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Final Report on the Safety Assessment of t-Butyl Hydroquinone

The original safety evaluation of t-Butyl Hydroquinone (*J. Am. Coll. Toxicol.* 5(5), 1986) concluded that data on the depigmentation potential of this ingredient were required before it could be concluded that this ingredient is safe for use in cosmetic products. The safety test data included in the original 1986 evaluation are summarized in this report. The data indicated that t-Butyl Hydroquinone was slightly toxic in oral feeding studies but was neither a human irritant nor sensitizer when tested at 0.14%. The results from subchronic, chronic, and teratogenic studies of t-Butyl Hydroquinone and hair dyes containing this ingredient were unremarkable.

The required new data included in this addendum to the original report indicate that t-Butyl Hydroquinone was a weak depigmentor at 1.0 and 5.0% but not at 0.1%. Although a threshold for depigmentation was not established, the dose–response relationship was adequate to conclude that t-Butyl Hydroquinone at concentrations of use of 0.1% and less would not be a human depigmentor. Other data indicated that this ingredient was not a phototoxic agent. Therefore, the conclusion in the original report is amended to conclude that t-Butyl Hydroquinone may be safely used as a cosmetic ingredient at concentrations not to exceed 0.1%.

INTRODUCTION

The CIR Expert Panel previously has reviewed the available safety test data on t-Butyl Hydroquinone. The data and the Expert Panel's conclusion were released on July 23, 1985, and subsequently were published as the Final Report on the Safety Assessment of t-Butyl Hydroquinone.[1] The Summary, Discussion and Conclusion as stated in the report was as follows:

SUMMARY

t-Butyl Hydroquinone is a crystalline solid that is prepared by the acid catalyzed reaction of hydroquinone with isobutylene or t-butanol. Reported impurities include t-butyl-*p*-benzoquinone, 2,5-di-t-butylhydroquinone, hydroquinone, toluene, lead, and arsenic. t-Butyl Hydroquinone is easily oxidized to quinones.

Noncosmetic applications of t-Butyl Hydroquinone include use as a food additive, antioxidant and stabilizer for chemicals. It is used also to retard polymerization of polyesters. In cosmetics, t-Butyl Hydroquinone is used as an antioxidant.

Data submitted to the FDA by cosmetic firms indicated that t-Butyl Hydroquinone was used in 1981 in at least 266 cosmetic products at concentrations of > 0.1 to 1.0% (19 products) and ≤ 0.1% (247 products). The greatest use of the antioxidant was in lipsticks (242 products). Cosmetic products containing this ingredient are normally applied to or have the potential to come in contact with skin, eyes and hair. Small amounts of the antioxidant could be ingested from lipstick.

[The 1989 FDA product formulation data indicated that the reported use of t-Butyl Hydroquinone had fallen to 11 uses. Four uses were reported in the Eye and Facial make-up products category, 1 at a concentration > 0.1 to 1%, and 3 at ≤ 0.1%. There were 7 uses in miscellaneous skin care products; 1 at a concentration > 0.1 to 1%, and 7 at ≤ 0.1%.][2]

t-Butyl Hydroquinone inhibits the growth of a broad spectrum of gram-negative and gram-positive bacteria and growth of certain yeast and protozoa. In studies with the ciliated protozoa *Tetrahymena pyriformis*, the antioxidant inhibited the biosynthesis of lipids, protein, RNA and DNA.

Induction of hepatic mixed function oxidases and liver enlargement were not observed following subchronic and chronic feeding of the antioxidant to rats and dogs. Inhibition of prostaglandin synthesis was noted in bovine seminal vesicles exposed *in vitro* to low concentrations of the antioxidant (5.49 and 6.07 μM).

In studies with rats, dogs and humans, oral doses of t-Butyl Hydroquinone were excreted predominantly in the urine, primarily as sulfate conjugates and glucuronides, with smaller amounts excreted as unchanged t-Butyl Hydroquinone. It was suggested that the metabolic pathway for t-Butyl Hydroquinone in rats, dogs and humans was similar to that of dihydroxybenzenes. Results of subchronic and chronic feeding studies with rats and dogs indicated no significant accumulation of the antioxidant in tissues.

t-Butyl Hydroquinone was slightly to moderately toxic to rats by the oral and intraperitoneal routes of administration. The acute oral LD_{50} in rats was 480 mg/kg and 800 mg/kg, whereas, the acute oral LD_{50} in rats of 5.0 or 10.0% t-Butyl Hydroquinone in corn oil was between 700 and 1000 mg/kg. The intraperitoneal LD_{50} in rats of a 5.0 or 10.0% suspension of the antioxidant in corn oil was between 300 and 400 mg/kg.

Subchronic and chronic studies were conducted with rabbits, rats and dogs. A hair dye formulation containing 0.3% t-Butyl Hydroquinone produced no systemic toxicity when applied to the skin of rabbits twice a week for 13 weeks. Reduced weight gain was noted in rats fed a diet containing 1.0% of the antioxidant for 22 days. Rats fed a diet containing 0.016, 0.05, 0.16 or 0.5% t-Butyl Hydroquinone for 20 months were comparable to control animals in terms of behavior, growth rate, feed intake, mortality, hematologic parameters, clinical chemistry, urinalyses and tissue changes. A slight decrease in the brain weight of male rats fed 0.5% was noted; however, this decrease was not

associated with any pathologic or behavioral change. No other organ weight changes were observed. In a 6 month feeding study with rats, the antioxidant was added to heated and unheated cottonseed oil at concentrations of 0.02, 0.10 or 0.5%. The oil and antioxidant were then added to the diet at a 5.0% concentration. An increase in liver weight and a decrease in serum glutamic oxaloacetic transaminase activity were observed in the 0.5% group; no other toxicological effects were reported. Dogs fed diets containing 0.05, 0.158 or 0.5% t-Butyl Hydroquinone for 2 years were comparable to control animals with respect to hematologic values, clinical chemistry, urinalyses, and organ weights. Selected tissues and organs were histologically normal in the treated dogs.

t-Butyl Hydroquinone was mutagenic in both the "rec-assay" with wild and recombinationless strains of *Bacillus subtilis,* and in the "sensitivity test" with wild and rad mutant strains of yeast. No teratogenic effects were observed when the antioxidant was administered at doses of 970, 1878 or 3599 mg/kg in the diet of pregnant rats. Application of a hair dye containing 0.3% t-Butyl Hydroquinone to the skin of pregnant rats caused no embryotoxic or teratogenic effects. Results of a 3 generation reproduction study indicated no differences between control animals and rats fed 0.5% t-Butyl Hydroquinone with respect to gonadal function, estrus, mating, conception rates, gestation times, parturition, lactation, soft tissue, skeletal and liver abnormalities, and accumulation of the antioxidant in amniotic fluid and uteri.

In clinical tests with 271 subjects, lipstick products containing 0.054, 0.11, 0.14 and 0.15% by weight t-Butyl Hydroquinone were nonirritating and nonsensitizing to the skin.

DISCUSSION

There are clinical data to support that t-Butyl Hydroquinone is nonsensitizing and nonirritating to the skin at concentrations used in cosmetics. Although there have been no studies on t-Butyl Hydroquinone as a depigmenter, structural similarity of this compound to hydroquinone raises significant concern about this possibility. Furthermore, there are no data regarding phototoxicity or photosensitization.

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 t-Butyl Hydroquinone 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 October 10, 1984 outlining the data needed to assess the safety of t-Butyl Hydroquinone. The types of data required included:

1. Ninety-day depigmentation study in black guinea pigs or other appropriate animal. At least 3 concentrations of t-Butyl Hydroquinone shall be evaluated. Appropriate positive controls shall also be employed.
2. *In vitro* human and animal melanocyte studies at 3 t-Butyl Hydroquinone concentrations. Appropriate positive controls shall be employed.

3. Photosensitization data—animal data are appropriate.

No response to the Notice of Insufficient Data Announcement was received within an appropriate time period.

On June 21, 1985 the Expert Panel reviewed a request to delay the issuance of the Final Report until the data previously requested could be supplied. 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 t-Butyl Hydroquinone as used in cosmetics.

The CIR Expert Panel has now received the additional data needed to complete its evaluation of the safety of t-Butyl Hydroquinone for use in cosmetic products. This report is issued as an Addendum to the Final Report on the Safety Assessment of t-Butyl Hydroquinone.

PHOTOSENSITIZATION

On June 1, 1987, the CIR Expert Panel reviewed additional photoallergic contact dermatitis and delayed contact hypersensitivity data in guinea pigs exposed to t-Butyl Hydroquinone.[3,4] They concluded that the submitted data were adequate to conclude that t-Butyl Hydroquinone is not a photosensitizer.

MELANOCYTE TOXICITY

At the June 1, 1987, meeting the Expert Panel also stated that the melanocyte toxicity testing could be delayed until after the animal depigmentation testing is completed. If the animal data lack sufficient interpretable results to reach a conclusion on depigmentation, the melanocyte toxicity tests may be required. This Addendum to the Final Report evaluates the potential of t-Butyl Hydroquinone to produce skin depigmentation.

DEPIGMENTATION

The irritation and depigmentation potential of t-Butyl Hydroquinone (TBHQ) was carried out in outbred male and female black guinea pigs with pigmented skin and pelage. Five males and five females were assigned to each treatment group.[5]

The test compound, TBHQ, and hydroquinone (HQ), the positive control, were mixed with a hydrophilic ointment at concentrations of 0.1, 1.0, and 5.0%. A second positive control, *p*-methoxyphenol was tested at 10.0%. The individual test mixture in

the amount of 0.1 ml was applied by a syringe to the skin and was spread over 3.2 cm^2 of shaved flank. The applications were made daily for 5 days/week for 13 weeks.

The applications sites were evaluated clinically and photographed, and samples of skin were taken for histopathological evaluation. Clinical evaluations were made before and after depilation. The reported results are summarized in Table 1.

TABLE 1. DEPIGMENTATION—t—BUTYL HYDROQUINONE

Concentration and Animal Number	*Clinical*		*Photography*	*Histopathology*
	Depilated	*No Depilation*		
0.1% tBHQ				
Male				
345	(−)	(−)	(−)	(−)
346	(−)	(−)	(−)	(−)
347	(−)	(−)	(−)	(−)
348	(−)	(−)	(−)	(−)
349	(−)	(−)	(−)	(−)
Female				
340	(−)	(−)	(−)	(−)
341	(−)	(−)	(−)	(−)
342	(−)	(−)	(−)	(−)
343	(−)	(−)	(−)	(−)
344	(−)	(−)	(−)	(−)
1.0% tBHQ				
Male				
360	(+)	(?)	(+)	(+)
376	(−)	(−)	(−)	—
377	(−)	(−)	(−)	(−)
379	(−)	(−)	(−)	(−)
300	(−)	(−)	(−)	(−)
Female				
335	(−)	—	(−)	(−)
336	(+)	(?)	(+)	(+)
337	(−)	(−)	(−)	(−)
338	(−)	(−)	(−)	(−)
339	(−)	—	(−)	(−)
5.0% tBHQ				
Male				
406	(−)	(−)	(−)	(−)
407	(−)	(−)	(−)	(−)
408	(−)	(−)	(−)	(−)
409	(−)	(−)	(−)	(−)
410	(+)	(?)	(+)	(+)
362	(+)	(+)	(+)	(+)
Female				
401	(−)	(−)	(−)	(−)
402	(−)	(−)	(−)	(−)
403	(+)	(+)	(+)	(+)
405	(−)	(−)	(−)	(−)
386	(+)	(+)	(+)	(+)

TBHQ applied in a hydrophilic ointment at 0.1% did not produce depigmentation. The compound at 1.0% concentration produced evidence of depigmentation in one male and one female black guinea pig when evaluated clinically and histopathologically. The compound at 5.0% concentration produced evidence of depigmentation in two male and two female guinea pigs as evidenced by clinical and histopathological evaluation. The data presented in Table 1 indicate that TBHQ has weak depigmentation potential in black guinea pigs. The observed depigmentation was limited to the treatment site.

Hydroquinone (HQ) at concentrations of 1.0 and 5.0% also was a weak depigmentor in female guinea pigs, but not in male guinea pigs. The test results are presented in Table 2.

The procedures for evaluation of the presence of irritation and depigmentation are documented in the report, and grading schemes were provided.

The data in this study do indicate that the black guinea pig is a suitable animal model for the evaluation of the depigmentation potential of chemicals. The black guinea pig was highly responsive to a potent depigmenting compound, *p*-methoxyphenol. Guinea pigs treated with a 10% preparation of this compound had clinical depigmentation of both hair and skin; the depigmentation was confirmed by microscopic examination.

Evidence of the weak depigmenting potential of TBHQ is the lack of loss of pigment from the hair in guinea pigs treated with this compound. These results can be compared to those obtained with the potent *p*-methoxyphenol, which produced loss of pigment from both the hair and skin. The depigmentation was complete as well in those guinea pigs treated with *p*-methoxyphenol, whereas it was described as incomplete in animals treated with TBHQ.

DISCUSSION

The depigmentation data indicated that t-Butyl Hydroquinone was a weak depigmentor at 1.0 and 5.0% but not at 0.1%. Although a threshold for depigmentation was

TABLE 2. DEPIGMENTATION BY HYDROQUINONE IN FEMALE GUINEA PIGS

Concentration and Animal Number	*Clinical*		*Photography*	*Histopathology*
	Depilated	*No Depilation*		
1% tBHQ				
330	(+)	(+)	(+)	(+)
332	(+)	(−)	(+)	(−)
333	(+)	(+)	(+)	(−)
5% tBHQ				
391	(+)	(+)	(+)	(+)
392	(+)	(+)	(+)	(−)
393	(+)	(+)	(+)	(+)
394	(+)	(+)	(+)	(−)
395	(−)	(−)	(+)	(−)
398	(−)	(+)	(+)	(−)

not established, the dose–response relationship was adequate to conclude that t-Butyl Hydroquinone at, concentrations of use of 0.1% and less would not be a human depigmentor. The melanocyte toxicity study that was tentatively requested will not be required.

CONCLUSION

On the basis of the data included in this report, the CIR Expert Panel has concluded that t-Butyl Hydroquinone may be safely used as a cosmetic ingredient at concentrations not to exceed 0.1%.

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