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The safety of tattoo inks: Possible options for a common regulatory framework

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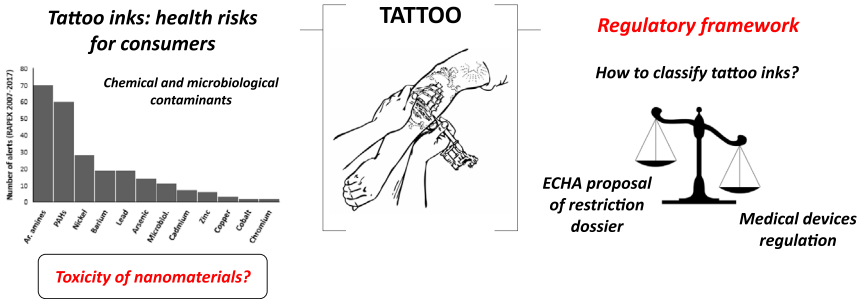
HIGHLIGHTS

- Considering the decorative purpose of most tattoos, risks should be minimised
- Supranational regulatory framework on tattoo inks is lacking in Europe
- Toxicity of nanomaterials contained in tattoo inks is not well-known
- Exposure to nanomaterials should be evaluated in the safety assessment of tattoo inks

GRAPHICAL ABSTRACT



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ABSTRACT

Tattoo prevalence has been increasing in the last 25 years, but specific regulations on tattoo inks are still missing. In the European Union, no supranational regulation is available and only few national provisions cover them. In the United States, tattoo inks are classified as cosmetics but are not approved for injection into the dermis.
Health risks for consumers may derive from microbiological contamination and the presence of toxic substances or nanomaterials. However, current regulations and non-binding recommendations, where present, only address the microbiological and chemical risks, completely overlooking nanotoxicity.
The aim of this paper is to promote awareness of the risks associated with tattoo inks and the nanomaterials contained therein. In particular, the need for a harmonised regulation or, at least, a set of minimal requirements is highlighted to improve the safety of tattoo inks and market surveillance by regulatory authorities.

1. Introduction

Tattoo prevalence among European and U.S. citizens is approximately 12% and 24%, respectively (Piccinini et al., 2016). Although tattoos mainly serve decorative or traditional purposes (e.g. tribal tattoos), in some cases they are made by medical professionals for medical reasons. For example, tattoos are used effectively as camouflage techniques in some pathological skin conditions (e.g. alopecia), in masking scars, or in plastic, reconstructive, and maxillofacial surgery (e.g. nipple-areola complex reconstruction and cleft lip) (Vassileva and Hristakieva, 2007). However, tattooing is not as safe as most consumers think (Rahimi et al., 2018). Indeed, adverse events associated with tattoo practices and products have been reported, although with low prevalence (Paprottka et al., 2018). However, considering the decorative purpose of most tattoos, the risk should be minimised to obtain an optimal risk-benefit ratio. Nevertheless, there is still no specific harmonised legislation on tattoo inks, and the subject matter ends up

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being regulated by non-specific laws, national legislation, or non-binding recommendations.

2. Scientific background

Tattoo inks generally contain pigments and dyes not specifically produced or authorised for subcutaneous use (Piccinini et al., 2016). In Europe, from 2007 to 2017, 190 tattoo inks or permanent makeup products (126 of which imported from the United States) were withdrawn from the market or banned following alerts by the European Rapid Alert System for dangerous non-food products (RAPEX) (RAPEX, 2018). Of those products, 37% contained aromatic amines (or azo pigments releasing aromatic amines upon UV-catalysed degradation), 32% contained polycyclic aromatic hydrocarbons, while 14% or fewer contained nickel, lead, barium, arsenic, cadmium, zinc, chromium, cobalt, and/or copper exceeding the recommended levels (RAPEX, 2018; De Cuyper, 2010; Forte et al., 2009).

Sterility is another important issue, as more than 10% of the banned inks posed microbiological risks (RAPEX, 2018). Considering the relevant risk of infection associated with subcutaneous injection, tattoo inks should comply with the same sterility requirements as parenteral medicinal products.

The figures extracted from RAPEX may not seem significant, as the majority of tattoo inks currently on the market assessed by the European Chemicals Agency (ECHA) meet the Council of Europe (CoE) recommendations of 2008 (Council of Europe, 2008; ECHA, 2017a). However, since tattoo inks do not have a therapeutic purpose but, similar to cosmetics, their aim is to change the appearance of the human body, they should meet the same safety requirements as cosmetic products, in the sense that any associated risk should be minimised (Regulation (EC) No 1223/2009).

Moreover, a fraction of the pigments is constituted by nanoparticles, which range from 10 nm to more than 1 μm in particle size (Piccinini et al., 2016; Hogsberg et al., 2011). Hogsberg et al. demonstrated that coloured and black pigments are particularly rich in nanomaterials (1–100 nm), whereas white pigments mainly contain particles bigger than 100 nm (Hogsberg et al., 2011). Nanomaterials possess peculiar physicochemical properties with respect to bulk materials and can be extremely hazardous to humans (Musazzi et al., 2017). Indeed, the nanoscale process modifies the bulk material, conferring to it new magnetic, optical, mechanical, and biological properties. Such novel physicochemical properties may be desirable, with the aim of technological improvements (e.g. higher stability of water-based ink), but they can also increase the potential toxicity of nanomaterials in humans and the environment. Concerns about so-called nanotoxicity arose after the first demonstration that nanoparticles can penetrate biological barriers and interact with intra- and extra-cellular targets, causing the disruption of tissue physiological functionalities and inducing inflammatory processes. For example, several published results documented that carbon-black nanoparticles (Hogsberg et al., 2011), which can be also found in tattoo inks, can be toxic for cells and animal models, affecting the functionalities of different organs (e.g. the cardiovascular system) (Yu et al., 2016). Carbon-black nanotoxicity seems to be caused by different mechanisms: the activation of pro-inflammatory pathways, the increase in radical species, the dysfunction in cellular metabolism, and DNA damage (Moller et al., 2015; Pandey and Prajapati, 2018).

Schreiver et al. demonstrated for the first time in humans that pigment nanoparticles in the range of 20–180 nm can be found in the lymph nodes of tattooed individuals. This provided strong evidence that a long exposure may cause biomolecular changes in cutaneous tissues (Schreiver et al., 2017). Although a cause-effect correlation has not been established, it is noteworthy that the higher incidence of tattoo-related side effects was observed in black tattoos, which are the richest inks in terms of nanomaterials (Hogsberg et al., 2011; Hoesberg et al., 2013). Hogsberg et al. observed a higher number of complaints about minor symptoms after tattooing in individuals with black tattoos compared to those tattooed with red inks (Hogsberg et al., 2011), which are known to have a high prevalence of side effects (Vasold et al., 2008), especially when mercuric salts were present as colourants (Mortimer et al., 2003).

Nanomaterials released from pigments in the tattooed area may trigger dermatologic adverse effects, such as papulo-nodular reactions, itching or skin elevation, and extremely rare granulomatous foreign material reactions, even after many years (De Cuyper, 2010; Gopee et al., 2007; Moreno-Horn and Gebel, 2014; Serup et al., 2016). Moreover, the significant loss of pigment mass from the tattooed area found in long-term studies suggests that pigment nanomaterials can reach the bloodstream, resulting in a higher risk of systemic exposure to nanomaterials (Engel et al., 2010). Indeed, some published evidence suggested that nanomaterials can distribute in different organs after an intra-dermal injection (Gopee et al., 2007), increasing concerns about the fate of pigments' nanomaterials and their impact on the physiology and functionality of organs and tissues.

Although there is no consensus regarding the real health risks to consumers due to the lack of standardised protocols for providing a toxicological assessment (Moreno-Horn and Gebel, 2014), the information available in the literature clearly demonstrates that nanomaterials cannot be classified a priori as safe or dangerous for human health. However, the risk assessment of nanomaterials cannot be extrapolated from the data available for bulk materials, since the toxicological profile is strongly influenced by its physicochemical properties (e.g. surface, shape, and chemical structure). As demonstrated by the recent EMA reflection papers on iron-core nanoparticles intended to treat severe iron deficiency, small differences in the physical properties of nanomaterials had a huge impact on their toxicological profiles, despite a similar chemical composition (Musazzi et al., 2017).

3. Regulatory framework

In both the United States and European Union, specific legislation on tattoos is lacking, and the current legislative framework is fragmented and mainly based on national laws. In the United States, tattoo inks are cosmetics, but none have been approved by the FDA for injection into the dermis (De Cuyper, 2010), and the colour additives are subject to the general provisions of the Federal Food, Drug, and Cosmetic Act (21 USC 361, 362, 381).

In Europe, while tattoo needles are regulated as medical devices following new regulations (Regulation (EU) 2017/745), tattoo inks are not covered by specific provisions. As such, they fall under the provision of the Directive on General Product Safety (Directive 2001/95/EC), which requires that only safe products are placed on the market. The non-binding CoE Resolution of 2008 provides limits to the nature and concentration of chemical compounds contained in tattoo inks. Other provisions include sterility, packaging, labelling, and risk assessment requirements (Council of Europe, 2008). In particular, the manufacturer or importer is identified for the first time as the person in charge of assessing the safety of inks that are placed on the market. However, guidelines on the toxicological assessment of tattoo products were issued only in 2017 by the European Directorate for the Quality of Medicines and Healthcare (EDQM) (EDQM, 2017). Recently, the ECHA along with the relevant authorities of Denmark, Italy, and Norway submitted a proposal for a restriction dossier under Annex XV of Regulation (EC) No. 1907/2006 (REACH) to regulate the use of hazardous substances in tattoo inks and permanent makeup (ECHA, 2017b). In line with the CoE Regulation of 2008, the proposal aims to reduce the potential health risks for people who get tattoos. The ECHA proposal, for which the public consultation ended on June 20, 2018, is to be submitted to the European Commission. It includes two options for the restriction dossier, which differ for the concentration limits for hazardous substances (ECHA, 2017c). In particular, the proposal contains a list of 4130 substances that should be restricted in the production of inks or pigments because of they are classified under REACH regulations. These include