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

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*All interested persons are provided 60 days from the above release date (i.e., by **May18, 2026**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

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

ABSTRACT

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

INTRODUCTION

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

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

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

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

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

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

CHEMISTRY

Definition and Structure

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

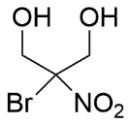

Figure 1. 2-Bromo-2-Nitropropane-1,3-Diol

Chemical Properties

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

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

Method of Manufacture

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

Degradation

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

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

Nitrosation

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

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

USE

Cosmetic

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

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

When determining whether to re-open this safety assessment, the Panel considered FDA Voluntary Cosmetic Registration Program (VCRP) data submitted to CIR in 2023 as compared to that stated in the previous report. In 2023, 2-Bromo-2-Nitropropane-1,3-Diol was reported to be used in 36 cosmetic formulations,[18] as opposed to 1 use reported in 2002.[4] Additionally, the reported maximum concentration of use has decreased; in 2003, the maximum reported concentration of use was 0.1%.

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

In the European Union, 2-Bromo-2-Nitropropane-1,3-Diol is included in Annex V, the List of Preservatives Allowed in Cosmetic Products.[19] The maximum concentration allowed in ready for use preparations is 0.1%, and the formation of nitrosamines is to be avoided.

Non-Cosmetic

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

TOXICOKINETIC STUDIES

Dermal Absorption

In Vitro

An in vitro skin penetration study to determine the skin permeability of 2-Bromo-2-Nitropropane-1,3-Diol was conducted following Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428 using porcine ear skin.[22] Three formulations (aqueous (aq.) solution, oil-in-water (o/w) emulsion, and a hydrogel) containing 4% (w/w) 2-Bromo-2-Nitropropane-1,3-Diol (> 98% pure) were evaluated over a 24 – 25-h period using vertical Franz-type diffusion cells with an effective area available for diffusion of 0.79 cm^2, and a receiver compartment with a 6 ml capacity. One ml of the formulation was placed in the donor compartment, while the receptor compartment was filled with phosphate buffered saline (PBS) or 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)/saline (20/150 mM) buffer. It was evident that the transdermal absorption was dependent on the formulation, with absorption being greatest from the aq. solution and lowest with the hydrogel; transdermal flux was 11.0 and 0.8 $\mu g/cm^2/h$, 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 quantified. 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) was absorbed relatively slowly (approximately 11% in 24 h) when applied to the skin of rats and rabbits.[2,5] The rate of absorption "remained low" even when the material was applied using an occlusive dressing. A slightly more rapid and greater absorption was observed when 2-Bromo-2-Nitropropane-1,3-Diol was dissolved in acetone. (No further information was available.)

Absorption, Distribution, Metabolism, and Excretion

Animal

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

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In Vitro

Inhalation

The inhalation toxicity potential of 0.02, 0.1, and 1.0% 2-Bromo-2-Nitropropane-1,3-Diol was evaluated in the airway model SoluAirway™.[23] Based on the effect on tissue viability, concentrations of 0.1 and 1.0% induced toxicity.

Animal

Dermal

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

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

Oral

2-Bromo-2-Nitropropane-1,3-Diol administered orally to rats (307 – 342 mg/kg) and mice (327 – 374 mg/kg) caused gastrointestinal lesions.[2] The LD_{50} values reported for mice were 374 mg/kg (male) and 307 mg/kg (female), whereas for rats, 327 mg/kg (male) and 342 mg/kg (female).[2] In another study, the oral LD_{50} of 2-Bromo-2-Nitropropane-1,3-Diol was determined to be 180 mg/kg in rats, 270 mg/kg in mice, and 250 mg/kg in dogs. The oral toxicity of 2-Bromo-2-Nitropropane-1,3-Diol (2 samples) was tested in rats; the LD_{50} values were 292 and 320 mg/kg. The oral LD_{50} for an aqueous solution of the test material in mice and rats was reported as 350 and 400 mg/kg, respectively. The oral LD_{50} in another study in rats was 193 mg/kg; symptoms observed at 4 h included decreased motor activity and respiratory rates. Single doses of 40 or 100 mg/kg of 2-Bromo-2-Nitropropane-1,3-Diol in dogs caused transient gastric irritation.

Inhalation

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

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

deaths were reported in rats exposed to 2-Bromo-2-Nitropropane-1,3-Diol (5000 mg/m^3) for 6 h. It caused labored breathing and decreased body weight.

In an acute inhalation study conducted with Sprague-Dawley rats in three test groups and one control group, each group had 5 female rats and 5 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 2-Bromo-2-Nitropropane-1,3-Diol at concentrations of 120 and 1140 mg/m^3 for 4 h, in accord with OECD TG 403.[6] The mass median aerodynamic diameters (MMAD) were 3.29 ± 1.64 and ≤ 9.34 ± 4.67 µm for the low and high concentrations, respectively. The acute inhalation LC_{50} was determined to be > 120 but < 1140 mg/m^3. An MMAD of 1 - 4 µm could not be maintained at concentrations of 2-Bromo-2-Nitropropane-1,3-Diol >1 mg/l due to agglomeration. At low-dose level, one male rat died whereas 4/5 males and 3/5 females died during exposure. The remaining high-dose 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 (further details not available) developed eye irritation, dyspnea, profuse mucus production and lethargy.[8] Chronic pneumonitis was also observed after the test duration. There were no mortalities; the acute inhalation LC_{50} was identified as > 5000 mg/m^3.

Short-Term Toxicity Studies

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

Subchronic Toxicity Studies

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

2-Bromo-2-Nitropropane-1,3-Diol (98% pure) was administered by gavage in acidified (pH 4) water to groups of 24 mated Sprague-Dawley rats at dose levels of 0, 10, 28 or 80 mg/kg/d from day 6 – 15 of gestation.[5] *Marginal evidence of maternal toxicity was reported at the highest dose tested as indicated by decreased body weight gain. No animal was reported as having dose-related clinical signs. The no-observable-effect-level (NOEL) for both maternal toxicity and developmental toxicity was ≥ 80 mg/kg/d. In another developmental toxicology study, groups of 18, 19, or 20 mated female New Zealand white rabbits received 2-Bromo-2-Nitropropane-1,3-Diol by gavage during gestation days 7- 19, and were killed on day 28. Aqueous solutions of the test substance were administered daily at nominal dose levels of 0 (vehicle control), 5, 20, 40, or 80 mg/kg/d and the dose volume of 2 ml/kg. Based on the finding of these studies, the NOEL and lowest-observable-effect-level (LOEL) for developmental toxicity were 40 and 80 mg/kg/d, respectively. In another study 2-Bromo-2-Nitropropane-1,3-Diol was administered via the drinking water of Charles River COBS CD strain rats (13 males and 26 females in a group) during premating (80 - 87 d), mating, gestation, and lactating periods at 0, 0.25, 7,0 and 200 mg/kg/d, respectively. Reproductive toxicity was observed only in the high dose group, and the NOEL and LOEL for systemic toxicity (based on changes in organ weight and nephropathy) were 25 and 70 mg/kg/d, respectively. The NOEL and LOEL for reproductive toxicity (a decrease in the female fertility index) were 70 and 200 mg/kg/d, respectively.*

GENOTOXICITY STUDIES

In Vitro

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

An Ames test was conducted to determine the mutagenicity of 2-Bromo-2-Nitropropane-1,3-Diol.[24] Negative test results were reported for all the 31 trials conducted with 0 - 166 µg/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.

The genotoxic potential of 2-Bromo-2-Nitropropane-1,3-Diol was evaluated in an in vitro mammalian cell gene mutation assay performed in accord with OECD TG 476.[6] Chinese hamster lung fibroblast cells (V79) were exposed to 2-Bromo-2-Nitropropane-1,3-Diol at concentrations of 3 - 27 µg/ml and 1 – 21 µg/ml with and without metabolic activation, respectively. 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). 2-Bromo-2-Nitropropane-1,3-Diol induced a reproducible increase of mutant frequency without metabolic activation at concentrations of 6 – 15 µg/ml, while the statistically significant increase of mutant frequency observed with metabolic activation at concentrations of 6 – 18 µg/ml, was not reproducible. 2-Bromo-2-Nitropropane-1,3-Diol is considered 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 µg/ml, but not in the presence of S9 at 40 µg/ml top dose; the observed clastogenic effect 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 which male and female CD1 mice that received single oral doses of 2-Bromo-2-Nitropropane-1,3-Diol (80 or 160 mg/kg bw) were killed 24, 48, and 72 h after dosing.[5] *At all sampling times, the mice treated with 2-Bromo-2-Nitropropane-1,3-Diol and the negative control (sterile double-distilled water) had similar number of micronuclei per 1000 polychromatic erythrocytes of femur bone marrow examined per animal, while the positive control cyclophosphamide (75 mg/kg) demonstrated significant increases in the micronuclei in both sexes. Based on these observations, the result of the mutagenicity test was negative.*

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

An in vitro study was conducted to evaluate the potential dermal irritation of 11 commonly used biocides, including 2-Bromo-2-Nitropropane-1,3-Diol (in dimethyl sulfoxide (DMSO)), using the KeraSkin™ reconstructed human epidermis model.[23] The dermal irritation was assessed by a tissue viability study employing a 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl-tetrazolium bromide (MTT) assay and histological examinations. Control tissues were treated with 1% dimethyl sulfoxide in PBS (negative) or 5% sodium dodecyl sulfate. The degree of damage was scored by 6 examiners using visual evaluation in a blinded fashion, considering parameters such as erosion, vacuolation, and necrosis. The data analysis was performed following OECD TG 439. 2-Bromo-2-Nitropropane-1,3-Diol was tested at 0.02, 0.1, and 1.0%. With 1% 2-Bromo-2-Nitropropane-1,3-Diol, tissue viability was approximately 10%; however, tissue viability was acceptable for the other 2 concentrations tested, indicating that these concentrations were non-irritating.

Animal

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

When 2-Bromo-2-Nitropropane-1,3-Diol was applied to non-abraded, shaved skin of rabbits in a variety of solvents, the level of irritancy depended on the vehicle. Acetone solutions were non-irritating on single occluded application at 1%, while repeated application of 0.5% was highly irritating when not occluded. 2-Bromo-2-Nitropropane-1,3-Diol at 0.5% in aqueous methylcellulose gave similar results. In PEG 300, a 5% concentration of 2-Bromo-2-Nitropropane-1,3-Diol was non-irritating as a single occluded application. A single application of a 2% emulsion caused skin irritation, but a 0.5% emulsion applied on 4 successive days did not.

Human

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

Sensitization

Animal

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

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

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

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

OCULAR IRRITATION STUDIES

2-Bromo-2-Nitropropane-1,3-Diol (106 mg; crystalline) in the eyes of rabbits caused immediate irritation of the conjunctiva and delayed effects on the cornea and iris.[2] *These later effects noted on the fourth day, remained on the last day of observation (day 7). Scores, according to the Draize scale, on day 7 were maximum in all but 2 of 6 unwashed eyes. Washing with water did not modify the damage produced. A 0.1 ml dose of a 10 or 20% aq. solution of 2-Bromo-2-Nitropropane-1,3-Diol placed in the conjunctival sac of a rabbit eye produced severe ocular damage. Washing 4 s after application of the 20% solution reduced the reaction. Complete clearing of the damage required 35 d in the unwashed eye and 14 d in the washed eye. When 3 mg of the solid compound was placed in the eye, damage was severe and clearing again required 35 d. Washing reduced recovery time to 14 d in one test and 21 in another. 2-Bromo-2-Nitropropane-1,3-Diol, at 2% in solution and in an emulsion, was reported to be irritating to the rabbit eye. However, 4 daily applications of 0.5% solution and emulsion were not irritating. 2-Bromo-2-Nitropropane-1,3-Diol tested as a 0.5% solution in normal saline was non-irritating in the eyes of rabbits when applied daily for 4 successive days. A solution of 5% in PEG 400 was irritating on single application, but at 2 % did not produce irritation.*

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

CLINICAL STUDIES

Retrospective and Single or Multicenter Studies

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

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

A study examining trends in patch tests results from a tertiary referral dermatitis clinic found that positive patch test outcomes were statistically significantly decreased ($p = 0.03$) with 2-Bromo-2-Nitropropane-1,3-Diol.[25] Over the 2002 – 2012 time frame, patch test positivity with 2-Bromo-2-Nitropropane-1,3-Diol was 2.5% (1400 patients), while during 2016 – 2021, positivity was 0.75% (402 patients).

Clinical studies are described in Table 3. Retrospective studies (mostly performed by the North American Contact Dermatitis Group (NACDG)) indicated that the positivity rates with 2-Bromo-2-Nitropropane-1,3-Diol, 0.5% (pet) ranged from 1.3 – 4.8%;[26-44] the lowest rate (1.3%) was reported with NACDG analysis of testing conducted in 2015 – 2016.[39] Results for specific patient subgroups are also included,[45-47] as are several studies using pediatric test groups.[48-50] A retrospective study (2011 – 2014) determining the prevalence of wet wipes as a source of allergy found that 0.9% of patients with a positive patch test had an allergic reaction to a wet wipe source, and the reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these subjects 27.4%.[51] Co-reactivity to formaldehyde was also evaluated, with some studies showing little co-reactivity[52,53] while another found that 25% of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde.[43]

Case Reports

A 62-yr-old female presented with dermatitis of the face and neck resulting from use of baby wipes/towelettes.[54] Patch testing with 2-Bromo-2-Nitropropane-1,3-Diol produces positive results, as did testing with the wipes.

A 3-yr-old female developed a rash on her leg at the area of application of several antiseptic creams.[55] Patch testing showed ++ reactions to several substances, including 2-Bromo-2-Nitropropane-1,3-Diol. She was diagnosed as having allergic contact dermatitis (ACD) from this ingredient, but the relevance was unknown due to inadequate history details.

A 16-yr-old female with a history of childhood asthma and allergic rhinitis had eczematous eruptions of the flexor forearms.[56] Patch testing showed a ++ reaction to 2-Bromo-2-Nitropropane-1,3-Diol, an ingredient present in cat litter. In another case, a 70-yr-old male presented with a 6-wk history of an acute pruritic eruption in the axillary vaults, inguinal folds, and central lumbar area was suspected of having ACD due to the severity of symptoms.[57] The patch-testing results were positive for two known allergens and 2-Bromo-2-Nitropropane-1,3-Diol.

SUMMARY

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

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

When determining whether to re-open this safety assessment, the Panel considered 2-Bromo-2-Nitropropane-1,3-Diol was reported to be used in 36 cosmetic formulations in 2023 (VCRP data), as opposed to 1 use reported in 2002, indicating an increase in frequency of use. RLD obtained from the FDA in 2025 reported that it is used in 572 cosmetic formulations; 143 of these uses were in disposable wipes. The reported maximum concentration of use has decreased. According to the results of a survey conducted by the Council in 2025, the maximum reported concentration of use is 0.05% in disposable wipes; in 2003, the maximum reported concentration of use was 0.1%. The use of 2-Bromo-2-Nitropropane-1,3-Diol is

regulated in the European Union. It is included in Annex V, the List of Preservatives Allowed in Cosmetic Products and the maximum use concentration in ready for use preparations is restricted to 0.1%, with caution to avoid formation of nitrosamines. It was evident that the transdermal absorption of 2-Bromo-2-Nitropropane-1,3-Diol was dependent on the formulation, with absorption being greatest from an aq. solution and lowest from a hydrogel; transdermal flux was 11.0 and 0.8 $\mu g/cm^2/h$, respectively. However, lag time for diffusion was 6.34 h from the aq. solution, while there was no lag time for diffusion when applied in a hydrogel or emulsion.

In an acute inhalation study with Sprague-Dawley rats using three test groups and one control group, the animals were nose/head-exposed to the test atmosphere for 4 h at concentrations of 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.. 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 a cytogenicity/chromosome aberration assay, it was suggested that the observed clastogenic effect 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 in DMSO was not predicted to be irritating, but tissue viability was not acceptable with 1%. 2-Bromo-2-Nitropropane-1,3-Diol, at 1% was 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.

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

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously issued reports approximately every 15 years. In 1980, the Panel evaluated the safety of 2-Bromo-2-Nitropropane-1,4-Diol concluded that it was safe as a cosmetic ingredient at concentration up to and including 0.1% except under the circumstance where its action with amines or amides can result in the formation of nitrosamines or nitrosamides. Due to the availability of new scientific data, an addendum to the report was published in 1984; the Panel reaffirmed its 1980 conclusion, and further stated that the additional data suggested the possibility that on absorption, 2-Bromo-2-Nitropropane-1,3-Diol may contribute to the endogenous formation of nitrosamines in humans. The Panel previously considered a re-review of this report in September 2003 and reaffirmed the conclusion, as published in 2006. In June 2024, since more than 15 years have passed since the last review, the Panel considered another re-review and determined to reopen the safety assessment to re-evaluate existing endpoints, and to reassess the possibility of the formation of endogenous nitrosamines in humans due to dermal penetration. After evaluation of previous and new data (including 2025 RLD), and in accordance with the product categories and concentrations of use identified in the Use section and Use table, the Panel issued a revised conclusion stating this ingredient is safe in cosmetics when formulated to be non-sensitizing, which may be determined based on a QRA or similar methodology.

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

The Panel expressed concern about the inconsistency of some of the toxicological data, as the dermal LD_{50} value reported for 2-Bromo-2-Nitropropane-1,3-Diol was lower than the oral LD_{50} values. The observed severe acute dermal toxicity can be attributed to the corrosive effects of 2-Bromo-2-Nitropropane-1,3-Diol used in a high concentration, which may have compromised the barrier function and accelerated systemic toxicity. Also, the small sample size (2 rats per dose) also limits the reliability of this study. Thus, the observed lower dermal LD_{50} may not indicate higher systemic toxicity. The

Panel also noted that this ingredient did not demonstrate developmental and reproductive toxicity. It was also observed that there was no carcinogenicity found in dermal (80-wk; mouse) or oral (2-yr; rats) studies.

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

2-Bromo-2-Nitropropane-1,3-Diol should not be used in cosmetic products in which *N*-nitroso compounds can be formed. It is a known *N*-nitrosating agent for secondary and tertiary amines. Additionally, antioxidant use in formulations reduces potential *N*-nitrosating activity.

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

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

CONCLUSION

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

TABLES

Table 1. Chemical properties

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

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

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

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

	# of Uses	Max Conc of Use
	RLD (2025)[15,16]	% (2025)[17]
Nail Creams and Lotions	2	NR
Nail Extenders	1	NR
Nail Polishes and Enamels	5	NR
Nail Polish and Enamel Removers	1	NR
Other Manicuring Preparations	9	NR
Personal Cleanliness		
Bath Soaps and Body Washes	22	NR
Deodorants (underarm)	1	NR
Douches	4	NR
Disposable Wipes	143	0.04 - 0.05
Other Personal Cleanliness Products	20 (l.o.); 82 (r.o.)	NR
Shaving Preparations		
Beard Softeners	1	NR
Pre-shave lotions (all types)	1	NR
Shaving Creams (aerosol, brushless, and lather)	1	NR
Shaving Soaps (cakes, sticks, etc.)	1	NR
Other Shaving Preparation Products	8	NR
Skin Care Preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	27	NR
Face and Neck (excluding shaving preparations)	26 (l.o.); 7 (r.o.)	NR
Body and Hand (excluding shaving preparations)	37 (l.o.); 7 (r.o.)	NR
Moisturizing	22	NR
Paste Masks (mud packs)	7	NR
Skin Fresheners	1	NR
Other Skin Care Preparations	1 (l.o.); 2 (r.o.)	NR
Other Preparations (i.e., those preparations that do not fit another category)	4	NR

NR – not reported

l.o. – leave-on; r.o. – rinse-off

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

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

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

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

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

Years	# patients	Study Details	Results	Reference
		Retrospective Studies		
1984-2014	54,348	Examined NACDG patch test records to analyze reaction trends over time; 13 evaluable records	positivity decreased between 1984 and 2014; - 0.6% change positive reactions, 1984 – 2.6%; positive reactions, 2014 – 2%	26
1994-2006	26,948	NACDG; PR (percentage of + (weak) reactions among the sum of all positive reactions (+, ++, +++)) and RI (number of positive reactions minus questionable and irritant reactions divided by the sum of all 3) were determined to evaluate proportion of weak, irritant, and questionable reactions	PR was considered "problematic," indicating a high proportion of weak, irritant, and questionable reactions PR – 73.5% RI – 0.45 + only reactions – 2.0%; +, ++, and +++ reactions – 2.8% allergic reactions, minus irritant or questionable reactions – 1.7%; allergic reactions, with irritant or questionable reactions – 3.8%	27
1994-2013	2111 with AD 342 without AD	Examined NACDG patch test records to compare the rates of positive patch test reactions among patients with and without AD; 2 clinics	positive reactions for patients with atopic eczema – 4.7% positive reactions for patients without atopic eczema – 2.0%	28
1994-2016	50,623	retrospective cross-sectional analysis of NACDG patch testing results	linear regression model reported decreasing trend in positive reactions (-0.33%, p = 0.024) positive reactions, 1994-2016: 2.5% second read code: 24.2% ±; 52.0% +; 17.1% ++; 5.2% +++ relevance: definite – 1.7%; probable – 35.8%; possible – 46.3%	29
2001-2002	4897	NACDG; 48-h patches	positive reactions – 3.3%; irritant reactions – 0.3% relevance: definite – 0.6%; probable –13.2%; possible – 56.9%	30
2001 2004	see Results column	analysis of positive patch test reactions in NACDG testing associated with a cosmetic source (2-Bromo-2-Nitropropane-1,3-Diol was one of the top 20 NACDG standard screening allergens associated with cosmetic source in males, but not in females, so only data for males is included here)	29 reactions % with allergy to cosmetic source – 4.8% (n = 611 males) % reactions associated with cosmetic source – 2.3% (n = 1286 males)	31
		reactions for the category 'cosmetics, not otherwise specified'	Females – 41 reactions % patients – 3.8% (n = 1072) % reactions – 2.1% (n = 2003) Males – 28 reactions % patients – 6.0% (n = 1072) % reactions – 2.7% (n = 1025)	
		reactions for the category 'moisturizer source'	Females – 18 reactions % patients – 3.4% (n = 5292) % reactions – 1.9% (n = 946) Males – 20 reactions % patients – 6.5% (n = 529) % reactions – 2.9% (n = 946)	
2001-2004	1493	retrospective cross-sectional analysis of NACDG data, comparing patients with SGD to those without SGD.	patients with SGD positive reactions – 4.8% relevance: definite –0%; probable 8.3%; possible – 47.2% It was found that patients with SGD had statistically significant more relevant responses	32
2003-2004	5140	NACDG; 13 test centers; 48-h patches	positive reactions – 2.3%	33
2005-2006	4435	NACDG; 13 test centers; 48-h patches	positive reactions: 3.4%; one of the top 20 allergens in the series for the first time relevance: definite – 2.0%; probable 17.2%; possible – 47%	34

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

Years	# patients	Study Details	Results	Reference
2006-2010	2142	Mayo Clinic; 3 clinical sites; 48-h patches	allergic reactions – 2.5% reaction grades: macular erythema – 35.6%; weak – 56.6%, strong – 5.7%, extreme – 1.9% irritant reactions – 0.8% relevance: allergic, relevant – 30.2%; allergic, not relevant - 0%; allergic, questionably relevant – 69.8%	35
2007-2008	5081	NACDG; 13 test centers; 48-h patches	positive reactions: 3.1% relevance: definite – 0.6%; probable – 12.5%; possible – 53.8% SPIN - 83	36
2011-2012	4231	NACDG; 12 test centers; 48-h patches	positive reactions: 1.6% second read code: 4.5% ±; 35.8% +; 32.8% ++; 19.4% +++ relevance: definite – 4.5%; probable – 35.8%; possible – 46.3% SPIN - 69	37
2013-2014	4859	NACDG; 13 test centers; 48-h patches	positive reactions: 2.1% second read code: 5.0% ±; 57.4% +; 26.7% ++; 10.9% +++ relevance: definite – 5.0%; probable – 22.8%; possible – 60.4% SPIN - 84	38
2015-2016	5593	NACDG; 13 test centers; 48-h patches	positive reactions: 1.3% second read code: 9.6% ±; 53.4% +; 30.1% ++; 6.8% +++ relevance: definite – 0%; probable – 13.7%; possible – 60.3% SPIN - 38	39
2017-2018	4938	NACDG; 14 test centers; 48-h patches	positive reactions: 1.5% final reading grade: 4.1% ±; 64.0% +; 26.0% ++; 5.5% +++ relevance: definite – 1.4%; probable – 11.0%; possible – 53.4% SPIN - 39	40
777777777 777777777 777777777 777777777 777777777 777777777 777777777 777777777 777777777 777777777 72017-2021	2688	Mayo Clinic; 3 clinical sites; 48-h patches	allergic reactions – 4% reaction grades: weak - 3.3%, strong - 0.6%%, extreme – 0.1% irritant reactions – 0.9%	41
2019-2020	4117	NACDG; 13 test centers; 48-h patches	positive reactions: 2.1% final reading grade: 12.8% ±; 59.3% +; 16.3% ++; 11.6% +++ relevance: definite – 1.2%; probable – 4.7%; possible – 73.3% SPIN - 60	42
2019-2021	748	Clinical trial conducted to evaluate allergens for inclusion in the EBS baseline series; single center study; 48-h patch	positive reactions – 2.7% ICDRG scoring of positive reactions: 0.7% ?+; 70% +; 25% ++, 5% +++ irritant reactions – 0.1% 11.9% of patients with patch test reactivity to formaldehyde co-reacted with 2-Bromo-2-Nitropropane-1,3-Diol 25% of patients with of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde	43
2021-2022	3052	NACDG; 12 test centers; 48-h patches	positive reactions: 2.7% final reading grade: 4.9% ±; 64.2% +; 24.7% ++; 4.9% +++ relevance: definite – 1.2%; probable – 2.5%; possible – 40.7% SPIN - 43	44
Results for Specific Patient Subgroups				

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

Years	# patients	Study Details	Results	Reference
1994-2014	2611; 165 were health care workers	only patients with suspected ACD were evaluated; 2 clinics	relevant positive reactions in healthcare workers – 3.0% relevant positive reactions in non- healthcare workers – 1.3%	45
2011-2020	148 Black patients	Mayo Clinic; 3 clinical sites; 48-h patches	positive reactions – 4.7%	46
2010-2022	18 solid organ transplant recipients	retrospective analysis of patch test data from adult transplant recipients; 20 tests performed Mayo Clinic; 3 clinical sites; 48-h patches were scored at 48 – 72 h and from 96 – 168 h	positive reactions – 5% (1 liver transplant patient using the immunosuppressant tacrolimus)	47
Pediatric Test Groups				
2012-2015	116 (ages 6 - 17 yr)	(concentration of 2-Bromo-2-Nitropropane-1,3-Diol not stated) TRUE test; multicenter study; suspected ACD 48-h patches; readings at 48, 72, and 96 h and at 1 and 3 wk	positive reactions – 17.1%	48
2016-2020	89 (ages 1 -18 yr)	Retrospective analysis of patch test data Mayo Clinic; 3 clinical sites; 48-h patches	positive reaction rate – 7.9% relevant positive reaction rate – 3.4%	49
2019-2023	13 (0 - 5 yr) 139 (6 - 16 yr)	Prospective multicenter study based on the REIDAC registry; patients were patch-tested according to ESCD guidelines with the GEIDAC baseline and extended series	positive reaction rate: 0 – 5 yr - 0% 6-16 yr - 1.44%	50
Studies with Wet Wipes				
2011-2014	9037 patients	NACDG retrospective cross-sectional study to determine the prevalence of wet wipes as a source of allergy during patch testing.	0.9% of patients with a positive patch test had an allergic reaction to a wet wipe source. reaction rate to 2-Bromo-2-Nitropropane-1,3-Diol in these subjects - 27.4% relevance: definite – 3%; probable – 11%; possible – 6%	51
Co-Reactivity with Formaldehyde				
2005-2009	2-Bromo-2-Nitropropane-1,3-Diol: 1192 formaldehyde: 7838	6 Spanish hospitals; examined co-reactivity between to 2-Bromo-2-Nitropropane-1,3-Diol and formaldehyde	Among the 2 patients allergic to 2-Bromo-2-Nitropropane-1,3-Diol, one was also allergic to formaldehyde Among the 135 patients allergic to formaldehyde, one (0.74%) was also allergic to 2-Bromo-2-Nitropropane-1,3-Diol	52
2015-2018	8139	Retrospective multicenter study examining sensitization to 2-Bromo-2-Nitropropane-1,3-Diol (0.5% pet) and co-reactivity to 2% aq. formaldehyde	2-Bromo-2-Nitropropane-1,3-Diol had a sensitization prevalence of 0.49% Very little co-reactivity with formaldehyde: 96.3% of the reactions to 2-Bromo-2-Nitropropane-1,3-Diol were isolated reactions	53
2019-2021	748	Single-center study described above evaluating allergens for inclusion in the EBS baseline series; 48-h patch	11.9% of patients with patch test reactivity to formaldehyde co-reacted with 2-Bromo-2-Nitropropane-1,3-Diol 25% of patients with of patients with positive reactions to 2-Bromo-2-Nitropropane-1,3-Diol co-reacted with formaldehyde	43

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

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