Safety Assessment of Hydroxypropyl Bis(N-Hydroxyethyl-p-Phenylenediamine) HCl as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this Scientific Literature Review and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 Director, Dr. F. Alan Andersen.

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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INTRODUCTION

This is a review of the available scientific literature and unpublished data provided by industry relevant to assessing the safety of the oxidative hair dye hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl and used in cosmetics.

CHEMISTRY

Definition and Structure

The structure of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (CAS no. 128729-28-2) is shown in Figure 1.

Physical and Chemical Properties

The physical and chemical properties are provided in Table 1. Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl is a substituted aromatic amine salt. The logP of this hair dye is -5.

Ultraviolet light absorption, in the range of 200 – 400 nm, of a solution (0.01 g/L in deionized water) has a peak at 258 nm.[1] There is a less well-defined peak at 302 nm. The visible light absorbance, in the range of 350 – 800 nm, of a solution (10 g/L in deionized water) has a peak at 415.5 nm. There is a less well-defined peak at 570 nm.

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[2] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group.[3] Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was reported to be used in 75 hair dyes and colors at a maximum concentration of 0.28%.

Because this ingredient is only used in one category, no use table was developed.

The Scientific Committee on cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) opinion of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl states that this hair dye may be used up to 3.0% (before mixing with hydrogen peroxide for application) so that the final concentration applied by the consumer does not exceed 1.5%.[4]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

^{14}C-Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (25 mg/kg) administered to the clipped skin of Wistar Hans rats was primarily recovered in the application site wash and the dressing (males, 94.2 ± 3.91%; females, 96.86 ± 2.96%).[5] Recovery in urine and feces was < 1%. Recovery in the skin (dermis and epidermis) was < 0.2%. Of the small amount that was absorbed, most of the test substance was eliminated in the feces (> 80%) within 72 h. There were no gender differences in the results.

When applied to human skin in a diffusion cell, < 0.2% of a radio-labeled hair dye (20 mg/cm^2) containing hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (3.67 ± 0.25%) mixed with either hydrogen peroxide or water was recovered in the receptor cell.[6] The receptor fluid was sampled at 0, 0.5, and 1 h then every hour up to 24 h. Most of the dye was recovered from the skin surface (93.9 ± 2.7% and 98.2 ± 4.0%, respectively). The stratum corneum contained 1.78 ± 0.87% and 1.32 ± 0.96% of the dye and the epidermis/dermis contained 0.55 ± 0.33% and 1.85 ± 1.68%, respectively.

When applied to human skin in a diffusion cell, ~0.01% of a radio- labeled hair dye (14.0 µL; ~20 mg/cm^2) containing hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (0.34%, 0.8%) mixed with either hydrogen peroxide or water was recovered in the receptor cell.[7] Most of the dye was recovered from the skin surface (98.31 ± 2.68% and 98.72 ± 2.27%, respectively). The epidermis/dermis contained 0.90 ± 0.92% and 0.80 ± 0.77% of the applied dye, respectively.

Oral

When ^{14}C-hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was orally administered to Wistar Han rats, the mean plasma total radioactivity levels increased from time 0 until the c_{max} (1558 ± 157 ng-eq/g for males and 1678 ± 540 ng-eq/g for females) at 1 h (males) or 2 h (females), and then decreased until the last quantifiable time points at 6 h (281 ± 15 ng-eq/g) or 8 h (224 ±53 ng-eq/g), respectively.[8] Blood samples (n = 3/sex/time point) were collected at 0, 1, 2, 4, 6, 8, 24, 48, and 72 h after treatment.

Other rats (n = 3/sex) were weighed and urine/feces/cage wash collected for 0 - 6 h and 6 – 24 h then every 24 h up to 168 h. Following oral gavage of the isotope mixture at 100 mg/kg, the mean total cumulative excretion of the radioactive dose in the summed excreta over the 168-h period was 98.3 ± 2.7% and 96.3 ± 3.4% for the males and females, respectively. A mean of 2.5 ± 0.3% and 95.4 ± 2.5% of the absorbed test substance was eliminated in the urine and feces, respectively, for the males and 3.7 ± 0.3% and 88.6 ± 9.3% for the females. The cage contained < 5% absorbed test substance for both sexes.

Most of the radioactivity (90.7% and 72.9 %, respectively) was eliminated in the summed urine and feces within 24 h, > 95% of which was in the feces.[8]

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal – Non-Human

The dermal LD_{50} for hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was > 2000 mg/kg for Sprague-Dawley rats (n = 5/sex).[9] One rat had a slight decrease in spontaneous activity at 4 and 6 h after treatment.

Oral – Non-Human

The oral LD_{50} of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was reported to be 2186 mg/kg (C.I. 1797-2965) for Sprague-Dawley rats (n = 5/sex).[10] The fasted rats were administered the test substance (1100, 1600, 2000, 2600 mg/kg in water; 10 ml/kg). No deaths occurred in the 1100 and 1600 mg/kg female groups. In the 2000 mg/kg group, 2/5 females and 3/5 males died. In the 2600 mg/kg group, 4/5 females died. Except for 2 animals which died on day 3, all deaths occurred within 30 minutes of treatment. Hypoactivity, sedation, piloerection and dyspnea were observed in both sexes. Males exhibited lateral decubitus. The first signs were observed at 30 min after treatment. For those that did not die, recovery was complete on day 7 for the females and day 5 for the males.

Wistar HanIbm:WIST (SPF) rats (n = 2) exhibited a reduction of spontaneous activity eyelid closure, and apathy when orally administered 1500 mg/kg hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl.[11] At 2000 mg/kg, there was a reduction of spontaneous activity eyelid closure, apathy, abdominal position, and one death observed.

Repeated Dose Toxicity

Oral – Non-Human

In a range finding study where Sprague-Dawley rats (n not provided) were administered hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (50, 200, 800 mg/kg/d) for 2 weeks, the rats in the high dose group had a slight decrease in body weight gain, glucose level, and total proteins.[12,13] A dose of 800 mg/kg/d resulted in: ptyalism and signs of poor clinical condition in both sexes, slightly lower body weight gain in males (-11% compared to controls), lower glucose (-26%) and higher triglyceride (x 1.5) levels in males, and in the kidneys, minimal to slight brownish pigment in the tubular epithelium and slightly higher incidence and severity of tubular dilatation in both sexes. The mid dose group had a slight decrease in glucose level. There were no effects observed in the low dose group.

The NOAEL for hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was 25 mg/kg/d when administered to rats for 13 weeks.[13] The test substance (25, 100, 400 mg/kg/d in water) was administered to Sprague-Dawley rats (n = 10/sex) by gavage; the rats were then killed and necropsied. There were no clinical signs in the low dose group.

There was ptyalism, loud breathing, and/or vomiting in the mid and high dose groups from week 4. Pink urine, brown colored tails, and brown or black feces were also observed in these groups. One male from each of the mid and high dose groups died; aspiration pneumonia due to vomiting was considered a contributing factor. Body weights and feed consumption were similar to controls. Opacification of the lens was observed in one female in the high dose group. Females in the high dose group had higher activated partial thromboplastin time and higher urea and creatinine levels were observed in females in the mid and high dose groups. Urinalysis and macroscopic examination of tissues were unremarkable. Microscopic examination revealed tubular basophilia in the kidneys of the males in the high dose group and many of the organs and tissues had a brownish pigmentation, probably due to the color of the test material. Subacute to chronic aspiration pneumonia was observed in the mid and high dose group.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The NOAEL for reproductive and developmental toxicity was > 800 mg/kg/d for Crl CD (SD) BR Sprague-Dawley rats (n = 25) orally administered hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl.[12] The test substance (50, 200, 800 mg/kg/d in water) was orally administered on days 6 – 15 of pregnancy. On day 20, the dams were killed and necropsied. Other than colored urine in one dam in the low dose group and all the dams in the mid and high dose groups, there were no clinical signs. The necropsies were unremarkable. The mean number of corpora lutea, implantation sites, post-implantation loss, number of live fetuses, sex ratio, and fetal body weights were similar to controls. There were no treatment related anomalies in the fetuses.

GENOTOXICITY

In Vitro

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (312.5, 625, 1250, 2500, 5000 µg/plate with metabolic activation; 62.5, 125, 250, 500, 1000 µg/plate without) was not mutagenic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537) and *Escherichia coli* (strain WP2uvrA) except for weak mutagenic activity observed (2.2 fold increase in revertant colonies) at 5000 µg/plate in the TA100 strain.[14] The test with metabolic activation was repeated

with higher concentrations (125, 250, 500, 1000, 2000 µg/plate) with the same result. The test without metabolic activation was repeated at the same concentrations with the same result.

In a mammalian cytogenetic assay using Chinese hamster ovary (CHO) cells, hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (30, 100, 300, 1000, 3000, 5000 µg/mL with metabolic activation; 12.5, 25, 50, 100, 150 µg/mL without) did not induce an increase in aberrant cell frequency with metabolic activation but did at 100 µg/mL without metabolic activation.[15]

When this assay was repeated (125, 250, 500, 750, 1000 µg/mL with metabolic activation; 12.5, 25, 50, 75, 100 µg/mL without), the test substance did not induce an increase in aberrant cell frequency with metabolic activation.[15] However, without metabolic activation, the test substance increased the instances of cells with structural chromosome aberrations at 75 µg/mL.

In Vivo

In an unscheduled DNA synthesis (UDS) assay of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (150, 1500 mg/kg in distilled water; 10 ml/kg) using Wistar HanIbm:WIST (SPF) rats (n = 4), there was no induction of UDS in the hepatocytes of the treated rats.[11] The hepatic samples were collected at 2 h (1500 mg/kg) and 16 h (150, 1500 mg/kg) after the rats were administered the test substance. The hepatocytes were cultured and the cells examined for UDS.

In a micronucleus test, hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (375, 750, 1500 mg/kg/d) orally administered for 2 days to Swiss OF1 mice (n = 5/sex) did not induce damage to the chromosomes or the mitotic apparatus of the bone marrows cells of the mice.[16]

In a micronucleus test, hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (500, 1000, 2000 mg/kg/d) orally administered for 2 days to Sprague-Dawley rats (n = 5/sex) did not induce damage to the chromosomes or the mitotic apparatus of the bone marrows cells of the mice.[17]

CARCINOGENICITY

Studies

No published reproductive or developmental toxicity studies were discovered and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (10% in purified water; 0.05 ml) was not irritating in a repeated application irritation test using Dunkin-Hartley guinea pigs (n = 3/sex).[18] The test substance was administered to the clipped skin daily for 14 days. The guinea pigs were killed and the test site examined microscopically. There were no clinical signs. There was a very slight erythema on all guinea pigs on day 9 and two on days 10 and 15. Almost all of the animals had dry skin at the test site. There was a slight black coloration of the skin starting on days 3 and 4 that could have masked very slight erythema.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (5% in distilled water; 0.05 ml) was not irritating in a patch test using New Zealand White rabbits (n = 3).[19] The test substance was administered to clipped skin under semiocclusion for 4 h and observed at 1, 24, 48, and 72 h and then daily up to day 9. No skin reactions were observed in one rabbit. Very slight or well-defined erythema was observed at 24 or 72 h after treatment in the other two rabbits. No edema was observed. There was dryness of the skin observed on days 5 - 8 in one rabbit. Mean scores over 24, 48 and 72 h for each animal were 0.0, 1.7, and 0.3 out of 4 for erythema and 0.0 for edema.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (100% dampened with water; 500 mg) was an irritant to male New Zealand White rabbits.[20] The test substance was administered to clipped skin under occlusion for 3 min (n = 1), 1 h (n = 1), and 4 h (n = 3). After 3 min, erythema (masked by a black coloration of the test site) was observed and persisted up to day 10. Slight edema was noted 1 h after removal of the dressing. After 1 h, slight to severe erythema was observed on days 1- 11. Severe to slight edema was observed on days 1 - 6. After 4 h, erythema (masked by a black coloration of the test site) persisted up to day 15. Slight to severe edema was observed on days 1 - 5 in two rabbits. The third rabbit had slight edema 1 h after removal of the dressing. The mean scores over 24, 48 and 72 h for individual rabbits were 0.0, 2.7 and 3.3 out a possible 4 for edema. Due to the skin coloration, scores for erythema could not be calculated.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (0.5 g in 0.5 mL distilled water) had a primary irritation index of 3.4 when administered to the intact and abraded clipped skin of New Zealand White rabbits (n = 3).[21] Slight to well-defined erythema and slight to severe edema were observed.

Ocular

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (100%; 0.1 mL) caused opalescent corneal opacity, iridial inflammation, and severe conjuctival irritation as well as sloughing of the cornea, hemorrhage, and a pale appearance

of the nictitating membrane when administered to the eye of one New Zealand White rabbit.[22]

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (5% in water; 0.1 mL) was not an ocular irritant to New Zealand White rabbits (n =3).[23] The eyes were not rinsed and were observed at 1, 24, 48, and 72 h after administration.

Sensitization

Dermal – Non-Human

In a Buehler test, hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (50% in distilled water; 0.5 mL) administered to the clipped skin of Dunkin-Hartley guinea pigs (n = 10/sex) did not induce sensitization when challenged (5% and 20%).[24] During the induction period, very slight to slight cutaneous reactions were observed in 8/20 guinea pigs.

In a guinea pig maximization assay using Dunkin-Hartley guinea pigs (n = 10), hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (0.1% in a sterile isotonic aqueous NaCl solution; 0.5 mL) administered by subcutaneous injections did not induce sensitization when challenged at 25% administered in a dermal patch.[25]

In a Magnusson-Kligman maximization test using Dunkin-Hartley guinea pigs (n = 10/sex), hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (1% in sterile isotonic saline) administered by intradermal injections and challenged at 50% in a dermal patch was classified as a sensitizer.[26] At 24 h, very slight, well-defined, and marked erythema were observed in 2/20, 11/20 and 7/20 guinea pigs, respectively. There was also slight edema observed in 11 guinea pigs and severe edema in one animal. Dryness of the skin was observed in 9/20 guinea pigs. Very slight black coloration of the skin was observed in 3 guinea pigs. At 48 h, very slight, well-defined, marked, and severe erythema were noted in 1/20, 4/20, 1/20 and 2/20 guinea pigs, respectively. Crust formation was observed in 3 guinea pigs. Dryness of the skin was observed in 14/20 guinea pigs. The dryness was severe enough to mask the evaluation of erythema in 5/20 treatment sites. Very slight to slight black coloration of the skin was observed in 5 guinea pigs. The very slight erythema which did not persist at the 48-h reading in two guinea pigs was attributed to a possible slight irritant reaction. All of the other skin lesions were attributed to a sensitization effect.

Phototoxicity

Dermal administration of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl (10% in purified water; 0.2 mL) to Dunkin Hartley guinea pigs (n = 10) did not cause phototoxicity or photosensitization when exposed to UVA or UVB light.[27] For the phototoxicity assay, the test substance was gently massaged into the shaved backs of the guinea pigs and 30 min later they were irradiated by UVB (312 nm) then UVA (365 nm). For the photosensitization assay, the guinea pigs were administered the test substance and irradiated 6 more times. After a 20-day rest, the test substance was administered and the test sites were irradiated again (left flank UVA, right flank UVB). The test sites were scored for reactions at 1, 6, 24, and 48 h after application.

SUMMARY

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl is an oxidative hair dye used in 75 hair dyes and colors at a maximum concentration of 0.28%.

Very little hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl penetrated the skin of rats and humans. Most of orally administered test substance was eliminated through urine and feces and cleared from the blood of rats within 6 – 8 h.

The dermal LD_{50} was > 2000 mg/kg for rats. The oral LD_{50} for rats was 2186 mg/kg.

The NOAEL for hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was 25 mg/kg/d for 13 weeks for rats.

The NOAEL for reproductive and developmental toxicity was > 800 mg/kg/d orally administered to rats on gestation days 6 – 15.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was not genotoxic to *S. typhimurium* and *E. coli* in an Ames test and a mammalian cytogenetic assay using CHO cells. The test substance was not genotoxic in an unscheduled DNA synthesis assay and two micronucleus tests.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was not irritating to guinea pigs up to 10% and rabbits up to 5%. It was severely irritating to rabbits at 100%.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was a severe ocular irritant to rabbits at 100% but was not an irritant at 5%.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was not sensitizing to guinea pigs up to 50% when applied dermally. However, when applied by intradermal injection, the test substance was sensitizing at 1%.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was not phototoxic at 10% when exposed to either UVA or UVB light.

DATA NEEDS

CIR is asking for submissions of characterization, toxicity, and dermal penetration data on the reaction products of this hair dye with hydrogen peroxide.

TABLES AND FIGURES

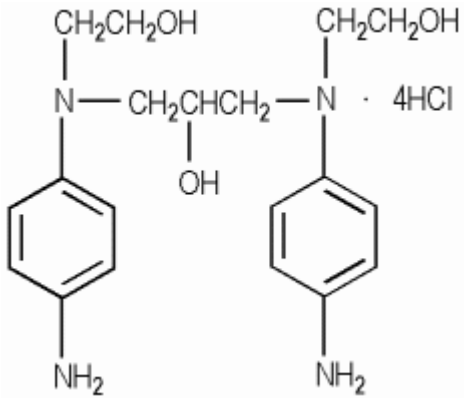

Figure 1. Chemical structure of hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl.

Table 1. Physical and chemical properties of hydroxypropyl bis(N-hydroxyethel-p-phenylenediamine) HCl.

Property	Value	Reference
Physical Form	Powder	[22]
Color	Blue-grey White-grey Beige	[22] [7] [9]
Odor	Strong, irritating	[1]
Molecular Weight g/mol	506.3	[7]
Water Solubility g/L	760	[7]
Other Solubility g/L @ 22°C		
Ethanol	< 1	[1]
DMSO	≥ 20	[1]
log K_{ow} @ 20 °C	-5	[7]

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