

REVIEW

The safety of hydroquinone: A dermatologist's response to the 2006 *Federal Register*

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Recently, the US Food and Drug Administration proposed a ban on over-the-counter hydroquinone mainly on the basis of high absorption, reports of exogenous ochronosis in humans, and murine hepatic adenomas, renal adenomas, and leukemia with large doses over extended time periods. Systemic exposure to hydroquinone from routine topical application is no greater than that from quantities present in common foods. While murine hepatic adenomas increased, murine hepatocellular carcinomas decreased, suggesting a protective effect. Renal tumors are sex, species, and age specific and therefore do not appear relevant to humans after decades of widespread use. Murine leukemia has not been reproducible and would not be expected from small topical doses. Finally, a literature review of exogenous ochronosis and clinical studies employing hydroquinone (involving over 10,000 exposures under careful clinical supervision) reveal an incidence of exogenous ochronosis in the United States of 22 cases in more than 50 years. Therefore, the proposed ban appears to be unnecessarily extreme. (J Am Acad Dermatol 10.1016/j.jaad.2007.02.020.)

On August 29, 2006, the US Food and Drug Administration (FDA) released a statement proposing a ban on over-the-counter (OTC) hydroquinone. Specifically, the FDA proposes to “establish that over-the-counter (OTC) skin bleaching drug products are not generally recognized as safe and effective (GRASE).” The FDA also “intends to consider all skin bleaching products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.”¹ This article will demonstrate that the undisputed efficacy of hydroquinone in conjunction with a historically low risk/benefit ratio supports a status quo regulatory approach with respect to prescription hydroquinone. In examining the FDA's arguments for banning hydroquinone, 5 categories are worthy of consideration: absorption, fertility, carcinogenicity,

Abbreviations used:

CPN:	chronic progressive nephropathy
DESI:	drug efficacy safety implementation
FDA:	Food and Drug Administration
NDA:	new drug application
NTP:	National Toxicology Program
OTC:	over-the-counter
TFM:	tentative final monograph

exogenous ochronosis, and risk-benefit. The reasoning of the FDA is summarized in the bulleted text after each section heading and is followed by an evidence-based rebuttal.

REGULATORY AND MARKET HISTORY OF HYDROQUINONE

Drug regulatory law has grown over the years, empowering the FDA to make various demands of manufacturers wishing to sell drug products in the United States. Between 1906 (when FDA was created) and 1938, drugs were allowed to be sold in the United States without prior demonstration of safety or efficacy. The “New Drug Application” (NDA) did not exist at that time. In 1938, Congress passed the federal Food, Drug and Cosmetics Act of 1938. This act required safety, but not efficacy, data and required submissions to meet the requirements of a standardized NDA. In 1962, Congress empowered the FDA to require efficacy in addition to safety. All drugs approved prior to 1962 required re-review for efficacy. The process of re-review was termed *drug efficacy safety implementation* (DESI). Safety data

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could also be reconsidered for DESI drugs in the context of updated scientific methods. In 1983, a list of all prescription drugs being marketed without an NDA was made and became known as the “DESI II list.” Prescription-strength hydroquinone is on the DESI II list.

On Sept 3, 1982, in a tentative final monograph (TFM), FDA proposed that OTC hydroquinone 1.5% to 2% be generally recognized as safe and effective (GRASE).¹ In 1983, as mentioned above, prescription-strength hydroquinone was listed on the DESI II list. On Aug 29, 2006, FDA withdrew the TFM of 1982, proposing to ban OTC hydroquinone and to require any currently marketed hydroquinone product to be submitted as an NDA or face withdrawal from the market.

Hydroquinone was first noted to be a bleaching agent by Oettel in 1936.² In the 1950s, hydroquinone was available without a prescription as a sunscreen. It was observed, fortuitously, also to bleach the skin.³ In 1961 Spencer⁴ reported the first clinical trial with hydroquinone as a bleaching agent. Since that time, hydroquinone has been marketed in the United States in various strengths in both OTC and prescription products.

ABSORPTION

- Dermal absorption in rats was estimated at 10.5% to 11.5%. *In vivo*, hydroquinone 2% in an ethanol vehicle “...was found to penetrate readily in human forehead skin,” with absorption ranging from 26% to 66% depending on the presence of other excipients.¹

The *in vivo* absorption study cited by FDA measured the absorption of 2% hydroquinone in a 71% ethanol vehicle through the forehead skin of 6 adult male volunteers. This preparation was 57% absorbed following a single topical exposure of 24 hours’ duration. When a sunscreen was added, absorption fell to 26%.⁵ Absorption of many compounds is vehicle dependent. In the case of hydroquinone, an alcoholic vehicle allows for high absorption, and the addition of sunscreen decreases absorption. In this case, no prescription hydroquinone preparation on the US market contains a predominantly ethanolic vehicle, making this particular study less relevant to the real-world situation faced by users of these products. Indeed, some currently marketed hydroquinone preparations contain sunscreen.

Arguably more relevant is the *in vivo* absorption study of a 2% [¹⁴C]hydroquinone cream (Kiwi Brands, Inc) performed on 14 healthy volunteers by applying 0.125 g of cream (2.5 mg hydroquinone) to their foreheads. Absorption was determined to be

45.3%, with peak plasma concentration at 4 hours of 0.04 $\mu\text{g-Eq/mL}$. Also, excretion was determined to be primarily via the urine as the glucuronide and was essentially complete by 24 hours after application. Absorption from forearm skin was estimated at 24%, raising the possibility that forehead application is a worst-case scenario in terms of exposure.⁶ This study is significant in that it rigorously measures absorption *in vivo* in humans using a relevant hydroquinone preparation, specifically, one that is actually on the market.

Interestingly, in the FDA-approved cream containing hydroquinone 4% in combination with two other active ingredients (Tri-Luma, Galderma Laboratories, L.P.), absorption was shown to be negligible. Negligible absorption was demonstrated by applying to 14 healthy volunteers 3 g of Tri-Luma cream to each forearm once daily for 8 weeks. The 6 g/d dosage was believed to be a dose in excess of that expected in the treatment of facial melasma, which typically requires less than 1 g/d. Blood was sampled at 0, 2, 4, 6, 8, 12, and 24 hours postdose on days 1, 7, and 14. Blood was also sampled before dosing on days 4, 21, 35, and 56. “[None] of the subjects had measurable plasma concentrations of hydroquinone.”⁷ In a separate study where 1 g of cream was applied to the forearms of 44 subjects for 8 weeks, only 8 subjects (18%) had quantifiable plasma concentrations.⁸ Individual data for plasma concentrations are not publicly available; however, pharmacokinetic parameters were as follows: T_{max} for hydroquinone ranged from 0 to 24 hours, C_{max} ranged from 2.555 to 8.652 $\mu\text{g/mL}$, and AUC_{last} ranged from 2.63 to 36.4 $\mu\text{g.h/mL}$.^{7,8} Steady state was achieved by day 4.

Comparing results from the 2% and 4% hydroquinone preparations, 0.125 g of 2% hydroquinone yielded peak plasma concentrations of 0.04 $\mu\text{g-Eq/mL}$, and 1 g of 4% hydroquinone yielded peak plasma concentration of 8.652 $\mu\text{g/mL}$. Comparing “apples to apples” in Table I, we see that Tri-Luma, which is FDA approved, has a 10-fold greater peak plasma concentration per gram of hydroquinone than Kiwi. Even high absorption of hydroquinone has little clinical significance, given the small absolute quantities in consideration, as it is rapidly eliminated via urine in the form of the glucuronide, preventing appreciable residual sequestration or binding to tissue.^{6,9}

We can translate these findings to a 2-oz (56.8-g) tube of a hydroquinone 4% cream, which contains 2.272 g, or 2272 mg, of hydroquinone. The tube typically lasts for 60 days, meaning about 1 g/d of cream is used, or 40 mg hydroquinone per day is applied to the skin. In a worst-case scenario, imagine

Table I. Peak plasma concentration per gram hydroquinone applied

Brand	% HQ	Cream applied (μ g)	HQ applied (μ g)	Peak plasma concentration (μ g/mL)	Peak plasma concentration per gram HQ applied
Kiwi	2	125,000	2,500	0.04	2×10^{-5}
Tri-Luma	4	1,000,000	40,000	8.652	2×10^{-4}

HQ, Hydroquinone.

that the tube were used up in 2 weeks, amounting to about 4 g of cream per day, or 162 mg/d of hydroquinone. Assuming a minimum volume of distribution of 3 L (plasma volume of a man weighing 70 kg)¹⁰ and 50% absorption,⁶ 81 mg would be absorbed, resulting in a plasma concentration of 81 mg/3000 mL equaling 0.027 mg/mL, or 27 μ g/mL.

Deisinger, Hill, and English¹¹ determined that common foodstuffs contain significant amounts of arbutin, which readily hydrolyzes in weak acid (such as can be found in the stomach) to yield free hydroquinone. Table II,¹² adapted from Deisinger, Hill and English,¹¹ shows the total hydroquinone content (ie, free hydroquinone plus arbutin) in some common foodstuffs. Blood levels of hydroquinone after ingestion of a meal high in arbutin were measured at 0.15 μ g/g. Of note, in one patient, $T_{\max}$ was determined to be 1 hour for a 4 mg/kg oral dose of free hydroquinone, with 90% elimination by 5.6 hours.¹¹ From Table II, eating a D'Anjou pear, a cup of coffee, and a bowl of wheat cereal (say, 10 biscuits) yields about 2800 μ g, or 2.8 mg, of hydroquinone. This compares to 40 mg hydroquinone from 1 g of a 4% cream. DeCaprio⁹ asserts that hydroquinone is extensively absorbed by the oral route. Assuming oral administration is 100% bioavailable, and topical administration is 50% bioavailable, then relative exposure is 2.8 mg from the diet versus 20 mg topically. Predicted worst-case scenario blood levels would be 0.9 μ g/mL (2800 μ g/3000 mL) from the diet, and 7 μ g/mL (20000 μ g/3000 mL) for the topical route.

The total amount of hydroquinone absorbed, given the percent creams and quantities applied, is important. Were one concerned about absolute hydroquinone exposure per dose, if we take the $T_{\max}$ to be 8 hours,⁷ one could argue for a labeling change that would limit the application to no more than 0.5 g of a 4% cream in any, say, 12-hour period. As this amount is basically equivalent to the amount of hydroquinone one might ingest in a meal, which presumably has 100% bioavailability, then applying the cream might be no more dangerous than eating a

Table II. Hydroquinone content in common foodstuffs

Foodstuff	Hydroquinone/gram (μ g/g)	Average serving size (g) ¹²	Hydroquinone (μ g)/serving
Tea	0.14	100 (just under 1/2 cup)	14
Coffee	0.31	99 (just under 1/2 cup)	31
Wheat cereal	1.04	46 (2 biscuits Shredded Wheat cereal)	48
Whole wheat bread	2.04	28 (one slice)	57
Pear (Bosc)	3.84	166 (one pear)	637
Wheat germ	10.65	7 (1 tbsp)	75
Pear (D'Anjou)	15.09	166 (one pear)	2505

pear with its skin, a bowl of wheat germ, and a cup of coffee.

We can assume that total exposure over a lifetime is not at issue here, given the amounts of coffee some people consume in a lifetime. So, the main concern must revolve around $C_{\max}$, which is only slightly higher than that of a high-hydroquinone meal. The cumulative lifetime exposure to hydroquinone from 6 months of heavily used 4% cream (say, six 56.8-g tubes = 13.6 g hydroquinone, of which, say, half is absorbed, yielding 6.8 g) is comparable to a lifetime exposure to hydroquinone from coffee (62 μ g/cup $\times$ 1 cup per day $\times$ 365 days/y $\times$ 40 years = 0.9 g) or pears (2500 μ g/pear $\times$ 1 pear/wk $\times$ 52 weeks/y $\times$ 10 years = 1.3 g).

What may be more significant is that humans have a baseline excretion of 115.4 μ g/h or 2770 μ g/d of hydroquinone without exposure to skin lighteners. Over 60 years, this amounts to 61 g of hydroquinone in the urine, which presumably found its way there after systemic exposure, such as from food.^{2,11,13} The mean background plasma level of hydroquinone in humans after an 8-hour fast is 0.038 μ g/g.¹¹ To compare, after a high-arbutin meal, the plasma level of hydroquinone is 0.15 μ g/g, and the $C_{\max}$ of TriLuma ranged from 0.285 to 0.575 μ g/mL.⁷

FERTILITY

- "Because some studies showed fertility was impaired and others did not, . . . [additional] studies are needed to make a better assessment."¹

Recent fertility data suggest a lack of toxicity for hydroquinone. Studies implicating hydroquinone in reproductive toxicity were old (some dating back to the 1950s) and used high doses and nonstandard protocols. Modern studies with standardized teratogenicity and reproduction bioassays fail to demonstrate reproductive toxicity. Details are given in the extensive review of hydroquinone toxicology by DeCaprio.⁹

CARCINOGENICITY

- “[Carcinogenesis] studies on orally administered hydroquinone... have indicated ‘some evidence’ of carcinogenicity in [rodents.]” Specifically, male rats had increased renal tubular cell adenomas, female rats had increased mononuclear cell leukemia, and female mice had increased hepatocellular adenomas.¹

Nephrotoxicity

The reproducibility of hydroquinone-induced renal adenomas in male F344 rats is thought to be species-, strain-, and sex-specific. That is, they do not appear to be relevant to predicting human carcinogenicity, especially in light of decades of widespread human use of hydroquinone and no reports of associated human nephrotoxicity.⁹ Aged male F344 rats are prone to “chronic progressive nephropathy” (CPN), characterized histopathologically by, among other findings, degeneration and regeneration of tubular epithelium and renal papillary hyperplasia.⁹ When given hydroquinone, this subset was found to have an increase in renal adenomas.¹⁴ “[The] high correlation between the presence of hyperplasia or adenomas and that of severe to end-stage grade CPN [suggests] that [hydroquinone] acts in an epigenetic manner to accelerate the spontaneous CPN process.”⁹

In explaining these findings, one must consider 3 distinctions between the aged male F344 rat and humans. First, humans do not develop CPN. Second, human metabolism of hydroquinone yields different and less toxic hydroquinone conjugates than those of the rat. Third, humans have less vigorous cellular responses than rats to continuing proliferative stimulation.⁹

With respect to hydroquinone conjugates, rats have a lower capacity than humans for detoxification of hydroquinone through the glucuronidation pathway. Rather, rats make more glutathione conjugates, which are not seen in humans after dermal application of hydroquinone.¹³ In rats, these glutathione conjugates are detoxified primarily to mercapturic acid conjugates, which are nephrotoxic in rats. The little glutathione conjugates of hydroquinone

formed in humans are metabolized to cysteine conjugates, which are presumably not nephrotoxic.¹³ The lack of mercapturic acid conjugates in humans after ingestion suggests that humans would not have a toxic reaction after dermal application of hydroquinone.¹³ Furthermore, given the relatively low dosages encountered with dermal absorption, conjugation reactions would not get saturated, unlike that potential when gavage or intraperitoneal routes are employed.

With respect to the effect of hydroquinone on the kidney function of humans after *in vivo* topical and oral exposures, no evidence of toxicity has ever been documented.^{2,9,11,13} With respect to mutagenicity, hydroquinone has not been found to be carcinogenic in Ames tests.² Therefore, DeCaprio⁹ astutely observes: “Based on the absence of evidence for similar predisposing factors in other species, the lack of demonstrated renal effects in humans exposed to significant levels of [hydroquinone], and the minimal direct mutagenic potential of [hydroquinone], it is unlikely that nephrotoxicity or renal carcinogenesis represent relevant risk extrapolation endpoints for [hydroquinone] in man.”

Leukemia

Concerns about leukemia stem from two observations: (1) mononuclear cell leukemia was observed in female rats exposed to hydroquinone orally over 2 years, and (2) hydroquinone is a metabolite of benzene, which is leukemogenic.

In evaluating the human relevance of the first concern, one must appreciate that, while the bone marrow is considered to be the origin of benzene-induced leukemia in humans, leukemia in rats originates in the spleen. That is, rat and human leukemia have different biological origins. Additionally, the rat leukemia occurred with an oral hydroquinone exposure of 50 mg/kg over 2 years. “[Bone] marrow and hematologic effects are generally not characteristic of [hydroquinone] exposure in animal bioassays employing routes of exposure other than parenteral. In addition, myelotoxic changes have not been reported in humans as a result of long-term occupational [hydroquinone] exposure.”⁹

The scientific relevance of the first concern is also questionable as the results do not appear to be reproducible. The demonstration of leukemia in the National Toxicology Program (NTP) contrasts with the absence of leukemia in two long-term studies exposing rats to chronic, high-dose, oral hydroquinone. Furthermore, “the reported historical control incidence of mononuclear cell leukemia observed in the (NTP) bioassays using female F344 rats increased progressively during the 1980s. This trend, in

addition to the isolated nature of the NTP finding, weakens the strength of evidence for a significant leukemogenic potential for [hydroquinone].”⁹

With respect to the relative leukemogenicity of benzene versus hydroquinone, hydroquinone is only leukemogenic in the presence of phenol, which serves to stimulate the oxidation of hydroquinone by myeloperoxidase. The two are present simultaneously when benzene is metabolized, but phenol is absent when hydroquinone is administered alone. “[No] single benzene metabolite, including phenol, [hydroquinone], or [benzoquinone], has exhibited the potency and level of myelotoxic effect of benzene itself in animal studies.”⁹ In considering direct exposures isolated to hydroquinone (ie, no benzene and no phenol), the “degree of myelotoxicity will depend only on the level of unchanged [hydroquinone] present in bone marrow,” which is dependent on route of exposure and, specifically, is low with dermal administration.⁹

Importantly, our knowledge of hydroquinone metabolism derives from studies of animals exposed to high levels of parenteral hydroquinone. “[This] technical approach, while experimentally convenient, results in lower overall [hydroquinone] detoxification (via conjugation) by the liver and increased levels of unchanged [hydroquinone] available to the bone marrow for activation by myeloperoxidase and other oxidative enzymes.”⁹ With respect to clastogenicity, mice data suggest a no-effect level at 12.5 mg/kg, which is 875 mg for a 70-kg man, far in excess of the average 40-mg dose (1 g of a 4% cream) of topically applied hydroquinone.⁹ Therefore, leukemia “...would not be expected to occur under reasonably anticipated conditions of human exposure,” such as topical application, which result in lower levels of exposure that do not overwhelm the body’s capacity to detoxify hydroquinone.⁹

Hepatotoxicity

Despite female and male mice being noted to have increased hepatocellular adenomas by the NTP, there is evidence to suggest that hydroquinone is protective against hepatocellular carcinoma.¹⁴ Indeed, NTP observed a decrease in the incidence of hepatocellular carcinomas in the same cohort of mice that had increases in noncancerous adenomas.¹⁴ In separate rat studies, O’Donoghue¹³ points out that hydroquinone “...has an inhibitory effect (29% reduction) in naturally occurring preneoplastic hepatic foci in F-344/DuCrj rats when fed at 0.8% for 2 years.” He also indicates that hydroquinone is “reported to reduce the number of preneoplastic lesions and DNA adducts induced by 2-acetylaminofluorene, a potent hepatic carcinogen.” Therefore,

with respect to the liver, hydroquinone is at best hepatoprotective and, at worst, innocuous.

HUMAN EXPOSURE

There have been numerous reports of both large and small cohorts of human exposures to hydroquinone, and in no instance were any carcinogenic adverse events noted. DeCaprio⁹ cites a study whereby two male volunteers ingested 500 mg/d of hydroquinone for 5 months, and no renal or marrow abnormalities were noted. DeCaprio cites another study in which 17 volunteers ate 300 mg of hydroquinone per day for 3 to 5 months, again with no renal or marrow toxicity. Friedlander et al studied 478 photographic processors over 16 years, where hydroquinone exposure was typically less than 0.01 mg/m³, and found no increase in cancer relative to controls (cited in Nordlund, Grimes, and Ortonne² and DeCaprio⁹). Pifer et al studied 9000 workers at a hydroquinone manufacturing facility and found cancer rates to be lower than those of control groups (cited in Nordlund, Grimes, and Ortonne).² Similarly, Pifer et al studied a cohort of 879 workers from 1942 to 1990 specifically exposed to significant levels of hydroquinone and representing 22,895 person-years of exposure, and they found no evidence of increased rates of leukemia or renal cancer. Indeed, cancer mortality rates were lower than that of a control population (cited in Nordlund, Grimes, and Ortonne² and O’Donoghue¹³). Sterner et al studied a cohort of hydroquinone production workers exposed to up to 30 mg/m³ of hydroquinone dust and found no systemic toxicity despite hydroquinone-induced corneal abnormalities (cited in DeCaprio⁹ and O’Donoghue¹³).

More directly to the issue at hand, hydroquinone has been in use topically for more than 50 years, and no cases of skin cancer or internal malignancy related to this use have been reported.² In the few case reports (*vide infra*) of hydroquinone-induced exogenous ochronosis, a condition in which the use and overuse of hydroquinone appears to be the most egregious, no reports of associated dermal or internal malignancies are noted. One simply cannot conclude that hydroquinone is a carcinogen when applied topically to humans. There is, however, overwhelming historical and epidemiological human data supporting the safety of topical hydroquinone.

- “The evidence of carcinogenicity in animals in combination with the high absorption rate of hydroquinone in humans does not allow FDA to rule out the potential carcinogenic risk from topically applied hydroquinone in humans.... [A]

dermal carcinogenicity study, conducted in an appropriate model with functioning melanocytes [sic], must be performed on hydroquinone to assess both its topical and systemic tumorigenicity.”¹

In the above section, we have demonstrated that the absorption of hydroquinone from a 4% cream is comparable to that absorbed from common foods that contain hydroquinone. More significantly, the FDA has approved one hydroquinone-containing prescription product, Tri-Luma, for use as recently as 2002. The hydroquinone in this product, at a level of 4%, was deemed safe and noncarcinogenic. According to FDA’s postmarketing commitments database,¹⁵ Galderma committed to performing dermal carcinogenicity testing of Tri-Luma. It is unclear what steps Galderma has taken to fulfill this commitment; however, from the stated FDA deadlines, this process should be near completion. The results of this study, if negative, would obviate the need for further dermal toxicity studies with hydroquinone 4% (and would spare the testing of additional animals). Therefore, if nothing else, the FDA should hold judgment pending receipt of these results.

Galderma’s dermal toxicity study aside, O’Donoghue¹³ outlines a number of dermal toxicology studies done by the NTP and others with rats and mice whereby no dermal or systemic toxicity was elicited. Topical application of hydroquinone to the dorsal skin of F344 rats at 3840 mg/kg per day and pigmented B6C3F1 mice at 4,800 mg/kg per day for 14 days resulted in no significant toxicity despite recognized absorption.¹⁴ The NTP itself concluded that “since no toxic effects were seen, [topical application] is inappropriate for evaluation of the systemic toxicity of this compound.” Thus they turned to oral gavage.¹⁴ The fact is topical application of hydroquinone does not produce systemic toxicity. Because hydroquinone is not meant to be given orally, oral toxicity studies are irrelevant, especially at higher oral doses, which cause significantly more exposure than would ever be encountered with normal topical use. That no carcinogenicity is demonstrated via dermal administration is more relevant than data gathered from excessive and biologically irrelevant oral dosing in determining carcinogenicity.

Other studies also support the lack of dermal toxicity in rodents. David et al¹⁶ applied 2.0, 3.5, or 5.0% hydroquinone in a skin lightener formulation (Kiwi Brands, Inc.) to the skin of male and female F344 rats 5 days per week for 13 weeks. Neither the female nor the male rats showed aberrations in body weight, food consumption, water consumption, hematologic profile, clinical chemistries, kidney histopathology, or the rate of renal cell proliferation.¹⁶

While the study is quite old (1959), “a solution of 20% [hydroquinone] in acetone applied twice a week for 12 weeks to the dorsal skin of mice did not promote the development of tumors in skin that had been initiated with dimethyl benzanthrane.”¹³ More recently, a dermal toxicity study of hydroquinone 2% cream (886 mg/kg/d) in Sprague-Dawley rats administered for 13 weeks failed to show effects on clinical pathology end points, histopathology, organ weights, or urinalysis.¹³ Lastly, a year-long dermal cancer bioassay using ICR/HA Swiss mice was conducted by applying hydroquinone to the skin 3 times per week. Three groups of mice were tested: hydroquinone alone, hydroquinone plus tumor initiator (benzo[a]pyrene), and tumor initiator alone. The hydroquinone group did not develop any tumors, and the combination group developed fewer tumors than the tumor initiator alone group.¹³ O’Donoghue¹³ concludes, correctly, that “[none] of the existing data for [hydroquinone] indicates that it has any significant toxicity following dermal application, even in the sensitive male F344 rat.”

The challenge of interpreting human relevance to results from animal toxicology studies is at the core of the hydroquinone issue. In deciding what is relevant and what is not, one must consider relevance of dose, relevance of route of exposure, and comparative biology with respect to species-specific metabolic and biologic processes. Central to FDA’s consideration must be that, when absorbed topically, absolute exposure is orders of magnitude less than the oral exposure that caused cancers in rodents.⁶ The 2-year carcinogenicity data, on their own merit, as acknowledged by FDA itself, were deemed by FDA, NTP, and the Carcinogenicity Assessment Committee (CAC), to be inconclusive.¹ The International Agency for Research on Cancer (IARC) concluded that hydroquinone is “not classifiable as to its carcinogenicity to humans (Group 3)” on the basis of “inadequate evidence in humans for the carcinogenicity of hydroquinone [and] limited evidence in experimental animals for the carcinogenicity of hydroquinone.”¹⁷ This limited evidence is based on renal tumors and leukemia in rats, both of whose biology with respect to hydroquinone are species-specific and dose dependent (specifically, occurring at irrelevantly high exposures of hydroquinone) and therefore is not applicable to humans.

EXOGENOUS OCHRONOSIS

- “Hydroquinone has been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1 to 2 percent. . . . Exogenous ochronosis was not extensively reported in the United States. . . until after publication of the

[tentative final monograph] for these drug products in 1982.”¹

Ochronosis refers to deposition of polymerized homogentisic acid in collagen-containing structures and is found in alkaptonuria. The polymer appears grossly as a blue-black pigment. Exogenous or pseudo-ochronosis is a skin condition in which foreign substances cause homogentisic acid to be deposited in the dermis, causing macular and papular hyperpigmentation. A number of chemicals have been implicated in causing exogenous ochronosis: hydroquinone,¹⁸ phenolic compounds (especially phenol [carbolic acid] and resorcinol),^{19,20} antimalarials such as quinine injections,²¹ and oral antimalarials, benzene substances,²⁰ picric acid,²² mercury,²³ and L-dopa.²⁴

A thorough survey of the world literature on the topic of human exposure to topical pharmaceutical hydroquinone preparations and exogenous ochronosis was performed using PubMed (encompassing the years of 1966 to present). Terms searched were “hydroquinone hyperpigmentation,” “melasma therapy,” “ochronosis hydroquinone,” and “hydroquinone laser.” Cases cited in the *Federal Register*¹ were included. Finally, relevant references found in articles from the above search were also included, allowing for the identification of relevant articles published before 1966. As the use of hydroquinone is not mentioned in all abstracts involving laser procedures, it is possible that some references describing human exposure to topical hydroquinone were missed.

Studies involving the use of hydroquinone in a clinical setting are summarized in Table III.^{3-7,25-96} In none of these studies, many of which had close physician follow-up, is exogenous ochronosis reported. Total patient exposures number 20,767, heavily biased by one author who claims to have followed up more than 10,000 patients. Excluding these patients, the number is 10,767. (In the 3 instances where the number of subjects used was unclear, the lower of the two values was used to calculate the above total.) Duration of exposure ranged from 1 day to 240 months. Hydroquinone concentrations ranged from 1% to 30%. Limiting those cases that had at least 1 month's exposure yields exposures numbering 19,632, and 9,632 excluding the 10,000 from the single study described above. Those studies explicitly using 2% hydroquinone or lower concentration yield total exposures of 1,182, and of those, 982 exposures were of at least 1 month's duration. Those studies explicitly using 3% to 5% hydroquinone yield 7,346 exposures, and of those, 7,267 exposures were of at least 1 month's

duration. Those studies explicitly using 4% hydroquinone yield 6,066 exposures, and of those, 6,015 were of at least 1 month's duration. Those studies explicitly using hydroquinone of 5% or higher yield 265 exposures, and of those, 65 were of at least 1 month's duration. These figures are found in Table IV.

Cases of exogenous ochronosis can be found in Table V.^{18,22,97-133} There are 789 cases of exogenous ochronosis reported worldwide. (It appears that Olumide et al^{105,106} and Jordaan et al^{114,115} reported their cases twice, so that only one of each of their case series was counted in the present analysis.) Of these, only 22 are reported from the United States. Of the total 789 cases, 652 fail to specify the percentage of hydroquinone used. In 116 cases, 1% to 2% hydroquinone was used. In 22 cases, 3% or higher concentration hydroquinone was used. The duration of use for the vast majority of cases was on the order of years, if specified at all. That is, it would appear that inappropriately extended use, more than concentration used, is a risk factor for exogenous ochronosis. Paradoxically, more cases are seen with lower concentrations, but that may be due to the wider availability of lower concentration products. Without knowing an exact denominator of exposures to $\leq 2\%$ and $\geq 3\%$ products, relative rates of exogenous ochronosis cases per exposure cannot be determined. Therefore, at this time, it is unclear how risky high- versus low-concentration hydroquinone preparations are with respect to the development of exogenous ochronosis.

Of the 789 cases reported, 756 arise from Africa. Of the 756 African cases, 503 are biopsy proven and 253 are based on clinical impression, which is subject to overdiagnosis. In only 116 cases was the hydroquinone concentration known. This particular statistic is important because few, if any, reports arising from Africa contain specific information about what agent was used. Indeed, one report from South Africa cites 68 cases of exogenous ochronosis but only 60 cases of hydroquinone exposure!¹¹⁹ Therefore, how can FDA implicate hydroquinone when the ingredients of the implicated agent cannot even be identified in nearly 85% of the cases and when definitive diagnosis (ie, histological confirmation) is unavailable in over 30% of cases?

Focusing on the 22 US cases, it is evident that exogenous ochronosis was *never* extensively reported in the United States, either before or after the publication of the tentative final monograph for these drug products. Of the 22 cases, 21 cases were associated with the use of 1% to 2% hydroquinone, whereas only one clearly resulted from 4% hydroquinone. The duration of use was typically on the

Table III. Clinical studies involving exposures to topical hydroquinone

Reference, Year	No. of patient exposures	Duration	% HQ used	Frequency	Reports of ochronosis	Notes
Yoshimura et al, ²⁵ 2002	19	16.6 wk on average	5	bid	0	
Yoshimura et al, ²⁶ 1999	61	Up to 3 mo	4 or 5	bid	0	Not clear on percentage HQ used
Yoshimura et al, ²⁷ 2006	225	Up to 32 wk	5	bid	0	
Yoshimura et al, ²⁸ 2003	18	Up to 12 wk	5	bid	0	
Yoshimura et al, ²⁹ 2000	136	At least 12 wk	5	bid	0	
Yoshimura and Harii, ³⁰ 1997	26	12 wk	5	bid	0	
Wester et al, ⁶ 1998	14	Up to 1 day	2	once	0	
West and Alster, ³¹ 1999	25	2 wk	4	bid	0	
Wang et al, ³² 2004	33	Up to 7 mo	4	NS	0	
Verallo-Rowell et al, ³³ 1989	78	24 wk	2	bid	0	
Vazquez and Sanchez, ³⁴ 1983	59	3 mo	3	bid	0	
TriLuma SBOA ⁷	88	8 wk	4	qd	0	Data are composite of two separate studies reported in the same document: 59 and 29 patients
Torok et al, ³⁵ 2005	389	6 mo	4	qd	0	
Torok et al, ³⁵ 2005	327	12 mo	4	qd	0	
Torok et al, ³⁶ 2005	228	6 mo	4	qd	0	
Taylor et al, ³⁷ 2003	480	8 wk	4	qd	0	
Swinyer and Wortzman, ³⁸ 2000	28	Up to 16 wk	4	qd or bid	0	
Stanfield, Feldman, and Levitt, ³⁹ 2006	20	1 day	4	once	0	
Spencer and Becker, ⁴⁰ 1963	380	Up to 6 mo	1.5 to 2	bid	0	
Spencer, ⁴¹ 1965	60	3 mo	2	bid	0	
Spencer, ⁴¹ 1965	26	3 mo	3	bid	0	
Spencer, ⁴¹ 1965	22	3 mo	5	bid	0	
Spencer, ⁴ 1961	380	2 to 4 mo	1 to 10	bid	0	
Sarkar et al, ⁴² 2002	40	Up to 21 wk	2 or 5	NS	0	Not clear on percentage of HQ used
Sanchez and Vazquez, ⁴³ 1982	46	3 mo	3	bid	0	
Ross et al, ⁴⁴ 1997	11	2 to 3 mo	3	NS	0	
Ross et al, ⁴⁴ 1997	28	2 wk	3	NS	0	
Rizer et al, ⁴⁵ 1999	69	Up to 12 wk	3 or 4	bid	0	
Rizer et al, ⁴⁶ 1999	6	3 wk	4	bid	0	
Rendon, ⁴⁷ 2004	797	12 mo	4	qd	0	415 used it for at least 80 days; 92 used it for at least 360 days*
Rendon, ⁴⁷ 2004	1400	8 wk	4	qd	0	Referencing Grimes (Summer AAD poster, 2003)
Piamphongsant, ⁴⁸ 1998	Up to 10,000	Up to 5 y	2 or 4	NS	0	
Petit and Pierard, ⁴⁹ 2003	30	2 mo	2	qd	0	
Pathak et al, ⁵⁰ 1981	221	12 wk	2 to 5	NS	0	

Table III. Cont'd

Reference, Year	No. of patient exposures	Duration	% HQ used	Frequency	Reports of ochronosis	Notes
Pathak et al, ⁵¹ 1986	200	3 mo	2	bid	0	Total of 300 patients were exposed, so it appears that 82 patients were exposed twice
Pathak et al, ⁵¹ 1986	20	3 mo	3	bid	0	
Pathak et al, ⁵¹ 1986	62	3 mo	4	bid	0	
Pathak et al, ⁵¹ 1986	100	3 mo	5	bid	0	
Nanda, Grover, and Reddy, ⁵² 2004	25	2 wk	2	qd	0	
Murad, Shamban, and Moy, ⁵³ 1993	50	Up to 6 wk	2	bid	0	
Momosawa et al, ⁵⁴ 2003	19	Up to 24 wk	5	bid	0	
Mills and Kligman, ⁵⁵ 1978	66	1 to 4 mo	5	qd to bid	0	Data are composite of 3 separate experiments reported in one paper
Melli, ⁵⁶ 1987	26	2 mo	2	bid	0	
Martin, de Arocha, and Loker, ⁵⁷ 1988	30	24 wk	4	NS	0	
Mahe, ⁵⁸ 1993	21	NS	NS	NS	0	Survey study of HQ users in Mali
Lim and Tham, ⁵⁹ 1997	10	26 wk	2	bid	0	
Lim, ⁶⁰ 1999	40	12 wk	2	bid	0	
Lawrence, Cox, and Brody, ⁶¹ 1997	16	Up to 7 mo	4	bid	0	
Lam et al, ⁶² 2001	4	14 to 21 wk	4	NS	0	
Kligman and Willis, ⁶³ 1975	15	8 wk	5	bid	0	
Kligman and Willis, ⁶³ 1975	28 to 35	NS	5	bid	0	No. of patients unclear
Kligman and Willis, ⁶³ 1975	52	5 to 7 wk	5	bid	0	
Kligman and Willis, ⁶³ 1975	100	3 to 7 wk	5	bid	0	
Kligman and Willis, ⁶³ 1975	12	6 mo	5	bid to qd	0	
Kligman and Willis, ⁶³ 1975	10 to 18	3 mo	5	bid	0	
Kligman and Willis, ⁶³ 1975	6	5 wk	5	bid	0	
Kang, Chun, and Lee, ⁶⁴ 1998	25	4 mo	5	2× wkly	0	
Kang, Chun, and Lee, ⁶⁴ 1998	7	4 wk	5	2× wkly	0	
Kakita and Lowe, ⁶⁵ 1998	34	24 wk	4	bid	0	
Javaheri et al, ⁶⁶ 2001	25	3 mo	2	qhs	0	
Jarratt, ⁶⁷ 2004	44	16 wk	3	bid	0	
Hurley et al, ⁶⁸ 2002	21	8 wk	4	bid	0	
Ho et al, ⁶⁹ 1995	30	8 to 12 wk	5	qhs	0	
Herndon, Stephens, and Sigler, ⁷⁰ 2006	71	Up to 24 wk	4	bid	0	
Herndon, Stephens, and Sigler, ⁷⁰ 2006	79	Up to 24 wk	4	qd	0	
Haddad et al, ⁷¹ 2003	30	3 mo	4	qhs	0	
Gupta and Ryder, ⁷² 2003	41	12 wk	4	NS	0	
Guevara and Pandya, ⁷³ 2003	39	12 wk	4	bid	0	
Guevara and Pandya, ⁷⁴ 2001	6	8 wk	6	qhs	0	
Grimes et al, ⁷⁵ 2006	1290	8 wk	4	qhs	0	
Grimes, ⁷⁶ 1999	25	~9 wk	4	NS	0	
Grimes, ⁷⁷ 2004	28	12 wk	4	bid	0	

Continued

Table III. Cont'd

Reference, Year	No. of patient exposures	Duration	% HQ used	Frequency	Reports of ochronosis	Notes
Goh and Dlova, ⁷⁸ 1999	111	NS	1.7	NS	0	
Goh and Dlova, ⁷⁸ 1999	44	NS	2	NS	0	
Goh and Dlova, ⁷⁸ 1999	39	NS	4	NS	0	
Glenn et al, ⁷⁹ 1991	12	3 mo	3 and 6	bid	0	
Gladstone et al, ⁸⁰ 2000	19	12 wk	4	bid	0	
del Giudice and Yves, ⁸¹ 2002	534	1 to 240 mo (mean, 50.5 mo)	2 to 5	NS	0	
Gilchrest and Goldwyn, ⁸² 1981	12	6 wk	4	bid	0	
Garcia and Fulton, ⁸³ 1996	39	3 mo	2	bid	0	
Gans and Christensen, ⁸⁴ 1999	19	12 wk	4	bid	0	
Gano and Garcia, ⁸⁵ 1979	25	10 wk	2	qhs	0	
Fitzpatrick et al, ³ 1966	93	≥ 1 mo	2 or 5	bid	0	
Espinal-Perez and Moncada, ⁸⁶ 2004	16	16 wk	4	qd	0	
Draeos, ⁸⁷ 2005	22	16 wk	4	bid	0	
Denton, Lerner, and Fitzpatrick, ⁸⁸ 1952	7	30 days	10 and 30	continuous	0	Patch testing
Burns et al, ⁸⁹ 1997	19	22 wk	2	bid	0	
Bucks et al, ⁵ 1988	6	4 days	2	once	0	
Bernstein et al, ⁹⁰ 1997	104	2 to 6 wk	4	bid	0	
Bentley-Phillips and Bayles, ⁹¹ 1975	200	48 h	5, 6, and 7	continuous	0	Open patch testing
Bentley-Phillips and Bayles, ⁹¹ 1975	52	12 wk	7.5	bid	0	
Bentley-Phillips and Bayles, ⁹¹ 1975	578	48 h	1, 2.5, 3.5, 5, and 7	continuous	0	Closed patch testing
Balina and Graupe, ⁹² 1991	165	Up to 24 wk	4	bid	0	
Astaneh, Farboud, and Nazemi, ⁹³ 2005	32 or 64	12 wk	4	qhs	0	No. of patients unclear
Arndt and Fitzpatrick, ⁹⁴ 1965	56	≥ 1 mo	2 or 5	bid	0	
Amer and Metwalli, ⁹⁵ 1998	70	Up to 12 wk	4	bid	0	
Abramovits, Barzin, and Arrazola, ⁹⁶ 2005	16	12 wk	4	bid	0	

bid, Twice a day; *h*, hour(s); *HQ*, hydroquinone; *qd*, daily; *qhs*, at night; *mo*, month(s); *NS*, not specified; *wk*, week; *y*, year(s).

*This figure includes the patients from Torok¹³⁶; hence that reference is not included in this table.

order of years, with the exception of two cases where reported 3-month exposures of 2% and 4% hydroquinone proved causal. Hydroquinone has been used in clinical situations since 1961 (ie, for 45 years) and has been available in over-the-counter formulations since about 1956 (ie, for about 50 years).⁹⁴ It has been estimated that 10 million to 15 million tubes of skin lightening formulations containing hydroquinone are sold annually in the United States.¹³⁴ The 22 cases were reported over a 23-year period (1983-2006). This averages one case per year for that period, or one in ten million tubes sold. Looking at the period from 1956 to present, the rate would be less than half that.

One difference between US and African cases of hydroquinone-induced exogenous ochronosis may stem from differences in formulation and use. In Africa, formulations often contain penetration enhancing vehicles (ie, hydroethanolic preparations), high concentrations of hydroquinone that are sometimes mislabeled as lower concentrations, and other ingredients, such as phenol and resorcinol, that are known to cause exogenous ochronosis.^{1,2} As antimalarials are a known cause of exogenous ochronosis, the assessment of the number of cases of ochronosis attributed to hydroquinone is confounded by the high relative use of antimalarials in Africa. Antimalarial use was not examined in these

Table IV. Summary of hydroquinone exposures in clinical studies*

HQ concentration (%)	Total No. of exposures	No. of exposures of at least 1 mo
1 to 30	10,767	9,632
≥ 2	1,182	982
3 to 5	7,346	7,267
4	6,066	6,015
>5	265	65

HQ, Hydroquinone.

*Excluding Piamphongsant⁴⁸ (1998).

reports. Concomitant use of phenol or resorcinol products was also never controlled for in the cases reported out of Africa.

Cultural practices of skin bleaching^{58,109,110,135} lead to grossly excessive, unsupervised use. Indeed, it is the excessive, unsupervised use, and not the compound itself, that is dangerous. This speaks in favor of placing all concentrations of hydroquinone under the auspices of a learned intermediary (ie, making all hydroquinone products prescription medications). Other factors accounting for the low incidence of cases in the United States include a less sunny average climate, more time spent indoors, and more regular use of sunscreens.²

RISK-BENEFIT

- “The benefit of removing OTC skin bleaching products from the market will be a reduction in the number of cases of ochronosis that would otherwise occur each year.” FDA alludes to the direct and indirect costs of “psychological suffering... resulting from disfigurement due to ochronosis.”¹

As stated above, the number of cases of exogenous ochronosis per year in the United States is about one. The incidence is extremely rare, at best. The vast majority of cases stem from Africa, with the attendant differences in the African situation as discussed above. Many disorders of pigmentation have the potential to be disfiguring and can produce roughly equivalent psychological suffering. While reported cases of exogenous ochronosis are rare, disorders of pigmentation such as melasma, photo-damage, and postinflammatory hyperpigmentation are common. In a survey of 2000 black patients seeking dermatologic care, postinflammatory hyperpigmentation and melasma were among the commonest complaints.⁷⁶ Among Asians, melasma incidence may be as high as 40% in women and 20% in men and can account for up to 4% of dermatology visits.⁷⁷ These common conditions are

probably best treated with hydroquinone, and no other more satisfactory treatment is available. The FDA can mitigate psychological suffering from disorders of pigmentation by assuring ready access to safe products. While only a handful of people might experience a rare and unlikely adverse effect of hydroquinone therapy, many millions of people can potentially benefit from having appropriate treatment options. In short, the FDA overstates the risks and minimizes the benefits of hydroquinone therapy.

- “Where the benefit appears low and use of the drug is proposed for an otherwise healthy target population, the risks should be minimal. . . . [The] sole intended benefit would be to improve the user’s appearance by bleaching the skin.” The FDA deems this benefit “insignificant,” concluding “there is no benefit to physical health that would justify [hydroquinone’s] continued marketing. . . . when compared to the potential risks. . . .”¹

One must caution against trivializing the psychological effects of dyschromia. The false assumptions in the statement are “an otherwise healthy population” and “the sole intended benefit would be to improve the user’s appearance.”¹ Taking melasma as the prototypical dyschromia, a variety of investigators demonstrated, using validated quality of life instruments, that social interactions, recreation, emotional well-being, and functioning at work or school are all adversely affected by melasma.¹³⁶⁻¹³⁸ Some concerns of melasma patients are: “People may see me as ‘dirty’ or ‘socially unacceptable,’” “I feel disfigured and deteriorated,” “I have to avoid people,” and “People focus on my skin and not on me.”¹³⁷ As is evidenced by these concerns, a large predictor of reduced health-related quality of life in women with melasma is an increased fear of negative evaluation by others. As might be expected, those whose quality of life is compromised by melasma typically have more severe disease and feel that life would be better without it.^{137,139} Of note, in the early clinical studies of hydroquinone, the end point was the “remedy of social embarrassment.”⁶³

Successful treatment of melasma—indeed, with a hydroquinone-containing product—was demonstrated to lessen dramatically self-consciousness, feelings of being scrutinized by others, feeling unattractive, the use of cosmetics to conceal the hyperpigmentation, and the limitation of social or leisure activities because of the skin’s appearance.^{136,137} In general, with successful treatment, melasma patients feel less embarrassed, younger, and more attractive.¹³⁷ For example, 73% of patients who initially felt “very much” or “a lot” embarrassed at baseline felt

Table V. Reported cases of exogenous ochronosis through December 31, 2006

Reference, Year	No. of ochronosis cases reported	Duration	% HQ used	Frequency	Geography	Notes
Zawar, ⁹⁷ 2004	1	NS	4	Many times per day	India	
Weiss, del Fabbro, and Kolisang, ⁹⁸ 1990	84	At least 1 y; mean, 3 y	At most 2	NS	South Africa	Clinical diagnosis
Tidman et al, ⁹⁹ 1986	1	10 y	2	Intermittently	UK	
Snider and Thiers, ¹⁰⁰ 1993	1	Many years, then 3 mo, then 6 mo	2, then 3, then 4	qd, then bid, then bid	US	Used 3 concentrations, dominant one was years of 2%
Raynaud, Cellier, and Perret, ¹⁰¹ 2001	4	>2 y	NS	NS	Senegal	Not biopsy proven
Phillips, Isaacson, and Carman, ¹⁰² 1986	395	Many years	NS	NS	South Africa	
Petit et al, ¹⁰³ 2006	5	12 to 14 y, on average	Up to 16.7	NS	France, but possible emigrants from Africa	Only one biopsy proven
Penneys, Smith, and Allen, ¹⁰⁴ 1985	1	NS	NS	NS	US	Unclear if biopsy proven
Olumide and Elesha, ¹⁰⁵ 1986	15	2 to 8 y	2 to 3	NS	Nigeria	Only 6 biopsy proven; some exposure may have been to monobenzylether of HQ
Olumide, ¹⁰⁶ 1987	15	2 to 6 y	2	NS	Nigeria	It appears these are the same reported cases in Olumide and Elesha, ¹⁰⁵ 1986
Menke et al, ¹⁰⁷ 1992	2	Not sure	Not sure	Not sure	Netherlands	Article in Dutch, cannot interpret
Martin et al, ¹⁰⁸ 1992	2	2 to 3 y; 30 y	NS, "OTC"	NS	Puerto Rico	
Mahe, Keita, and Bobin, ¹⁰⁹ 1994	3	Prolonged application	NS	NS	Mali	
Mahe et al, ¹¹⁰ 2003	14	1 mo to 35 y (median, 4 y)	4 to 8.7	NS	Senegal	Not biopsy proven
Lawrence et al, ¹¹¹ 1988	2	2 to 3 y; unspecified	1	NS	US	
Lang, ¹¹² 1988	1	Many years	NS	NS	US	Also applied mercury-containing bleaching creams
Kramer et al, ¹¹³ 2000	1	30 y, then not stated	2, then 4	NS	US	Successfully treated with Q-switched ruby laser
Jordaan and Van Niekerk, ¹¹⁴ 1991	2	Many years; 5 y	6.5 to 7.5; NS	NS	South Africa	
Jordaan and Mulligan, ¹¹⁵ 1990	1	Many years	NS	NS	South Africa (presumably)	Possibly the same case as reported in Jordaan et al, ¹¹⁴ 1991

Table V. Cont'd

Reference, Year	No. of ochronosis cases reported	Duration	% HQ used	Frequency	Geography	Notes
Jacyk, ¹¹⁶ 1995	6	NS	NS	NS	South Africa (presumably)	Unclear if HQ was used in these patients
Hull and Procter, ¹¹⁷ 1990	1	2 y	2	NS	South Africa (presumably)	
Howard and Furner, ²² 1990	1	4 mo	2	bid	US	
Hoshaw, Zimmerman, and Menter, ¹¹⁸ 1985	2	2 y, then NS; 3 mo	2, then 4; 2	NS	US	
Hardwick et al, ¹¹⁹ 1989	68	>6 mo, some to 16 y	NS	NS	South Africa	Of note, only 60 patients used HQ; cases not biopsy proven
Gonul et al, ¹²⁰ 2006	1		<i>Not due to hydroquinone</i>			
Fisher, ¹²¹ 1988	1	18 mo	4	NS	US	
Findlay, Morrison, and Simson, ¹⁸ 1975	35	Up to 8 y	"Strong"	NS	South Africa	
Dogliotti and Leibowitz, ¹²² 1979	43	Up to 10 y	NS	NS	South Africa	
Diven et al, ¹²³ 1990	1	2 to 3 mo	2, possibly others	NS	US	Successfully treated with dermabrasion and CO ₂ laser
Davis, Trapp, and Grimwood, ¹²⁴ 1990	1	NS	NS	NS	US	
Cullison, Abele, and O'Quinn, ¹²⁵ 1983	1	2.5 y	2	Up to 6 times/d	US	
Connor and Braunstein, ¹²⁶ 1987	1	Decades	NS	NS	US	
Carey et al, ¹²⁷ 1988	3	NS	2	NS	US	
Camarasa and Serra-Baldrich, ¹²⁸ 1994	1	NS	2	NS	US	Not biopsy proven
Huerta Brogeras and Sanchez-Viera, ¹²⁹ 2006	1	6 y	2	NS	US	
Bowman and Leshner, ¹³⁰ 2001	1	NS	OTC (presumably 2)	NS	US	
Bongiorno and Arico, ¹³¹ 2005	2	4 y; NS	2; NS	NS	Africa	Unclear if the second case involved HQ
Bellew and Alster, ¹³² 2004	2	Several months; 1 y	NS	NS	US	Successfully treated with Q-switched alexandrite laser
Adebajo, ¹³³ 2002	83	>6 mo for 90% of patients	NS	NS	Nigeria	Not biopsy proven

OTC, Over the counter; UK, United Kingdom; US, United States; for other abbreviations, see legend for Table III.

“a little” or “not at all” embarrassed after 8 weeks of therapy. Eighty percent of patients who initially felt “very much” or “a lot” unattractive to others at baseline felt “a little” or “not at all” unattractive to others after 8 weeks of therapy.¹³⁷

Numerous renowned dermatologists have acknowledged the negative impact that dyschromia has on people's lives. Fitzpatrick et al³ note: “Pigmentary disfigurement can have a devastating effect on the social behavior of the individual. . . .” Kligman and Willis⁶³ put it most eloquently:

Pigmentary changes are an important source of human misery. They immediately set one apart and consequently threaten psychological and psychosexual identity. Pigmentary nonconformists are never praised and are generally viewed as odd and unattractive. The lack of physical impairment is but slight compensation for the mental anguish of the outcast with too little or too much melanin, especially when the changes occur in bizarre patterns. Physicians have lagged considerably behind laymen in appreciating that these afflictions merit medical attention; even today scientists of high ability and low sensitivity refer to pigmentary abnormalities as ‘cosmetic.’ One untoward effect of such cavalier ‘put-downs’ is to divert individuals with pigmentary problems to beauticians rather than physicians. Dermatologists, happy to say, generally accord these patients the sympathy they need and are well schooled in the utilization of available remedies.

Kligman and Willis raise several issues. The first is the comment that “scientists of high ability” inappropriately categorize dyschromia as merely a cosmetic problem. Eliminating appropriate therapies for dyschromia perpetuates this misconception. The second issue raised is that individuals are diverted to nonphysician intermediaries. The third issue is that physicians, more so than any other group, are best trained in treating these patients on both a psychological and pharmaceutical basis.

The FDA has set a precedent with the approval of such drugs as isotretinoin for acne or botulinum toxin for rhytides, acknowledging that benefits of drugs with perhaps even more potential danger than hydroquinone can outweigh the risks. In these instances, the benefit is a life-altering psychological one that stems from improved cosmesis. Hydroquinone has an arguably similar benefit profile with a very favorable safety profile. Therefore, the FDA should consider hydroquinone no differently than such other approved drugs.

Finally, disorders of hyperpigmentation are notoriously difficult to treat. Hydroquinone is recognized as the “gold standard for hyperpigmentation treatment in the United States.”¹⁴⁰ Without hydroquinone,

patients are left with few alternatives for its effective treatment. Available agents include mequinol; chemical peels (that have the risk of resulting in further posttraumatic hyperpigmentation); laser therapy (which is often ineffective for melasma); off-label use of retinoids or azelaic acid; topical vitamin C, E, and niacinamide preparations; kojic acid; licorice extracts; aloesin; and arbutin.¹⁴⁰ Triple combination therapy with Tri-Luma is indeed effective, but some patients cannot tolerate the irritation of the retinoid component or the potential side effects of the steroid component. A hydroquinone ban would merely limit the safe therapeutic options of such patients. Furthermore, it is difficult to understand how the FDA can approve a cream containing hydroquinone 4% as safe, allow it to be marketed, yet simultaneously declare that self-same ingredient as so unsafe as to require its removal from the marketplace.

The FDA should be aware that, given the high demand for bleaching creams, patients will probably secure these products from unregulated sources. Proof that this occurs was published as recently as 2005, where people in France illegally obtain skin-bleaching agents containing clobetasol, use them indiscriminately, and suffer disfigurement such as skin atrophy, striae, infection, and acne.¹⁰³ Were hydroquinone to be banned in the United States, consumers would be forced to buy from less regulated sources in which mislabeled products can be found, including high-potency topical steroids, mercurial compounds, and hydroquinone compounds. One cannot ignore that hydroquinone preparations are available over the counter in Canada and can be purchased by mail. Patients would also be able to obtain hydroquinone from compounding pharmacies with a prescription. Here, the concentration and quality of product are essentially unregulated relative to those currently available branded prescription products, which are manufactured under FDA-regulated, current good manufacturing practice protocols. Sometimes, people have used caustic agents, such as Clorox, to effect bleaching. This is inherently dangerous.

With respect to the treatment of exogenous ochronosis, many case reports have labeled it as irreversible or permanent. However, these reports largely antedated the existence of modern laser therapy. Indeed, recent studies report that the Q-switched alexandrite laser (750 nm) effectively treats ochronosis.¹³² Q-switched ruby laser (694 nm) was also remarkably effective in two cases (Mark Nestor, MD, personal communication and Kramer et al¹¹³).

- “[B]ecause of the carcinogenic and ochronotic potential of hydroquinone, its use in skin

bleaching drug products should be restricted to prescription use only, and users of such products should be closely monitored under medical supervision.”¹

Because 21 of 22 cases of exogenous ochronosis that have occurred in the United States were the result of prolonged, unregulated use of hydroquinone, one could argue for physician supervision of this treatment. Interestingly, 21 of the 22 cases occurred with $\leq 2\%$ hydroquinone. The relative proportion of 2% versus 4% products used in the United States may account for this association; however, one cannot ignore that 4% products, requiring a prescription, are used under more careful patient supervision relative to the 2% products and, perhaps, are more often used in combination with sunscreen.

By taking action to ban OTC hydroquinone and to make further marketing of prescription hydroquinone products contingent upon NDA submissions, the FDA creates the perception of a medicolegal risk in the eyes of the physician who would otherwise prescribe hydroquinone-containing products, be it Tri-Luma or the current DESI formulations. Decreased use of these agents by physicians results only in decreased treatment of dyschromia, translating to a greater burden of disease in the general public. It would not result in any less cancer or exogenous ochronosis.

As hyperpigmentation is disproportionately a problem of skin of color (ie, non-Caucasians), and as many people with skin of color belong to uninsured, low-income populations, a governmental edict to ban hydroquinone in the absence of genuine safety concerns could well be interpreted as discriminatory on many levels. The ban would deny low-income groups access to effective therapy (OTC or prescription) for hydroquinone-responsive dyschromias, as Tri-Luma is not readily affordable and often requires an expensive physician visit to obtain. It is often these groups for whom dyschromia causes the most psychological burden and is a particularly negative social stigma.

- FDA “intends to consider all skin bleaching products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.”¹

There are numerous barriers to an NDA submission for hydroquinone, making the FDA request unreasonable. First, the cost of an NDA submission is prohibitive given the lack of patentability of the hydroquinone molecule itself. Costs include a user submission fee, any further safety and efficacy

studies, and the opportunity cost of being off the market during the time that the preparation of the NDA submission takes place. Excluding the latter, these could amount to as much as \$2,000,000. The market for the branded, non-Tri-Luma products is somewhere on the order of only \$15 million annually. Patent protection associated with hydroquinone is limited. While formulation patents might offer some protection from immediate release of lower priced generic products, it would be relatively straightforward to formulate a bioequivalent preparation. With the high cost of an NDA submission in mind, companies have little incentive to stay in the market supporting quality products for the long term in the absence of patent protection of a new molecular entity.

CONCLUSION

When making decisions to protect the public interest with respect to pharmaceutical agents, the FDA itself states that it does so on a case-by-case basis, performing a balancing act of the public need, medical necessity, safety, and regulatory requirements. The FDA states it will “... be mindful of the effects of its action on consumers and health professionals and set its priorities according to their public health impact.”¹⁴¹ The FDA states that it will make “... every effort... to avoid adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the drug supply.”¹⁴² With respect to DESI drugs, a category to which hydroquinone belongs:

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period, [FDA] may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration.¹⁴³

It is clear that there is a public need for hydroquinone, at the very least, as a prescription agent. It is clear that removing hydroquinone from the prescription market will impose an undue burden on those many patients that depend on the drug for relief of

dyschromia. It has been demonstrated in the discussion related in this article that legally marketed products would not meet the needs of all patients using DESI hydroquinone products. On the basis of cost and market considerations, there is little economic incentive for pharmaceutical companies to pursue NDA submission. Immediate disruption of the drug supply of hydroquinone by forcing prescription drugs off the market would constitute an unwarranted overreaction, as the above discussion has demonstrated a marginal risk relative to life-altering benefits of hydroquinone availability. Given the stated considerations of the FDA, it would seem inconsistent for FDA to proceed with the proposed final rule as stated.

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