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## 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
- Noting regulatory gap, Council of Europe Committee of Experts on Cosmetic Products (P-SC-COS) has taken up the issue → ResAp(2003)2 and ResAp(2008)1

# 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  $MOS_{\text{repeated dose tox}}$
- 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 1<sup>st</sup> trimester should not be accepted for tattooing (similar warning optional for 2<sup>nd</sup> and 3<sup>rd</sup> 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 =

$$\text{Animal}_{\text{NOAEL}} [\text{mg/kg bw}] / \text{exposure mg/kg bw}$$

- Animal NOAEL from intravenous or oral study

- Exposure estimate requires figures for:

- Tattoo area, pigment/cm<sup>2</sup>, % 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 fulfil 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?