

2nd Meeting of the BfR Commission on Tattoo Inks

The BfR Commission on Tattoo Inks advises the German Federal Institute for Risk Assessment (BfR) as an honorary and independent expert body on issues of tattoo ink safety and risk assessment by giving counsel 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 (ISO) or the Organisation for Economic Co-operation and Development (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 decisions or expert opinions and is not authorized to issue instructions to the BfR (and vice versa) nor involved in its risk assessments.

Item (TOP) 1 Welcome and adoption of the agenda

The vice chairperson opens the commission's 2nd meeting and welcomes the participants acknowledging the subcommission meetings held the previous day and the last meeting in March 2023. She highlights the presence of all subcommissions together for the current meeting and invites attendees to raise objections or propose additions to the agenda if any.

Item (TOP) 2 Declaration on conflicts of interest

Participants are invited to declare any conflicts of interest, especially if changes occurred since the last meeting. The participants declare to have no conflict of interest. The consent of the participants to record the sessions is obtained.

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Item (TOP) 3 Summary of previous subcommission meetings on 15.11.2023

A commission member provides insights into advancements in analytical methods regarding tattoo pigments. The discussion covers updates on the development of analytical approaches, specifically focusing on the status of liquid chromatography coupled with mass spectrometry or diode array detector (LC-MS/DAD) and Fourier-transform infrared spectroscopy (FTIR) methods. Another commission member gives a presentation on the current analytical work carried out at their institute. Next, results of analyses aimed at identifying impurities and non-declared substances in tattoo inks are presented. Findings include reports of metals, formaldehyde, and incorrectly declared pigments in inks. However, no chemical identification and quantification of pigments is currently carried out on a routine basis. The average ratio of incorrectly declared pigments is assumed to be approximately 50%. The labelling accuracy varies depending on the supplier or manufacturer. It is also discussed how to further develop the analysis of inks and pigments. Considerations on how to dissolve and analyse them effectively are expressed. Additionally, concerns are raised about the lack of comprehensive information on commercially used pigments and emphasis is put on the need for details beyond common identifiers like the "Colour Index Generic Name". The difficulty to obtain essential information about pigment finishing by manufacturers is acknowledged.

Two talks on toxicology are given. In one presentation about skin models, work on artificial inflows and organ-on-a-chip modelling is shown. These methods are welcomed by commission members and are proposed for testing in combination with pigments. As the immune system differs across different organs due to unique microenvironments, cell compositions, and functional requirements, it is challenging to mimic dendritic cell activity and T-cell activation in these *in vitro* systems. Another commission member presents an overview report on the risk assessment for the endpoint of skin sensitisation within a pilot project. Additionally, the focus is put on the uncertainties related to the solubility and the purity of pigments as well as the need for further studies to establish limit values for each pigment. In the following discussion it is noted that this approach might be interesting not only for skin sensitisation but also for other endpoints. Furthermore, members agree upon the need of studies from which limit values can be derived and that those studies need to be performed for every relevant pigment.

Next, a commission member presents the priority list of pigments. Participants are invited to provide any additional points to or corrections on the priority list of pigments which was circulated by the BfR beforehand.

An expert presentation by the Fraunhofer Institute for Microengineering and Microsystems (IMM) is given on the experimental determination of dynamic solubility using a prototype setup. This will be used in a cooperation between BfR and Fraunhofer IMM for the assessment of the dynamic solubility of tattoo pigments.

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Item (TOP) 4 BfR – Key pigments in today’s tattoo inks

BfR shares insights into the tattoo pigment market and presents data from the Danish company “Inkbase” which is operating since 2018. It is a data management system for tattoo studios, linking information on ink bottles to barcodes or numbers. The detailed information can include distributor, producer, colourant, log number, expiration date and basis and is provided by the tattoo studios. The system's advantages, such as direct and time-correlated mapping of pigment applications in populations, and limitations, including the lack of information about additives or ingredient ratios and the reliance on the honesty and accuracy of the tattoo studios when entering the data, are noted.

Based on Inkbase data, the pigment usage in 2018/2019 and 2022/2023 is analysed and compared while the pigments are categorised and their regulatory status is assessed. The genotoxic potential is discussed, focusing on aromatic amines and links in certain pigments. Based on the 2022/2023 data, new pigments are found on the market: red diketopyrrolopyrrole compounds, Pigment Yellow 138 and Pigment Blue 60 (Indanthrone) which is known to be used as replacement for Pigment Blue 15. It is summarised that the 13 most important pigments - including carbon black and titanium dioxide - cover 92% of all tattoo applications.

During the discussion, potential biases or errors in the data regarding several pigments or colours are highlighted. The participating tattoo studios and correctness of information provided by these studios are mentioned as possible reasons. The importance of considering biases in data collection, inaccuracies in ink labelling by the manufacturers and the need for continued analysis of new pigments is emphasised.

Based on the comparison of the pigment lists from 2018/2019 and 2022/2023 it is noted that some studios still enter the use of inks with declared, forbidden pigments into the system. On the other hand, azo pigments are less often declared. The introduction of new pigments on the market is acknowledged, underlining the need for a toxicological assessment of these substances. The importance of addressing impurities in new pigments, especially those without harmonised classification, is stressed.

Potential differences regarding the tattoo ink market between Denmark and Germany are mentioned. It is cautioned against putting too much faith in current market share data, and the need to focus on future developments is emphasised. One commission member introduces a study regarding tattoos from the Information Network of Departments of Dermatology (IVDK) that focusses on sensitisation. The challenges related to false declarations of pigments in tattoo inks and the lack of available patch tests are mentioned. A possible collaboration with the BfR to provide patch testing is discussed briefly.

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The lack of knowledge about pigments used in tattoo inks in the past 20 - 30 years and the uncertainty in any study related to tattooing or samples from that period is recognised. An ongoing analysis in Switzerland of over 150 tattoo ink samples from 2004 to understand historical pigment use is mentioned. Concerns are raised about the absence of an inventory system among tattoo studios. The ongoing discussions with the German tattooing association to collect voluntary inventory data is mentioned. One member advocates for a chemical survey to explore the current use of pigments in tattoo inks, emphasising the need for data.

A joint action in Europe on the analysis of tattoo inks is mentioned, but concerns are raised that the focus might be more on analysing contaminants than identifying pigments. The need for collaboration and sharing information regarding market information and methods is emphasised and the voluntary inventory of the German tattooing association is mentioned as an example. Participants express their hope regarding the potential of the Danish tattoo registry as a starting point for assessing pigments on the market but emphasise the importance of responsibility of ink producers and tattoo studios. A survey conducted by the group members to gather information on pigments used in tattoo inks is discussed and members are encouraged to participate and contribute accurate data. The challenges of implementing analytical methods for pigment identification and the importance of the survey as a practical starting point are acknowledged.

Item (TOP) 5 BfR – Data and sample submission

BfR emphasises the importance of collecting data and samples for the development and adjustment of analytical methods. Commission members highlight the need of detecting pigments and soluble components in tattoo inks, as well as developing methods for pigment dissolution and toxicological studies with a focus on human studies and new approach methodologies (NAMs). The collection of data sheets for pigments is mentioned and the need for corresponding analytics and physicochemical data is discussed. Handling of intellectual property and trade secrets and the obligation of commercial members to maintain confidentiality are discussed. It is noted that access to business or trade secrets may not be granted without consent. The involvement of members in the decision-making process in cases of doubt was discussed. BfR provides information on how to handle data submission and sample collection and shares the commission's functional email address for communication.

Item (TOP) 6 Next Generation Risk Assessment (NGRA): A concept and case study for skin sensitisation

In the next presentation, a commission member provides an overview of skin sensitisation, outlining its principles, and of the use of Adverse Outcome Pathways (AOPs) in the context of Next Generation Risk Assessment (NGRA) principles. The historical approach to risk

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assessment is discussed, which focussed on *in vivo* animal data, and the paradigm shift toward using *in vitro* and *in silico* data is highlighted. Emphasis is placed on adopting Defined Approaches (DAs) that integrate *in vitro* tools for assessing the risk of skin sensitisation. The presentation further explains AOPs related to skin sensitisation, outlining key events and mechanistic approaches. The speaker mentions the publication of a revised NGRA framework for skin sensitisation in the journal ALTEX (Alternatives for Animal Experimentation) and its adoption by regulatory institutions. A case study focussing on methyl dibromoglutaronitrile (MDBGN) and its use as a preservative in a face cream is discussed.

The presentation outlines the steps taken in the NGRA framework, including Tier 0, which involves identifying the use scenario and chemicals of concern; Tier 1, which focuses on hypothesis generation based on *in silico* alerts and physical-chemical properties; and Tier 2, which includes conducting *in vitro* testing to derive the point of departure for risk assessment. Commission members discuss the identified hazards and existing data, including *in silico* predictions, molecular structure and physicochemical properties. The limitations of read-across approaches are acknowledged, and the focus shifted to *in vitro* testing for skin sensitisation. The presentation covers the use of NAMs for skin sensitisation testing, referencing OECD-accepted tests, such as the Direct Peptide Reactivity Assay (DPRA), the KeratinoSens assay, and the h-CLAT. The shared results of *in vitro* testing on MDBGN confirm its sensitiser status.

During the following discussion several defined approaches are discussed and it is noted that one approach may not fit all cases. The importance of a detailed look is stressed, as a clear yes-or-no answer may not always be available or appropriate. The importance of concordant data for more confident risk assessments is acknowledged, as non-concordant data would lead to greater uncertainty. The risk assessment, including the determination of acceptable exposure limits, is discussed in more detail and nine principles for NGRA applicable to skin sensitisation and human safety are introduced. The need to address uncertainties at different levels (Tier 1, Tier 2, etc.) and to document them thoroughly is emphasised. Solubility issues and other limitations in the DAs and NAMs and the need to check for them are noted. Ongoing efforts to address more complex case studies and different chemical types as well as an initiating work on mixtures of lipophilic chemicals are mentioned.

Item (TOP) 7 BfR - Partnership for the Assessment of Risks from Chemicals (PARC)

A member of BfR provides an overview of the European Partnership for the Assessment of Risks from Chemicals (PARC) and its relevance to the BfR Commission on Tattoo Inks. He emphasises the collaborative nature of PARC, as a partnership between the European Commission and the Member States and further affiliated entities. He highlights PARC's mission to address chemical safety challenges as well as the transition to NGRA. The key points are summarised below:

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PARC includes work packages focusing on data generation, monitoring exposure, hazard assessment, regulatory risk assessment, and toolbox conception. The emphasis on synergies, cooperation, and awareness in PARC to connect partners within and outside of the project is mentioned. Some work packages are shortly outlined to explain the project in more detail. The NGRA roadmap activity “NGRARoute” and framework principle are introduced and the need for NGRA is stressed. Information on collaboration with the European Commission and on phasing out animal testing is shared.

The recently launched knowledge management and community platform PARCopedia (<https://parcopedia.eu>) is introduced as a means to connect and to exchange among chemical risk assessment professionals, to serve as a knowledge base, community hub and network. As its goal is to strengthen the scientific discussion and enable knowledge sharing, the commission members are invited to register at PARCopedia and participate in its community. In particular, PARCopedia also offers the possibility to create private discussion groups which may be used by activities focusing on chemical risk assessment (such as the tattoo ink commission) for timely communication between meetings.

Item (TOP) 8 Any other business

All members are satisfied with the discussion and no further points are raised.

Item (TOP) 9 Planning of the next meeting

A next round of online meetings is proposed and members agree that these smaller meetings help to stay in contact and updated. It is agreed to schedule them in February and that these meetings do not have to be on consecutive days. BfR has already distributed a poll to find the best date for each meeting.

Possible dates for the next general meeting of the BfR Commission on Tattoo Inks are discussed and after voting for different options it is decided that the next meeting of the BfR Tattoo Commission for Tattoo Inks will take place on the 17th and 18th of April, 2024, via an online conference.

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