Science for Communities

HEALTH RISK ASSESSMENT: CHROMIUM IN LEATHER

February 2023

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ACRONYMS AND ABBREVIATIONS

ADI	Acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
bw	Body weight
CSF	Cancer slope factor
DAD	Dermal absorbed dose
DL	Detection limit
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
ESR	Institute of Environmental Science and Research Limited
EU	European Union
HQ	Hazard quotient
IARC	International Agency for Research on Cancer
ICP-OES	Inductively coupled plasma optical emission spectroscopy
LASRA	Leather & shoe research association
LCR	Lifetime cancer risk
LD_{50}	Lethal dose (which causes death in 50% animals)
LCR	Lifetime cancer risk
LOAEL	Lowest observed adverse effect level
MET	Minimal elicitation threshold
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
NZ EPA	New Zealand's Environmental Protection Authority

OSF	Oral slope factor
osRfD	Organ/system specific reference dose
POD	Point of departure
QRF	X-ray fluorescence
RfD	Reference dose
TWA	Time weighted average
USEPA	United States Environmental Protection Agency
UV-VIS	Ultraviolet-visible spectroscopy

EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for incidental exposure to chromium (Cr) while using leather or leather goods. This report will only consider domestic, non-occupational, routine, and incidental exposure to hexavalent chromium [Cr (VI)].

Leather is a versatile material and has many different uses. It is both durable and fashionable, and therefore its applications are nearly endless. It may be used to make clothing, footwear, furniture, gloves, wristwatch straps, baseball gloves, bags, smartphone cases, personal accessories (belts, bracelets) etc.

Tanning is the process of treating the skin or hide of an animal to make leather. It is done to keep the animal skin or hide from rotting, decomposing, and putrefying. Most of the leather made today is chrome-tanned i.e uses Cr (III) salts such as chromium sulfate. Cr (VI) salts are never used in leather tanning as they are more toxic to humans than Cr (III). However, Cr (VI) may end up in the leather. The exact origin of Cr (VI) in leather is not well understood but its formation can occur in several stages of leather's lifetime i.e during leather and product manufacturing or during storage and transportation.

The most stable and commonly occurring oxidation states of Cr are trivalent [(chromium +3, Cr (III)], a form which is considered an essential element to humans and found in food, and hexavalent [(chromium +6, Cr (VI)], which is toxic and a known carcinogen.

There are restrictions for the concentration of Cr (VI) in leather goods in the European Union (EU). In the EU, leather articles coming into contact with the skin cannot be placed on the market if they contain Cr (VI) in concentrations equal to or greater than 3 mg/kg. In New Zealand, there are no specific regulatory concentration limits or restrictions for Cr(VI) in leather. However, New Zealand tanners are aligned with international standards through involvement with the international Leather Working Group and the limits are consistent with the EU.

Leather goods (shoes, sandals, belts wallets, mobile covers, gloves, clothing, dog leads, bracelets, and handbags) have been recalled in the United States (US), United Kingdom (UK) and EU due to the detection of high levels of Cr (VI). Most of these products were manufactured in the People's Republic of China. Concentrations of Cr (VI) as high as 414 mg/kg were detected in gloves and prompted a recall in the EU in 2013. The restriction of 3 mg/kg of Cr (VI) in leather products to be placed in the EU market was adopted from 2015. The concentration levels in products have decreased markedly but products containing a concentration above 3 mg/kg are still occasionally identified.

Exposure to Cr (VI) while using leather goods is considered incidental. The dermal route of exposure is considered relevant as the products (shoes, bags, purse) may come in contact with skin. Exposure via the inhalation and oral routes is likely to be negligible. For the current risk assessment, the maximum concentrations of bioavailable Cr (VI) detected in a Danish EPA survey (33 and 62 mg/kg in baby shoes and adult shoes, respectively) were used to carry out a risk assessment.

In this assessment, non-carcinogenicr health risks of Cr (VI) in leather shoes (adult and children) through dermal exposure was evaluated by calculating hazard quotient (HQ). The HQ was greater than 1 for children and adults, which indicates that Cr (VI) in leather shoes

may be of toxicological concern for non-carcinogenic risks. However, there are some limitations in the risk assessment and some of the assumptions made were highly conservative. Factors such as wearing socks with the shoes, the same shoes may not be used over a lifetime, and seasonal variations (different shoes worn in summer vs winter) would mitigate exposure to and absorption of Cr (VI) from leather goods and will decrease risks.

Lifetime carcinogen risk was not estimated as there is no evidence of carcinogenicity of Cr(VI) by the dermal route of exposure.

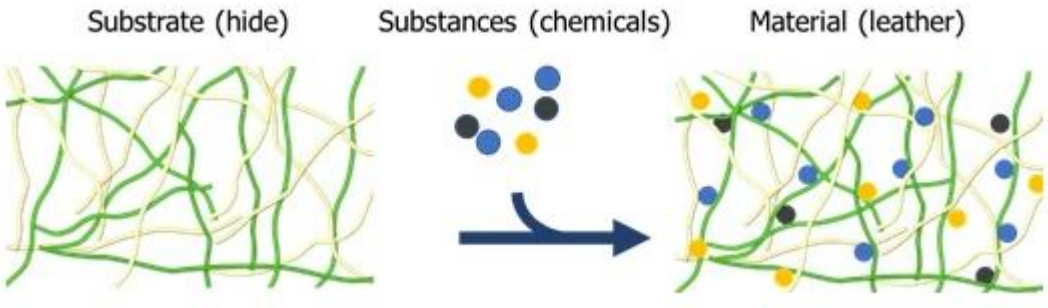
1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for chromium (Cr) (contaminant, by-product) in leather or leather products (shoes, belts, and clothing etc). This report will only consider domestic, non-occupational, incidental exposure (dermal) to Cr in leather or leather goods. Exposure scenarios will be developed for the most common or likely exposure events. It is well known that hexavalent chromium [Cr (VI)] is more toxic than trivalent chromium [Cr (III)] as Cr (VI) is a skin irritant and contact sensitiser and is genotoxic and a human carcinogen. Hence, this assessment report will focus primarily on risks associated with Cr (VI) in leather.

1.1 LEATHER TANNING

Leather is a versatile material and has many different uses. It is both durable and fashionable, and therefore its applications are nearly endless. It may be used to make clothing, footwear, furniture, gloves, wristwatch straps, baseball gloves, bags, mobile phone cases, personal accessories (belts, bracelets) etc.

Tanning is the process of treating the skin or hide of an animal to make leather. It is done to keep the animal skin or hide from rotting, decomposing, and putrefying. There are both microbiological and chemical factors which cause animal skin to breakdown and decompose. Tanning prevents all of these degradation processes and makes the leather durable (SteelHorseLeather, 2021).



Source: https://www.neratanning.com/leather-tanning/

Figure 1. Graphical representation from hide to leather

Two main leather tanning techniques are used:

1) Vegetable tanning: This is the oldest method and involves usage of tannins extracted from various parts of a plant. It usually takes longer to tan leather using this method, but the result is a leather with a distinctive aroma and patina, which ages well (Sai Bhavya *et al.*, 2019; SteelHorseLeather, 2021).

2) Chrome tanning: Unlike the ancient practice of vegetable tanning, chrome tanning or chromium tanning is relatively recent. About 75% of leather made today is chrome-tanned. It is one of the most practiced methods of tanning leather. This is because it has certain advantages in comparison to other techniques of tanning, especially vegetable tanning. It uses Cr (III) sulfate which has been considered as the most effective and efficient tanning agent. It forms poly chromium compounds by a process called olation which acts as active

compounds in tanning by crosslinking the collagen subunits in the hide (Sai Bhavya *et al.*, 2019; SteelHorseLeather, 2021).

1.2 PHYSICO-CHEMICAL PROPERTIES OF CHROMIUM

Cr (atomic number 24, relative atomic mass 51.996) is a grey hard metal, occurs in the oxidation state from -2 to +6, but only the 0 (elemental metal form), +2, +3 and +6 states are common (Dayan and Paine, 2001). The most stable and commonly occurring states are trivalent [(chromium +3, Cr (III)], a form which is considered an essential element to humans and found in food, and hexavalent [(chromium +6, Cr (VI)], which is toxic and a known carcinogen (EFSA, 2014a; b). The relationship between the hexavalent and trivalent states of Cr is described by the equation:

$Cr_2O_7^{2-} + 14H^+ + 6$ electrons $\rightarrow 2Cr\ [III] + 7H_2O + 1{:}33$ eV

Cr (VI) has strong oxidising potential due to the difference in electric potential between Cr (VI) and Cr (III) and the substantial energy (1.33 eV) required to oxidise the trivalent Cr to the hexavalent form. Thus, oxidation of Cr (III) never occurs in biological systems. However, spontaneous reduction of Cr (VI) occurs in organisms unless Cr (VI) mis present in an insoluble form. For example, in blood, Cr (VI) is rapidly reduced to Cr (III). Thus, once Cr (VI) has penetrated the membrane of the red blood cell it is reduced and Cr (III) becomes bound to cellular constituents making it unable to leave the erythrocyte (Dayan and Paine, 2001).

1.3 SOURCES OF CHROMIUM (VI) IN LEATHER

Most of the leather made today is chrome-tanned, using Cr (III) salts such as chromium sulfate. Cr (VI) salts are never used in leather tanning as they are more toxic to humans than Cr (III). However, Cr (VI) may end up in the leather. The exact origin of Cr (VI) is not well understood but its formation can occur in several stages of leather's lifetime (Babu *et al.*, 2005; Hauber and Buljan, 2000; Hendan, 2019):

a) Leather manufacturing process

Uncontrolled process conditions are the main reason for conversion of Cr (III) to Cr (VI). These conditions may be:

1. Uncontrolled high pH and high temperatures at certain steps even if strong oxidising agents are not used.
2. Use of inappropriate process chemicals such as strong bleaching agents, metal complex dyes containing Cr (VI), fat liquor having high amounts of fatty acids. Fat liquors based on oils with a high degree of unsaturation and other post-tanning and finishing auxiliaries bearing uncured oxidative catalysts used in the processing of leather could, theoretically, aid in the conversion of free Cr (III) to Cr (VI). The hydroperoxide formed during auto-oxidation of the fat/oil, oxidises Cr (III) to Cr (VI) in chrome-tanned leather.

b) Product manufacturing process

1. Uncontrolled high temperatures at shaping at assembling steps can convert Cr (III) to Cr (VI).
2. Use of inappropriate process chemicals such as glues, dyes, finishing agents which contain alkaline and oxidising agents.
3. Use of UV radiation in polymerisation initiation. Exposure to UV light is one of the best known ways in which species such as lipid peroxide and radicals such as the

hydrogen peroxide and hydroxyl radical can be formed, which was reported to account for the oxidation of Cr (III) to Cr (VI).

c) During storage and transport of leather or leather products

1. Uncontrolled conditions such as high temperatures, low humidity and exposure to sun or artificial light can convert Cr (III) to Cr (VI).
2. Insufficient protection against mold and other microorganism can also contribute to formation of Cr (VI).

1.4 SURVEYS FOR CHROMIUM (VI) IN LEATHER

There are a number of surveys and studies conducted to evaluate the content of Cr (III) and Cr (VI) in leather or leather products. These are summarised below:

1) The Danish EPA investigated the presence of Cr (III) and Cr (VI) in leather products (n = 43) (Rydin, 2002). The products sampled were watch-straps, shoes, gloves, baby-shoes, working gloves, leather jackets, trousers, leather-tops, skirts, and leather hats. A colorimetric determination method (DIN 53314) was used to determine the content of Cr (VI) in leather. The detection limit (LOD) for this method was 3 mg/kg. The DIN method extracts Cr (VI) from 2 g of finely cut-up leather using a potassium hydrogen phosphate buffer at pH 7.7 for 3 hr. The survey found that 35% (15 out of 43) of the leather products contained Cr (VI) in levels above the LOD. The Cr (VI) content was in the range of 3.6 – 14.7 mg/kg. The highest concentration of Cr (VI) was found in working gloves. This was expected as working gloves are quite often low-cost products. Two of the five shoes tested had a detectable content of Cr (VI) of 10.4 and 6.3 mg/kg.

   Items were also analysed for total Cr content. The total Cr contents, expressed as $\%Cr_2O_3$, were in the range of 2 – 5.6%. Ten additional baby shoes were subjected to further analysis of total Cr and Cr (VI). Two of these shoes (upper and sole) were then analysed for migration of Cr according to DS/EN 71 part 3: Dec 1994. Cr (VI) was not detected in any of these samples at concentrations above the LOD. The total chromium, as $\%Cr_2O_3$, was in the range of 4 – 5%. There were large variations in the migration of Cr from the shoes and also from the sole and upper leather of the shoe. Migrating Cr was in the range of 370 – 980 mg/kg. All the results are summarised in Table 1.

   Table 1: Mean values of chromium content and migration analysis

Samples	Cr (VI), mean (range) (mg/kg)	Total Cr, mean (range)($\%Cr_2O_3$)	Migration of total Cr (mg/kg)
Leather products (n = 43)*	7.5* (3.6 – 14.7)	3.8* (1.8 - 5.6)	-
Baby shoes (n= 10)*	<DL	4.6* (4 – 5.2)	-
Baby shoes (n= 2), Sole and upper*	-	-	585* (370 – 980)

Cr: Chromium
*Mean of quantifiable values only

2) The Danish EPA conducted a further survey and health assessment (sensitisation only) of Cr in leather shoes (Johansen *et al.*, 2011). For this, 60 pairs of leather shoes were purchased from well-known shoe store chains in Denmark. The shoes

bought were planned to be approximately 50% sandals (or similar) within each category (children's shoes, men's shoes, and lady's shoes), but due to the season (autumn), it was not possible to reach that number, especially within the categories children's shoes and men's shoes. X-ray fluorescence (XRF) was used to screen the shoes for Cr. There was different leather in the inner-sole and the upper-leather. Hence, the shoes were screened at two different places - the sole (from inside the shoe) and the upper leather (from inside the shoe). It should be noted that the results from QRF screening do not give any information about the state or form (ex. Cr (VI) or Cr (III)) of the chemical element present. However, it is judged that the results from the XRF screening were usable for selection of leather shoes for further migration analysis (for release of Cr (VI) and Cr (III) compounds).

Of the purchased shoes, 50 of the 60 had Cr content between 1 and 3% in the upper leather parts. XRF screening of the soles (from the inside of the shoes) showed that 51 of the 60 purchased shoes also had Cr content between 1 and 3%. Hence, the typical range of Cr in both soles and leather surrounding the foot was 1 to 3%. Three shoes did not seem to have any detectable Cr (<LOD). The LOD was 0.01% Cr, and it cannot be ruled out that these three shoes may have contained very small amounts of Cr. It is also possible that these shoes might have been tanned without using Cr. The results indicated no correlation between content of Cr and shoe category (lady's, men's, or children's shoes) or shoe type (sandals, boots or ordinary shoes).

Samples for migration analysis were selected based on proportional equal distribution between shoe categories, shoe types and price range. The proportion of equal distribution of amount of Cr was also considered. Eighteen shoes (boot, sandal and ordinary) were selected for migration analysis. The International ISO Standard ISO 17075 method was used for determining Cr (VI) in solutions leached from leather. In this method, soluble Cr (VI) is extracted from the specimen of leather in a water-based solution containing a phosphate salt at a carefully controlled pH of 7.5 to 8. The extraction is carried out in this solution, as it contains the constituents of perspiration, and therefore is likely to be present on the surface of a person's skin. This method is suitable to quantify the Cr (VI) content in leathers with a concentration of 3 mg/kg (3 ppm) or higher. The Cr (III) content was determined by performing an analysis by inductively coupled plasma – optical emission spectrometry (ICP-OES) of the total Cr content in the extraction solution used for determining the Cr (VI) content and then subtracting the value for the Cr (VI) content (

Table 2).

Table 2: Total Cr and Cr (III and VI) (mg/kg) migrating from leather shoes

Sample	Cr migrating from leather shoes, mean (range) (mg/kg)		
	Total Cr	**Cr (VI)**	**Cr (III)**
Leather shoes (n =18)	153* (1 – 277)	18* (3 – 62)	154* (1 – 303)

*Mean of quantifiable values only

Eight of the 18 shoes (44%) analysed leached Cr (VI) in an amount equal to or above the LOD of 3 mg/kg. The highest value detected was 62 mg/kg Cr (VI).

3) The Danish EPA conducted another survey for the presence of Cr in leather goods (Barbara Kolarik, 2019). A total of 21 products were selected for Cr chemical analysis, including shoes for adults, shoes for babies/children, shoe sole, handbags/purses, belts, watch straps/bracelets, and key string. Total Cr and Cr (VI) were determined based on the ISO 17075 method and a modified version of DS/EN 259:2003, respectively (Table 3). In the DS/EN 259:2003 method, leather is subjected to a digestion solution consisting of diluted *aqua regia* (nitric acid and hydrochloric acid). The LODs for determining total Cr and Cr (VI) were 5.0 mg/kg dry matter and 1.0 mg/kg dry matter, respectively.

Table 3: Total Cr and Cr (VI) in different leather product categories (mg/kg)

Product category	Total Cr- XRF	Total Cr (DS/EN 259:2003)	Cr (VI) (ISO17075)
Footwear (n =14)	7878 (2970 – 16487)	19910 (8750 – 31500)	3 (1.5 – 5.5)
Handbags and purses (n = 4)	10915 (7041 – 13000)	23125 (20500 – 25000)	14 (1.3 – 28)
Belts and straps (n = 3)	4463 (500 – 6564)	17350 (9050 – 22500)	3.4 (1.6 – 5.0)

The concentration of Cr (VI) was highest in the handbags (16, 1.3, 28, 11 mg/kg). There was no correlation between the amounts of total-Cr and Cr (VI) in the leather samples.

4) Pantazi *et al.* (2012) investigated whether Cr (VI) and Cr (III) are released from leather shoes in a quantity leading to a risk of causing allergic reactions. For this, 10 pairs of leather shoes (4 pairs of children's footwear, 3 pairs women's footwear and 3 pairs of men's footwear) were analysed for Cr (VI) migration according to the SR EN ISO 17075:2008 Leather – Chemical Tests – Determination of Cr (VI) Content, and determination of total Cr in leather was done according to the SR EN ISO 5398/1:2008 Leather - Chemical Determination of Chromic Oxide Content - Part 1: Quantification by Titration. The LOD for Cr (VI) was 3.0 mg/kg. Cr (VI) concentrations were below the LOD in all the samples (

5) Table 4).

Table 4: Mean of total Cr and Cr (VI) in footwear (mg/kg)

Product category	Total Cr	Cr (VI)
Children's footwear (n = 4)	25315 (21073 – 21073)	<3
Women's footwear (n = 3)	31496 (30173 – 32636)	<3
Men's footwear (n = 3)	27934 (19215 – 37221)	<3

6) Total Cr content was determined in leather samples (n = 10) used in car accessories like seat covers, belts etc (Zeiner *et al.*, 2011). The samples were analysed by inductively coupled plasma – optical emission spectrometry (ICP-OES) after acidic microwave assisted digestion. The mean concentration of total Cr in the ten samples analyzed was 25000 mg/kg (18700 – 32000 mg/kg).

7) Total Cr and Cr (VI) content was determined by ultraviolet-visible (UV-VIS) spectroscopy in leather products that were intended to be used in the textile industry (Rezić and Zeiner, 2009). The mean content of total Cr extracted from leather materials (n = 6) was 56 mg/kg. The mean Cr (VI) content extracted from leather material was 2 mg/kg (0.30 – 3.30 mg/kg). It should be noted that these concentrations relate to Cr extractable from the leather.

1.4.1 Product recalls due to chromium (VI) in leather products

There have been product recalls of various leather products (shoes, gloves. clothes) in the US, UK, and EU due to the presence of Cr (VI) at high levels and some of these recalls are summarised in Table 5. The EU Safety Gate alert system contains around 640 recalls of leather products for elevated Cr (VI) content, with products including shoes (adult and childrens), sandals, belts, wallets, mobile phone covers, gloves, clothing, dog leads, bracelets, and handbags. Most of these products were manufactured in the Republic of China. The concentration of Cr (VI) was found up to the level of 414 mg/kg in gloves which were recalled in the year 2013. There has been a limit of 3 mg/kg of Cr (VI) in leather products to be placed in the EU market since 2015. The concentration levels in products have since then significantly dropped but have still occasionally been found at concentrations above 3 mg/kg.

Table 5: Product recalls due to high levels of Cr (VI)

Name of Product	Hazard	Risk	Reference
Wide Fit Kitten Heel Court Pumps 	Leather insock had elevated levels of Cr (VI)	Skin irritant	(CPSC, 2020)
Ashwood women's red leather gloves 	Leather had an elevated level of a Cr (VI)	Skin irritant	(UKGOV, 2022)
Crocodilino anatomic shoes 	Leather had Cr (VI) (measured values: up to 8.8 mg/kg). .	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2022e)
Black, coated leather belt, 100 cm long. 	Inner layer of the belt contains chromium (VI) (measured values: up to 8 mg/kg).	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2022d)
Chiba Gloves for Sports 	Cr (VI) (measured value up to 17.5 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2022c)
Children's sandals 	Cr (VI) (measured value up to 5.6 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2022b)

Children's Lederhose (leather breeches) 	Cr (VI) (measured value up to 7.1 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2022a)
Dog lead 	Cr (VI) (measured value up to 12.4 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2021b)
Red leather wallet with RFID protection 	Cr (VI) (measured value up to 6.5 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2021a)
Pink leather key pouch with zip fastener and pink textile lining 	Cr (VI) (measured value up to 12.4 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2020a)
Black leather bracelet 	Cr (VI) (measured value up to 6.8 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2020b)
Brown leather case for Iphone 	Cr (VI) (measured value up to 4 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2020c)
Black leather scarf	Cr (VI) (measured value up to 19.2 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2019)

			
Black leather handbag 	Cr (VI) (measured value up to 13.6 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2018a)
Handbag 	Cr (VI) (measured value up to 6.6 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2018b)
Baseball glove 	Cr (VI) (measured value up to 9.6 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2017)
Women's trousers 	Cr (VI) (2.4 to 19.2 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2010a)
Children dress 	Cr (VI) (0.6 to 5 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2010b)
Men shoes 	Cr (VI) (11.4 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2011a)
Leather wristbands	Cr (VI) (10.5 to 12.0 mg/kg)	Skin sensitising, can trigger allergic	(SafetyGate, 2011b)

		reactions and can cause cancer	
Babies' shoes "Leather first-walker shoes for chil 	Cr (VI) (22.0 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2011c)
baby's slip-on shoes/slippers 	Cr (VI) (28.7 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2011d)
Ladies' shoes (lace-up) 	Cr (VI) (20.5 to 38.3 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2011f)
Ladies' leather jackets 	Cr (VI) (3 to 50 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2011e)
Ladies' gloves 	Cr (VI) (414 mg/kg)	Skin sensitising, can trigger allergic reactions and can cause cancer	(SafetyGate, 2013)

1.5 REGULATORY LIMITS FOR CHROMIUM (VI) IN LEATHER

1.5.1 New Zealand

ESR staff contacted New Zealand Leather & Shoe Research Association (LASRA) to check if there are any concentration limits or restrictions for Cr (VI) in leather or leather products in New Zealand. The response from LASRA was "There are no concentration limits or restrictions that are specific to New Zealand and the tanners follow international standards due to the Leather Working Group requirements. All tanners in New Zealand manufacture chrome tanned leather to a specification of less than 3 mg/kg of Cr (VI) and this is regularly tested by LASRA or other international laboratories".

1.5.2 European Union (EU)

Cr (VI) in leather is regulated under Registration, Evaluation, Authorisation and Restriction (REACH) regulation (ECHA, 2016) in the EU.

The condition of restriction is:

a) "Leather articles coming into contact with the skin shall not be placed on the market where they contain Cr (VI) in concentrations equal to or greater than 3 mg/kg (0.0003% by weight) of the total dry weight of the leather".

b) "Articles containing leather parts coming into contact with the skin shall not be placed on the market where any of those leather parts contains Cr (VI) in concentrations equal to or greater than 3 mg/kg (0.0003 % by weight) of the total dry weight of that leather part".

The above restrictions do not apply to the placing of second-hand articles on the market which were in end-use in the Union before 1 May 2015 (ECHA, 2016).

1.5.3 United States of America (USA)

There is no federal regulation in the USA for Cr (VI) in leather products. California's Proposition 65 regulates Cr (VI) on the basis of carcinogenicity and reproductive toxicity. Proposition 65 is a right-to-know act that is intended to protect citizens in consumer, occupational, and community exposure settings. Over the last few years, there has been a substantial increase in the number of Proposition 65 notices issued for Cr (VI) compounds in leather goods. In 2019, 39 notices were issued for Cr (VI)-containing substances, 25 of which were issued for leather goods such as gloves, aprons and footwear. In 2020, four notices were issued for Cr (VI)-containing articles, all of which were leather gloves. The covered products were identified as containing Cr (VI) and did not have Proposition 65 warning labels (TUV_SUD, 2022).

1.6 HUMAN HEALTH HAZARD CLASSIFICATIONS OF CHROMIUM (VI) AND COMPOUNDS CONTAINING CHROMIUM (VI)

1.6.1 New Zealand

ESR notes that the NZ EPA has not evaluated the toxicity of Cr (VI) (CAS RN 18540-29-9) and hence, there are no human health hazard classifications in New Zealand.

1.6.2 European Union (EU)

There is no harmonized (official) human health hazard classification for Cr (VI; CAS RN 18540-29-9) in the EU. However, some compounds containing Cr (VI) have harmonised classifications which provide indications of the toxicity of Cr (VI). These are summarised in Table 6:

Table 6: Human health hazard classification of Cr (VI) and Cr (VI) compounds

Compound (CAS RN)	Hazard classification	Reference
Cr (VI) (18540-29-9)* and Chromic acid (7738-94-5)*	Skin Sens 1; H317: May cause an allergic skin reaction Carc 1B; H350: May cause cancer by inhalation route	(C&L_Inventory, 2022c)
Potassium dichromate (7778-50-9)	Acute Tox 3; H301: Toxic if swallowed Acute Tox 4; H312: Harmful in contact with skin Skin Corr 1B; H314: Causes severe skin burns and eye damage Skin Sens 1; H317: May cause an allergic skin reaction Muta 1B; H340: May cause genetic defects Carc 1B; H350: May cause cancer by inhalation route STOT RE 1; H372: Causes damage to organs Repr 1B; H360DF: May damage fertility or the unborn child	(C&L_Inventory, 2022b)
Potassium chromate (7789-00-6)	Skin Irrit 2; H315: Causes skin irritation Eye Irrit 2; H319: Causes serious eye irritation Skin Sens 1; H317: May cause an allergic skin reaction STOT RE 1; H372: Causes damage to organs Muta 1B; H340: May cause genetic defects Carc 1B; H350: May cause cancer by inhalation route	(C&L_Inventory, 2022a)

*Classification is not harmonised (not official) in the EU but has been notified by several companies to the C&L inventory

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments for Cr (VI) in leather were found for New Zealand.

2.2 HEALTH EFFECTS – CHROMIUM IN LEATHER

2.2.1 Incident surveillance and case reports

There was one clinical report found in the literature where Cr in a leather glove caused contact dermatitis. This is summarised below:

A 27-year-old professional woman golfer presented with recurrent, pruritic, erythematous plaques that had been occurring on both the dorsal and palmar sides of the hand for several years (Lim *et al.*, 2010). The lesions appeared whenever she had worn golf gloves for an extended period of time, especially during tournament season. Patch tests were performed to identify the causal agent and the results demonstrated a strong positive reaction to 0.5% potassium dichromate at 48 hours and 72 hours and to her own glove. A moderately positive reaction to 7.5% nickel sulfate was also observed. Chromium content in the glove was analysed and it was found to be 309 mg/kg. Nickel was found to be 10 mg/kg. Based on the results, she was diagnosed with allergic contact dermatitis due to a chromium-tanned leather glove. The skin lesions improved following administration of oral antihistamines and topical steroids. The case was advised to wear chromium-free leather gloves and it was explained that re-exposure to chromium-containing leather gloves could cause a recurrence of contact dermatitis.

2.3 TOXICITY OF CHROMIUM

The toxicity data on Cr (VI) compounds is extensive and has been reviewed by various regulatory agencies such as the European Chemicals Agency (ECHA), the U.S. Environmental Protection Agency (US EPA), and the European Food Safety Authority (EFSA) (ECB, 2005; EFSA, 2014b; USEPA, 2010). Most of the toxicology data available is on sodium chromate, dichromates of sodium, potassium and ammonium, and chromium (VI) trioxide, the substances are all highly water-soluble hexavalent compounds.
Toxicity studies were mostly based on oral administration of Cr, with little information available on the toxicity of Cr compounds following dermal exposure.

2.3.1 Absorption, Distribution, Metabolism and Excretion of Chromium

Absorption: Cr (VI) is absorbed to a greater extent than Cr (III) following oral administration. Cr (III) is very poorly absorbed via the gastrointestinal tract in both rats and humans after oral administration. The absorption rate of Cr (III) is 0.4 to 2.8% in both rats and humans. Studies report that 1 to 6.9% of the administered dose of Cr (VI) was recovered in the urine in humans and 2% in rats (ATSDR, 2012; EFSA, 2014b).

Animal studies have shown that after inhalation exposure, 20 to 30% of the administered Cr (VI) is absorbed via the respiratory tract (ECB, 2005).

Cr (VI) salts penetrate through the skin especially if the skin is damaged. Studies with volunteers showed that the reductive capacity of the skin is not sufficient to prevent systemic uptake of Cr VI from locally applied Cr. The dermal absorption ranged from 3.4 to 10.6% for a 0.2 M sodium chromate solution and from 7.7 to 23% for a 0.01 M sodium chromate

solution (ATSDR, 2012; SCHER, 2015). Dermal absorption of highly soluble Cr (VI) compounds in guinea pigs was <1 and 4% of applied doses (ECB, 2005).

Distribution: Several *in vivo* and *in vitro* studies that reported that negligible amounts of Cr (III) are taken up by red blood cells (RBCs), but rather compete for one of the binding sites on the iron-transport plasma protein transferrin. Cr (III) can subsequently be transferred to a low molecular-weight chromium binding substance, or chromodulin and transported to the liver, a process partly regulated by insulin. Tissue uptake is also limited for Cr (III). Following oral administration in rats, very small amounts of Cr (IIII) was detected in the liver, spleen, and bone (marrow) but a substantial amount was detected in the kidney (but at much lower levels than Cr (VI)) (EFSA, 2014b).

Following absorption, Cr (VI) is found in both RBCs and plasma. Inside the RBCs, Cr (VI) is rapidly reduced to Cr (III) by glutathione, becoming irreversibly bound to haemoglobin for the lifespan of the cell. Cr (VI) is also reduced to Cr (III) in plasma (ECB, 2005; EFSA, 2014b). Animal studies have shown that Cr (VI) accumulates mainly in liver, kidneys, spleen, and bone marrow. Autopsy data on humans both occupationally and non-occupationally exposed showed the highest concentrations of Cr (VI) in lungs followed by spleen, liver, and kidneys. The half-life of chromium in various tissues (other than plasma) of rats administered Cr (VI) exceeds 20 days (EFSA, 2014b).

Metabolism: Cr (III) in biological environments is converted to Cr (VI) to a limited extent only. This may be since this conversion requires strong oxidising agents (ATSDR, 2012; EFSA, 2014b).

Cr (VI) is reduced to Cr (III) by saliva and gastric juices. This process may become saturated at high oral doses of Cr (VI) and can result in increased absorption, elevated blood levels and the appearance of toxicity that may not occur at lower doses. In the RBC, Cr (VI) is reduced to Cr (III) by glutathione.

Excretion: Following oral exposure, Cr (III) is primarily excreted in faeces in humans and rats as its intestinal absorption is poor. Small amounts are also excreted in urine. Cr (III) is rapidly cleared from the blood and plasma and urinary Cr also rapidly declines. Cr (III) is removed from tissues at a slower rate. The estimated half-time of Cr (III) for whole-body elimination in rats after gavage administration was 92 days (EFSA, 2014b).

Cr (VI) is rapidly taken up by RBCs and does not decline rapidly and remains elevated for quite some time. The decrease in Cr (VI) levels is more rapid when administered orally, likely reflecting the conversion to Cr (III) before GI absorption. The estimated half-time for whole-body Cr elimination is 22 days following administration of Cr (VI) (ATSDR, 2012; EFSA, 2014b).

2.3.2 Acute toxicity

Acute oral toxicity in humans was 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. Fatalities observed were due to respiratory distress with severe hemorrhages, multiple organ failure (metabolic acidosis, gastrointestinal hemorrhage and necrosis, fatty degeneration of the liver, and acute renal failure and necrosis) (EFSA, 2014b).

Laboratory rats were found to have lethal oral acute toxicity (LD_{50} mg/kg bw) to Cr (VI) from potassium dichromate of 16.9 (F) and 26.2 (M), sodium chromate 13 (F) and 28 (M), and calcium chromate 108 (F) and 249 (M), respectively (EFSA, 2014b; Gad, 1989). Nephrotoxicity was the primary cause of death from acute exposure of Cr (VI).

Very limited data was found on acute toxicity by the dermal route of exposure. However, based on LD_{50} values, Cr (VI) compounds with high water solubility were toxic following dermal application. The dermal LD_{50} values for different Cr (VI) compounds in rabbit were: sodium dichromate 960 mg/kg (380 mg Cr (VI)/kg bw); potassium dichromate 1,150 mg/kg (410 mg Cr (VI)/kg bw); ammonium dichromate 1,860 mg/kg (770 mg Cr(VI) /kg bw) and sodium chromate 1,330 mg/kg (430 mg Cr (VI)/kg bw). In another study, percutaneous doses of 207 mg/kg sodium chromate (66 mg Cr (VI)/kg bw) and 170 mg/kg sodium dichromate (66 mg Cr (VI)/kg bw) produced death in guinea pigs. A dermal LD_{50} value of 57 mg/kg (30 mg Cr (VI)/kg bw) has been reported for chromium (VI) trioxide in rabbits (ECB, 2005).

Cr (VI) compounds are toxic by inhalation. The inhalation LC_{50} values in rats for several compounds ranged from 29 to 45 mg Cr (VI)/m^3 for females and from 33 to 82 mg Cr (VI)/m^3 for males (ATSDR, 2012). Female rats were found to be more sensitive than male rats. Major signs of toxicity were reduced body weight, respiratory distress, irritation of the respiratory tract, lung oedema, inflammation and tracheal epithelium necrosis (ECB, 2005).

2.3.3 Skin and eye irritation

Skin irritation: 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. Chrome ulcers were also reported in leather tanners who handled dichromate salts (ATSDR, 2012).
Corrosivity is also dependent on pH of the Cr (VI) compound solution. Aqueous chromium (VI) trioxide is a corrosive substance due to its low pH. In guinea pigs, concentration dependent erythema was observed after repeated applications were made daily for 4 days on unabraded skin using potassium dichromate solution. Skin inflammation, oedema, and necrosis was reported after dermal application of Cr (VI) compounds to the clipped, non-abraded skin of rabbits. (ECB, 2005)

Eye irritation: 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 to the human eye. Corneal vesication was reported in workers after accidental splashing of a crystal of potassium dichromate or a drop of a potassium dichromate solution in his eye.
Sodium dichromate and sodium chromate (pH 7.4) solution was not irritating or corrosive to the eyes of rabbits (ATSDR, 2012; ECB, 2005).

2.3.4 Skin sensitisation

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. Cross reactivity has been observed in the guinea pig; animals sensitised to Cr (VI) responded positively to Cr (III) compounds and vice versa. This is consistent with the current mechanistic understanding which indicates that Cr (III) is the ultimate hapten, following reduction of Cr (VI) in the skin (ECB, 2005).

Cr (VI) is also reported to cause contact allergic dermatitis in sensitive individuals. It has been reported that concentrations of 0.5% and below, potassium dichromate elicited a response in patch testing studies. In one study a minimum (10% reacting) elicitation concentration of 0.09 µg Cr (VI)/cm^2 was calculated after 54 Cr (VI)-sensitive volunteers were exposed to potassium dichromate (ECB, 2005; EFSA, 2014b).

2.3.5 Subchronic/chronic toxicity

No adverse or toxic effects were observed up to the highest dose tested in animals after oral administration of Cr (III). This may be due to the poor oral absorption of Cr (III). NOAELs of 506 and 286 mg Cr (III)/kg bw/d for sub-chronic and long-term toxicity in the rat, respectively, were reported from well conducted studies carried out by the US National Toxicology Program (NTP).

Repeated toxicity studies have shown that the major target organs after exposure to Cr (VI) compounds in rats and mice are the haematological system (microcytic, hypochromic anemia), the liver (biochemical and histopathological changes: vacuolation, lipid accumulation, chronic inflammation and focal necrosis), the kidney (biochemical and histopathological changes) and the gastrointestinal tract (irritation and histopathological changes to tissues) (EFSA, 2014b).

There were several studies in the literature regarding repeated oral exposure (dietary or via drinking water) to Cr (VI). The details of these studies are in the EFSA, US EPA, and ECHA reports (ECB, 2005; EFSA, 2014b; USEPA, 1998; 2010).

There are three drinking water studies (90-d to 2-year) conducted by the National Toxicology Program which provide dose-response data on the effects of Cr (VI) exposure based on a comprehensive assessment of toxicological endpoints. Several other studies do not provide data suitable for dose-response evaluation, because either only one dose was tested and/or comprehensive toxicological endpoints were not evaluated (EFSA, 2014b).

The lowest NOAEL identified in these studies for non-cancer effects was approximately 0.2 mg/kg bw/d. However, in some studies the lowest dose was greater than this NOAEL and no NOAEL could be determine.

In three 90-d studies conducted in rats and mice, a NOAEL was not identified because effects were observed at the lowest dose tested (EFSA, 2014b; NTP, 2007; USEPA, 2010). In rats, the mean effective doses of sodium dichromate dihydrate [Cr (VI)] based on drinking water intake was estimated to be 0, 1.7, 3.5, 5.9, 11.2, and 20.9 mg/kg bw/d for both males and females. The LOAEL in male and female rats was 1.7 mg hexavalent chromium/kg-day based on observations of microcytic, hypochromic anemia, increased serum liver enzyme activities and histopathological changes to pancreatic lymph nodes (in males). Histopathological changes to the duodenum (histiocytic infiltration) was observed from 3.1 mg hexavalent chromium/kg-day.

In mice, the mean effective doses of sodium dichromate dihydrate [Cr (VI)] based on drinking water intake was estimated to be 0, 3.1, 5.3, 9.1, 15.7, and 27.9 mg/kg bw/d for both males and females. The LOAEL in male and female mice was 3.1 mg hexavalent chromium/kg bw/d based on histopathological changes (histiocytic cellular infiltration) in the duodenum in both sexes at daily doses ≥3.1 mg hexavalent chromium/kg-day. Histopathological changes in mesenteric lymph nodes (histiocytic infiltration) was observed from 5.2 mg hexavalent chromium/kg bw/d (EFSA, 2014b; NTP, 2007; USEPA, 2010).

Similarly, in another comparative 90-d drinking water study in mice, a NOAEL was not identified. A LOAEL of 2.8 mg hexavalent chromium/kg-day was identified based on histopathological changes in the duodenum in B6C3F1 mice (histiocytic cellular infiltration and diffuse epithelial hyperplasia), BALB/c mice (histiocytic cellular infiltration), and *am*3-C57BL/6 mice (diffuse epithelial hyperplasia).

In a 2-year chronic toxicity study in rats, based on measured water consumption rates and body weights in rats, males received time-weighted average doses of hexavalent chromium of 0.21, 0.77, 2.1, or 5.9 mg/kg bw/d, while female rats received 0.24, 0.94, 2.4, or 7.0 mg/kg bw/d of hexavalent chromium (NTP, 2008; USEPA, 2010). The NOAEL for non-cancer effects in male rats was 0.21 mg/kg bw/d of hexavalent chromium based on increased incidence of nonneoplastic histopathological changes to the liver (basophilic foci), duodenum (histiocytic cellular infiltrate), and mesenteric lymph nodes (histiocytic cellular infiltrate and hemorrhage) observed at 0.77 mg/kg bw/d of hexavalent chromium. In female rats, a NOAEL was not identified as the effects were observed at the lowest dose tested. The LOAEL for noncancer effects of 0.24 mg hexavalent chromium/kg bw/d was identified based on the increased incidence of chronic inflammation of the liver in all treatment groups.

In a 2-year chronic toxicity study in mice, a NOAEL was not identified because effects were observed at the lowest dose tested (NTP, 2008; USEPA, 1998). A LOAEL for noncancer effects of 0.38 mg hexavalent chromium/kg bw/d was determined for both male and female B6C3F1 mice. The LOAEL in males was based on increased incidence of histopathological changes to the duodenum (diffuse epithelial hyperplasia) and mesenteric lymph nodes (histiocytic cellular infiltration). In females, the LOAEL was based on increased incidence of histopathological changes to the duodenum (diffuse epithelial hyperplasia), mesenteric lymph nodes (histiocytic cellular infiltration), liver (histiocytic cellular infiltration), and pancreas (depletion of cytoplasmic zymogen granules).

2.3.6 Genotoxicity

Data on the mutagenic potential of Cr (III) and Cr (VI) is extensive and has been thoroughly reviewed (ATSDR, 2012; EFSA, 2014b).

Cr (III) was not genotoxic in bacterial assays (*Salmonella* Typhimurium, *Escherichia coli)* but gave mixed, often positive, results with mammalian cells (human lymphocytes, Chinese hamster ovary, human diploid fibroblasts). In contrast, negative results were observed in *in vivo* animal models. Cr (III) compounds did not affect the micronuclei frequency and was negative in *in vivo* micronucleus assays in mice after oral and intraperitoneal administration.

In humans, tannery workers exposed to Cr (III) compounds, no significant differences in the frequency of chromosomal aberrations in peripheral lymphocytes were detected between healthy Cr-exposed workers and controls. However, the interpretation of results is difficult due to the presence of other chemicals (possibly also Cr (VI)) in the work environment. There are conflicting results on genotoxicity of Cr (III) but most of the studies were largely negative in *in vitro and in vivo* studies.

Cr (VI) compounds were found to be mutagenic in bacterial (strains of *S*. Typhimurium, *E. coli*), in yeast (*Saccharomyces cerevisiae*) and in mammalian systems. Clastogenic[1] activity (micronuclei, chromosomal aberrations and sister chromatid exchange) of Cr (VI)

[1] A clastogen is a mutagenic agent that disturbs normal DNA related processes or directly causes DNA strand breakages, thus causing the deletion, insertion, or rearrangement of entire chromosome sections

compounds (i.e. calcium chromate, chromic acid, potassium chromate, potassium dichromate, sodium chromate and sodium dichromate) was reported by several groups in cultured Chinese hamster ovary (CHO) cells. Cr (VI) is a direct-acting mutagen and metabolic activation is not required to detect the mutagenic/clastogenic effects in mammalian cells.

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.

2.3.7 Carcinogenicity

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 the 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, 2010). This is based on a statistically significant increase in the incidence of tumors 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.

2.3.7.1 PROPOSED MECHANISMS OF CARCINOGENICITY

Cr (VI) has been shown to be carcinogenic in animal experiments via oral and inhalation administration. Cellular uptake of Cr (VI) is likely to be the first stage of Cr (VI)-induced carcinogenesis. Cr (VI) is similar in structure to tetrahedral sulphate and phosphate anions, and therefore can readily pass into cells via non-specific sulphate and phosphate anion transport channels (Bridges and Zalups, 2005). Cr (III), and Cr (VI) reduced to Cr (III) before entering cells, is not tetrahedral in structure and does not readily pass into cells. Intracellular reduction of Cr (VI) takes place following intermediate reduction to thermodynamically unstable Cr (V) and Cr (IV) and finally stable Cr (III) (USEPA, 2010).

DNA damage and mutagenicity occurs via the reduced species of Cr (V) and Cr (IV). They have been shown to be reactive with DNA, leading to DNA strand breaks, chromium-DNA adducts, chromosomal aberrations, and genomic instability. If inadequately repaired, mutations can occur (USEPA, 2010). Oxidative stress takes place with the formation of reactive intermediates (EFSA, 2014b).

3 DOSE-RESPONSE INFORMATION

In the current context, concerns associated with exposure to Cr (VI) will be related to chronic exposure events.

3.1 NON-CANCER EFFECTS

3.1.1 Contact dermatitis:

There was one survey and health risk assessment (sensitisation endpoint) carried out in Denmark by the Danish EPA which is summarised below and, in the risk characterisation section.

Contact allergy is also known as type IV-allergy and consists of two phases- the induction phase and the elicitation phase. In the induction or sensitization phase, changes in the immune system are induced. This phase is without symptoms. Subsequent exposure to sufficient amounts of allergens, the immune system will react to the substance and symptoms will appear. This phase is called elicitation (Pantazi *et al.*, 2012). The threshold values for risk assessment of allergens are expressed as $MET_{10\%}$ (minimal elicitation threshold) - which represents the estimated dose causing a reaction in 10% of sensitised individuals. $MET_{10\%}$ is derived from exposure to an allergen dose over an area of 0.5 cm^2 for 48 hours. The $MET_{10\%}$ values for Cr available in the literature are given below in **Error! Reference source not found.**

Table 7: Estimated MET for 10% of sensitized individuals

$MET_{10\%}$	Number of test subjects	References
0.09 µg Cr (VI)/cm^2/2 days = 3 mg/kg	54	(Hansen *et al.*, 2002; Pantazi *et al.*, 2012)
0.35 µg Cr (VI)/cm^2/2 days = 11.67 mg/kg	14	
0.90 µg Cr (VI)/cm^2/2 days = 30 mg/kg	17	
0.02 µg Cr (VI)/cm^2/2 days = 0.67 mg/kg	5	
0.03 µg Cr (VI)/cm^2/2 days = 1 mg/kg	18	

$MET_{10\%}$ values for Cr (VI) were estimated to be between 0.02-0.9 µg/cm^2. The value of 0.09 µg/cm^2 corresponding to 3 ppm was used in the assessment as it was the largest study with a sample size of 54 subjects. Cr (III) has higher threshold levels as compared to Cr (VI). From the same study, the estimated $MET_{10\%}$ for Cr (III) was 0.18 µg/cm^2 (6 ppm)

3.1.2 Non-cancer systemic effects

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 for a year in water containing between 0.45 and 11 ppm. No effects (water intake, food consumption or weight gain, hematology) were observed at monthly intervals or examination of tissues at 6 months or a year show any significant differences between any of the groups

given chromium and the control group. Two other groups 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). 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 for the rat (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 8.

Table 8: Reference dose for chromium

Study / key effect	POD	UF / MF	RfD	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/d (adj.)	300 / 3	0.003 mg/kg bw/d	(IRIS, 1998)

POD: point of departure, UF: uncertainty factor, MF: modifying factor, BMCL: Lower 95th percentile confidence limit of the benchmark dose, bw: body weight

Proposed organ organ/system specific reference doses

As discussed in section 2.3.4, NTP conducted studies which provide dose-response data on the effects of Cr (VI) exposure based on a comprehensive assessment of toxicological endpoints. The US EPA has proposed new organ/system specific reference doses (osRfD) based on BMDL, NOAEL or LOAEL approaches using chronic toxicity studies which are summarised in Table 9 (IRIS, 2022; USEPA, 2010).

A LOAEL analysis was used to derive an organ/system-specific point of departure (POD) for GI tract effects. Hyperplasia in the small intestine of female B6C3F1 mice was selected as the basis for the overall chronic RfD of 9×10^{-4} mg/kg bw/d (IRIS, 2022; USEPA, 2010). However, it should be noted that the proposed osRfD are in draft stage and yet to be reviewed by expert toxicologists.

Table 9: Organ organ/system specific reference doses

Effect	Basis	osRfD (mg/kg bw/d)	Exposure Description
GI tract toxicity	Diffuse epithelial hyperplasia in small intestine (female mice)	9×10^{-4}	Chronic
Hepatic toxicity	Chronic inflammation (female rats)	7×10^{-4}	Chronic
Developmental toxicity	Decreased F1 offspring postnatal growth (mice)	0.07	Continuous breeding
Hematological toxicity	Decreased Hgb (male rats)	0.01	Subchronic
Overall RfD	**GI tract effects**	**9×10^{-4}**	**Chronic**

osRfD: organ/system specific reference dose, bw: body weight

The overall RfD is derived to be protective of all types of noncancer effects for lifetime exposure and is intended to protect the population as a whole including potentially susceptible subgroups. While the osRfD for liver effects was slightly lower, the osRfD for GI effects is still lower than most other candidate values considered for the liver osRfD. With

the exception of chronic liver inflammation in female rats, candidate values for the osRfD for liver effects that were based on chronic exposure data (12 months or 2 years;) were above 9×10^{-4} mg/kg bw/d. Candidate liver values derived from subchronic data that were lower than 9×10^{-4} mg/kg bw/d had cumulative uncertainty factors of 300, whereas other candidate values had uncertainty factors of 100 or less. Because the GI tract is exposed to higher concentrations of un-reduced Cr (VI) than the liver, it is likely to be more susceptible to the effects of ingested Cr (VI). Thus, the osRfD for GI effects was selected as the overall RfD. Hence, once finalised the value (9×10^{-4} mg/kg bw/d) may be used in general population risk assessments (IRIS, 2022; USEPA, 2010).

Proposed oral slope factor for cancer:

The oral slope factor (OSF) is a plausible upper bound on the estimate of risk per mg/kg bw/d of oral exposure. The OSF can be multiplied by an estimate of lifetime exposure (in mg/kg bw/d) to estimate the lifetime cancer risk (IRIS, 2022).

A chronic 2-year drinking water bioassay in male and female rats and mice found "clear evidence of carcinogenic activity" of Cr (VI). There was increased incidence of squamous cell neoplasms in the oral cavity of rats, and increased incidence of neoplasms (adenomas or carcinomas) in the small intestine of mice (NTP, 2008).

A benchmark dose (BMD) approach was used to model the dose-response data and derive a point of departure (POD) (Table). The multistage model was selected for extrapolation from the POD to the low dose range because it is consistent with low dose linearity, it is sufficiently flexible for most cancer bioassay data, and its use provides consistency across cancer dose-response analyses (IRIS, 2022).

For tumors of the small intestine of mice, a physiologically-based pharmacokinetic (PBPK) model was used to convert the rodent dose-response model results to a human equivalent dose.

For tumors in the oral cavity of rats, in the absence of an adequately developed theory or information to develop and characterise an oral portal-of-entry dosimetric adjustment factor, application of $BW^{3/4}$ (BW = body weight) scaling was performed (IRIS, 2022).

Table 10: Summary of the oral slope factor derivations

Species/ sex	BMDL mg/kg bw/d	Extrapolation Method	Internal rodent dose mg/kg-d	Internal dose POD mg/kg bw/d	POD_{HED} mg/kg-d	OSF Per mg/kg bw/d
Adenomas or Carcinomas in the mouse small intestine						
Mice (M)	1.05	PK	0.173	0.0274	0.319	0.313
Mice (F)	1.03		0.17	0.0267	0.316	0.317
Squamous cell carcinoma or squamous cell papilloma in oral mucosa or tongue						
Rats (M)	3.37	$BW^{3/4}$	NA	NA	0.923	0.108
Rats (F)	2.70				0.645	0.155

POD: point of departure, OSF: Oral slope factor, BMDL: Lower 95th percentile confidence limit of the benchmark dose, bw: body weight, PK: physiologically-based pharmacokinetic, BW: body weight

The highest OSF for Cr (VI) was derived for occurrence of small intestine tumors in male and female mice using PBPK modeling, with a rounded value of 0.3 per mg/kg bw/d (IRIS, 2022).

As Cr (VI) is both genotoxic and carcinogenic, EFSA use the MOE approach for the risk characterisation of neoplastic effects of Cr (VI). A $BMDL_{10}$ of 1.0 mg Cr(VI)/kg bw/d was derived for the combined incidence of adenomas and carcinomas in the mouse small intestine (EFSA, 2014b). The US EPA also derived similar $BMDL_{10}$ values of 1.05 and 1.03 mg/kg bw/d for male and female mice, respectively based on adenomas or carcinomas in the mouse small intestine (IRIS, 2022).

4 EXPOSURE ASSESSMENT

As previously discussed, only Cr (III) compounds are used in the tanning process. Cr (VI) compounds are not used in tanning as it is more toxic than Cr (III). A direct oxidation of fixed Cr (III) to the Cr (VI) form under standard conditions is very unlikely because the reaction speed is extremely slow. Only at temperatures greater than 800°C would the oxidation reaction start shifting towards Cr (VI). This means that for normal leather and under consumer conditions the likelihood of conversion of Cr (III) to Cr (VI) is very low. However, detectable concentrations of Cr (VI) have been detected in leather products and exposure estimates were derived, based on these measured concentrations.

4.1 EXPOSURE ASSESSMENT APPROACH

4.1.1 Relevant exposure scenarios

The consumer exposure to Cr from leather products is considered incidental. The scenarios considered in the exposure assessment depend on the intended uses of the products. The products recalled from the market (EU) were generally those which will come in contact with the skin. The products were- adult and children's shoes, sandals, gloves,' wallets, handbags, bracelets, mobile phone case, child's dress, trousers, and jackets. For most of these products, dermal exposure was considered relevant as some products may come in direct contact with the skin e.g sandals may be worn without socks during summer. Oral and inhalation exposure to Cr from such leather products was considered to be negligible (Table 11).

Table 11. Exposure routes considered for Cr in leather products

Population	Product type	Exposure Pathway		
		Inhalation	Dermal	Oral
Adults	Shoes		X	
Children			X	

For the current exposure assessment, the maximum concentrations of Cr (VI) detected in the Danish EPA survey (**33 and 62 mg/kg** in baby shoes and adult shoes, respectively) were used (Johansen *et al.*, 2011). These concentrations were for Cr (VI) that migrated out of the shoe leather into a simulated sweat solution, thus mimicking the most likely exposure route for humans.

4.1.2 Exposure models (tier 1 approach)

Risk assessment may follow a tiered approach. Under a tiered approach, initial exposure estimates are derived using highly conservative assumptions. If such estimates indicate no cause for concern, then more refined approaches are unnecessary.

Tier 1 assessment is usually used to screen consumer exposure based on the summation of high percentile product use levels and maximum concentrations of the substance of interest in products, to give a worst-case exposure scenario. Due to the lack of data on a number of inputs to the exposure assessment, a tier 1 approach was used in the current situation.

Assessment of dermal exposure results in estimation of internal (systemic) doses. However, the available toxicological reference values are external doses, relating to oral exposure.

Internal doses from dermal exposure can be converted to oral external doses through application of an estimate of the orally absorbed proportion.

4.1.2.1 Dermal exposure

Dermal exposure occurs when a chemical cross' the dermal barrier and enters the portal circulation. The amount of chemical absorbed will depend on the concentration in the external medium (sweat in the current case), the duration and frequency of exposure to the external medium and the characteristics of the chemical. The proportion of the skin surface that contacts the external medium will also have an impact on dermal exposure.

The stratum corneum is generally considered to be the rate-limiting diffusion barrier for most compounds. Dermal absorption is considered to occur through passive diffusion of chemicals through the stratum corneum, the outermost layer of the skin. After a chemical has absorbed into the stratum corneum it can pass through it into the viable epidermis (the next skin layer) and then into the dermis where it can be transported systemically by the dermal blood supply.

Compounds that come in contact with the skin are potentially subject to three processes.

- Evaporation from the skin surface,
- Uptake into the stratum corneum, followed by reversible or irreversible binding, and
- Penetration into the viable epidermis, followed by metabolism.

For the currently considered case of dermal absorption during shoe wearing, evaporation was assumed to be unimportant and the concentration of the Cr (VI) at the skin surface was considered to be constant and equal to the maximum migratable Cr (VI) concentrations from the Danish EPA study.

In the absence of objective information on patterns of shoe wearing, a highly conservative approach was taken of calculating exposure from wearing shoes 8 hours per day, 365 days per year, without wearing socks, which would mitigate exposure to migrating Cr (VI). Exposure was averaged over a 30 year averaging time.

The dermal absorbed dose (DAD) is calculated as:

$$DAD = \frac{DA_{event} \times EV \times ED \times EF \times SA}{BW \times AT} \qquad \textbf{Equation 1}$$

Where:

Absorbed dose per event (DA_{event})	See calculation below	-
Skin surface area available for contact (SA, area of the feet)	Adult: 1400 cm^2 Child (2-<3 years): 400 cm^2	(Cressey, 2016)
Event frequency (EV)	1 event/day	assumed
Exposure frequency (EF)	365 days/year	assumed
Exposure duration (ED)	30 years	assumed
Body weight (BW)	Adult: 70 kg (default weight of an adult)	(Cressey, 2016)

	Child: 13 kg (default weight of a child, 2-<3 year)	
Averaging time (AT)	30 x 365 days	

DA_{event} is a function of chemical- and site-specific factors. For inorganic chemicals or highly ionised organic chemicals in water, DA_{event} is calculated from:

$$\boldsymbol{DA_{event} = K_p \times C_w \times t_{event}} \qquad \textbf{Equation 2}$$

Where:

K_p = dermal permeability coefficient of Cr (VI) (cm/h)
Chromium Compounds (USEPA, 1992)
Sodium chromate: 2×10^{-3}
Sodium dichromate: 1×10^{-3}

C_w = concentration of chemical in medium (mg/cm^3)
For adult shoes: 62 mg/kg or ppm (1 ppm = 0.001 mg/cm^3) or 0.06 mg/cm^3
For children shoes: 33 mg/kg or 0.03 mg/cm^3

T_{event} = event duration (hours/event)
8 hours/event (assumed)

This is a steady-state approach where absorption begins at the beginning of exposure (no lag phase) and ends when exposure ends (no reservoir). These assumptions are considered to be adequate for inorganic compounds or ionised organic compounds.

For adults:
DA_{event} = 0.002 x 0.06 x 8 = 0.0009 mg/cm^2 per event

For children:
DA_{event} = 0.002 x 0.03 x 8 = 0.0005 mg/cm^2 per event

Using equation 1

$$DAD\ (adult) = \frac{0.0009\,\frac{mg}{cm2} \times 1\ \times 30\ yr \times 365\ d \times 1400\ cm2}{70\ kg \times (30 \times 365\ d)} = 0.018\ \text{mg/kg bw/d}$$

$$DAD\ (child) = \frac{0.0005\,\frac{mg}{cm2} \times 1\ \times 30\ yr \times 365\ d \times 400\ cm2}{13\ kg \times (30 \times 365\ d)} = 0.015\ \text{mg/kg bw/d}$$

5 RISK CHARACTERISATION

5.1 NON-CANCER RISK

The potential for non-cancer health risks posed by Cr (VI) contaminated leather shoes were assessed based on hazard quotient (HQ), which is the ratio of the estimated exposure of Cr (VI) to the reference dose (RfD). However, in the current situation the exposure was estimated as an internal dose, while the RfD is an external dose. In order to accommodate these differences, the RfD was converted to an internal RfD by multiplying by the orally absorbed proportion (0.1 or 10%). The HQ was calculated for the leather shoes based on the following equation:

$$HQ = \frac{DAD}{RfD}$$

HQ ≤ 1 indicates that there would be no adverse health effects whereas HQ ≥ 1 indicates possible adverse health effects.

Table 10. Hazard quotient (HQ) for non-carcinogenic risk

Product	Population	Exposure (mg/kg bw/d)	Rfd (mg/kg bw/d)	HQ
Shoes	Adult	0.018	0.003 x 10% (oral absorption) = 0.0003	60
	Child	0.015		50

The HQ was much greater than 1 for children and adults using both the current and proposed osRfD, which indicates that the presence of Cr (VI) in leather shoes at the maximum concentrations reported may be a cause for concern with respect to non-cancer effects, based on this tier 1 assessment.

However, it should be noted that there are some limitations and uncertainties in the exposure assessment and risk characterisation:

1) Shoes are often worn with the socks which may decrease or limit the direct exposure with skin. Hence, there may be less absorption of Cr (VI) through the skin of the feet.

2) We have assumed that the same or equivalent leather shoes are worn daily for 30 years, which is very conservative. People usually have multiple pairs of shoes, and a single pair of shoes will usually be discarded after a period much less than 30 years. It is also unlikely that the same individual would own multiples pairs of shoes with equivalent high levels of migratable Cr (VI). All these factors can limit the exposure to Cr (VI) from this source.

3) Seasonal variations were also not taken into consideration in the current risk assessment. Cr (VI) migrating from leather and contacting the dermal surface is dependent on many factors such as moisture, and pH. Migration of Cr (VI) from the leather will mainly be in the presence of an extraction medium such as moisture from sweat. But in cooler weather, Cr (VI) would be less likely to migrate due to the absence of moisture from sweat. Also, in winter socks are used that limit the direct exposure to the skin. Therefore, there will be less exposure and absorption of Cr (VI).

4) The leaching of Cr (VI) from the shoes will decrease over time. This will decrease the exposure during the use of shoes.

5.2 CANCER RISK

Lifetime cancer risk (LCR) was not investigated for Cr (VI) as there was no evidence of carcinogenicity of Cr (VI) following dermal exposure.

5.3 RISK CHARACTERISATION FROM OTHER STUDIES

5.3.1 Contact dermatitis:

1. The Danish EPA conducted a survey and health assessment (sensitisation only) of Cr in leather shoes (Johansen *et al.*, 2011). The assessment focused on allergy caused by release of Cr from leather shoes. The threshold values for risk assessment of allergens are expressed as $MET_{10\%}$ (minimal elicitation threshold) - which are summarised in Table 7. It was concluded that all the shoes with Cr (VI) may pose a risk of causing allergy in consumers. This is because the analytical method only gives reliable results above 3 ppm (3 mg/kg) and the threshold limit for causing Cr (VI) allergy lies around 1 – 3 ppm, thus below the DL. Thus, shoes, which do not seem to contain/release Cr (VI), may in fact still pose a risk of causing allergic reactions.

2. In a study, (Pantazi *et al.*, 2012) investigated whether the Cr compounds released from leather shoes lead to a risk of causing allergic reactions. $MET_{10\%}$ value (**Error! Reference source not found.**) was used to assess the skin senstisation potential of Cr. Low levels of Cr (VI) can cause allergic contact dermatitis. Patients allergic to Cr (VI) may react to a single exposure of 1-3 mg/kg Cr (VI). As discussed in section 1.4, all pairs of shoes were found to have low levels (<1 mg/kg, below DL) of Cr (VI), which falls within the product standard limits, without the risk of allergy to chromium.

6 CONCLUSIONS

Tanning is the process of treating the skin or hide from an animal to make leather. It is done to keep the animal skin or hide from rotting, decomposing, and putrefying. Most of the leather made today is chrome-tanned i.e uses Cr (III) salts such as chromium sulfate. Cr (VI) salts are never used in leather tanning as they are more toxic to humans than Cr (III). However, Cr (VI) may end up in the leather. The exact origin of Cr (VI) is not well understood but its formation can occur in several stages of leathers lifetime i.e during leather and product manufacturing or during storage and transportation.

Exposure to Cr (VI) while using leather goods is considered incidental. The dermal route of exposure is considered relevant as the products (shoes, bags, purse) may come in contact with the skin. Exposure via the inhalation and oral routes is likely to be negligible. For the current risk assessment, the maximum concentrations of bioavailable Cr (VI) detected in a Danish EPA survey (33 and 62 mg/kg in baby shoes and adult shoes, respectively) were used to carry out a risk assessment.

Non-carcinogen health risks of Cr (VI) in leather shoes (adult and children) through dermal exposure was evaluated by calculating hazard quotients (HQ). The HQ was greater than 1 for children and adults, which indicates that Cr (VI) in leather shoes may be of toxicological concern for non-carcinogen risks. However, there are some limitations in the risk assessment and some of the assumptions made were highly conservative. Factors such as wearing socks with the shoes, the same shoes may not be used over a lifetime, and seasonal variations (different shoes worn in summer vs winter) would mitigate exposure to and absorption of Cr (VI) from leather goods and will decrease risks.

The Danish EPA survey concluded that all pairs of shoes may pose a risk of causing Cr (VI) allergy in consumers. The analytical method (ISO 17075) had a DL of 3 mg/kg and the threshold limit for causing Cr (VI) allergy lies around 1 – 3 ppm, below the DL. Hence, shoes which did not seem to contain or release Cr (VI) may still pose a risk of allergic reactions. However, it was also pointed out that the risk of using shoes that release chromium will be influenced by use conditions, such as moisture, pH, and pre-existing skin diseases in a not yet determined way.

Lifetime cancer risk was not estimated as there is no evidence of carcinogenicity by the dermal route of exposure.

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