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**NOMINATION OF CHEMICAL/AGENT/SCIENTIFIC ISSUE FOR TESTING
CONSIDERATION BY THE NATIONAL TOXICOLOGY PROGRAM**

NOMINATING CENTER/OFFICE/BRANCH:

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CHEMICAL/AGENT NAME:

Permanent makeup inks.

CAS NUMBER:

Not applicable. Permanent makeup inks consist of a variety of pigments suspended in a vehicle.

SOURCE OF DRUG/COMPOUND:

The terms “cosmetic tattooing” or “permanent makeup” (*e.g.* micropigmentation) refer to mechanical application of pigmented materials to the area of the eye, lips and face for the purpose of changing the color or appearance of that facial feature. This is a rapidly growing business in the United States becoming mainstream in many sociological circles. The inks and methods used for application of permanent makeup are similar to those used for general body tattooing; however, many manufacturers of inks make the distinction between inks that should or should not be used in the area of the eyes.

The inks used for permanent makeup are widely available in the US. These inks are generally a complex mixture of pigments suspended in a vehicle/diluent which also contains multiple components. While recipes exist for “home-made” tattoo inks and tattooing devices are available on the internet (About.com, 2004a,b; Tattoo FAQs, 2004), permanent makeup is typically applied by a professional. The application of permanent makeup (and tattoos) is regulated as a commercial business in most states, requiring licensing and/or registration by most state health departments. In the United States, regulation of the composition of permanent makeup inks is under the authority of the Food & Drug Administration (FDA). The FDA has considered intradermal permanent makeup to be cosmetics because they are applied to the body for the purpose of altering appearance or promoting attractiveness (FDA, 1994). No pigments are approved by the FDA for use in permanent makeup (FDA, 1994, 2004a), although many pigments have been approved as color additives for use in other FDA-regulated products (Code of Federal Regulations, Title 21, Parts 73, 74, and 82).

MAGNITUDE OF HUMAN EXPOSURE:

Magnitude of exposure

There are currently no published estimates of the number of individuals in the United States who

have received permanent makeup; however, the popularity of this practice and the wide availability of businesses that offer permanent makeup application, suggest the number of individuals with permanent makeup will increase over the next several years.

There have been recent estimates of the number of individuals who have tattoos. A recent survey in Germany indicated that 10% of the population has tattoos (German Federal Institute for Risk Assessment, 2004). A Harris Poll conducted in the United States in July 2003 determined that 16% of US adults have at least one tattoo (Harris Interactive, 2003). Since the US population is approximately 280 million, this poll indicates that as many as 45 million US citizens have at least one tattoo. The poll also indicated that 13% of 18-24 year olds, 36% of 25-29 year olds, and 28% of 30-39 year olds have at least one tattoo.

Pigments in inks used in permanent makeup manufacture

While there have been several publications regarding the chemicals used for coloration in tattoo inks (Lehmann and Pierchalla, 1988; Bäumlner et al., 2000; Timko et al., 2001; Danish EPA, 2002; Cui et al., 2004) little has been published regarding the composition of permanent makeup inks.

Fate of pigments used in tattooing and permanent makeup application

Permanent makeup application involves using a needle or needle assembly to mechanically force pigments through the epidermis into the dermis. The pigment deposited in the epidermis is eventually lost due to differentiation and clearance of epidermal keratinocytes. The pigment deposited in the dermis is either removed by phagocytic cells (neutrophils or macrophages; Gopee et al., 2004a,b) or remains in the dermis providing the makeup color. The fate of pigments removed by neutrophils and macrophages remains largely unknown. There have been reports of tattoo pigments in the lymph nodes of humans (*e.g.*, Dheansa and Powell, 1997; Moehrle et al., 2001; Zirkin et al., 2001), and the tattooing of mice has resulted in the accumulation and persistence of tattoo inks in lymph nodes (Gopee et al., 2004a,b). The effect of long-term exposure of the dermis and lymph nodes to the remaining pigment is not known.

EVIDENCE FOR CENTER/OFFICE CONCERN:

Regulation of permanent makeup inks

There is a paucity of toxicological data on the safety of inks used in this country for permanent makeup. The FDA has not listed (*i.e.* permitted) for use any color additives for injection. A recent event and several publications regarding tattoo inks (see below) have warranted increased concern regarding the lack of toxicological data.

Infection hazard associated with tattooing

The primary hazard regarding the application of permanent makeup is infection. Historically, bacterial and viral infections were the most common complaint associated with the related practice of tattooing (reviewed in Long and Rickman, 1994). Tattooing is a risk factor for transmission of viral infections (*e.g.*, hepatitis C, HIV) in prison (Loimer and Werner, 1992;

Holsen et al., 1993; Long and Rickman, 1994; Thompson et al., 1996; Hellard et al., 2004). The prevalence of bacterial and viral infections in the general population receiving tattoos is unknown; however, the regulation of permanent makeup application and tattooing by state health departments and the enforcement of good hygiene practices is thought to have reduced this danger.

Adverse reactions to components in permanent makeup inks

Adverse reactions to components of permanent makeup and tattoo inks have been reported; however, no epidemiological studies have been conducted to substantiate cause and effect, or to document the magnitude of the problem. Many of the early reports regarding adverse skin reactions to tattoo inks have been attributed to the use of cinnabar (mercury sulfide; Silverberg and Morris, 1970), chromium salts (Verdich, 1981), cobalt salts (Rorsman et al., 1969), manganese salts (Schwartz et al., 1987), cadmium salts (cadmium sulfide, cadmium selenide; Björnberg, 1963), and aluminum-containing pigments (McFadden et al., 1989). Since many of the current tattoo inks still contain aluminum and cobalt (Timko et al., 2001), it is possible that adverse reactions could still be due to these minerals.

Hazard of tattoos causing misdiagnoses

The misidentification of black tattoo pigment in lymph nodes for metastatic melanoma has been reported by Dheansa and Powell (1997) and Moehrle et al. (2001). It is unknown if the application of permanent makeup would result in a similar diagnostic complications.

Magnetic hazard of iron pigments

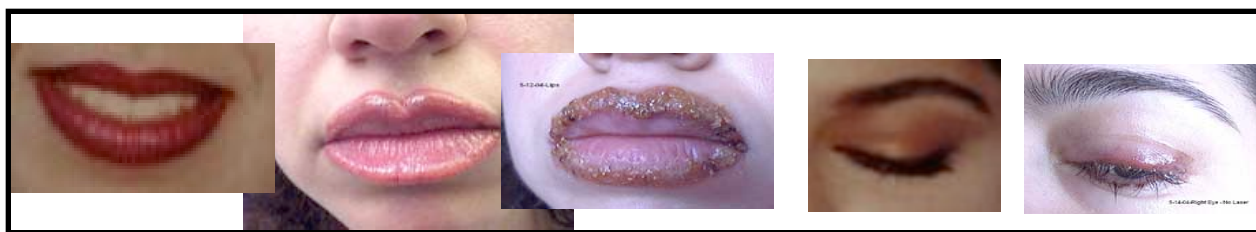
There are some reports of intense burning during magnetic resonance imaging of tattooed individuals (Jackson and Acker, 1987; Carr, 1995; Wagle and Smith, 2000). In the latter report (Wagle and Smith, 2000) the authors attribute the burn to the loop design of a specific tattoo as opposed to a generalized phenomenon associated with tattoos containing iron oxide.

Complications associated with permanent makeup (micropigmentation)

There have been reports of adverse skin reactions following micropigmentation or application of permanent makeup. Duke et al. (1998) reported a case where the second application of red permanent makeup (naphthanil red) on the lips of a patient resulted in edematous, erythematous, and crusted lips. Topical steroid treatment for over a year did not completely clear the condition.

Recently, the FDA has been informed of numerous adverse event reports (>50) regarding a permanent makeup product line (Premier True Color Concentrates) manufactured by the Premier Products, in Arlington, TX. These adverse event reports prompted an “FDA talk paper” (FDA, 2004b) to be released in July 2004. The FDA is continuing its investigation into the magnitude of the problems associated with use of these products (a list of the Premier Products’ ink shades that were recalled as a result of the adverse event complaints are listed in Table 1, and available at <http://www.premierpigments.com/tcrecall.ivnu> or <http://www.cfsan.fda.gov/~dms/cos-tat2.html>; FDA, 2004c).

One of the recipients of the Premier Products' permanent makeup has published her story on several Internet sites (Erfan, N.; see images below). The patient complaints are best summarized by quoting from one of the articles *"The swelling didn't really go down and my lips became more irritated until it was obvious that something was wrong. My allergic reaction symptoms consisted of burning, itching, swelling, bumps or so-called 'granulomas', dryness, peeling, bleeding, and the constant formation of yellowish fluids around my eyes and lips that were impossible to completely remove. My lips were sensitive to the touch and my eyes hurt when I blinked. I still can't open my mouth wide enough to floss my teeth and I have to use baby utensils in order to eat. In addition, I still have swollen lymph nodes because I have big lumps under my chin and the sides of my face. At one point, my eyes and lips were infected and I was on antibiotics."*



The images in the above picture are available on-line, published in the article "Permanent make-up tattoos: taboos or time saver?" by Nancy Erfan at <http://www.lucire.com/2004a/0703110.shtml>, and were copied from that site for the purpose of this presentation. The images depict from left to right: **1**, patient's lips prior to permanent makeup application; **2**, swollen lips following permanent makeup application; **3**, lips approximately 1 month after picture 2, and prior to laser treatment; **4**, eye prior to permanent makeup; **5**, eye after reaction to permanent makeup (picture taken at same time as picture 2).

Whether the response of Nancy Erfan is characteristic of the numerous complaints of recipients of Premier Products True Color Concentrates remains to be established; however, the complaints communicated by Nancy Erfan fit the pattern of either an allergenic or photoallergenic response to the pigments used to formulate the inks. Despite extensive efforts, CFSAN has been unable to find toxicological data on the pigments used in these inks. The regulatory responses available to CFSAN have been limited due to this lack of toxicological data.

The Center for Disease Control and Prevention is collaborating with the FDA and is investigating the complaints associated with the use of Premier Products True Color Concentrate permanent makeup inks.

RECOMMENDED STUDIES:

The FDA requires toxicological data to determine the safety of permanent makeup inks. The FDA recommends that studies be conducted to examine the toxicity, phototoxicity, allergenicity and photoallergenicity of permanent makeup inks, including the pigments and/or the solvents or diluents. The experimental approaches used in these studies should allow identification of the allergenic and photoallergenic components of inks (*i.e.* identification of pigments and components

of the vehicle/diluent contributing to toxicity/phototoxicity).

The following toxicological studies are recommended, and will focus on components of the shades of Premier Products that are identified by the Center for Disease Control and Prevention study as causative shades in the cases of adverse reactions to Premier Pigment True Color Concentrate inks. The studies will be limited to the components of the implicated shades in an attempt to identify the etiological agent(s).

(1) In animal studies determine the allergenicity and photoallergenicity of the ink components identified by the Center for Disease Control and Prevention as probable causative agents. The investigation by the Center for Disease Control and Prevention should also suggest the type of immunological reaction that occurred. The specific studies to be conducted will depend on the outcome of the Center for Disease Control and Prevention investigation. For instance, there are four main classifications to allergic reactions to drugs (Gell and Coombs, 1963): Type I, immediate hypersensitivity or anaphylaxis; Type II, antibody-mediated cytotoxic reactions; Type III, immune complex-mediated reactions; Type IV, delayed hypersensitivity. The model used to investigate the possible allergenicity (or photoallergenicity) will need to be delineated since the candidate allergen is deposited into the skin with a tattoo needle. While a classical approach to allergic contact dermatitis such as the local lymph node assay (Dearman et al., 1999; Gerberick et al., 2000; Kimber, 2001) would be useful in determining if the candidate agent elicits contact dermatitis, the assay might not be useful if the candidate agent was introduced by tattooing, which will induce inflammation at the tattoo site and at the local lymph node (Gopee et al., 2004b).

Since tattoo pigment has been reported to be present in lymph nodes, the deposition of pigments in the regional lymph nodes in the animal studies, and any toxicity to the lymph nodes should be addressed.

(2) Determine the *in vitro* toxicity and phototoxicity of the pigments identified in the Premier Products True Color Concentrate products in cells *in vitro* (e.g. mouse 3T3 fibroblasts or keratinocytes) with or without illumination by ultraviolet A (UVA)/visible light. While this approach does not address the immunologic components of the inks, it will determine if any of the ink pigments are potential photosensitizers. This information will augment the data derived in approach, and if correlative with the *in vivo* data, could serve as a short-term *in vitro* screen for future products.

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Table 1
Shades of Premier True Color Concentrates that were Recalled^a

Areola Highlighter	Light Pink Areola	Pink Areola	Dark Pink Areola
Light Natural Areola	Natural Areola	Dark Natural Areola	Light Brown Areola
Brown Areola	Dark Brown Areola	Light Ebony Areola	Ebony Areola Dark
Ebony Areola	Sheer Bronze	Bliss	Cherry Cheek
Half Naked	Peach Glow	Dark Taupe Shadow	Taupe Mist
Taupe Halo	Taupe Smudge	Antique Pink	Cherry Red
Spiced Cider	Hot Fuchsia	Blush	Hot Coral
Peaches and Creme	Pink Passion	Poetic Wine	Dark Brown Creme
Brown Crème	Tropical Passion	Electric Plum	Cherrywood
Indian Summer	Chestnut	Dark Pecan	Black Fudge
Light Brown Creme	Scarlet	Black Velvet	Wheat
Ash	Khaki Creme	Baby Blue	Purple Slate
Electric Blue	Rich Raspberry	Violet Smoke	Dark Cherry Red
Crimson	Autumn Sunset	Spiced Nude	Dark Chestnut
Light Wheat	Electric Violet	Dark Wheat	Light Sandalwood
Dark Sandalwood	Cognac	Light Brown Suede	Chocolate Spice
Dark Smoke	Chocolate Mauve	Double Fudge	Black Suede
Double Dark Fudge	Chocolate Raspberry	Chocolate Kiss	Rosewood
Mochaccino	Plum	Flaming Red	Dark Brown Suede
Copper Kiss	Black Chestnut	Double Black Fudge	Indigo Teal
Toasted Smoke	Bright Blue	Cobalt Blue	Emerald Green
Iced Spice	Blue Slate	Mocha Mauve	Dark Autumn
Autumn	Light Autumn	Warm Blonde	Chocolate Cinnamon
Dusty Rose	Chocolate Ruby	Dark Champagne	Champagne
Light Champagne	Dark Ash	Ash	Light Ash
Caramel	Light Caramel	Mahogany	Cotton Candy
Spice	Electric Fuchsia	Warm Blush	Spiced Melon
Evergreen	Sandalwood	Light Pecan	Pecan
Sage	Chocolate Orchid	Purple Passion	Teal
Dark Fudge	Black Brown Suede	Fudge	Black Slate
Babies Breathe	Burgundy Wine	Candied Raisin	Rich Russet
Blue Bonnet	Double Black Magic	Soft Smoke	Coffee Bean
Naturally Nude	Electric Orchid	Chocolate Grape	Toasted Almond
Rustic Rose	Sienna	Brown Suede	Cool Blonde
Blonde Taupe	Umber	Dark Umber	Black Umber
Beautiful Brown	Lip Highlighter	Dark Brown Sugar	Toasted Taupe

Table 1 (continued)
Shades of Premier True Color Concentrates that were Recalled^a

Black Magic	Dark Caramel	Light Porcelain	Porcelain
Buff	Ivory Crème	Shell	Light Beige Creme
Beige Crème	Dark Beige Creme	Cool Beige	Dark Cool Beige
Light Suntan	Suntan	Dark Suntan	Light Bronzing Creme
Bronzing Creme	Dark Bronzing Crème	Honey Bisque	Dark Honey Bisque
Honey Brown	Chocolate Honey	Dark Chocolate	White Linen
Tangerine	Lemon Creme	True Red	Orange Creme
Black to Brown Eyeliner Corrector			
Blue to Black/Brown Corrector			
Orange/Peach Eyebrow Corrector			
Purple Lip Corrector			
Gray/Ash Eyebrow Corrector			
Green Eyebrow Corrector			
Blue Lip Corrector			
Purple Eyebrow Corrector			
Pink Eyebrow Corrector			
Blue Eyebrow Corrector			

^a The products listed in this Table are the True Color Concentrate shades recalled by Premier Products, and listed in the order listed at the Premier Products website <http://www.premierpigments.com/tcrecall.ivnu>