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Final Report on the Safety Assessment of 5-Bromo-5-Nitro-1,3-Dioxane

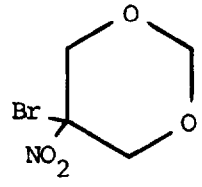
5-Bromo-5-Nitro-1,3-Dioxane is used as a preservative in cosmetic products. The chemical can be metabolized to 2-bromo-2-nitropropane-1,3-diol, a nitrosating agent, whose safety of use has already been substantiated. 5-Bromo-5-Nitro-1,3-Dioxane has an LD_{50} of 455 mg/kg for rats and 590 mg/kg for mice. Significant skin and eye irritation was observed in animal studies at 0.5%, but not at 0.1%. The compound was neither a sensitizer nor a photosensitizer in guinea pig studies. This ingredient was neither mutagenic nor teratogenic. Sensitization was observed in clinical patients at 0.1 and 0.5%, but not in a study on nonclinical volunteers. It is concluded that 5-Bromo-5-Nitro-1,3-Dioxane can be safely used in cosmetic products at concentrations up to and including 0.1%, except when it may react with amines and amides to form nitrosamines or nitrosamides.

INTRODUCTION

5-Bromo-5-Nitro-1,3-Dioxane is reviewed in this document. The CIR Panel has previously reviewed 2-bromo-2-nitropropane-1,3-diol.[1,2]

CHEMICAL AND PHYSICAL PROPERTIES

5-Bromo-5-Nitro-1,3-Dioxane (CAS No. 30007-47-7) is the substituted cyclic ether with the following chemical formula:[3]



The pure compound is a white crystalline powder and has the tradename of Bronidox K. 5-Bromo-5-Nitro-1,3-Dioxane is available commercially as a colorless 10% (w/v) solution in 1,2-propylene glycol that is known as Bronidox L.[4]

5-Bromo-5-Nitro-1,3-Dioxane has a molecular weight of 212, a melting point of 58–60°C, and a boiling point of 113–116°C at a pressure of 13 Torr. Decomposition occurs upon boiling at this pressure.[5,6]

The solubility of 5-Bromo-5-Nitro-1,3-Dioxane in water is 0.46% at 20°C and is 1.70% at 50°C. At 20°C, its solubility is greater than 25% in ethanol, greater than 10% in isopropanol, greater than 10% in 1,2-propylene glycol, and greater than 50% in chloroform. 5-Bromo-5-Nitro-1,3-Dioxane is soluble in vegetable oils and is insoluble in paraffin oil. The pH of 5-Bromo-5-Nitro-1,3-Dioxane as a 10% solution in 1:1 water:acetone is 6.5.[7]

5-Bromo-5-Nitro-1,3-Dioxane is light-stable and is stable at temperatures of less than 50°C. The compound is unstable at a pH of less than 5 and is stable at pHs between 5 and 9. 5-Bromo-5-Nitro-1,3-Dioxane is corrosive to metal containers.[5,6,8,9]

The *N*-nitrosation potential of 5-Bromo-5-Nitro-1,3-Dioxane with morpholine as a secondary amine is comparable to that of 2-bromo-2-nitropropane-1,3-diol. The greatest yields of *N*-nitrosomorpholine were observed at pHs of 8 to 9.[10]

5-Bromo-5-Nitro-1,3-Dioxane is manufactured by polyphosphoric acid-catalyzed condensation of 2-bromo-2-nitropropane-1,3-diol and paraformaldehyde.[11,12] 5-Bromo-5-Nitro-1,3-Dioxane contains less than 0.2% sodium sulfate. Less than 0.3% of the total bromine content of the compound is present in an ionic form.[5,6]

Qualitative and quantitative determinations of 5-Bromo-5-Nitro-1,3-Dioxane are made by colorimetry, infrared spectroscopy, ultraviolet spectroscopy, thin-layer chromatography, two-dimensional thin-layer chromatography, column chromatography, gas chromatography with capillary columns, gas chromotography–mass spectrometry, and high-voltage agar gel electrophoresis.[13–16]

COSMETIC USE

5-Bromo-5-Nitro-1,3-Dioxane is used as an antimicrobial preservative in cosmetics. It is a broad-spectrum preservative that is useful at pHs of 5 to 9. The antimicrobial effect of 5-Bromo-5-Nitro-1,3-Dioxane is due to the oxidation of thiol groups contained in mercaptoamino acids to disulfides, and the subsequent inhibition of enzyme activity and microbial growth; it is not due to the formation of formaldehyde.[5,6,17]

A 10% 5-Bromo-5-Nitro-1,3-Dioxane solution in propylene glycol is miscible with water. It can be added by cosmetic formulations at room or higher temperatures. It is compatible with emulsifiers, surfactants, polymeric materials, oil components, and plant and organ extracts. Lorenz[5,6] has stated that 5-Bromo-5-Nitro-1,3-Dioxane is not a formaldehyde donor, and that it does not affect the odor, color, or consistency of cosmetic products. Major decomposition products of 5-Bromo-5-Nitro-1,3-Dioxane were formaldehyde, 2-hydroxymethyl-2-nitro-1,3-propanediol, and bromonitroethanol.[1,2] The preservative activity of a 10% solution of 5-Bromo-5-Nitro-1,3-Dioxane in propylene glycol is augmented in media by antioxidants.[18]

The manufacturer of 5-Bromo-5-Nitro-1,3-Dioxane recommends its use in shampoos and foam baths and other cosmetic rinse-off products in concentrations of up to 0.2%.[4–6]

Product types and the number of product formulations containing 5-Bromo-5-Nitro-1,3-Dioxane and reported voluntarily to the Food and Drug Administration (FDA) in 1988 are presented in Table 1. Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset

TABLE 1. Product Formulation Data for 5-Bromo-5-Nitro-1,3-Dioxane[19]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
			>0.1–1	≤0.1
Bath and other personal cleanliness products	1008	19	16	3
Hair conditioners, sprays and shampoos (noncoloring)	1315	24	12	12
Skin care and facial cleansing preparations	2004	3	2	1
1988 Totals		46	30	16

concentration ranges and product types as described in the Code of Federal Regulations 21 CFR 720.4. Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration. In 1988, 5-Bromo-5-Nitro-1,3-Dioxane was reported as an ingredient in 46 cosmetic formulations at concentrations ranging from ≤0.1% to between 0.1% and 1% (Table 1)[19]. The FDA has reported that 5-Bromo-5-Nitro-1,3-Dioxane was used as a preservative in no cosmetic formulations in 1977, 12 in 1980, 17 in 1984, and 44 in 1987. Most of these formulations were products of foreign manufacture.[20]

The European Economic Community (EEC) permits the use of 5-Bromo-5-Nitro-1,3-Dioxane in rinse-off products only, at a concentration of 0.1%. The formation of nitrosamines should be avoided.[21]

Cosmetic products containing 5-Bromo-5-Nitro-1,3-Dioxane may be applied to or come in contact with skin, eyes, hair, nails, and mucous membranes (Table 1).[19]

Product formulations containing 5-Bromo-5-Nitro-1,3-Dioxane may be applied as many as several times a day and may remain in contact with the skin for variable periods following application. Daily or occasional use may extend over many years (Table 1).[19]

ABSORPTION, METABOLISM, AND EXCRETION

5-Bromo-5-Nitro-1,3-Dioxane is metabolized by rats and rabbits to 2-bromo-2-nitropropane-1,3-diol, 2-nitro-1,3-propanediol, and 2-nitroethanol. Within 4 days of administration to rats, 44.1, 56, or 17% of oral, intraperitoneal, or dermal doses were excreted in the urine and feces as unchanged 5-Bromo-5-Nitro-1,3-Dioxane or its metabolites (Fig. 1).[7]

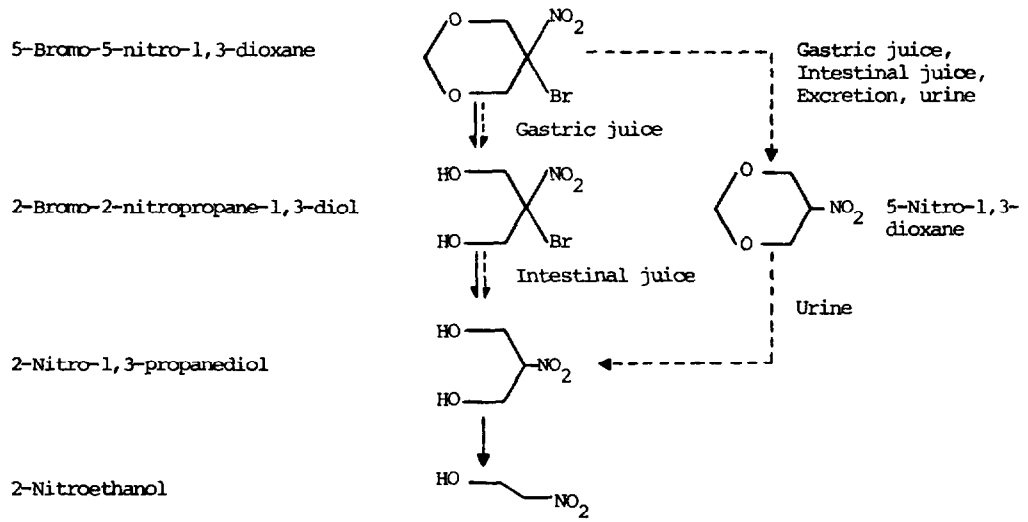


FIGURE. 1 Metabolism of 5-Bromo-5-Nitro-1,3-Dioxane in rats and rabbits (--- *in vitro,* —— *in vivo*).[7]

To determine the effect of the vehicle on the absorption and excretion of 5-Bromo-5-Nitro-1,3-Dioxane, one rabbit each was treated dermally with 100 mg/kg 5-Bromo-5-Nitro-1,3-Dioxane in olive oil or Tween 60, respectively. Twenty-four hours after application, 0.2 and 1.3% were recovered from the treated skin. Two days after the application, 7 and 16.4% of the bromide, applied in the form of the test compound, was recovered from the urine (6.5 and 16.2%) and from the feces.[22]

A 0.5% concentration of 5-Bromo-5-Nitro-1,3-Dioxane was applied in a cream to a 20 × 30-cm area on the backs of 5 male volunteers. The total amount applied was 1.85 to 2.5 g. Four hours later, the remaining cream was wiped off. Urine samples were collected 24 h after application of the cream. The urine contained 10.8 to 75.3% of the applied dose as unchanged 5-Bromo-5-Nitro-1,3-Dioxane or its metabolites, determined as bromides.[7]

Incubation of 5-Bromo-5-Nitro-1,3-Dioxane with urine, feces, stomach juices, or intestinal fluids results in the formation of 2-bromo-2-nitropropane-1,3-diol; this compound is debrominated to 2-nitro-1,3-propanediol and then is metabolized to 2-nitroethanol. On the basis of these findings, it appears likely that the degradation of 5-Bromo-5-Nitro-1,3-Dioxane to various metabolites occurs not only in the acidic medium of the stomach but, upon absorption, in other organs as well.[22]

ANIMAL TOXICOLOGY

Oral Studies

The acute oral LD_{50} of 5-Bromo-5-Nitro-1,3-Dioxane in 100% olive oil is 455 mg/kg for male Wistar rats and 590 mg/kg for CF_1 mice.[5–7]

Groups of 10 male and 10 female SPF Wistar rats were given 10, 50, and 100 mg/kg/day of 5-Bromo-5-Nitro-1,3-Dioxane 5 times a week for 17 weeks. At 6 weeks,

the high dose was increased from 100 to 200 mg/kg. Control rats were untreated. No differences were found between the control group and the groups receiving 10 and 50 mg/kg/day in body weight, hematologic values, and urine composition. Some animals in both the 10 and 50 mg/kg/day groups had mild irritation of the mucous membrane of the stomach. No differences were observed in the biochemical studies. The rats given 200 mg/kg/day of 5-Bromo-5-Nitro-1,3-Dioxane died within a few days.[5–7]

Dermal Studies

No adverse dermal reactions were observed in rabbits when 5-Bromo-5-Nitro-1,3-Dioxane was applied repeatedly to the skin in a concentration of 0.5%, or was applied as a 24-h patch containing a concentration of 0.5%.[5–7]

5-Bromo-5-Nitro-1,3-Dioxane was applied to the skin of hairless mice in vaseline and two creams at 0.1 and 0.5% concentrations each day for 3 to 5 days, and at a 1% concentration each day for 2 to 3 days, and at a 2.5% concentration in a single application. No changes in the skin were observed following the applications of 0.1% 5-Bromo-5-Nitro-1,3-Dioxane. At the higher concentrations, necrosis was observed in the skin of 1 to 5 of the mice in each group.[7]

5-Bromo-5-nitro-1,3-Dioxane was applied to the skin of groups of 5 rats in vaseline and two creams at a 0.1% concentration each day for 5 days, and at a concentration of 0.5% for 3 to 4 days. No changes in the skin were observed following the applications of 0.1% 5-Bromo-5-Nitro-1,3-Dioxane. At a 0.5% concentration, sloughing of the skin was observed in 3 to 5 rats in each group.[7]

5-Bromo-5-Nitro-1,3-Dioxane was tested for sensitization in 25 guinea pigs. The compound was administered in two 0.1 ml intradermal injections of 0.1% into the shoulder region. This was followed by two intradermal injections of 1:1 0.1% 5-Bromo-5-Nitro-1,3-Dioxane:Freund's adjuvant and then, two intradermal injections of Freund's adjuvant into the same site. Eight days after the intradermal injections, an occlusive patch containing 2.5% 5-Bromo-5-Nitro-1,3-Dioxane was applied to the shoulder for 24 h. After a 14-day nontreatment period, an epicutaneous challenge of 2.5% 5-Bromo-5-Nitro-1,3-Dioxane in 45% methylcellusolve, 45% ethanol, and 10% Tween was applied to the flank and the vehicle alone was applied to the other flank. Skin reactions were observed 24, 48, and 72 h after the epicutaneous open application. There were no adverse reactions to the chemical; 5-Bromo-5-Nitro-1,3-Dioxane was not a sensitizer in this test.[23]

A nonirritating and nonsensitizing concentration level (0.05%) solution of 5-Bromo-5-Nitro-1,3-Dioxane in propylene glycol was used in a photosensitizing test. Ten occlusive patches containing the solution were applied to the skin on the backs of guinea pigs for 6 h per day over a 14-day period. The second and fifth applications of the 5-Bromo-5-Nitro-1,3-Dioxane were followed by a 10 min exposure to ultraviolet light of 300 to 400 nm (150-W Xenon Solar simulator with filter to eliminate UVB radiation). There were 5 control guinea pigs treated with the test solution, but without UV exposure, and 5 negative controls. After a 5-day nontreatment period, the animals were challenged with occlusive patches containing 5-Bromo-5-Nitro-1,3-Dioxane, and at another site, 5-Bromo-5-Nitro-1,3-Dioxane and ultraviolet light (site UV exposure similar to that used during the induction). The guinea pigs were challenged twice in a 24-h period, and the skin reactions were observed at 15 min and 24 and 72 h. Mild irritation was observed at the test sites; this was possibly due to skin fatigue. There was

no evidence of increased irritation due to photosensitivity at challenge between the test and control animals.[24]

Ocular Irritation

A 0.05% solution of 5-Bromo-5-Nitro-1,3-Dioxane in carboxymethycellulose was placed in the eyes of rabbits each day for 10 days over a 2-week period. No eye irritation was observed. A single application of 0.1% 5-Bromo-5-Nitro-1,3-Dioxane in carboxymethylcellulose did not produce significant irritation when placed in the eyes of rabbits. A 0.5% solution in carboxymethylcellulose was a strong eye irritant after one application.[7]

Intraperitoneal Study

The acute intraperitoneal LD_{50} of 5-Bromo-5-Nitro-1,3-Dioxane is 31.5 mg/kg for rats.[7]

Teratology Study

5-Bromo-5-Nitro-1,3-Dioxane was administered orally in doses of 5, 15, and 45 mg/kg to groups of 30 pregnant Sprague-Dawley SPF rats on days 6 to 15 of gestation. All three doses caused maternal toxicity; vocalization, ataxia, piloerection, decreased activity, and dyspnea were observed. One death was reported in the middle dose group. Retardation of maternal body weight gain and four deaths were observed in the high-dose group. For fetal parameters, there were an increased resorption rate after implantation and an increased rate of retardations in the high-dose group but not in the control, low-, and mid-level dose groups. Under the conditions of this study, 5-Bromo-5-Nitro-1,3-Dioxane was not considered to be teratogenic.[25] This experimental conclusion is consistent with that previously reported.[1]

MUTAGENESIS

Concentrations of 1 to 35 ppm solutions of pure 5-Bromo-5-Nitro-1,3-Dioxane and 10% 5-Bromo-5-Nitro-1,3-Dioxane in propylene glycol were tested for mutagenicity in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 with and without metabolic activation. The compound was not mutagenic. The positive control, 50 ppm *o*-nitro-*p*-phenylenediamine, was positive, with and without metabolic activation in *S. typhimurium* TA1537, TA1538, TA98, and TA100.[26]

A dose of 20 mg/kg 5-Bromo-5-Nitro-1,3-Dioxane was administered intraperitoneally to male and female mice. A second dose was administered 24 h later. Six hours later, the animals were sacrificed, and the bone marrow was examined for micronuclei. 5-Bromo-5-Nitro-1,3-Dioxane did not significantly increase the number of micronuclei.[27]

CLINICAL ASSESSMENT OF SAFETY

A 24-h patch test was conducted with vaseline and two creams containing 0, 0.1, and 0.5% 5-Bromo-5-Nitro-1,3-Dioxane on the backs of 40 patients from a dermatol-

ogy clinic. Skin reactions were evaluated 20 min and 24 and 48 h after patch removal. One subject reacted to vaseline alone, and 1 subject reacted to a cream alone. Eleven of the remaining 38 subjects had positive reactions to at least one of the 5-Bromo-5-Nitro-1,3-Dioxane formulations.[7]

A bubble bath and a shampoo, containing 0.1% 5-Bromo-5-Nitro-1,3-Dioxane, were used at least once a week for 6 weeks by 114 volunteers. The shampoo produced skin irritation in 3 subjects. However, none of the 3 had positive skin sensitization reactions to 5-Bromo-5-Nitro-1,3-Dioxane.

SUMMARY

5-Bromo-5-Nitro-1,3-Dioxane is the substituted cyclic ether that is manufactured by polyphosphoric acid-catalyzed condensation of 2-bromo-2-nitropropane-1,3-diol and paraformaldehyde. The *N*-nitrosation potential of 5-Bromo-5-Nitro-1,3-Dioxane with morpholine as a secondary amine is comparable to that of 2-bromo-2-nitropropane-1,3-diol.

5-Bromo-5-Nitro-1,3-Dioxane is used as an antimicrobial preservative in cosmetics. The antimicrobial effect of 5-Bromo-5-Nitro-1,3-Dioxane is due to the oxidation of thiol groups contained in mercaptoamino acids to disulfides, and the subsequent inhibition of enzyme activity and microbial growth and is not due to the formation of formaldehyde.

5-Bromo-5-Nitro-1,3-Dioxane was reported as an ingredient in 46 cosmetic formulations at concentrations ranging from $\leq 0.1\%$ to between 0.1 and 1% in 1988. It was reported to be used as a preservative in no cosmetic formulations in 1977, 12 in 1980, 17 in 1984, and 44 in 1987.

5-Bromo-5-Nitro-1,3-Dioxane is metabolized by rats and rabbits to 2-bromo-2-nitropropane-1,3-diol, 2-nitro-1,3-propanediol, and 2-nitroethanol. Unchanged 5-Bromo-5-nitro-1,3-dioxane and its metabolites are found in the urine and feces of rats following oral, intraperitoneal, and dermal application, and is found in the urine of humans following dermal application. Incubation of 5-Bromo-5-Nitro-1,3-Dioxane with urine, feces, stomach juices, or intestinal fluids results in the formation of 2-bromo-2-nitropropane-1,3-diol followed by 2-nitro-1,3-propanediol and then, 2-nitroethanol.

The acute oral LD_{50} of 5-Bromo-5-Nitro-1,3-Dioxane is 455 mg/kg for rats and 590 mg/kg for mice. No differences were observed between control rats and rats given 10 and 50 mg/kg/day 5-Bromo-5-Nitro-1,3-Dioxane orally 5 times a week for 17 weeks. Rats given 100 and then 200 mg/kg/day 5-Bromo-5-Nitro-1,3-Dioxane died within a few days.

No adverse dermal reactions were observed when 0.5% 5-Bromo-5-Nitro-1,3-Dioxane was applied to the skin of rabbits, and 0.1% was applied to the skin of hairless mice and rats. Skin necrosis was observed in hairless mice when 0.5% and greater concentrations were applied dermally. Skin sloughing was observed in rats when 0.5% was applied dermally. 5-Bromo-5-Nitro-1,3-Dioxane was not a dermal sensitizer nor a photosensitizer in guinea pigs.

5-Bromo-5-Nitro-1,3-Dioxane was not irritating to the eyes of rabbits at a concentration of 0.05%, was not significantly irritating at 0.1%, and was strongly irritating at 0.5%.

Maternal toxicity was observed when 5 to 45 mg/kg 5-Bromo-5-Nitro-1,3-Dioxane was administered orally to pregnant rats on days 6 to 15 of gestation. An increased resorption rate after implantation and an increased rate of retardations were observed in the high-dose group. However, 5-Bromo-5-Nitro-1,3-Dioxane was not embryolethal or teratogenic.

5-Bromo-5-Nitro-1,3-Dioxane was not mutagenic to *Salmonella typhimurium* strains and did not significantly increase the number of micronuclei in the bone marrow of mice following intraperitoneal administration.

Eleven of 38 patients from a dermatology clinic had positive reactions to patch tests with 0.1 or 0.5% 5-Bromo-5-Nitro-1,3-Dioxane in vaseline or in two creams. None of 114 volunteers were sensitized to 5-Bromo-5-Nitro-1,3-Dioxane following a 6-week use test of a bubble bath and a shampoo containing 0.1% of the chemical.

DISCUSSION

5-Bromo-5-Nitro-1,3-Dioxane is manufactured from 2-bromo-2-nitro-propane-1,3-diol and paraformaldehyde. The chemical can be metabolized to 2-bromo-2-nitropropane-1,3-diol, a nitrosating agent. The manufacturer of 5-Bromo-5-Nitro-1,3-Dioxane recommends its use in shampoos and other cosmetic rinse-off products in concentrations of up to 0.2%. A recent computer search by the FDA indicates that 5-Bromo-5-Nitro-1,3-Dioxane is used in 34 cosmetic preparations in concentrations of > 0.1 to 1%.

2-Bromo-2-nitropropane-1,3-diol is the major metabolite of 5-Bromo-5-Nitro-1,3-Dioxane. The Cosmetic Ingredient Review Expert Panel has reviewed 2-bromo-2-nitropropane-1,3-diol previously. The data from the Cosmetic Ingredient Review report on 2-bromo-2-nitropropane-1,3-diol has been considered in this 5-Bromo-5-Nitro-1,3-Dioxane report. The conclusion to the most recent Cosmetic Ingredient Review report on 2-bromo-2-nitropropane-1,3-diol (BNPD) is an addendum to the first report, and is as follows:

> The major manufacturer of BNPD recommends that it not be used in concentrations above 0.1%[28] and this agrees with the recommendation of the CIR Expert Panel.[1] However, in a recent computer search by the FDA . . . 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.

The NACDG reported that, during 1977 to 1983, 16 of 626 patients, with suspected cosmetic-related dermatitis, had positive reactions to patch tests with 2-bromo-2-nitropropane-1,3-diol.[29]

> 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-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.[30]

The conclusion to the same report is as follows:

The conclusion to the original CIR report is: "The evidence at hand indicated 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 affirms 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.

The Panel has relied on toxicity data obtained from 2-bromo-2-nitropropane-1,3-diol where such data were not available for 5-Bromo-5-Nitro-1,3-Dioxane to make its judgment on the safety of use of this compound in cosmetic formulations.

CONCLUSION

The evidence at hand indicates 5-Bromo-5-Nitro-1,3-Dioxane 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.

ACKNOWLEDGMENT

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REFERENCES

1. COSMETIC INGREDIENT REVIEW (CIR). (1980). Final report of the safety assessment for 2-bromo-2-nitropropane-1,3-diol. J. Environ. Pathol. Toxicol. **4**(4), 47–61.

2. CIR. (1984). Addendum to the Final report on the safety assessment of 2-bromo-2-nitropropane-1,3-diol. J. Am. Coll. Toxicol. **3**(3),139–55.
3. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (EDITORS). (1982). *CTFA Cosmetic Ingredient Dictionary*, 3rd. ed. Washington, DC: The Cosmetic, Toiletry and Fragrance Association.
4. POTOKAR, M. (April 1987). Henkel Institut fuer Toxikologie-5-Bromo-5-nitro-1,2-dioxane (sic) (Bronidox) - Special Toxicity Studies. Archive no. 870171. Submission from Henkel Corporation.
5. LORENZ, P. (1977). 5-Bromo-5-nitro-1,3-dioxane. A preservative of cosmetics. Cosmet. Toilet. **92**, 89–91.
6. LORENZ, P. (1977). 5-Bromo-5-nitro-1,3-dioxane—a new preservative for cosmetics. J. Soc. Cosmet. Chem. **28**, 427–39.
7. POTOKAR, J., GREB, W., IPPEN, H., MAIBACH, H.I., SCHULZ, K.H., LORENZ, P., and GLOXHUBER, C. (1976). Bronidox, a new preserving agent for cosmetics: properties and toxicological-dermatological assays. Fette, Seifen, Anstrichm. **78**(7), 269–76.
8. ANONYMOUS. (1977). A new shampoo preservative. Soap, Perfum. Cosmet. **50**(4), 133–7.
9. KABARA, J.J. (EDITOR). (1984). *Cosmetic and Drug Preservation Principles and Practice*. New York: Marcel Dekker, Inc., p. 613.
10. PROKOPCZYK, B. (1987). Personal communication. American Health Foundation. Valhalla, NY.
11. LAPPAS, L.C., HIRSCH, C.A., and WINELY, C.L. (1976). Substituted 5-bromo-5-nitro-1,3-dioxanes: correlation of chemical structure and antimicrobial activity. J. Pharm. Sci. **65**(9), 1301–5.
12. MILSTEIN, S., ORTH, D.S., and LICHTIN, J.L. (1984). Organic synthesis, anti-bacterial evaluation and quantitative structure-activity relationship (QSAR) of cosmetic preservatives related to 5-bromo-5-nitro-1,3-dioxane. I. Aliphatic analogs. J. Soc. Cosmet. Chem. **35**, 73–93.
13. MATISSEK, R. (1983). Analysis of 5-bromo-5-nitro-1,3-dioxane (Bronidox) - an antimicrobial agent for cosmetics. Z. Lebensm.-Unters. Forsch. **177**(4), 271–7.
14. MATISSEK, R. and DROSS, A. (1983). Thin-layer-chromatographic detection of the preservative 5-bromo-5-nitro-1,3-dioxane (Bronidox) in nonemulsifiable, surfactant-containing cosmetics. Dtsch. Lebensm.-Rundsch. **79**(8), 269–71.
15. MOORE, K.E. and STRETTON, R.J. (1978). Detection of preservatives in pharmaceutical and cosmetic products using agar gel electrophoresis. J. Chromatogr. **156**(1), 211–7.
16. SCHMAHL, H.J. and HIEKE, E. (1980). Separation and identification of some antimicrobials used also in cosmetic products by means of thin-layer chromatography. Fresenius' Z. Anal. Chem. **304**(5), 398–404.
17. GHANNOUM, M., THOMSON, M., BOWMAN, W., and AL-KHALIL, S. (1986). Mode of action of the antimicrobial compound 5-bromo-5-nitro-1,3-dioxane (bronidox). Folia Microbiol. (Praha) **31**(1), 19–31.
18. ZEELIE, J.J. and McCARTHY, T.J. (1983). Antioxidants - multifunctional preservatives for cosmetic and toiletry formulations? Cosmet. Toilet. **98**(12), 51–5.
19. FOOD AND DRUG ADMINISTRATION (FDA). (1988). Cosmetic product formulation data. Washington, DC.
20. DECKER, R.L., JR. and WENNINGER, J.A. (1987). Frequency of preservative use in cosmetic formulas as disclosed to FDA—1987. Cosmet. Toilet. **102**, 21–4.
21. DUPUIS, J. (EDITOR AND COLIPA SCIENTIFIC OFFICER). (June 1986). the EEC Cosmetics Directive Updated Version—Incorporating All Amendments Until 15th June 1986.
22. SALKA, B.A. (August 3, 1988). Letter to Dr. McEwen, CTFA, Resorption und metabolismus von Bronidox. Dr. W. Greb.
23. SCHULZ, K.H. (March 5, 1975). Bericht ueber das Sensibilisierungsvermoegen des Praparates Bonidox. As cited in Potokar, 1987. Appendix 2. Submission from Henkel Corporation.
24. CONSUMER PRODUCT TESTING COMPANY. (April 11, 1978). Guinea pig photosensitivity—Bronidox L,R-2691, Expt. Ref. No. 783. As cited in Potokar, 1987. Appendix 3. Submission from Henkel Corporation.
25. HENKEL INSTITUT FUER TOXIKOLOGIE. (June 25, 1984). 5-Brom-5-nitro-1,3-dioxan (Bronidox K) - Prufung auf embryotoxische Wirkung nach wiederholter oraler Verabreichung an Ratten Abschlussbericht. Archive No. 84 0240. As cited in Potokar, 1987. Appendix 6. Submission from Henkel Corporation.
26. GLOXHUBER, CH. and WALLAT, S. (May 21, 1981). Bronidox (5-Brom-5-nitro-1,3-dioxan)-Pruefung auf Mutagenitaet im Ames-Test. As cited in Potokar, 1987. Appendix 5. Submission from Henkel Corporation.
27. GLOXHUBER, CH. and GREB, W. (June 23, 1978). Untersuchung von Bronidox im Mikrokerntest. As cited in Potokar, 1987. Appendix 4. Submission from Henkel Corporation.
28. HOLLAND, V.R. (Jan. 26, 1983). 2-Bromo-2-nitropropane-1,3-diol (BNPD). Letter to G.N. McEwen, 3 pp.
29. ADAMS, R.M. and MAIBACH, H.I. (1985). A five-year study of cosmetic reactions. J. Am. Acad. Dermatol. **13**(6), 1062–9.
30. TANNENBAUM, S.R. (1983). N-nitrosos compounds: a perspective on human exposure. Lancet 629–32.