Science of the Total Environment 651 (2019) 634–637

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

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

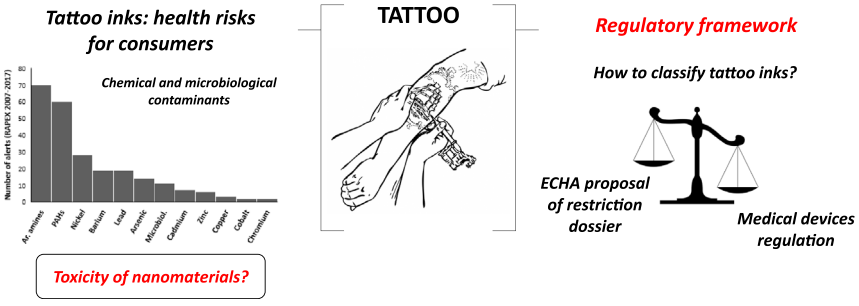
Paola Minghetti [a,*], Umberto M. Musazzi [a], Rossella Dorati [b], Paolo Rocco [a]

[a] Department of Pharmaceutical Sciences, Università degli Studi di Milano, via G. Colombo, 71-20133 Milan, Italy
[b] Department of Drug Sciences, Università di Pavia, Viale Taramelli, 12-27100 Pavia, Italy

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



ARTICLE INFO

Article history:
Received 3 May 2018
Received in revised form 13 September 2018
Accepted 13 September 2018
Available online 15 September 2018

Editor: Adrian Covaci

Keywords:
Tattoo ink
Nanomaterials
Heavy metal
Tattoo license
Legislation

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

* Corresponding author.
E-mail address: paola.minghetti@unimi.it (P. Minghetti).

https://doi.org/10.1016/j.scitotenv.2018.09.178
0048-9697/

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

carcinogenic and mutagenic substances, reproductive toxicants, skin/eye sensitisers, skin/eye irritants, and corrosive substances. In the case of substances for which reliable safety limits are defined (e.g. zinc, copper, barium, and methanol), acceptable concentration limits were defined. For other substances a qualitative approach was proposed. These include chemicals that, under Regulation (EC) No. 1223/2009, are prohibited in cosmetic products (Annex II) or are not allowed in cosmetics that come into contact with the mucous membranes, including colourants (Annex IV). Acceptable concentration limits were defined based on a model of exposure assessment after the intra-dermal injection of tattoo inks.

Because of the large number of substances involved, the submitters of the dossier did not include specific statements about the impact of each substance's physicochemical properties on risk assessment. The missing information is particularly critical for safety assurance of nanomaterial-containing tattoo inks. Although the impact of nanoparticles on human health was highlighted in the proposal, neither a general guidance about their physicochemical characterisation nor a restriction was included. In particular, no specific restriction was stated for ZnO nanoparticles. Indeed, the ECHA postponed the risk assessment of ZnO nanoparticles in tattoo inks until after the final results of the REACH Substance Evaluation that started in 2017 are available (ECHA, 2017b). On the contrary, carbon black nanoparticles were included in the restricted list. In agreement with their inclusion in Annex IV of Regulation (EC) No. 1223/2009, their use in tattoo inks was considered acceptable if their maximal concentration does not exceed 10% and their primary particle size is more than 20 nm. Even if such a particle size cut-off is effective to preserve consumer health by nanomaterial exposure via transdermal absorption, it is not if nanoparticles were intra-injected into the dermis (Baroli, 2010).

The steps toward regulatory harmonisation in Europe still rely upon the willingness of individual member states to comply with non-binding recommendation provisions. In this context, the ECHA proposal of a restriction dossier is a positive signal for improving the safety of tattooing. However, the existing provisions address only the chemical and microbiological risks for estimating the margin of safety (MOS) of tattooing, overlooking the risk associated with nanoparticles. The lack of expertise on nanomaterial properties, characterisation, and toxicology makes the risk assessment of the nanomaterials contained in inks very difficult (Musazzi et al., 2017). The health risk assessment of tattoo inks containing nanomaterials should be improved, taking into account the impact of physicochemical properties and systemic and prolonged exposure to their health risks for consumers.

4. Conclusion

Although tattooing has entered the mainstream, it maintains the appeal of an underground practice. In this context, an approach based on a prohibitionist regulation could prove counter-productive and peoples' safety could be initially pursued with complementary measures. For example, mandatory training of tattoo artists and awareness campaigns for the public should be developed, as already suggested (Piccinini et al., 2016), possibly integrated with a third-party certification/inspection of body art facilities for compliance with hygiene requirements, and/or licensing of tattoo artists, as already required by some U.S. states, e.g. Texas (Texas Department of State Health Services, 2018) and Michigan (Michigan Department of Community Health, 2018), cities, e.g. New York City (NYC Department of Health and Mental Hygiene, 2018), and tattoo artists' associations.

The efforts of ECHA are welcome because the restriction proposal establishes a basic supranational regulation on the grade of chemicals used in tattoo inks. However, the ECHA proposed limits only for chemical substances contained in the industrial-produced tattoo inks, but such restrictions cannot be considered sufficient to protect consumers' health. Indeed, since tattoo inks are intra-dermally injected, those with tattoos are exposed to chemicals in a more critical matter with respect to other types of marketed inks. Therefore, rules on tattoo inks should be integrated into a systematic regulation comprising a health risk assessment based on the real exposure to chemicals and on the possible consequences on human health. The Medical Devices Regulation (MDR) seems to be a reasonable choice. Indeed, unlike the current regulatory framework on cosmetics, the MDR regulates the assessment of the risk/benefit balance of injectable products. This would not be in contrast with the purpose of reaching a harmonisation of EU regulations with U.S. regulations.

With regard to which regulatory framework would be more appropriate, the two most obvious choices are the regulations on cosmetic products, as is the case in the United States, or on medical devices. Indeed, the FDA's approach to the safety of nanomaterials in cosmetic products is already sufficiently flexible to account for the risks associated with long exposure to tattoo inks (FDA, 2014). On the other hand, as tattoo inks are injected into the dermis using a needle, they are formally excluded from the scope of the European regulations on cosmetic products (Regulation (EC) No 1223/2009), even considering the power of the commission to determine whether or not a specific product falls within the definition of “cosmetic product” introduced by a recent amendment to the European MDR (*Regulation (EU) 2017/745*).

Tattoo inks are also explicitly excluded from the MDR's scope, indicating that they were at least considered for inclusion. Now that its scope includes products without an intended medical purpose, we believe that the MDR could represent an appropriate framework for tattoo inks if a special rule is provided to avoid compliance with all if the requirements of class IIb (Regulation (EU) 2017/745).

If tattoo inks were classified as medical devices in the EU, given that they are considered cosmetics in the United States, an international harmonisation would still be possible on the grounds of a binding set of minimal requirements. Moreover, the identification of a European authority responsible for market surveillance and providing guidance to manufacturers and importers of tattoo-related products would be desirable, both to assure the health of European consumers and to improve international cooperation with the FDA.

Funding sources

None.

Conflict of interest disclosure

None declared.

Abbreviations

EU	European Union
FDA	U.S. Food and Drug Administration
PAHs	polycyclic aromatic hydrocarbons
RAPEX	Rapid Alert System for dangerous non-food products
EDQM	European Directorate for the Quality of Medicines and Healthcare (EDQM)
MDR	Medical Devices Regulation
MOS	margin of safety
ECHA	European Chemicals Agency

References

Baroli, B., 2010. Penetration of nanoparticles and nanomaterials in the skin: fiction or reality? J. Pharm. Sci. 99 (1), 21–50.

Council of Europe, 2008. Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up (superseding Resolution ResAP(2003)2 on tattoos and permanent make-up). Available at:. https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016805d3dc4, Accessed date: 18 April 2018.

De Cuyper, C., 2010. Cosmetic and medical applications of tattooing. In: De Cuyper, C., Perez-Cotapos, M.L. (Eds.), Dermatologic Complications with Body Art, Tattoos, Piercings and Permanent Make-Up. Dermatologic Complications With Body Art. Springer, Heidelberg.

Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on General Product Safety. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0095&from=en.
ECHA, 2017a. Public Consultation. ECHA proposes a restriction on substances in tattoo inks. https://echa.europa.eu/documents/10162/2b217418-1bd9-7e00-7355-a9fb792d68b3, Accessed date: 24 April 2018.
ECHA, 2017b. Proposal for a Restriction for Substances in Tattoo Inks and Permanent Make Up. Available at:. https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/18114/term, Accessed date: 18 April 2018.
ECHA, 2017c. Proposal for Annex XV Restriction Report – Substance in Tattoo Inks and Permanent Make Up. Version 1.2. Available at:. https://echa.europa.eu/documents/10162/49ca957f-86ca-5eda-1aed-5835a72f8ac9, Accessed date: 24 July 2018.
EDQM, 2017. Consumer Health Protection Committee (CD-P-SC). Safer Tattooing. Overview of Current Knowledge and Challenges of Toxicological Assessment. Edition 1st. EDQM, Strasbourg.
Engel, E., Vasold, R., Santarelli, F., Maisch, T., Gopee, N.V., Howard, P.C., Landthaler, M., Baumler, W., 2010. Tattoooing of skin results in transportation and light-induced decomposition of tattoo pigments – a first quantification in vivo using a mouse model. Exp. Dermatol. 19, 54–60.
RAPEX, 2018. Available at:. https://ec.europa.eu/consumers/consumers_safety/safety_products/rapex/alerts/?event=main.listNotifications, Accessed date: 18 January 2018 (Search string: “free text=tattoo” & “category = chemical products” (189 matches). Added tattoo ink with alert number 0358/08 classified in “category = cosmetics”).
FDA, 2014. Guidance for industry–safety of nanomaterials in cosmetic products. https://www.fda.gov/cosmetics/guidanceregulation/guidancedocuments/ucm300886.htm, Accessed date: 18 April 2018.
Forte, G., Petrucci, F., Cristaudo, A., Bocca, B., 2009. Market survey on toxic metals contained in tattoo inks. Sci. Total Environ. 407 (23), 5997–6002.
Gopee, N.V., Roberts, D.W., Webb, P., Cozart, C.R., Siitonen, P.H., Warbritton, A.R., Yu, W.W., Colvin, V.L., Walker, N.J., Howard, P.C., 2007. Migration of intra-dermally injected quantum dots to sentinel organs of mice. Toxicol. Sci. 98, 249–257.
Hoesberg, T., Hutton Carlsen, K., Serup, J., 2013. High prevalence of minor symptoms in tattoos among a young population tattooed with carbon black and organic pigments. J. Eur. Acad. Dermatol. Venereol. 27, 846–852.
Hogsberg, T., Loechner, K., Lof, D., Serup, J., 2011. Tattoo inks of general usage contain nanoparticles. Br. J. Dermatol. 165, 1210–1218.
Michigan Department of Community Health, 2018. Tattoo parlor-required state license(s) https://www.michigan.gov/statelicensesearch/0,4671,7-180-24786_24826-81538–,00.html, Accessed date: 27 April 2018.
Moller, P., Jensen, D.M., Christopheresen, D.V., Kermanizedeh, A., Jacobsen, N.R., Hemmingsen, J.G., Danielsen, P.H., Karottki, D.G., Roursgaard, Cao Y., Jantzen, K., Klingberg, H., Hersoug, L.-A., Loft, S., 2015. Measurement of oxidative damage to DNA in nanomaterial exposed cells and animals. Environ. Mol. Mutagen. 56, 97–110.
Moreno-Horn, M., Gebel, T., 2014. Granular biodurable nanomaterials: no convincing evidence for systemic toxicity. Crit. Rev. Toxicol. 44, 849–875.
Mortimer, N.J., Chave, T.A., Johnston, G.A., 2003. Red tattoo reactions. Clin. Exp. Dermatol. 28, 508–510.
Musazzi, U.M., Marini, V., Casiraghi, A., Minghetti, P., 2017. Is the European regulatory framework sufficient to assure the safety of citizens using health products containing nanomaterials? Drug Discov. Today 22 (6), 870–882.
NYC Department of Health and Mental Hygiene, 2018. Tattoo license. Available at:. https://www1.nyc.gov/nycbusiness/description/tattoo-license, Accessed date: 27 April 2018.
Pandey, R.K., Prajapati, V.K., 2018. Molecular and immunological toxic effects of nanoparticles. Int. J. Biol. Macromol. 107, 1278–1293.
Paprottka, F.J., Krezdorn, N., Narwan, M., Turk, M., Sorg, H., Noah, E.M., Hebebrand, D., 2018 Feb. Trendy tattoos-maybe a serious health risk? Aesthet. Plast. Surg. 42 (1), 310–321.
Piccinini, P., Pakalin, S., Contor, L., Bianchi, I., Senaldi, C., 2016. Safety of tattoos and permanent make-up. Final report. Joint Research Commission (JRC) Science for Policy Report. https://doi.org/10.2788/011817.
Rahimi, I.A., Eberhard, I., Kasten, E., 2018. Tattoo: what do people really know about the medical risks of body ink? J. Clin. Aesthet. Dermatol. 11, 30–35.
Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02009R1223-20171225&qid=1524648533299&from=IT.
Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017. Available at:. http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN.
Schreiver, I., Hesse, B., Seim, C., Castillo-Michel, H., Villanova, J., Laux, P., Dreiack, N., Penning, R., Tucoulou, R., Cotte, M., Luch, A., 2017. Synchrotron-based ν-XRF mapping and μ-FTIR microscopy enable to look into the fate and effects of tattoo pigments in human skin. Sci. Rep. 7 (1), 11395. https://doi.org/10.1038/s41598-017-11721-z.
Serup, J., Sepehri, M., Hutton, Carlsen K., 2016. Classification of tattoo complications in a hospital material of 493 adverse events. Dermatology 232, 668–678.
Texas Department of State Health Services. Licensing Requirements - Tattoo and Body Piercing Studios. https://www.dshs.texas.gov/tattoo-piercing/licensing.aspx, Accessed date: 27 April 2018.
Vasold, R., Engel, E., Konig, B., Landthaler, M., Baumler, W., 2008. Health risks of tattoo colors. Anal. Bioanal. Chem. 391, 9–13.
Vassileva, S., Hristakieva, E., 2007. Medical applications of tattoing. Clin. Dermatol. 25, 367–374.
Yu, X., Hong, F., Zhang, Y.-Q., 2016. Bio-effect of nanoparticles in the cardiovascular system. J. Biomed. Mater. Res. A 104, 2881–2897.