December 21, 2006

Division of Dockets Management (HFA – 305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

Attached is the American Health & Beauty Aids Institute (AHBAI) response to Docket No. 1978N-0065 and RIN number 0910-AF53. AHBAI is a national trade association representing the leading manufacturers of ethnic beauty products.

If you have any questions or require additional information, please feel free to contact me at 708-633-6328 or via e-mail at gjonesahbai@sbcglobal.net.

Sincerely,

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Executive Director

78N-0065 C 66

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Department of Health and Human Services
Food and Drug Administration
21 CFRE Part 310

Response to Docket No. 1978N-0065 (formerly Docket No. 78N-0065)
RIN 0910-AF53

Skin Bleaching Drug Products for Over-the-Counter Human Use; Proposed Rule

Agency: Food and Drug Administration, HHS

Action: Proposed rule; withdrawal of previous proposed rule.

Respondents: NMA (National Medical Association) Dermatology Section
AHBAI (American Health and Beauty Aids Institute)

Response to II New Data:

Toxicology

The Federal Register document refers to toxicology data received subsequent to publication of the TFM in 1982 stating that NTP data indicates, " 'some evidence' of carcinogenicity in male and female rats and in female mice ".

Recommendation (1) We suggest that the Agency consider all of the available hydroquinone toxicology data including the more recent: developmental, reproduction, neurotoxicology, metabolism, pharmacokinetic, genotoxicity, tumorigenicity and exposure testing as listed in the following references.

TABLE IV: Additional Data for FDA Review

Reference (year)	Study classification	Miscellaneous
Pifer *et al.* (1995)	epidemiological	HQ workers
Murphy *et al.* (1992)	animal	rabbit developmental toxicity study with HQ
Krasavage *et al.* (1992)	animal	rodent developmental toxicity study with HQ
Blacker *et al.* (1993)	animal	rodent two-generation reproduction study with HQ
Krasavage *et al.* (1984)	animal	rodent dominant lethal assay with HQ
Topping *et al.* (2006)	chemistry/basic science	subchronic neurotoxicity study with HQ
Deisinger *et al.* (1996)	basic science	metabolism study
Deisinger and English (1999)	basic science	metabolism study
Boatman *et al.* (2000)	basic science	metabolism study
English and Deisinger (2005)	basic science	metabolism study
Corlet *et al.* (2000)	pharmacology	pharmacokinetic study with HQ
Poet *et al.* (2004)	pharmacology	pharmacokinetic study with HQ
English, Perry *et al.* (1994)	animal	mechanistic study with rodents on HQ
English, Hill *et al.* (1994)	animal	mechanistic study with rodents on HQ
Boatman *et al.* (1996)	animal	mechanistic study with rodents on HQ
Hard *et al.* (1997)	animal	mechanistic study with rodents on HQ
David *et al.* (1998)	animal	toxicity study of HQ in sking lightener formulation in albino animals
O'Donoghue *et al.* (1999)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Doepker *et al.* (2000)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Williams *et al.* (2006)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Whysner *et al.* (1995)	review	data for HQ, tumorigenicity
DeCaprio *et al.* (1999)	review	data for HQ, toxicology, environmental and occupational exposure

Recommendation (2) In consideration of the seriousness and widespread effect of the proposed ban, we request that the Agency consider undertaking a pharmacoepidemiology study of the risks associated with prescription use of hydroquinone products. Said study may be able to be performed if such products are captured by existing administrative or medical record databases (e.g. General Practice Research Database, Kaiser, etc). In particular, potentially large numbers of individuals who received hydroquinone prescriptions (e.g. exposed) could be retrospectively reviewed in these systems, with appropriate control patients (e.g. unexposed) to determine if the rates of malignancies of interest vary between those using prescription hydroquinone products and those not using prescription hydroquinone products.

Exogenous Ochronosis

Hydroquinone containing creams are the mainstay of therapy for Caucasian, Black, Asian, and Hispanic American male and female consumers suffering from hyperpigmenting skin diseases. Melasma, post-inflammatory hyperpigmentation, and lentigines have responded well to treatment with over the counter and prescription hydroquinone formulations for over 60 years in the United States of America without any significant, irreversible adverse reactions reported. During the period from 1961 to 1995, there were less than 30 adverse events reported to the FDA related to use of hydroquinone. The majority of these reports were minor skin irritations, allergic reactions and 1 case of hyperpigmentation. According to Maibach, approximately 10 – 15 million skin tone cream units were sold in the United States in 1997. This volume of hydroquinone equates to over 550 million potential exposures annually and therefore billions of exposures since introduction of hydroquinone into the US market. In the United States of America hydroquinone is widely used with less than 1 adverse reaction for every billion exposure generating an extremely favorable benefit to risk profile.[8]

According to the Proposed Rule, "hydroquinone has been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1 to 2 percent." Support for this statement includes 21 referenced articles covering the period from 1975 to 2001. We have formulated and formatted Table 1 to highlight the relevant demographic, clinical, histological and patient outcomes from each of the 21 references (in the same order) to facilitate review of the pertinent data.

Comment: It is well known that the use of skin bleaching in products in Africa prior and subsequent to the partial ban in South Africa is very different than in the United States of America, as illustrated in the table and the Agencys' review.[8,26] Black Africans tend to use hydroquinone over entire cutaneous surfaces, for much longer periods of time, at higher concentrations (6.5 to 8.5%) and in hydro-alcoholic formulations (t-butyl alcohol) that may also contain ochronotic mercuric compounds. The American experience differs in that hydroquinone is generally used on isolated areas of skin for specific hyperpigmenting disorders (as opposed to trying to have a lighter colored skin), duration of use is usually limited to correction of the underlying pigment problem, hydroquinone is the only active ingredient in the product and the formulations are 'cream' based. It is noteworthy that the desire to bleach the skin is so great in South Africa that subsequent to the partial hydroquinone ban, the use of anti-acne products containing synergistic resorcinols, that lighten skin color, has increased dramatically.[8,26]

The clinical descriptions of exogenous ochronosis associated with hydroquinone in the rare American 'case reports' are less striking (Stage 1) than the more severe African (Stage III) 'series'. Similarly, skin histology in the African population with hydroquinone-associated

ochronosis demonstrates more pathology (colloid milium, collagen and elastin degeneration, pseudoepithelomatous hyperplasia, transepidermal elimination of pigment, sarcoidal like granulomas, giant cells, plasma cells, and histiocytes) than patients from the United States. Histopathology specimens obtained from patients in the United States with the rare diagnosis of exogenous ochronosis exhibit much less aggressive pathology displaying ochronotic fibers not laden with inflammatory cells, destruction, transepidermal elimination or granulomas.(Table 1)

The rare cases of exogenous ochronosis in Americans generally respond to effective treatment: avoidance, dermabrasion, and laser therapy. (Table 3). Treatments were not offered or described in the African series. (Table 1)

We have reviewed the English literature available to date on hydroquinone associated exogenous ochronosis, which includes 1 United States case report that was not included in the Agency references (Table 1a). The small number of cases reported compared with the volume of hydroquinone sold in the United States support the rarity of exogenous ochronosis in the American population.

Under the Freedom of Information Act, we have submitted a request for adverse events reports of hydroquinone associated ochronosis received by the Food and Drug Administration. The information has not been received as of this date.

Recommendation: We recommend that the agency reconsider the proposed ban of over the counter hydroquinone on the basis of exogenous ochronosis as the association in the United States is extremely rare, generally mild, responds to
treatment, and will impose an undue burden on the American consumer.

IV. Analysis of Impact

According to Executive Order 12866 agencies are directed to access all costs and benefits of available regulatory alternatives ....to select regulatory approaches that maximize net benefits.... The proposed rule states, "FDA tentatively concludes that the benefits of OTC skin bleaching drug products are insignificant when compared to the potential risks and that the proposed rule would benefit society....The benefit or removing OTC skin bleaching products from the market will be a reduction in number of cases that would otherwise occur each year....FDA has limited information to assign a monetary value to the prevention and treatment of ochronosis and the direct medical costs and indirect medical costs, such as psychological suffering resulting from disfigurement due to ochronosis."

...The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer and more affordable and helping the public get accurate, science based information they need to use medicines and foods to improve their health."

FDA Mission Statement

National Ambulatory Care Survey Data suggests that 3 million patients visit dermatologists offices each year for concerns related to pigment abnormalities. The unrecorded cases who are treated by non-dermatologists or use over the counter drugs is at least equally prevalent. The FDA underestimates the significance of pigment abnormalities and overestimates the incidence and severity of hydroquinone-associated ochronosis in the American consumer.

Recommendation The FDA withhold any action on the proposed rule until all the pharmacological, clinical and epidemiologic data have been reviewed and appropriately weighted in addition to completing a human epidemiologic study to access the incidence, if any, of hydroquinone associated ochronosis and cancer risk.

TABLE I: ORIGINALLY CITED REFERENCES FROM FDA					
Reference (Year) [country of origin]	**# EO pts**	**Patient age (yr), race, gender**	**Suspected causative agent**	**Duration of use**	**Clinical Description**
Findlay *et al.* (1975) [South Africa]	35	30-39/B/F	HQ cream, 6-8%	continuously, up to 8yr	Reticulated, sooty hyperpigmentation, blue tint, chloasma, colloid milia
Olumide (1987) [Lagos]	15	unk/B?/unk	HQ , unk%	not stated	none
Jordaan and Mulligan (1990) [South Africa]	1	39/B/F*	HQ cream, unk %	"many years"	"papular ochronosis", annular atrophic lesions
Hoshaw *et al.* (1985) [U.S.]	2	1. 75/B/F 2. 49/B/F	1. HQ, 2%, then 4% 2. Brightening cream	1. 2yr; then few weeks 2. 3 mos.	1. pigmented papules, macular pigmentation 2. sharply demarcated blue-black hyperpigmentation, papules
Tidman *et al.* (1985) [U.K.]	1	45/B/F	HQ, 2%	10 yr	symmetric hyperpigmentation
Connor and Braunstein (1987) [U.S.]	1	72/B/F	HQ cream, unk %	since childhood	confluent blue-black macules/patches
Lawrence *et al.* (1988) [U.S.]	2	1. 62/B/F 2. 46/B/F	1. HQ cream, 1% 2. HQ cream, 1%	1. 2-3 yr 2. 2 mos.?	1. speckled hyperpigmentation 2. hyperpigmented macules
Howard and Fumer (1990) [U.S.]	1	36/Mex/F	HQ cream, 2%	4 mos.	macular hyperpigmentation
Diven *et al.* (1990) [U.S.]	1	53/B/F	HQ cream, 2%	2-3 mos.	sooty black macules and patches, hypopigmented macules
Jordaan and Van Niekerk (1990) [South Africa]	2	1. 56/B/M 2. 39/B/F*	1. HQ, 6.5-7.5% 2. skin lightening cream, unk %	1. "many years" 2. 5 yr	1. "papular ochronosis",annular hypopigmented patches with raised borders 2. "papular ochronosis"
Martin *et al.* (1992) [Puerto Rico]	2	1. 44/PR/F 2. 56/B/F	1. HQ + RA; HQ cream, unk % 2. OTC bleaching cream, unk %	1. 3-4 yr 2. 30 yr?	1. grayish black pigmentation & papules 2. hyperpigmented, purplish black macules
Snider and Thiers (1993) [U.S.]	1	59/B/F	HQ cream, 2%, then 3%, then 4% + sunscreen	many years, then 3 mos., then 3 mos.	blue-black macules, mild hypopigmentation
Camarasa (1994) [U.S.]	1	45/unk/F	HQ, 2%	?9 mos.	hyperpigmentation/"melasma"
Bowman and Lesher (2001) [U.S.]	1	75/B/F	bleaching cream	not stated	yellowish papulonodules with surrounding hyperpigmentation
ADDITIONAL CASE REPORTS					
Cullison *et al.* (1983) [U.S.]	1	50/B/F	HQ cream, 2%	2.5 yr	uniform, blue-black sooty hyperpigmentation
Pennys (1985) [U.S.]	1	?/Black?/?	not stated	not stated	not stated
Jordaan and Mulligan (1990) [South Africa]	1	39/B/F*	HQ cream, unk %	"many years"	"papular ochronosis", annular atrophic lesions
Carey *et al.* (1990) [U.S.]	3	not stated	HQ bleaching creams	not stated	not stated
Davis *et al.* (1990) [U.S.]	1	40/Caj/M	HQ bleaching cream, unk%	?9mos.	punctate hyperpigmentation
Jacyk (1995) [South Africa]	6	1. 49/B/F 2. 50/B/F 3. 70/B/F 4. 40/B/F 5. 49/B/F 6. 43/B/F	not stated	not stated	1. 2 annular lesions, raised rim, satellite lesions 2. 4 annular lesions 3. 2 annular lesions 4. 7 lesions, 2 annular 5. 2 annular lesions 6. >20 annular lesions
Kramer *et al.* (2000) [U.S.]	1	50/Hisp/F	HQ cream 2%; then 4%	30 years; unk	speckled grey-brown patches
Bellew and Alster (2004) [U.S.]	2	1. 47/B/F 2. 46/NA/M	1. Bleaching creams, unk % 2. HQ bleach, unk %	1. several mos. 2. 1 yr	1. diffuse dark-brown patches; grouped pinpoint slate gray macules 2. slate gray hyperpigmented patches
Bongiorno and Aricò (2005) [Italy]	2	1. 45/B/F 2. 35/B/F	1. HQ cream, 2% 2. bleaching agents, unk % + steroid cream	1. 4 yr 2. 10 yr	1. blue-black macules, hyperpigmentation 2. hyperpigmentation; hypopigmentation; striae
Brogeras and Sánchez-Viera (2006) [Spain]	1	70/Hisp/F	HQ cream, 2%	6 yr	bluish gray hyperpigmentation

Legend: EO=exogenous ochronosis; HQ=hydroquionone; unk=unknown; yr=years; mos=months; B=Black; Hisp=Hispanic; NA=Native American; PR=Puerto Rican; F=female; M=male

TABLE I: ORIGINAL REFERENCES FROM FDA					
Reference (Year) [country of origin]	**Location**	**Histology**	**EM findings**	**Treatment**	**Outcome**
Findlay *et al.* (1975) [South Africa]	orbital margin to zygoma, anterior neck	Skin: elastosis, ochronosis of papillary dermis, colloid degeneration, colloid milium, pigmentary incontinence; Ear: ochronosis, elastosis, pigment granulae laden superficical chondrocytes	none	HQ avoidance, sunscreen, topical steroids	mild improvement, smooth skin
Olumide (1987) [Lagos]	unknown	none	none	unknown	none
Jordaan and Mulligan (1990) [South Africa]	forehead, cheeks, neck	thinned epidermis, granulomatous infiltrate, giant cells, asteroid bodies, sparse ochronotic fibers	none	none	none
Hoshaw *et al.* (1985) [U.S.]	1. Forehead, temples, malar cheeks 2. cheeks, nose, chin	1. clumped yellow-brown deposits in upper dermis 2. banana-shaped brown clumps in upper dermis	1. none 2. none	1. none 2. none	1. 1yr: no change; 6yr: decrease in #/size of papules; background malar hyperpigmentation 2. 9 mos: no change
Tidman *et al.* (1985) [U.K.]	zygomatic cheek, nose, chin	solar elastosis, dermal yellow-brown structures, histiocytes	Active phagocytosis	cosmetic camouflage	11mos-no change
Connor and Braunstein (1987) [U.S.]	Forehead, temples, malar cheeks	free/phagocytized yellow-brown granules in dermis	none	none	none
Lawrence *et al.* (1988) [U.S.]	1. malar cheeks 2. forehead, periorbital area, malar cheek, nose	solar elastosis, brown structures in upper dermis, swollen collagen, finely granular brown pigment	1. none 2. none	1. HC 2.5% cream, sunscreen 2. HC cream, sunscreen	1. unknown 2. forehead: some decreased pigmentation
Howard and Furner (1990) [U.S.]	forehead, cheeks, chin, gingival and buccal mucosa?	upper dermal numerous banana-shaped clumps of golden brown material, solar elastosis	none	0.1% retinoic acid gel, 1% HCV and 5% bp gel w sunscreens	minimal lightening
Diven *et al.* (1990) [U.S.]	Forehead, periorbital area, malar cheeks	Yellow-brown pigment in papillary dermis	none	A. cryo, tretinoin gel & tca B. dermabrasion C. CO2 laser	A. PIH B.&C. pt pleased
Jordaan and Van Niekerk (1990) [South Africa]	1. Face, neck, cheeks 2. Face, forehead, neck, auricular cartilage	1. ochrophages, melanophages, free melanin, ochronotic pigment, colloid milium, ochronotic fibers 2. atrop	1. none 2. none	1. none 2. none	1. none 2. none
Martin *et al.* (1992) [Puerto Rico]	1. forehead, nose, cheeks 2. temples, left infraorbital area	1. yellow-brown ochronotic fibers in papillary dermis 2. yellow-brown ochronotic fibers in papillary dermis	1. ochronotic globules around/within collagen bundles	1. avoid HQ cream, HC 1% cream, sun avoidance 2. avoid bleaching cream, sunscreen	1. 8 mo:no change 2. unknown
Snider and Thiers (1993) [U.S.]	Periorbital area, nasolabial fold	yellow-brown globules, swollen/degenerated collagen in dermis	none	not stated	unknown
Camarasa (1994) [U.S.]	cheeks, periorbital	none	none	none	none
Bowman and Lesher (2001) [U.S.]	forehead, cheeks, chin	yellow-brown pigment in upper dermis overlying bony nodule	none	punch excision, adapalene gel	improvement of hyperpigmentation
ADDITIONAL CASE REPORTS					
Cullison *et al.* (1983) [U.S.]	Face, accentuation over forehead, malar cheek, skin creases of cheeks	banana-shaped clumps, yellow-brown pigment and swollen collagen in upper dermis	large ochronotic fibers	HC 2.5% cream, sun avoidance	Remarkable clearing, residual periorbital pigment
Pennys (1985) [U.S.]	not stated	none	none	not stated	none
Jordaan and Mulligan (1990) [South Africa]	forehead, cheeks, neck	thinned epidermis, granulomatous infiltrate, giant cells, asteroid bodies, sparse ochronotic fibers	none	none	none
Carey *et al.* (1990) [U.S.]	not stated	completed, not stated	completed, not stated	not stated	none
Davis *et al.* (1990) [U.S.]	infraorbital	yellow-brown broad ochronotic fibers, upper dermis	none	not stated	none
Jacyk (1995) [South Africa]	1. Face 2. Face 3. Face 4. Face 5. Face 6. Face	1. Ochronotic zone: yellow-brown thickened collagen bundles, elastosis 2. same 3. same 4. same 5. same 6.same	none	not stated	none
Kramer *et al.* (2000) [U.S.]	zygomatic cheek	yellow-brown pigment in swollen collagen bundles of dermis	none	Q-switched 694 nm ruby laser	lightening in treated areas
Bellew and Alster (2004) [U.S.]	1. cheeks; forehead, infraorbital region, nose, cheeks 2. temples, malar cheeks	1. yellow-brown depositions in dermis 2. "ochronosis"	none	1. QS 755nm Alexandrite laser -- bimonthly, 6 sessions, sun avoidance, sunscreen 2. QS 755 nm Alexandrite laser--	1. 0-12mos: progressive fading; H&E: no residual pigment 2. 16mos: marked lightening
Bongiorno and Aricò (2005) [Italy]	1. face (forehead, temples, nose), neck 2. face, neck; dorsa hands; flexural areas	1. yellow-brown banana-shaped fibers, swollen collagen, free brown pigment granules, macrophages in papillary/ reticular dermis 2. thinned epidermis & collagen; yellow-brown banana-shaped fibers and granules in dermis	none	not stated	none
Brogeras and Sánchez-Viera (2006) [Spain]	Cheeks, eyebrows	ochronotic pigment in dermis	none	Q-switched Nd:YAG laser	not assessed

Legend: EO=exogenous ochronosis; HQ=hydroquinone; unk=unknown; yr=years; mos=months; B=Black; Hisp=Hispanic; NA=Native American; PR=Puerto Rican; F=female; M=male

Table II. Published cases of exogenous ochronosis (EO) in the US*

No. of patients	Patient age (y) race and gender	Suspected causative agent	Reference (year)
1	58 B/F	2% Hydroquinone for 2.5 years (used 5 to 6 x daily)	Cullison et al. (1983)
2	75 B/F	2% Hydroquinone for 2 years	Hoshaw et al.(1985)
	49 B/F	OTC skin lightening cream for 2 months	
1	Not stated	Not stated	Pennys (1985)
1	72 B/F	One month of darkening after using skin lightening creams since childhood	Conner and Braunstein (1987)
2	62 B/F	1% Hydroquinone for 2 to 3 years	Lawrence (1988)
	46 B/F	1% Hydroquinone (duration unknown)	
1	47 B/F	4% Hydroquinone for 18 months	Fisher (1988)
3	Not stated	Not stated	Carey et al.(1990)
1	36 Hisp/F	2% Hydroquinone for 4 months	Howard and Furner (1990)
1	53 B/F	2%Hydroquinone for 2 to 3 months	Diven et al. (1990)
1	40 Cajun/M	Not stated	Davis et al. (1990)
2	56 B/M	6 5-7 5% Hydroxyquinone for 'many' years	Jordaan and Niekerk (1991)
	39 B/F	Skin lightening cream for 5 years (unkown hydroquinone concentration)	
2	44 B/F	2% hydroquinone for 3 to 4 years	Martin et al. (1992)
	56B/F	Over the counter skin lightening creams for 30 years	
1	72 C/M	Secondary to alkaptonuria which the patient had for 37 years	Albers et al. (1992)
1	59 B/F	2 to 4% Hydroquinone for many years	Snider and Theirs (1993)
	45 race not stated/F	2% Hydroquinone used to treat melasma; EO associated with allergic	Camarasa (1994)
1		hypersensitivity to hydroquinone	
6	40-70 B/F	Not stated	Jacyk (1995)
1	50 Hisp/F	2% Hydroquinone for 30 years	Kramer (2000)

B = Black; **C** = Caucasian; **Hisp** = Hispanic; **F** = female; **M** = mate.

*Adapted with permission from Levin CY, Maibach H. Exogenous Ochronosis. Am J Clin Dermatol; 2(4):213-217.

Table III. Efficacy of treatments used for exogenous ochronosis*

Therapy	Clinical Efficacy	References
Avoidance of offending agent	Beneficial, but slow improvement	Findlay et al. (1975), Cullison et al. (1983), Hoshaw et al. (1985), Snider and Thiers (1993)
Retinoic acid	Helpful for some individuals; caused transient hyperpigmentation in others	Howard and Furner (1990), Diven et al. (1990), Schultz et al. (1988)
Retinoic acid and sunscreen	Beneficial, infrequently utilized	Camarasa (1994)
Sunscreen	Variable efficacy	Hoshaw et al. (1985), Martin et al. (1992), Whilliams (1992)
Trichloroacetic acid	Ineffective	Diven et al. (1990)
Low-potency corticosteroids	Variable efficacy	Lawrence (1988), Cullison et al. (1983), Howard and Furner (1990), Martin et al (1992)
Dermabrasion	Beneficial, infrequently utilized	Lang (1988)
Dermabrasion and CO2 laser	Beneficial, infrequently utilized	Diven et al. (1990)
Cryotherapy	Ineffective	Diven et al. (1990)
Q-switched ruby laser	Beneficial, infrequently utilized	Kramer (2000)
Q-switched alexandrite laser	Beneficial, infrequently utilized	Bellew and Alster (2004)
Tetracycline	Beneficial in sarcoid-like ochronosis	Fisher (1988)

a The results of evidence-based studies assessing the efficacy of potential treatments for exogenous ochronosis are required

CO_2 = carbon dioxide

*Adapted with permission from Levin CY, Maibach H. Exogenous Ochronosis. Am J Clin Dermatol 2001; 2(4):213-217.

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Blacker *et al.* (1993)	animal	rodent two-generation reproduction study with HQ
Krasavage *et al*. (1984)	animal	rodent dominant lethal assay with HQ
Topping *et al.* (2006)	chemistry/basic science	subchronic neurotoxicity study with HQ
Deisinger *et al.* (1996)	basic science	metabolism study
Deisinger and English (1999)	basic science	metabolism study
Boatman *et al.* (2000)	basic science	metabolism study
English and Deisinger (2005)	basic science	metabolism study
Corlet *et al.* (2000)	pharmacology	pharmacokinetic study with HQ
Poet *et al.* (2004)	pharmacology	pharmacokinetic study with HQ
English, Perry *et al.* (1994)	animal	mechanistic study with rodents on HQ
English, Hill *et al.* (1994)	animal	mechanistic study with rodents on HQ
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Hard *et al.* (1997)	animal	mechanistic study with rodents on HQ
David *et al.* (1998)	animal	toxicity study of HQ in sking lightener formulation in albino animals
O'Donoghue *et al*. (1999)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Doepker *et al.* (2000)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Williams *et al.* (2006)	chemistry/toxicity	genotoxicity, preventative action of HQ on mutagenicity and tumorigenicity
Whysner *et al.* (1995)	review	data for HQ, tumorigenicity
DeCaprio *et al.* (1999)	review	data for HQ, toxicology, environmental and occupational exposure

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