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Tattooing: immediate and long-term adverse reactions and complications

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Tattooing has become a popular global trend in industrialised countries, with the highest prevalence rates of up to 30–40 % in the adult population younger than 40 years. Common tattoo inks may contain heavy metals, polycyclic aromatic hydrocarbons, and primary aromatic amines, toxic if exceeding permissible limits. It is estimated that about 14.36 mg of ink is injected per cm^2 of skin, at a depth of 1–3 mm. The injected pigment is internalised by neutrophils, fibroblasts, and macrophages or dendritic cells. About 60–90 % of the pigment is then transported to the lymph nodes via the lymphatic system and to other organs, such as the liver, spleen, and lung, through blood. Adverse reactions can be immediate (irritation, infection, inflammation of the skin), delayed (hypersensitivity reactions), and can result in long-term complications (fibrosis, granulomatous changes, systemic inflammation, and sometimes malignant diseases such as lymphoma). Pigments in tattooed skin can be identified by skin biopsy, chemical imaging, and histochemical and immunohistochemical analyses. Harmful effects of tattoo inks have been investigated *ex vivo*, *in vitro*, *in vivo*, and recently *in silico*. Studies in humans mainly refer to case reports, but there are no epidemiological studies that would evaluate the potential links between tattoos and cancer or other disorders. As the safety of people getting tattoos primarily depends on the quality of tattooing products, it is necessary to create a general regulatory framework.

KEY WORDS: fibrosis; granulomatous changes; hypersensitivity reactions; infection; inflammation of the skin; irritation; malignant diseases; systemic inflammation; tattoo ink

Tattooing is an invasive procedure by which tattoo ink is injected into the skin or mucosa. Archaeological research shows that tattooing is as old as human history. Tattoos have been discovered on numerous mummies in many countries, and one of the oldest examples is a tattoo on an ancient mummy known as Ötzi the Iceman, dating back to 3,300 BC, found in the Tyrolean Alps in 1991 (1). Tattoos have also been found on Egyptian mummies dating back to around 2000 BC. Ancient Romans tattooed slaves and criminals. In ancient Israel, tattooing was forbidden, at first probably because of infection, and then for religious reasons (Lev. 19:28). This ban was continued by Christian Europeans until they encountered Native Americans and Polynesians during the era of exploration.

Today, millions of people around the world wear tattoos. Tattooing has become a popular global trend of body art in industrialised countries, prevailing in about 10–20 % of the population in the early 2000s. More than 8 % of the German population aged 14–90 has a tattoo (2). In 2019, the reported prevalence of tattoos among US adults was 30 % (3). Today, tattoos are a major part of mainstream fashion among young people. According to the World Health Organization (WHO), the highest prevalence (30–40 %) is recorded in the in the USA and Europe among adult population younger than 40 years (4).

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Unfortunately, tattoo inks have been reported to cause adverse reactions such as skin inflammations, skin infections, allergic reactions, foreign body reactions, blood-borne diseases, skin reactions to magnetic resonance imaging (MRI), autoimmune diseases, and cancers. This has raised the issue of the quality and safety of tattoo inks and how to regulate it (5, 6).

The aim of this article is to give a brief review of tattooing practice and to point out the immediate, delayed, and long-term effects of tattoo inks, including changes in some biochemical parameters.

TATTOO INKS

Ancient tattooing procedures involved rubbing pigment into incisions in the skin or manually applying ink to the skin using a sharp tool. Dark pigments were obtained from plant and animal materials. Today, tattoo inks are a mixture of inorganic and organic pigments, including precursors and by-products of pigment synthesis and various additives (7). Average tattoo pigment particle size may vary from about 100 nm to about 1 μm (8). Most current tattoo inks contain carbon-based pigments obtained from natural or synthetic minerals (9, 10) and are injected into the skin with a

tattoo machine through needles. Some Asian and African cultures use a natural reddish-brown dye obtained from the henna plant (*Lawsonia inermis*) (11). Unlike tattoo inks that remain in the dermis (the middle layer of the skin between the epidermis and the subcutis, rich in blood and lymphatic vessels) forever, a henna tattoo begins to fade two to three days after application, and can last up to three weeks on the skin.

Table 1 lists some pigments contained in tattoo inks by colour. This colour depends on the composition and amount of certain heavy metals (12, 13–15). In addition to heavy metals, tattoo inks contain carbon black, phthalocyanines, polycyclic aromatic hydrocarbons (PAHs), and the primary aromatic amine (PAA) *p*-phenylendiamine. All these substances can have a toxic effect, if their levels in the ink exceed the permissible limits (9, 16–18).

In addition to pigment, tattoo inks contain solvents/carriers, whose task is to keep the pigment evenly distributed in a fluid, to prevent clumping, and to inhibit the growth of pathogenic microorganisms (19, 20). The most common and safest among them are ethanol, distilled water, methanol, propylene glycol, glycerine (glycerol), and isopropyl alcohol (21). Harmful carriers include benzisothiazolinone (a skin irritant), formaldehyde (classified as a carcinogen), or ethylene glycol (antifreeze) and glutaraldehyde, which are toxic.

Furthermore, tattoo inks differ in quality, especially the professional ones (brands) from cheap tattoo inks of unknown composition, which contain even more hazardous substances than professional inks (22). Tattoo artists and people who want to get a tattoo should be aware of these facts.

Distribution of tattoo ink after injection into the skin

During tattooing, about 14.36 mg of ink is injected into the skin per cm^2 at a depth of 1–3 mm (23). About one third ink remains in the epidermis (the outer, visible layer of the skin), and about one fourth migrates to the regional lymph nodes through lymph or to other organs through blood (22). While epidermal pigment is eliminated by desquamation, dermal pigment is internalised by neutrophils, fibroblasts and macrophages or dendritic cells.

The injury sustained by needle puncture is followed by inflammation (within 10 days), tissue formation (within three months), and tissue remodelling (within one year). Inflammation involves haemostasis (the process that stops bleeding) and the activity of neutrophils and macrophages. Neutrophils are the first cells that react to skin needle damage, blood loss, and inflammation. These cells are present for about 24 hours, and then they are eliminated. Macrophages, as the main phagocytic cells, ensure the lifelong presence of pigments in the dermis due to continuous successive cycles of pigment release and recapture by newly created macrophages (14). Finally, a small amount of pigment is entrapped and immobilised by connective tissue fibroblasts (11). Over time, 60–90 % of the applied pigment is transported via the lymphatic system or blood to the lymph nodes and other organs, such as the liver, spleen, and lung (Figure 1).

Animal research has shown that, besides passive transport with lymph and blood, tattoo pigment is actively transported to the lymph nodes and then to various organs by dendritic cells, neutrophil granulocytes, and macrophages (18).

Research on mouse macrophage cell culture showed that cobalt and zinc pigments have a moderate intrinsic pro-inflammatory effect (11), which permanently affects the immune system by reducing the ability to defend against bacterial skin infections (reduced phagocytosis) and by weakening the ability to recognise cancer cells. Such chronic inflammation is a consequence of increased nitric oxide (NO) and decreased tumour necrosis factor (TNF) levels during infection. The possibility of skin recovery is also reduced due to lower macrophage migration caused by monocyte chemoattractant protein-1 (MCP-1) deficiency (14).

Research on tattoos older than 40 years shows that ink particles remain in the deep dermis and local lymph nodes. According to the WHO data from animal experiments, black and red tattoo ink

Table 1 Pigments contained in tattoo inks

Colour	Pigments	Ref.
Black	Iron oxide (Fe_3O_4), iron oxide (FeO), carbon, logwood	9, 15, 17, 18
White	Titanium dioxide (TiO_2), zinc (Zn), lead (Pb)	9
Brown	Ochre (an ancient pigment), iron (Fe)	9, 11
Red	Cinnabar (HgS), cadmium red (CdSe), iron oxide (Fe_2O_3), napthol-AS pigment ($C_{26}H_{22}N_4O_4$), quinacridone ($C_{20}H_{12}N_2O_2$), azo compounds	9, 11
Purple	Cobalt (Co), manganese (Mn)	17, 18
Orange	Disazodiarylide ($C_{34}H_{30}Cl_2N_6O_4$) and/or disazopyrazolone ($C_{32}H_{24}Cl_2N_8O_2$), cadmium selenide sulphide (Cd_2SeS)	17, 18,
Yellow	Cadmium sulphide (CdS), azo compounds, lead (Pb)	17, 18
Brown	May contain iron oxides, e.g., ochre, iron (Fe)	17
Green	Cobalt oxide (CoO) or chromium oxide (Cr_2O_3), phthalocyanine green ($C_{32}Cl_{16}CuN_8$), a mix of cobalt chromate ($CoCr_2O_4$) and lead chromate ($PbCrO_4$)	17, 18
Blue	Aluminium cobalt oxides ($Al_2Co_2O_5$), copper phthalocyanine ($C_{32}H_{16}CuN_8$), nickel (Ni)	16, 17, 18

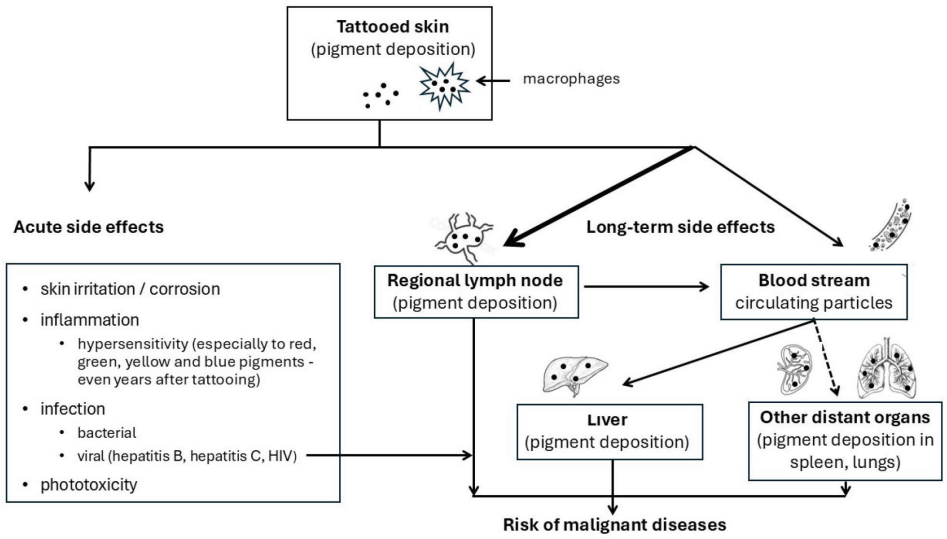

Figure 1 Distribution of tattoo pigments after injection into the skin. HIV – human immunodeficiency virus

particles reach the liver, and titanium dioxide (white pigment) reaches the liver, spleen, and lung (4).

ADVERSE EFFECTS AND COMPLICATIONS OF TATTOOING

In view of the distribution discussed above, tattoo pigments can remain in the skin for life, some PAHs in particular. If present above permissible limits, many components of tattoo inks can have a toxic effect and cause various diseases, including cancer. Among these hazardous components are PAAs, PAHs, heavy metals, and their compounds. PAAs can form inside the skin as a result of reductive cleavage of organic tattoo azo pigments – a process that takes place under the influence of UV radiation. Lead, mercury, cadmium, beryllium, and arsenic can cause cardiovascular, gastrointestinal, lung, liver, kidney, endocrine, and bone diseases. Cadmium, compounds of cadmium, cobalt sulphate, as well as soluble cobalt salts and carbon black can also cause cancers (24). Adverse effects and complications of tattooing can be acute (immediate), delayed, and long-term, as shown in Table 2.

Immediate and delayed adverse effects

Some persons undergoing MRI may experience pain and a subjective sensation of burning at the tattoo site (25). Transient skin irritation followed by inflammation and infection due to skin damage are the main immediate/acute adverse effects of tattooing. Inflammation includes local oedema, pruritus, papules, or nodules at the tattoo ink injection site.

Bacterial, viral, and rare mycotic infections can affect the surface or the deeper layer of the skin. Bacterial infection can appear in the first few days after tattooing, viral infection develops after a few weeks or months, and mycotic infection becomes visible after a few months. The most common bacterial infections are those with the *Staphylococcus*, *Streptococcus*, *Pseudomonas*, and *Clostridium* species and nontuberculous mycobacteria (26). Primary infections may result from poor hygiene standards during tattooing, and secondary infections may result from poor skin care during healing (27). Also, the tattoo ink itself can be contaminated with various pathogenic microorganisms.

Possible complications of tattooing are acute contact dermatitis, hypersensitivity reactions, chronic inflammatory reactions, or papulo-nodular reactions (28). In the case of poor hygienic conditions during tattooing, there is a risk of infection with blood-borne viruses such as hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV). The disease can develop within several weeks to several months.

Histological exam of skin inflammation most often shows fibrosis followed by granulomatous reactions, lichenoid reactions, epithelial hyperplasia, psoriasis, pseudolymphomas, and spongiotic reactions (11, 28). It can also show foreign body giant cells (pigment), histiocytes, lymphocytes, granulocytes, and eosinophilic granulocytes, while immunohistochemical analysis can show a subpopulation of cells such as CD^{3+} T cells. It often takes an experienced cytologist to distinguish pigment particles from melanin in the histological preparation.

The most common adverse effects of tattooing are allergic and granulomatous skin reactions. Hypersensitivity reaction most often occurs to red, black, and green pigments and their combinations. According to some reports (29, 30), coloured inks, especially the red ones, are far more often associated with adverse effects than black inks. Before tattooing, it is recommended to test the person for hypersensitivity by applying coloured pigment on a small area of the skin. This will lower the risk of a hypersensitivity reaction (11). Allergic reactions that occur only a few days after tattooing indicate that the patient was already sensitised to some component of the tattoo ink (28). Allergic reactions can also develop during or after the wound has healed, depending on which immune cells have

Table 2 Immediate, delayed, and long-term adverse effects and complications of tattooing

Adverse effects / complications	Cause / Clinical features	Onset
Immediate		
Iritation/inflammation	Skin damage, lymphadenopathy	Shortly after tattooing
MRI burn	Pain, subjective sensation of burning	During MRI
Delayed		
Infection		
Bacterial	*Staphylococcus*, *Streptococcus*, *Psudomonas*, *Clostridium* species, nontuberculous mycobacteria, etc.	First few days
Viral	Hepatitis B, C, human immunodeficiency virus, papilloma, and herpes simplex viruses	Weeks to months
Mycotic	Zygomicota	After months
Other		
Allergy	Tattoo ink ingredients (e.g., nickel)	Days / weeks / years
Photoallergic reaction (hives-like reaction)	Tattoo ink with cadmium sulphide; possibly ROS-mediated	After sun exposure
Skin disease in tattooed area	Clinical features: psoriasis, lichen planus, pseudolymphoma, pseudoepitheliomatous hyperplasia	Weeks to years
Long-term		
Idiopathic benign accumulation of inflammatory cells	Cutaneous pseudolymphoma	Weeks to years
Malignant diseases	Carcinoma basocellular, melanoma, keratoacanthoma, lymphoma	Weeks to years

MRI – magnetic resonance imaging; ROS – reactive oxygen species

reacted to which tattoo ink ingredients. In sensitised persons this may take four to twenty days after the first exposure (31). Such delayed allergic reactions, usually of type IV, have been reported upon immunohistochemical analysis which demonstrated the presence of CD^{3+} and CD^{8+} lymphocytes (28). An allergic reaction can also be caused by a henna tattoo, if some colouring agents (additives) are added to natural henna (32).

However, allergy to tattoo ink cannot be reliably diagnosed with patch tests due to poor penetration of the pigment through the skin and its slow haptenisation (the reaction between antigenic hapten and carrier protein to stimulate immune response). In addition, not all tattoo pigments are available as test allergens in the patch test (16).

Long-term effects and complications

Long-term adverse effects depend on pigment colour, i.e., its chemical composition and additives that are an integral part of tattoo inks. Black inks containing iron oxides or carbon can cause chronic inflammation such as granulomatous inflammation or sarcoidosis. Red inks containing mercury, cadmium, or azo compounds can trigger delayed type IV allergy. Blue inks (containing cobalt, nickel, aluminium, or copper compounds or compounds), purple inks (containing cobalt or manganese), or white inks (containing titanium dioxide, zinc, or lead) are also associated with sarcoidosis (10).

Photo-induced reaction has been reported for yellow, red, black, and blue pigments (33, 34) particularly in older tattoos (35). Exposure of tattooed skin to UV radiation or laser light may cause decomposition of tattoo pigment molecules to new, potentially harmful chemical compounds (36).

Long-term effects of tattoo ink include fibrosis and granulomatous changes (formation of nodules and fibrous tissue), which point to a chronic inflammatory response of the skin (37). In addition, tattoo ink can cause systemic inflammation, such as uveitis, arthritis, and enteritis (38).

Another complication can be the development of cutaneous pseudolymphoma. Although its pathogenesis is still unknown, it is believed that through chronic inflammation tattoo pigment triggers polyclonal proliferation of B and T lymphocytes. Fortunately, they seldom become monoclonal and malignant (39, 40). The latest research (41) has shown that cutaneous tumours (squamous cell carcinoma and keratoacanthoma) within tattoos occur most often after red pigment is applied.

Needle or ink-associated infections with HCV and HBV pose a higher risk of developing non-Hodgkin lymphomas and liver cancer, whereas HIV infection has been associated with the development of Hodgkin and non-Hodgkin lymphomas, liver cancer, cervical cancer, and Kaposi sarcoma (7, 11, 42).

Psycho-social complications after tattooing cannot be ignored either. Tattooing is often associated with deviant social behaviour and the consequent negative attitude toward tattooed people (43, 44). Tattooed people sometimes regret having done a tattoo, as they

feel in dissonance with their social environment, and some may even experience depression (3).

Tamez and Özlü (45) also refer to isolated systemic complications of tattooing, such as systemic infections (e.g., acquired immunodeficiency syndrome, HBV, HCV, tuberculosis, sepsis, and endocarditis), neoplasms (melanoma, lymphoma, basal cell carcinoma, and squamous cell carcinoma), psychosocial complications (depression, dissatisfaction, internalised stigma), and other rare complications such as vasculitis, uveitis, and burning after magnetic resonance imaging.

Methods for detection and identification of harmful effects and complications of tattooing

The harmful effects of tattoo inks can be determined *ex vivo*, *in vivo*, *in vitro*, and since recently, predicted *in silico* (Table 3). *Ex vivo* methods investigate the effects of tattoo inks on human cells, such as lymphocytes and monocytes (46) or on animal tissue maintained under optimal conditions that mimic the natural state (*in vivo*) (47).

Several *ex vivo* (histological) and *in vitro* methods have identified enhanced sensitisation and reduced metabolic potential of certain pigments (49, 50). Some studies test tattoo pigment effects on cell cultures and reconstructed human skin (RHS) models (48–50). According to one such study on RHS (48), some tattoo pigments – red, black, and white in particular – are cytotoxic and cause inflammation and the release of cytokines interleukin-1α (IL-1α), interleukin-8 (IL-8), and interleukin-18 (IL-18).

In vivo research on mice has shown that besides the skin, ingredients of tattoo ink can be found in the liver, spleen, kidney, and the lungs (51).

Human studies mainly refer to case reports of harmful effects in people tattooed with different types of inks. Pigment components in tattooed skin can be identified with skin biopsy, chemical imaging techniques such as micro-X-ray fluorescence (μ-XRF), and laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS). The last two methods can accurately identify and quantify iron, nickel, copper, titanium, chromium, zirconium, niobium, and chlorine, as reported by van der Bent et al. (52). The main disadvantage of case reports is that they focus on a single patient or a small number of cases. They may highlight rare and atypical conditions, but may not apply to a larger population.

Epidemiological studies of adverse effects and complications of tattooing have the potential to yield useful data for a larger population but are not easy to conduct and therefore scarce. Epidemiological research has so far investigated potential associations between tattoos and cancer (7, 53, 54). Warner et al. (53) found no statistically significant association between tattoos and the risk of non-Hodgkin's lymphoma or multiple myeloma. As the main limitation of their finding, they noted the lack of data on the chemical composition of tattoo inks (heavy metals or organic dyes). A retrospective study by Serup et al. (29), which covered ten years and was based on medical histories and clinical examinations, showed that about 70 % of 405 tattooed patients had acute skin reactions, 7 % systemic harmful effects, and 6 % persistent complications.

Another potential venue of identification and prediction of adverse effects and complications of tattoing is *in silico* research (Figure 2), a fast and cost-effective method of screening for toxicological properties of tattoo ink substances that relies on available databases describing relationships between substances, their levels, and activity as well as on data analysis and interpretation tools, machine learning models, and network analysis tools to predict the outcome of specific toxic substances (e.g., drugs, plasticisers)

Table 3 Methods for detection and identification of adverse effects of tattooing

Test	Principle	Method
Ex vivo on cells	Addition of tattoo ink (component) to isolated cells (lymphocytes, macrophages)	Flow cytometry
Ex vivo on cell culture or reconstructed human skin models (RHS)	Application of tattoo ink (component) on RHS	Reflectance spectroscopy
Experiments on sacrificed animals (a year after injection of tattoo ink)	Detection of deposits of tattoo pigments in the Kupfer cells	Light microscopy and transmission electron microscopy
Human trials		
Skin biopsy	Qualitative and quantitative analysis	histology analysis; immunohistochemistry analysis; micro-X-ray fluorescence analysis (μ-XRF); laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS)
Case reports	Description of side effects in individual patients	Clinical identification and laboratory testing
Epidemiological research	Description of side effects on a large number of subjects	Examining the connection between tattooing and side effects (e.g., link between ink and cancer)
In silico	Computer models of cellular behaviour	Computer simulation software

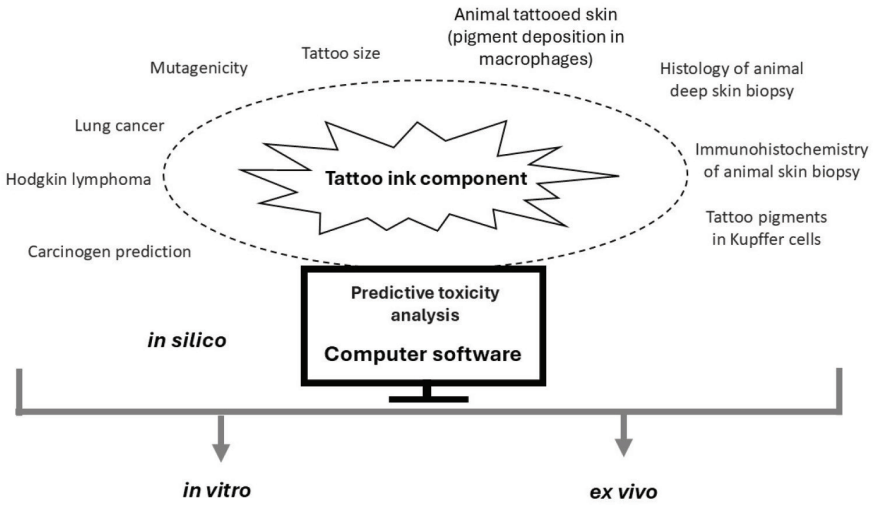

Figure 2 Possible avenues of *in silico* analysis to predict the adverse effects of tattoo ink components

(54). This model can also be a starting point for other tests such as *in vitro* and *ex vivo*. Considering the benefits of such research, we expect that it will play an important role in predicting the adverse effects of tattoo inks in the future.

REGULATORY FRAMEWORK FOR TATTOO INK APPLICATION

Public awareness about tattoo safety issues is increasing every day, but there are still no uniform regulations to control them (9). The United States Food and Drug Administration (US FDA) considers tattoo inks to be cosmetic products (55). As such, they are subject to marketing approval. However, the US FDA does not currently have the regulatory authority over colour additives for pigments used in tattoo inks, but their use is regulated by local jurisdictions. For now, it has issued a non-binding guideline which focuses on microbial contamination during tattooing and healing (47, 56) and is expected to establish good manufacturing practice designed to protect public health and ensure that cosmetic products are not adulterated as part of the implementation of the 2022 Cosmetic Product Regulatory Modernization Act (57).

In contrast, the European Union has in place stricter regulations, including the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation 2022/477 (58). This regulation bans more than 4000 substances and restricts many others. Another relevant European Commission regulation 2020/2081 regulates dyes for tattooing and permanent makeup (59).

In Croatia, the composition of tattoo inks is currently tested against these regulations by the Department for General Use Items of the Croatian Institute of Public Health. To reduce exposure to hazardous substances, the new 2022 restrictions stipulate that they shall not be marketed in mixtures used for tattooing and permanent makeup. Suppliers marketing mixtures must ensure that the mixture is labelled accordingly.

CONCLUSION

As tattooing has become widely accepted across all demographic groups around the world, it is important to raise awareness about the numerous adverse effects and complications that can occur, some of which can be prevented. The most important thing is to ensure the safety of those who will undergo tattooing by producing quality tattoo inks, professional training of tattoo artists, and raised awareness of people who consider having a tattoo. Patients with skin diseases should definitely consult a dermatologist before tattooing, and patients with chronic disorders/diseases or compromised immunity must consult their physician about the of which tattoo pigments are safe for their health condition.

In the future, it will certainly be necessary to i) standardise the composition and quality of tattoo inks; ii) harmonise methods for chemical and physical analysis of tattoo ink; iii) stipulate by law that tattooing can only be performed by licensed tattoo artists; iv) instruct tattoo candidates to check their health before tattooing; and v) run longitudinal studies to identify the cause-and-effect relationship between tattoo pigments and disorders in the lymph nodes and organs in which they are retained for life.

Conflict of interests

None to declare.

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Tetoviranje: neposredne i dugoročne nuspojave

Tetoviranje je postalo popularan sveopći trend u industrijaliziranim zemljama, s najvišim stopama prevalencije, do 30–40 % u odrasloj populaciji do 40 godina. Uobičajene tinte za tetoviranje mogu sadržavati toksične metale, policikličke aromatske ugljikovodike i primarne aromatske amine, kemijske spojeve koji imaju toksični učinak ako su prisutni u tinti iznad dopuštenih granica. U kožu se tijekom tetoviranja ubrizgava oko 14,36 mg tinte po cm^2 u dubinu od 1 do 3 mm. Pigment ubrizgan u kožu internaliziraju neutrofili, fibroblasti i makrofagi ili dendritične stanice. Oko 60–90 % pigmenta prenosi se limfotokom ili krvotokom od kože do limfnih čvorova, a zatim dijelom do drugih organa, npr. jetre, slezene i pluća. Nuspojave unošenja boje za tetoviranje u kožu mogu biti neposredne (iritacija, infekcija, upala kože), odgođene (reakcije preosjetljivosti) ili dugoročne (fibroza, granulomatozne promjene, sistemske upale, ponekad i zloćudne bolesti, npr. zloćudni limfomi). Štetni učinci boja za tetoviranje mogu se istražiti *ex vivo* i *in vivo*, a odnedavno i *in silico* testovima. Studije na ljudima uglavnom se odnose na prikaze slučajeva. Identifikacija pigmenata u tetoviranoj koži može se obaviti biopsijom kože, tehnikama kemijskoga oslikavanja te histokemijskim i imunohistokemijskim analizama. Epidemiološko istraživanje moglo bi procijeniti potencijalne veze između tetovaža, karcinoma i drugih poremećaja. Za sigurnost ljudi koji se tetoviraju potrebno je stvoriti opće regulatorne okvire.

KLJUČNE RIJEČI: fibroza; granulomatozne promjene; iritacija; reakcije preosjetljivosti; sistemske upale; tinta za tetoviranje; upala kože; zloćudne bolesti