPD was not considered a mutagen.[1]

BNPD was not mutagenic in the Ames test with *Salmonella typhimurium* strains TA1535, TA1536, TA1537, and TA1538 with metabolic activation and with these strains and strain G46 without metabolic activation.[1]

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Carcinogenesis

Oral administration of BNPD to rats in drinking water at doses as high as 160 mg/kg/day for two years did not affect the incidence of tumors. BNPD, in concentrations of up to 0.5%, applied topically to mice three times per week for 80 weeks, did not have a carcinogenic effect.[1]

CLINICAL ASSESSMENT OF SAFETY

Dermatologic Evaluation

Human subjects were tested for skin irritation with closed patches of BNPD at 0.0%, 0.5%, 1.0%, and 2.0% in soft paraffin, and at 0.0%, 0.05%, 0.1%, and 0.25% in aqueous buffer at pH 5.5. Slight erythema was produced in two of 10 subjects at 1% BNPD in paraffin and moderate erythema was produced in four of 10 subjects at 2% BNPD. Slight erythema was produced in one of the 10 subjects at 0.25% aqueous BNPD. BNPD was considered slightly irritating to human skin at these concentrations in these vehicles.[1]

Another study indicated that BNPD is an irritant to human skin at concentrations greater than 1%. Contact sensitization was not demonstrated in any of 93 normal subjects on whose skin 5% BNPD in yellow paraffin was applied 10 times in three weeks followed by a two-week rest period prior to challenge with 0.25% BNPD.[1]

Occupational Exposure

The occupational exposure to BNPD of 50 workers was investigated. Twenty-three of the 50 had reported rashes and/or superficial burns secondary to exposure to saturated aqueous solutions or powder of BNPD on at least one occasion. Eight reported a second occurrence, six a third, and three a fourth. These were described as irritant reactions rather than contact allergy. No employee terminated employment as a consequence of these injuries.[1]

Clinical Experiences

Patients attending a dermatology clinic were tested with closed patches containing BNPD at 0.25% in soft paraffin. Three of 149 patients had a slight transient erythema. There was no evidence of sensitization or of cross-sensitization with formalin.[1]

Fisher[35] found that in three of four formaldehyde-sensitive patients, results of patch tests with BNPD were positive. He also observed three patients with allergic hypersensitivity to BNPD in cosmetics; all three patients also reacted to formaldehyde.

Storrs and Bell[36] found seven patients who had developed acute allergic contact dermatitis after using a BNPD-containing cream on their previously dermatitic skin for periods of time varying from five weeks to two years. At the time of testing, the cream was a 50% oil-in-water emulsion containing 0.05% BNPD in a base composed of wood wax alcohols, petrolatum, mineral oil, ceresin, and water. All seven patients had a dermatitis which worsened while using the BNPD-containing cream; with avoidance of the cream their dermatitis either returned to its original condition, or cleared completely. All the patients had positive patch tests to one and usually to two concentrations of BNPD, in

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petrolatum or water (all had positive reactions to 1% BNPD in petrolatum, at least) and to the cream containing BNPD, and had negative patch tests to 2% aqueous formaldehyde. Six of the patients participated in a use test; they used the cream on their normal skin. Four of these six had positive reactions to the cream within two weeks. The other two patients did not complete the use test; at five days, one patient had no reaction, and the test site of the other patient was beginning to itch. These researchers patch tested 228 patients during 1979 and 1980 and found eight BNPD-sensitive patients, of which four were sensitive to the cream containing BNPD. The other four of the eight were formaldehyde positive. In this group of 228 patients, 14 were allergic to formaldehyde and four of the BNPD-positive patients were among the 14. During 10 months in 1982 and 1983, 127 patients were patch tested; six patients had allergic reactions, and eight had irritant reactions to BNPD (tested at 0.5% and 1% in petrolatum). Two patients were positive at 1% BNPD, but were negative when tested with 0.5% BNPD, and one patient was positive with the 0.5% concentration, and was negative at the 1% concentation. Storrs and Bell[36] also reported on two machinists who had positive patch tests for BNPD; they were sensitive to a BNPD breakdown product used in cutting oils. Storrs and Bell warned against the prematue condemnation of BNPD which they describe as a superior preservative. They suggested that the use of products containing BNPD on normal skin does not result in sensitization and that such products might even be used by sensitive individuals on their normal skin or in wash-off products. Storrs and Bell state that they have seen no patients and have heard of none who developed an allergy to a cream containing BNPD used on normal skin.

Seventy-two patients were patch-tested with 0.25% and 0.5% BNPD.[37] Twelve (16.6%) had positive reactions. Nine of the 12 had used a BNPD-containing product for their dermatitis. Of these nine, three had a positive reaction to formaldehyde. Following these results, the authors discontinued use in their practice of the cream containing BNPD. They then noticed a drop in the number of positive reactions to BNPD. During the period of January to June, 1980, 12.5% of the patients tested had positive reactions to 0.25% and/or 0.5% BNPD. During the period of January to June 1981, 7.8% and 10.7% of the patients tested had positive reactions to 0.25% and 0.5% BNPD, respectively. During the period January to June 1982, 2.0% and 2.3% of the patients tested had positive reactions to 0.25% and 0.5% BNPD, respectively. The researchers suggested that caution should be exercised in the prolonged and widespread use of products containing BNPD by patients with dermatitis. When flare-ups occur or dermatitis is difficult to control in patients using such products, contact sensitivity to BNPD should be considered.

A report for 1975 to 1976 by the North American Contact Dermatitis Group (NACDG) gives the incidence of contact dermatitis among dermatology patients. The NACDG found that 13.2% of 190 patients responded with contact dermatitis when tested with 1% aqueous BNPD and 3.8% of 900–2,000 patients had contact dermatitis when tested with 2% aqueous formaldehyde.[1]

During 40 months in 1977 to 1980, the NACDG identified 487 cases of cosmetic-related contact dermatitis (of 8,093 total cases of contact dermatitis) and performed patch tests on 149 of these patients. They found eight cases (5.4%) in which BNPD was responsible for the dermatitis, and 10 cases (6.7%) in which formaldehyde (in one case identified as paraformaldehyde) was responsible.[38]

The 1978 to 1979 patch test results of the NACDG indicated that 20 of 910

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subjects (2%) had positive reactions to 0.25% BNPD and that of 124 of 2,374 subjects (5%) had positive reactions to 2% aqueous formaldehyde. The 1979–1980 results indicated that 20 of 628 subjects (3%) had positive reactions to 0.25% BNPD, and that 142 of 2,103 subjects (7%) had positive reactions to 2% aqueous formaldehyde.[39]

DISCUSSION

The major manufacturer of BNPD recommends that it not be used in concentrations above 0.1%[8] and this agrees with the recommendation of the CIR Expert Panel.[1] However, in a recent computer search by the FDA (Table 3), BNPD, in at least 10 cases, is used in concentrations between 0.1% and 1%. Such concentrations may induce allergic contact dermatitis in people with sensitive skin. Recent studies have indicated that 5.4%–16.6% of subjects with damaged skin are sensitive to BNPD and that no subjects with normal skin are sensitive. The NACDG reported, for 1978–1979, that 2% of subjects have positive reactions to patch tests with BNPD.

BNPD is an in vitro N-nitrosating agent for secondary and tertiary amines, as are nitrite and nitrogen dioxide. Thus, it is likely that in cosmetic products BNPD would react with amines, such as triethanolamine, diethanolamine, and morpholine, with the formation of carcinogenic N-nitrosamines.

Perhaps the greatest uncertainty exists in regards to the potential of BNPD for endogenous formation of N-nitrosamines in humans. However, a long-term mouse skin bioassay and a rat feeding study indicated that BNPD is not carcinogenic in laboratory animals.[1] Other N-nitrosating agents, nitrite and nitrogen dioxide, are involved in the endogenous formation of N-nitrosamines in laboratory animals. The ingestion of nitrite and inhalation of cigarette smoke contributes to the endogenous formation of N-nitrosoproline in humans.

It has been suggested that safer nitrogen-containing compounds could be designed for use in pharmaceuticals and industrial and agricultural chemicals, and that compounds with the ability to prevent the formation of N-nitroso compounds particularly under endogenous conditions could be judiciously used.[40]

CONCLUSION

The conclusion to the original CIR report is: "The evidence at hand indicates 2-Bromo-2-Nitropropane-1,3-Diol to be safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides."

An update of the scientific literature available since 1979 reaffirms the earlier concerns of the Panel. It suggests, furthermore, the possibility that on absorption, BNPD may contribute to the endogenous formation of nitrosamines in humans.

ACKNOWLEDGMENT

Karen Brandt, Scientific Analyst and writer prepared the literature review used by the Expert Panel in developing this Addendum.

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2-BROMO-2-NITROPROPANE-1,3-DIOL (BRONOPOL)

A safety assessment of 2-Bromo-2-Nitropropane-1,3-Diol was published in 1980 with the conclusion that this preservative is safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides (Elder 1980).

In 1984, a report addendum considered newly available data that use concentrations were reported at levels up to 1%. In addition, the action of 2-Bromo-2-Nitropropane-1,3-Diol as a nitrosating agent was emphasized and data provided demonstrating that it was present in formulations with amines such as Triethanolamine. The CIR Expert Panel reaffirmed the concentration limitation at 0.1% and the need to avoid use where nitrosamines or nitrosamides could be formed (Elder 1984).

Studies available since the addendum was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

2-Bromo-2-Nitropropane-1,3-Diol was used in 323 products in 1976 (Elder 1980), with the largest single use in makeup fixatives at concentrations of $\leq$0.1%. Frequency of use data provided by industry to FDA in 2002 indicated that 2-Bromo-2-Nitropropane-1,3-Diol was used in only one noncoloring hair preparation (FDA 2002). Use concentration data provided from an industry survey in 2003 indicated use in several other product categories (CTFA 2003). The current maximum use concentration was 0.1%. Complete information is included in Table 2.

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TABLE 2

Historical and current cosmetic product uses and concentrations for 2-Bromo-2-Nitropropane-1,3-Diol

Product category	1976 use (Elder 1980)	2002 use (FDA 2002)	1976 concentrations (Elder 1980) %	2003 concentrations (CTFA 2003) %
Bath				
Bath oils, tablets, and salts	1	—	≤0.1	—
Bubble baths	4	—	≤0.1	—
Bath soaps and detergents	1	—	≤0.1	—
Other bath	5	—	≤0.1	—
Eye makeup				
Eyebrow pencil	14	—	≤0.1	—
Eyeliner	11	—	≤0.1	—
Eye shadow	3	—	≤0.1	0.1
Eye makeup remover	—	—	—	0.05
Mascara	6	—	≤0.1	—
Other eye makeup	2	—	≤0.1	—
Fragrances				
Colognes and toilet waters	—	—	—	0.03
Perfumes	—	—	—	0.1
Other fragrances	2	—	>0.1–1	—
Noncoloring hair care				
Hair conditioners	22	—	≤0.1–1	—
Rinses	6	—	≤0.1–1	—
Shampoos	9	—	≤0.1	—
Hair tonics, dressings, etc.	3	—	≤0.1–1	—
Wave sets	1	—	≤0.1	—
Other noncoloring hair care	1	1	≤0.1	—
Hair coloring				
Hair dyes and colors	3	—	>0.1–1	—
Shampoos	6	—	≤0.1	—
Makeup				
Blushers	20	—	≤0.1	0.1
Foundations	6	—	≤0.1	—
Leg and body paints	2	—	≤0.1	—
Lipstick	—	—	—	0.1
Makeup bases	3	—	≤0.1	—
Makeup fixatives	134	—	≤0.1	—
Other makeup	1	—	≤0.1	—
Personal hygiene				
Underarm deodorants	2	—	≤0.1	—
Shaving				
Aftershave lotion	1	—	≤0.1	0.03
Skin care				
Cleansing creams, lotions, etc.	17	—	≤0.1	0.02
Depilatories				
Face and neck skin care preparations	3*	—	>0.1–1*	—
Body and hand skin care preparations		—		—
Moisturizers	9	—	≤0.1	—
Night skin care preparations	3	—	≤0.1	—
Paste masks/mud packs	8	—	≤0.1	—
Skin fresheners	3	—	≤0.1	0.01
Other skin care	6	—	≤0.1	0.009
Suntan preparations				
Suntan gels, creams, and liquids	3	—	≤0.1–1	0.05
Indoor tanning preparations	1	—	≤0.1	—
Other suntan	1	—	≤0.1	—
Total uses/ranges for 2-Bromo-2-Nitropropane-1,3-Diol	**323**	**1**	**≤0.1–1**	**≤0.1**

*These categories were originally combined, but are now separate.

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BUTYLATED HYDROXYANISOLE (BHA)

A safety assessment of Butylated Hydroxyanisole was published in 1984 with the conclusion that this ingredient is safe as a cosmetic ingredient in the practices of use (Elder 1984). New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The name of Butylated Hydroxyanisole as listed in the *International Cosmetic Ingredient Dictionary and Handbook* has been changed to BHA (Pepe et al. 2002).

BHA functions in cosmetics include antioxidant and fragrance ingredient. It was used in 3217 cosmetic products in 1981, with the largest use occurring in lipstick at concentrations of $\leq$10% (Elder 1984). In 2002, BHA was used in 1224 cosmetic products (FDA 2002), at a maximum use concentration of 0.2% in colognes, toilet waters, and perfumes (CTFA 2003). Table 3 presents the available use information for BHA. The most recent information now constitutes the present use of this ingredient.

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BUFF BOOK 2

ISOSTEARYL NEOPENTANOATE

BHA

p-HYDROXYANISOLE

2-BROMO-2-NITROPROPANE-1, 3 DIOL

CIR Expert Panel Meeting
September 8-9, 2003

RE-REVIEW DOCUMENT ON: 2-Bromo-2-Nitropropane-1,3-Diol

2-Bromo-2-Nitropropane-1,3-Diol (BNPD) is a substituted aliphatic diol (Pepe et al., 2002). The CIR Expert Panel has evaluated the safety of this ingredient in cosmetics, and a Final Report with the following conclusion was published in 1980: The evidence at hand indicates 2-Bromo-2-Nitropropane-1,3-Diol to be safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides (Elder, 1980).

It is important to note that, in 1984, a report Addendum reaffirming the Final Report conclusion was published. Furthermore, the following statements are inserted after the original conclusion in this Addendum: An update of the scientific literature available since 1979 reaffirms the earlier concerns of the Panel. It suggests, furthermore, the possibility that on absorption, BNPD may contribute to the endogenous formation of nitrosamines in humans (Elder, 1984).

An updated search of the literature was performed to identify studies on 2-Bromo-2-Nitropropane-1,3-Diol that have been published since the Panel's Addendum to the Final Safety Assessment was issued. These studies, summarized in text, will be used to determine whether reevaluation of the safety of this ingredient in cosmetics by the Panel is warranted.

CHEMISTRY

DEFINITION

According to Pepe et al. (2002), 2-Bromo-2-Nitropropane-1,3-Diol (CAS No. 52-51-7) is a substituted aliphatic diol. Other names for this chemical include Bronopol

and 1,3-Propanediol, 2-Bromo-2-Nitro.

UV ABSORBANCE

An intense UV absorption band at 244 nm was observed when an aqueous solution of spectrophotometrically inactive Bronopol was made alkaline with NaOH (0.1 M). The absorbance band disappeared under acidic conditions (Sanyal et al., 1996).

HYDROLYSIS

An adequate hydrolysis study on Bronopol exists (Boots co., Ltd, 1986; Crampton, 1986; EPA, 1995). Hydrolysis is strongly correlated with temperature and pH. Hydrolysis may or may not occur appreciably, depending on conditions. An acceptable study, conducted under conditions different from EPA's present testing guidelines, concluded that Bronopol is stable against hydrolysis in "typical" natural settings. At elevated temperatures (30, 40, 50, and 60°C), in ambient laboratory light, and at concentrations of 2000 ppm or higher, the half-life was extrapolated to be the following at 20°C: approximately 18 years at pH 4, approximately 1.5 years at pH 6, and approximately 2 months at pH 8. At higher temperatures and/or pHs, as may occur in industrial applications, hydrolysis is greatly accelerated. At 60°C (140°F), half-lives range roughly from 4 days at pH 4 to only 3 hours at pH 8. Under accelerated conditions, degradation is extensive and formaldehyde is the major hydrolysate. Other degradates produced under these circumstances are: 2-hydroxymethyl-2-nitropropane-1,3-diol (tris); 2-bromo-2-nitroethanol; unidentified products that were possibly polymeric; bromide; nitrite (not nitrate); and other trace products such as aliphatic nitro compounds and lightweight gases, but not carbon dioxide.

Bronopol hydrolyzes in aqueous medium to give tris(hydroxymethyl)-

nitromethane, glycolic acid, formic acid, methanol, and 2,2-dinitrophenol. It also releases NO_2^- and Br^- ions, but not BrO^- (Challis and Yousaf, 1991).

DEGRADATION

A partially satisfactory photodegradation in water study (Jackson et al., 1992; EPA, 1995) indicates that Bronopol rapidly photodegrades at pH 4 under continuous xenon irradiation; approximately one-half of its activity remained after about 24 hours. An equivalent exposure time under natural sunlight would be approximately 2 days (assuming 12 hours each of light and dark). Tris (2-hydroxymethyl-2-nitropropane-1,3-diol), also named tris-hydroxymethyl-nitromethane, is a tentatively identified major degradate (up to approximately 60%) that appears to degrade further, but at a slower rate. Another major, but unidentified, "relatively polar" product (component "B") steadily increased, and, at the end of the one-week study, was up to approximately 30% of the dose. Steadily increasing levels of labeled carbon dioxide derived from the central carbon atom of Bronopol indicate that at least one reaction leads to extensive degradation. Although carbon dioxide increased in parallel with unknown component "B," formation of component "B" and carbon dioxide appears to occur by separate pathways (Jackson et al., 1992; EPA, 1995).

Bronopol standard solution, 0.02 mg/ml, in different solvents (acetonitrile, methanol, acetonitrile/water [50:50, v/v] and methanol/water [50:50, v/v]) was analyzed by HPLC, and the effects of the solvents compared (Wang et al., 2002). Bronopol degradation was observable after 1 hour when the sample was prepared with methanol/water (50:50, v/v), and the decrease in Bronopol continued with time. After storage at ambient temperature for 24 h, the content of Bronopol had decreased by

approximately 20%. As a result, bromonitroethanol (degradation product of Bronopol) initially increased and then, with time, decreased slightly due to degradation to produce bromonitromethane. The same situation was observed when Bronopol solutions were prepared with acetonitrile/water (50:50, v/v). No decomposition of Bronopol could be detected when methanol was used, and the Bronopol content remained unchanged over one month. Furthermore, no degradation was found in a Bronopol standard solution prepared with methanol after it had been stored in a refrigerator at 4°C for one year (Wang et al., 2002).

In the same study, the content of Bronopol in eight commercial products, four shampoos included, was determined using high performance liquid chromatography. The content of Bronopol was between 0.011 and 0.08% w/w. Bromonitromethane and bromonitroethanol were also detected in some products in various amounts, indicating that the degradation of Bronopol took place to a different extent in these products. 2-bromoethanol was not detected in any of the samples (Wang et al., 2002).

NITROSAMINE FORMATION

According to the FDA (2003), Cosmetics containing as ingredients amines or amino derivatives, particularly diethanolamine, or ingredients that are derived from diethanolamine or possibly contain diethanolamine as a contaminant, may form nitrosamines if they also contain an ingredient that acts as a nitrosating agent, such as 2-bromo-2-nitropropane-1,3-diol (Bronopol). Amines and their derivatives are mostly present in creams, cream lotions, hair shampoos, and cream hair conditioners. Nitrosamines are avoidable by proper formulation: by not using amines or amino derivatives in combination with a nitrosating agent and by testing the product under use

conditions to make sure that nitrosamines do not form under customary conditions of use.

USE

PURPOSE IN COSMETICS

2-Bromo-2-Nitropropane-1,3-Diol functions as a preservative in cosmetic products (Pepe et al., 2002).

SCOPE AND EXTENT OF USE IN COSMETIC PRODUCTS

Current frequency of use data provided by FDA in 2002 and use concentration data (from cosmetics industry survey) provided by CTFA in 2003 are summarized in Table 1 along with similar data from the CIR Final Report on 2-Bromo-2-Nitropropane-1,3-Diol.

The 2002 FDA data indicate that Bronopol (tradename for 2-Bromo-2-Nitropropane-1,3-Diol) is being used in only one cosmetic product (hair preparation). The chemical name, 2-Bromo-2-Nitropropane-1,3-Diol is not listed in the 2002 FDA database. However, current use concentration data indicate that 2-Bromo-2-Nitropropane-1,3-Diol is being used in 11 different product categories (number of products/category not included) at concentrations ranging from 0.009% to 0.1% (CTFA, 2003).

The content of Bronopol in eight commercial products, four shampoos included, has been determined using high performance liquid chromatography. The content of Bronopol in these products was between 0.011 and 0.08% (Wang et al., 2002). Results from an earlier study, using high performance liquid chromatography, indicated

Table 1. Product Formulation Data on 2-Bromo-2-Nitropropane-1,3-Diol

Product Category (Number of Formulations Reported to FDA) (FDA, 2002)	Number of Formulations Containing Ingredient (Elder, 1980)	Number of Formulations Containing Ingredient (FDA, 2002)	Concentration of Use (Elder, 1980)	Concentration of Use (CTFA, 2003)
Bath Oils, Tablets, and Salts (143)	1	-	≤ 0.1%	-
Bubble Baths (215)	4	-	≤ 0.1%	-
Other Bath Preparations (196)	5	-	≤ 0.1%	-
Eyebrow Pencil (102)	14	-	≤ 0.1%	-
Eyeliner (548)	11	-	≤ 0.1%	-
Eye Shadow (576)	3	-	≤ 0 1%	0.1%
Eye Makeup Remover (3E)	-	-	-	0.05%
Mascara (195)	6	-	≤ 0.1%	-
Colognes and Toilet Waters (684)	-	-	-	0 03%
Perfumes (235)	-	-	-	0.1%
Other Fragrance Preparations	2	-	> 0.1 to 1%	-
Other Makeup Preparations (201)	2	-	≤ 0.1%	-
Hair Conditioners	22	-	≤ 0.1 to 1%	-
Rinses (noncoloring)	6	-	≤ 0.1 to 1%	
Shampoos (non-coloring)	9	-	≤ 0.1%	-
Tonics, Dressings, and Other Hair Groom (598)	3	-	≤ 0.1 to 1%	-
Wave Sets (53)	1	-	≤ 0.1%	-
Other Hair Preparations (277)	1	1	≤ 0.1%	-
Hair Dyes and Colors (1690)	3	-	> 0.1 to 1%	-
Hair Shampoos (coloring)	6	-	≤ 0.1%	-
Blushers (all types)	20	-	≤ 0.1%	0.1%
Foundations (324)	6	-	≤ 0.1%	-
Leg and Body Paints (4)	2	-	≤ 0.1%	-
Lipstick (962)	-	-	-	0.1%
Makeup Bases (141)	3	-	≤ 0.1%	-
Makeup Fixatives (20)	134	-	≤ 0.1%	-
Other Makeup Preparations (201)	1	-	≤ 0.1%	-
Bath Soaps and Detergents (421)	1	-	≤ 0.1%	-
Deodorants (underarm) (247)	2	-	≤ 0.1%	-
Aftershave Lotion (231)	1	-	≤ 0.1%	0.03%
Cleansing (775)	17	-	≤ 0.1%	0.02%
Depilatories (34)				
Face and Neck (excluding shaving) + Body and Hand (excluding shaving) (1150) - the 2 separate product categories were combined in 1980	3	-	> 0.1 to 1%	-
Moisturizing (905)	9	-	≤ 0.1%	-
Night (200)	3	-	≤ 0.1%	-

Table 1 - Continued. Product Formulation Data on -Bromo-2-Nitropropane-1,3-Diol

Product Category (Number of Formulations Reported to FDA) (FDA, 2002)	Number of Formulations Containing Ingredient (Elder, 1980)	Number of Formulations Containing Ingredient (FDA, 2002)	Concentration of Use (Elder, 1980)	Concentration of Use (CTFA, 2003)
Paste Masks (mud packs) (271)	8	-	≤ 0.1%	-
Skin Fresheners (184)	3	-	≤ 0.1%	0.01%
Other Skin Care Preparations (725)	6	-	≤ 0.1%	0.009%
Suntan Gels, Creams, and Liquids (131)	3	-	≤ 0.1 to 1%	0.05%
Indoor Tanning Preparations (71)	1	-	≤ 0.1%	-
Other Suntan Preparations (38)	1	-	≤ 0.1	-
Totals	323	1		

the following cosmetic product concentrations of Bronopol: liquid soap (0.023% w/w), shampoo (0.010% w/w), and cream (0.015% w/w) (Scalia et al., 2001).

Table 2, from the Addendum to the CIR Final Report on 2-Bromo-2-Nitropropane-1,3-Diol (Elder, 1984), contains FDA data on the concomitant occurrence of this ingredient and a number of amines in cosmetic products.

INTERNATIONAL USE

2-Bromo-2-Nitropropane-1,3-Diol (Bronopol) is listed among the preservatives that are allowed provisionally in cosmetic products marketed in the European Union, at a maximum authorized concentration of 0.1% and with the following limitation/requirement: Avoid formation of nitrosamines (European Commission, 2003).

NONCOSMETIC USE

Indirect Food Additives

2-Bromo-2-Nitropropane-1,3-Diol is listed among the components of adhesives that may be used safely as components of articles intended for use in packaging, transporting, or holding food under the conditions that have been prescribed. It is

Table 2. Product Formulation Data. Cosmetic Formulations Containing Amines and 2-Bromo-2-Nitropropane-1,3-Diol (BNPD)

Product Category	Number of Formulations Containing Ingredient	Concentration of Use
Triethanolamine and BNPD		
Other Bath Preparations	2	≤ 0.1%
Eyeliner	2	≤ 0.1%
Eye Shadow	11	≤ 0.1 to 1%
Sachets	2	≤ 0.1%
Hair Conditioners	1	≤ 0.1%
Tonics, Dressings, and Other Hair Grooming Aids	1	≤ 0.1%
Blushers (all types)	7	≤ 0.1%
Makeup Foundations	3	≤ 0.1%
Makeup Bases	31	≤ 0.1%
Skin Cleansing Preparations (cold creams, lotions, liquids, and pads)	10	≤ 0.1%
Face, Body, and Hand Skin Care Preparations (excluding shaving preparations)	23	≤ 0.1%
Moisturizing Skin Care Preparations	12	≤ 0.1%
Night Skin Care Preparations	9	≤ 0.1%
Skin Lighteners	1	≤ 0.1%
Wrinkle Smoothers (removers)	1	≤ 0.1%
Other Skin Care Preparations	11	≤ 0.1 to 1
Suntan Gels, Creams, and Liquids	5	≤ 0.1%
1983 Total for Triethanolamine and BNPD	132	
1981 Total Number of Formulations Containing Triethanolamine	2720	
TEA Lauryl Sulfate and BNPD		
Bath Oils, Tablets, and Salts	3	≤ 0.1%
Hair Shampoos (noncoloring)	3	≤ 0.1%
Other Personal Cleanliness Products	2	≤ 0.1%

Table 2 - Continued. Product Formulation Data on Cosmetic Products Containing Amines and BNPD

Product Category	Number of Formulations Containing Ingredient	Concentration of Use
TEA Lauryl Sulfate and BNPD - Cont'd		
Skin Cleansing Preparations (cold creams, lotions, liquids, and pads)	1	≤ 0.1to 1%
1983 Total for TEA Lauryl Sulfate and BNPD	9	
1981 Total Number of Formulations Containing TEA-Lauryl Sulfate	400	
TEA Coco Hydrolyzed Animal Protein and BNPD		
Skin Cleansing Preparations (cold creams, lotions, liquids, and pads)	1	≤ 0.1%
Other Skin Care Preparations	1	≤ 0.1%
1983 Total for TEA-Chap and BNPD	2	
1981 Total Number of Formulations Containing TEA-Chap	18	
Morpholine and BNPD		
Mascara	4	≤ 0.1%
1983 Total for Morpholine and BNPD	4	
Total Number of Formulations Containing Morpholine	38	

limited to use only as an antibacterial preservative in these adhesives (21CFR 175.105).

2-Bromo-2-Nitropropane-1,3-Diol is listed among the components of paper and paperboard that may be used safely as components of the uncoated or coated food-contact surface or paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods, subject to the provisions that have been established. It is limited to use

only as an antimicrobial/preservative in fillers, pigment slurries, starch sizing solutions, and latex coatings at levels not to exceed 0.01 percent by weight of those components (21CFR 176.170).

2-Bromo-2-Nitropropane-1,3-Diol is listed among the components of paper and paperboard (i.e., slimicides) that may be used safely in the manufacture of paper and paperboard that contacts food, in accordance with the prescribed conditions that have been established. It is limited to a maximum level of 0.6 pound per ton of dry weight fiber (21CFR 176.300).

Other Uses

2-Bromo-2-Nitropropane-1,3-Diol has the following uses: microbiocide/microbiostat in oil field systems, air washer systems, air conditioning/humidifying systems, cooling water systems, papermills, absorbent clays, metal working fluids, printing inks, paints, adhesives, and consumer/institutional products (Environmental Protection Agency [EPA], 1995).

A pesticide product containing 2-Bromo-2-Nitropropane-1,3-Diol as an active ingredient was first registered in the United States in 1984 for use in industrial bactericides, slimicides, and preservatives (EPA, 1995).

BIOLOGICAL PROPERTIES

METABOLISM

Rat metabolism data for Bronopol consist of four separate studies conducted with male and female Sprague-Dawley rats (Glass and Hewerston, 1993; EPA, 1995). Animals were treated by gavage with ^{14}C Bronopol (radiochemical purity: > 95 to 100%).

In the first study, animals received a single dose of 10 mg/kg. The second study employed a higher dose of 50 mg/kg. Doses higher than 50 mg/kg caused respiratory problems and death. The third study's dose was 10 mg/kg (14 daily doses of nonradioactive, 100% pure Bronopol , followed by one dose of ^{14}C-Bronopol). Urine, feces, and CO_2 were collected for seven days after dosing, at which time the rats were killed and tissues examined for radioactivity. Because, irrespective of the dose, most of the administered ^{14}C was excreted in the urine (64 to 78% in 24 hours and 68 to 83% in 7 days), urine was used for the identification of metabolites in the fourth study. Feces, CO_2, and tissues represented minor routes of excretion of ^{14}C. Very little ^{14}C was also detected in the whole blood and plasma.

From the results of these four studies, EPA concluded that Bronopol administered orally was rapidly absorbed and rapidly excreted by the rats of both sexes, with urine being the major route of excretion. The only metabolite identified in urine was BTS 23 913 (2-nitropropane-1,3-diol or desbromo-bronopol), accounting for 45 to 50% of the radioactivity taken for analyses. The remaining radioactivity was not identified (one radioactive peak and radioactivity not resolved into peaks). Unchanged Bronopol was not detected (Glass and Hewerston, 1993; EPA, 1995).

PERCUTANEOUS ABSORPTION

Bronopol (aqueous solution), applied to the skin of rats and rabbits, was absorbed relatively slowly (approximately 11% in 24 hours). A slightly more rapid and greater absorption was observed when Bronopol was dissolved in acetone (no further details available) (BIBRA International Ltd,1995).

TOXICOLOGY

Unpublished toxicity/pharmacokinetic data included in the Environmental Protection Agency's reregistration eligibility decision document on 2-Bromo-2-Nitropropane-1,3-Diol (Bronopol) will be referenced as EPA (1995) as well as the primary reference.

ACUTE INHALATION TOXICITY

No deaths were reported when rats were exposed to Bronopol (5000 mg/m^3) for 6 hours. Bronopol (concentrations of 500 mg/m^3 or greater) caused labored breathing and decreased body weight (BIBRA International Ltd, 1995).

In an inhalation study, piloerection, hunched posture, and hydronephrosis were observed in male and female rats at the 0.089 mg/L concentration of Bronopol (≥ 98.8%). Clinical signs observed in the 0.588 mg/L group included diffuse red lungs, sore eyelids, and severe dermatitis and ulceration of the head (attributed to dermal exposure). Particle size was 1.3 to 6.7 µm. The EPA concludes from the results of this study that Bronopol is slightly toxic, with an acute inhalation LC50 of > 0.588 mg/L (Collins, 1986; EPA, 1995).

ACUTE ORAL TOXICITY

In a report by Hindmarsh (1990), eight Jersey calves (3 months old) were each fed 2 liters of a mixture consisting of a milk residue (from sampling procedures) mixed with an equal volume of tap water. The residue of Bronopol in the milk mixture was calculated to be 8 mg/kg. Seven of the eight calves died. Three calves died at 12 hours post-feeding and two died at 16 hours. The sixth and seventh calves died at days 15 and 30 post-feeding, respectively. Histopathology of tissues from the calves

that died suddenly showed severe hemorrhagic abomasitis and enteritis, with congestion and edema in the brain, liver, and kidneys. The two calves that died at 15 and 30 days post-feeding, respectively, had severe necrotizing and ulcerative abomasitis, with areas of calcification. Hepatocellular necrosis, moderate chronic glomerulonephritis, and severe distal tubular necrosis were also observed. Two hundred mg/kg Bronopol was detected in the abomasum content. Bronopol was not detected in the liver, kidney, or colon content. The presence of substantial amounts of Bronopol in the abomasal content suggests that overdosing with Bronopol caused the gastrointestinal, hepatic, and renal changes and the subsequent deaths (Hindmarsh, 1990).

ACUTE DERMAL TOXICITY

Results from an acute dermal toxicity study, while inadequate, suggest Bronopol is highly toxic by the dermal route. Bronopol (≥98.8%) was administered to two male rats per dose at the dose levels of 0, 64, 160, 400, or 1000 mg/kg. Clinical signs noted were edema, hemorrhage, labored breathing, prostration, and lung congestion. The results of this study suggest that the acute dermal LD50 is 64 to 160 mg/kg. A new study is not required due to the corrosive properties of Bronopol (Smithson, 1984; EPA, 1995).

OCULAR IRRITATION

In a primary eye irritation study, Bronopol (≥98.8%) was instilled as a 5% solution in polyethylene glycol 400 into the eyes of rabbits (number not stated). Strongly irritating (redness and swelling to the conjunctiva, with moderate discharge) effects were noted 1 hour after dosing and subsided in all but one rabbit by the seventh day

after treatment. The results of this study determined that Bronopol is a corrosive eye irritant, placing it in toxicity category I (corosive; corneal opacity not reversible within 7 days) (Liggett and Parcell, 1984; EPA, 1995).

SKIN IRRITATION

Concentrations of 2 or 4% Bronopol in 90% acetone, applied daily to the shaved skin of mice for one week, produced severe (but unspecified) toxic effects. A concentration of 0.5% similarly applied for four weeks was "well tolerated" (no further details available) (BIBRA International Ltd., 1995).

SKIN SENSITIZATION

In a study to determine the dermal sensitization potential of Bronopol (≥98.8%), guinea pigs received dermal applications of 1% in acetone. Bronopol was determined not to be a skin sensitizer after three induction treatments on the outer surface of each ear, and, one week later, one challenge treatment on the back and flank. A positive control response was obtained with DNCB (dinitrochlorobenzene) (Smithson, 1984: EPA, 1995).

CYTOTOXICITY

Carrara et al. (1993) evaluated the cytotoxicity of Bronopol in mouse fibroblast cells (L929 cells) using the neutral red uptake assay *in vitro*. At all concentrations tested (0.1%, 0.05%, 0.025%, and 0.0125%), Bronopol induced lysosomal membrane modifications and morphologic alterations, without killing the cells, and a statistically significant increase ($p < 0.01$) in neutral red uptake.

In a study by Jantova et al. (2001), Bronopol had a cytotoxic effect on the proliferation of V79 and VH10 fibroblast cell lines. IC100 values were 10 mg/ml

throughout the experiment.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Bronopol (98% pure) was administered by gavage in acidified (pH 4) water to groups of 24 mated Sprague-Dawley rats at dose levels of 0, 10, 28 or 80 mg/kg/day from gestation day 6 through 15 (gestation day 0 = detection of sperm in vaginal lavage). Females were observed for appearance of clinical signs and mortality, and body weight and food consumption were determined at intervals during gestation. Animals were killed on gestation day 20 and reproductive observations were made. Uteri were weighed and examined for live fetuses and intrauterine deaths. Fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations (Steele, 1994; Palmer, 1995; EPA, 1995).

Marginal evidence of maternal toxicity was reported at the highest dose tested and was evidenced by decreased body weight gain (80% less than that for the control; $P \leq 0.01$) during gestation days 6 through 7, and slightly reduced (1%) body weight at day 7 when compared with the controls. No animals were described in the report as having dose-related clinical signs. There were no developmental effects that could be attributed to the administration of Bronopol. Based on these findings, the NOEL for maternal toxicity is $\geq$80 mg/kg/day, and the NOEL for developmental toxicity is also $\geq$80 mg/kg/day. The highest dose tested is considered adequate because the results of a range-finding study indicated that doses $\geq$100 mg/kg/day, administered by gavage, caused severe gastrointestinal irritation that led to death (Steele, 1994; Palmer, 1995; EPA, 1995).

In another developmental toxicology study (Irwine, 1992a, b; EPA, 1995), groups

of 18, 19, or 20 mated female New Zealand White rabbits received Bronopol (98.8% pure) by gavage during gestation days 7 through 19 and were killed on gestation day 28. Aqueous solutions of Bronopol, prepared just before use and acidified to pH 4, were administered daily at the nominal dose levels of 0 (vehicle control), 5, 20, 40, or 80 mg/kg/day and the dose volume of 2 mL/kg. Separate solutions were prepared for each dose level and individual body weights were obtained daily during the treatment period. The analytical concentrations of Bronopol in dosing solutions were very close to the nominal concentrations (95 to 100%). The dose levels of Bronopol used in this study were selected by the sponsor after examination of data from a range-finding study in mated rabbits.

The following maternal effects were observed only in the 80 mg/kg/day group: decreased fetal body weight in both sexes (10%, $P < 0.05$); increase in fetuses with major external/visceral and skeletal abnormalities (6.9% vs. 0% in the concurrent control group and 1.8% in the historical controls); increase in fetuses with minor skeletal abnormalities (29.5%, $P < 0.01$ vs. 10.2% in the concurrent control group); and an increased incidence of fetuses with skeletal variants (unossified forelimb [8%] and hindlimb [16%] epiphyses). Based on these findings, the NOEL and LOEL for maternal toxicity are 40 mg/kg/day and 80 mg/kg/day, respectively. The developmental NOEL and LOEL are also 40mg/kg/day and 80 mg/kg/day, respectively (Irwine, 1992a, b; EPA, 1995).

In another study (EPA, 1995; unpublished data: primary reference not provided), Bronopol (99.9% pure) was administered in drinking water to Charles River COBS CD strain rats (13 males and 26 females/group) during the premating (80 to 87 days),

mating, gestation, and lactation periods. The water was adjusted to pH 4 with hydrochloric acid to ensure the stability of Bronopol. The study involved parental group F_0 and litters F_{1a} and F_{1b}, and parental group F_1 and litters F_{2a} and F_{2b}. The F_{1b} rats were used as the F_1 parents. The target concentrations of Bronopol were 0, 0.025, 0.07, and 0.2%, corresponding to 0, 25, 70, and 200 mg/kg/day, respectively. The mean achieved doses of Bronopol for the F_0 and F_1 males and females were 0, 22.5, 55.2, and 147 mg/kg/day, respectively. Dose concentrations were based on the results of a range-finding study.

Nothing remarkable was observed in the low-dose (25 mg/kg/day) group. Systemic toxicity was observed mostly in the mid-dose (70 mg/kg/day) and high-dose (200 mg/kg/day) groups, in both generations. Compared to the concurrent controls, toxic signs observed in the mid-dose group included an increase in kidney weight of the F_0 females (14.5%, $P < 0.01$), decreased liver weight of the F_1 males (11%) and females (11%, $P < 0.05$, relative weight or organ/body weight ratio), and an increased incidence of nephropathy in the F_0 males (4/10 vs. 2/10 in the controls) and the F_0 females (3/10 vs. 0/10 in the controls) (EPA, 1995; unpublished data: primary reference not provided).

Toxic signs noted in the high-dose group were: decreased body weights of the F_0 and/or F_1 females during the premating (7 to 24%, $P < 0.05$ or 0.01), gestation (5 to 16%), and/or lactation (8 to 11%) periods; decreased body weights of the F_1 males (11 to 22%, $P < 0.05$ or 0.01); decreased food consumption of the F_0 males (5 to 18%) and the F_0 and F_1 females (6 to 16%); increases in organ weights as follows: adrenals (22%, $P < 0.05$, F_0 females), kidneys (36%, $P < 0.01$, F_0 females and 14%, $P < 0.05$, F_1 males,

both relative), and thyroid/parathyroid (26%, $P < 0.05$, F_1 males); decreases in liver weight of the F_1 males (21%, $P < 0.01$); and an increased incidence of nephropathy in the F_0 males (6/10 vs. 2/10 in the controls) and females (9/10 vs. 0/10 in the controls) (EPA, 1995; unpublished data: primary reference not provided).

Reproductive toxicity was observed only in the high-dose group, as evidenced by a slight decrease in the female fertility index during the F_{1a} mating (75% vs. 87.5% in the controls) (EPA, 1995; unpublished data: primary reference not provided).

Based on the above findings, the NOEL and LOEL for systemic toxicity are 25 mg/kg/day and 70 mg/kg/day, respectively. The NOEL and LOEL for reproductive toxicity are 70 mg/kg/day and 200 mg/kg/day, respectively (EPA, 1995; unpublished data: primary reference not provided).

MUTAGENICITY

Bronopol was negative for mutagenicity in the Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, with and without metabolic activation. The metabolic activation system was obtained from the liver of male rats induced with Aroclor 1254. The highest concentrations of Bronopol tested were 125 µg and 62.5 µg/plate, in the presence and absence of S-9, respectively. Concentrations of Bronopol higher than those tested were cytotoxic. The following positive controls were used: cyclophosphamide (TA1535), neutral red (TA1537), and 2-aminofluorene (TA1538, TA98, and TA100). Distilled water was the solvent for Bronopol and, dimethyl sulfoxide (DMSO), for positive controls. It was stated that this study satisfies the requirements for genetic effects, gene mutations (Everest and Williams, 1986a; EPA, 1995).

In another study (Everest and O-Donovan,1986; EPA, 1995), Bronopol was negative for mutagenicity in the V79 cell mutation assay (Chinese hamster lung fibroblasts), with and without metabolic activation, when tested at concentrations up to 8 µg/ml (the maximum allowed by cytotoxicity). The metabolic activation system (S-9 microsomal fraction) was obtained from the livers of male rats induced with Aroclor 1254. N-methyl-N'-nitro-N-nitrosoguanine (MNNG) was used as a positive control in the absence of S-9 and, 7,12-dimethylbenz(a)anthracene (DMBA), in the presence of S-9. Distilled water was the solvent for the positive controls. Mutagenic potential was evaluated by comparing the frequencies of the 6-thioguanine (6-TG)-resistant mutants observed in the treated cultures with those observed in the negative control (distilled water) cultures. It was stated that this study satisfies the requirements for genetic effects, gene mutations.

In the cytogenetic assay (human lymphocytes) (Everest and Williams, 1986b; EPA, 1995), Bronopol was not clastogenic in the presence of the metabolic activation system (S-9 microsomal fraction) and was clastogenic in the absence of S-9, but only at 30 µg/ml, the highest concentration allowed by cytotoxicity. Other concentrations of Bronopol tested were 10 and 20 µg/ml without S-9 and 20, 30, and 40 µg/ml with S-9. Positive controls used were mitomycin C (0.5 µg/ml) in the absence of S-9 and cyclophosphamide (25 µg/ml) in the presence of S-9. Distilled water was a solvent for all test compounds and was also a negative control. The observed clastogenicity (significant increases in the percentage of cells with aberrations, relative to the negative control values) was attributed by the testing facility to formaldehyde, one of the degradation products of Bronopol and a known clastogen. Other degradation products

of Bronopol were not identified. It was stated that this study satisfies the requirements for genetic effects, structural chromosomal aberrations (Everest and Williams, 1986b; EPA, 1995).

In the *in vivo* micronucleus assay (Everest and Williams, 1986c; EPA, 1995), male and female CD1 mice received single oral doses of Bronopol (80 or 160 mg/kg of body weight) and were killed at 24, 48, and 72 hours post-dosing. At all sampling times, the Bronopol-treated and negative control mice had similar numbers of micronuclei per 1000 polychromatic erythrocytes of femur bone marrow examined per animal. The 160 mg/kg dose was the maximum tolerated dose (MTD), as judged by mortality (4/24 males and 4/24 females) and by reduced numbers of polychromatic erythrocytes (indicative of a reduction in hemopoiesis) in some surviving mice, 72 hours after treatment. The positive control, cyclophosphamide (75 mg/kg), significantly increased the numbers of micronuclei in both sexes. Sterile double-distilled water was used as solvent for the test materials and was also the negative control. Results for Bronopol were negative (Everest and Williams, 1986c; EPA, 1995).

CLINICAL ASSESSMENT OF SAFETY

SKIN IRRITATION AND SENSITIZATION

Clinical skin irritation/sensitization data are included in Table 3.

CROSS-SENSITIZATION

Eight-thousand one-hundred forty-nine patients were patch-tested with the preservative Bronopol (0.5% in petrolatum) in seven European contact clinics. Reactivity was low, with a total of ten irritant (0.12%) and 38 allergic reactions (0.47%).

Table 3. Irritation/Sensitization Data on Bronopol

Test Substance	Number of Subjects	Test Protocol	Results	References
Provocative Tests				
Bronopol	Case Reports: 11 dermatology patients	- -	2 patients sensitized to Bronopol	Campiglio et al., 1984
Bronopol	713 contact dermatitis patients with cosmetic-related reactions in multicenter (12 centers) study. 626 patients patch-tested	64-month study (1977 to 1983). 48-hour patch tests (Al test or Finn chamber). Reactions read at 48 and 72 hours. Additional readings at 96 or 120 hours	16 cutaneous (allergic sensitization) reactions	Adams and Maibach, 1985
0.25% aqueous Bronopol	50 patients (19 controls - no history of skin problems; 15 with eczematous dermatitis; 16 with cosmetic sensitivity)	45-minute open test (filter paper discs secured with Scanpor tape). 48-hour patch test (Finn chambers on Scanpor tape). 48- and 96-hour readings	8 of 50 with contact urticaria. No positive patch test reactions	Emmons and Marks, 1985
1% Bronopol in petrolatum	2,298 patients	Finn chambers on Scanpor tape. 2-day application. Patients routinely and consecutively patch tested over period of approximately 2 years (1983-84)	20 subjects (0.8%) with positive reactions	Ford and Beck, 1986
0.25% Bronopol in petrolatum; 1% Bronopol in petrolatum	627 patients in study by Dutch Contact Dermatitis Group	Patch test - ICDRG recommendations	One positive reaction to 0.25% and 5 positive reactions to 1%. One patient reacting to both concentrations also reacted to formaldehyde	DeGroot et al., 1986
0.25% Bronopol in Petrolatum	Case Report: 36-year-old male with acute erythroderma	48 h patch test	+++ reaction	Camarasa, 1986
Bronopol (0.1%, 0.25%, and 1% in yellow soft paraffin)	Case Reports: 3 patients (milk recorders) with hand dermatitis	Patch tests	+ reaction (0.1% Bronopol;+ to ++ (0.25% Bronopol); ++ to +++ (1% Bronopol)	Grattan et al., 1986

Table 3 - Continued. Irritation/Sensitization Data on Bronopol

Test Substance	Number of Subjects	Test Protocol	Results	References
0.5% Bronopol in petrolatum	15 workers at milk testing laboratory (8 with hand dermatitis)	Finn chambers applied for 48 h. Readings at 48 h and 2 days later	No positive reactions	Herzog et al., 1988
0.5% Bronopol in petrolatum	652 patients (mean age = 42.9 years) with suspected allergic contact dermatitis in multicenter study (10 centers)	Finn chambers on Scanpor tape	Allergic reactions (17 patients). Doubtful reactions (6 patients). Irritant reaction (1 patient). Bronopol among the most common allergens on vehicle and preservative tray	Storrs et al., 1989
0.5% Bronopol in petrolatum	8149 contact dermatitis patients in multicenter study (7 clinics) in Europe	Finn chambers on Scanpor tape. 48 h application. Readings at 48 h and either 72 or 96 hours (or both)	Irritation in 10 subjects. Positive allergic reactions in 38 subjects; 17 classified as clinically relevant.	Frosch et al., 1990
Bronopol (% not stated)	Case Report: 35-year-old veterinary surgeon with history of erythematous swelling of left arm	Patch test	Positive patch test (allergic reaction)	Wilson and Powell, 1990
Bronopol	4718 dermatologic patients	Finn chambers on Scanpor tape. 48 h application. Readings at 2 and 4 days	27 of 4718 patients (1%) with allergic reactions	Shehade et al., 1991
0.25% Bronopol in petrolatum	3700 to 4780 dermatologic patients	48 h patch tests - Finn chambers on Scanpor tape. Readings at 48, 72, and 96 hours post-application.	244 patients (5.1%) with allergic reactions	Fransway and Schmitz, 1991
0.5% Bronopol in petrolatum	2 makers of cosmetic creams with occupational dermatitis	Patch test	Positive reaction: dermatitis	Rudzki et al., 1993
0.5% Bronopol in petrolatum	2295 outpatients (mean age = 42 years) with suspected allergic contact dermatitis	Finn chambers applied to upper back for 2 days	Sensitization rate of 1.2% (medium to low sensitization rate)	Perrenoud et al., 1994
0.5% Bronopol in petrolatum	21,265 patients (Patch test results in England: 1982-1993)	ICDRG guidelines. Finn chambers on Scanpor tape	Allergy rate fluctuates between 0.3 and 1%	Jacobs et al., 1995

Table 3 - Continued. Irritation/Sensitization Data on Bronopol

Test Substance	Number of Subjects	Test Protocol	Results	References
0.5% Bronopol in petrolatum	11,516 eczema patients in Austrian multicenter study (14 centers)	Patch test	Sensitization reactions (36 females; 7 males)	Kränke et al., 1996
0.2% Bronopol in petrolatum	Case report: 42-year-old nurse with urticaria and intermittent hand eczema	Open patch test	Strong positive reaction (contact urticaria)	Torresani et al., 1996
Bronopol (% not stated)	204 reports of possible adverse effects of cosmetics and toiletries (years 1989-1994) registered in Sweden. Majority from physicians (mostly dermatologists)	Patch test	Of the 79 positive patch test results to individual cosmetic ingredients, one positive patch test reaction to Bronopol	Berne et al., 1996
Bronopol (0.25%, 0.5%, and 1% in petrolatum)	93 patients evaluated during 1982 to 1986	Patch tested with 1% Bronopol in petrolatum	2 allergic responses and 4 presumed irritant responses	Shaw, 1997
	1996 patients evaluated since 1986	Patch tested with 0.5% Bronopol in petrolatum	8 allergic responses and 11 irritant responses	"
	63 patients	Patch tested with 0.25% Bronopol in petrolatum	1 positive allergic response [Note: overall prevalence of allergic reactivity for entire study (all 3 concentrations; total of 2152 patients) = 0.46%	"
0.5% Bronopol in petrolatum	11,443 patients with suspected allergic contact dermatitis in multicenter study in Germany (24 centers)	Nine of 24 centers applied patch tests for 24 h. The remaining 15 applied patch tests for 48 hours. Only 72 h readings considered.	134 patients (1.2%) with irritation. 87 patients: question-able/irritative reactions. Age-adjusted frequency of sensitization: 0.7% (women < 40 years), 12.4% (women > 40), 1% (men < 40), 1.5% (men 40).	Schnuch et al., 1998

Table 3 - Continued. Irritation/Sensitization Data on Bronopol

Test Substance	Number of Subjects	Test Protocol	Results	References
0.5% Bronopol in petrolatum	1781 patients with suspected allergic contact dermatitis in same study	Nine of 24 centers applied patch tests for 24 h. The remaining 15 applied patch tests for 48 hours. Only 72 h readings considered.	32 patients: irritation reactions. 8 patients: questionable/irritative reactions. Age-adjusted frequency of sensitization: 1.7% (men < 40 years) and 2.2% (men > 40).	Schnuch et al., 1998
Bronopol (% not stated)	475 patients with contact allergy to cosmetic ingredients in multicenter study (European survey - Germany, UK, and Belgium)	Method not stated	10 subjects with cutaneous allergic reactions	Goossens et al., 1999
0.5% Bronopol in petrolatum	3477 patients suspected of having allergic contact dermatitis	Patch testing over two-year period: 1992 to 1994. 48-hour patch tests (See Marks et al., 2000 below)	Allergic reactions: 2.2%	Marks et al., 1995
0.5% Bronopol in petrolatum	3074 patients suspected of having allergic contact dermatitis	Patch testing over two-year period at 12 centers: 1994 to 1996. 48-hour patch tests (See Marks et al., 2000 below)	Allergic reactions: 2.3%	Marks et al., 1998
0.5% Bronopol	4094 patients with suspected allergic contact dermatitis	Patch testing over two-year period (1996 to 1998) at 12 centers - 48-hour patch tests - Finn chambers on Scanpor tape. Sites evaluated at 48 to 72 h and between 72 and 168 hours post-application	Allergic reactions: 3.2%. Relevant reactions (definite, probable, or possible relevance to patient's present dermatitis): 68.5%	Marks et al., 2000
0.25% Bronopol in petrolatum	Case report: 40-year-old female employee of yarn manufacturing plant with rash on fingers.	Patch test	Positive reaction: allergic contact dermatitis	Podmore, 2000
Bronopol (% not stated)	Case Report: 59-year-old female with history of rosacea	Patch test	++ reaction	Choudry et al., 2002

In only 17 cases (0.21%) was the patch test reaction to Bronopol considered to be of current or past clinical relevance. Concomintant sensitization to formaldehyde was present in approximately one-third of the patients (Frosch et al., 1990).

In a study by Fransway and Schmitz (1991), dermatologic patients (3700 to 4780) were patch tested with 0.25% Bronopol in petrolatum (48 h patch tests; Finn chambers on Scanpor tape). Two-hundred forty-four patients (5.1%) had allergic reactions to Bronopol. Six of 20 Bronopol-sensitive patients reacted to formaldehyde.

FORMALDEHYDE EXPOSURE AND RISK

EPA has looked at potential formaldehyde exposure to products containing Bronopol, since formaldehyde has been identified as a degradate of Bronopol under aqueous, alkaline conditions. However, the agency is not concerned about handlers or post-application exposures to formaldehyde because of Bronopol's slow decomposition rate. When mixed with water, the half-life of Bronopol decomposition to formaldehyde is 18 years at pH 4; 1.5 years at pH 6; and 2 months at pH 8 at 20°C (EPA, 1995).

HUMAN RISK ASSESSMENT

Since no food or feed uses of Bronopol are registered, dietary risk is not expected. However, a reference dose of 0.1 mg/kg/day was established because of possible long-term exposure to Bronopol-containing products. Bronopol is severely, acutely toxic by the dermal route and is a corrosive eye irritant (Toxicity Category 1: corrosive; corneal opacity not reversible within 7 days). Based on an unacceptable margin of exposure for handlers using open pour application methods of liquid formulations to water cooling systems, the Agency is requiring metered pump systems for all water cooling system uses (EPA, 1995).

EPA is requiring that labels contain a statement advising workers to wear personal protective equipment, consisting of a long sleeved shirt and long pants, socks plus shoes, and chemical resistant gloves. Chemical resistant gloves are required for application of the end-use product to protect applicators' skin (EPA, 1995).

Although Bronopol may release formaldehyde in aqueous solutions, minimal risk is expected due to the chemical's slow decomposition, and because the Occupational Safety and Health Administration (OSHA) has a standard to monitor workers' exposure to formaldehyde during industrial uses of Bronopol in occupational settings. No additional human health risk of concern is expected (EPA, 1995).

REGULATORY CONCLUSION

According to EPA (1995), all pesticides sold or distributed in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered years ago be re-registered to ensure that they meet today's more stringent standards.

EPA has concluded that the uses of currently registered Bronopol products, with the established limitations (application restrictions, handler personal protective equipment instructions for occupational use products, and labeling requirements for all Bronopol end-use products), will not pose unreasonable risks to humans or the environment. Therefore, all uses of these products are eligible for re-registration (EPA, 1995).

As cited in the *Federal Register* (EPA, 2002), EPA has received a pesticide petition from BASF Corporation proposing, persuant to section 408(d) of the Federal

Food, Drug, and Cosmetics Act, 21 U.S.C. (United States Code) 346a(d), to amend 40 CFR (Code of Federal Regulations) part 80 to establish an exemption from the requirement of a tolerance for 2-Bromo-2-Nitro-1,3-Propanediol (Bronopol) in or on all raw agricultural commodities when used as an in-can preservative in pesticide formulations applied to growing crops, raw agricultural commodities after harvest, and animals.

The following clarification of the petition referred to in the preceding paragraph was received: "At this time, there is not a tolerance exemption for Bronopol. The notice of filing is the process by which the public is made aware that someone (the petitioner) is requesting to use Bronopol as an inert ingredient (not as the active ingredient) in a pesticide product. The use pattern specified is as a preservative applied to growing crops or to animals. 40 CFR 180.1001 is the section of the Federal Register where tolerance exemptions for inert ingredients are usually established. The Agency must complete its review and evaluation of the available information before determining whether or not the tolerance exemption should be established." (EPA, 2003).

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