Necessary specifications of tattoo ink ingredients: Expert discussion at the BfR

Communication No 014/2022 from the BfR of 16 June 2022

On 3 March 2022, the expert meeting on the necessary specification of tattoo ink ingredients took place at the German Federal Institute for Risk Assessment (BfR) via video conference. Experts from the field of analytics, state surveillance agencies, governmental organizations, tattoo ink manufacturers, and tattooists participated in the meeting.

In 2020, BfR was asked by the German Federal Ministry of Food and Agriculture (BMEL)[1], which was responsible for tattooing products at the time, to develop a strategy for risk assessment of tattoo inks in order to enhance consumer safety. The strategy developed by the BfR comprises a set of minimum requirements, which were published in October 14, 2021 (https://www.bfr.bund.de/cm/349/tattoo-inks-minimum-requirements-and-test-methods.pdf).

These requirements were presented at the 2nd International Conference on Tattoo Safety (https://www.bfr-akademie.de/english/archive/2021/tattoo.html), which took place in Berlin on November 18-19, 2021. The next step was to specify these requirements. Therefore, the experts discussed the selection of suitable pigments, the characterisation of contaminants and leachable substances, and which compounds should be prioritised for analysis of tattoo ink ingredients.

1 Introduction of the BfR minimum requirements and test methods with emphasis on necessary tattoo ink specifications

The framework for risk reduction and its relevance along with the restriction of substances in tattoo inks under REACH was introduced. The specifications for ingredients of tattoo inks include substance characterisation and information on purity. Contaminants and leachable substances should be quantified. Furthermore, the homogenity and stability of the inks during storage and exposure towards light are addressed. There is a requirement to perform a five-batch-analysis due to the fact that small changes in substance purity may lead to significant differences in toxicity.

The minimum toxicological requirements were presented. Endpoints taken into account are: skin irritation/corrosion, eye irritation/damage, skin sensitization, phototoxicity, and mutagenicity/genotoxicity, including phototoxicity. A set of test guidelines and evaluation criteria are recommended for each endpoint. Based on the current state of science and technology, the risks can be reduced correspondingly.

There will be, however, no recommendation on pigments for use in tattoo inks yet. Data missing for a comprehensive characterisation of risks shall be collected. This includes the development of analytical methods, the evaluation of clinical data and development of suitable toxicological methods to mimic the intradermal application of pigments. Some of the important projects to achieve this goal include the epidemiological study within the LIFE-Adult

[1]Since 2022, the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection has been responsible for this issue.

cohort,[2] a short-term biokinetics study for exposure assessment,[3] tattoos in cancer epidemiology,[4] and data collected in the frame of information network of dermatological clinics (IVDK). A review of the integrity of the delivered information should follow after the ink manufacturers have fulfilled the requirements on a voluntary basis. The implementation of the requirements is to be discussed and further elaborated in the frame of the International BfR-Committee on Tattoo Inks.

2 Feedback from Participants on the minimum requirements

Participants express significant interest and recognise the need for minimum requirements while also acknowledging the challenges associated with their implementation. There is a consensus that both parts, i.e., the required specification as well as the toxicological testing, shall be addressed. It is also emphasized that the discussion should start from the very beginning by considering the origins of the pigments on the market. The development of standard analytical methods on international level is mentioned as a major objective for achieving comparable results. Moreover, the required test guidelines should be implemented. Existing restrictions within the frame of the REACH regulation should be enforced. Due to the large variability of impurities it is suggested to develop a checklist of impurities, which must be analysed. It was asked whether these requirements should be dynamic, meaning if they should apply to pigments already on the market and to those likely to enter the market in the future.

Experts raised concerns regarding the situation that no information is provided by pigment manufacturers. The limits set in the restriction under REACH were addressed. Most limits were set as group limits without a toxicological evaluation. Non-classified substances do not fall into the frame of the restriction.

Removal of tattoos was not addressed in the minimum requirements; however, producers of tattoo inks should consider the fate of the pigments upon irradiation.

3 Discussion on: which pigments do you consider essential for tattooing?

- How would you select suitable pigments?

The most important criteria for the selection of pigments mentioned by manufacturers is that they should be suitable for application in the skin resulting in a desired coloration as well as for the tattoo ink manufacturing procedure. Furthermore, the experts mentioned the safety of the selected pigments as an important criterion. It was discussed as a problem that pigments with one CI (Colour Index) number may have different origins and impurity profiles. Hence,

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[2] Loeffler M, Engel C, Ahnert P, et al. The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. BMC Public Health. 2015; 15(1):691. https://www.uniklinikum-leipzig.de/einrichtungen/life

[3] Schreiver I. Bioavailability of tattoo inks by quantifying the marker substances 4-aminobenzoic acid, 2-phenoxyethanol and iodide in blood and urine after tattooing 24 male test persons with black or red color: German Clinical Trials Register, 2021.

[4] (a) Zins M, Bonenfant S, Carton M, et al. The CONSTANCES cohort: an open epidemiological laboratory. BMC public health 2010; 10: 479. (b) Hoffmann W, Jöckel K-H, Kaaks R, et al. The National Cohort. A prospective epidemiologic study resource for health and disease research in Germany. 2011.

also their safety profiles are different. This holds true especially for carbon black-based pigments (acetylene black, furnace black, lamp black or gas black etc.).

Pigments were also reported to be chosen based on their compliance with the BfR recommendations from 2013 (https://mobil.bfr.bund.de/cm/349/requirements-for-tattoo-inks.pdf). Toxicological data available for pigments is being evaluated. Pigments are chosen according to their quality based on criteria such as: indication of purity, read-across, availability of guideline conform studies. According to the manufacturers, pigments with most toxicological data and without obvious concerns are chosen for the usage in tattoo inks.

The missing information that can only be provided from pigment manufacturers includes manufacturing processes, composition and contaminants. For example, the addition of barium sulphate in phthalocyanine-based pigments is not declared. No pigment manufacturers are ready to produce pigments for the tattoo market. Purification of pigments is possible but at very high costs. The main issue with selecting safe pigments is not the pigment itself, but the impurities present in the pigment. Their profile changes depending on the production process.

As another aspect for the pigment selection, stability and possible metabolism in the human body were mentioned. Lightfastness is important but degradation products must be considered too.

- **Can the colour spectrum be covered without azo pigments?**

Azo pigments can be avoided in tattoo inks. However, diazo pigments might not have proper alternatives yet. It is generally agreed that the number of azo pigments used for tattooing can be drastically reduced.

- **How to acquire representative test materials?**

No source is as yet known for providing test reference substances with a known purity.

4 Characterisation of contaminants and leachable substances

- **Can formaldehyde be measured at 0.5 ppm?**

It was mentioned that formaldehyde and acetaldehyde limits in tattoo inks are stricter than for medical devices. It was further brought up that, even if high purity ethanol or glycerol are used, contaminations with formaldehyde and acetaldehyde cannot be avoided. Some participants called for a toxicological evaluation to justify the limit of 0.5 ppm.

It was discussed, that formaldehyde and acetaldehyde may be formed in the products during storage; hence, analytical results are time dependant. Analytically, the threshold of 0.5 ppm can be implemented according to some laboratories while others see difficulties. Many of the inks on the market contain levels of formaldehyde slightly above 0.5 ppm, making them uncompliant with REACH. The origin is from liquid tattoo ink components and not from the pigments.

Three methods exist for analysis of formaldehyde in tattoo inks with variability in results. Therefore, standardization of formaldehyde analysis is considered necessary.

- **What is the limit of quantification for nickel measurement?**

The quantification of nickel at 0.5 ppm is possible. Even lower limits of detection are possible. However, manufacturers mentioned that nickel is a main impurity in iron oxide based pigments and hence purification is required. They would prefer a limit of quantification set by convention. Technically achievable limits of quantification might result in different labelling requirements.

- **Ring trials – for what methods to be performed?**

For comparable results, standardized methods were discussed as an essential prerequisite. In addition, standard deviations are very high without standardised methods. Standardisation is necessary when the sample preparation procedure has a major impact on the analysis. With regard to the implementation of the REACH restriction of tattoo ink ingredients, the non-existent definitions of metal solubility and their analytical implementation were questioned. The extraction conditions should be precisely described, as otherwise different amounts of metals will be detected. This must be addressed on EU level as member states can come to different conclusions. However, as tattoo inks are injected into the dermis and thus become 100% systemically available, also a consideration of the total metal content was discussed.

Due to the very large amount of substances restricted, standard methods should be developed only for selected substances which can be easily analysed. Here a prioritisation is required.

As for the detection of metals, analytical results might differ depending on the sample preparation methods (e.g., microwave digestion, temperatures used). Here methods were adopted from the analysis of cosmetic products. Two different ring trials were seen necessary – one for metals using ICP-MS/OEC for total metal content and another ring trial for the soluble metal fraction of copper, zinc and barium for the definition of the extraction/solubility procedure. A method for the detection of chromium VI was developed. Adaptation by other laboratories is needed for the confirmation of results.

Not all laboratories have the appropriate equipment to participate in ring trials, for example, for PAH extraction.

5 Five-batch-analysis of tattoo ink ingredients

- **Which compounds should be prioritised?**

To ensure chemical and technical equivalence, the ingredient specifications are to be determined with five different batches. The reason is that small changes in the chemical composition or the physical properties of the pigments may lead to significant toxicological changes. Toxicological test results can only be considered when performed with a substance of a known purity. Alternatively, test results are acceptable when the purity of the substance and the impurities fall within a predefined concentration range. This range is determined from five independent analysis and the calculated standard deviations.

The problem arises when different batches of a pigment have very different impurity profiles. Specifications based on data achieved with existing analytical methods should be considered

for this analysis. At present, a standard set of analytical testing involves PAHs, heavy metals, PAAs and the requirements as stated in ResAP (2008). Screenings are also conducted for unknown impurities. The mean and median sizes of nanoparticles as well as the graphical representation of the size distribution of pigment particles should be determined. The aggregation behaviour should be described. Fraction of particles with sizes lower than 100 nm should be determined. A combination of techniques should be used. A medium should be defined for studying these parameters.

Scientific judgment would be required to decide which impurities are expected and should be included in the five-batch-analysis. This applies also for the crystallinity, which is only relevant for selected pigments.

The importance of the five-batch-analysis is generally acknowledged; however, concern was raised that currently appropriate methods for implementation may be missing.

6 Concluding remarks and next steps

The specification requirements and the initiatives for method development and harmonisation represent a major element of tattoo ink safety. Further meetings will be dedicated to toxicological requirements. Experts are welcome to join these upcoming meetings. These meetings will lay the framework for the implementation of the requirements. An International BfR-Committee on Tattoo Inks will be established in due time.

Further information, please visit BfR-Website:

Tattoo: BfR publications in English

https://www.bfr.bund.de/en/a-z_index/tattoo-130164.html#fragment-2

Tatowierung: BfR publication in German

https://www.bfr.bund.de/de/a-z_index/taetowierung-4929.html

„Stellungnahmen-App“ des BfR

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