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

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.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. 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., Scientific Analyst/Writer, CIR.

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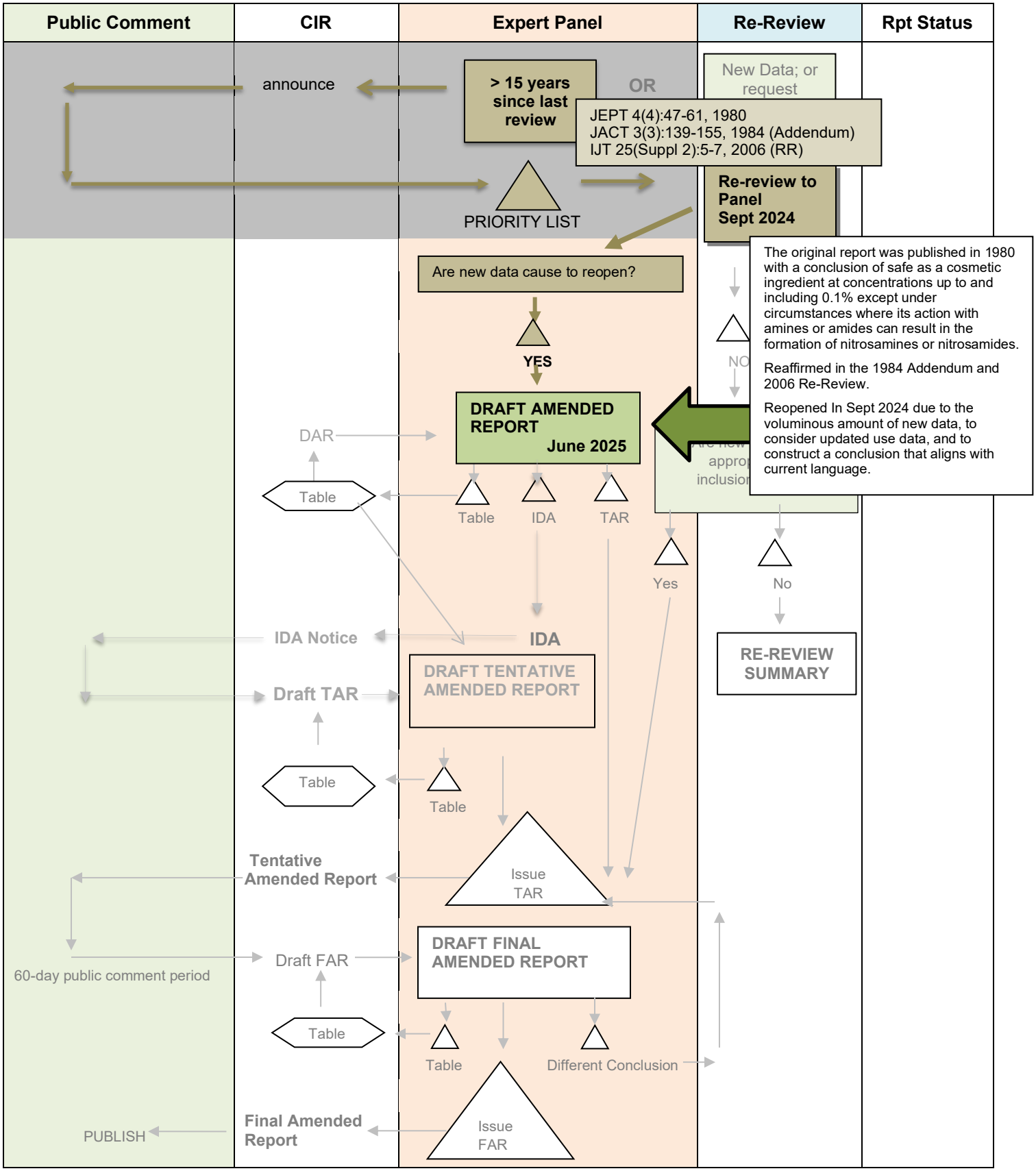
RE-REVIEW FLOW CHART

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

MEETING June 2025



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Scientific Analyst/Writer, CIR
Date: May 16, 2025
Subject: Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of 2-Bromo-2-Nitropropane-1,3-Diol in 1980 (identified as *originalreport1980_2-Bromo-2-Nitropropane-1,3-Diol_062025* in the pdf). The Panel concluded that *2-Bromo-2-Nitropropane-1,3-Diol was safe as a cosmetic ingredient at concentrations up to and including 0.1% except under 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 their 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* (*addendum1984_2-Bromo-2-Nitropropane-1,3-Diol_062025*). The Panel previously considered a re-review of this report in 2003 after studying the data submitted (*RRdata2003_2-Bromo-2-Nitropropane-1,3-Diol_062025*) and reaffirmed the conclusion, as published in 2006 (*rereview2006_2-Bromo-2-Nitropropane-1,3-Diol_062025*).

Because it had been at least 15 years since the previous re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, in August 2024 an extensive search of the world's literature was performed for studies dated 2000 forward related to 2-Bromo-2-Nitropropane-1,3-Diol. After reviewing that information at the meeting in September 2024, the Panel decided to reopen its safety assessment due to the voluminous amount of new data, to consider updated use data, and to construct a conclusion that aligns with current language. The Panel also wants to re-assess the possibilities of the formation of endogenous nitrosamines in humans due to dermal penetration.

RLD submitted in 2024 showed that 2-Bromo-2-Nitropropane-1,3-Diol is used in 167 cosmetic formulations. The highest use category was hair preparations (non-coloring; 64 total uses). According to the results of Council surveys that were submitted in 2023 and 2025 (*data1_2-Bromo-2-Nitropropane-1,3-Diol_062025; data2_2-Bromo-2-Nitropropane-1,3-Diol_062025*, respectively), the maximum reported concentration of use is 0.05% (in leave-on skin cleansing hand wipes, eye makeup removers, and disposable wipes); in 2003, the maximum reported concentration of use was 0.1% (in eye shadow, perfumes, blushers, and lipsticks).

Enclosed with this Draft Amended Report is the following information.

1. flow chart *(flow_2-Bromo_2-Nitropropane-1,3-Diol_062025)*
2. literature search strategy (*search_2-Bromo-2-Nitropropane-1,3-Diol_062025)*
3. history (*history_2-Bromo-2-Nitropropane-1,3-Diol_062025)*
4. data profile (*dataprofile_2-Bromo-2-Nitropropane-1,3-Diol_062025)*
5. transcripts from the recent meeting at which reopening this report was discussed *(transcripts_2-Bromo-2-Nitropropane-1.3-Diol_062025)*
6. minutes from the meetings at which the original reports were discussed *(originalminutes_2-Bromo-2-Nitropropane-1,3-Diol_062025)*

If no further data are needed to reach a conclusion of safety, the Panel should formulate a Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

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.

2-Bromo-2-NitroPropane-1,3-Diol* – March 2025 – Thushara Diyabalanage																														
	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**	**O**	X	X	X	O	O	O	X	X	O	X		O	X	O		O	X	O	O		X	O			X	X	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/

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

Belsito Team Meeting– 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.

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:	Draft Amended Report for Panel Review
Release Date:	May 16, 2025
Panel Meeting Date:	June 9-10, 2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.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. 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., Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

AD	atopic dermatitis
Aq.	aqueous
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
EBS	European baseline series
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FOU	frequency of use
HPLC	high-pressure liquid chromatography
l.o.	leave-on
LOEL	lowest-observable-effect-level
MED	minimum erythema dose
MoCRA	Modernization of Cosmetics Regulation Act
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 of Economic Co-operation and Development
o/w	oil in water
Panel	Expert Panel for Cosmetic Ingredient Safety
RLD	Registration and Listing Data
r.o.	rinse-off
TG	test guideline
US	United States
UVA	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of 2-Bromo-2-Nitropropane-1,3-Diol as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*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 their 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] and that National Industrial Chemical Notification and Assessment Scheme (NICNAS)[7] 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.

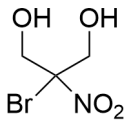

Figure 1. 2-Bromo-2-Nitropropane-1,3-Diol

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.[8] 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. (Methods of manufacture data were not included in the original report, no additional methods were found in the published literature, and unpublished data were not submitted.) Bishydroxymethylation of nitromethane using formaldehyde in the presence of a base gives the salt corresponding to 2-nitropropane-1,3-diol.[2,9] This salt is subsequently reacted with bromine to from 2-Bromo-2-Nitropropane-1,3-Diol.

Degradation

2-Bromo-2-Nitropropnae-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 Environmental Protection Agency (EPA) have shown a minimal risk of formaldehyde exposure for the handlers of 2-Bromo-2-Nitropropnae-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-Nitropropnae-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.[10] Chemicals such as citric acid and sodium dodecylsulfate, and physical factors such as elevated temperature, sunlight, ultraviolet (UV) light radiation, 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.[11]

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 Food and Drug Administration (FDA), cosmetic ingredients that contain diethanolamine, 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.*

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. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, 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.[12] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to 2023 FDA VCRP data, 2-Bromo-2-Nitropropane-1,3-Diol was reported to be used in 36 cosmetic formulations,[13] as opposed to 1 use reported in 2002[4] (Table 2), indicating an increase in frequency of use. RLD received in 2024 reported that is used in 167 cosmetic formulations.[14] The reported maximum concentration of use has decreased. According to Council survey results submitted in 2023[15] and 2025,[16] the maximum reported concentration of use is 0.05% (in hand wipes (a leave-on), disposable wipes and eye makeup removers); in 2003, the maximum reported concentration of use was 0.1%.

2-Bromo-2-Nitropropane-1,3-Diol is used in products that are applied near the eye (concentration not reported) and in products that result in mucous membrane exposure (e.g., douches). It is also reported to be used in baby products (e.g. baby wipes and other baby products; concentration of use not reported).

Some products containing 2-Bromo-2-Nitropropane1,3-Diol may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, 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 using airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, the Council currently surveys the cosmetic industry for maximum reported

use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available, when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, 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. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

In the European Union, 2-Bromo-2-Nitropropane-1,3-Diol is included in Annex V, the List of Preservatives Allowed in Cosmetic Products.[17]

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] It is used in pharmaceuticals, non-agricultural and agricultural pesticides, paints, coloring agents, cleaning and washing agents, adhesives, (21 CFR 175.105) solvents, fillers (21 CFR 176.170) and as a component in the paper and paper board that contacts food according to prescribed conditions (21 CFR 176. 300).[18]

TOXICOKINETIC STUDIES

Dermal Absorption

In Vitro

An in vitro skin penetration study to determine the skin permeability of 2-Bromo-2-Nitropropane1,3-Diol was conducted following Organisation of Economic Co-operation and Development (OECD) test guideline (TG) 428 using porcine ear skin.[19] Three formulations (aqueous (aq.) solution, 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, and 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 $\mu g/cm^2/h$, 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.

Because 2-Bromo-2-Nitropropane-1,3-Diol is a formaldehyde-releaser, the amount of formaldehyde in the receptor fluid was also measured. The mass balance of 2-Bromo-2-Nitropropane-1,3-Diol at the end of the studies was less than 100%, indicating 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 $\mu g/cm^2/h$, respectively).

Animal

An aqueous solution of 2-Bromo-2-Nitropropane-1,3-Diol (4 mg/ml) applied to the skin of the rats and rabbits was absorbed relatively slowly (approximately 11% in 24 h).[2,5] *A slightly more rapid and greater absorption was observed when it was dissolved in acetone.*

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 2-Bromo-2-Nitropropane-1,3-Diol, 3-[^{14}C] 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 ^{14}C was excreted in urine. The feces and tissues represented minor routes. The fourth study used urine to identify the metabolites, 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

Dermal

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 and mice 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] Another study determined the oral LD_{50} of 2-Bromo-2-Nitropropane-1,3-Diol to be 180 mg/kg in rats, 270 mg/kg in mice, and 250 mg/kg in dogs. Two samples of 2-Bromo-2-Nitropropane-1,3-Diol tested in rats reported LD_{50} values of 292 and 320 mg/kg. The oral LD_{50} for aqueous solution of th etest material the mice and rats were reported as 350 and 400 mg/kg. 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.

When 2-Bromo-2-Nitropropane-1,3-Diol was administered orally, both male and female rats produced clinical signs of sedation, nasal exudate, gasping, wheezing, cyanosis, and convulsions.[7] The study reported an acute oral LD_{50} of 307 and 342 mg/kg bw for males and females, respectively.

Inhalation

2-Bromo-2-Nitropropane-1,3-Diol showed a 4-h LC_{50} of 18 mg/m^3 when administered to 10 male and 10 female rats per exposure concentration.[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 reg 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.

In an acute inhalation study conducted with Sprague-Dawley rats in three test groups and one control group, each test group had 5 female rats and five male rats.[6] The animals were exposed nose/head only to 38, 89, and 588 mg/m^3 of 2-Bromo-2-Nitropropane-1,3-Diol for 4 h. Control animals received filtered air without test substance. 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. Body weight was assessed prior to test initiation, at the end of the 4-h exposure, once daily between days 1 and 7 of observation, on day 14, and prior sacrifice. 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 5 male and 5 female Fisher 344 rats were exposed nose-only to two doses of 2-Bromo-2-Nitropropane-1,3-Diol at 120 and 1140 mg/m^3 for 4 h, according to OECD TG 403.[6] The mass median aerodynamic diameter (MMAD) was ≥ 3.29 and ≤ 9.34 µm. The acute inhalation LC_{50} was determined to be > 120 but < 1140 mg/m^3. At low-dose level, one male rat died whereas 4/5 males and 3/5 females died during exposure. The remaining animals died by the end of the day 3.

During another study, rats exposed to 0, 50, 500, or 5000 mg/m^3 of 2-Bromo-2-Nitropropane-1,3-Diol developed eye irritation, dyspnea, profuse mucus production and lethargy.[7] 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.

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™.[20] Based on the effect on tissue viability, concentrations of 0.1 and 1.0% induced toxicity.

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 fed 100 and 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

Rats tolerated daily oral doses of 2-Bromo-2-Nitropropane-1,3-Diol,20 mg/kg, for 90 d; 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

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 to 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 to 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. 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 to 15 of gestation produced local skin reaction at the site of application but had no other adverse effects on the dams or the fetuses. Administration of daily oral doses of Bromo-2-Nitropropane-1,3-Diol at up to 100 mg/kg to pregnant rats and doses of up to 10 mg/kg to rabbits from day 8-16 of gestation, indicated no embryotoxic or teratogenic effects.*[3] *There was no effect on the young, in rats given up to 40 mg/kg 2-Bromo-2-Nitropropane-1,3-Diol orally from day 15 of gestation throughout lactation. Similar doses given to male rats for 63 d prior to mating and to female rats 14 d prior to mating had no effect on reproduction. Up to 8 mg/kg 2-Bromo-2-Nitropropane-1,3-Diol in gum acacia given orally to rats on days 6-15 of pregnancy had no teratogenic effects. Dermal application of up to 2% Bromo-2-Nitropropane-1,3-Diol to rats from day 6 - 15 of gestation showed no adverse effects.*

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 evidenced by decreased body weight gain. No animal was reported as having dose-related clinical signs. The no-observable-effect-levels (NOEL) for maternal toxicity and developmental toxicity were ≥ 80 mg/kg/d. In another developmental toxicology study, groups of 18, 19, 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 solution of the test substance were administered daily at normal dose level of 0 (vehicle control), 5, 20, 40 or 80 mg/kg/d and the dose volume of 2 ml/kg. Based on the finding of these studies, the NOEL and lowest-observable-effect-level (LOEL) for maternal toxicity were 40 and 80 mg/kg/d, respectively. In another study 2-Bromo-2-Nitropropane-1,3-Diol was administered to 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 0.25, 70 and 200 mg/kg/d, respectively. Reproductive toxicity was observed only in the high dose group and the NOEL and LOEL for systemic toxicity was 25 and 70 mg/kg/d. The NOEL and LOEL for reproductive toxicity 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.[2,5] *In a V79 cell mutation assay conducted with Chinese hamster lung fibroblasts with and without metabolic activation 2-Bromo-2-Nitropropane-1,3-Diol was tested negative for mutagenicity.*[5]

An Ames test was conducted to determine the mutagenicity of 2-Bromo-2-Nitropropane-1,3-Diol.[21] Negative test results were reported for all the 31 trials conducted with 0 - 166 ug/plate 2-Bromo-2-Nitropropane-1,3-Diol in *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98 with and without metabolic activation employing positive controls.

In a gene mutation study conducted using an in vitro mammalian cell transformation assay, 2-Bromo-2-Nitropropane-1,3-Diol was tested in the V79/HPRT-test at concentrations ranging from 1 - 21 µg/ml without S9 mix and from 3 - 27 µg/ml with S9 mix.[6] Under both activation conditions, clear cytotoxic effects were induced (at concentrations ≥15 µg /ml in the absence of activation and ≤ 18 µg/ml with activation). Due to this sensitivity, 2-Bromo-2-Nitropropane-1,3-Diol is considered to be genotoxic in the V79/HPRT forward mutation assay.

2-Bromo-2-Nitropropane-1,3-Diol was investigated by an in vitro cytogenicity/chromosome aberration study on mammalian cells.[6] A weak but reproducible clastogenic effect was seen in absence of S9 mix at 30 ug/ml, but not in the presence of S9 at 40 ug/ml top dose. The authors of the study suggested that the observed clastogenic effect rather might have been due to formaldehyde liberated from the degradation of 2-Bromo-2-Nitropropane-1,3-Diol, not from 2-Bromo-2-Nitropropane-1,3-Diol itself.

In Vivo

An in vivo micronucleus assay was conducted in male and female CD1 mice that received single oral doses of 2-Bromo-2-Nitropropane-1,3-Diol (80 or 160 mg/kg bw).[5] *There was no increase in the number of micronuclei as compared to the positive control cyclophosphamide (75 mg/kg,) which demonstrated significant increases in both sexes.*

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 the 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, using KeraSkin™, a reconstructed human epidermis model.[20] The dermal irritation caused by these biocides 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. The degree of damage was scored by visual evaluation of 6 examiners in a blinded fashion using the parameters such 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 (5mg, 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 moderately to severely irritation. 2-Bromo-2-Nitropropane-1,3-Diol in 0.5 and 2% emulsions and solutions were tested on rabbit skin and produced irritation at 2% from one application while no irritation was produced from four daily applications of 0.5% concentrations. When applied to non-abraded, shaved skin of rabbits in a variety of solvents, 2-Bromo-2-Nitropropane-1,3-Diol 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 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.

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 toxic effects.[5] A concentration of 0.5% applied similarly for 4 wk was well tolerated.

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%. The aqueous patches showed slight erythema in one volunteer at 0.25% concentration.

Sensitization

Animal

2-Bromo-2-Nitrtopropane-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 by an occluded patch of 1.5% 2-Bromo-2-Nitropropane-1,3-Diol in water which was left in place for 48 h. 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 and observations were repeated for a total of 4 applications. 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. Another test using a 1% solution 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 2-Bromo-2-Nitropropane-1,3-Diol (98.8% purity) in 1% acetone.[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 dinotrochlorobenzene.*

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

Dermal application of 1% 2-Bromo-2-Nitropropane-1,3-Diol (> 98.8%) in acetone to guinea pigs did not show any sensitization effects.[7] Three induction treatments on the outer surface of each ear and, 1 wk later, one challenge treatment on the back and flank, did not produce any sensitization effects.

Human

Ten volunteers were tested for skin irritation with closed patches of 2-Bromo-2-Nitropropane-1,3-Diol at 0, 0.5, 1.0, and 2.0% in soft paraffin and 0, 0.05, 0.1, and 0.25% in aqueous buffer at pH 5.5.[2] *The paraffin patches produced slight erythema in 2 volunteers at 1% and moderate erythema in 4 volunteers at 2% concentrations. The aqueous patches produced slight erythema in 1 of the volunteers at 0.25%.*

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% aqueous 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 2% in solution and in 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 nonirritating 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 show 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.[7] The effects subsided in most of the animals after 7 d.

CLINICAL 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.*

Retrospective and Single or Multicenter Studies

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

Clinical studies are described in Table 3. Retrospective, single-center, multi-center studies evaluated the prevalence of reactions to 2-Bromo-2-Nitropropane-1,3-Diol.[22-28]

Case Reports

A 16-yr-old girl with a history of childhood asthma and allergic rhinitis had eczematous eruptions of the flexor forearms. [29] Patch testing showed a +2 reaction to 2-Bromo-2-Nitropropane-1,3-Diol, an ingredient present in family cat litter. A 70-yr-old white man presented with a 6-wk history of an acute pruritic eruption in the axillary vaults, inguinal folds, and central lumbar area, was suspected for having allergic contact dermatitis due to the severity of symptoms.[30] The patch-testing results were positive for two known allergens and 2-Bromo-2-Nitropropane-1,3-Diol. A patient who had consumed several bottles of a topical antiseptic solution containing 2-Bromo-2-Nitro-Propane-1,3-Diol, showed the presence of bilateral putaminal necrosis.[31] The observation of permanent necrotic lesion of putamina was ascribed to the accumulation of formic acid derived from 2-Bromo-2-Nitropropane-1,3-Diol.

SUMMARY

The Panel conducted a safety assessment on 2-Bromo-2-Nitro-1,3-Diol in 1980 and concluded that it 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. Due to the availability of new scientific literature, an addendum to the report was published in 1984 where the Panel reaffirmed their 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. A re-review of this report in 2004/2005, reaffirmed that conclusion, as published in 2006. In September 2024, since more than 15 years have passed since the last review, the Panel reviewed the 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, and 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 *N*-nitrosodiethanolamine (NDELA) and of morpholine to form *N*-nitrosomorpholine. Studies conducted by FDA had shown the cosmetic products such as creams, cream lotions, hair shampoos, and cream hair conditioners are known to contain such amines and their derivatives. Endogenous formation of nitrosamines can be avoided by proper formulation preventing the combination of such ingredients with 2-Bromo-2-Nitropropane-1,3-Diol and testing the products under use conditions for the presence of nitrosamines.

According to 2023 FDA VCRP data, 2-Bromo-2-Nitropropane-1,3-Diol was reported to be used in 36 cosmetic formulations, as opposed to 1 use reported in 2002 (Table 2), indicating an increase in frequency of use. RLD received in 2024 reported that it is used in 167 cosmetic formulations. The reported maximum concentration of use has decreased. According to Council survey results submitted in 2023 and 2025, the maximum reported concentration of use is 0.05% (in hand wipes (a leave-on), disposable wipes and eye makeup removers); in 2003, the maximum reported concentration of use was 0.1%.

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 the aq. solution and lowest with the 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 aq. solution, while there was no lag time for diffusion when applied in a hydrogel or emulsion.

Metabolic breakdown of 2-Bromo-2-Nitropropane-1,3-Diol includes reductive de-halogenation resulting in the formation of 2-nitropropane-1,3-diol. This in turn may be further metabolized to glycerol and eventually carbon dioxide. ^{14}C radio labeling studies indicated that ingested 2-Bromo-2-Nitropropane-1,3-Diol is mostly expelled with urine

Percutaneous applications of 2-Bromo-2-Nitropropane-1,3-Diol at doses of 160 mg/kg or greater caused death in rats. In another acute toxicology study, the dermal application at the doses of 0, 64, 160, 400, and 1000 mg/kg bw, produced edema, hemorrhage, labored breathing, prostration, and lung congestion. The acute dermal LD_{50} was reported to be 64 – 160 mg/kg bw.

The oral LD_{50} values for 2-Bromo-2-Nitropropane-1,3-Diol administered mouse were 374 mg/kg (male) and 307 mg/kg (female) whereas for rats, 327 mg/kg (male) and 342 mg/kg (female).

In an acute inhalation study with Sprague-Dawley rats in three test groups and one control-group, the animals were nose/head-exposed to the test atmosphere for 4 h and given doses 38, 89, and 588 mg/m^3. Three deaths were reported from the high dose group and most animals showed clinical signs of toxicity. The LC_{50} in rats was > 120 mg/m^3 but < 1140 mg/m^3. In another acute inhalation study, rats were exposed to various aerosolized concentrations of 2-Bromo-2-Nitropropane-1,3-Diol. No mortalities occurred. During another study, rats were exposed to 0, 50, 500, or 5000 mg/m^3 of 2-Bromo-2-Nitropropane-1,3-Diol, 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.

2-Bromo-2-Nitropropane-1,3-Diol was not mutagenic in an Ames test (0 - 166 ug/plate, with or without metabolic activation). 2-Bromo-2-Nitropropane-1,3-Diol is considered to be genotoxic in the V79/HPRT forward mutation assay, and a weak but reproducible clastogenic effect was seen in an in vitro cytogenicity/chromosome aberration study on mammalian cells. In the cytogenicity/chromosome aberration assay, the authors of the study suggested that the observed clastogenic effect rather might have been due to formaldehyde liberated from the degradation of 2-Bromo-2-Nitropropane-1,3-Diol, not from 2-Bromo-2-Nitropropane-1,3-Diol itself.

In an in vitro reconstructed human epidermis model (KeraSkin™) study, ≤ 0.1% 2-Bromo-2-Nitropropane-1,3-Diol was not predicted to be irritating, but tissue viability was not acceptable with 1%. 2-Bromo-2-Nitropropane-1,3-Diol ws not a sensitizer in guinea pig assays.

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. 2-Bromo-2-Nitropropane-1,3-Diol 106 mg (crystalline material) placed in the eyes of rabbits caused immediate irritation of the conjunctiva and delayed effects on the cornea and iris. These later effects were noted on the fourth day and remained on the last day (7^{th}) of observation. Scores, according to the Draize scale, on the d-7 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. A 0.1 ml dose of a 10 or 20% aqueous solution of 2-Bromo-2-Nitropropane-1,3-Diol placed in the conjunctival sac of a rabbit's eye produced severe ocular damage. 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 d. Washing reduced recovery time to 14 d in one test and 21 in another. 2-Bromo-2-Nitropropane-1,3-Diol 2% in solution and in emulsion was reported to be irritating to the rabbit eye. However, four daily applications of 0.5% solution and emulsion was not irritating. 2-Bromo-2-Nitropropane-1,3-Diol was also tested as a 0.5% solution in 1 normal 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% under the same conditions did not show irritation.

PREVIOUS DISCUSSION - 1984 ADDENDUM

The major manufacturer of 2-Bromo-2-Nitropropane-1,3-Diol recommends that it not be used in concentrations above 0.1% and this agrees with the recommendation of the CIR Expert Panel.[2,3] *However, in a recent computer search by the FDA, 2-Bromo-2-Nitropropane-1,3-Diol, 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 2-Bromo-2-Nitropropane-1,3-Diol 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 2-Bromo-2-Nitropropane-1,3-Diol.*

2-Bromo-2-Nitropropane-1,3-Diol 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 2-Bromo-2-Nitropropane-1,3-Diol 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 2-Bromo-2-Nitropropane-1,3-Diol for endogenous formation of N-nitrosamines in humans. However, a long-term mouse skin bioassay and a rat feeding study indicated that 2-Bromo-2-Nitropropane-1,3-Diol 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-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.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

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 (g/mol)	199.99	2
Specific Gravity (@	1.9	8
Melting Point (ºC)	130	8
Flash Point (ºC)	167	8
Water Solubility (g/l @ 23ºC & pH)	Freely soluble	2
Other Solubility (g/l @ ºC & pH)	Soluble in ethanol, tetrahydrofuran and propylene glycol, slightly soluble in mineral oil and vegetable oils	2
log P_{ow} (@ ºC)	0.18	8
UV Absorption (λ) (nm) (0.1 M NaOH)	244	5

Table 2. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*	
	RLD (2024)[14]	**VCRP (2023)[13]**	**VCRP (2002)[4]**	**% (2023[15], 2025[16])**	**% (2003)[4]**
Totals*	**167**	**36**	**1**	**0.00045-0.05**	**0.009-0.1**
summarized by likely duration and exposure**					
Duration of Use					
Leave-On	***	*7*	*1*	*0.001-0.05*	*0.009-0.1*
Rinse-Off	***	*29*	*NR*	*0.00045-0.05*	*0.02-0.05*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*
Exposure Type					
Eye Area	***	NR	NR	0.05	0.05-0.1
Incidental Ingestion	***	NR	NR	NR	0.1
Incidental Inhalation-Spray	***	1[a]	NR	NR	0.03-0.1; 0.01-0.05[b]
Incidental Inhalation-Powder	***	1[a]	NR	NR	NR
Dermal Contact	***	35	NR	0.00045-0.05	0.009-0.1
Deodorant (underarm)	***	NR	NR	NR	NR
Hair - Non-Coloring	***	1	1	NR	NR
Hair-Coloring	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR
Mucous Membrane	***	21	NR	0.00045-0.026	0.1
Baby Products	***	3	NR	NR	NR
as reported by product category					
Baby Products	***1***				
Baby Shampoos	NR	NR	NR	NR	NR
Baby Wipes	1	NA	NA	NR	NA
Other Baby Products	NR	3	NR	NR	NR
Bath Preparations	***3***				
Bath Oils, Tablets, and Salts	3	NR	NR	NR	NR
Eye Makeup Preparations (not children's)	***3***				
Eyeliner	2	NR	NR	NR	NR
Eye Shadow	NR	NR	NR	NR	0.1
Eye Makeup Remover	NR	NR	NR	0.05	0.05
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	1	NA	NA	NA	NA
Fragrance Preparations					
Cologne and Toilet Water	NR	NR	NR	NR	0.03
Perfumes	NR	NR	NR	NR	0.1
Hair Preparations (non-coloring)	***64***				
Hair Conditioners	1 (l.o.)	NR	NR	NR	NR
Permanent Waves	3	NR	NR	NR	NR
Shampoos (non-coloring)	3 (r.o.)	NR	NR	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids	27	NR	NR	NR	NR
Other Hair Preparations	31	1	1	NR	NR
Makeup Preparations (not eye; not children's)					
Blushers and Rouges (all types)	NR	NR	NR	NR	0.1

Table 2. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*	
	RLD (2024)[14]	**VCRP (2023)[13]**	**VCRP (2002)[4]**	**% (2023[15], 2025[16])**	**% (2003)[4]**
Lipstick and Lip Glosses	NR	NR	NR	NR	0.1
Other Makeup Preparations	NR	1	NR	NR	NR
Personal Cleanliness	***56***				
Bath Soaps and Body Washes	4	5	NR	0.00045-0.026	NR
Douches	3	NR	NR	NR	NR
Disposable Wipes	49	NA	NA	0.04-0.05	NA
Other Personal Cleanliness Products	2 (r.o.)	16	NR	NR	NR
Shaving Preparations	***7***				
Aftershave Lotions	NR	NR	NR	NR	0.03
Other Shaving Preparation Products	7	NR	NR	NR	NR
Skin Care Preparations	***37***				
Cleansing	7	4	NR	0.001-0.05 (handwipes; l.o)	0.02
Face and Neck (excluding shaving preparations)	3 (l.o.); 1 (r.o.)	NR	NR	NR	NR
Body and Hand (excluding shaving preparations)	18 (l.o.)	1	NR	NR	NR
Moisturizing	12	NR	NR	NR	NR
Paste Masks (mud packs)	1	4	NR	NR	NR
Skin Fresheners	NR	NR	NR	NR	0.01
Other Skin Care Preparations	1 (l.o) 1 2 (r.o.)	1	NR	NR	0.009
Suntan Preparations					
Suntan Gels, Creams, and Liquids	NR	NR	NR	NR	0.05

NR – not reported; NA – not applicable (this category was not part of the VCRP)

l.o. – leave-on; r.o. – rinse-off

*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.

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

*** In the RLD each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

[a] 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

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

Table 3. Retrospective and single or multicenter studies				
Study Protocol	**Number of Participants**	**Period**	**Result**	**Reference**
Retrospective Studies				
Retrospective cross-sectional study to determine the prevalence of wet wipes as a source of allergy. Patents were patch tested.	9037 patients		0.9% had a positive patch test for an allergy identified. Most commonly associated allergens included 2-Bromo-2-Nitropropane-1,3-Diol (27.4%). Anal/genital dermatitis was 15 times more likely ($P < 0.0001$) in those with wet wipe allergy	22
Single Center Studies				
Clinical study to determine the trends and changes of allergens that cause contact dermatitis. Patch tests were conducted.	3115 patients	2006-2010	Observed a mean of 73.0 allergens. Rates were lower for 10 allergens including 2-Bromo-2-Nitropropane-1,3-Diol which was 0.25%.	23
Clinical study to investigate the predisposition of patients with atopic dermatitis to develop cutaneous delayed-type hypersensitivity to skincare products containing preservatives. Patch testing to Patch testing to NACDG standard screening series	2453 patents, 2111 with AD 342 without AD		Higher incidence of positive patch test reaction among patients with AD were statistically significant. AD occurrences showed associated with contact hypersensitivity to 2-Bromo-2-Nitropropane-1,3-Diol	24
Clinical trial conducted to evaluate the European baseline series (EBS) for contact allergens. Routine patch test were administered to the upper back and removed by the patients after 48 h. Readings were done in days 3, 6, and 7.	748 adults		Eight allergens including 2-Bromo-2-Nitropropane-1,3-Diol not listed in EBS had $\geq 0.5\%$ prevalence rate.	25
Multi Center Studies				
Multi-center clinical study involving 12 centers in North America. Patients were tested against 70 allergens in standard manner	4238 patients	2013 and 2014	Compared with previous decade positivity of all formaldehyde-releasing agents have decreased. 2-Bromo-2-Nitropropane-1,3-Diol showed 1.6% with risk rate of 0.60.	26
Multi-center clinical study conducted at 13 centers in North America. Patients were tested against 70 allergens in standard manner	4871 patients	2013 and 2014	2-Bromo-2-Nitropropane-1,3-Diol did not appear as a key allergen.	27
Multi-center clinical study conducted in 12 centers in North America	5597 patients	2015 and 2016	2-Bromo-2-Nitropropane-1,3-Diol was not observed as a key allergen and its positive reaction rate has not increased.	28
A multi-center retrospective study conducted in 14 centers in North America. Series of 70 allergens tested in standard manner	4947 patients with dermatitis	2017 and 2018	2-Bromo-2-Nitropropane-1,3-Diol was not observed as a key allergen	26

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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.

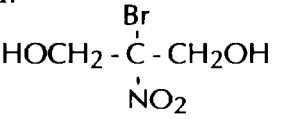
BNPD had no effect on reproduction, was not a teratogen, and had no embryotoxic effects. It was not a mutagen by the standard mouse dominant lethal test nor by the bacterial reverse mutant system.

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

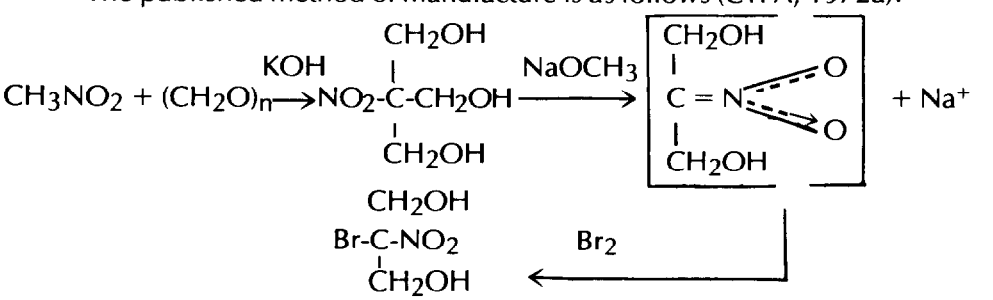
Structure

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):



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

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

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

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).

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.

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).

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).

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

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).

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

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.

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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5

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

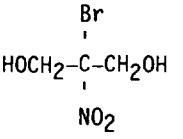
A literature review of test data that have become available since the 1979 toxicological safety report on 2-Bromo-2-Nitropropane-1,3-Diol (BNPD) is presented and discussed. The earlier conclusion that BNPD is safe as a cosmetic ingredient at concentrations up to 0.1% except under circumstances where 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]

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

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).

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.

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]

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

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

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

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-

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]

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]

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]

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

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

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.

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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

C I R

September 9, 2003

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Re-review of 2-Bromo-2-Nitropropane-1,3-Diol (Bronopol)

In 1980, CIR published a Final Report on 2-Bromo-2-Nitropropane-1,3-Diol with the following conclusion: 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. It is important to note that, in 1984, a report addendum reaffirming the conclusion in this Final Report was published. Furthermore, the following statement is inserted after the original conclusion: 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. Copies of the published Final Report and Addendum are included

A search of the currently available scientific literature resulted in numerous publications on 2-Bromo-2-Nitropropane-1,3-Diol, most addressing its irritation/sensitization potential. The available data are summarized in the attached re-review background document along with use/concentration data that have been provided.

The task for the Panel at this meeting is to determine whether the conclusion on 2-Bromo-2-Nitropropane-1,3-Diol is still valid. If it is not, an amendment should be initiated. If the conclusion is still valid, then the Panel should decide if there is a need for an addendum to add significant new safety or other data. If there is no such need, the Panel may simply describe the new information considered and reaffirm the original conclusion.

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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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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Concentration of Use by FDA Product Category – 2-Bromo-2-Nitropropane-1,3-Diol

Product Category	Maximum Concentration of Use
Eye makeup removers	0.05%
Bath soaps and detergents	0.00045-0.026%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) Hand wipes (leave-on)	 0.001-0.05%

Information collected in 2022-2023

Table prepared: February 23, 2023

Concentration of Use by FDA Product Category[1]

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

Product Category	Maximum Concentration of Use
Disposable wipes	0.04-0.05%

Information collected in 2025

Table prepared: March 27, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.