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Final Report on the Safety Assessment of Disperse Violet 1

Disperse Violet 1 is a diamino-anthraquinone dye that is used as an ingredient in both semi-permanent and permanent hair coloring formulations at concentrations at or below 1%.

In acute oral toxicity tests, Disperse Violet 1 was practically nontoxic. In a subchronic feeding study, no adverse clinical or untoward pathological changes were found. Disperse Violet 1 was practically nonirritating in ocular studies at a concentration of 5.0%. A formulation containing Disperse Violet 1 was nonirritating to the skin.

In Ames assays using concentrations of Disperse Violet 1 that ranged from 10 to 1000 $\mu\text{g}/\text{plate}$, Disperse Violet 1 was not mutagenic. In one other Ames assay at concentrations ranging from 100 to 2000 $\mu\text{g}/\text{plate}$, some mutagenic activity of Disperse Violet 1 was seen both without and with metabolic activation. In a long-term test, a hair dye formulation containing 0.033% Disperse Violet 1, dermally applied, was not carcinogenic.

At a concentration of 5%, Disperse Violet 1 was not a human skin irritant. Hair dyes containing Disperse Violet 1 are exempt from the principal adulteration provision and from the color additive provisions in Sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when cautionary statements and skin patch test instructions are conspicuously displayed on the labels. On the basis of the animal and clinical data presented in this report, it is concluded that Disperse Violet 1 is safe as a cosmetic ingredient in the present practices of use and concentration.

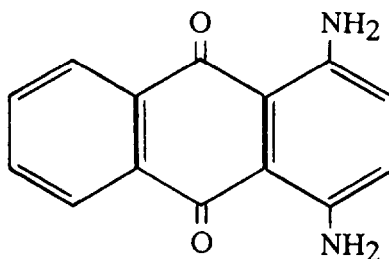
INTRODUCTION

Disperse Violet 1 is a diamino-anthraquinone dye used as a cosmetic ingredient in hair dyes. It is included in semipermanent and permanent hair coloring formulations.

CHEMISTRY

Definition and Structure

Disperse Violet 1 (CAS No. 128-95-0, CI No. 61100) conforms to the following formula⁽¹⁾:



Other names for this dye are 1,4-Diaminoanthraquinone, 1,4-Diamino-9,10-Anthracenedione, Disperse Violet K, and Krisolamine. Numerous other trade names are also available.^(1,2)

Disperse Violet 1 occurs in the form of dark violet crystals that are soluble in pyrimidine,⁽³⁾ alcohol, benzene,^(3,4) acetone, and linseed oil.⁽⁴⁾ According to Cosmair,⁽⁵⁾ Disperse Violet 1 has a weak odor and occurs as a black powder that forms a suspension with water at 25°C. Chemical and physical properties are summarized in Table 1.

Analytical Methods

Disperse Violet 1 has been identified through thin layer chromatography⁽⁸⁾ and chemical ionization (CI) mass spectrometry using ammonia and deuterated ammonia as reagent gases.⁽⁹⁾ A UV spectrum has been performed using a solution of Disperse Violet 1 in a water/methanol/30% alcohol (40:50:10) solvent. At a dye concentration of 0.0083 g/kg, the absorption maxima observed were: 0.720 at 225 nm, approximately, and 0.390 at 255 nm, approximately.⁽⁷⁾

Method of Manufacture

The most commonly reported method of manufacture used by industry is the pressurized condensation of quinzarin with aqueous ammonia and sodium hydrosulfite and then oxidizing the resulting leuko-1,4-diaminoanthraquinone in a mixture of σ -dichlorobenzene and nitrobenzene or sulfuric acid with chlorine.⁽⁴⁾

Disperse dyes get their names from the fact that they are used in the dye bath as colloidal dispersions. In 1979, the U.S. produced approximately 25 tons of Disperse Violet 1 and imported approximately 1.5 tons.^(6,10)

USE

Cosmetic Use

Disperse dyes are used in temporary hair color preparations in the form of rinses and colored setting lotions as well as in semipermanent preparations. In permanent hair colorants (the oxidation dyes), the presence of anthraquinone dyes in the formulation provides a wide range of color shades difficult to obtain by oxidation dyes alone.⁽¹¹⁾

Disperse Violet 1 is used as an ingredient in all types of hair dyes and colors. In 1988, Disperse Violet 1 was used in 133 formulations at a concentration of $\leq 1\%$.⁽¹²⁾

The FDA cosmetic product formulation information⁽¹²⁾ is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.⁽¹³⁾ Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide 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 ten-fold error in the assumed ingredient concentration. Table 2 includes the most updated product formulation data for Disperse Violet 1 as reported by the FDA.⁽¹²⁾

Use of hair dyes may result in contact with the hair, skin (particularly the scalp), eyes, and nails. For the individual user, the contact time of a dyeing solution on the scalp and hair is between 5 and 40 min. The amount of solution used varies from 15 to 100 ml, based on the individual. The frequency of use is once a week for temporary colorants and about once every 4 weeks for more permanent colorants. Use may extend over many years. Hairdressers are exposed to greater concentrations more frequently than their clients. It is estimated that 40% of the women in the U.S. are regular users of hair dyes.^(11,14)

The hair dyes containing Disperse Violet 1, as coal tar hair dye products, are exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF DISPERSE VIOLET 1

<i>Property</i>	<i>Description</i>	<i>Reference</i>
Physical appearance	Dark violet crystals	3
	Black powder	5
Odor	Weak	5
Formula	$C_{14}H_{10}N_2O_2$	1
Molecular weight	238.25	3
Log K_{ow}	1.25	6
Melting point (°C)	268	3
Solubility	Soluble in alcohol, benzene, and pyrimidine	3
	Soluble in acetone, alcohol, benzene, and linseed oil	4
	Forms a suspension with water at 25°C	5
UV spectrum (λm /absorbance)	225 nm/0.500 ^a	5
	250 nm/0.300 ^a	5
	290 nm/0.085 ^a	5
	≈225 nm/0.720 (dye conc. 0.0083 g/kg)	7
	≈255 nm/0.390 (dye conc. 0.0083 g/kg)	7

^aConcentration not given.

TABLE 2. PRODUCT FORMULATION DATA FOR DISPERSE VIOLET 1⁽¹²⁾

<i>Product category</i>	<i>Total no. of formulations in category</i>	<i>Total no. containing ingredient</i>	<i>No. of product formulations within each concentration range (%) ≤ 1</i>
Hair dyes and colors (all types requiring caution statement and patch test)	1056	133	133
1988 Totals		133	133

their label bears a caution statement as well as patch test instructions to determine whether the product causes skin irritation.⁽¹⁵⁾ The following caution statement should be displayed on all coal tar hair dye products:

Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Consumers are strongly urged to patch test for sensitivity 24 h prior to every application of the hair dye. Instructions are to apply a few drops of the hair dye with a cotton swab to a small area (the size of a quarter) behind either ear or inside the elbow. This area is to be left uncovered and undisturbed for 24 h and then evaluated for irritation.⁽¹⁶⁾

Noncosmetic Use

Disperse Violet 1 is used as a dye for plastics, textiles, wool, and furs and as a solvent dye when in a pure state.⁽¹⁷⁾ In 1980, disperse dyes composed the largest single group of dyes used in the U.S. Their main use was for dyeing synthetic fibers.⁽⁶⁾

BIOLOGICAL PROPERTIES

General Effects

Disperse Violet 1 inhibited respiration in microbial cells; respiratory inhibition increased with increases in concentration.⁽¹⁸⁾

Production of microsomal Ca^{2+} -dependent serine protease was promoted by Disperse Violet 1. Male F344 rats weighing approximately 150 g were fed a basal diet including 0.25% Disperse Violet 1. Control adult rats were fed a basal diet. All animals were killed following 15 h of fasting, and the liver was removed. Microsomes were prepared by standard fractionation techniques. Protease activity was measured by spectrophotometry. Disperse Violet 1 increased the activity of protease and elevated the activity of cytochrome P-450 by 150-fold. Results of a previous study related increased protease activity to tumor promotion.⁽¹⁹⁾

Cutaneous Absorption

Cutaneous absorption of a 10% solution of Disperse Violet 1 was studied using anesthetized animals. The number, species, and sex were not stated.⁽²⁰⁾ The animals were immobilized, and a thick layer of solution was applied to a shaved area of the abdomen. After 3 h, there were no indications that this ingredient was absorbed.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Acute toxicity studies were conducted in four tests using groups of 10 fasting rats (5 males and 5 females per group).⁽²¹⁾ Each animal received a single oral 5.0 g/kg dose of a hair color preparation containing Disperse Violet 1. Each group was observed for 14 days. No signs were reported, and no rats died during the study. The LD₅₀ for this cosmetic formulation was not reached.

Subchronic Toxicity

Oral

Twenty rats (10 males and 10 females) were administered feed containing 500 ppm of Disperse Violet 1 daily (approximately 30–50 mg/kg/day) for 13 weeks.⁽²⁰⁾ A similar number of untreated animals served as the control. Samples of blood and urine were analyzed at the beginning and end of the experiment. No observations of illness were made during the test period. On completion of the study, test animals were killed, organ weights were recorded, and histopathological examinations were performed. Animal and organ weights did not vary significantly from controls. No pathological changes were found. All test material was eliminated in the urine.

Ocular Irritation

An acute ocular irritation study was conducted on an unspecified number of rabbits.⁽²²⁾ Using the Draize procedure, a single 500 mg dye sample was instilled into the conjunctival sac of the rabbits' eyes, and the eyes were examined 24 h later.⁽²³⁾ The investigators concluded that Disperse Violet 1 was a moderate ocular irritant in rabbits.

Two drops of a 5% suspension of Disperse Violet 1 in water were instilled into the conjunctival sac of the eyes of an unspecified number of rabbits to test acute ocular irritation.⁽²⁰⁾ (It is not stated whether or not controls were used.) Little or no conjunctival irritation was reported by the investigators.

A hair color preparation containing Disperse Violet 1 was used to study ocular irritation in albino rabbits.⁽²⁴⁾ In four tests, an undiluted 0.1 ml application was instilled into the conjunctival sac of the eyes of 6 rabbits per test. Clinical observations under white light and long-wave ultraviolet light after fluorescein staining were conducted daily for 1 week. Corneal opacity was monitored for 14 days in each test. Twenty of the 24 rabbits had no signs by day 7. Slight transitory irritation was observed in some rabbits. The final Draize eye irritancy scores for the four tests were 2.67, 2.67, 5.97,

and 6.33. The Disperse Violet 1 hair preparation was considered practically nonirritating.

Dermal Irritation

A hair preparation containing Disperse Violet 1 was tested for dermal irritation using the Draize procedure.⁽²⁵⁾ In four tests, a 0.5 ml dose was applied to the intact and abraded skin of 6 albino rabbits per group. Erythema and edema were scored at 24 and 72 h. The primary irritation scores for the four tests were 0.2, 0.6, 0.8, and 0.8 (score range 0.0–8.0). The hair color preparation was nonirritating.

MUTAGENICITY

An Ames test was conducted to assay the mutagenic potential of Disperse Violet 1 using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA100, and TA98.⁽²⁶⁾ Disperse Violet 1 was tested at doses of 10, 20, and 40 µg/plate. (It is not stated whether metabolic activation was present.) Investigators reported that Disperse Violet 1 was not a mutagen at these concentrations. No evidence of mutagenicity was found in a study by Shahin and von Borstel⁽²⁶⁾ using *Saccharomyces cerevisiae* to test Disperse Violet 1 at concentrations of 20 to 100 µg/plate.

Brown and Brown⁽⁸⁾ tested high concentrations of Disperse Violet 1 (100, 500, 1000, and 2000 µg/plate) using *S. typhimurium* following the Ames procedure. Tester strains included TA1537, TA1538, TA100, TA98, and TA1978. The experiment was conducted with and without metabolic activation. Without metabolic activation, only in strain TA1537 was mutagenic activity produced by Disperse Violet 1. With metabolic activation, the number of reactants of the frameshift mutants generally increased. The data indicated that mutagenic activity in some *S. typhimurium* strains (TA98, TA1538) required the biochemical conversion of Disperse Violet 1 to an active substance.

Venturini and Tamaro⁽²⁷⁾ conducted a similar Ames study using *S. typhimurium* strains TA1535, TA1538, TA100, and TA98 at doses of 100 to 1000 µg/plate with and without metabolic activation. Disperse Violet 1 was not mutagenic.

Mutagenicity tests of Disperse Violet 1 were conducted using *S. typhimurium* strains TA1535, TA1538, TA1978, TA98, and TA100.⁽²⁸⁾ Repeated tests used doses ranging from 10 to 1000 µg/plate. No mention of metabolic activation was made. No evidence of mutagenic activity was found when Disperse Violet 1 was compared to controls.

Mutagenic potential of Disperse Violet 1 was assayed using the induction of rapid lysis mutants in bacteriophage T4D. *Escherichia coli* strains B, Bb, CR63m, and K12 (λh) were used.⁽²⁹⁾ Disperse Violet 1 significantly increased the frequency of rapid lysis mutants in bacteriophage T4D at 12.8, 30.5, and 61.0 µg/ml. Concentrations ranging from 0.3 to 291.0 µg/ml did not affect mutant frequency when compared to the controls.

CARCINOGENICITY

A carcinogenicity test of a hair dye formulation containing 0.033% Disperse Violet 1 was conducted using 8-week-old Eppley Swiss mice.⁽³⁰⁾ The experimental group and

two control groups each contained 60 male and 60 female mice. Three times a week for 20 months the dye was applied, 0.05 ml per application, via a calibrated Hamilton syringe. The application site was an approximately 1 cm² area of skin in the interscapular region that was clipped free of hair. The control animals were shaved but did not receive any treatments. After 9 months of treatment, 10 males and 10 females were selected randomly from each group for clinical tests, hematology, and necropsy. Urine samples were analyzed for color, pH, occult blood, albumin, and glucose. At the end of the 20-month treatment period, all animals were killed, and blood samples were taken via cardiac puncture from 5 males and 5 females in each group. Complete blood counts and differential counts were determined on the samples taken. There were no significant differences in either the urinalysis or hematology parameters when the treated group was compared to the control groups. Necropsy was performed on all mice found dead, killed due to moribund condition, killed after 9 months, or killed at the termination of the study. Neoplasms that commonly occur in Eppley Swiss mice, such as pulmonary adenomas, hepatic hemangiomas, and malignant lymphomas, were observed in both the treated and untreated groups. A statistical analysis of neoplasm incidence by use of chi-square and Fisher exact tests indicated no significant increase in any of these common neoplasms in the treated males and females when compared to the control groups. No skin tumors were cited as occurring in either the test or control groups.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Seven human subjects were used in a skin irritation study.⁽²⁰⁾ A 5% solution of Disperse Violet 1 was applied to the upper arm of test subjects for 3 h. The test area was observed 24 h after patch removal, and the results were negative.

SUMMARY

Disperse Violet 1 is a diamino-anthraquinone dye that occurs as either dark violet crystals or as a black powder and is used as an ingredient in both semipermanent and permanent hair coloring formulations. It is used in the dye bath as a colloidal dispersion. In 1988, Disperse Violet 1 was reported to the FDA as being used in 133 hair dye and color formulations at a concentration of $\leq 1\%$.

Coal tar hair dyes, including those containing Disperse Violet 1, are exempt from the principal adulteration provision and the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The following caution statement should be displayed conspicuously on the label of coal tar hair dyes:

Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Noncosmetic uses of Disperse Violet 1 include its use as a dye for plastics, textiles, wool, and furs. It can be used as a solvent dye when in a pure state.

Disperse Violet 1 inhibits respiration in microbial cells; the inhibition increased with increased concentration. Production of microsomal Ca^{2+} -dependent serine protease was promoted by feeding 0.25% Disperse Violet 1 to rats. The activity of cytochrome P-450 was increased by 150-fold.

A solution of 10% Disperse Violet 1 was not cutaneously absorbed.

Four acute oral toxicity tests determined that, at most, according to the methods of Hodge and Sterner,⁽³¹⁾ Disperse Violet 1 is practically nontoxic. In a feeding study in which 500 ppm Disperse Violet 1 was fed to rats for 13 weeks, no clinical signs were observed and no pathological changes were found. All test material was eliminated in the urine. Disperse Violet 1 was a moderate ocular irritant in rabbits following a single 500 mg application. In tests using either a 5% solution or 0.1 ml application of Disperse Violet 1, Disperse Violet 1 was practically nonirritating. In four dermal irritation tests, a 0.5 ml dose of Disperse Violet 1 was nonirritating.

In a number of mutagenic assays using concentrations of Disperse Violet 1 that ranged from 10 to 1000 $\mu\text{g}/\text{plate}$, Disperse Violet 1 was not mutagenic. In an Ames test using concentrations ranging from 100 to 2000 $\mu\text{g}/\text{plate}$, some mutagenic activity of Disperse Violet 1 was seen without and with metabolic activation.

A 20-month test in which a hair dye formulation containing 0.033% Disperse Violet 1 was dermally applied produced no carcinogenic activity.

Negative results were obtained in a skin irritation study using a 5% solution of Disperse Violet 1.

DISCUSSION

The CIR Expert Panel recognizes that there are limited human sensitization and irritation data on Disperse Violet 1. Hair dyes containing Disperse Violet 1 are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when cautionary statements and patch test instructions are conspicuously displayed on the labels. Prophetic patch testing of hair dye formulations with open patches is less predictive of skin reactions than patch testing with closed patches. False negative reactions may occur. Some persons may be sensitized even under the proper conditions of use.

CONCLUSION

On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes that Disperse Violet 1 is safe as a cosmetic ingredient in the present practices of use and concentration.

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