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To Whom It May Concern:

I have extensively reviewed the worldwide literature on ochronosis and it's relation to hydroquinone. I respectfully disagree with the FDA and their views on hydroquinone. Hydroquinone is one of the most effective molecules for the treatment of hyperpigmentary disorders, with over 40 years of efficacy and safety data. Concerns over its safety have been raised by the FDA as it is a derivative of benzene. Additional safety issues are due to the infrequent long term side effects observed with some cosmetic products from outside the US containing high concentrations of hydroquinone. However, despite 40-50 years use of hydroquinone for medical conditions, there has not been a single documented case of either a cutaneous or internal malignancy associated with this drug.

Prescription topical hydroquinone has been used safely and without significant adverse events. It appears to have a good risk: benefit ratio for those suffering from hyperpigmentation disorders. Over the counter (OTC), but not prescription use of hydroquinone has been banned in Europe secondary to cosmetic concerns mainly. The focus is on a rare disorder called ochronosis which occurs in less than 1% of hydroquinone users. There is no correlation between ochronosis and cancer. Typical side effects of any OTC or prescription hydroquinone may include irritation, stinging and redness.

It could be postulated that because most humans are exposed daily to hydroquinone in common foods and drinks such as wheat, berries, coffee and tea, the body has gained the capacity to detoxify it into inert compounds. This may partly explain why hydroquinone may produce deleterious effects in vitro not seen in vivo. A few studies of hydroquinone in culture or in rodents suggest that it may have the capacity to damage DNA. These studies are not conclusive. Thus, at this point in time regulatory groups have concluded that there are insufficient data to classify hydroquinone as a carcinogen.

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FDA proposed rule would establish that over the counter (OTC) skin bleaching products containing hydroquinone are not safe and effective and are misbranded. FDA is also considering that existing skin bleaching products be required to provide a new drug application regardless of whether or not the product is currently marketed as a prescription or an OTC product.

This would significantly impede the excellent clinical care that we can now give patients with dark spots as there is no other drug on the market that can effectively fade dark spots as well as hydroquinone. Kojic acid, vitamin C, grape seed extract and soy all even skin tone but are used to enhance hydroquinone and will not be effective replacements.

Arbitrary scattered reports in the worldwide literature discuss ochronosis in several different forms. In Turkey, a case of pigmented colloid milium associated with exogenous ochronosis was determined to be secondary to an interaction between sunlight and exposure to chemical fertilizers. In Japan, Greece, Rome, Chicago, and Georgia ochronotic arthropathy also called ochronosis is the articular manifestation of alkaptonuria, a rare metabolic disease that leads to the deposition of homogentisic acid in the joints and causes articular degeneration. In San Francisco, exogenous ochronosis is attributed to use of hydroquinone, antimalarials, resorcinol, phenol, mercury or picric acid. In this article, it was noted that exogenous ochronosis is much more prevalent in South Africa, due to the fact that they are using significantly higher percentages of hydroquinone, 6%, 8% and 10% compounded with mercury in many cases which makes the dark pigment worse. The same discussion noted that exogenous ochronosis is relatively uncommon in the United States and occurs at a rate of less than 1%.

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Out of Rochester, Minnesota, is a study that discussed melanosis oculi that is associated with choroidal melanomas and that ochronosis is non-melanin conjunctival pigmentation. Exenteration is warranted in cases with stromal invasion. This type of ochronosis has nothing to do with use of hydroquinones. In India, a female farmer with melasma used a high percentage of hydroquinones without sunscreen and had exogenous ochronosis. Failure to follow proper sun protection measures and usage of concentrations above 4% most likely caused the ochronosis.

I am a member of the American Society of Dermatologic Surgery task force working on this hydroquinone issue. As a whole, we respectfully request that you kindly reconsider your position on hydroquinones and allow them to stay on the market without an NDA. If there are any questions or comments, please feel free to reach me directly at my office. Thank you kindly for your time and attention.

Very truly yours,

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To the Food and Drug Administration:

In August, the Food and Drug Administration (FDA) proposed a rule change to over-the-counter (OTC) skin bleaching products containing hydroquinone based on new evidence of carcinogenicity in rats and mice. Therefore, the FDA stated that it cannot rule out the potential carcinogenic risk from topically applied hydroquinone in humans. In addition, the FDA cited hydroquinone as having been shown to cause ochronosis after use of concentrations as low as 1 to 2 percent. Based on these data, the FDA has tentatively concluded that there is no health benefit of OTC skin bleaching products that would justify their continued marketing.

The FDA also stated that skin bleaching products sole purpose is for cosmetic improvement. Consequently, the health risks outweigh the benefits. Therefore, the FDA's position is that OTC hydroquinone products are no longer recognized as safe and effective and their use cannot be justified. The FDA proposed that hydroquinone in skin bleaching products be restricted to prescription use only, and users of such products should be closely monitored under medical supervision.

As a member of the American Society for Dermatologic Surgery (ASDS) I oppose the FDA's proposed rule changes for the following reasons:

- Dermatologists frequently use hydroquinone-containing products both to treat and prevent post inflammatory hyperpigmentation which is common after resurfacing procedures in darker skin types.
- Abnormal pigmentation of the skin, also known as dyschromia, is an important cutaneous disorder with significant patient morbidity.

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- Dyschromias affect millions of Americans including those from minority groups including African Americans, Latinos, and Asians.

- Treatments for dyschromias, whether self-treatment by patients with OTC hydroquinones or by dermatologists with prescription hydroquinones, should not be denied to the American population.

- Eliminating safe, effective, readily accessible and affordable OTC hydroquinone products is injurious to millions of dyschromia patients particularly those from minority groups who are less likely to see a dermatologists for treatment.

- Requiring a new drug application for all prescription hydroquinone products would severely limit treatment for more severe dyschromias.

- In marked contrast to the African experience, in the United States , exogenous ochronosis is a remarkably uncommon adverse event from the use of hydroquinone containing products, and the exceedingly low risk does not support removal from the market.

- The association of cancer in humans from the use of hydroquinone is unproven and existing animal data do not support removal of these products from the market.

As a practicing dermatologist who regularly treats dyschromia patients with hydroquinone products, I strongly believe the FDA has underestimated the health benefit of OTC and prescription hydroquinone treatments.

I urge the FDA to reconsider its position on withdrawing OTC and limiting prescription hydroquinone treatment. If this proposal is passed it will have deleterious effects for dyschromia patients. The action is in many respects punitive in nature for dyschromia patients and is potentially inequitable for patients of various minority groups.

Very truly yours,

Joanne B Dorn