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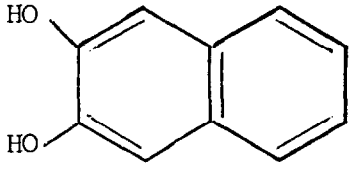
4

Final Report on the Safety Assessment of 2,3-Naphthalenediol

The safety of 2,3-Naphthalenediol has not been documented and substantiated. The Cosmetic Ingredient Review Expert Panel cannot conclude that *t*-Butyl Hydroquinone is safe for use in cosmetic products until such time as the appropriate safety data have been obtained and evaluated. The data that were available are documented in the report, as well as the types of data that are required before a safety evaluation may be undertaken.

DEFINITION AND STRUCTURE

2,3-Naphthalenediol is the dicyclic aromatic compound that conforms to the formula[1]:



2,3-NAPHTHALENEDIOL

Other names for 2,3-Naphthalenediol (CAS No. 92-44-4) include 2,3-Dihydroxynaphthalene and Rodol 23N.[1]

ANALYTICAL METHODS

2,3-Naphthalenediol may be analytically determined by high-performance liquid chromatography.[2]

COSMETIC USE

2,3-Naphthalenediol is used in cosmetics as a component of oxidative hair dyes.[3] Data submitted to the Food and Drug Administration (FDA) in 1983 by cosmetic firms participating in the voluntary cosmetic registration program indicated that 2,3-Naphthalenediol was used at concentrations of ≤0.1% in 37 hair dyes (Table 1).[4]

TABLE 1. Product Formulation Data for 2,3-Naphthalenediol[4]

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
Hair dyes and colors	946	42	4	38
1986 TOTALS		42	4	38

Hair dye products formulated with 2,3-Naphthalenediol are applied to hair but have the potential to come in contact with skin and eyes.

TOXICOLOGY

Acute Oral Toxicity

A propylene glycol solution containing 5% 2,3-Naphthalenediol was given by oral intubation to five groups of fasted Sprague-Dawley rats. Doses consisted of 10.0, 12.6, 15.9, 20.0, and 25.0 of an unspecified unit. The animals were observed daily over 14 days for general health and activity after the single oral dose. These observations were not reported. The LD_{50} of the test solution, as calculated by the method of Weil,[5] was 675.5 mg/kg.[6]

Ocular Irritation

One percent 2,3-Naphthalenediol in propylene glycol was assessed for ocular irritation in 3 female albino rabbits. The test material (0.1 ml) was instilled into the conjunctival sac of each left eye. The right eye served as untreated control. Eyes were examined for irritation 1 h after the single instillation and daily thereafter until the eye became clear. Irritation of the conjunctivae was noted at both the 1-h and 24-h evaluations; however, the eye appeared normal by day 2. No irritation of the cornea or iris was observed. It was concluded that 2,3-Naphthalenediol was "slightly irritating" at 1.0% concentration.[7] (It was not reported whether or not the treated eyes received a water rinse after exposure to 2,3-Naphthalenediol.)

Intravenous Toxicity

The intravenous LD_{50} of 2,3-Naphthalenediol in mice has been reported as 56 mg/kg.[8]

Guinea Pig Sensitization

The skin sensitization potential of 1.0% 2,3-Naphthalenediol in propylene glycol was evaluated in 10 female Hartley guinea pigs. The test material was applied to a 1.8 cm diameter circular area on the preshaven back of each animal.

Applications (0.1 ml) were made every other day over a 3-week period for a total of 9 induction exposures. Reactions were evaluated 24 h after application. After a 2-week nontreatment period, challenge applications were made to the original test site and to an adjacent site. Reactions were graded for erythema and edema 24 and 48 h after the challenge application according to the method of Draize.[9] As stated by the investigator: "Four out of 10 guinea pigs exhibited an erythemal response of at least a one grade greater during the challenge period than observed in the induction." It was concluded that 2,3-Naphthalenediol "elicited positive contact allergic responses" at 1.0% concentration.[10] (Details relating to the severity of induction and challenge reactions, as well as to the length of challenge exposure were not specified.)

Teratogenicity

2,3-Naphthalenediol was evaluated for teratogenic potential. The diol was dissolved in propylene glycol and administered by gavage to pregnant Sprague-Dawley rats on days 6–15 of gestation. Three groups of rats consisting of 10–13 animals per group were given doses of either 110, 220, or 450 mg/kg. No statistically significant differences between diol-treated and vehicle-treated groups were noted with respect to mean number of corpora lutea, total implantations, viable fetuses, mean fetal body weight, or fetal external, visceral, and skeletal anomalies. However, a significant decrease in mean maternal weight gain on days 6–16 of gestation was observed in rats of the high dose group. Oral administration of 100,000 units of vitamin A, the positive control, on day 9 of gestation resulted in a significant increase in abnormal fetuses. The investigators concluded that 2,3-Naphthalenediol produced maternal toxicity but that the oxidative dye was nonteratogenic. Doses employed in the study were reported to exceed human exposure levels by 100-fold.[3]

Mutagenicity

2,3-Naphthalenediol (1000 μg) was nonmutagenic in *Salmonella typhimurium* strains TA-1538 and TA-98 when evaluated according to the methods of Maron and Ames.[11] The ingredient was tested with and without activation at a 1% concentration in DMSO.[12]

Human Skin Irritation

A single insult patch test was used to evaluate an unspecified "finished product" containing 0.1% 2,3-Naphthalenediol for skin irritation. The product was applied in a 0.1 ml dose by means of an occlusive patch to the back of 100 female subjects aged 18–65. The patch remained in place for 48 h. Skin erythema and edema were evaluated 15 min and 24 h after patch removal. No reactions were observed.[13]

SUMMARY

2,3-Naphthalenediol is a dicyclic aromatic compound that is used in cosmetics as a component of oxidative hair dyes.

The ingredient has an oral LD_{50} of 675 mg/kg and an intravenous LD_{50} of 56 mg/kg. 2,3-Naphthalenediol was slightly irritating to the eye at 1.0%. The ingredient was a sensitizer when tested at 1.0% on guinea pigs. Test data indicate that the ingredient is neither a mutagen nor a teratogen.

A formulation containing 0.1% 2,3-Naphthalenediol was not a human skin irritant.

DISCUSSION

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the CIR Procedures, the Expert Panel informed the public of its decision that the data on 2,3-Naphthalenediol are insufficient to determine whether this ingredient, under each relevant condition of use, is either safe or not safe. The Panel released a Notice of Insufficient Data Announcement on September 23, 1986, outlining the data needed to assess the safety of 2,3-Naphthalenediol. The types of data required included:

1. Dermal irritation data (animals)
2. Photosensitization data (animals)
3. 90-Day subchronic dermal data (animals)
4. Chemical description and impurity data

No response to the Notice of Insufficient Data Announcement was received within an appropriate time period. The Panel decided to issue the Final Report in accordance with Section 45 of the CIR Procedures. When new data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of 2,3-Naphthalenediol as used in cosmetics.

REFERENCES

1. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (1982). *CTFA Cosmetic Ingredient Dictionary*, 3rd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association, p. 179.
2. CHIAVARI, G., CONCIALINI, V., and VITALI, P. (1982). High-performance liquid chromatography of some hydroxy-substituted aromatic compounds. J. Chromatogr. **242**(2), 385–92.
3. DINARDO, J.C., PACCIANO, J.C., SCHNETZINGER, R.W., MORRIS, W.E., and WOLF, B.A. (1985). Teratological assessment of five oxidative hair dyes in the rat. Toxicol. Appl. Pharmacol. **78,** 163–6.
4. FOOD AND DRUG ADMINISTRATION (FDA). (1986). Cosmetic product formulation data–ingredients used in each product category. Section 06A: Hair dye. Washington, DC: Computer printout.

5. WEIL, C.S. (1952). Tables for convenient calculation of median effective dose (LD_{50}, ED_{50}) and instruction for their use. Biometrics **8,** 249–63.
6. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (Jan. 20, 1982). Submission of unpublished data by CTFA. CIR safety data test summary response form. Acute oral toxicity test. CTFA Code No. 3-14-1.*
7. CTFA. (Dec. 20, 1978). Submission of unpublished data by CTFA. CIR safety data test summary response form. Rabbit eye irritation. CTFA Code No. 3-14-2.*
8. REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES. (1982). National Institute for Occupational Safety and Health. U.S. Dept. of Health and Human Services, p. 796.
9. DRAIZE, J.H. (1959). Dermal toxicity. In: *Appraisal of the Safety of Chemicals, Foods, Drugs, and Cosmetics*. Austin, TX: Association of Food and Drug Officials of the US, pp. 46–59.
10. CTFA. (Nov. 4, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Contact allergy testing in guinea pigs. CTFA Code No. 3-14-4.*
11. MARON, D.M., and AMES, B.N. (1975). Test. Mut. Res. **31,** 347–64.
12. CTFA. (July 3, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Ames testing. CTFA Code No. 3-14-5.*
13. CTFA. (Dec. 13, 1982). Submission of unpublished data by CTFA. CIR safety data test summary response form. Human patch-single insult. CTFA Code No. 3-14-3.*

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