# 1st Meeting of the BfR Commission on Tattoo Inks

Minutes of March 23rd, 2023

The BfR Commission on Tattoo Inks counsels the Federal Institute for Risk Assessment (BfR) as an honorary and independent expert body on issues of tattoo ink safety and risk assessment by giving advice to the BfR on the development and adjustment of analytical and toxicological methods (focus on human studies and NAMs) suitable for inks and pigments. The activities will be performed in close cooperation with the existing bodies of standardization such as the International Organization for Standardization or the OECD. Furthermore, the Commission ensures a continuous dialogue with the state surveillance agencies.

With its scientific expertise, the Commission advises the BfR and can assist the Institute as a network of experts in the event of a crisis. The Commission consists of 23 members appointed for a four-year term through an open tender and application procedure. They distinguish themselves through scientific expertise in their respective field. The members of the Commission are obliged to preserve confidentiality towards third parties and to fulfil their duties impartially. Any conflicts of interest regarding individual agenda items (TOPs) discussed in the meeting are subject to transparent queries and disclosure. The meeting minutes below reflect the scientific opinion of the BfR Commission. The Commission's recommendations are entirely advisory in nature. The Commission itself does not issue any orders or expert opinions and is not authorized to issue instructions to the BfR (and vice versa) nor involved in its risk assessments.

**Previous note**

The 1st meeting of the BfR Commission for tattoo inks has been video recorded. The language is English.

**Item (TOP) 1 Welcome and adoption of the agenda**

The managing director opens the commission meeting and welcomes the participants of the newly appointed BfR-Commission. He asks for desired changes of the suggested agenda items. A change in the agenda is not necessary and the quorum of the commission is asserted. The president of the BfR, Prof. Dr. Dr. Hensel, and the head of the Department of Chemical and Product safety, Prof. Dr. Dr. Andreas Luch, welcome the participants of the newly appointed BfR-Commission for tattoo inks and its guests. Furthermore, they inform the audience to the background and aim of the commission. The current activities of the BfR related to tattoo inks are introduced.

**Item (TOP) 2 Declaration on conflicts of interest**

The commission manager asks if the participants want to claim any conflict of interest regarding the items of the agenda or the topics going to be discussed. The participants declare to have no conflict of interest. The consent of the participants to record the sessions is obtained.

**Item (TOP) 3 Introduction to BfR Commissions**

The BfR gives an informative presentation about the tasks and functions of the BfR Commission work, with focus on potentially arising conflicts of interest and transparency of the BfR Commissions.

**Item (TOP) 4 Round of introduction of all commission members**

BfR participants introduce themselves, followed by the commission members and guests. The attendees gives a brief summary of their work and expertise on tattoo inks. 19 of the 23 appointed

commission members are present at the online session, 4 commission members do not participate. In addition, 6 BfR employees and 3 guests from the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection participate in the meeting.

**Item (TOP) 5 Election of the chairperson and vice chairperson**

Prof. Marilena Carbone is running for the commission president and Mrs. Carina Wolf for the vice president. There are no further candidates. With an online election tool (TedMe) an anonymous election is carried out. Prof. Marilena Carbone is elected as commission president with 18/19 votes, Carina Wolf is elected as vice president with 18/19 votes.

**Item (TOP) 6 Tattoo inks: minimum requirements/test methods- Analytics, Toxicology**

The minimum requirements and test methods (MR) for tattoo inks[1] published in 2021 are introduced by the BfR. The requirements do not comprise a full toxicological assessment of tattoo inks. Instead, their aim is to reduce potential health risks by achieving constant chemical purity and fully declared identity of the pigments used in tattoo inks as well as by an obligatory toxicological assessment. It is pointed out that the minimum requirements are not legally binding, but intend to support producers of tattoo inks to achieve a better product quality. A voluntary compliance of the producers is pursued.

Tattoo inks and their individual components are restricted by the REACH-Regulation (in the following REACH), Annex XVII, Entry 75 since January 2022. For substances that are classified by the globally harmonized system (GHS) concentration limits are set. Those apply to carcinogenic, mutagenic or reprotoxic (CMR) substances as well as to substances that are skin sensitisers, or are damaging or irritant to the skin and eye. However, tattoo inks may contain unclassified substances (including those substances lacking of data) that are potentially hazardous.

Besides the pigments themselves, additives as well as impurities and metabolites may play a role. To fill this information gap, the BfR has published the minimum requirements and test methods for tattoo inks. Therein, specifications for components of tattoo inks are demanded. Furthermore, a set of operable minimum toxicological requirements for tattoo ink pigments is laid down.

The identity of a tattoo ink ingredient should be defined in accordance with good laboratory practice (GLP). It should comprise its chemical characterization, an indication of contaminants and leachable substances, as well as information on homogeneity and stability.

Reference to an expert panel on specifications[2] for tattoo ink ingredients is made which was part of a series of three expert panels previously organized and held by BfR. The BfR Commission will provide additional support for implementation of these topics. It is summarized that information on the exact composition of the tattoo pigments and impurities as well as on the manufacturing process is urgently needed. Furthermore, analytical strategies for the identification and quantification of the relevant toxic components need to be developed.

[1] Tattoo inks: minimum requirements and test methods, Opinion No 031/2021 of the BfR of 14 October 2021, DOI 10.17590/20211021-115214, https://mobil.bfr.bund.de/cm/349/tattoo-inks-minimum-requirements-and-test-methods.pdf

[2] Necessary specifications of tattoo ink ingredients: Expert discussion at the BfR
Communication No 014/2022 from the BfR of 16 June 2022
https://www.bfr.bund.de/cm/343/notwendige-spezifikationen-fuer-inhaltsstoffe-von-taetowiermitteln-expertengespraech-im-bfr.pdf

During the commission meeting, the BfR gives the example of Pigment Red 170 to illustrate the deficiencies regarding declaration and composition of colorants, which are used to produce tattoo inks. Several Pigment Red 170 products containing the pigment are available on the market, even from one supplier. These are in most cases not specifically produced to be used in tattoo inks. Although the products have varying product names and colour shades, they share identical identifiers such as CAS, EC, or C.I. numbers. Additional information on the composition is missing. The safety data sheet (SDS) may only contain information according to the Regulation (EU) 2020/878. This information is incomplete for analytical profiling and therefore inadequate for a toxicological assessment and, thus, ink producers cannot guarantee the product quality according to the restriction on hazardous substances contained in tattoo inks (Entry 75 of Annex XVII, Regulation (EC) No 1907/2006).

Therefore, a harmonization according to the identity and the declaration is aspired. In addition, the BfR raises the topic that reference and standards materials are needed for analytical methods and any investigation of tattoo pigments and inks, especially for qualitative and quantitative determination. Furthermore, the long-term stability and metabolites of the pigments need to be investigated.

Current research projects regarding tattoo pigment analytics at the BfR are shortly introduced. The BfR is developing techniques for pigment analytics: HPLC-DAD- and -MS analyses of the soluble fraction after tattoo pigment extraction into organic solvents as well as FT-IR-analysis of the tattoo pigments and inks. Additionally, the BfR plans a study for the assessment of the dynamic solubility of tattoo pigments. During this study, in addition to the identification of potentially toxic substances released during pigment dissolution under physiological conditions, the influence of UV-radiation and temperature will be taken into account. In general, issues regarding the analysis of tattoo inks will be addressed in the analytical subcommission.

During the toxicological part of the presentation, the BfR introduces the sequential testing procedure described in the minimum requirements to the commission members. It is pointed out that toxicological *in vitro* testing is only required if data gaps are identified during collection and assessment of available data.

The relevant endpoints for tattoo inks from the BfR minimum requirements, which were discussed in the 2nd and 3rd meeting of the expert panels[3,4], are reviewed during the 1st BfR commission meeting. Because toxicological data for tattoo pigments are available under REACH and during the expert panels tattoo ink producers have suggested to trust this data, the overlap of REACH requirements and the BfR MRs is shown by BfR. BfR raises the question if and to which extend REACH data can be used to fulfil the BfR minimum requirements. Therefore, the BfR has started two pilot studies for the endpoints genotoxiticity / mutagenicity and skin sensitisation. In these pilot studies the data submitted according to REACH requirements for specific pigments and the data publically available at ECHA´s dissemination site[5] have been evaluated. For genotoxicity / mutagenicity the following issues have been identified:

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[3] Operable minimum toxicological requirements: 2nd Expert discussion at BfR on tattoo inks - Communication No 030/2022 of the BfR from 8 November 2022 https://www.bfr.bund.de/cm/349/operable-minimum-toxicological-requirements-2nd-expert-discussion-at-bfr-on-tattoo-inks.pdf

[4] Toxicological testing requirements to be developed: 3rd Expert discussion at the BfR on tattoo inks, Communication No 031/2022 of the BfR from 9 November 2022 https://www.bfr.bund.de/cm/349/toxicological-testing-requirements-to-be-developed-3rd-expert-discussion-at-the-bfr-on-tattoo-inks.pdf

5 https://echa.europa.eu/de/information-on-chemicals/registered-substances

1. The cellular uptake of (nano-)particulate substances is a premise for genotoxic testing. Confirmation of cellular uptake is only available for a minority of the investigated studies. Many pigments are nanoparticles. Therefore, acceptability of the studies needs to be discussed.
2. The information about the purity of test substance used in the *in vitro* tests analyzed is inconsistent or not available.
3. The pigment titanium dioxide was assessed by EFSA[6] recently. As a result, the European Commission banned its use in food from summer 2022. It needs to be clarified what consequences can be drawn for its use in tattoo inks.

For the endpoint skin sensitisation, data available from the ECHA´s dissemination site has been reviewed by the BfR to assess their acceptability to fulfil the BfR minimum requirements. As tattoo inks are injected intradermally, no conclusion about the sensitising potential of the pigments can be drawn from a negative outcome of tests that use dermal (topical) application like patch tests, the local lymph node assays (LLNA) or Bühler tests, because insufficient dermal absorption through the skin barrier could lead to false-negative test results. Therefore, negative test outcomes are considered as not acceptable for the risk assessment of tattoo inks. In contrast, positive test results will be considered as predictive because sensitising properties following topical application are also expected to occur after intradermal application. For the application of read-across approaches and the consideration of test results from studies that have not been performed according to the OECD-test guidelines, guidance needs to be developed in the Subcommission Toxicology. So far, the only acceptable *in vivo* test is the guinea pig maximisation test (GMPT) according to Magnusson und Kligman[7].
Preliminary observations of the information for the endpoint skin sensitisation available on ECHA's dissemination site for selected pigments are:

1. Identity and purity of the test substance were often inconclusive or unknown.
2. For the majority pigments no useful data for risk assessment of tattoo inks for the endpoint skin sensitisation were available.
3. For some of the data expert judgement is necessary.
4. *In vivo* experiments (animal data) with sensitising pigments were not found, even for pigments that have been tested positive in humans.
5. Guidance for nanomaterials is needed.

**Item (TOP) 7 Questions to the BfR Commission and formation of subcommissions**

A summary of the questions from the previous presentations (TOP 6) is given as a basis for the foundation of the subcommissions for analytics and toxicology. Additional potential subcommissions for technology and hygiene, exposure and clinics are suggested. The BfR comments that the focus should lay on analytics and toxicology for now and further subcommissions can be founded in the future. Commission members of the United States Food and Drug Administration (FDA) explain that the FDA is currently working on a guidance document regarding hygiene of tattooing. Regarding the topics of the Hygiene Subcommission the BfR suggests only discussing ink hygiene, since other aspects of hygiene, for instance in tattoo studios, are not in the remit of the BfR commission. Furthermore, a subcommission of technology is suggested, in which questions like the sources and processing of pigments and inks as well as technical practicability of limit values could be discussed. The discussion concludes with the understanding that technology and hygiene are highly connected topics and thus a combined Subcommission Technology & Hygiene will be founded. A subcommission for clinical aspects is refused because clinical aspects are the basis of toxicological assessment and should be addressed in the Subcommission Toxicology. In conclusion, the following three subcommissions are established:

6 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2021.6585

7 https://www.oecd-ilibrary.org/environment/test-no-406-skin-sensitisation_9789264070660-en

- Analytics
- Toxicology
- Technology & Hygiene

Furthermore, it is decided that commission members can participate in more than one subcommission. The BfR asks the commission members to select the subcommissions in which they want to participate and a short poll is conducted to record their vote. Commission members which have not been able to participate in the 1st commission meeting will be asked via E-mail.

The result of the formation of the subcommissions of the BfR Commission on tattoo inks is as follows:

| Member | Subcommissions | | |
|---|---|---|---|
| | Analytics | Toxicology | Technology & Hygiene |
| Nathalie Alépée | | X | |
| Wolfgang Bäumler | | X | |
| Marilena Carbone | X | | |
| Greta Dau | X | | X |
| Michael Dirks | X | | X |
| Marco Famele | X | | |
| Milena Foerster | | X | |
| Stephan Große-Büning | | X | |
| Birgit Gutsche | X | | |
| Urs Hauri | X | | |
| Sarah Hedtrich | | X | |
| Cornelia Hildebrandt | X | | X |
| Veit Houben | X | | |
| Carola Jagota | X | | |
| Robert McGowan | | | X |
| Ralf Michel | X | | X |
| Bhakti Petigara Harp | X | | |
| Frederike Reischies | | X | X |
| Steffen Schubert | | X | |
| Olaf Seidel | | X | X |
| Zemin Wang | | X | |
| Carina Wolf | X | | |
| Yu (Janet) Zang | | X | X |

**Item (TOP) 8 Date of next meeting and meetings of the subcommissions**

It is discussed, if the 2nd commission meeting should be held in presence. The participants of the meeting give their consent. Additionally, members suggested a 2-day meeting, because the subcommissions have to meet on the first day to then present their results on the 2nd day. The members endorsed the proposal to facilitate arrivals and departures. The BfR suggests two options 14th / 15th and 15th / 16th of November 2023. The commission members agree on 15th / 16th November with 15 of 18 votes. At the time point of discussion, only one member excludes a participation. Some members offer a venue. The commission president invites to Dept. of Chemical Science and Technologies, University of Rome Tor Vergata, Italy. Alternatively, Frankfurt (Main) and Köln are suggested.

The commission members inquire whether it would be feasible to schedule subcommission meetings separately and prior to the main commission meeting, to focus and define the scope and reduce workload of the subsequent 2nd commission meeting. The BfR explains that the subcommission meetings shall be held directly before the commission meeting and results will be presented in summary for discussion in the commission meeting. Prior to the subcommission meeting, online calls of the subcommission members can be held to prepare for the upcoming subcommission meeting. The organisation of the meeting should be coordinated soon. Upon request the BfR confirms, that the agenda of the 2nd commission meeting will be send in advance and that external experts can be invited to the commission meetings. Members inquire if heads for each subcommission will be elected or if these will be organised by the BfR. BfR confirms that it will coordinate the individual subcommission – including possible prior online calls – and that no subcommission heads will be elected.

**Item (TOP) 9 Presentation of the BfR Dermatotoxicology Study Centre**

The lead of the BfR Dermatotoxicology Study Centre presents the current research with regard to allergy, phototoxicity, biokinetics, biodistribution and exposure of tattoo inks. At the end of the presentation potential impurities and purification of the investigated pigments are discussed. The lecturer points out that pure pigments are difficult to access and information on pigment identity and purity is sparse. Furthermore, analytical test methods are largely missing. From the commission members it is asked, if the BfR is able to analyse impurities. The lecturer answers that the impurities have not been quantified, because of missing capacities. Nevertheless, impurities like Naphthol AS and primary aromatic amines were identified. Subsequently, the sensitising potential of Naphthol AS was discussed.

**Item (TOP) 10 Further current research activities at BfR**

BfR presents the work on Quantitative Structure Analysis (QSAR) and the ongoing project on the applicability of *in silico* New Approach Methods (NAMs) for the risk assessment of components of tattoo inks. A newly developed QSAR model specific for tattoo pigments for the endpoint genotoxicity is presented. It is remarked that experimental data are available for Pigment Green 7 and Pigment Blue 15:3. The presenter expresses interest in the origin of those data to use it for further improvement of the model. Secondly, BfR presents the ongoing research on mutagenicity testing of tattoo pigments, especially the work on the Ames Test. Different aspects according to solvents as dispersion medium (water vs. DMSO) and leachable substances are discussed, which could be tested in further experiments.

**Item (TOP) 11 AoB**

The commission manager summarises the formation of the subcommissions and declares that the activities of the commission will start soon. In parallel, the BfR will update the minimum requirements. The BfR asks if further points need to be discussed or if there are comments or suggestions of the commission members.

The BfR comments on a request for a time line, that REACH data are revised for pigments included in aforementioned pilot project at the moment. Until the end of the year, a selection of the most important pigments will be prepared in cooperation with the Subcommission Hygiene & Technology. Furthermore, a consultation with the FDA is planned.

Commission members indicate with regard to the 5-batch analysis of pigments that changes in the composition and impurity profile of pigments have been detected, recently. These changes may be caused by shifts or modifications of the supply chains over the last years. Furthermore, it is mentioned that for Pigment Blue 15 at least two different manufacturing methods are used and

result in individual impurities. Commission members propose that batches can also be different. The BfR confirms that there is an urgent need of appropriate standards for tattoo pigments.

Purification with the goal to develop standards or cleaner pigments is in general considered difficult. However, this approach is considered as useful by some members. The BfR emphasises again, that - because of the intradermal application of tattoo inks - open questions regarding the identity and potential standards of tattoo ink pigments have to be addressed urgently. The BfR suggests that pigments with defined specifications within composition boundaries could be used.

The commission members point to the fact that common identifiers, like the C.I.-number, give no information about additional components that may be present in tattoo pigments. In addition, the trade name of the pigment is not reliable in terms of pigment identity and other identifiers are missing. Upon request of the BfR, if the SDS of the pigment producers or distributors are helpful, the commission members state that helpful information is not always available or partially even inadequate.

The BfR asks if there are suggestions by the ink manufactures for improvement with regard to the characterisation or purification of pigments or if the ink manufacturers would perform such activities in cooperation. However, the cooperation with the pigment producers is considered difficult by the ink manufactures. In addition, the so-called finishing of pigments by the pigment producers is seen as an issue. Additional components are added during the process that are not specified in the original SDSs of the pigments. One member suggests two solutions: Either the ink producers are analysing and purifying the pigments they use or they synthesise the pigments on their own. In general, a pharmaceutical purity is desired for tattoo pigments. The opinion of one member is that as long as tattoo ink producers buy pigments from big companies they will not know the exact composition of these tattoo pigments.

The decision of ECHA to restrict tattoo pigments under REACH is criticised by some commission members. It is further mentioned, that the downstream user does not receive sufficient information. The commission manager, thanking all participants for their attendance and the fruitful discussion, closes the session.