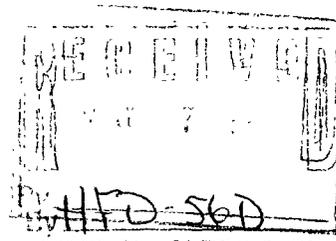


Carcinogenicity Assessment Committee
Open Public Meeting - Hydroquinone (OTC monographed ingredient)
December 4, 1996



Attendees: See Attachment

Division of Over-the-Counter Drug Products Presentation

Dr. Arthur Baker provided a brief summary of the industrial and pharmaceutical uses of hydroquinone as well as the regulatory history of hydroquinone as an over-the-counter (OTC) drug product.

In 1982, a tentative final monograph for hydroquinone was published. The intended use included gradual fading of dark discolorations in the skin such as: freckles, age and liver spots, pigment in the skin due to pregnancy or birth control pills (melasma). In 1989, the National Toxicologic Program (NTP) released a technical report documenting the carcinogenicity finding of oral hydroquinone in F344/N rats and B6C3F1 mice. The NTP reported a significant increase in renal tubular cell adenomas in male rats, mononuclear cell leukemia in female rats, and hepatocellular neoplasm in female mice. The CAC concurred with the NTP's finding in 1991 and recommended additional pharmacokinetic and toxicokinetic studies to evaluate the absorption and exposure via dermal application.

Dr. Baker further summarized the various studies and literature reviews conducted by the Non-prescription Drug Manufacturers Association (NDMA). To date, a 2-year dermal carcinogenicity study at clinically relevant doses has not been conducted, an assessment that the division believes necessary to adequately measure the potential carcinogenic risk to humans.

Based on the data available, the Division of OTC Drug Products recommended that NDMA conduct a 2-year dermal carcinogenicity study in B6C3F1 or CD-1 mice using up to a maximum tolerated dose; clinical relevant study in humans assessing the bioavailability, pharmacokinetics, and metabolism based on chronic OTC use. The comparative metabolism data will be important, especially if the rodent dermal study produces tumors.

NDMA Presentation

Dr. John O'Donoghue presented data from a collection of studies designed to assess the safety of hydroquinone and subsequently address the concerns raised by the CAC and division. Specifically, NDMA focused on the chemical mechanism of hydroquinone; hydroquinone's potential to act as a tumor initiator or promoter; whether tumor induction is present in other animal species; the absorption of hydroquinone following oral and dermal applications to animals and humans; and the histologic pattern of renal tubular adenomas seen in the aging male rats.

NDMA also presented epidemiologic mortality data collected from Eastman Chemical Company on workers exposed to hydroquinone in the HQ production/ use areas of the company between

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1941 and 1980. Mortality follow up data was collected through 1991. The data compared expected deaths with observed deaths in major diagnostic categories, as well as subcategories of cancer. The findings suggest that the workers in the chemical company had fewer deaths than expected in most cancer categories. NDMA believes this data lends support to the relative safety of HQ in comparison to the rodent bioassay findings.

NDMA summarized the presentation indicating that HQ is not mutagenic and may not be clastogenic, they believe the mechanism of action of the kidney tumors associated with HQ exposure is similar to that of alpha-2u-globulin, and the human epidemiologic data presented do not support the bioassay results found in the NTP study.

Division of Dermal and Dental Drug Products Presentation

Dr. Abby Jacobs, Pharmacology Team Leader, presented published data supporting the genotoxicity of hydroquinone under both in vitro and in vivo conditions as well as the mutagenicity of the hydroquinone metabolite, p-benzoquinone. She also presented data from the NTP report and published literature further supporting the immunotoxicity of hydroquinone. Dr. Jacobs addressed several issues of concern related to the differences in study design and methods between the NTP and Shibata study and noted that alpha-2-u-globulin was not detected in either the NTP or the Shibata studies.

Dr. Barbara Hill, Pharmacology Reviewer, presented data on the nephrotoxicity of the glutathione conjugates of hydroquinone. The data suggested that the severity of renal necrosis in rats correlates with an increase in the extent of glutathione substitution. In another rat toxicity study, in vivo formation of glutathione conjugates were detected in bile and urine samples. Based on this data, the susceptibility to nephrotoxicity appears to be similar across species (Fisher 344 rats and Sprague-Dawley rats) following administration of bromohydroquinone, 2-Br-(diGSyl)HQ, and 2,3,5-(triGSyl)HQ. The data further suggest that the potential factors involved in hydroquinone nephrotoxicity include the level of renal gamma-glutamyl transpeptidase activity and the ratio of deacetylase/acetylase activity.

Dr. Jacobs summarized the FDA presentation by concluding that hydroquinone is mutagenic, clastogenic, and immunotoxic. The data presented support the formation of reactive intermediates with the administration of hydroquinone. Also, based on the data considered, hydroquinone exposure resulted in renal tubule adenomas in male rats, an increased incidence and severity of mononuclear cell leukemia in female rats, and an increased incidence of hepatocellular adenomas in female mice. Finally, the evidence suggest that hydroquinone can covalently bind to proteins in the blood and kidney.

CAC Questions:

1. Hydroquinone and/or its metabolites have been reported by NTP (1989) to be clastogenic. Based on the available data, is it also genotoxic/clastogenic?

Yes - 13 No - 1 Abstained - 1

2. After reviewing the additional studies performed on hydroquinone by NDMA, does hydroquinone have potential tumorigenicity in humans by dermal route?

Yes - 8 No - 2 Maybe - 5

3. a.) Are there additional studies recommended by the CAC in order to better assess hydroquinone's safety as a topically applied skin bleaching drug product?

Yes - 14 No - 1

Additional safety studies recommended by the committee:

Noncarcinogenic assessment:

- **Comparative Metabolism (topical) - 13**
- **PK - 1**
- **Skin DNA Adducting - 2**

- b.) Should a an assay by dermal route in rodents be required to establish the safety (i.e., potential risk of cancer) of 2% hydroquinone cream as dermal product in humans? If so, which rodent model or alternative model does the CAC recommend?

- **Two-year bioassay needed - 8 Two-year bioassay not necessary - 2**
- **Alternative assay - 15**

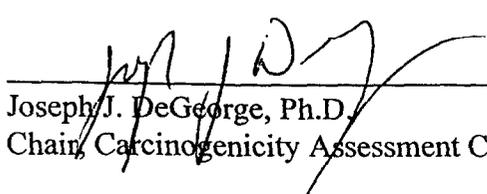
Recommended models:

- **TGAC - 7**
- **Initiation/Promotion - 5**
- **P53 +/- mouse - 1**

4. Are the available data adequate to assess potential carcinogenic risk of topical hydroquinone (2%) cream in humans? If so, what is the likelihood that, under OTC conditions of use, humans would develop cancer from topically applied 2% hydroquinone skin bleaching drug products?

Yes - 4* No - 11

- * **Two committee members believe the data presented may not be sufficient to fully characterize the risk; however, there is enough data to assess some risk.**

 3/14/97

Joseph J. DeGeorge, Ph.D.
Chair, Carcinogenicity Assessment Committee

cc: Docket file
HFD-24/JDeGeorge
HFD-105/MWeintraub
HFD-560/DBowen/ABaker/RCook/DDobbs
CAC file
CAC members

Attachment I

List of Meeting Attendees
CAC - 12/4/96

Committee members:

David Bailey, HFD-160
Conrad Chen, HFD-550
Lois Freed, HFD-120
Charles Resnick, HFD-110
William Fairweather, HFD-710
James Farrelly, HFD-530
Robert Osterberg, HFD-520
Abby Jacobs, HFD-540
Joseph Contrera, HFD-900
Ke Zhang, HFD-180
Ronald Steigerwalt, HFD-510
Hilary Sheevers, HFD-570
Wendy Schmidt, HFD-150
Lucy Jean, HFD-170
Joseph Sun, HFD-570
Sharon Olmstead, HFD-006, Exec Sec (non-voting member)
Joseph DeGeorge, HFD-24, Chair

Division members (HFD-560):

Michael Weintraub, Office Director, HFD-105
Rosemary Cook, Supervisory Project Manager
Linda Katz, Deputy Division Director
Debra Bowen, Division Director
William Gilbertson, Deputy Division Director
Lee Geismar, Team Leader
Ella Toombs, Medical Officer
Arthur Baker, Medical Officer
Donald Dobbs, Interdisciplinary Scientist

FDA Staff:

Barbara Hill, Pharmacologist, HFD-540
Jeffrey Yourick, Research Chemist, HFS-128
Robert Bronaugh, Supervisory Pharmacologist, HFS-128
Jennifer Fan, Staff Fellow, HFD-560
Liza Takiya, Staff Fellow, HFD-560
Terry Peters, Veterinary Pathologist, HFD-520

NDMA representatives:

Lorna Totman, Director of Scientific Affairs

Caroline English, Manager, Biochemical Toxicology, Eastman Kodak Co.

John O'Donoghue, Director, Health & Environmental Labs, Eastman Kodak Co.

Attendees:

Ed Stracuch, VP, Research and Development, Kivi Brands

Gene Gans, Chairman, Medicis Pharmaceuticals

E. John McKenna, FDC

John Bucher, Deputy Director, NTP, NIEHS

Gary Williams, Director, American Health Foundation

Attachment II

List of Presenter - Overheads
CAC - 12/4/96

- A. **Arthur Baker, M.D.**
Division of Over-the-Counter Drug Products, CDER, FDA
- B. **John L. O'Donoghue, V.M.D., Ph.D.**
Eastman Kodak Company
- C. **Abby Jacobs, Ph.D.**
Division of Dermatologic and Dental Drug Products, CDER, FDA
- D. **Barbara Hill, Ph.D.**
Division of Dermatologic and Dental Drug Products, CDER, FDA