

**Department for Environment, Food and Rural Affairs  
and the Environment Agency**

**CONTAMINANTS IN SOIL:  
COLLATION OF TOXICOLOGICAL DATA AND  
INTAKE VALUES FOR HUMANS.  
CHROMIUM**

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This publication details the derivation of tolerable daily soil intakes or Index Doses for chromium. The report has been written for technical professionals who are familiar with the risks posed by land contamination to human health but who are not necessarily experts in risk assessment. It is expected to be of use to all parties involved with or interested in contamination, but in particular to those concerned with the assessment of land contamination.

## **Keywords**

Tolerable daily soil intake, Index Dose, land contamination, risk assessment, human health, chromium.

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## 1 Introduction

- 1.1 This report, one of a number on the assessment of risks to human health from contaminants in soil, presents key data and expert opinions on the toxicology and intake of chromium. It may be necessary to update this report in the future to incorporate new toxicological data as science advances.
- 1.2 The aim is to derive an oral tolerable daily intake (TDI) and an inhalation Index Dose, which in turn are needed to derive Soil Guideline Values (SGVs) for chromium, that is concentrations of chromium in soil that will pose no significant threat to health.
- 1.3 There is a general discussion of TDIs and Index Doses in CLR9 *Contaminants in Soils: Collation of Toxicological Data and Intake Values for Humans. Consolidated Main Report*. Reference to CLR9 is necessary to understand the concepts and terms used in this report (Department for Environment, Food and Rural Affairs, DEFRA, and Environment Agency, 2002a).
- 1.4 The computer model used for deriving Soil Guideline Values is described in CLR10 *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms* (DEFRA and Environment Agency, 2002b). The derivation of the Soil Guideline Values for chromium is given in *SGV 4 Guideline Values for Chromium Contamination in Soils* (DEFRA and Environment Agency, 2002c).
- 1.5 In general, the literature up to March 1998 has been reviewed in this report. A number of more recent publications have also been consulted, including 2001 records of the Integrated Risk Information System (USEPA, 2001a,b), the revised WHO air quality guidelines for Europe (WHO, 2000) and the most recent report of the Agency for Toxic Substances and Disease Registry (ATSDR, 2000).

## 2 Identity

- 2.1 Chromium is a hard, silvery white metal. It is a transition element with possible oxidation states from  $-2$  to  $+6$ , but only the 0 (elemental),  $+2$ ,  $+3$  and  $+6$  states are common.
- 2.2 Elemental chromium does not occur naturally. It is virtually insoluble in water, and very resistant to chemical attack (although it dissolves in dilute hydrochloric and sulphuric acids); the stability of metallic chromium is largely due to the protective film of trivalent chromium oxide that forms on its surface. Divalent compounds are relatively unstable as they are readily oxidised to the trivalent form. Trivalent compounds are stable and most naturally occurring chromium is in the trivalent (chromic) state. Although hexavalent chromium (chromate) rarely occurs naturally, it is produced from anthropogenic sources. The pentavalent and tetravalent compounds are generally unstable; an exception is tetravalent chromium in the dioxide,  $\text{CrO}_2$  (widely used in magnetic recording tape). The focus of this report is on the trivalent, Cr(III), and hexavalent, Cr(VI), forms.
- 2.3 Chromium compounds show a wide range of water solubilities, but the general rule is that the trivalent chromium salts are insoluble and the hexavalent ones are soluble. There are clear exceptions in that chromium(III) chloride and nitrate are both very soluble, whereas zinc and lead chromates, both Cr(VI) salts, are virtually insoluble. Hexavalent compounds are reduced to the trivalent form in the presence of oxidisable organic matter. The anaerobic decomposition of plant matter may increase the mobilisation of trivalent chromium due to the formation of soluble complexes. The mobility of any soluble chromium in soil will depend on the sorption characteristics of the soil. In general, most of the chromium in soil is strongly adsorbed onto soil particles, poorly soluble and of very limited mobility. The processes that chromium in soil may undergo, and the effects on its mobility, are discussed by Bartlett (1991) and by Palmer and Wittbrodt (1991).
- 2.4 Chromium occurs naturally in the Earth's crust and can be detected in all environmental media. The continental dust flux is the main natural source of chromium in the atmosphere, but much larger amounts are released by human activities. These include metal industries, the combustion of coal and oil, cement works, waste incineration, and fugitive emissions from road dusts.
- 2.5 The fraction of chromium present in the hexavalent form is greater in the industrial than the ambient environment; for example, the fraction Cr(VI)/Cr(total) in air samples taken in the chromium industry is typically around 20% (Axelsson *et al*, 1980; Bonde and Christensen, 1991; Langård *et al*, 1980), but values of up to 100% have been reported in some welding operations (van der Wal, 1985). There appear to be no reliable, general data on the oxidation states of chromium in the ambient air, soil and water, or in food and drinking water. The Cr(VI) fraction in samples from the ambient environment will, in general, be less than that in industrial samples – how much less depending on the relative proportions of natural and industrial chromium. The two oxidation states are in dynamic equilibrium, with the degree of oxidation depending on various factors; for example – in soil – moisture content, pH and the presence of reducing and oxidising agents (Bartlett, 1991). However, in most circumstances,

Cr(VI) tends to be converted to Cr(III) when in contact with the natural environment, and – for all practical purposes – the oxidation of Cr(III) to Cr(VI) never occurs in biological systems. Chromium in foodstuffs is generally considered to be in the trivalent form.

- 2.6 The lack of data on the speciation of chromium in environmental samples reflects the analytical difficulties in such measurements. Storage and preparation of environmental and biological samples often allow or promote interconversion between Cr(III) and Cr(VI). Gochfeld (1991a) notes that two different laboratories analysing the same soil sample have been known to report the chromium content as almost entirely hexavalent in one case, and entirely trivalent in the other.
- 2.7 The metallurgical, refractory and chemical industries are the prime users of chromium. In the metallurgical industry, it is used to produce stainless steels, non-ferrous alloys and alloy cast irons. In the refractory industry, Cr(III) oxide is a component of the lining material for high-temperature furnaces. In the chemical industry, chromium is used in pigments, wood preservatives, leather tanning, metal finishing and a number of other products and processes.

### 3 Toxicity

- 3.1 Reviews of the literature on the toxicity of chromium have been published by the World Health Organization (WHO, 1987, 1988, 1996), the Health and Safety Executive (HSE, 1989), the International Agency for Research on Cancer (IARC, 1990, 1999), the Agency for Toxic Substances and Disease Registry (ATSDR, 1993, 2000), Katz and Salem (1993), Hughes *et al* (1994), Costa (1997) and the United States Environmental Protection Agency (USEPA, 2001a,b). This section is largely based on these reviews; particular mention is made of those studies that have been used in deriving TDIs and Index Doses. In general, the primary literature has not been consulted.
- 3.2 The toxicity of chromium depends upon its oxidation state. Hexavalent chromium is more toxic than the trivalent form. Cr(VI) compounds penetrate biological membranes much more readily than do Cr(III) compounds. After crossing cellular membranes, Cr(VI) may be reduced to Cr(III) via a number of hypothesised reactions. Several reactive intermediates – pentavalent and tetravalent chromium species, and oxygen radicals – are thought to be involved in the reduction process. These intermediates may interact with essential constituents of the cells (including genetic material), which they can damage through oxidation and complexation with the resulting Cr(III) species. As well as the inherently greater toxicity of hexavalent compared with trivalent chromium, the former is the more readily absorbed by both the inhalation and oral routes.
- 3.3 **Essentiality.** Studies on humans and experimental animals have shown that trivalent chromium has an essential role in the maintenance of normal glucose and fat metabolism. The biologically active form of an organic Cr(III) complex is believed to function by facilitating the interaction of insulin with its cellular receptor sites. Studies have shown that chromium supplementation in deficient and marginally deficient subjects results in improved glucose, protein and lipid metabolism. A number of authors consider that many people do not have an adequate intake of chromium (Hunt and Stoeker, 1996, and references therein; Anderson, 1997). The signs of chromium deficiency, which are often alleviated by increased dietary chromium, are similar to those of maturity-onset diabetes and cardiovascular diseases. Supplementation of the diets of subjects showing symptoms of chromium deficiency with up to  $1000 \mu\text{g Cr day}^{-1}$  (micrograms of chromium per day) has usually shown benefits (Anderson, 1989, 1997).
- 3.4 The US National Research Council have recommended a dietary intake for adults of  $50\text{--}200 \mu\text{g Cr(III) day}^{-1}$  (NRC, 1989). The UK Committee on Medical Aspects of Food Policy have suggested rather lower figures for a “safe and adequate intake”: above  $25 \mu\text{g Cr(III) day}^{-1}$  for adults, and between  $0.1$  and  $1 \mu\text{g Cr(III) kg}^{-1} \text{ bw day}^{-1}$  (micrograms of chromium per kilogram body weight per day) for children and adolescents (DoH, 1991); for a 15-year-old weighing 50 kg, this range of intakes is equivalent to  $5\text{--}50 \mu\text{g Cr(III) day}^{-1}$ . The Committee does not suggest an upper limit for a “safe and adequate intake” for adults.
- 3.5 **Absorption.** The presence of chromium in the urine and serum of men occupationally exposed to airborne, soluble Cr(III) or Cr(VI) compounds shows that chromium can be absorbed via the



inhalation route, but the data do not permit a quantitative estimate of the amount absorbed. Both human and animal studies suggest that, once deposited in the lungs, Cr(VI) compounds are generally transferred to the systemic circulation more readily than Cr(III) compounds. For any inhaled aerosol, the main determinants of the fractional deposition and the fractional transfer to the systemic circulation are the particle size and *in vitro* solubility. For chromium, there is the additional consideration that Cr(VI) compounds are more able to cross biological membranes than are Cr(III) compounds.

- 3.6 Both human and animal studies have shown that there is a difference in the efficiency of absorption of ingested Cr(VI) and Cr(III) compounds. For all the species examined, the absorption of hexavalent chromium is generally greater. The results usually quoted from human studies are that the fractions of ingested Cr(VI) and Cr(III) transferred across the gut are about 2% and 0.5% respectively. However, in one study of a group of elderly subjects, the absorption of Cr(III) in the diet was estimated to be about 2.5% (Anderson *et al*, 1983). In another study, of volunteers who received Cr(VI) as chromate in drinking water, a wide range of uptake values was found, but most were in the range 3–6% (Kerger *et al*, 1997); most of the ingested Cr(VI) was thought to be reduced to Cr(III) organic complexes in the gastrointestinal tract before absorption. There is evidence that the extent of absorption is dependent on the dietary intake (being higher at low levels of chromium intake), that absorption is greater in immature than in adult animals, and that absorption is usually greater in fasting animals than when taken with food (ATSDR, 1993). However, if the chromium ion binds to certain ligands (some of which may be present in some foodstuffs), absorption may be increased by up to a factor of 5 (WHO, 1988). It seems likely that the relatively poor transfer of Cr(VI) compounds across the gut is a consequence of the reduction of some or most of the Cr(VI) to Cr(III) in the stomach.
- 3.7 Systemic toxicity has been observed in humans following dermal exposure to chromium compounds, indicating significant transfer across the skin. A number of animal and human studies of the dermal penetration of chromium have been reported. The rate of transfer to the systemic circulation depends upon a number of variables, such as the solubility of the compound, its concentration, the solvent used and the oxidation state of the chromium (ATSDR, 1993). Transfer rates were generally higher with organic solvents than with aqueous solutions, and increased with increasing concentration. Rates were usually, but not always, higher for Cr(VI) than for Cr(III) compounds. In a study with human volunteers, transfer rates across the forearm skin using 0.01 M, 0.1 M and 0.2 M solutions of sodium chromate were about 1, 6 and 10  $\mu\text{g Cr(VI) cm}^{-2} \text{ h}^{-1}$  respectively (Baranowska-Dutkiewicz, 1981).
- 3.8 **Distribution.** Some of the chromium that enters the systemic circulation will reach all organs and tissues, but there appears to be little long-term accumulation. In a series of autopsy studies in the USA, Schroeder *et al* (1962) measured chromium concentrations (as total chromium) in various tissues in subjects of various ages. It was found that the concentrations were highest at birth and tended to decrease with age. The decrease was most pronounced during the first and second decades, and (except for the lung) was followed by a more gradual decrease for the remainder of life. It is not known whether this decrease is a consequence of some physiological mechanism, or of a dietary deficiency; an alternative explanation could be that, as all the samples were taken over a relatively short time interval, the observed decrease in tissue

concentration with age was a consequence of a lower historical dietary chromium intake for older subjects. Schroeder *et al* found that the concentration of chromium in the lung began to increase again during middle and old age, but did not regain its initial high value. In several rodent studies, higher tissue levels of chromium were found after administration of Cr(VI) than after administration of Cr(III). This presumably reflects the greater tendency of Cr(VI) to cross biological membranes and bind to intracellular proteins in the various tissues.

- 3.9 **Excretion.** Absorbed chromium is excreted primarily in the urine as Cr(III). The half-life for urinary excretion of chromium orally administered as potassium chromate in drinking water was estimated to be 35–40 hours in humans. Hair and nails are minor pathways of excretion.
- 3.10 **Acute oral toxicity.** Cases of both intentional and accidental ingestion of fatal doses of Cr(VI) compounds by humans have been reported. The acute effects leading to death have included haemorrhages in the gastrointestinal tract, generalised oedema, pulmonary oedema, and severe liver and kidney damage. The lethal oral dose is usually considered to be in the range 1–5 g, but a value as low as 300 mg has been reported (ATSDR, 1993).
- 3.11 **Repeated oral toxicity.** There are few human data on the adverse effects of chronic intakes of smaller doses. In a study conducted in 1965 of 155 villagers outside Jinzhou, China, whose well-water was contaminated with Cr(VI) at a level of about 20 mg L<sup>-1</sup>, associations were found between the consumption of the water and various health effects principally affecting the gastrointestinal tract (oral ulcer, diarrhoea, vomiting, abdominal pain and indigestion) and the blood (leucocytosis and immature neutrophils) (Zhang and Li, 1987). It is not possible to derive a dose–effect relationship from this study.
- 3.12 Several animal studies entailing chronic or sub-chronic oral exposure to chromium have been reported. Effects on the liver and kidney were detected in rats given potassium dichromate by gavage for 20 days at a dose of 13.5 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> (Kumar and Rana, 1982, 1984). There was an increased accumulation of lipids in both liver and kidneys, and inhibition of membrane enzymes in the kidneys.
- 3.13 The administration of Cr(VI), as potassium dichromate, in the drinking water to female dogs (two per dose group) at 0.012–0.30 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> for four years produced no signs of toxicity (Anwar *et al*, 1961). Appearance, body weight gain, organ weights, urinalysis, haematology and histopathology were unaffected.
- 3.14 Toxicity was also absent when either Cr(VI), as potassium dichromate, or Cr(III), as chromic chloride, was given in the drinking water of groups of 20 rats for one year (MacKenzie *et al*, 1958). No significant adverse effects were seen on appearance, weight gain, or food consumption, and there were no treatment-related pathological changes in the blood or other tissues examined (livers, kidneys and femurs). The highest tested doses were about 2.5 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup>.
- 3.15 In a six-month feeding study, rats received doses of up to about 5 mg Cr(III) kg<sup>-1</sup> bw day<sup>-1</sup> of either chromium chloride or another more bioavailable form of Cr(III), chromium tripicolinate (Anderson *et al*, 1997). There were no statistically significant differences in body weight, organ weights or blood variables among all the groups tested at 11, 17 and 24 weeks. Blood

- variables measured were glucose, cholesterol, triglycerides, blood urea nitrogen, lactic acid dehydrogenase, transaminases, total protein and creatinine. Histological evaluation of tissues from the liver and kidney of control and high-dose animals found no treatment-related differences.
- 3.16 In a long-term feeding study, rats received Cr(III), as the insoluble Cr<sub>2</sub>O<sub>3</sub> at dose levels up to about 1500 mg Cr(III) kg<sup>-1</sup> bw day<sup>-1</sup>. The chromium salt was given, baked in bread, on 600 occasions over a 840-day period. Tissues from all major organs were examined histologically. There were no signs of toxicity at any dose level (Ivankovic and Preussmann, 1975). The corresponding 90-day study used the same dose levels, but recorded additional toxicological end-points – including haematology, serum protein, bilirubin, urinalysis and organ weights. The only treatment-related findings were reductions (12–37%) in the absolute weights of the livers and spleens of animals in the high-dose group (Ivankovic and Preussmann, 1975).
- 3.17 Iraqi investigators have claimed that potassium dichromate or chromium sulphate administered in the diet of mice for 35 days reduced the sperm count and produced testes degeneration at the lowest tested dose of around 25 mg kg<sup>-1</sup> bw day<sup>-1</sup> of each compound. Cr(VI) was marginally more active than was Cr(III) (Zahid *et al*, 1990). The USEPA have been critical of the quality of the study report, the test and statistical methods used, and the lack of biological coherence of the sperm effects (a reduction in spermatogonia was observed, even though spermatocyte and spermatid numbers were unchanged) (USEPA, 2001a).
- 3.18 **Oral reproductive/developmental toxicity.** Exposure of pregnant mice to potassium dichromate in drinking water at the lowest tested dose level of about 50 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> caused severe developmental effects: deaths of embryos, decreased litter sizes and gross abnormalities. There were indications also of mild maternal toxicity (Trivedi *et al*, 1989). Foeto- and embryotoxicity were reported by Junaid *et al* (1996) in pregnant mice given potassium dichromate in the drinking water. There was some suggestion of an effect even at the lowest tested dose of approximately 67 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup>, which did not produce any overt sign of toxicity in the mothers. The administration of potassium dichromate in the drinking water for 12 weeks to female rats produced foeto- and embryotoxicity at the lowest tested and maternally toxic dose of about 40 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> (Kanojia *et al*, 1996).
- 3.19 A reduced fertility in both males and females was reported in mice exposed for 12 weeks to potassium dichromate in the drinking water. The tested doses were in the order of 70–150 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> (Elbetieha and Al-Hamood, 1997).
- 3.20 A three-part study on the reproductive toxicity of hexavalent chromium has been conducted as part of the National Toxicology Program of the USA. The latest IRIS record notes that potassium dichromate administered in the diet at up to 400 ppm was not a reproductive toxicant in mice or rats (USEPA, 2001b). The maximum tested doses of the dichromate would have been about 60 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> in the mice and 20 mg Cr(VI) kg<sup>-1</sup> bw day<sup>-1</sup> in the rats.
- 3.21 No reproductive or developmental toxicity was seen when male and female rats were given 1500 mg kg<sup>-1</sup> bw day<sup>-1</sup> of Cr(III) in the diet for 60 days before mating, and throughout the female gestational period (Ivankovic and Preussmann, 1975). Chromium chloride administered

in the drinking water of mice for 12 weeks reduced both male and female fertility. The tested dose was in the order of  $150 \text{ mg Cr(III) kg}^{-1} \text{ bw day}^{-1}$  (Elbetieha and Al-Hamood, 1997).

- 3.22 **Repeated inhalation toxicity.** The respiratory tract is the primary target organ for inhaled chromium, although effects on the kidney (paragraph 3.23), gastrointestinal tract and liver have also been claimed. The respiratory toxicology is probably due to the direct action of chromium at the site of contact. The symptoms produced by occupational exposure to airborne Cr(VI) compounds include nasal itching and soreness, persistent runny nose and nose-bleeding, nasal mucosal atrophy, perforations and ulceration of the nasal septum, decreased pulmonary function, bronchitis, pneumoconiosis and pneumonia. Asthma has also been reported in some chromium-sensitised workers. The effects most likely to occur at relatively low concentrations of Cr(VI) are nasal irritation and mucosal atrophy, and decreases in pulmonary function. Lindberg and Hedenstierna (1983) found these in workers subject to long-term occupational exposure ( $8 \text{ h day}^{-1}$ ) to  $2 \mu\text{g Cr(VI) m}^{-3}$  and above of chromic acid. There was a much lower incidence of nasal abnormalities at  $1 \mu\text{g Cr(VI) m}^{-3}$ .
- 3.23 Some studies of workers exposed to airborne Cr(VI) and Cr(III) have found increased levels of low-molecular-weight (LMW) proteins, indicative of effects on the kidney. In one study of chrome-platers, whose exposure was mainly due to Cr(VI), elevated levels of  $\beta_2$ -microglobulin, a LMW protein, were found in the urine of current platers but not in former platers (Lindberg and Vesterberg, 1983); the “lowest observed adverse effect” level (LOAEL) was  $4 \mu\text{g Cr(VI) m}^{-3}$ . This appears to be the lowest level at which such effects have been reported.
- 3.24 The effect of Cr(VI) particulates on the lung of rats has been examined by Glaser *et al* (1985, 1990). Rats were exposed to sodium dichromate at concentrations of  $0.025\text{--}4 \text{ mg Cr(VI) m}^{-3}$ ,  $22 \text{ h day}^{-1}$ ,  $7 \text{ day week}^{-1}$  for 28–90 days. The critical toxicity end-point was an increase in lactate dehydrogenase activity in bronchioalveolar lavages (which was considered to be an early indication of lung injury and inflammation). An analysis of the dose–response was the basis of the USEPA inhalation reference dose.
- 3.25 There is limited information on the inhalation toxicity of Cr(III). Some lung effects were reported in rabbits exposed to aerosols of chromium nitrate at  $0.6 \text{ mg Cr(III) m}^{-3}$ ,  $6 \text{ h day}^{-1}$  for 4–6 weeks (Johansson *et al*, 1980).
- 3.26 **Sensitization.** There are many reports, going back over 50 years, on chromium’s ability to sensitise humans. Chromium-containing substances of various chemical compositions and chromium oxidation states have been shown to cause sensitisation, or to produce reactions (skin or respiratory effects) in already sensitised people. The ultimate allergen is believed to be a Cr(III)–protein complex, but it is the Cr(VI) compounds that most readily produce sensitisation because of their ability to cross biological barriers and subsequently be reduced to the trivalent form. In the context of environmental exposure, it is skin allergies that are of most concern. Cases of occupational allergic contact dermatitis have been reported in a wide range of situations involving skin contact with materials containing water-soluble Cr(VI) compounds. In non-occupational situations, skin sensitisation has been induced by contact with Cr(VI) in tattoo pigments, tanned leather and matches (HSE, 1989).

- 3.27 The dermatological literature contains many reports of human patch-testing studies with chromium. However, the lack of any general standardised procedure, and in particular the lack of information on the mass of allergen per unit area of skin, limit the value of the earlier studies in the derivation of soil guidelines (Horowitz and Finley, 1994). A number of investigators (Bagdon and Hazen, 1991; Sheehan *et al*, 1991; Gochfeld, 1991b; Paustenbach *et al*, 1992; Horowitz and Finley, 1994; and references therein) have discussed the problems involved in deriving guidelines based upon allergic contact dermatitis.
- 3.28 Horowitz and Finley (1994) have outlined a method for deriving soil guidelines, and have given worked examples for Cr(VI) and Cr(III). These were based on the study findings of Nethercott *et al* (1994) of 54 Cr(VI)-sensitised volunteers who were patch-tested with serial dilutions of Cr(VI) (as potassium dichromate) and Cr(III) (as chromium trichloride). Five of the volunteers developed a local reaction when their skin was in 48 h covered contact with a Cr(VI) concentration of  $0.088 \mu\text{g Cr(VI) cm}^{-2}$ . At  $0.18 \mu\text{g Cr(VI) cm}^{-2}$ , the cumulative response was 10 out of 54. Since Cr(VI)-related allergic contact dermatitis is thought to occur in less than 1% of the general population, the  $0.088 \mu\text{g Cr(VI) cm}^{-2}$  concentration would be expected to be health protective for greater than 99.9% of the general population. An additional safety margin is introduced by the fact that the experimental conditions involved 48 h closed contact with the volunteers' skin, a much more extensive exposure than would occur under environmental conditions. None of the 54 Cr(VI)-sensitised volunteers gave an unequivocal response to the maximum patch-test concentration of  $33 \mu\text{g cm}^{-2}$  of Cr(III). There was one individual who gave a weak reaction, but who did not respond in a confirmatory retest.
- 3.29 In sensitised people, skin reactions can flare up following an oral intake of Cr(VI), but there are few quantitative data. Hostýnek *et al* (1993) note that as little as  $50 \mu\text{g}$  of chromate given orally to chromate-sensitive patients gave a positive skin reaction in all those tested.

## 4 Carcinogenicity and Genotoxicity

- 4.1 The carcinogenicity of chromium and its compounds is discussed in the reviews mentioned in paragraph 3.1. In addition, useful reviews or comments have been published by Cross *et al* (1997), Jones (1990), Langård (1990), Mancuso (1997) and Steenland *et al* (1996).
- 4.2 The IARC state that “there is sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate production, chromate pigment production and chromium plating industries”. Cr(VI) is described by the USEPA “as a known human carcinogen by the inhalation route of exposure”. Both organisations place Cr(VI) in their highest cancer category, Group 1 and Group A respectively (IARC, 1990; USEPA, 2001b). There is also agreement on Cr(III), not classifiable (or not classified) as to its human carcinogenicity, Group 3 in the IARC scheme and Group D under the USEPA guidelines (IARC, 1990; USEPA, 2001a). IARC have similarly assigned metallic chromium to Group 3 (IARC, 1990, 1999).
- 4.3 Epidemiological studies carried out in a number of countries have shown an association between exposure to chromium and lung cancer. Among the industries investigated are chromate production, chromate pigment production and use, chromium plating, stainless steel welding, ferrochromium alloy production and leather tanning. Studies of chromate production workers (who are exposed to both hexavalent and trivalent chromium compounds) and of chromate pigment workers (who are exposed mainly to hexavalent compounds) have consistently shown excess risks for lung cancer. Studies in the chromium plating industry, where exposure is mainly to Cr(VI), generally support the conclusion that Cr(VI) is carcinogenic. Studies of stainless steel welders, exposed to Cr(VI) and other chemicals, and of ferrochromium workers, who are exposed mainly to Cr(0) and Cr(III) but also to some Cr(VI), have been inconclusive. Studies of leather workers, who are exposed mainly to Cr(III), have been negative.
- 4.4 Cases of sinonasal cancer have been reported in studies of workers in the chromate production, chromate pigment production and chromium plating industries, indicating a pattern of excess risk for these rare tumours.
- 4.5 Excess risks for cancers other than of the respiratory system have been reported in a number of studies of chromium workers. These have been reviewed by Costa (1997), who concluded that chromium has a causative role in the production of these other cancers. IARC (1990) commented that: “For cancers other than of the lung and sinonasal cavity, no consistent pattern of cancer risk has been found among workers exposed to chromium compounds.”
- 4.6 There is some suggestion that chromium-induced cancer of the respiratory tract may be an exclusively high-dose phenomenon and that there would therefore be a dose threshold below which the cancer risk would be zero (De Flora, 2000; Jones, 1990). Nevertheless, most regulatory authorities continue to assume a non-threshold approach to cancer risk assessment.

- 4.7 Various Cr(VI) compounds have been shown to be carcinogenic in experimental animals. The routes of exposure for which positive results were found included inhalation, intrapleural and intrabronchial implant, and subcutaneous injection.
- 4.8 There appear to be no high-quality data on the carcinogenic potential of ingested Cr(VI) compounds. Forestomach tumours have been reported in a long-term study in mice given potassium chromate in their drinking water (Borneff *et al*, 1968). Problems with the conduct of the study and the interpretation of the results have undermined the study's value for the purposes of risk assessment. Cr(III) compounds have been administered to rodents by various routes, including a limited oral study in rats (Schroeder *et al*, 1965) and the mouse study of Ivankovic and Preussman (1975) (paragraph 3.16); no increases in the incidence of tumours have been observed.
- 4.9 Hexavalent chromium compounds have been shown to have mutagenic potential. Positive results have been obtained with soluble chromate salts in assays for gene mutation in bacteria as well as clastogenicity and DNA damage in mammalian cells. In addition, activity has been shown *in vivo* in both marrow (chromosome aberrations and micronuclei induction) and germ cells (dominant lethal assay) in rats. There is no consistent evidence that water soluble trivalent chromium compounds have genetic activity. Negative results were obtained in assays for gene mutation or DNA damage *in vitro*; equivocal results were obtained in assays for clastogenicity *in vitro*, but negative results were obtained in *in vivo* studies (HSE, 1989).

## 5 Derivation of a Tolerable Daily Intake

### The WHO guidelines for drinking-water quality

- 5.1 The WHO (1993, 1996) have recommended a provisional guideline value for chromium in drinking water of  $50 \mu\text{g L}^{-1}$  “which is considered to be unlikely to give rise to significant risks to health”. This was unchanged from the earlier value (WHO, 1984a,b), because “the available toxicological data do not support the derivation of a new value” (WHO, 1993, 1996). No explicit derivation of the guideline is given in the 1984 reports. It is clear that the usual practice of assuming that 10% of an overall tolerable daily intake comes via drinking water was not followed.
- 5.2 Although the guideline is based upon general considerations of the toxicity of Cr(VI), it is given in terms of total chromium. This is because “... of difficulties in analysing for the hexavalent form only (WHO, 1984a), and “... current analytical methods and the variable speciation of chromium in water favour a guideline value for total chromium” (WHO, 1996).

### The WHO Environmental Health Criteria report

- 5.3 A WHO Task Force did not derive a TDI for chromium in their Environmental Health Criteria report (WHO, 1988). These are largely based upon pre-1980 measurements and are probably overestimates. However, in the final section of the report (Evaluation of health risks for man), they noted that: “The daily human intake through food varies considerably between regions. Typical values range from 50 to 200  $\mu\text{g day}^{-1}$ . They do not represent a toxicity problem.” Later in the same section they wrote: “In the form of trivalent compounds, chromium is an essential nutrient and is relatively non-toxic for man and other mammalian species.”

### The WHO air quality guidelines for Europe

- 5.4 A WHO Working Group in 1994 reviewed four sets of data for chromate production workers to estimate the lung cancer risk posed by the presence of Cr(VI) in the atmosphere (WHO, 2000). The “best estimate” of the risk resulting from a lifetime exposure at a concentration of  $1 \mu\text{g m}^{-3}$  was  $4 \times 10^{-2}$ . On this basis, an excess lifetime risk of  $10^{-4}$  would be associated with  $2.5 \text{ ng m}^{-3}$ . The lifetime risk of  $10^{-6}$  would be posed by  $0.025 \text{ ng m}^{-3}$ . The guidelines emphasised that “information on the speciation of chromium in ambient air was essential since, when inhaled, only hexavalent chromium is carcinogenic in humans”.
- 5.5 An earlier WHO air quality guideline (WHO, 1987) had also estimated that the attributable risk of lung cancer from lifetime inhalation exposure to Cr(VI) at  $1 \mu\text{g m}^{-3}$  was  $4 \times 10^{-2}$ .



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## The recommendations of COT

- 5.6 The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) have reviewed chromium as part of the UK Food Surveillance Programme (MAFF, 1998). They concluded that the “current levels of exposure to chromium in the diet, which is mainly in the trivalent form, do not warrant any major concern in terms of toxicity, or deficiency”. At that time the estimated intake of a “high-level” consumer was  $380 \mu\text{g day}^{-1}$ . No proposals on a TDI were made.

## The recommendations of the USEPA

- 5.7 The USEPA (2001b) have derived a reference dose (RfD) for chronic oral exposure to soluble Cr(VI) salts from the one-year drinking-water study of MacKenzie *et al* (1958) (paragraph 3.14). This rat study was said to indicate a “no observed adverse effect” level (NOAEL) of  $2.5 \text{ mg Cr(VI) kg}^{-1} \text{ bw day}^{-1}$ . An uncertainty factor of 300 (10 each for inter- and intra-species variations, and an additional factor of 3 to take account of the less-than-lifetime duration of the experiment), and a modifying factor of 3 to take account of the concerns/uncertainties raised by the study of Zhang and Li (1987), produced an RfD of  $3 \mu\text{g Cr(VI) kg}^{-1} \text{ bw day}^{-1}$ . The USEPA assigned a low overall confidence rating to this figure. There was a low confidence in the key study, because of the small number of animals tested, the small number of parameters measured and the lack of toxic effect at the highest dose tested. Confidence in the Cr(VI) database was also low because the supporting studies were of poor quality, and the developmental end-points were not well studied.
- 5.8 A chronic oral RfD for insoluble Cr(III) salts was based on the chronic dietary study of Ivankovic and Preussmann (1975) (paragraph 3.16). The NOAEL was taken to be  $1468 \text{ mg Cr(III) kg}^{-1} \text{ bw day}^{-1}$ . An uncertainty factor of 100 (10 each for inter- and intra-species variations), and an additional modifying factor of 10, was applied to produce (after rounding) an RfD of  $1.5 \text{ mg Cr(III) kg}^{-1} \text{ bw day}^{-1}$ . The modifying factor was said to reflect database deficiencies, including the lack of a toxicity study in a non-rodent species, lack of unequivocal data evaluating reproductive impacts, and the concern over reproductive toxicity raised by the study of Elbetieha and Al-Hamood (1997). There were also reservations about the study of Ivankovic and Preussmann (1975): the effects observed in the 90-day study were not explicitly addressed in the two-year study; the effect of the vehicle, the baked bread, on the absorption of chromium was uncertain, and the relevance of this dosing regime to environmental exposures was unclear; animals were allowed to die naturally after feeding stopped (two years), and only then was histology performed. The USEPA assigned a low confidence rating to the RfD because of the lack of explicit detail on the protocol and results of the key study used, and the lack of high-dose supporting data (USEPA, 2001a).
- 5.9 The USEPA (1998) recommended a maximum contaminant level (MCL) of total chromium in drinking water of  $100 \mu\text{g L}^{-1}$ . It was said to be necessary to set an MCL for total chromium based on the toxicology of Cr(VI) “since the two states are in dynamic equilibrium with the degree of oxidation depending on factors such as pH, dissolved oxygen, or presence of reducing agents” (USEPA, 1989). On the assumption that a 70 kg adult consumes 2 L of water

a day and there are no other dietary sources of chromium, this MCL is equivalent to a tolerable daily intake of  $3 \mu\text{g Cr kg}^{-1} \text{ bw}$ .

- 5.10 The USEPA have derived two RfDs for chronic inhalation exposure to Cr(VI), one for chromic acid mists and dissolved Cr(VI) aerosols, and the other covering Cr(VI) particulates. The former RfD is based on the study of Lindberg and Hedenstierna (1983) of workers exposed to chromic acid mists (paragraph 3.22). The LOAEL for nasal septum atrophy of  $2 \mu\text{g Cr(VI) m}^{-3}$ , adjusted downwards to its 24 h continuous exposure equivalent ( $0.714 \mu\text{g Cr(VI) m}^{-3}$ ), and an uncertainty factor of 90, was used to derive the RfC of  $0.008 \mu\text{g Cr(VI) m}^{-3}$ . USEPA confidence in this figure was described as “low” because of uncertainties on exposure characterisation and the role of direct contact within the key study, and similar weaknesses on exposure characterisation in the database on chromium as a whole. For Cr(VI) particulates, the key studies were those of Glaser *et al* (1985, 1990) in which rats were exposed to sodium dichromate (paragraph 3.24). A benchmark concentration approach generated an RfC of  $0.1 \mu\text{g Cr(VI) m}^{-3}$ . The benchmark dose of  $0.016 \text{ mg Cr(VI) m}^{-3}$  (the lowest 95% confidence limit on the dose corresponding to a 10% change in the key end-point) was adjusted to  $0.034 \text{ mg Cr(VI) m}^{-3}$  to take account of the differences in the deposition pattern of inhaled chromium dusts in the respiratory tract of humans and rats. This adjusted value was then divided by uncertainty factors of 3 for other pharmacodynamic differences, of 10 to account for inter-individual variations, and of 10 to account for the less-than-lifetime exposure of the rat studies. There was said to be a medium level of confidence in the RfC. There remained uncertainties over upper respiratory tract toxicity, as well as on reproductive and kidney effects.
- 5.11 The USEPA (2001b) have derived quantitative estimates of the risk of lung cancer resulting from exposure to airborne Cr(VI) based upon a study of chromate production workers (Mancuso, 1975). The lifetime unit risk (the cancer risk from  $1 \mu\text{g m}^{-3}$ ) was estimated to be  $1.2 \times 10^{-2}$ . This is equivalent to a lifetime lung cancer risk of  $10^{-4}$  from an airborne concentration of Cr(VI) of  $8 \times 10^{-3} \mu\text{g m}^{-3}$  or a lifetime cancer risk of  $10^{-6}$  from  $8 \times 10^{-5} \mu\text{g Cr(VI) m}^{-3}$ .

### The recommendations of the ATSDR

- 5.12 The ATSDR (2000) have not derived any minimal risk levels (MRLs) for oral exposure to Cr(VI) or Cr(III), because “the available data on reproductive and developmental effects are insufficient or too contradictory to establish ... intermediate or chronic-duration oral NOAELs or LOAELs ... However, the upper range of the estimated safe and adequate daily dietary intake ... of  $200 \mu\text{g}$  of chromium ... (NRC, 1989) has been adopted as provisional guidance for oral exposure to Cr(VI) and Cr(III).”
- 5.13 No inhalation MRL was considered appropriate for chronic exposure to Cr(VI) “because concern that carcinogenicity associated with chronic exposure to hexavalent chromium compounds takes precedence”. (MRLs are by definition based on non-cancerous health effects only.) An MRL “for intermediate (15–364 days) exposure [to] chromic acid (chromium trioxide mist) and other dissolved hexavalent chromium aerosols and mists” was derived from the study of Lindberg and Hedenstierna (1983). The LOAEL of  $2 \mu\text{g m}^{-3}$  was “adjusted for

intermittent occupational exposure”, and two uncertainty factors of 10 applied (one for intra-species variability, the other because of extrapolation from a LOAEL), so arriving at an MRL of  $0.005 \mu\text{g Cr(VI) m}^{-3}$ . A separate intermediate exposure MRL of  $1 \mu\text{g m}^{-3}$  was set for particulate Cr(VI) compounds. This was based on an analysis (using the benchmark concentration) of the 90-day study of Glaser *et al* (1990) in which rats were exposed to sodium dichromate particulates. An uncertainty factor of 30 was invoked to take account of pharmacodynamic differences between rats and humans, and 10 for human variability. It was emphasised that the MRL may not be applicable to particle sizes that differ appreciably from those used by Glaser *et al* (which had, for example, a mass median aerodynamic diameter of  $2.8 \mu\text{m}$ ).

## Conclusions

- 5.14 The derivation of the WHO’s guideline concentration for chromium in drinking water is unclear, and it is not possible to derive a TDI from it. It is noteworthy that both the WHO and the USEPA give their reference levels for chromium in drinking water in terms of total chromium. This is because of the limitations of the analytical methods, and the ease with which in water one oxidation state can be transformed to the other. The analytical difficulties in differentiating between the different oxidation states in environmental samples are certainly considerable.
- 5.15 The only explicitly derived safety limits for oral exposures to chromium appear to be those of the USEPA, who proposed an RfD of  $3 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for Cr(VI) and  $1500 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for Cr(III).
- 5.16 The ATSDR had reservations about the derivation of a tolerable oral intake of either Cr(VI) or Cr(III) because of uncertainties over reproductive toxicology. Nevertheless, the studies fuelling these doubts did not generally indicate that the foetus was more susceptible to chromium’s toxicity than was the mother, and the observed effects were occurring at doses about 1000 times higher than the RfD, the TDI equivalent, proposed by the USEPA for Cr(VI).
- 5.17 The oral RfD of  $1500 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  adopted by the USEPA for Cr(III) is based on the results of a long-term oral study that found no signs of toxicity despite high tested doses and the introduction of an additional safety factor (or modifying factor) to take account of various reservations with the chromium database in general. In addition, there have been no documented signs of chromium toxicity in any of the nutritional chromium studies conducted in humans over the past three decades, using supplemental Cr(III) at levels up to  $1000 \mu\text{g day}^{-1}$  or about  $14 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ . In fact, there do not appear to be any published reports of adverse effects in humans resulting from ingested Cr(III). Almost all toxicological opinion, of both individual authors and organisations, is that Cr(III) compounds are of low oral toxicity.
- 5.18 Because of the difficulties in characterising the oxidation state of chromium in an environmental sample, it is recommended that, as a starting point, the USEPA RfD of  $3 \mu\text{g kg}^{-1} \text{bw}$  for Cr(VI) is applied to all the chromium content of an environmental sample. However, it is expected that much of the chromium present in soil will be as Cr(III) rather than Cr(VI) (see

DEFRA and Environment Agency, 2002c, for further detail). Therefore, in applying this health criteria value to land contamination it is important to obtain information on the oxidation state of chromium in the soil. To this aim, consideration should be given to how the soils have been sampled and analysed as well as to any information available about the site and soil conditions to inform on likely speciation. It is recognised that to start from the position that all chromium in soil is present as Cr(VI) is highly conservative. Given that most of the chromium in soil is expected to be Cr(III) – an essential element, and of much lower toxicity than Cr(VI) – it is considered appropriate to treat the RfD of  $3 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  as a TDI rather than an Index Dose, even though Cr(VI) is an *in vivo* mutagen.

- 5.19 For chronic exposure to airborne Cr(VI) compounds, it would be prudent to set an inhalation Index Dose to minimise the risk of lung carcinogenesis. The WHO air quality guidelines note that a lifetime lung cancer risk of  $10^{-4}$  is posed by an atmospheric concentration of Cr(VI) of  $2.5 \text{ ng m}^{-3}$  and is recommended here as the basis of an inhalation Index Dose. If a 70 kg adult inhales  $20 \text{ m}^3$  of air daily, the  $\text{ID}_{\text{inh}}$  is therefore  $0.001 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  (rounded up from  $0.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ ).

## 6 Intake of Chromium from Food, Water and Air

- 6.1 The most recently reported survey of chromium in food in the UK is that carried out as part of the 1997 Total Diet Study (MAFF, 1999; Ysart *et al*, 2000). The results are given in terms of total chromium. This is because, at the time of the survey, a reliable analytical method that could distinguish between the two forms was not available. The mean daily intake (MDI), from food, for the total population was estimated to be 100  $\mu\text{g}$ . Coincidentally the MAFF (1999) estimate of the MDI for adults is also 100  $\mu\text{g}$ . The 97.5th percentile of daily adult exposure is 170  $\mu\text{g}$ .
- 6.2 The estimated intake of chromium from foodstuffs is based on an assumed adult body weight of 60 kg. Using updated Department of Health data, a mean body weight of 70 kg is assumed in CLEA (DEFRA and Environment Agency, 2002b). Advice from the Food Standards Agency (FSA) suggests that the MDI should be scaled accordingly. The mean daily intake of chromium assumed for an adult from food sources is therefore approximately 117  $\mu\text{g day}^{-1}$ .
- 6.3 The value found in the 1997 survey is significantly lower than the 340  $\mu\text{g day}^{-1}$  figure reported for the 1994 survey. However, the 1994 value is considered anomalous and due to unusually high chromium concentrations in the Oils and Fats, Milk, Dairy Produce and Nuts food groups (MAFF, 1999; Ysart *et al*, 2000). In the 1997 survey, chromium concentrations in these food groups were stated to be in line with pre-1994 Total Diet Surveys. Measurements of chromium in foodstuffs sampled in the 1991 and 1984 Total Diet Surveys have been carried out, and the total population MDIs for these two years were 250 and 73  $\mu\text{g}$  respectively (MAFF, 1997, 1999).
- 6.4 Though chromium is regularly monitored in drinking water in the UK for regulatory purposes, this information is not generally published. The WHO (1996) notes that, in a survey of drinking water in the Netherlands, the chromium concentration of 76% of the supplies was below 1  $\mu\text{g L}^{-1}$ , and that of 98% of supplies was below 2  $\mu\text{g L}^{-1}$ . In the USA, background levels in water are reported as 1  $\mu\text{g L}^{-1}$ ; in a survey of 3834 tap waters, chromium concentrations were found to range from 0.4 to 8  $\mu\text{g L}^{-1}$  (USEPA, 1998). Chromium concentrations in the water supply to some cities in the European Community are reported to range between 1 and 5  $\mu\text{g L}^{-1}$  (MAFF, 1985). It will be assumed that the mean concentration of chromium in drinking water in the UK is no more than 5  $\mu\text{g L}^{-1}$ , that is, that the daily intake (via drinking water) for an adult that ingests 2 L  $\text{day}^{-1}$  is no more than 10  $\mu\text{g}$ .
- 6.5 For the adult, the MDI of total chromium from food and water combined is therefore about 127  $\mu\text{g day}^{-1}$ . It is usually considered that almost all the chromium in food is in the trivalent form (MAFF, 1999). The speciation of chromium in drinking water is less certain. For the present purposes, it will be conservatively assumed that no more than 10% of the chromium intake via food and water is in the hexavalent form, that is, about 13  $\mu\text{g}$  of Cr(VI)  $\text{day}^{-1}$ . On this basis, the mean daily intake of Cr(VI) for an adult is about 0.2  $\mu\text{g kg}^{-1} \text{bw}$ .
- 6.6 The average annual concentration of chromium in urban air in the UK varies with location; site means range from about 0.5 to 3  $\text{ng m}^{-3}$  (DETR, 1997). A concentration of 3  $\text{ng m}^{-3}$  and the

inhalation of 20 m<sup>3</sup> of air in a day would lead to daily intakes of about 0.06 µg for the adult or 0.9 ng kg<sup>-1</sup> bw day<sup>-1</sup>.

## 7 Conclusions

7.1 The oral tolerable daily intake (TDI<sub>oral</sub>) and mean daily intake (MDI) of chromium are given in Table 7.1.

**Table 7.1 TDI<sub>oral</sub>, oral MDI and TDSI for an adult and six-year-old child**

<b>TDI<sub>oral</sub></b> <b>(µg kg<sup>-1</sup> bw day<sup>-1</sup>)</b>	<b>Oral MDI</b> <b>(µg day<sup>-1</sup>)</b>	<b>TDSI for an adult</b> <b>(µg kg<sup>-1</sup> bw day<sup>-1</sup>)</b>	<b>TDSI for a six-year-old child</b> <b>(µg kg<sup>-1</sup> bw day<sup>-1</sup>)</b>
3	13	2.8	2.6

7.2 In applying these health criteria values to land contamination reference should be made to the discussion of chromium speciation in paragraph 5.18 (see also DEFRA and Environment Agency, 2002c, for further details).

7.3 An oral tolerable daily soil intake (TDSI) is defined as the difference between the TDI<sub>oral</sub> and the oral MDI (TDI – MDI). As an example, the MDI for a 70 kg adult is equivalent to 0.2 µg kg<sup>-1</sup> bw day<sup>-1</sup> and therefore the TDSI would correspond to 2.8 µg kg<sup>-1</sup> bw day<sup>-1</sup> (Table 7.1). Similarly, for a 20 kg child (aged six) who ingests 62% of the adult dietary intake, the TDSI would be 2.6 µg kg<sup>-1</sup> bw day<sup>-1</sup>.

7.4 The Index Dose derived from inhalation studies (that is, ID<sub>inh</sub>) of chromium is summarised in Table 7.2. This value is of an approximately similar order to the exposures arising from the present atmospheric concentrations of chromium (see paragraph 6.7 above).

**Table 7.2 Index Dose for Chromium derived from inhalation studies**

<b>ID<sub>inh</sub></b> <b>(µg kg<sup>-1</sup> bw day<sup>-1</sup>)</b>
0.001

7.5 The Index Dose represents a dose that poses a minimal risk level from possible exposure to a particular substance from a source, with the additional requirement that exposure needs to be reduced to as low a level as reasonably practicable (DEFRA and Environment Agency, 2002a). Therefore, background exposure to chromium is not considered, and the Index Dose itself is the toxicological assessment parameter used for deriving Soil Guideline Values for inhaled chromium (see DEFRA and Environment Agency, 2002c, for details).

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