Science for Communities

# HEALTH RISK ASSESSMENT: HEAVY METALS (ANTIMONY, ARSENIC, BARIUM, CADMIUM, CHROMIUM, LEAD, MERCURY, AND NICKEL) IN TATTOO INK (INTRA-DERMAL CONTACT)

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Abhishek Gautam

ESR Risk Assessment, Food and Social Systems Group

**PREPARED FOR:** Manatū Hauora/Te Whatu OraT

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**REVIEWED BY:** Dr Rob Lake

| Peer reviewer | Management Reviewer | Project Manager |
| --- | --- | --- |
|  |  |  |
| **Dr Rob Lake**<br>Risk Assessment, Food and Social Systems Group | **Daniel Bohnen**<br>Manager, Risk Assessment, Food and Social Systems Group | **Peter Cressey**<br>Science Leader, Risk Assessment and Social Systems Group |

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# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| AAS | Atomic Absorption Spectrometry |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMD | Benchmark dose |
| bw | Body weight |
| CIR | Cosmetic Ingredient Review |
| CPR | Cosmetic Products Regulation |
| ECHA | European Chemicals Agency |
| ESR | Institute of Environmental Science and Research Limited |
| EU | European Union |
| FDA | US Food and Drug Administration |
| GC-MS | Gas Chromatography–Mass Spectrometry |
| HPLC-UV | High-performance Liquid Chromatography with UV detection |
| HSNO | Hazardous Substances and New Organisms Act 1996 |
| IARC | International Agency for Research on Cancer |
| ICP-MS | Inductively Coupled Plasma-Mass Spectroscopy |
| $LD_{50}$ | Lethal dose (which causes death in 50% of animals) |
| LOAEL | Lowest observed adverse effect level |
| MET | Minimal Elicitation Threshold |
| MOS | Margin of Safety |
| NACD | Nickel Allergic Contact Dermatitis |
| NOAEL | No Observed Adverse Effect Level |
| NPs | Nanoparticles |
| NPC | National Poisons Centre |
| NZ EPA | New Zealand's Environmental Protection Authority |

| | |
|---|---|
| PAHs | Polycyclic Aromatic Hydrocarbons |
| POD | Point of departure |
| REACH | Registration, Evaluation, Authorisation and Restriction of Chemicals (European Union) |
| RfD | Reference dose |
| SED | Systemic Exposure Dose |
| SCCP | Scientific Committee on Consumer Products (European) |
| TDI | Tolerable Daily Intake |
| TGA | Therapeutic Goods Administration (Australia) |
| TWA | Time weighted average |
| US | United States |
| USEPA | United States Environmental Protection Agency |
| WHO | World Health Organization |

# EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for heavy metals [Barium (Ba), lead (Pb), nickel (Ni), hexavalent chromium [Cr (VI)], mercury (Hg) cadmium (Cd), antimony (Sb) and arsenic (As)] in tattoo inks. While risks associated with other metals have occasionally been examined in relation to tattoo inks, these eight metals are of consistent concern and the current study is restricted to consideration of these eight metals. This report will only consider exposure to heavy metals in tattoo inks applied by professional tattoo artists. Temporary tattoos such as henna and risks involving self-tattooing are not under the scope of this report. This report also only includes common commercial tattoo inks and does not include other inks such as traditional tattoo ink from organic material or alternative ink such as fluorescent tattoo ink. Exposure scenarios will be developed for the most common or likely exposure events to permanent tattoos.

Tattoo application is regarded as one of the oldest forms of personal decoration and is widely performed all over the world. People get tattoos for many reasons: for fashion purposes (body art), religious purposes (for protection or as a source of power), as an indication of group membership, as a status symbol, as an artistic expression, for permanent cosmetics, and as an adjunct to reconstructive surgery. New Zealand is one of the most tattooed nations in the world. It is estimated that nearly one in five adult New Zealanders have been tattooed.

Tattoo inks may have high levels of heavy metals such as arsenic (As), hexavalent chromium [Cr (VI)], mercury (Hg), lead (Pb), cadmium (Cd), Nickel (Ni), antimony (Sb) and barium (Ba). This has led to product recalls over the years from the European market. There was no information available on product recalls in New Zealand. The source of heavy metals in tattoo inks is not exactly known. They may occur as components of pigments, coformulants and/or chemical impurities during the manufacturing of tattoo inks.

The regulation of tattoo inks varies around the world. In New Zealand, tattoo inks require approval under the Hazardous Substances and New Organisms Act 1996 (HSNO Act) implemented by the Environmental Protection Authority (EPA). For tattoo inks and permanent makeup substances, the approval is the Tattoo and Permanent Makeup Substances Group Standard. The NZ EPA has recommended maximum impurity concentration limits for some heavy metals.

There is some clinical evidence that heavy metals in inks might be responsible for allergic reactions, swelling, erythema and redness of the tattooed arm, cheek and lips as well as tongue. However, the evidence is very limited that the clinical symptoms were solely due to heavy metals as tattoo inks are mixtures of a variety of potentially hazardous substances.

In New Zealand, the National Poisons Centre (NPC) provided information that there were only 11 incidents of harm potentially linked to tattoo ink exposure (oral and intradermal) from years 2008 to 2022. In only two of these incidents the respondent was advised to seek medical attention. Both of these cases involved self-applied tattoos.

Exposure to heavy metals through tattoo inks is considered to be incidental. Tattoo ink is injected into the dermis and releases pigments (with other chemicals, impurities) that permanently stain the skin. Chemical components in the ink can migrate from the site of application through blood vessels and lymph nodes in the body and be deposited in different organs. Hence, the intra-dermal route is the main route of exposure to heavy metals in tattoo inks. Inhalation and oral exposure are not considered as relevant routes of exposure.

For exposure assessment, the concentrations of the respective heavy metals in tattoo inks were taken as the maximum concentrations from a New Zealand Ministry of Health (MoH) survey in 2012 of heavy metals in tattoo ink. It was assumed that a person receives a tattoo at an age of approximately 20 years and will have the tattoo throughout adulthood, that is, the balance (50 years) of a 70-year lifetime. It was further assumed that all heavy metals in the tattoo would eventually migrate from the dermis and that this process of migration would be constant. The exposure to heavy metals through tattoo ink was calculated following an approach used by the Danish Environmental Protection Agency on the safety of tattoo ink, with minor modifications. A daily systemic exposure dose (SED) was calculated for each heavy metal and combined with a suitable toxicological point of departure to give a margin of safety (MoS) to allow characterisation of risk. Human health risks from exposure to heavy metals in tattoo inks were evaluated by a MoS approach. The MoS was much greater than 100 for Ba, Ni, Pb Cd, Hg, As and Sb, which indicates that the presence of these metals in tattoo inks at the maximum concentrations reported is not a cause for health concerns.

# 1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for heavy metals [Barium (Ba), lead (Pb), nickel (Ni), hexavalent chromium [Cr (VI)], mercury (Hg) cadmium (Cd), antimony (Sb) and arsenic (As)] in tattoo inks. While risks associated with other metals have occasionally been examined in relation to tattoo inks, these eight metals are of consistent concern and the current study is restricted to consideration of these eight metals. Copper (Cu) and Zinc (Zn) were not considered in this assessment as both of these metals are micronutrients and are present in the diet and also available in supplements.

This report will only consider exposure to heavy metals in tattoo inks applied by professional tattoo artists. Temporary tattoos such as henna and scenarios involving self-tattooing are not within the scope of this report. This report also only includes common commercial tattoo inks and does not include other inks such as traditional tattoo ink from organic material or alternative ink such as fluorescent tattoo ink. Exposure scenarios will be developed for the most common or likely exposure events from permanent tattoos.

## 1.1 CONSUMER SERVICE DESCRIPTION – TATTOOS

Tattoo application is regarded as one of the oldest forms of body decoration and is widely performed all over the world (Karadagli *et al.*, 2022). The word ‘tattoo’ comes from a Samoan word ‘tatau’, which mimics the tapping sound of tools during tattooing. It is a permanent form of body modification in which pigments are inserted into the skin (dermis) with needles, bone or knives in order to create a design (DeMello, 2014).

The reasons for getting tattoos are numerous and varied around the world. They can be for fashion purposes (body art), religious purposes (for protection or as a source of power), as an indication of group membership, as a status symbol, as an artistic expression, for permanent cosmetics, and as an adjunct to reconstructive surgery. In New Zealand, traditional tattoos (Tā moko) are a customary form of a tattooing tradition for Māori and it is a widespread component of contemporary New Zealand culture (Martins, 2019). Tā moko reflects an individual's whakapapa (ancestry) and personal history and are taonga (treasure), protected by the Treaty of Waitangi (ArchivesNZ, 1840). In earlier times, it was an important signifier of social rank, knowledge, skill and eligibility to marry (Spasić, 2012).

In the past 20 years tattoos have gained significant popularity among young people in developed countries. In the US, 26% of the population have received at least one tattoo (USStatista, 2023). This proportion is at least 12% in the European population. The 18-35 age group is the most likely to have a tattoo (ECHA, 2022; Piccinini *et al.*, 2016). In New Zealand, it is estimated that nearly one in five adult New Zealanders have been tattooed, with tattoos more likely among women than men, and young people more likely than older individuals (NZEPA, 2020a; Sunsettattoo, 2016). A survey of New Zealanders aged 18 years or above found that 19% of all adults have been tattooed, with the rate among adults under 30 years being 36% (Sunsettattoo, 2016).

## 1.2 CONSUMER PRODUCT DESCRIPTION – TATTOO INKS

Tattoo inks consist of pigments combined with a carrier solution. A healed tattoo is a complicated array of ink particles trapped within dermal fibroblasts, macrophages, and mast cells.

### 1.2.1 Composition of tattoo inks

The exact composition of tattoo inks is not publicly available as it is a trade secret. In general, however, tattoo inks may contain vehicles (water, glycerine, alcoholic derivatives), additives (e.g surfactants and polymers) and pigments. The pigments used can be inorganic metallic salts (including salts of barium, cadmium, cobalt, copper, iron, nickel, manganese, mercury, titanium and zinc) or organic dyes, such as azo compounds (Kluger and Koljonen, 2012). The vehicle or carrier is used to keep the pigment evenly distributed in a fluid matrix, to inhibit the growth of pathogens, to prevent clumping of pigment, and to aid in application to the skin. Some other common ingredients in inks (irrespective of colour) are aluminium, titanium, and carbon. It should be noted that components may vary between brands, even in pigments with the same base colour (Arl *et al.*, 2019; Kluger and Koljonen, 2012).

### 1.2.2 Heavy metals in tattoo inks

Toxic heavy metals, Pb, Cd, As, Cr, Hg and Ni, may be found in tattoo inks. The presence of heavy metals has led to product recalls in the European Union (EU).

Many pigments in the tattoo inks are manufactured from heavy metal salts and/or their oxides. These are generally used in bright colours such as red to give a more vibrant colour that will last a long time without fading (Forsberg, 2023; Tighe *et al.*, 2017). They may occur as components of pigments, coformulants and/or chemical impurities during the manufacturing of tattoo inks. Some of the heavy metals that may be present in specific ink colours are:

- Blue – cobalt (Co), copper (Cu)
- Green – chromium (Cr), lead (Pb), aluminum (Al)
- White – barium (Ba), zinc (Zn), lead (Pb), titanium (Ti)
- Red – iron (Fe), cadmium (Cd), mercury (Hg)
- Yellow – zinc (Zn), lead (Pb), cadmium (Cd)
- Brown – iron (Fe)
- Orange – cadmium (Cd)

Several studies have determined the concentrations of heavy metals in tattoo inks:

1. The Danish EPA conducted a survey in which 61 tattoo inks were analysed for metals and other elements (Miljøstyrelsen, 2012). The inks purchased were of 10 different colour series. Samples were available in Europe, but from a variety of international manufacturers. Analyses were conducted by inductively coupled plasma-mass spectrometry (ICP-MS). Ni, Cu and Pb were detected in all samples. The highest concentrations of Ni, Cu and Pb were 18, 140 and 10 mg/kg, respectively. Cr was detected in 57 samples, with the highest concentration being 31 mg/kg. Because ICP-MS was used for the analysis, it was not possible to distinguish between Cr (III) and Cr (VI). Hg was detected in two samples at 0.11 mg/kg (peach) and 0.038 mg/kg (blue). Cd was detected in 45 samples and the highest concentration was 0.27 mg/kg.

2. The New Zealand Ministry of Health (MoH) conducted a survey of heavy metals in tattoo ink samples (n = 169) in 2012 (MoH, 2013). Only the metals with limits recommended by the Environmental Protection Authority (NZ EPA) (Table 1) were analysed. The aim of the survey was to determine whether the tattoo inks complied with the maximum impurity limits of heavy metals (Table 1) recommended by the NZ EPA. The majority of heavy metals were analysed by microwave digestion in acid, followed by ICP-MS analysis. Cr (VI) was analysed using a modified version of the US EPA Method 218.7, which involves ion chromatographic separation, post-column derivatisation, and ultraviolet-visible detection of Cr (VI). This method is primarily

intended for Cr(VI) detection in drinking-water samples, and the limit of detection (LoD) for ink matrices was not reported.

All the samples were compliant with Co, Se and Cr (VI) guideline levels (0.5, 2 and 0.5 mg/kg, respectively). The highest levels of total Hg, As, Cd, Pb, Ni, Ba and Sb were 0.6, 60, 0.8, 45, 23, 17000 and 147 mg/kg, respectively.

3. Heavy metal concentrations in four brands of tattoo ink samples (n = 56) available in the Italian market have been reported (Forte *et al.*, 2009b). The heavy metals were quantified by ICP-MS. The metal concentrations were highly variable between samples, brands and even among like-coloured pigments. Among the allergenic metals, Cr showed the highest concentration followed by Ni and then Co. The following concentration ranges were observed (in mg/kg): Cr, 0.3 - 147; Ni, 0.04 - 9.6; Co, 0.003 - 6.4; Pb, 0.02 - 14.8 and Cd, 0.001 - 3.0. Hg was either present at trace[1] levels or was undetectable.

4. In another study by the same Italian research group, metal content was quantified in tattoo inks (n = 13) purchased online from one Italian tattoo ink supplier (Forte *et al.*, 2009a). The heavy metals were quantified using ICP-MS. As in the study in the preceding paragraph, the metal concentrations in tattoo inks were highly variable between samples, brands and like-coloured pigments. The metal present at the highest concentration was Cr in all the pigments (0.3 - 4.7 mg/kg) followed by Ni (0.04 - 2.3 mg/kg) and Cd (0.007 - 1.2 mg/kg). Co (0.003 - 0.13 mg/kg) and Hg (<limit of quantification - 0.18 mg/kg) were present at substantially lower concentrations.

5. Tattoo inks were analysed for heavy metals (Zn, Cd and Pb) in 100 samples of different colours of tattoo inks purchased from cosmetic stores and markets in Tehran, Iran (Eghbali *et al.*, 2014). The samples were analysed by flame emission spectrophotometry. Cd and Pb were detected in all the samples. The black inks had the highest mean concentration of Pb (57 mg/kg). The highest mean concentration of Cd was found at 2.14 mg/kg in the white tattoo inks.

6. Heavy metals (including As, Ni, Cd, Cr, Pb, and Hg) were quantified in tattoo ink samples (n = 16) of different colours by ICP-MS (Di Gaudio et al., 2023). This study by Italian researchers used samples from two Chinese manufacturers. The total concentrations of metals in the 16 analysed tattoo ink samples ranged from 60 to 16900 mg/kg. Allergenic metals (Cr, Ni and Co) were present in all the samples. The mean (range) concentrations of the metals Co, Ni and Cr all the ink samples were- Co: 0.2 (0.02 - 0.57); Ni: 7 (0.43 - 43); Cr: 2.2 (0.57 - 5.6); Cd: 0.63 (0.02 - 2.6) and Pb: 0.54 (0.12 - 1.6) mg/kg.

7. Tattoo ink samples (n = 16) of different colours purchased from various shops in the Republic of Korea, were analysed for heavy metals (Cd, Pb, Sb As and Ni) by ICP-MS (Lim and Shin, 2015). The analytical results showed a great variation in the concentration of the chemical substances detected in the tattoo inks. Hg was found in all samples, with the mean concentration (range) of 0.0027 (0.0003 - 0.014) mg/kg. Cd was found in 8 of the 16 samples, with a mean concentration (range) of 0.6 (0.1 - 7.8) mg/kg. Cr was found in 14 out of 16 of the analysed tattoo ink samples, with a mean concentration (range) of 6.1 (1.4 - 23.5) mg/kg. It was not possible to distinguish between Cr(III) and Cr(VI) with the ICP-MS method used. Pb and Sb were found in only 2 out of 16 of the analysed tattoo ink samples. The mean concentration (range)

[1] Trace refers to concentrations above the limit of detection but below the limit of quantification

of Pb and Sb in the samples was 1.6 (6.2 - 20.1) and 1.6 (6.5 - 20.1) mg/kg, respectively.

8. Tattoo inks of different colours (tsunami blue, black, white, violent violet, tomato red, forest green and deep yellow) were analysed for heavy metals (Cd, Cr, Cu, Ni and Pb) using atomic absorption spectrometry (AAS) (Manso *et al.*, 2019). The brand of the samples in this European study was given but not the country of manufacture. The concentration ranges for Pb and Cu were 0.0008-0.009 mg/kg and 0.003-13.9 mg/kg, respectively. Cr (0.003 mg/kg), Ni (0.0004 mg/kg) and Cd (0.0002 mg/kg) were detected above the LoD in the black ink only.

9. Cr (VI) was quantified in tattoo inks (n = 22) of different colours using ion chromatography and ICP-MS (Bocca *et al.*, 2018). The total Cr and Cr (VI) levels in all inks ranged from 0.22 to 4.72 and 0.16 to 4.09 mg/kg, respectively. The total Cr and Cr (VI) levels were not statistically different with respect to the origin of samples.

## 1.3 RELEVANT LEGISLATION

### 1.3.1 New Zealand

Tattoo inks are hazardous substances and hence, require approval to import or manufacture under the Hazardous Substances and New Organisms Act 1996 (HSNO Act) implemented by the NZ EPA (NZEPA, 2020a). For tattoo inks and permanent makeup substances, approval is provided through compliance with the Tattoo and Permanent Makeup Substances Group Standard. The group standard sets out rules and conditions to manage the chemical risks associated with tattoo inks and permanent makeup substances (NZEPA, 2020c). The NZ EPA has recommended the maximum impurity limits for some heavy metals(Table 1) (NZEPA, 2020b).

**Table 1: Maximum concentrations of heavy metals in tattoo inks**

| Substance name | CAS Number | Concentration limit (ppm) |
|---|---|---|
| **As** | 7440-38-2 | 0.5 |
| **Ba** | 7440-39-3 | 500 |
| **Cd** | 7440-43-9 | 0.5 |
| **Cr (VI)** | 7440-47-3 | 0.5 |
| **Co** | 7440-48-4 | 0.5 |
| **Cu** | 7440-50-8 | 250 |
| **Hg** | 7439-97-6 | 0.5 |
| **Ni** | 7440-02-0 | 5 |
| **Pb** | 7439-92-1 | 0.7 |
| **Sb** | 7440-36-0 | 0.5 |
| **Sn** | 7440-31-5 | 0.5 |
| **Se** | 7782-49-2 | 2 |
| **Zn** | 7440-66-6 | 2000 |

Sb: Antimony; As: Arsenic; Ba: Barium; Cd: Cadmium; Cr: Chromium; Co: Cobalt; Cu: Copper; Pb: Lead; Hg: Mercury; Ni: Nickel; Sn: Tin; Se: Selenium; Zn: Zinc; CAS: Chemical abstract service

There are also requirements for packaging and labelling of tattoo inks. For example, if there are traces of Cr (VI) and Ni in the tattoo ink or permanent makeup, a warning statement “Contains Cr (or Ni). Can cause allergic reactions” should appear on the package (NZEPA, 2020b).

### 1.3.2 United States (US)

In the US, tattoo inks and permanent makeup are considered as cosmetics and are regulated under the Federal Food, Drug and Cosmetic Act sections 601 and 602, administered by the U.S. Food and Drug Administration (FDA) (FDA, 2022). Since tattoo inks are cosmetics they do not require pre-market review or approval. The FDA only intervenes in the tattoo ink market when an issue with a specific product becomes apparent. This happened in 2019 when the FDA learned that three tattoo ink products had been contaminated with bacteria. This led to voluntarily recalls of products from the market (FDA, 2021).

### 1.3.3 European Union / European Economic Area (EU / EEA)

In the EU, chemicals used in tattoo inks are restricted under the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation (ECHA, 2022). The restriction covers chemicals:

1) that have an EU-wide classification of carcinogen, mutagen or as toxic to reproduction; skin sensitiser; skin corrosive; skin irritant; eye irritant; or eye damaging,

2) are included in the Cosmetic Products Regulation (CPR (EC) No 1223/2009).

In 2020, the EU adopted legislation (1907/2006) that restricts the use of certain substances in tattoo ink. The restriction introduced concentration limits for a range of chemicals, including metals (EU, 2020). The EU limits are the same as the New Zealand limits as shown in table 1.

## 1.4 PRODUCT RECALLS

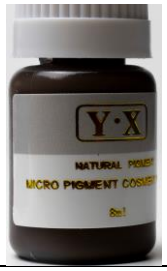
Tattoo inks may contain toxic heavy metals such as Pb, Ni and Cd above regulatory limits. This has led to product recalls of various tattoo inks in the EU. There were other alerts related to tattoo inks which were due to polycyclic aromatic hydrocarbons (PAHs) and other organic contaminants which are not covered under the scope of this report. While product recalls of tattoo inks have occurred in the US, these were due to microbial contamination rather than high levels of heavy metals (FDA, 2021).

In the EU, the Safety Gate alert system contains around 313 alerts or recalls of tattoo inks (from year 2010 to the present). Out of the 313 alerts, 88 of them were due to high levels of metal contaminants, 194 were due to organic contaminants, 23 were due to both metal and organic contaminants, and 8 were due to microbiological contamination. A representative selection of the recent recalls due to heavy metal contamination are summarised in Table 2. All the products did not comply with the REACH regulation.

**Table 2: Product recalls from the EU (from year 2010)**

| Name of Product | Hazard |
|---|---|
| Dynamic viking Ink, colours co.  | Excessive concentration of lead; up to 25% by weight (250,000 mg/kg). |
| | |

| | |
|---|---|
| Fleis academy expert SERIES  | Excessive concentration of cobalt; up to 0.000178% by weight (1.78 mg/kg). |
| Imperial tattoo ink florentine roof  | Excessive concentration of cobalt; up to 1.5 mg/kg. |
| DLD Permanent tattoo  | Excessive concentration of lead; up to 1.8 mg/kg. |
| Quantum future eyebrow pigment  | Excessive concentrations of nickel and cobalt; 12 mg/kg and 2.4 mg/kg, respectively. |
| Premium tattoo ink Tomato is red  | Excessive concentrations of lead and arsenic; 18 mg/kg and 0.54 mg/kg, respectively. |
| Kuro sumi colours tattoo ink Deep yellow  | Excessive concentration of lead; up to 1.1 mg/kg. |
| XLNT Brows Milano brown  | Excessive concentration of cobalt; up to 1.8 mg/kg. |

| | |
|---|---|
| Stigma True Black  | Excessive concentration of lead; up to 0.96 mg/kg. |
| Solong tattoo True black  | Excessive concentration of lead; up to 1.3 mg/kg. |
| Natural Pigment Brown Coffee  | Excessive concentrations of arsenic, cobalt, lead and nickel; 2.6 mg/kg,11 mg/kg, 0.90 mg/kg and 12 mg/kg, respectively. |
| Dimension Dark Brown Tattoo Ink  | Excessive concentrations of arsenic, antimony, cobalt, lead and nickel; 8.1 mg/kg, 1.3 mg/kg, 9.2 mg/kg, 3.4 mg/kg, and 60 mg/kg, respectively). |
| Eternal Ink Deep Red  | Excessive concentration of arsenic and nickel; 0.91 and 1.5 mg/kg, respectively. |
| Natural Pigment Black Coffee  | Excessive concentration of cobalt and nickel; 16 mg/kg and 12 mg/kg, respectively. |

| | |
|---|---|
| Micro pigment gray  | Excessive concentration of lead and has nickel; 1.7 mg/kg and 0.66 mg/kg, respectively. |
| Doré 225 Burnt Sienna  | Excessive concentration of cobalt; up to 1.2 mg/kg. |
| Bevaro Kola   | Excessive concentrations of cobalt and nickel; up to 14 mg/kg and 60 mg/kg, respectively. |
| International Seduction Colours  | Excessive concentration of cobalt; up to 4.71 mg/kg. |

### 1.4.1 New Zealand

There were no reports of tattoo ink recalls in New Zealand due to heavy metal contamination based on general search performed on google and Product Safety NZ website.

# 2 HAZARD IDENTIFICATION

## 2.1 PREVIOUS ASSESSMENTS

The New Zealand MoH conducted a survey of heavy metals in tattoo ink samples and compared the concentrations to the maximum impurity limits recommended by the NZ EPA. However, no health impact assessment was performed.

## 2.2 HEALTH EFFECTS – HEAVY METALS IN TATTOO INKS

### 2.2.1 Observations In humans

#### *2.2.1.1 Incident surveillance – New Zealand*

The National Poisons Centre (NPC) provided surveillance information on reported exposures to tattoo inks (Lucy Shieffelbien, National Poisons Centre, personal communication). From the years 2008 to 2022, a total of 11 human exposure records were identified. All the subjects aged 0-5 years (n=7) ingested small amounts of tattoo ink, while other patients had been tattooed and had concerns.

Seven patients were female, three were male, and one was of unknown gender. A total of 8 patients were asymptomatic and one had minor effects (headache). These patients were advised on home treatment or that no treatment was necessary (9 of 11; 82%). Two (adult) patients were cases of self-tattooing which are not under the scope of this assessment. These patients suffered skin burn – the skin was blistering, swelling and paralysis, which may be related to the tattooing process rather than the ink used. However, no information is available on the source of tattoo inks used.

#### *2.2.1.2 Incident surveillance – International*

1) A 31-year old person was tattooed over the entire trunk and both arms with red, yellow, green and black pigments (Hanada *et al.*, 1985). After one year, numerous pruritic nodules developed at red tattoo sites. Skin lesions, fatigue, high fever, non-productive cough and enlargement of right axillary and bilateral inguinal lymph nodes also developed. Several eyesight disorders also occurred. A patch test with 2% mercuric sulphate and 10% tattoo pigments in petrolatum album (petroleum jelly) was negative after 48 hours indicating that the symptoms were not due to an allergic response. Clinical chemistry and haematological parameters were all normal.

   Electron microscopic appearance of some red pigment in the skin lesions had both fibrous elements with high electron density and large crystal particles with low density, which were intermingled in the cytoplasm. Crystal particles were observed in yellow pigment and also irregular shaped granules were interdigitated in green pigment. Electron microscopic observation of the lung tissue revealed the existence of fine fragments of pigment granules, similar to those of red and black pigments in the skin lesions. Electron-probe microanalysis showed several significant peaks in the skin specimens; Si, Al and Hg in the red pigment; only Si in the yellow pigment; Pb and Ba in the green pigment. Fibrous fragments from the lung specimens showed peaks of Si, Al and Hg or Pb (the sections were stained by lead citrate), indicating a similarity to those in the red pigment. It was inferred that tattoo pigments were responsible for sarcoidal granuloma formation in multiple organs, since all lesions appeared after tattooing. Silica granuloma of the skin as well as pulmonary silicosis and tattoo granuloma brought about by red pigment containing mercury are also well documented.

2) In another case, a 59-year old man presented with rapidly progressing swelling and redness of the tattooed left arm, left cheek and lips as well as his tongue (Jungmann *et al.*, 2016). These effects appeared 5 hours after receiving the tattoo. Another hour later he appeared in the emergency room with a grade 3 systemic anaphylaxis. The patient was able to get ink samples (n = 2) from his tattooist, which were analysed using ICP-MS, HPLC-UV and GC-MS. Two allergenic elements, Ni and Mn, were detected in the black and white ink at concentrations of 5.2 and 60 mg/kg, respectively. Formaldehyde was also detected in the black ink. Since, Ni and Mn are known allergens, a combined effect of the preservative and metal impurities was proposed as triggers for the observed symptoms, however, the patient refused further sensitivity testing.

3) An unusual case of mercury poisoning was reported in a 14-year old male adolescent who underwent amateur tattooing to his left arm, with the tattoo completely disappearing after three weeks (Prantsidis *et al.*, 2017). After 20 days, he developed persistent inflammation and erythema in the arm. X-ray imaging of the arm showed multiple confluent subcutaneous opaque deposits in the soft tissues of the arm. Metallic foreign bodies were found in the incised lesions and identified as metallic (elemental) Hg. Biological sample (whole blood, urine and hair) analyses were carried out at the time and after three months. During this period, the patient underwent several surgical procedures to remove the Hg particles. Blood mercury decreased from 218 µg/L at presentation to 112 µg/L after three months. The Hg concentration in 24-hour urine decreased from 5400 µg to 580 µg. The red colouring of the tattoo consisted of mercury sulfide. It was assumed that by some process, the $Hg^{2+}$ was reduced to elemental Hg.

## 2.3 TOXICITY OF HEAVY METALS

### 2.3.1 Cadmium (Cd)

Acute toxicity data for Cd in humans are very scarce and there are no reliable human studies following acute-duration oral exposure. Acute exposure to high doses of Cd in laboratory animals results in a variety of effects, including altered haematological parameters, focal necrosis and degeneration of the liver, focal necrosis in renal tubular epithelium, necrosis and ulceration in the stomach and intestines, decreased motor activity, and testicular atrophy and necrosis.

Cd is primarily toxic to the kidneys and bones after repeated exposure in animals and humans (EFSA, 2009). Chronic exposure to Cd by the oral or inhalation routes has produced proximal tubule cell damage, proteinuria, glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The renal damage produced by Cd is often cumulative and has been related to lifetime Cd dose (Chiyoda *et al.*, 2003; Nogawa *et al.*, 2018). Therefore, episodic exposures at any age contribute to a person's lifetime accumulated Cd exposure and risk. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney. After prolonged and/or high exposure the tubular damage may progress to decreased glomerular filtration rate, and eventually to renal failure. Cd can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. In severe cases this may result in "itai itai" disease , involving osteomalacia and osteoporosis (JECFA, 2011b).

The International Agency for Research on Cancer (IARC) has classified Cd as a human carcinogen (Group 1) on the basis of animal and occupational studies and concluded that

“there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds”. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and the prostate (IARC, 1993).

### 2.3.2 Lead (Pb)

Studies of Pb exposure in humans as well as laboratory animal studies have reported effects on the nervous system, cardiovascular effects, renal effects, immune system effects, haematologic effects, reproductive and developmental effects, and cancer (EFSA, 2010; JECFA, 2011b).

The acute toxicity of Pb is low (JECFA, 2011b). Ingestion of large amounts of Pb can produce gastrointestinal symptoms, including colic, constipation, abdominal pain, anorexia and vomiting.

The critical effects that occur as a result of exposure to Pb are developmental neurotoxicity in young children and cardiovascular and kidney effects in adults. Changes in systolic blood pressure (SBP) and prevalence of chronic kidney disease (CKD) in adults are the critical endpoints in adults.

Long-term exposure to Pb in workers has shown effects on glomerular filtration rate (GFR) and biomarkers of renal tubular toxicity which ultimately lead to CKD. Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis. Depressed GFR, proteinuria and impaired transport of organic anions and glucose have been associated with lead exposure in humans (EFSA, 2010). Studies show consistent evidence of renal damage and reduced renal function associated with a wide range of blood lead levels (PbB) (≤10–>50 µg/dL), with the overall dose-effect pattern suggesting an increasing severity of nephrotoxicity associated with increasing PbB (ATSDR, 2007b).

Changes in systolic blood pressure (SBP) was the most sensitive endpoint in lead exposure. An association between PbB and elevated blood pressure has been shown. The changes in SBP and its association with lead measured in blood and in tibia bone was measured longitudinally from 1994 to 1998 three to four times in current and former employees of a US chemical manufacturer. Changes in SBP were statistically significantly associated in 496 workers (mean age 55.8 years) with PbB, year 3 tibia lead and peak past tibia lead. For this effect, the shape of the dose–response relationship is not well characterised, particularly at low levels of lead exposure. The lowest level of lead exposure associated with no effect on blood pressure is unknown, and available studies provide little evidence for a threshold. The increase in SBP is also supported by animal studies (EFSA, 2010).

Exposure to Pb during pregnancy has been associated with toxic effects on the human foetus, including increased risk of preterm delivery, low birthweight, and impaired mental development, including decreased IQ scores (CDC, 2012). Human studies are inconclusive regarding the association between lead exposure and other birth defects, while animal studies have shown a relationship between high lead exposure and birth defects (ATSDR, 2007b).

Human studies are inconclusive regarding Pb exposure and an increased cancer risk. Animal studies have reported kidney tumours in rats and mice exposed to lead via the oral route. IARC has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) (IARC, 2006).

### 2.3.3 Nickel (Ni)

The main human health effects of concern associated with Ni exposure include Ni allergic contact dermatitis, respiratory carcinogenicity, reproductive toxicity, immunotoxicity, and non-cancer respiratory effects. Acute ingestion of Ni compounds may cause nausea, vomiting, diarrhoea, headache, cough and shortness of breath. In severe cases, ingestion of large amounts of a Ni compound may cause death. Chronic oral exposure to Ni or Ni compounds has not been characterised in humans (ATSDR, 2005).

Ni is of low acute toxicity by the oral route in animals. The acute $LD_{50}$ is greater than 9000 mg/kg bw. Generally, soluble Ni compounds are more toxic than insoluble compounds: single dose oral lethality studies indicated that soluble Ni compounds are acutely toxic to rats whereas less soluble compounds or insoluble Ni compounds are not acutely toxic to rats (ECHA, 2018). Acute oral $LD_{50}$ values of 46 and 39 mg/kg bw for Ni sulphate were reported in male and female rats, respectively. In rats, the oral $LD_{50}$ values for the less soluble Ni compounds Ni oxide and subsulfide were >3,930 and >3,665 mg/kg bw, respectively.

Some forms of Ni may be acutely toxic to humans in large doses. Acute inhalation exposure of humans of Ni compounds may produce headache, nausea, respiratory disorders, and death. Asthmatic conditions have also been documented for inhalation exposure to Ni compounds.

Ni is a well-known skin sensitiser and allergic contact dermatitis is a commonly reported effect in humans exposed to Ni. Exposure through skin or airways may lead to Ni sensitisation (i.e. the type of sensitisation is associated with the route of exposure). A combination of Ni with circulating or tissue protein gives rise to new antigens and acts as a contact allergen and causes sensitisation.

IARC concluded that there is sufficient evidence in humans for the carcinogenicity of mixtures that include Ni compounds and Ni metal. These agents cause cancers of the lung and of the nasal cavity and paranasal sinuses. Ni compounds are classified as carcinogenic to humans (Group1) by the inhalation route. However, the inhalation route of exposure is not relevant to metals in tattoo inks. In view of the overall findings in animals, there is sufficient evidence in experimental animals for the carcinogenicity of nickel compounds and nickel metal (IARC, 1990).

### 2.3.4 Chromium (Cr)

Chromium occurs in the environment primarily in two valence states, trivalent chromium (Cr III) and hexavalent chromium (Cr VI). Chromium III is much less toxic than chromium (VI).

Acute oral toxicity in humans has been studied after intentional or accidental poisoning at high doses of Cr (VI). Sources of Cr (VI) were chromic acid, potassium chromate, and ammonium dichromate. Clinical effects of the high dose poisoning in humans included haematological, hepatic and renal injury. Respiratory and gastrointestinal lesions were also observed. Lethal doses of Cr (VI) were reported to range from 4 to 360 mg/kg bw (EFSA, 2014).

In humans, acute dermal exposure to Cr (VI) causes chrome holes or chrome ulcers i.e. skin burns, blisters, and skin ulcers. Necrosis and sloughing of the skin are also reported in individuals at the site of application of a salve containing potassium chromate. Multiple skin ulcers were observed on the legs of occupational workers after exposure to chromic acid for approximately 10 minutes (ATSDR, 2012).

Cr (VI) compounds can cause serious eye irritation. The severity of response is increased by low pH or high temperature. In humans, accidental splashing of highly water-soluble Cr (VI) compounds in solution into the eye has resulted in damage (ATSDR, 2012; ECB, 2005).
Cr (VI) compounds (sodium/potassium dichromate) are highly hydrophilic and have been found to be skin sensitisers in the modified guinea pig maximisation test and the mouse ear swelling test. Cr (VI) is also reported to cause contact allergic dermatitis in sensitive individuals. It has been reported that at concentrations of 0.5% and below, potassium dichromate elicited a response in patch testing studies (ECB, 2005; EFSA, 2014).

Cr (VI) compounds were found to be mutagenic in bacterial (strains of *S. Typhimurium*, *E. coli*), in yeast (*Saccharomyces cerevisiae*) and in mammalian systems. Numerous *in vivo* studies in rats and mice following parenteral, intratracheal or inhalation administration of Cr (VI) compounds have reported positive results for genotoxicity. Oral studies have been negative, but these employed lower dose levels and absorption is known to be poor by the oral route. Overall, water soluble Cr (VI) compounds are *in vivo* somatic cell mutagens in animal studies (ATSDR, 2012; EFSA, 2014).

Cr (VI) compounds have been evaluated by several IARC working groups in different years (1973, 1979, 1980, 1982, 1987, 1990 and 2012). IARC concluded that there was sufficient evidence in humans for the carcinogenicity of Cr (VI) compounds, with respect to cancer of the lung and also cancer of the nose and nasal sinuses from occupational studies. There was sufficient evidence in experimental animals for the carcinogenicity of Cr (VI) compounds. Therefore, Cr (VI) compounds are carcinogenic to humans (Group 1). The USEPA has proposed that Cr (VI) is “likely to be carcinogenic by oral route” (USEPA, 1998). This is based on a statistically significant increase in the incidence of tumours of the oral mucosa and tongue of rats and of the small intestine of mice; and evidence of an association between oral exposure to Cr (VI) and stomach cancer in humans. There is no evidence of carcinogenicity of Cr (VI) by the dermal route of exposure.

### 2.3.5 Mercury (Hg)

The toxicity of mercury salts depends on their solubility. Mercury salts are corrosive which enhances gastrointestinal permeability and absorption. Acute exposure to mercuric salts at high doses primarily causes burning chest pain, darkened discoloration of the oral mucous membrane and severe gastrointestinal symptoms due to extensive corrosive damage to the gastrointestinal tract (Park and Zheng, 2012). Following acute inorganic mercury poisoning, impaired renal function and damage has been reported. This is also supported by studies in animals where there is consistent evidence of dose- and duration-dependent increases in severity of renal toxicity, including damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, and necrosis (ATSDR, 1999).

The kidney is the target organ for inorganic mercury, mainly the proximal convoluted tubules. Neurological and renal toxicity have been consistently observed in animals after oral exposure to inorganic mercury salts (ATSDR, 1999). Clinical symptoms and signs of inorganic mercury poisoning include polyuria and proteinuria (especially low molecular proteinuria), which can develop into nephritic syndrome in severe cases, with haematuria and anuria. Inorganic mercury salts generally do not cross the blood-brain barrier to induce neurotoxicity or cross the blood-placenta barrier to cause developmental toxicity as they are not lipid soluble (Park and Zheng, 2012).

Mercuric chloride induced forestomach and thyroid tumours in male rats in carcinogenicity studies. There is limited evidence of renal tumours in male rats exposed to phenylmercuric acetate. IARC concluded that inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3) based on inadequate evidence in humans for mercury

and mercury compounds and limited evidence for carcinogenicity of mercuric chloride in experimental animals (forestomach tumours in rats) (ATSDR, 1999). The USEPA concluded that mercuric chloride is a possible human carcinogen (Group C) based on no human data and limited evidence of carcinogenicity in animals (forestomach and thyroid tumours in male rats) (IRIS, 2012).

### 2.3.6 Arsenic (As)

Inorganic arsenic is found throughout the environment; it is released into the air by volcanic activity, the weathering of arsenic-containing minerals and ores, and commercial and industrial processes. General population exposure occurs through ingestion of contaminated drinking water or food. For most people, diet is the largest source of arsenic exposure, with smaller intakes from drinking water and air.

Most of the toxicology data available for As is from industrial workers (ATSDR, 2007a). Acute oral exposure to lower levels of As has resulted in effects on the digestive tract (constriction of the throat, dysphagia, nausea, vomiting, watery diarrhoea), respiratory tract (respiratory distress, hemorrhagic bronchitis), central nervous system (CNS) (encephalopathy, weakness, delirium), cardiovascular system (hypotension, shock), the liver (increased enzymes and size), and blood (anemia, leukopenia). Inhalation exposure to high levels of As over a short period have resulted in respiratory tract symptoms (cough, chest pain, dyspnea, pulmonary edema), gastrointestinal effects (nausea, diarrhoea, abdominal pain), and central and peripheral nervous system effects (peripheral neuropathy, frank encephalopathy).

Chronic oral exposure of humans to elevated levels of inorganic arsenic has been associated with effects on the gastrointestinal system, blood, skin, eyes, lungs, heart, CNS, liver, and kidneys. Such effects include anaemia, peripheral neuropathy, skin lesions, hyperpigmentation, gangrene of the extremities, vascular lesions, and liver or kidney damage. Chronic inhalation exposure of humans to elevated levels of inorganic arsenic has been associated with effects on the cardiovascular system and skin (including dermatitis, conjunctivitis, pharyngitis and rhinitis) and with nerve damage.

The IARC has determined that inorganic arsenic is carcinogenic to humans (Group 1). The USEPA also has classified inorganic arsenic as a known human carcinogen (Group A) by the inhalation and oral routes (ATSDR, 2007a; IRIS, 1991b). By the inhalation route, the primary tumour types are respiratory system cancers, although a few reports have noted increased incidence of tumours at other sites, including the liver, skin, and digestive tract. In humans exposed chronically by the oral route, skin tumours are the most common type of cancer. In addition to skin cancer, there are a number of case reports and epidemiological studies that indicate that ingestion of arsenic also increases the risk of internal tumours (mainly of bladder and lung, and to a lesser extent, liver, kidney, and prostate).

### 2.3.7 Antimony (Sb)

Chronic exposure to several antimony compounds by inhalation, dermal and oral routes in industrial workers has led to respiratory, dermal, cardiovascular and gastrointestinal effects (ATSDR, 2019). Respiratory effects observed after exposure to antimony trioxide and/or pentoxide dust (8.87 mg antimony/$m^3$ or greater) is reported to cause pneumoconiosis chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions, and respiratory irritation. Dermal effects consist of a condition known as antimony spots, which is a rash consisting of pustules around sweat and sebaceous glands, while effects on the eye include ocular conjunctivitis. Airborne antimony trichloride, antimony trisulfide or antimony oxide can also cause abdominal pain, diarrhoea, vomiting, and ulcers in humans. It should be noted that a causal relationship to antimony exposure has not been definitely established as workers

were also exposed to a variety of other compounds including arsenic oxide, iron oxide, hydrogen sulfide, and sodium hydroxide.

There is inadequate evidence for carcinogenicity of antimony trioxide and trisulphide in humans but both have been reported to cause lung tumours in rats. Antimony trioxide is classified as possibly carcinogenic to humans (Group 2B) by IARC. US EPA has not classified antimony for carcinogenicity (IRIS, 1991b).

### 2.3.8 Barium (Ba)

Barium is an alkaline earth metal and its toxicity depends on the solubility of its compounded form. Barium is found in many food groups but in a relatively low concentration (<3 mg/100 g) with the exception of Brazil nuts (150-300 mg/100 g). Barium sulfate is insoluble and is used as a radiopaque contrast compound to visualize the digestive tract in humans. Other Ba salts (chloride, carbonate, sulfide, oxide and acetate) are soluble which are bioavailable and hence toxic after ingestion.

There are many case reports of Ba poisoning in humans. Ba can be fatal and can ultimately lead to death (ATSDR, 1998; Copeland et al., 2023). Acute poisoning with barium chloride ($BaCl_2$) in humans cause symptoms like nausea, vomiting, stomach burning feeling, dizziness, and weakness. It can also cause hypokalemia and atrioventricular blocking, ventricular tachycardia (Tao et al., 2016). Intravenous infusion of $BaCl_2$ into anesthetized dogs or guinea pigs resulted in increased blood pressure and cardiac arrhythmias (ATSDR, 1998).

Chemical-related nephropathy was observed at high doses of $BaCl_2$ after sub-chronic and chronic drinking water exposure in mice and rats. These lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. Significant mortality (26-75%) was also observed at high dose in a 2-year study in mice which were attributed to renal lesions (ATSDR, 1998). The lesions observed in the high dose group were mild to severe whereas in the intermediate group they were characterised as mild or moderate. A LOAEL of 160 mg/kg bw/day was identified for a statistically significantly increased incidence of chemical-related renal lesions. The next lower dose was not identified as the NOAEL because a low level of chemical-related nephropathy was also observed in this treatment group. For this reason, a NOAEL of 30 mg/kg bw/day was identified for the absence of chemical-related renal lesions.

There are some conflicting reports that Ba may induce a hypertensive state in dogs. However, NTP did not find any association in their sub-chronic and chronic studies in rats and mice (ATSDR, 1998).

No *in-vivo* studies have been conducted to evaluate the genotoxicity of barium compounds (ATSDR, 1998). Based on the limited *in-vitro* studies, $BaCl_2$ and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation. In mouse lymphoma cells, $BaCl_2$ induced gene mutations with metabolic activation but not in the absence of metabolic activation. In mammalian cells, $BaCl_2$ did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation.

### 2.3.9 Summary

This risk assessment primarily considers absorption through the skin into lymph and blood, and non-cancer end points. Dermal exposure to metals (Ba, Ni, Cr, Co, Mn) in inks may cause allergic reactions. Ni and Cr seem to be most commonly associated with these effects, but the evidence for the metals in inks causing these effects is limited.

# 3 DOSE-RESPONSE INFORMATION

Point of departure (POD) is defined as the point on a toxicological dose-response curve established from experimental data or observational data generally corresponding to an estimated low effect level or no effect level. It marks the beginning of extrapolation to toxicological reference dose (RfD) or reference concentration (RfC). The most common PODs used are the no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or statistical benchmark dose (BMD).

The BMD approach is preferred as the dose descriptor for the POD as it has distinct advantages over the NOAEL approach in that the modelled BMD ($BMD_{05}$ or $BMD_{10}$) reflects the shape of the dose–response curve and is less affected by the choice of experimental concentrations. However, the BMD approach requires a robust data set and additional knowledge of statistical modelling. When no BMD can be calculated or is available, usually NOAEL or LOAEL values are applied.

## 3.1 NICKEL (Ni)

The USEPA has derived an oral RfD for Ni soluble salts. The RfD was based on a NOAEL of 5 mg/kg/day and a LOAEL of 50 mg/kg/day for decreased body weight and organ weight in rats exposed to dietary Ni for 2 years (Table 3).

In this chronic study, body weights were significantly decreased as compared to controls in high dose male and female rats. The dose of 50 mg Ni/kg bw represents a LOAEL for this study. High mortality occurred in the controls in both sexes (44/50) raising some concern about the interpretation of the results of this study. However, this study was supported by a sub chronic study in which the NOAEL was also 5 mg/kg/day.

EFSA (2020) derived a tolerable daily intake (TDI) of 0.013 mg/kg/day based on reproductive and developmental toxicity observed in rats. Developmental toxicity was also observed in mice (decreased fetal weight, malformations) but at higher doses than for rats suggesting that rats may be more sensitive than mice to developmental toxicity of nickel. Based on the available data, the increased incidence of post-implantation loss in rats was considered a critical effect for the risk characterisation of chronic oral exposure to nickel.

**Table 3: Reference dose for nickel**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Rat Chronic Oral Study/ Decreased body and organ weights | NOAEL: 5 mg/kg/day<br><br>LOAEL: 50 mg/kg/day | 300 | 0.02 mg/kg bw/day (20 µg/kg bw/day) | (IRIS, 1991a) |
| One- and two-generation studies in rats/ increased incidence of post-implantation loss. | $BMDL_{10}$: 1.3 mg Ni/kg | 100 | TDI: 0.013 mg/kg/day (13 µg/kg bw/day) | (EFSA, 2020) |

BMDL: Benchmark dose level (subscript denotes benchmark response of exposure dose associated with 10% extra risk), NOAEL: No observed adverse effect level, LOAEL: lowest observed adverse effect level, bw: body weight, TDI: Tolerable daily intake

The US EPA has not evaluated soluble salts of Ni, as a class of compounds, for potential human carcinogenicity.

### 3.2 CADMIUM (Cd)

The USEPA has derived an oral RfD for Cd. The RfD is based on an estimated NOAEL of 0.005 mg/kg bw/day for Cd in drinking-water Table 4. The NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of Cd in both humans and animals. These data also permit calculation of pharmacokinetic parameters of Cd absorption, distribution, metabolism and elimination.

The EFSA Panel did not consider the dose-response data for cancer as a sufficient basis for quantitative risk assessment and based their assessment on kidney effects. A meta-analysis was conducted on the relationship between urinary cadmium (a measure of cadmium body burden) and urinary β-2-microglobulin (B2M; a biomarker of renal tubular damage). A urinary reference point of 1 µg cadmium/g creatinine was derived, equating to a tolerable weekly intake (TWI) of 2.5 µg/kg bw per week. Creatinine enters urine at a fairly constant rate and is used to standardise biomarker measurements.

EFSA subsequently reviewed the approach and assumptions used in deriving the TWI and compared them to the approach and assumptions employed by JECFA (see below). The JECFA health-based guidance values (HBGV) is more than twice the EFSA value, when considered in the same time frame.

JECFA published an addendum to their assessment of cadmium in 2011 (JECFA, 2011a). JECFA followed a similar approach to EFSA but concluded that for those aged 50 years or older (a point at which cadmium in the body would have achieved a steady state) there was no evidence of increased B2M urinary excretion at urinary cadmium concentrations less than 5.24 µg/g creatinine. This equates to a provisional tolerable monthly intake (PTMI) of 25 µg/kg bw per month.

**Table 4: Reference dose for cadmium**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Human studies involving chronic exposure/ Significant proteinuria | NOAEL (water): 0.005 mg/kg/day | 10 | 0.0005 mg/kg bw/day (0.5 µg/kg bw/day) | (IRIS, 1989) |
| Human studies-meta-analysis / urinary cadmium levels and beta-2-microglobulin | 1 µg cadmium/g creatinine | Not required | TWI: 0.0025 mg/kg bw (2.5 µg/kg bw, equivalent to 0.36 µg/kg bw/day) | (EFSA, 2009) |
| Human studies-meta-analysis / urinary cadmium levels and beta-2-microglobulin | - | - | PTMI: 25 µg/kg bw per month, equivalent to 0.82 µg/kg bw/day | (JECFA, 2011a) |

NOAEL: No observed adverse effect level, bw: body weight, TWI: tolerable weekly intake, PTMI: provisional tolerable monthly intake

Cadmium is classified as B1 carcinogen (probable carcinogen) by the USEPA and IARC, and is classified 1B (may cause cancer) by ECHA (ECHA, 2023; IRIS, 1989). Experimental studies in animals and *in vitro* mammalian cell lines have indicated that several cadmium compounds are genotoxic. In humans, data are conflicting but seem to indicate a genotoxic potential, at least in occupational settings, but it is unclear whether these effects are solely attributable to cadmium (ECHA, 2020; IRIS, 1989).

### 3.3 CHROMIUM [Cr (VI)]

The US EPA has derived an oral reference dose (RfD) based on the NOAEL in a one year chronic toxicity study in rats. Animals (8/sex/group) were given chromium as chromate ion in water containing between 0.45 and 11 mg/kg, for 1 year. No effects (water intake, food consumption, weight gain, or hematology) were observed at monthly intervals. Examination of tissues at 6 months and a year did not show any significant differences between any of the dose groups and the control group. Two other groups were given water containing 25 ppm of chromium as Cr (VI) and Cr (III), respectively, for 1 year. No toxic symptoms were observed in either group. However, tissue concentrations of chromium were approximately 9 times higher in the group given Cr (VI) compared to the groups given Cr (III). There was an approximately 20% reduction in water consumption. Based on the body weight of the rat (0.35 kg) and the average daily drinking water consumption (0.035 L/day), this dose was converted to give an adjusted NOAEL of 2.5 mg/kg bw/d Cr (VI) (USEPA, 1998). The oral RfD for chromium is summarised in Table 5.

**Table 5: Reference dose for chromium**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor / Modifying Factor | Reference dose | Reference |
|---|---|---|---|---|
| Rat, 1-year drinking water study / No effects observed | NOAEL: 25 mg/L of chromium as $K_2CrO_4$ 2.5 mg/kg bw/day (adj.) | 300 / 3 (total adjustment factor = 900) | 0.003 mg/kg bw/d | (IRIS, 1998) |

### 3.4 LEAD (Pb)

According to the USEPA, the degree of uncertainty regarding the health effects of Pb is very low. The critical effects that occur as a result of exposure to Pb (changes in levels of certain blood enzymes, elevation of blood pressure, and neurobehavioral deficits in children) occur at exposure levels (measured as blood lead) so low as to be essentially without a threshold. Therefore, the USEPA's RfD Work Group considered it inappropriate to develop an RfD for inorganic Pb (IRIS, 2004). This is consistent with the conclusions of other evaluations (EFSA, 2010; JECFA, 2011b). Consequently, exposure to Pb should be kept as low as reasonably achievable (ALARA). In New Zealand, the health advice is that there is no safe level of lead and lead exposure needs to be avoided as much as possible (Ministry of Health, 2021).

For non-threshold effects, modelling benchmark doses (BMD) for selected benchmark response (BMR), typically 1-10% extra risk of the critical effect is derived. Developmental neurotoxicity was identified as a critical effect in young children. In adults, cardiovascular effects and nephrotoxicity were identified as the critical effects for the risk assessment. The respective BMDLs derived from blood lead levels in µg/L (corresponding dietary intake values in µg/kg bw/d) were: developmental neurotoxicity $BMDL_{01}$, 12 (0.50); effects on systolic blood pressure $BMDL_{01}$, 36 (1.50); effects on prevalence of chronic kidney disease $BMDL_{10}$, 15 (0.63) (EFSA, 2010). The current risk assessment assumes that tattoos will not be applied to very young children, the age group at risk of developmental neurotoxicity. Consequently, the $BMDL_{01}$ value of 0.63 µg/kg bw/d, based on effects on prevalence of chronic kidney disease was used in the risk assessment.

**Table 6: PODs dose for lead**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Long term exposure in workers/ Depressed GFR, Proteinuria and impaired transport of organic anions and glucose leading to CKD | $BMLD_{10}$: 0.00033 mg/kg bw/day | - | - | (EFSA, 2010) |
| Long term exposure in workers/ increased systolic blood pressure | $BMLD_{10}$: 0.0015 mg/kg bw/day | - | - | |
| Long term exposure in workers/ developmental toxicity | $BMLD_{10}$: 0.0005 mg/kg bw/day | - | - | |

bw: body weight: BMDL: = 95% lower confidence limit on the BMD (subscript denotes benchmark response of exposure dose associated with 10% extra risk)

### 3.5 MERCURY (Hg)

Following oral exposure to mercuric chloride in a sub chronic toxicity study in rats, increased relative kidney weight in male and female rats was considered as the critical effect for deriving health based guidance values (JECFA, 2011a).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived a Provisional Tolerable Weekly Intake (PTWI) for inorganic mercury of 4 μg/kg bw (JECFA, 2011a). The PTWI was derived from the $BMDL_{10}$ (lower 95th percentile confidence limit for a benchmark dose giving a 10% change in response over baseline) of 0.11 mg/kg bw/d as Hg (II) chloride for kidney weight changes in male rats. This corresponds to 0.06 mg/kg bw/d as Hg, adjusted from a 5 days/week dosing schedule to an average daily dose and for the per cent contribution of inorganic mercury to Hg (II) chloride dose μg/kg bw, or about twice the USEPA oral RfD (JECFA, 2011a).

**Table 7: Reference dose for mercury**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Rats, 6-month drinking water study / No effects observed | $BMLD_{10}$: 0.112 mg/kg bw/day corresponding to 0.06 mg/kg bw/day | 100 | 0.004 mg/kg bw/d | (JECFA, 2011a) |

bw: body weight, BMDL: = 95% lower confidence limit on the BMD (subscript denotes benchmark response of exposure dose associated with 10% extra risk)

### 3.6 ARSENIC (As)

The USEPA has derived an oral RfD for inorganic arsenic. The RfD was based on a NOAEL of 0.0008 mg/kg/day and a LOAEL of 0.014 mg/kg/day for hyperpigmentation, keratosis and possible vascular complications in humans.

Tseng (1977) reported a high prevalence of chronic arsenicism (hyperpigmentation, keratosis, and cancer) on the southwest coast of Taiwan, where artesian well water with a high concentration of arsenic had been used for more than 60 years. The arsenic content of the well water, including water from four shallow wells, ranged from 0.01 to 1.82 ppm. There was a dose response in the prevalence of cancer and blackfoot disease with the concentration of As in water. The incidence of blackfoot disease also increased with age. The prevalences (males and females combined) at the low dose was 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group (IRIS, 1991b). The studies showed that skin lesions were the most critical and sensitive effect (IRIS, 1991b; Tseng, 1977).

**Table 8: Reference dose for arsenic**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Human Chronic oral exposure / Hyperpigmentation, keratosis and possible vascular complications | NOAEL: 0.0008 mg/kg bw/day | 3 | 0.0003 mg/kg bw/d | (IRIS, 1991b) |

bw: body weight, NOAEL: No observed adverse effect level

### 3.7 ANTIMONY (Sb)

The USEPA has derived an oral RfD for antimony. The RfD was based on a LOAEL of 0.35 mg/kg/day for longevity, blood glucose, and cholesterol in rats.

In this study, rats (n = 50/sex/group) were administered 5 ppm potassium antimony tartrate in water from the time of weaning until natural death (Schroeder *et al.*, 1970). There were negligible effects on growth and mature weight. Antimony was innately toxic, males surviving 106 days and females 107 days less than the controls at median life spans, and 70 and 165 days less when 90% were dead. In the treatment group, the ages were significantly reduced compared to control ages. Non-fasting blood glucose levels were decreased in treated males, and cholesterol levels were altered in both sexes. Since there was only one dose level, the NOAEL was not identified. Hence, 5 ppm or 0.35 mg/kg bw/day was the LOAEL.

**Table 9: Reference dose for antimony**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Chronic toxicity study-rat / longevity, blood glucose, and cholesterol | LOAEL: 0.35 mg/kg bw/day | 1000 | 0.0004 mg/kg bw/d | (IRIS, 1970; Schroeder *et al.*, 1970) |

bw: body weight, LOAEL: Lowest observed adverse effect level

### 3.8 BARIUM (Ba)

The USEPA has derived an oral RfD for Ba and its compounds.

As summarised in section 2.38, kidneys appear to be the target organ for Ba toxicity. Chemical-related nephropathy was observed at high doses of $BaCl_2$ after sub-chronic and chronic drinking water exposure in mice and rats. Hence, nephropathy was considered as the sensitive effect from a 2-year drinking water study in mice.

The RfD was derived by the benchmark dose approach using renal lesions in mice as the critical effect. The benchmark response predicted to affect 5% of the population ($BMR_{05}$) was selected for the point of departure. The $BMD_{05}$ for males was 84 mg/kg bw/day and the lower 95% confidence limit (i.e., $BMDL_{05}$) was 63 mg/kg bw/d. The $BMD_{05}$ for females was 93 mg/kg bw/day and the $BMDL_{05}$ was 58 mg/kg bw/day. These $BMDL_{05}$ values are very similar, but since there is slightly less uncertainty in the estimate derived from the male mice (the $BMD_{05}$ and $BMDL_{05}$ are closer together), the male $BMDL_{05}$ was used for deriving the RfD.

**Table 10: Reference dose for barium**

| Study / key effect | Point of Departure (POD) | Uncertainty Factor (UF) | Reference dose (RfD) | Reference |
|---|---|---|---|---|
| Chronic (drinking) toxicity study-mice / Nephropathy | $BMDL_{05}$: 63 mg/kg bw/day<br>$BMD_{05}$: 84 mg/kg bw/day | 300 | 0.2 mg/kg bw/day | (IRIS, 2005) |

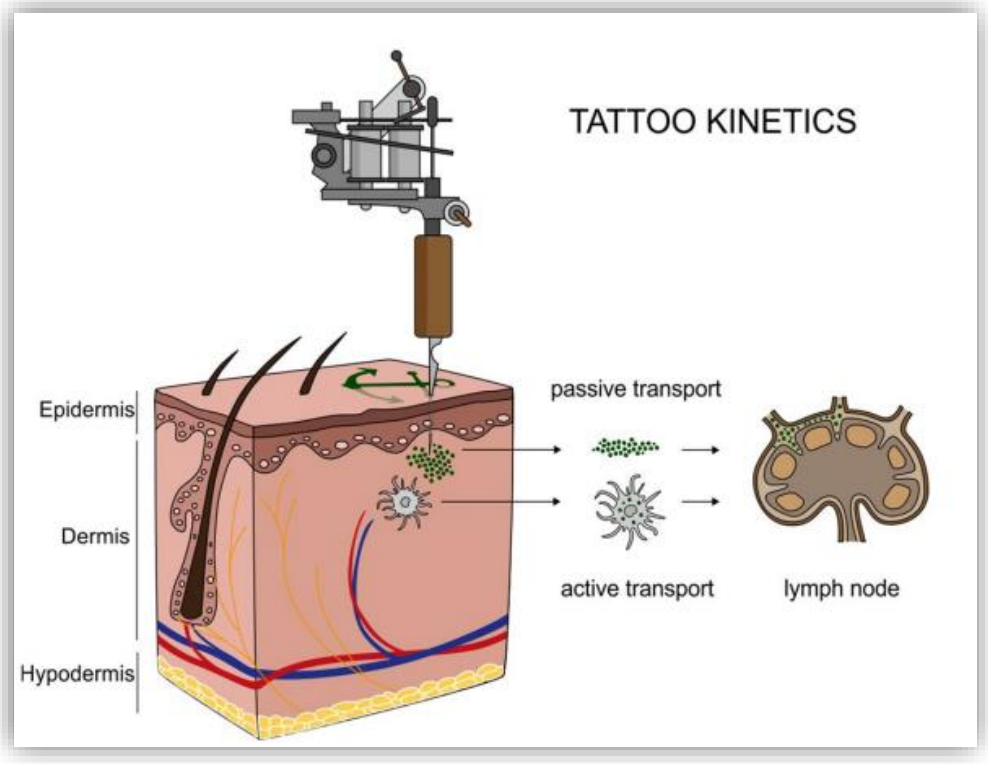
bw: body weight, BMDL: = 95% lower confidence limit on the BMD (subscript denotes benchmark response of exposure dose associated with 5% extra risk)

# 4 EXPOSURE ASSESSMENT

In order to consider the possible exposure pathways to tattoo inks, it is important to understand how tattoo inks are applied.

The skin has three layers, with the epidermis on the top, the dermis in the middle, and then the hypodermis, also known as the subcutaneous layer. Tattoo ink is injected into the dermis and releases pigments, which permanently stain the skin. The dermis has nerves, blood vessels, and hair follicles. The blood vessels drain to the venous system and the large vessels of the body. The lymphatics drain via larger vessels in the subcutis to the sentinel lymph nodes that function as a filter and the lymph then passes to the bloodstream. Hence, there are two potential drainage paths from a tattoo: one directly to the venous system, the other through the lymph tracts and lymph nodes to the bloodstream (Miljøstyrelsen, 2012). Schreiver *et al.* (2017) showed that toxic elements (Al, Cr, Fe, Ni and Cu) were quantitatively elevated in the tattooed skin and lymphatic tissues from human corpses.

Pigments and heavy metals may be transported to migrating cells and organs such as the liver, lungs or kidneys (Weiß *et al.*, 2021). Studies about the distribution of tattoo inks in the body are limited. In one study, tattoo ink pigment particles were detected in the skin, lymph nodes and kuffer cells (in the liver) of mice after one year of application. Pigment particles were not detected in any other organ (Sepehri *et al.*, 2017). It is unclear which pathway the particles follow but it may be dependent on their size. The macro particles mainly travel via the lymph fluid and subsequently get filtered in the lymph nodes (Miljøstyrelsen, 2012; Schreiver *et al.*, 2017).




Source: (Schreiver *et al.*, 2017)

## 4.1 Relevant Exposure Scenarios

The main route of exposure to heavy metals in tattoo inks in adults is intradermal (i.e. under the skin) as the tattoo ink is injected into the dermis. Some dermal exposure (epidermal) is also expected. However, it is reported that the epidermis is regenerated after a period of two weeks (Miljøstyrelsen, 2012). There are no exposure models available for assessing substances after intra-dermal exposure as the kinetics and absorption of heavy metals intradermally is not known. Hence, as a worst-case scenario, this exposure assessment was performed assuming 100% absorption intradermally. The tattoo ink is intended to remain in the dermis and for the current exercise it has been assumed that tattoo ink components will migrate slowly over the lifetime into the blood stream and then be distributed to different organs. That is, chronic exposure is expected.

Inhalation and oral exposure are not considered to be relevant routes of exposure to tattoo ink components.

### 4.1.1 Concentrations of heavy metals in tattoo inks

For the current exposure assessment, the following maximum concentrations of respective heavy metals in tattoo inks were considered from the survey undertaken by the New Zealand MoH (MoH, 2013). This survey is over ten years old but represents the only source of data for inks on the New Zealand market.

This survey sampled inks that appear to have been manufactured overseas and imported. No locally manufactured inks were sampled; it is uncertain whether such products exist.

**Table 11: Concentrations of heavy metals selected for risk assessment.**

| Heavy metal | Concentration (mg/kg) |
|---|---|
| Ba | 17000 |
| Cr (VI) | N.D* |
| Ni | 23 |
| Pb | 45 |
| Cd | 0.8 |
| Hg | 0.6 |
| As | 60 |
| Sb | 147 |

Ba: Barium; Cd: Cadmium; Cr: Chromium; Pb: Lead; Hg: Mercury; Ni: Nickel; As: Arsenic; Sb: Antimony; N.D: Not detected

*No limit of detection reported

The safety of any product is evaluated by developing exposure scenarios. For tattoo inks, parameters like normal and foreseeable use of the tattoo ink, estimated exposure by ink use, body surface area and absorption are considered, and are discussed below.

### 4.1.2 Quantity of ink applied

The normal and foreseeable use of tattoo ink is for introduction directly into the skin without dilution of the ink (Tordrup, 2014). There are few studies which provide information on the amount of tattoo ink injected during the tattooing process (Miljøstyrelsen, 2012). One study by Engel *et al.* (2008) is referred to for most exposure assessments and is also used in the recommendation from the Danish Environmental Protection Agency on the safety of tattoo ink (Tordrup, 2014). In this study, azo (red) pigments suspended in concentrations of 10% (w/v) and 25% (w/v) in a vehicle of 10% of glycerol in water were applied to rectangular pig and human skin samples (1 X 3 cm) (Engel *et al.*, 2008). The study revealed that the concentrations of red pigments placed in the human and pig skin ranged from approximately

0.60 to 9.42 mg pigment per skin cm². The mean value was 2.53 mg pigment/cm$^2$ and the median was 1.9 mg pigment/cm$^2$. The mean value of tattoo ink applied was 15 mg/cm$^2$.

### 4.1.3 Area of skin tattooed

While tattoos vary hugely in the body surface area affected, a clinical investigation of 72 tattooed persons, found that on an average 2.5% of the body surface area was covered with tattoos (Miljøstyrelsen, 2012). The mean surface area of the skin of an adult New Zealander is standard 18,400 cm$^2$ and 20,700 cm$^2$ for women and men, respectively (Cressey, 2016). If 2.5% of the skin is tattooed, then the tattooed area is on average 460 cm$^2$ for women and 517 cm$^2$ for men. Hence, an average of 488 cm$^2$ for both sexes is used in the assessment.

### 4.1.4 Duration of exposure

After application, tattoo inks sit in the dermis. From here, tattoo ink components may be transported through blood vessels and lymph nodes to different organs. It was assumed that this process is complete (all heavy metals are transported) and happens over the lifetime of an adult. It was assumed that a person gets a tattoo at an age of 20 years and adulthood is the balance (50 years) of a 70-year lifetime. Hence, the duration of exposure was taken as 50 years or 18,250 days.

### 4.1.5 Absorption

There was no information available on intradermal absorption of heavy metals. Hence, 100% absorption was considered for the exposure assessment. That is, all of the heavy metals applied with the tattoo ink will eventually enter the body.

## 4.2 EXPOSURE ASSESSMENT

The exposure to heavy metals through tattoo ink was calculated following recommendation from the Danish Environmental Protection Agency on the safety of Tattoo Ink (Tordrup, 2014).

$$SED = \frac{C\ X\ ink\ use\ X\ Area\ X\ DA}{BW\ X\ Time\ period} \text{ ----------(1)}$$

**Table 12: Parameters for exposure assessment**

| Parameter | Explanation/Value | Reference/comments |
|---|---|---|
| SED | Systemic Exposure Dose | - |
| C (mg/kg) | Concentration of heavy metal in the ink<br>Ba 17000<br>Cr N.D<br>Ni 23<br>Pb 45<br>Cd 0.8<br>Hg 0.6<br>As 60<br>Sb 147 | (MoH, 2013) |
| Ink use (mg/cm$^2$) | Estimated amount of ink containing heavy metals used during tattooing i.e. normal and foreseeable use of inks (15 mg/cm$^2$) | (Engel *et al.*, 2008; Tordrup, 2014) |
| Area (cm$^2$) | 2.5% of the surface area of the skin i.e. 488 cm$^2$ for both sexes | (Cressey, 2016) |
| DA (%) | Dermal Absorption expressed as a percentage of the test dose (100%). | (Tordrup, 2014) |
| BW (Kg) | Average body weight (70 kg) | (Cressey, 2016)<br>25$^{th}$ Percentile body weight for New Zealand adults, 66.8 kg, rounded off to 70 kg |
| Period | 50 years or 18,250 days | Assumption |

A daily average was calculated for heavy metal exposure to allow comparison with health-based guidance values.

Estimated daily systemic exposures to the eight heavy metals are summarised in Table 13.

**Table 13: Systemic Exposure Dose for heavy metals**

| Heavy metal | Concentration (µg/g) | SED (µg/kg bw/d) |
|---|---|---|
| Ba | 17 | 0.10 |
| Cr | N.D | - |
| Ni | 0.023 | 0.000132 |
| Pb | 0.045 | 0.000258 |
| Cd | 0.0008 | 4.58E-06 |
| Hg | 0.0005 | 2.86E-06 |
| As | 0.06 | 0.000344 |
| Sb | 0.14 | 0.000802 |

Ba; Barium; Cd: Cadmium; Cr: Chromium; Pb: Lead; Hg: Mercury; Ni: Nickel; As: Arsenic; Sb: Antimony; N.D: Not detected

Some metals can accumulate in the body. However, this is taken into account while deriving PODs for respective heavy metals.

# 5 RISK CHARACTERISATION

A margin of safety (MoS) approach was used to assess the expected level of safety associated with heavy metals in tattoo inks. MoS is the ratio between a $PoD_{sys}$ (systemic POD, usually the NOAEL or BMD values from oral studies) and an estimate of the exposure (SCCS, 2021).

$$MoS = \frac{POD_{sys}}{SED}$$

The BMD approach is preferred as the dose descriptor for the PoD and the MoS calculations. When no BMD can be calculated or is available, usually NOAEL values are applied. If a BMD or a NOAEL cannot be identified from the available data, other dose descriptors such as the LOAEL may be used in the MoS calculation.

For a chemical substance with health thresholds (i.e, not genotoxic and not carcinogenic), a MOS >= 100 is generally considered to be protective. If a LOAEL is used, the MOS should be at least 1000.

The PODs in Table 14 were used for the risk characterisation of heavy metals in tattoo inks.

**Table 14: Points of Departure for Margin of Safety (MoS) calculations**

| Heavy metal | POD (mg/kg bw/day) |
|---|---|
| Ba | $BMDL_{05}$: 63 |
| Cr | NOAEL: 2.5 |
| Ni | NOAEL: 5 |
| Pb | $BMDL_{10}$: 0.63 |
| Cd | NOAEL: 0.005 |
| Hg | $BMDL_{10}$: 60 |
| As | NOAEL: 0.0008 |
| Sb | LOAEL: 0.35 |

The MoS was calculated for each heavy metal in Table 15.

**Table 15: Margin of safety (MoS) for health risks**

| Heavy metal | Exposure (µg/kg bw/d) | PoD (µg/kg bw/d) | MoS |
|---|---|---|---|
| Ba | 0.1 | $BMDL_{05}$: 60000 | >10000 |
| Cr* | - | NOAEL: 2500 x 10% (oral absorption) = 25 | - |
| Ni* | 0.000132 | NOAEL: 5000 x 10% = 500 | >10000 |
| Pb** | 0.000258 | $BMDL_{10}$: 0.63 x 60% = 0.38 | 1465 |
| Cd | 4.58E-06 | NOAEL: 50 x 6% = 3 | >10000 |
| Hg*** | 2.86E-06 | $BMDL_{10}$: 60 x 7% = 4.2 | >10000 |
| As | 0.000344 | $BMDL_{10}$: 0.8 | 2300 |
| Sb* | 0.000802 | LOAEL: 350 x 1% = 3.5 | 4300 |

Ba: Barium; Cd: Cadmium; Cr: Chromium; Pb: Lead; Hg: Mercury; Ni: Nickel; As: Arsenic; Sb: Antimony; POD: point of departure

**10% oral absorption (ATSDR, 2019; Chain *et al.*, 2020; SCHER, 2015)

**60% oral absorption (EFSA, 2010)

*** 7% oral absorption (IRIS, 2012)

Human health risks from exposure to heavy metals in tattoo inks were evaluated by a MoS approach. The MoS was much greater than 100 for Ba, Ni, Pb, Cd, Hg, As and Sb, which

indicates that the presence of these metals in tattoo inks at the maximum concentrations reported is not a cause for health concern.

## 5.1 RISK CHARACTERISATION FROM OTHER STUDIES

Some of the studies reviewed did perform risk characterisation calculations and compared estimates of exposure to health-based guidance values for some metals. These are summarised below.

Bocca *et al.* (2018) conducted a risk assessment (sensitisation and systemic) of tattoo inks with respect to their Cr (VI) levels. The threshold limit for causing Cr (VI) allergy is 1 mg/kg. The results of this study showed that 21 of 29 tattoo inks (or 72.4%) contained Cr(VI) levels of ≤1 mg/kg; therefore, for the majority of samples, the likelihood of the induction of sensitisation may be very low. However, for a number of inks (27.6%), the Cr(VI) level (in the range 1.19-4.09 mg/kg) could represent a possible cause of skin reactions, especially if a consumer has already been sensitised to Cr(VI) from other sources. The systemic risks of Cr (VI) in tattoo inks were evaluated by calculating SED and then determining MoS. The SED of Cr(VI) resulting from the use of the tattoo inks ranged from $1.26 \times 10^{-7}$ to $3.17 \times 10^{-6}$ mg/kg bw/d for a 100% absorption scenario, as the worst case. The MoS values ranged from 2620 to 65 747. Since the MoS>100, it indicates that the presence of Cr (VI) in tattoo inks may not be cause for concern. It should be noted that the SEDs determined by Bocca *et al.* are substantially lower than those determined in the current study.

After their survey, the Danish EPA concluded that current knowledge is insufficient for a valid quantitative exposure assessment of the selected chemical substances in the analysed tattoo inks, as well as pigments, coformulants and chemical impurities that occur in tattoo inks in general (Miljøstyrelsen, 2012). It is also not known what the source of heavy metal impurities is, whether the detected elements occur as impurities in the pigments and/or coformulants or in the tattoo inks,or if the elements occuras a result of degradation of the pigments, coformulants and/or chemical impurities in the tattoo inks during the analytical process.

# 6 CONCLUSIONS

The purpose of this report is to develop a generic health risk assessment for heavy metals [lead (Pb), nickel (Ni), hexavalent chromium (Cr (VI)), mercury (Hg) cadmium (Cd), antimony (Sb), barium (Ba), and arsenic (As)] in tattoo inks. While other metals have occasionally been examined in tattoo inks, these eight metals are of consistent concern and the current study is restricted to consideration of these metals only. This report only considered exposure to heavy metals in tattoo inks applied by professional tattoo artists. Temporary tattoos such as henna and risks involving self-tattooing are not under the scope of this report. This report also only includes common commercial tattoo inks and does not include other inks such as traditional tattoo ink from organic material or alternative ink such as fluorescent tattoo ink. Exposure scenarios were developed for the most common or likely exposure events to permanent tattoos.

Tattoo inks may have high levels of heavy metals such as arsenic (As), hexavalent chromium [Cr (VI)], mercury (Hg), lead (Pb), cadmium (Cd), Nickel (Ni), antimony (Sb) and barium (Ba). This has led to the product recalls over the years from the European market. There was no information available on product recalls in New Zealand. The source of heavy metals in tattoo inks is not exactly known. They may occur as components of pigments, coformulants and/or chemical impurities during the manufacturing of the tattoo inks.

In New Zealand, tattoo inks require approval under the Hazardous Substances and New Organisms Act 1996 (HSNO Act) implemented by the Environmental Protection Authority of New Zealand. For tattoo inks and permanent makeup substances, the approval is the Tattoo and Permanent Makeup Substances Group Standard. The NZ EPA has recommended the maximum impurity limits for some heavy metals.

There is some clinical evidence that heavy metals in inks might be responsible for allergic reactions, swelling, erythema and redness of the tattooed arm, cheek and lips as well as tongue. However, the evidence is very limited that the clinical symptoms were solely due to heavy metals as tattoo inks are mixtures of a variety of potentially hazardous substances.

In New Zealand, the National Poisons Centre (NPC) provided information that there were only 11 incidents of harm potentially linked to tattoo ink exposure (oral and intradermal) from years 2008 to 2022. In only two of these incidents the respondent was advised to seek medical attention. Both of these cases involved self-applied tattoos.

The intradermal route is the main route of exposure to heavy metals in tattoo inks. Inhalation and oral exposure are not considered a relevant route of exposure. A systemic exposure dose (SED) was calculated for each heavy metal and combined with an appropriate toxicological point of departure to give a margin of safety (MoS) for characterisation of risk. Human health risks from exposure to heavy metals in tattoo inks was evaluated by a MoS approach. The MoS was much greater than 100 for Ba, Ni, Pb Cd, Hg, As and Sb, which indicates that, based on currently available data, the presence of these metals in tattoo inks at the maximum concentrations reported is not a cause for health concerns.

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INSTITUTE OF ENVIRONMENTAL
SCIENCE AND RESEARCH LIMITED

**Kenepuru Science Centre**
34 Kenepuru Drive, Kenepuru, Porirua 5022
PO Box 50348, Porirua 5240
New Zealand
**T:** +64 4 914 0700 **F:** +64 4 914 0770

**Mt Albert Science Centre**
120 Mt Albert Road, Sandringham, Auckland 1025
Private Bag 92021, Auckland 1142
New Zealand
**T:** +64 9 815 3670 **F:** +64 9 849 6046

**NCBID – Wallaceville**
66 Ward Street, Wallaceville, Upper Hutt 5018
PO Box 40158, Upper Hutt 5140
New Zealand
**T:** +64 4 529 0600 **F:** +64 4 529 0601

**Christchurch Science Centre**
27 Creyke Road, Ilam, Christchurch 8041
PO Box 29181, Christchurch 8540
New Zealand
**T:** +64 3 351 6019 **F:** +64 3 351 0010

**www.esr.cri.nz**