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Skin-lightening cosmetics: frequent, potentially severe adverse effects

- Skin-lightening cosmetics are used by many women and men around the world.

- The products contain a variety of substances, which are often unknown to the users. Most of these products include topical corticosteroids, *hydroquinone* and mercury salts. Many other substances may be added.

- Several surveys and cohort studies, including several thousand individuals, have shown that regular application of skin-lightening cosmetics to large surface areas can have irreversible cutaneous adverse effects, such as patchy hyper- or hypopigmentation, skin atrophy, stretch marks and delayed wound healing, and can also mask or, on the contrary, promote or reactivate skin infections.

- Cases of skin cancer have been attributed to skin-lightening cosmetics.

- A Senegalese cohort study of 147 women showed a statistically significant increase in the risk of hypertension and diabetes linked to the use of skin-lightening agents.

- Other systemic adverse effects attributed to skin-lightening cosmetics include Cushing's syndrome, adrenal insufficiency, nephrotic syndrome, neurological disorders, and ocular disorders. Hypersensitivity reactions, including anaphylaxis, have also been attributed to these products.

- Many skin-lightening cosmetics contain substances that can harm the unborn child. For example, *tretinoin* is teratogenic while *salicylic acid* is fetotoxic.

- In practice, users are often unaware of the risk of severe adverse effects associated with skin-lightening cosmetics. Users should be informed of these adverse effects and encouraged

to stop using these products, especially when skin disorders appear.

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Skin-lightening (or bleaching) cosmetics are widely used throughout the world, especially in Africa (including North Africa), the Middle East, the West Indies, the American continent (United States, South and Central America), Asia (India, Philippines). In Europe, they are used by some people originating from these regions. A lighter skin colour is often perceived to be linked to social success, respect, and better living conditions (1-8). These perceptions have created a large market for skin-lightening cosmetics (2-6). It has been estimated that skin-lightening products are used by about one-quarter of the urban population in Africa, especially women but also men, regardless of their social origin, level of education, age, family situation, and country of origin (3,9-12).

Skin-lightening cosmetics (often creams, but also gels, body lotions and soaps) are generally applied daily for several decades, usually to the face and the entire body (2,9). Users sometimes make their own concoctions, while the contents of commercial products are not always clearly stated on the labelling (11-13). Most products contain more or less potent topical corticosteroids (especially *betamethasone* and *clobetasol*), sometimes combined with *hydroquinone* or one of its derivatives, *mequinol*, or mercury salts (14-16). Other substances include *salicylic acid*, *glycolic acid*, *tretinoin*, *azelaic acid*, *ascorbic acid*, *kojic acid*, bleach, hydrogen peroxide, and lemon juice (see inset p.211) (2,4,7,11, 12,17).

What health risks do skin-lightening cosmetics carry, both for the user and, in pregnant women, for the unborn child?

To answer this question, we reviewed the available data using the standard *Prescrire* methodology (see page 215).

A difficult assessment

The adverse effects of skin-lightening cosmetics are difficult to assess, for a number of reasons.

There are a wide variety of products. They are not pharmaceuticals and therefore do not fall within the scope of pharmacovigilance activities. There are a plethora of brand names (a). Banned substances are sometimes used. For example, in France, cosmetic products based on mercury salts are banned, as are those containing *hydroquinone* (with certain exceptions) (b,c,d)(18-23). In addition, skin lightening is a practice that is often kept secret and that users are reluctant to discuss with health professionals (24,25).

To assess the risks associated with these products, it is essential to examine the known adverse effect profile of their individual components. The adverse effects of some of these components are summarised in the inset on pages 212-213.

Some substances may have both cutaneous and extracutaneous adverse effects. The dangers of exposure in utero are outlined in the inset on page 214. ▶▶

a- Depending on the country, this practice is referred to as "Keesal", "tcha tcho", "leeral", "caco", "maquillage", etc. (ref 2,7).

b- Since the French ministerial decree of 5 February 2009, implementing European directive 2008/88/EC, *hydroquinone* is no longer included on the list of substances that can be used in cosmetic products in France, except for artificial nails, at a maximum concentration of 0.02%, for professional use only and avoiding contact with the skin (ref 20). The Commission banned the use of *hydroquinone* because of the lack of safety data (ref 62).

c- In March 2011, five products intended for topical application and based on *mequinol*, a substance closely related to *hydroquinone*, were granted marketing authorisation in France: *Any 8 pour cent*®, *Any 5 pour cent*®, *Leucodinine B 10 pour cent*®, *Crème des trois fleurs d'orient 5 pour cent*®, and *Crème des trois fleurs d'orient 10 pour cent*® (refs 15,62). *Any 8 pour cent*® is currently on the market (ref 63).

d- Five cutaneous adverse effects following the use of skin-lightening cosmetics possibly containing illicit substances were reported to the French authorities in 2009: there were 2 cases of atypical acne, 2 cases of pseudo-acromegaly, and 1 case of hypertrichosis and acne. Tests of the cosmetic products implicated in the two cases of pseudo-acromegaly revealed that they contained *hydroquinone* (ref 23).

Sometimes irreversible cutaneous adverse effects

Skin-lightening cosmetics have numerous cutaneous adverse effects (2,7).

Patchy or confetti-like hyper- and hypopigmentation. Among the many cutaneous adverse effects attributed to skin-lightening cosmetics, heterogeneous skin colour changes are the most frequent, including patchy or confetti-like hyperpigmentation or hypopigmentation, resembling ochronosis (e)(1,7,13).

Severe forms usually leave permanent traces (7).

Initially used to lighten the skin, these products are subsequently used to mask the stains they provoke (26).

The amount and duration of application varies from day to day, and marked depigmentation may occur in areas where the product accumulates, such as under rings (7).

Local hyperpigmentation is frequent. A Senegalese prospective study lasting 6 months examined problems encountered by people who said they used bleaching creams (unspecified compositions). The problems included hyperpigmentation of joints (70 reports), periorbital hyperpigmentation (45 reports), and lilac erythema of eyelids (8 reports) (27).

In a survey conducted in the Paris region among more than 1000 users, a bluish hue of the outer ear was noticed in 6 persons from Africa or the West Indies who said they used a bleaching cream of unknown composition (8). Bluish-grey discolouration of the ear is evocative of pseudo-ochronosis linked to the use of bleaching creams (7).

Abnormal pigmentation provoked by bleaching creams can be aggravated by interaction with medications, especially antimalarials (2,28).

Rebound effect. Rebound hyperpigmentation has also been reported. In a survey conducted in a Senegalese hospital and including 147 women aged 15 to 60 years, 41 patients said they used bleaching creams and 6 of them experienced rebound hyperpigmentation after they stopped using the products (29).

Skin atrophy, stretch marks, delayed wound healing. Skin atrophy (thinning), stretch marks, telangiectasia, and delayed wound healing are among the plethora of cutaneous adverse effects associated with skin-lightening cosmetics that contain topical corticosteroids. Severity depends on the frequency and duration of use and the treated surface area (4,7,27,30).

Other reported cutaneous adverse effects include dry skin (especially on the shin), eczema, pruritus and purpura (2,4,31-34).

Skin infections: mycoses, parasitoses. Fungal, parasitic, bacterial and viral skin infections may occur in users of skin-lightening cosmetics. These infections are favoured by the immunosuppression induced by topical corticosteroids (9,30).

Two reviews of cohort studies or surveys in a total of about 4000 persons living in several African countries (Senegal, Mali, Togo, Burkina Faso, etc.) examined skin infections affecting users of skin-lightening cosmetics.

Mycoses were the most frequent infectious complications, affecting 22% to 30% of users (7,9). Axillary and submammary tinea and intertrigo of fungal or bacterial origin were also reported. Tinea was often masked by traction alopecia, making it difficult to diagnose (7). Often extensive fungal infections of the face have been reported (9). Disseminated pityriasis versicolor associated with marked achromia and atrophy was often found in unusual locations, such as the lower limbs (7,9).

Scabies lesions were crusted, hyperpigmented, disseminated and profuse in users of skin-lightening cosmetics (7,9,35).

Bacterial and possibly viral infections. Severe infectious dermohypodermatitis, often affecting the lower limbs and buttocks, sometimes with bullous and necrotic lesions, was responsible for 10% of admissions to hospital dermatology units in Dakar (7,9,29,36).

Other bacterial infections such as disseminated folliculitis and impetigo were frequent (9).

Lesions of viral origin, such as herpes, molluscum contagiosum, warts and condylomata, were less frequent (7).

Acne, nodules. Skin rash is more frequent when skin-lightening cosmetics are used along with greasy cosmetics (1,33,37).

A cohort study conducted at a Dakar hospital in 1999, in a sample of 147 women aged from 15 to 60 years, showed that 19.5% of women using skin-lightening cosmetics consulted for acne, compared to 4.7% of non-users ($p < 0.02$) (29).

The two above-mentioned reviews of cohort studies or surveys in a total of about 4000 people showed that acne affected between 17% and 34% of users (7,9). There are no available comparisons with non-users.

Other types of skin rash included rosacea, nodules on the upper back and,

more rarely, lupus-like lesions that regressed after *hydroquinone* exposure stopped (1,2,4,9,29,38).

Hydroquinone can also cause ochronosis-like lesions with clusters of papules or micropapules that are lighter or darker than the surrounding skin, giving the temples, cheeks, and nape of the neck a heterogeneous grey colour (9).

Irritation, with redness, pain, pruritus. A number of substances contained in skin-lightening cosmetics can cause skin irritation or peeling.

This irritation may be accompanied by symptoms such as redness (or, on black skin, a darker skin tone), pain, a burning sensation, or pruritus (37,39).

Skin irritation has been reported with bleaching creams, especially around the mouth, palms and soles (2,4,26,37,40-42).

Cancer? Several long-term animal studies indicate that *hydroquinone* can cause cancer (43). In the US, in 2006, based on the results of animal studies, the FDA decided to make *hydroquinone* available by prescription only (26).

Four cases of squamous cell carcinoma were described in patients who used bleaching creams containing topical corticosteroids or *hydroquinone*, for more than 10 years in two cases (4,44,45). In two patients, the carcinoma was located on the neck, in a sun-exposed area or on a plaque of ochronosis-like lesions. One of the patients, whose lesions had reached the soft tissues and collarbone, died after a relapse of the initial skin cancer (44).

Several mechanisms have been proposed, including immunosuppression, reduced photoprotection, or a carcinogenic effect of *hydroquinone*, which is a metabolite of benzene, a chemical known to cause leukaemia (46,47).

Extracutaneous adverse effects

In addition to cutaneous disorders, skin-lightening cosmetics can have systemic adverse effects depending on the components they contain.

The degree of absorption of topically applied products depends on the active substance(s), the excipient(s) (48), the treated surface area, and the integrity of the epidermis (48).

Cushing's syndrome and adrenal insufficiency. Adrenal insufficiency and Cushing's syndrome have both been attributed to skin-lightening cosmetics containing topical corticosteroids (48-54).

Mechanisms of action of skin-lightening products

Many substances lighten skin tone, through a variety of more or less well documented mechanisms, mainly involving either melanin or keratin.

Melanin, a pigment synthesised by melanocytes, gives the skin and hair their colour (1). Melanocytes, situated in the basal layer of the epidermis, transfer part of the melanin they produce to keratinocytes. Keratinocytes differentiate as they progress from the basal layer of the epidermis to the horny layer (1,2).

Keratin is composed of a mass of dead cells that have migrated from the basal layer of the epidermis, thus forming the horny layer (3).

Reduction in melanin synthesis and skin colour. *Hydroquinone* and *mequinol* are chemically related substances that inhibit melanin synthesis in melanocytes (4-7). *Monobenzene*, another substance chemically related to *hydroquinone*, has a similar mechanism of action and may cause destruction of melanocytes (8).

Mercury salts appear to inhibit melanin formation by competing for the copper necessary for tyrosinase activity, which is required for melanin synthesis (1). *Kojic acid* inhibits melanin synthesis (9).

Tretinoin, a vitamin A derivative, lightens the skin through several mechanisms, notably by inhibiting melanin synthesis (1).

Hydrogen peroxide and *ascorbic acid* bleach melanic pigments (1).

Inhibition of keratin synthesis. Corticosteroids and *azelaic acid* inhibit keratin production (10,11). An antiproliferative effect on keratinocytes has been observed with corticosteroids and could explain the lightening and atrophic effects of these compounds (1,12).

Salicylic acid and *tretinoin* have a keratolytic (peeling) effect. *Glycolic acid*, an organic alpha-hydroxy acid derived from sugar cane, accelerates cell turnover in the horny layer, leading to a lighter skin colour (1,12-16).

Drug interactions. Concomitant use of antimalarial drugs and bleaching creams increases the risk of pigmentation disorders (16,17).

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1- Batchily-Plat F "Dépigmentants". In: Martini MC et Seiller M "Actifs et additifs en cosmétologie" 3^e édition. Lavoisier, Paris 2006: 697-724.

2- "Pigmentation disorders". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 3 pages.

3- "Keratinisation disorders". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 1 page.

4- Prescrire Rédaction "Les crèmes "éclaircissantes"" Rev Prescrire 1989; 9 (89): 393-394.

5- "Hydroquinone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, Lon-

don. www.medicinescomplete.com accessed 15 March 2011: 4 pages.

6- "Mequinol". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

7- "Metyrapone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 3 pages.

8- "Monobenzene". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 3 pages.

9- "Kojic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

10- "Adverse effects of corticosteroids and their treatment". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

11- "Azelaic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 3 pages.

12- Prescrire Rédaction "Psoriasis des adultes: des rémissions, mais pas de traitement curatif" Rev Prescrire 2005; 25 (266): 751-762.

13- "Glycolic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

14- "Salicylic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 9 pages.

15- "Tretinoin". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 14 pages.

16- Dadzie OE and Petit A "Skin bleaching: highlighting the misuse of cutaneous depigmenting agents" J Eur Acad Dermatol Venerol 2009; 23: 741-750.

17- Prescrire Editorial Staff "Drug-induced photosensitivity" Prescrire Int 2009; 18 (103): 208-211.

A 6-month prospective cohort study of 99 pregnant women, 68 of whom used skin-lightening cosmetics, showed a statistically significant reduction in plasma cortisol concentrations in women who used skin-lightening cosmetics containing *clobetasol* (53). Some cosmetics contained *hydroquinone*, corticosteroids and/or *salicylic acid*, and their composition was sometimes not known.

Diabetes and hypertension. Diabetes and hypertension have been reported after several years of use (29,54).

The above-mentioned cohort study of 147 hospitalised Senegalese women showed a statistically significant increase in the frequency of diabetes and hypertension in the 41 women who admitted using skin-lightening cosmetics, compared with the 85 women who said they had never used them. Twenty-one women refused to participate or were excluded.

Exposure for more than 10 years was associated with hypertension (29). The composition of the cosmetics in question was not known.

Renal disorders: glomerulopathies, tubulopathies. Serious renal disorders such as glomerulopathies and tubulopathies have been described in people using creams that contain mercury salts (19,40). Cases of haematuria and nephrotic syndrome have also been attributed to skin-lightening cosmetics (10, 40,55).

A 21-year-old African woman was hospitalised with facial and peripheral oedema, with marked proteinuria (110 g/24 h) and hypoalbuminaemia. Tests for malaria were negative. For the past 1 or 2 years she had applied a cream containing 10% to 15% of a mercury salt to her face, neck and hands every night. She also had a nephrotic syndrome. The syndrome dis-

appeared 6 to 9 months after withdrawal of the cream, but moderate proteinuria persisted (55).

In a descriptive survey conducted in Lagos, Nigeria, among 450 sellers of skin-lightening cosmetics, 77% said they had been using the products themselves, for an average of 1 to 3 years. Nine said they had blood in their urine (10).

Neurological disorders. Some substances contained in skin-lightening cosmetics can have neurological adverse effects (40), as illustrated by the following examples.

A 30-year-old woman experienced a burning sensation in her feet, progressive lower-limb weakness leading to diffi- ▶▶

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e- Some skin lesions associated with skin-lightening cosmetics resemble *acromelosis*, a very rare condition associated with *alkaptonuria* (ref.64).

Adverse effect profile of common components of skin-lightening cosmetics

Based mainly on the *Prescrire* database and *Martindale The Complete Drug Reference* (a clinical pharmacology textbook), the following is a brief summary of the adverse effects of substances often contained in skin-lightening cosmetics.

Topical corticosteroids

There are many topical corticosteroids. The intensity of their effects depends on their formulation, but the nature of their adverse effects is similar.

Cutaneous adverse effects. The main cutaneous adverse effects of corticosteroids include:

- skin thinning or atrophy (in the armpits and the groin skinfolds, areas where the skin is thinner, moist and often covered), stretch marks, delayed wound healing;
- dry skin (especially on the shins), eczema, pruritus, purpura, acne, rosacea, and nodules;
- fungal, parasitic, bacterial and viral skin infections, due to immunosuppression;
- rare hypersensitivity reactions, including anaphylaxis; the risk increases with prolonged or repeated application (1-13).



The typical systemic adverse effects of corticosteroids. Cutaneous application of corticosteroids

leads to a degree of systemic absorption, which varies according to the individual, the treated surface area, and the integrity of the epidermis, etc. This absorption can lead to the systemic adverse effects of corticosteroids, including:

- hypercorticism;
- adrenal insufficiency;
- hypertension;
- hyperglycaemia and hypercholesterolaemia;
- neuropsychological disorders;
- water-electrolyte disorders, hypokalaemia, and water-sodium retention;
- osteoporosis;

- ocular disorders (cataracts and glaucoma, etc.) (14-19).

Hydroquinone

Hydroquinone is a benzene metabolite (2). *Mequinol* is related to *hydroquinone*, and was still marketed in France in early 2011 (20).

Cutaneous adverse effects. The main cutaneous adverse effects of *hydroquinone* and *mequinol* include:

- pigmentation disorders (ochronosis-like lesions): blue-black hyperpigmentation, clusters of hyperpigmented papules, confetti-like or plaque hypopigmentation, which is often irreversible and appears about 6 months after beginning to use *hydroquinone*-based creams on sun-exposed areas; and brown discolouration of the nails (reversible after treatment cessation);
- skin thickening;
- skin irritation: darker colour, pain or burning sensation, and itching, around the mouth and on the palms and soles;
- cancer: animal studies have shown a carcinogenic risk associated with *hydroquinone*, and a few cases of cancer have been reported in long-term users (2,7,13,21-23).



Systemic adverse effects: liver. Cutaneous *hydroquinone* application leads to a degree of systemic absorption that depends on the individual, the treated surface area, the integrity of the epidermis, etc. This leads to a risk of systemic adverse effects, such as:

- liver damage in case of heavy exposure;
- a fishy body odour (7,21-23).

Mercury salts

Cosmetic preparations based on mercury salts were withdrawn from the

French market in the mid-1980s because of allergic cutaneous and systemic reactions (encephalopathy and renal impairment) (24).

Cutaneous adverse effects. The main cutaneous adverse effects of mercury salts include:

- rash: dermatitis, bullous rash;
- irritation: darker skin colour, pain or burning sensation, and pruritus, around the mouth and on the palms and soles (2,7,13,22,25).



Mercury poisoning. Cutaneous application of mercury salts leads to a degree of absorption that varies

depending on the individual, the treated surface area, the integrity of the epidermis, etc. This leads to a risk of systemic adverse effects such as:

- gastrointestinal disorders: nausea, vomiting, bloody diarrhoea, sialorrhoea;
- renal impairment: kidney failure, nephrotic syndrome, tubular necrosis;
- haematological disorders;
- neurological disorders: tremor, seizures, motor and sensory disturbances, intellectual impairment, ataxia, dysarthria and headache; transdermal absorption is increased in warm, humid climates, leading to a higher risk of neurological disorders;
- muscle disorders;
- hypersensitivity reactions, and occasional anaphylaxis (9,13,24,25).

Tretinoin

Tretinoin is a retinoid marketed mainly for local treatment of acne. Its adverse effect profile is that of retinoids in general (26).

Mainly cutaneous adverse effects. The cutaneous adverse effects of *tretinoin* mainly include:

- pigmentation disorders;
- skin rash;
- skin irritation: around the mouth, on the

– culty walking, and pain in the right forearm. Physical examination showed a loss of muscle strength and tendon reflexes, and abnormal lower-limb sensitivity. Blood and urine tests were normal, as was abdominal and pulmonary radiography. The disorders resolved 4 months after withdrawal of the *hydroquinone*-based cream she

had been using for about 4 years (56).

Similarly, a 30-year-old woman developed several health problems over a 3-year period, including a facial skin rash accompanied by a burning sensation, followed by erythema of the palms and soles, tremor, and finally sialorrhoea, pruritus, weakness and insomnia. Mercury

intoxication was confirmed by analysis of her urine and the cream she had applied daily to her face for about 5 years (40,57).

Hypersensitivity reactions. Hypersensitivity reactions and cases of anaphylaxis have been attributed to skin-lightening cosmetics (32-34).

palms and soles; black skin may take on a darker hue, with pain, a burning sensation, or pruritus (26,27).



Systemic adverse effects: mucosal and psychological disorders. *Tretinoin* application to the skin leads

to a degree of systemic absorption that depends on the individual, the treated surface area, and the integrity of the epidermis, etc. This leads to a risk of systemic adverse effects, including:

- mucosal dryness, epistaxis, cheilitis, colitis, sterile urethritis;
- psychological disorders, depression, suicide;
- ocular disorders, dry eye, conjunctivitis, keratitis; visual disturbances;
- bone and muscle disorders, hyperostosis, ligament and tendon calcification;
- intracranial hypertension;
- hyperlipidaemia, pancreatitis, hyperglycaemia;
- hepatic disorders.

Tretinoin is also teratogenic (see inset page 214) (26-28).

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Selected references from Prescrire's literature search (see details below).

- 1- "Adverse effects of corticosteroids and their treatment". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.
- 2- Dadzie OE and Petit A "Skin bleaching: highlighting the misuse of cutaneous depigmenting agents" *J Eur Acad Dermatol Venerol* 2009; **23**: 741-750.
- 3- Sène D et al. "Insuffisance surrénalienne haute symptomatique compliquant l'usage de dermocorticoïdes pour dépigmentation volontaire" *Rev Méd Interne* 2008; **29**: 1030-1033.
- 4- Mahé A et al. "Complications dermatologiques de l'utilisation cosmétique de produits dépigmentants à Bamako (Mali)" *Ann Dermatol Vénéréol* 1994; **121**: 142-146.
- 5- Prescrire Rédaction "Effets indésirables cutanés des corticoïdes inhalés" *Rev Prescrire* 2007; **28** (279): 25.
- 6- Morand JJ et al. "Complications de la dépigmentation cosmétique en Afrique" *Méd Trop* 2007; **67** (6): 627-634.
- 7- Olumide YM et al. "Complications of chronic use of skin lightening cosmetics" *Int J Dermatol* 2008; **47** (4): 344-353.
- 8- Prescrire Rédaction "hydrocortisone topique sans prescription - Dermaspraid démangeaison®, Mitocortyl démangeaisons®, Ni panacée, ni démon" *Rev Prescrire* 2001; **21** (213): 19-23.

Fetotoxicity and birth defects. Skin-lightening cosmetics are widely used by women of child-bearing age, yet they often contain unidentified substances that may harm the unborn child. Depending on the period of exposure, these substances may be fetotoxic or cause birth defects (see inset page 214).

9- Caroli UM et al. "Lymphocytic infiltration of the skin Jessner-Kanof after treatment with a hydroquinone-containing bleaching cream" *Arch Dermatol* 2006; **142** (12): 1655-1656.

10- Prescrire Editorial Staff "Local steroids in children: hypertrichosis" *Prescrire Int* 2008; **17** (97): 204.

11- "Effects on immune response". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 1 page.

12- Mahé A et al. "Irrational use of skin-bleaching products can delay the diagnosis of leprosy" *Int J Lepr Other Mycobact Dis* 2002; **70** (2): 119-121.

13- Prescrire Editorial Staff "Black skin, white masks" *Prescrire Int* 1993; **2** (5): 42.

14- Prescrire Rédaction "18-1-3. Patients sous corticoïde" *Rev Prescrire* 2010; **30** (326) (suppl. interactions médicamenteuses).

15- "Dexamethasone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 22 pages.

16- Druce M et al. "The pursuit of beauty" *Lancet* 2008; **371**: 596.

17- Bwomda P et al. "Glucocorticoid hypertension due to the use of bleaching skin cream, a case report" *Acta Clin Belg* 2005; **60** (3): 146-149.

18- Prescrire Rédaction "Psoriasis des adultes: des rémissions, mais pas de traitement curatif" *Rev Prescrire* 2005; **25** (266): 751-762.

19- Prescrire Rédaction "fluticasone dermique-Flixovate". Un Nième dermocorticoïde d'activité forte" *Rev Prescrire* 2003; **23** (238): 245.

20- Afsaps - Répertoire des spécialités pharmaceutiques "Any 5%" + "Any 8%" + "Crème des trois fleurs d'orient 5%" + "Leucodinine B 10%" + "Crème des trois fleurs d'orient 10%": updated 25 February 2011. www.afsaps.fr accessed 7 March 2011: 7 pages.

21- "Hydroquinone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 4 pages.

22- Prescrire Rédaction "Irritations localisées de la peau" *Rev Prescrire* 2008; **28** (299): 673-674 + (300): II de couverture.

23- Ly F et al. "Premiers cas de carcinomes épidermoïdes sur terrain de dépigmentation artificielle" *Ann Dermatol Vénéréol* 2010; **137** (2): 128-131.

24- Prescrire Rédaction "Attention aux usages détournés. Retrait du marché des crèmes contenant du chloramide de mercure" *Rev Prescrire* 1987; **7** (65): 217.

25- "Ammoniated mercury" + "Mercury". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 10 pages.

26- Prescrire Rédaction "3-1-4. Patients sous rétinoïde topique" *Rev Prescrire* 2010; **30** (326) (suppl. interactions médicamenteuses).

27- "Tretinoin". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 14 pages.

28- Prescrire Editorial Staff "Topical retinoids during pregnancy (continued)" *Prescrire Int* 2005; **14** (77): 100-101.

Tretinoin is a retinoid. Malformations resembling those associated with oral retinoids have been observed in babies born to women who applied *tretinoin* to their skin (37,58). The polymalformative syndrome provoked by oral retinoids includes a fairly characteristic triad of craniofacial, cardiac and central nervous

system malformations.

Other products such as mercury salts and salicylic acid are fetotoxic, potentially causing cataracts, tubulopathies, pulmonary arterial hypertension, etc. (59,60).

The risks to the unborn child associated with cosmetic use of *hydroquinone* and topical corticosteroids are poorly documented. Maternal adverse effects of topical corticosteroids include stretch marks, delayed wound healing after Caesarean section, and infections (4,33,61).

In practice, warn users of the risks and encourage them to stop using these products

Skin-lightening cosmetics can have serious cutaneous and systemic adverse effects. Women of child-bearing age who use these products run a risk of obstetrical complications, fetotoxicity and congenital malformations.

Patients are often reluctant to admit to using these products, but a number of cutaneous signs, such as pigmentation disorders, skin atrophy, stretch marks, etc., as well as systemic signs, can alert health professionals to this possibility.

Users should be warned of the dangers associated with skin-lightening cosmetics and encouraged to stop using them.

©Review prepared and translated by the Prescrire Editorial Staff (no conflicts of interest)

Literature search and methodology

Our literature search was based on continuous prospective monitoring at the Prescrire library, contents listings of the main international journals, Current Contents-Clinical Medicine, and member bulletins of the International Society of Drug Bulletins (ISDB), and consultation of Martindale The Complete Drug Reference, and Briggs' Drugs in Pregnancy and Lactation 2008. We also accessed Medline (1950-2011 March week 1), Embase/Excerpta Medica (1991-2011 week 10) and CIRC, Reprotox, Shepard's and Teris, up to 15 March 2011.

This review was prepared using the standard Prescrire methodology, which includes selection and analysis of documents by an editor, with verification by another editor; preparation of the first draft with input from several editors; external review by several specialists and non-specialists; verification and integration of the reviewers' comments and any further documents; and multiple quality controls, including a final control with the references to hand.

- 1- Prescrire Editorial Staff "Black skin, white masks" *Prescrire Int* 1993; **2** (5): 42.
- 2- Dadzie OE and Petit A "Skin bleaching: highlighting the issue of cutaneous depigmenting agents" *J Eur Acad Dermatol Venerol* 2009; **23**: 741-750.
- 3- De Souza MM "The concept of skin bleaching in Africa and its devastating health implications" *Clin Dermatol* 2008; **26**: 27-29.
- 4- Olumide YM et al. "Complications of chronic use of skin lightening cosmetics" *Int J Dermatol* 2008; **47** (4): 344-353. [continued on page 215]

Skin-lightening creams: warn women of child-bearing age about the risks

Women who use skin-lightening cosmetics are often young. The composition of these products is often unknown (see main article pages 209-215) and some components are capable of crossing the skin and the placenta. Depending on when the fetus is exposed, these products may cause malformations or fetotoxicity (1,2).

Tretinoin: teratogenic. *Tretinoin*, like *isotretinoin*, is a retinoid (3). Oral retinoids are teratogenic: about one-quarter of infants exposed to *isotretinoin* during the first trimester of pregnancy develop a malformative syndrome, characterised by craniofacial, cardiac and central nervous system defects.

Available epidemiological data do not rule out a risk of teratogenesis in children exposed in utero to cutaneous retinoids; several cases of malformation compatible with those induced by oral retinoids have been reported (4).

In practice, women of child-bearing age who are not using effective contraception should avoid *tretinoin*.

Salicylic acid: renal failure and pulmonary hypertension. *Salicylic acid* has the same fetotoxicity as *aspirin*: renal failure, pulmonary arterial hypertension and a risk of bleeding towards the end of pregnancy (5).

In practice, cutaneous application of *salicylic acid* should be avoided during pregnancy.

Inorganic mercury salts: likely fetotoxicity. Inorganic mercury salts do not seem to be transformed into organic mercury, i.e. methylmercury, a compound known for its teratogenic effects mainly affecting the central nervous system (6,7).

However, there are no animal or human studies of the fetotoxicity of inorganic mercury derivatives applied to the skin during the second or third trimester of pregnancy (7-9).

A case of bilateral cataracts with anaemia and renal tubular impairment was described in a 3-month-old baby. The baby and mother both had high mercury concentrations in their blood and urine. The mother had been using a soap containing mercury salts for 15 years, and had not stopped using it during pregnancy or during the one month

of breastfeeding. She did not use the soap on her child (10).

In practice, it is better to avoid using mercury salts during pregnancy.

Hydroquinone: skeletal disorders? Transplacental passage of *hydroquinone* has not been studied. Animal studies have yielded conflicting results concerning the risk of skeletal malformations (vertebrae and ribs), and microphthalmia (11).

In practice, *hydroquinone* should be avoided during pregnancy.

Corticosteroids: delayed healing of Caesarean section wounds. Topical corticosteroids can be absorbed systemically and corticosteroids are known to cross the placenta (2). Topical application of corticosteroids during pregnancy is indicated for some cutaneous disorders (12). In addition, corticosteroid therapy is sometimes indicated for severe asthma, autoimmune disorders, and, in a single dose, to prevent premature delivery (12-19).

Topical corticosteroids applied to the abdomen during pregnancy have been reported to delay the healing of Caesarean section wounds and to promote their infection (15,17).

In practice. Skin-lightening cosmetics have many, often poorly documented adverse effects and can contain unknown substances. Their use during pregnancy places the unborn child at risk of malformations. Women of child-bearing age must be informed of these risks and encouraged to stop using these products.

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Selected references from Prescrire's literature search.

- 1- Prescrire Rédaction "fluticasone dermique-Flixovate®. Un Nième dermocorticoïde d'activité forte" *Rev Prescrire* 2003; **23** (238): 245.
- 2- Briggs GG et al. "Hydrocortisone". In: "Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk" Lippincott, Williams & Wilkins, 2008: 879-886.
- 3- "Tretinoin". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 14 pages.
- 4- Prescrire Editorial Staff "Topical retinoids during pregnancy (continued)" *Prescrire Int* 2005; **14** (77): 100-101.
- 5- Prescrire Rédaction "Psoriasis des adultes: des rémissions, mais pas de traitement curatif" *Rev Prescrire* 2005; **25** (266): 751-762.

6- Prescrire Rédaction "Mercure: ne pas abuser de certains poissons" *Rev Prescrire* 2003; **23** (243): 697-698.

7- "Mercury". In: "Shepard's" Micromedex Healthcare Series. www.thomsonhc.com accessed 21 May 2010: 5 pages.

8- "Mercury, inorganic salts". In: "Teris" Micromedex Healthcare Series. www.thomsonhc.com accessed 21 May 2010: 3 pages.

9- Prescrire Rédaction "Inhalation de mercure après le bris d'instrument de mesure: connaître le risque d'intoxication et les procédures de décontamination" *Rev Prescrire* 2006; **26** (269): 126-129.

10- Lauwerys R et al. "Prenatal and early postnatal intoxication by inorganic mercury resulting from the maternal use of mercury containing soap" *Human Toxicol* 1987; **6**: 253-256.

11- Briggs GG et al. "Hydroquinone". In: "Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk" Lippincott, Williams & Wilkins, 2008: 888-890.

12- Prescrire Editorial Staff "Long-term asthma therapy" *Prescrire Int* 2007; **16** (91): 208-211.

13- Prescrire Editorial Staff "Risk of preterm delivery: a single course of antenatal corticosteroids" *Prescrire Int* 2010; **19** (108): 168-169.

14- Prescrire Editorial Staff "Treatment of rheumatoid arthritis" *Prescrire Int* 2001; **10** (52): 55-61.

15- Olumide YM et al. "Complications of chronic use of skin lightening cosmetics" *Int J Dermatol* 2008; **47** (4): 344-353.

16- Chi CC et al. "Systematic review of the safety of topical corticosteroids in pregnancy" *J Am Acad Dermatol* 2010; **62**: 694-705.

17- "Adverse effects of corticosteroids and their treatment". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

18- "Dexamethasone". In: "Teris" Micromedex Healthcare Series. www.thomsonhc.com accessed 21 May 2010: 6 pages.

19- Prescrire Rédaction "Spécialités à base de dermocorticoïde non associé disponibles en France" *Rev Prescrire* 2000; **20** (202): 4.

► 5- Easton A "Women have deadly desire for paler skin in the Philippines" *Lancet* 1998; **352**: 555.

6- AFP "La folie du "whitening" atteint le monde arabe". www.afp.pressedd.com accessed 20 August 2008: 2 pages.

7- Morand JJ et al. "Complications de la dépigmentation cosmétique en Afrique" *Méd Trop* 2007; **67** (6): 627-634.

8- Arsouze A et al. "Motifs de consultation en dermatologie des sujets de peau noire d'origine africaine et antillaise: enquête multicentrique en région parisienne" *Ann Dermatol Vénérol* 2008; **135**: 177-182.

9- Ly F "Complications dermatologiques de la dépigmentation artificielle en Afrique" *Ann Dermatol Vénérol* 2006; **133**: 899-906.

10- Adebajo SB "An epidemiological survey of the use of cosmetic skin lightening cosmetics among traders in Lagos, Nigeria" *West Afr J Med* 2002; **21** (1): 51-55.

11- Petit A et al. "Skin lightening and its complications among African people living in Paris" *J Am Acad Dermatol* 2006; **55** (5): 873-878.

12- Petit A "Prise en charge des complications de la dépigmentation volontaire en France" *Ann Dermatol Vénérol* 2006; **133**: 907-916.

13- Mahé A et al. "Skin diseases associated with the cosmetic use of bleaching products in women from Dakar, Senegal" *Br J Dermatol* 2003; **148**: 493-500.

14- Mahé A et al. "Systemic complications of the cosmetic use of skin-bleaching products" *Int J Dermatol* 2005; **44** (suppl. 1): 37-38.

15- Prescrire Rédaction "Les crèmes "éclaircissantes"" *Rev Prescrire* 1989; **9** (89): 393-394.

16- Prescrire Rédaction "Spécialités à base de corticostéroïdes non associés disponibles en France" *Rev Prescrire* 2000; **20** (202): 4.

17- Madhogaria S and Ahmed I "Leucoderma after use of a skin-lightening cream containing kojic palmitate, liquorice root extract and mitracarpus scaber extract: clinical dermatology concise report" *Clin Exp Dermatol* 2010; **35** (4): e103-e105.

18- AFP "Lancement à Paris de la première campagne sur les dangers du blanchiment de la peau". www.afp.pressedd.com accessed 4 November 2009: 2 pages.

19- Prescrire Rédaction "Attention aux usages détournés. Retrait du marché des crèmes contenant du chlorure de mercure" *Rev Prescrire* 1987; **7** (65): 217.

20- "Arrêté du 5 February 2009 modifiant l'arrêté du 6 Février 2001 fixant la liste des substances qui ne peuvent entrer dans la composition des produits cosmétiques" *Journal Officiel* du 13 February 2009: 3 pages.

21- Prescrire Rédaction "Hydroquinone dans un masque cosmétique" *Rev Prescrire* 2005; **25** (267): 822.

22- "Arrêté du 6 Février 2001 fixant la liste des substances qui ne peuvent être utilisées dans les produits cosmétiques en dehors des restrictions et conditions fixées par cette liste" *Journal Officiel* du 23 February 2001: 9 pages.

23- Afsaps "Cosmétovigilance: bilan des effets indésirables déclarés à l'Afsaps en 2009". www.afsaps.fr accessed 26 March 2010: 9 pages.

24- Mahé A et al. "Complications dermatologiques de l'utilisation cosmétique de produits dépigmentants à Bamako (Mali)" *Ann Dermatol Vénérol* 1994; **121**: 142-146.

25- Prescrire Editorial Staff "Adverse effects of cannabis. Inform psychologically vulnerable patients of the risk of serious, dose-dependent disorders" *Prescrire Int* 2011; **20** (112): 18-23.

26- "Hydroquinone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 4 pages.

27- Ly F "Aesthetic problems associated with the cosmetic use of bleaching products" *Int Journal of Dermatol* 2007; **46** (suppl.1): 15-17.

28- Prescrire Editorial Staff "Drug-induced photosensitivity" *Prescrire Int* 2009; **18** (103): 208-211.

29- Raynaud E et al. "Dépigmentation cutanée à visée cosmétique. Enquête de prévalence et effets indésirables, dans une population féminine sénégalaise" *Ann Dermatol Vénérol* 2001; **128**: 720-724.

30- "Effects on immune response". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 1 page.

31- Prescrire Editorial Staff "Hypertrichosis in children treated with steroids" *Prescrire Int* 2008; **17** (97): 204.

32- Prescrire Rédaction "hydrocortisone topique sans

prescription - Dermaspraid démangeaison°, Mitocortyl démangeaisons°. Ni panacée, ni démon" *Rev Prescrire* 2001; **21** (213): 19-23.

33- "Adverse effects of corticosteroids and their treatment". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 2 pages.

34- Caroli UM et al. "Lymphocytic infiltration of the skin Jessner-Kanof after treatment with a hydroquinone-containing bleaching cream" *Arch Dermatol* 2006; **142** (12): 1655-1656.

35- Prescrire Rédaction "Diagnosis and treatment of scabies in 2002" *Prescrire Int* 2002; **11** (61): 152-155.

36- Dieng MT et al "Dermohypodermite bactérienne et dépigmentation artificielle. À propos de 60 cas observés au Sénégal" *Nouv Dermatol* 2001; **20**: 630-632.

37- "Tretinoïn". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 14 pages.

38- Mahé A et al. "Utilisation de produits dépigmentants" *Images en dermatologie* 2010; **3** (1): 32-37.

39- Prescrire Rédaction "Irritations localisées de la peau" *Rev Prescrire* 2008; **28** (299): 673-674 + (300): II de couverture.

40- "Ammoniated mercury" + "Mercury". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 10 pages au total.

41- "Azelaic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 3 pages.

42- "Salicylic acid". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 9 pages.

43- International Agency for Research on Cancer "hydroquinone" 1987. www.iarc.fr accessed 27 September 2010: 29 pages.

44- Ly F et al. "Premiers cas de carcinomes épidermoïdes sur terrain de dépigmentation artificielle" *Ann Dermatol Vénérol* 2010; **137** (2): 128-131.

45- Addo HA "Squamous cell carcinoma associated with prolonged bleaching" *Ghana Med J* 2000; **34** (3): 144-146.

46- Kooyers TJ and Westerhof W "Toxicology and health risks of hydroquinone in skin lightening formulations" *J Eur Acad Dermatol Venerol* 2006; **20**: 777-780.

47- Prescrire Rédaction "1-1. Patients sous anticancéreux (généralités)" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).

48- Prescrire Rédaction "fluticasone dermique-Flixivate". Un Nième dermocorticoïde d'activité forte" *Rev Prescrire* 2003; **23** (238): 245.

49- Sène D et al. "Insuffisance surrénalienne haute symptomatique compliquant l'usage de dermocorticoïdes pour dépigmentation volontaire" *Rev Méd Interne* 2008; **29**: 1030-1033.

50- Bwonda P et al. "Glucocorticoid hypertension due to the use of bleaching skin cream, a case report" *Acta clin belg* 2005; **60** (3): 146-149.

51- Sobngwi E et al. "Adrenal insufficiency and diabetes mellitus secondary to the use of topical corticosteroids for cosmetic purpose" *Ann Endocrinol* 2003; **64** (3): 202-204.

52- Druce M et al. "The pursuit of beauty" *Lancet* 2008; **371**: 596.

53- Mahé A et al. "The cosmetic use of skin-lightening products during pregnancy in Dakar, Senegal: a common and potentially hazardous practice" *Trans R Soc of Trop Med Hyg* 2007; **101**: 183-187.

54- "Meiyrapone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 15 March 2011: 6 pages.

55- Kibukamusoke JW et al. "Membranous nephropathy due to skin-lightening cream" *BMJ* 1974; **2**: 646-647.

56- Karamagi C et al. "Hydroquinone neuropathy following use of skin bleaching creams: case report" *East Afr Med J* 2001; **78** (4): 223-224.

57- Tlacuilo-Parra A et al. "Percutaneous mercury poisoning with a beauty cream in Mexico" *J Am Acad Dermatol* 2001; **45** (6): 117.

58- Prescrire Editorial Staff "Topical retinoids during pregnancy (continued)" *Prescrire Int* 2005; **14** (77): 100-101.

59- Lauwerys R et al. "Prenatal and early postnatal intoxication by inorganic mercury resulting from the maternal use of mercury containing soap" *Human Toxicol* 1987; **6**: 253-256.


60- Prescrire Rédaction "Psoriasis des adultes: des rémissions, mais pas de traitement curatif" *Rev Prescrire* 2005; **25** (266): 751-762.

61- Briggs GG et al. "Hydrocortisone". In "Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk" Lippincott Williams & Wilkins, 2008: 888-890.

62- "Commission Directive 2008/88/EC of 23 September 2008 amending Council Directive 76/768/EEC, concerning cosmetic products, for the purpose of adapting Annexes II and III thereto to technical progress" *Official Journal of the European Union* 24 September 2008: 5 pages.

63- Afsaps - Répertoire des spécialités pharmaceutiques "Any 5%" + "Any 8%" + "Crème des trois fleurs d'orient 5%" + "Leucodine B 10%" + "Crème des trois fleurs d'orient 10%": updated 25 February 2011. www.afsaps.fr accessed 7 March 2011: 7 pages.

64- "Ochronose". In: Garnier M et al. "Dictionnaire illustré des termes de médecine" 30^e éd. Éditions Maloine, Paris, 2009: 618.



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