Pigment or Poison? A Comprehensive Look at Tattoo Ink in the U.S.

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I. INTRODUCTION AND BACKGROUND

Within the past decade there has been an increase in the popularity of tattooing. The image of tattoos being part of a rebel lifestyle is over. According to a Harris Poll, three in ten Americans have tattoos and the number of people with two or more tattoos has doubled in the past seven years (Breuner, Levine et al. 2017). Today, people of all ages and all personalities are getting tattoos for different reasons. Surveys of college students consistently show that about 20 to 25 percent of students have tattoos (Desai 2018). The numbers for young adults between ages 18 to 35 is slightly higher, ranging from 22 to 47 percent.

In the tattooing process, a needle pierces the skin and delivers ink into the dermis through that small wound. Tattoo ink is a mixture of large and small particles of pigment. The immune system recognizes ink as a foreign substance invading the body and uses macrophages to engulf and remove the particles. However, the ink particles that are too large for the macrophages to engulf remain. These large pigment particles stay in the dermis and become the permanent tattoo (Wood-Black 2017) . The particles engulfed by macrophages travel with the macrophage and may persist in sites distant from the tattoo.

Tattoo ink is composed of three categories of chemicals: chemicals responsible for the tattoo's color, chemicals that assist in its dispersal within the ink bottle and preserve the coloring agent before injection (generally listed under "carriers"), and chemicals that are considered contaminants. These contaminants arise from the ink manufacturing processes or from secondary reactions between chemicals composing the tattoo ink (Jacobsen 2012) .

To produce a diverse range of tattoo ink colors, many types of organic and inorganic compounds have been used. The most common tattoo color is black which arises primarily from the use of paracrystalline carbon (carbon black). The paracrystalline carbon used to produce black ink is often supplemented by iron oxides and titanium dioxide to produce different shades of black (Laux, Tralau et al. 2016). Recognized contaminants of carbon black include a group of

carbon-based molecules called polycyclic aromatic hydrocarbons, some of which have been shown to cause cancer (Jacobsen 2012). Several common colors of tattoo ink, including red, blue, and green, contain organic compounds and heavy metals to produce the coloration. Heavy metals used in non-black pigments include copper, titanium, barium, antimony, vanadium and aluminum (Jacobsen 2012). In addition, potentially toxic elements such as chromium, lead, nickel, cadmium, mercury and arsenic have been identified as intentional pigmentary elements in some inks and as contaminants in others (Laux, Tralau et al. 2016) Moreover, organic compounds used as pigments include phthalocyanines and azo compounds, which can be a source of chemical structures known as primary aromatic amines, molecules that can cause cancer through their ability to react with biological molecules like DNA, RNA, and proteins (Jacobsen 2012, IARC 2010).

In addition to chemical pigments, tattoo ink includes dispersant and preservant chemicals. Dispersants are chemical compounds used to separate or disperse the pigments throughout the dermis. Some include glycerin, isopropanol, ethyl alcohol and methanol (Jacobsen 2012) . Preservants are used to preserve the organic pigment compounds and to maintain sterility of the ink. Common preservants in use include benzoic acid, methylisothiazolinone, benzisothiazolinone, formaldehyde, and phenol (Jacobsen 2012, Laux, Tralau et al. 2016). The purpose of the preservatives is to maintain the sterility of the pigments in storage. However, the chemicals involved in preservation and dispersal are often as unregulated as the pigmentary compounds in the ink.

In the United States, most aspects of the tattoo industry are subject to minimal regulation and governmental oversight. Inks used in tattooing are considered to be cosmetics by the U.S. Food and Drug Administration, which should technically be subject to pre-market approval (US Food and Drug Administration 2018). However, the FDA has not exercised this authority over tattoo inks, and the industry is thus largely self-regulated (Dixon 2006). Additionally, as manufacturers are only required to disclose the ingredients of "consumer goods," and most tattoo inks are sold directly to professional parlors, the ingredients of tattoo inks do not have to be listed on product labels. In our research, we were unable to find any indication that ink manufacturers are required to disclose information on the exact ingredients in their products. Though manufacturers must provide Material Safety Data Sheets to tattoo parlors, in order to protect latex-gloved tattoo artists, paradoxically this requirement confers no protection to the consumer into whose skin the ink will be injected into (OSHA). Consequently, it is difficult for anyone to know the actual risks associated with getting a tattoo.

The FDA's hands-off approach with tattoo ink regulation often leaves regulation of tattooing businesses to individual state governments. Some states require that tattoo artists obtain their licensing from local or state health departments (Dixon 2006). In the past, attempts have been made to restrict the practice of tattooing to licensed physicians. However, such regulations have been challenged and removed. For instance, a court ruling in Massachusetts in 2000 held that the right to have a tattoo is protected by the First Amendment, and struck down the statutory

requirement that only physicians be allowed to provide tattoos (ACLU 2000). Many states do not require any formal licensing of tattoo artists or parlors. In a recent review, U.S. states were categorized based on regulations for the following (Yes/No) criteria: *Educational Standards for [tattoo] artists for infection control, Disclosure of potential risks to consumers, Standards for sterile technique, Tattoo artists required to wear gloves, Hepatitis B vaccine offered to tattoo artists, Artist health screening, including for hepatitis B, required, Artists required to report adverse events.* Arizona was one of only 4 states (along with Idaho, Utah and Wyoming) to have no requirements under any of these safety categories (Haugh, Laumann et al. 2015). Instead, in states such as Arizona, state law regulates who can *receive* a tattoo (only adults 18 and older, or parent-accompanied minors), and where a tattoo can be administered (only in legally allowed businesses per 13 Arizona Rev. Stat. Sec. 3721).

II. RISKS

Tattoo injection comes with the risk of adverse effects. When an individual acquires a tattoo, not only are they at risk from the immediate procedure, but also from unanticipated long-term effects of the chemicals involved in tattoo ink reacting with their body. Research on the occurrence and mechanism of adverse effects from tattoos is relatively limited, but does include several reports associating tattoos with adverse health outcomes. At least in some individuals, it appears that tattoos can damage health.

When ink is injected directly into the dermis (the deep layer of the skin) short-term pain, redness and swelling are almost guaranteed. These processes occur because of the physical damage done by the many injections, by the inflammatory immune response to that damage, and to the introduction of foreign chemicals. These immediate effects are common, well-documented, and often resolve in a matter of a few weeks. Microbial infection is always a risk in any procedure involving skin penetration, and tattoos are no exception. The focus of this report, however, is to shed light on potential long-term, adverse health effects from the chemical ingredients of tattoo ink following their injection into tattoo recipients. Surveying the scientific literature, we group health risks into three categories: immune system reactions, skin cancer, and diagnostic interference.

IIa. IMMUNE/ALLERGIC CONSEQUENCES

While short-term inflammation is a normal reaction to tattoo ink injection, studies have shown that an inflammatory-immune-allergic response to tattoos can occur months or even years after the procedure. This response manifests itself through numerous conditions, including an eczema-like skin inflammation. Immune reactions to tattoos can result in plaque-like (lichenoid) or firm, nodule-like (granulomatous) areas of inflammation and proliferation of skin and immune cells (McFadden, Lyberg et al. 1989). The onset of these reactions can range from weeks to years and these conditions may mimic skin cancer carcinomas and require skin biopsies to fully

diagnose (Malki, Onnis et al. 2017). Medical terms for these conditions include cutaneous pseudolymphoma, lichen planus, vasculitis, and sarcoidosis.

Cutaneous pseudolymphoma is a response that results in proliferation of immune cells and inflammation at the site of the affected area (Marchesi, Parodi et al. 2014). This reaction includes papules, nodules, and plaques that may form at the tattoo site. This reaction can occur from an allergic mechanism of hypersensitivity to the ink itself or to combined effects of ink and exposure to sunlight.

Lichen Planus is another condition characterized by immune cell infiltration (Aguayo-Leiva, Gonzalez-Garcia et al. 2011). This reaction has been found to occur in association with various ink colors, but is more common in red inks. Some reports indicate that the association with red inks may be due to the mercury-containing pigments. Patients who have underlying conditions such as sarcoidosis, lupus, lichen, etc.. may see their condition reactivated or flare up due to tattooing. Immune system reaction to the embedded "foreign bodies" of tattoo ink particles has been suggested to trigger the disease and may take weeks to decades to trigger (Piccinini 2016) .

Vasculitis, an inflammation of blood or lymph vessels has been documented in four cases involving tattoo ink, with the symptoms appearing over a variable period following the tattoo, from 10 days to 28 years after tattooing (Piccinini 2016) .

Sarcoidosis is an inflammatory autoimmune disease (the body's immune system inappropriately attacking itself) that can be triggered by tattoo ink injection, an effect first reported in the 1950s (Simunovic and Shinohara 2014). There is evidence to suggest that in nearly three-quarters of the cases of a local tattoo sarcoidosis reaction, the patient will subsequently develop systemic sarcoidosis affecting organs distant from the tattoo site (Antonovich and Callen 2005).

Heightened concern for the impact that tattoo inks can have on the immune system comes from work by scientists from Germany and the European Synchrotron Radiation Facility. These researchers have discovered that pigments and toxic impurities from tattoo inks may also travel from the tattoo site to lymph nodes (small immune system organs distributed throughout the body). Students in our course conducted a Tucson-Berlin tele-meeting with Dr. Ines Schreiver, lead author on this work. She explained that their group, studying cadavers who had been tattooed for varying durations prior to death, measured toxic particles that originated from tattoos in lymph nodes distant from the tattoo. In some cases, the lymph nodes become colored with the injected tattoo ink color as the pigment particles were engulfed by immune cells and transported to local lymph nodes. The research group is concerned that the movement of these nanoparticles may lead to chronic enlargement of the lymph nodes, and could potentially lead to other clinical problems such as a cancer, but more research is necessary in order to understand the movement of nanoparticles (Schreiver, Hesse et al. 2017). The researchers explained that they are unable to classify which tattoo inks contain these impurities as they only have access to a regulated white (approved) and black list (banned) for pigments that are approved and pigments that are cause

for concern. Pigments that are not found on this list have no regulations imposed but are still allowed to be used until they become cause for concern or are tested thoroughly enough to be added to the lists.

IIb. SKIN CANCER AND RELATED LESIONS

Tattoo inks contain substances that are classified as mutagenic (induce changes in the DNA code) and/or carcinogenic (cancer causing). Reported cases of tumors developing in tattooed areas include the skin cancer categories of squamous cell carcinoma and keratoacanthoma, as well as pseudoepitheliomatous hyperplasia, a non-cancerous proliferation of skin cells. Some evidence suggests that among tattooed individuals, these lesions appear most often in tattoo areas containing red ink (Piccinini 2016) .

In some individuals, wart-like plaques forming in tattooed areas can indicate the presence of pseudoepitheliomatous hyperplasia (PEH). There is a reported association of PEH with red and purple inks in particular (Breza, O'Brien et al. 2013). While this condition is benign, it often anatomically mimics squamous cell carcinoma, confusing the diagnosis between a benign condition and a cancer that needs to be treated aggressively (Chakrabarti, Chakrabarti et al. 2014). Squamous cell carcinoma is a form of skin cancer that develops in squamous cells which make up the middle and outer layer of the skin. While squamous cell skin cancer is usually not life-threatening, it can metastasize to other areas in the body if left untreated. Over the past 40 years, 23 cases of squamous cell carcinoma have been reported in tattooed areas of skin (Piccinini 2016). Relying on the number of literature-reported cases to estimate risk in the total population can be problematic. Nevertheless, 23 cases of tattoo-associated squamous cell carcinoma is a very small number relative to the total number of tattoos in the population. Researchers from the University of Copenhagen demonstrated that mouse skin tattooed with red ink was more prone to squamous cell carcinoma development from UV irradiation compared to non-tattooed skin exposed to UV irradiation, suggesting that red ink may enhance the ability of UV irradiation to cause skin cancer (Lerche, Heerfordt et al. 2017). While some inks do contain carcinogenic and mutagenic compounds, cancer is a multifactorial disease with many causes and modifying factors that can appear years or decades after causative exposures.

Keratoacanthomas (KA) are low-grade skin cancers arising from hair follicles. In a 2009, study, researchers reviewed all skin cancer cases at their institution over an 8 year period that included a skin cancer within a tattoo. Eight patients with tattoo site-KA were identified. One patient had four separate KA arising from two tattoos. Of the total number of KA biopsied, 82% arose from areas of red ink (Fraga and Prossick 2010).

Taken together, research suggests that tattoos may possibly increase the risk for cancer, though the actual magnitude of the risk is unknown. Given the extremely large number of tattoos and the relatively small number of reported tattoo-associated skin cancers, the skin cancer risk from tattoos is unlikely to be extremely large. Nevertheless, the lack of high-quality data makes the magnitude of the risk unknown.

IIc. TATTOO INTERFERENCE WITH MEDICAL DIAGNOSTICS

Two general areas of concern regarding interference of tattoos with medical diagnostics have been highlighted in the medical literature. Both relate to the accumulation of tattoo ink in lymph nodes receiving drainage from tattooed skin, a phenomenon we described previously in this report.

For women with breast cancer it is not uncommon for physicians to identify the most important lymph nodes to test for metastasis by injecting dyes into the affected breast tissue, and looking for the accumulation of that dye in lymph nodes. Those would be the lymph nodes (called "sentinel lymph nodes") more likely to have been infiltrated by breast cancer cells during their spread to distant sites; thus those are the lymph nodes that should be closely examined for the presence of cancer cells. Prior tattooing in areas of skin that have lymphatic drainage to lymph nodes that also drain breast tissue can result in lymph nodes that are colored by tattoo ink, confounding the procedure used for breast cancer metastasis detection (Schlager, Laser et al. 2008, Soran, Kanbour-Shakir et al. 2014).

Malignant melanoma, a skin cancer with a high mortality rate unless detected early, also undergoes metastasis to lymph nodes. Since the cancerous melanocytes are often dark-colored due to the presence of the melanin pigment that those cells normally produce, the presence of dark colored regions of draining lymph nodes is sometimes used as an indication of metastasis in malignant melanoma. The presence of dark colored tattoo ink in the lymph node is an obvious confounder in this surgical diagnostic technique and has been reported in the literature (Manganoni, Sereni et al. 2014).

III. CONCLUSIONS

More than 50 million Americans over the age of 18 have at least one tattoo. The amount of pigment in an average sized tattoo is about 460.5 mg. Assuming that 50 million Americans have only one tattoo of average size, then over 51,000 pounds of pigment have been injected into their bodies collectively, a weight equivalent to the size of 5 adult African elephants. Despite the massive scale of internalized human exposure to tattoo inks, we know very little about their health risks. This report was an effort to highlight some of the health effects that have been associated with tattoos, and it is important to recognize that the health effects described here are only a subset of the spectrum of problems associated with tattoos.

For a procedure performed on a daily basis that is comparable to receiving a shot at a doctor's office, the current regulations imposed on tattoo ink are shockingly limited. Almost every aspect of our lives is regulated in some manner by government agencies−from the food we eat to the cars we drive. Yet, when it comes to injecting various liquid chemicals into our bodies, the government has largely decided to adopt a "hands-off" approach. Given the lack of information available to the public on the primary compounds that compose the pigments and the secondary "carrier" compounds used as solvents and preservatives in tattoo ink, the minimal

regulations are simply not satisfactory. It is critical that the ingredients of substances injected into millions of people should be clearly declared, and should have their safety established. Finally, all of the related information should be made available to prospective tattoo recipients as part of a proper informed consent process.

Not only are the regulations limited, the research that has been conducted on potential health effects that result from injection of tattoo ink has limitations. Many of the studies are reliant on data collection methods such as surveys or requests for interviews. While these techniques can identify potential health risks, they are typically poor at quantifying the actual risk. In a survey of individuals with tattoo-related problems there may be little participation from participants who have never received tattoos (who may be having the same type of problem in the absence of a tattoo). As a result, despite the very large number of tattooed people, we do not have an accurate estimate of the true risk of tattoo-related health effects. Ideally, studies should follow tattoo recipients as well as comparable individuals without tattoos to evaluate incidence of disease over the long term. The experimental design has to be able to differentiate between the effects of the tattoo ink and the effects of other confounding risk factors that may have been involved in an adverse effect that is suspected to be caused by tattoos. These studies will be expensive and they will not produce immediate results. But consider the fact that 50 million Americans have already participated in an uncontrolled and unregulated medical procedure in which virtually unknown liquids that persist for decades have been injected into their bodies. The benefit from knowing more about the associated risks seems worth the cost of acquiring that knowledge.

Whatever the reason an individual has for getting a tattoo, the important thing is that the tattoo recipient is as well-informed as possible about the process and the risks that come along with tattoos and is capable of consenting to the procedure. The intent of this study is not to tell people whether or not to get a tattoo, but rather to summarize our current understanding of some of the risks involved so that an informed decision is possible.

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