Risk assessment and regulation of tattoo inks in the EU

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Current situation:

• Tattoo application in a regulatory ‘vacuum’:
  • Is not a medical treatment
  • Is not a cosmetic treatment

• No EU-regulation

Council of Europe ResAP(2008)1

• Harmful substances may be present in tattoo products

• No national regulations in most member states

• No European Community regulations

• As a first step towards ensuring that hazardous substances are avoided: a ‘negative’ list-approach
Council of Europe ResAP(2008)1 negative lists

• List of 27 azo dye-related aromatic amines
• CEN list of 35 colour pigments classified as carcinogenic, mutagenic, reprotoxic and/or sensitizing
• List in Annex II to the Cosmetics Directive 76/768/EEC (not acceptable in cosmetics)
• List of colourants with restricted use in cosmetics according to Directive 76/768/EEC
• Substances classified as carcinogenic, mutagenic or reprotoxic (CMR) of categories 1, 2 or 3 (categories 1A, 1B and 2 under the new CLP-classification)
• List of maximum allowed concentrations for metal and polycyclic aromatic hydrocarbon (PAH) impurities.
ResAP(2008)1 recommends:

- Member states take into account these negative lists in their national regulations

- Take steps towards an exhaustive list of substances proved safe for this use (“positive list”)

- Positive list based on safety assessments by competent bodies and harmonised at European level

- Q: What are the requirements for safety evaluation of tattoo ingredients?

- A subgroup of the CoE Committee of Experts on Cosmetic Products (P-SC-COS) is looking at this issue
Endpoints for safety assessment

1) Ink chemical and physical characterisation
2) Genotoxicity in vitro and in vivo assays
3) Local tolerance studies
4) Biokinetics
5) Repeated toxicity assay - Determination of the MOS_{repeated dose tox}
6) Carcinogenicity and/or reprotoxicity studies (if deemed necessary)
7) Exposure assessment and MOS calculation.
Genotoxicity

- Battery approach as used in many regulatory settings: in vitro assays followed by in vivo tests if necessary
- Tests identical to those used for cosmetic ingredients, pharmaceuticals
- In vivo Comet-assay suited for testing for local genotoxicity
- The formation of genotoxic photolytic degradation products to be evaluated on a case-by-case basis

Bottom line: genotoxicants should not be present in tattoo products
Local tolerance studies

• Initially, tattoo pigments in direct contact with tissue already damaged by tattooing process
• Skin irritation: question is, how much a skin-irritating tattoo ingredient would augment primary needle damage
• Typical skin irritation study with application on intact skin is incomplete model
• Intracutaneous Reactivity Test (developed in medical devices area) can be used
• Eye irritation with usual standard protocol
• Effect on wound healing
Local tolerance studies (cont’d)

• Phototoxicity (tiered approach with UV-absorption as initial test followed by in vitro tests)
  - In vitro 3T3 Neutral Red Uptake phototoxicity test (3T3 NRU-PT)
  - Further tests in human in vitro epidermis model
Local tolerance studies (cont’d)

• Sensitisation:
  - Magnusson Kligman Guinea Pig Maximisation Test (GPMT) with intradermal application
  - Data obtained with other tests with intradermal application

• Photo-sensitisation (in vitro, in vivo)
  - In vitro 3T3 NRU-PT photo toxicity test
  - In vivo intradermal test by Ichikawa et al (1981)

• Photo-genotoxicity: no adequate test available
  - In vitro clastogenicity test (chromosome aberrations or micronucleus test) oversensitive according to results evaluated by European Medicines Agency
Biokinetics

• Fate of pigments different from carrier fluid, including preservatives, conditioners etc.

• Soluble compounds will readily migrate into body fluids, with metabolism and excretion from the body

• Pigments: first distributed across epidermis and upper dermis area with some transepidermal loss

• Pigments end up ‘caught’ under basement membrane at epidermal/dermal border
Biokinetics cont’d

• Transport of pigment to lymph nodes both directly after application and over longer term
• Some pigment could migrate to blood stream, potentially causing systemic toxicity
• So (again): how much of the pigment leaks from tattooed skin site?
• Recommendation: carry out animal study for some representative pigments to find out
• Pigs or minipigs as test animal because pig skin is more representative of human skin than mouse or rat skin
Carcinogenicity

• Classified chemicals (1A, 1B, 2) should not be present in tattoo products
• Genotoxic chemicals already excluded
• New carcinogenicity studies needed in exceptional cases only
• Epigenetic carcinogens can be evaluated case-by-case (MOS-calculation)
Reproductive toxicity

• General warning needed that women planning pregnancy and women in their 1st trimester should not be accepted for tattooing (similar warning optional for 2nd and 3rd trimesters and during breastfeeding)

• R-classified chemicals should not be present in tattoo products

• For assessment of unclassified chemicals, teratogenicity study first priority

• If indications of reprotoxicity seen in repeated toxicity studies or endrocrine disruption shown, then specific reprotoxicity studies required

Bottom line: reproductive toxicants should not form part of tattoo inks.
Exposure assessment + Margin of safety calculation

• Similar as for cosmetics:
  • Margin of safety =
    \[
    \text{Animal}_{\text{NOAEL}} \text{[mg/kg bw]} \div \text{exposure mg/kg bw}
    \]

• Animal NOAEL from intravenous or oral study
• Exposure estimate requires figures for:
  - Tattoo area, pigment/cm², % leakage

→ Need for reasonable default values (initial estimates made based available information)
Where do we stand?

• Tension between wish for positive list and scarcity of data
• New experiments are needed to flesh out risk assessment but will want to fund them?
• If individual dossiers of pigments and ingredients were to be evaluated at the present stage of knowledge these evaluations would be incomplete
• Thus a positive list would be more of a ‘not so negative list’ (selection of the pigments with least unfavourable tox profile)
• Bottom line: pragmatism needed in any risk assessment at current state of knowledge
Possible EU-regulation

• Ongoing discussion within Consumer Safety Network of DG Health and Consumers
• Several member states favour legislation at EU-level
• “Costs for evaluation and legislation of products must be judged against expected health benefits”
• Because of increasing popularity of tattoos several member states consider matter urgent
• Scoping paper by EC in preparation to analyse cost and benefits of legislation
• New EU Commissioner to provide guidance on way forward
Aspects for possible regulation

Tattoo inks, chemical tattoo removers
• Chemical risks
• Microbiological risks

Tattooing needles
• Microbiological risks
• Chemical risks (nickel)?

Tattoo studios (service providers)
• Hygiene risks
• Qualification requirements

Permanent make-up

Ethical aspects

Such as a lower age limit for having a tattoo applied
Legislation on tattooing (and piercing) in the Netherlands

Colourants:

• Inks for tattooing and PMU have to fulfill CoE ResAP(2003)2, requirements of ResAP(2008)1 to be implemented shortly

Hygiene:

• A licence is required from the Dutch Minister of Health, Welfare and Sport (VWS) for tattoo/piercing shop, to be renewed after 3 years
Legislation on tattooing (and piercing) in the Netherlands cont’d

Regulations in force are:

• Materials must not harm safety and health of clients

• Application space must pose no danger for safety and health of clients

• Operators of tattoo and piercing materials must accomplish good personal hygiene

• Written information must be provided to clients about the risks of tattoo and piercing application and attended after care

• Age limits when a tattoo or piercing may be placed

Enforcement by the Netherlands GGD and the Netherlands Food and Product Safety Authority (NVWA)
Questions?