Scientific Committee Health and Environmental Risks

SCHER

Opinion on

Chromium VI in toys

SCHER approved this opinion at the 10th plenary meeting of 22nd January 2015

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SCHER

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ABSTRACT

The European Commission mandated the Scientific Committee on Health and Environmental Risks (SCHER) to consider whether a revision of the migration limits for chromium VI in toys or components of toys, is necessary in view of new available evidence, in particular, with regard to the potential carcinogenic effects of chromium VI. The SCHER evaluated recent data on the cancer potency of chromium VI after oral administration. The occurrence of oral and gastro-intestinal cancer in animals after oral uptake of chromium VI was shown. Due to the genotoxic mode of action there is evidence that carcinogenic effects observed in experimental animals may also be of relevance for humans.

A virtual safe dose of 0.0002 µg/kg bw/d was derived and new values for migration limits for chromium VI from toys were recommended accordingly. Given the relatively high background exposure, however, the SCHER is of the opinion that exposure to chromium VI from toys should be minimised to the lowest levels achievable. The SCHER acknowledges that current best available technology may not be sufficient to achieve the new migration limits.

Keywords: Scientific opinion, chromium VI, toys, virtual safe dose, migration limit, carcinogenicity, oral exposure.

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EXECUTIVE SUMMARY

The SCHER was asked to assess the safety of migration limits for chromium VI from toys based on recent data from animal studies on carcinogenicity after oral uptake by drinking water. Those data were used by the Californian Office of Environmental Health Hazard Assessment (OEHHA) to derive the level of chromium VI in drinking water that does not pose a significant health risk and by the European Food Safety Authority (EFSA) to evaluate the uptake of chromium VI from drinking water.

Recently the International Programme on Chemical Safety (IPCS) also assessed the same data regarding the safety of chromium VI compounds and concluded that chromium VI induces oral cancers in rodents but emphasised that there are uncertainties regarding the extrapolation of the results of the animal studies to low-level exposure of humans via drinking water.

However, due to the mode of action, there is evidence that carcinogenic effects observed in experimental animals may be also of relevance for humans. Although chromium VI may be rapidly converted to chromium III in biological tissues, under certain circumstances the reductive capacity may not be sufficient to exclude carcinogenic effects due to exposure to chromium VI.

Regarding the exposure of children to chromium VI from toys the oral exposure route is generally considered the most important with respect to potential carcinogenic effects. The SCHER is of the opinion, that children are a vulnerable subgroup and therefore the use of a safety factor of 10 for an exposure at early life stages is justified. Studies available enable for the quantification of the dose response relationship and to estimate a dose for oral uptake that leads to an additional cancer case of 1 in a million (1 in $10^{6,}$) by using different approaches. This dose could be considered as a virtual safe dose[1].

The current European Union (EU) migration limits were derived in 2008 on the basis of a "highly uncertain daily virtual safe dose" of 0.0053 µg/kg bw and in the absence of data for cancer potency after oral uptake (Toy Safety Directive 2009/48/EC). Based on recent studies, the virtual safe dose for an additional cancer case of 1 in 10^6 is 0.0002 µg/kg bw/d based on the approach of OEHHA and also 0.0002 µg/kg bw/d based on the "linearised" approach recommended by ECHA to derive DMELs. The SCHER is of the opinion that the current migration limits for chromium VI from toys should be revised to take into account the new, lower values.

[1] A virtually safe dose may be determined for those carcinogens not assumed to have a threshold. Virtually safe doses are calculated by regulatory agencies to represent the level of exposure to such carcinogenic agents at which an excess of cancers greater than that level accepted by society is not expected (Derelanko and Hollinger, 1995),

According to the current Toy Safety Directive 2009/48/EC, migration limits for chromium VI are allocated to 5% of the virtual safe dose. The SCHER proposes new migration limits of 0.0094 mg/kg toy material for scraped-off toy materials, 0.0008 mg/kg toy material for dry (powder like or pliable) toy materials and 0.0002 mg/kg toy material for liquid or sticky toy materials, taking into account the lower new virtual safe dose of 0.0002 µg/kg bw/d and the approach followed by the Toy Safety Directive.

The SCHER acknowledges limitations with respect to the analytical methods available for enforcement of the migration limits of chromium VI from toys and also of technical limitations to achieve these values applying the best available technology. However, considering the different sources for exposure to chromium VI and the background exposure, the virtual safe dose may be already reached or even exceeded for children via uptake of chromium VI from drinking water or through ambient air. For this reason, the SCHER recommends that for children additional exposure to chromium VI from toys should be reduced to the lowest levels achievable. The SCHER acknowledges that current best available technology may not be sufficient to achieve the new proposed migration limits.

1. BACKGROUND

The Toy Safety Directive[2] (TSD) establishes migration limits for 19 elements in toys or components of toys, depending on the toy material used. The migration limits may not be exceeded. However, they do not apply if the toy or the components of the toy clearly exclude any hazard due to sucking, licking, swallowing or prolonged contact with the skin when used as intended or in a foreseeable way, bearing in mind the young children's proclivity for mouthing objects.

The migration limits are based on a 2008 report from the Netherlands National Institute for Public Health and the Environment (RIVM)[3] and the Opinion of the Scientific Committee[4]. In the 2010 SCHER Opinion on the evaluation of migration limits for chemical elements in toys, the SCHER supports the RIVM approach as a starting point for risk assessment of chemical elements in toys, namely that the basis for all approaches presented in the report is the tolerable daily intake (TDI) as a health-based limit value. In accordance with an earlier Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE) Opinion[5] the SCHER also recommended that the amount allocated to exposure from toys be limited to a maximum of 10% of the health-based limit value[6].

Section 2.3.5 of the 2008 RIVM report states that the TDI value for chromium VI (hexavalent chromium) "*only takes into account non-carcinogenic effects by hexavalent chromium; for the carcinogenic effect by hexavalent chromium a highly uncertain Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/d has been proposed by OEHHA (1999). A new drinking-water cancer bioassay with hexavalent chromium is being conducted within the US-NTP (National Toxicology Program).*"

Based on findings of this recent study, a Public Health Goal (PHG) of 0.02 parts per billion (ppb) or 0.02 µg/L for hexavalent chromium in drinking water was proposed by OEHHA in December 2010 (OEHHA 2010). A PHG is the level of a chemical contaminant in drinking water that does not pose a significant health risk[7]. A final technical support document for the PHG was published in July 2011 (OEHHA, 2011).

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[2] http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1418044666974&uri=CELEX:02009L0048-20140721

[3] http://www.rivm.nl/bibliotheek/rapporten/320003001.pdf

[4] SCHER 2010, Evaluation of the Migration Limits for Chemical Elements in Toys http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_126.pdf

[5] http://ec.europa.eu/health/archive/ph_risk/committees/sct/documents/out235_en.pdf

[6] Please note, that in the current TSD the amount allocated to the health-based limit value is deviating from the 10% rule and is set to 5%.

[7] The "one-in-one million" risk level is widely accepted as "negligible risk" (for every million people consuming two liters of drinking water with that level of chromium VI daily for 70 years, one person would be expected to develop cancer from exposure to chromium VI

2. TERMS OF REFERENCE

Taking this new information into consideration, the SCHER is asked:

1. to review the available scientific data and conclusions drawn for chromium VI in the light of the OEHHA technical support document for the Public Health Goal for hexavalent chromium in drinking water, of July 2011;
2. to consider whether the migration limits for chromium VI in point 13 of section III of Annex II of the Toy Safety Directive 2009/48/EC are still appropriate to ensure the safety of toys;
3. to propose, if the current limits are no longer appropriate, new limits, clearly indicating the data on which they would be based.

3. SCIENTIFIC RATIONALE

3.1. Occurrence, Sources and Use of Chromium compounds

Chromium is a naturally-occurring element found in rocks, animals, plants, and soil. Chromium exists in multiple oxidation states, of which the hexavalent (chromium VI) and trivalent (chromium III) states are most prevalent biologically. Chromium is known to undergo various chemical and biological reactions in natural systems. Both oxidation of chromium III and reduction of chromium VI can occur in geologic and aquatic environments (ECB, 2005). In the atmosphere chromium VI may react with dust particles or other substances and may be converted to chromium III (EPA, 1998).

Chromium VI occurs in rare minerals and may be naturally occurring in groundwater (McNeill *et al*., 2012), however, chromium VI in the environment is almost totally derived from human activities (WHO, 1990; Kimbrough *et al*., 1999; Johnson *et al*., 2006). An important source is the production and use of chromium compounds (mainly chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate) as well as the disposal of commercial products containing chromium compounds. Major uses of chromium VI compounds include metal plating, manufacture of pigments and dyes, corrosion inhibitors, chemical synthesis, refractory production, leather tanning, and wood preservation (EPA, 2010). Chromium VI can be found in many consumer products such as wood treated with copper dichromate or leather tanned with chromic sulphate (EU Risk Assessment Report on chromates, ECB, 2005).

Major sources of chromium emissions to the air are the production of chromium VI compounds and metal treatment (6.2 t/y and 12 t/y, respectively). Important sources of chromium releases to water are metal treatment use (estimated at 2,342 t/y), chrome tanning salt production (38 t/y), chromium trioxide production (22t/y) and metal treatment formulations (12 t/y), while wood preservative application is the main source for chromium in soil (6.2 t/y) (all data valid for the EU; ECB, 2005).

As summarised by the United States Environmental Protection Agency (US EPA), elemental chromium is found in air, water, soil and biota with concentrations of 1.0–2,000 mg/kg soil (average of 40 mg/kg soil), 0.1−6.0 µg/L fresh water and 0.2−50 µg/L sea water (EPA, 2010). In contaminated sites, chromium concentrations may be higher, e.g. up to 30 µg/L in fresh water (ATSDR, 2000a). For the United States of America (USA) a median value of 10 µg/L in fresh water is reported (ATSDR, 2012). Chromium also enters groundwater by leaching from soil. Based on US data collected from 2,106 monitoring stations between 1977 and 1984, the arithmetic mean concentrations of total chromium in the ambient air (urban, suburban, and rural) were in the range of 0.005–0.525 µg/m^3 (ATSDR, 2000a). According to United States Agency for Toxic Substances

and Disease Registry (ATSDR), chromium VI accounts for approximately one third of the 2,700–2,900 tons of chromium emitted to the atmosphere annually in the USA (ATSDR, 2012).

3.2. Health effects

The SCHER based its assessment on information collected in recent reviews and assessments such as *Inorganic chromium VI compounds* (WHO/IPCS, 2013), *Toxicological Profile for Chromium* (ATSDR, 2012), *Establishing a reference dose response relationship for carcinogenicity of hexavalent chromium* (RAC, 2013), *Chromium in drinking water* (WHO, 2003), *Chemicals in toys* (RIVM, 2008) *Chromium VI compounds* (IARC, 2012), *Scientific Opinion on the risks to public health related to the presence of chromium in food and drinking water* (EFSA, 2014) and *Public Health Goal for Hexavalent Chromium in Drinking Water*, California Environmental Protection Agency (OEHHA, 2011). Recent literature (up to October 2014) was consulted with specific focus on new available evidence on the potential carcinogenic effects of chromium VI. The SCHER focused mainly on information on health effects following oral exposure and noticed that various chromium salts were used to administer chromium VI in animal studies as well as in *in vitro* studies. These include dipotassium-, disodium-, calcium-, strontium-, zinc- and diammonium salts which have different degrees of solubility. In epidemiological studies, co-exposure to chromium III and chromium VI occurred.

3.2.1. Kinetics

Chromium VI is highly reactive in biological systems and can rapidly be reduced to chromium III which is less readily absorbed and far less toxic than chromium VI.

Saliva and gastro-intestinal fluids reduce chromium VI within minutes (De Flora *et al*., 1997) with estimated reductive capacities of 0.7 to 2.1 mg/d for saliva and 80 to 84 mg/d for gastric juices (De Flora, 2000). Reductive capacities may be overestimated due to analytical limitations (Zhitkovich, 2005). The half-life of chromium VI is reported to be 23 minutes in artificial gastric juice (Gammelgaard *et al*., 1999). Saturation or exhaustion of the reducing capacity of saliva and gastric fluids has been suggested to result in increased absorption, elevated blood levels and the appearance of toxicity.

In humans there is a large inter- and intra-individual variability regarding absorption of chromium VI since the conversion depends on the concentrations of both chromium VI and the native reducing agents as well as on the gastric content and on pH. Especially acidic environments with high organic content promote the reduction of chromium VI to chromium III. Ascorbate and small thiols are the principal biological reducer of chromium VI, accounting for more than 80% of its metabolism (Zhitkovich, 2011).

Absorption of chromium VI in adult humans varies between 0.5% and 18% when studied in volunteer experiments. For chromium VI administered orally as potassium chromate or dichromate, absorption is reported to be approximately 2–8% with no clear dependence of the dose (Finley *et al.,* 1996; Finley *et al*., 1997; Kerger *et al*., 1996; Kerger *et al*., 1997). Less than 10% of the orally administered dose of chromium VI , with an average half-life of 39 hours was recovered in the urine in humans (Kerger *et al.,* 1996). Remarkable differences were evident between individuals in different studies, but also within the same study, and within the same individual in multiple administration study designs. Based on published literature it is assumed that 10-20 % of ingested low dose chromium VI would not be reduced in the gastro-intestinal tract of humans (Zhitkovich, 2011).

Chromium VI as chromate structurally resembles sulphate and phosphate and is readily taken up by all cells and organs throughout the body via sulphate transporters (Costa, 1997). This differs from chromium III which is not taken up by cells in the same way. The final uptake is determined by competition between extracellular reduction of chromium VI and its rapid intracellular absorption.

Reduction to chromium III also occurs in lung epithelial lining fluids and in skin. However complete conversion to chromium III does not occur since elevated chromium VI levels and related toxicity have been observed in animals and humans following chromium VI exposure by all exposure routes (O'Flaherty *et al*., 2001). Inhaled chromium VI is readily absorbed from the respiratory tract (Minoia and Cavalleri, 1988). The degree of absorption depends on the physical and chemical properties of the particles (size, solubility) while insoluble chromium compounds and particles above 5 µm can remain in the lungs for a very long time. Long-term retention of chromium was observed in the bronchial walls of chromate workers who developed lung cancer after an average exposure duration of 21 years (Ishikawa *et al*., 1994).

Penetration of chromium VI salts through the skin occurs especially if the skin is damaged (Gammelgaard *et al*., 1992). Studies with volunteers showed that the reductive capacity of the skin is not sufficient to prevent systemic uptake of chromium VI from locally applied chromium. The dermal absorption ranged from 3.4 to 10.6% for the 0.2-molar sodium chromate solutions and from 7.7 to 23% for the 0.01-molar sodium chromate solution (Baranowska-Dutkiewicz, 1981).

In the blood, chromium VI is mainly trapped in the red blood cells (RBC), reduced to chromium III and remains there for the life time of the RBC, making it a good biomarker for chromium VI exposure. However, reduction of chromium VI in blood is not rapid enough to prevent the uptake in other organs. Animal studies showed relatively increased levels of chromium VI in the liver, kidney, and spleen, while RBC and plasma

chromium levels were only modestly elevated after exposure to chromium VI (Costa, 1997; Thomann *et al*., 1994; Witmer *et al*., 1989; Collins *et al*., 2011; Witt *et al*., 2013). Thompson *et al*. (2011, 2012) reported significant increases in total chromium concentrations in the oral cavity, glandular stomach, duodenum, jejunum, and ileum of rats and mice following 90 days of exposure to sodium dichromate dihydrate in drinking water. The half-life of chromium in various tissues of rats who are administered chromium VI was long and exceeded 20 days.

Physiologically-based kinetic (PBK) models were developed for rats and mice orally exposed to chromium (Kirman *et al*., 2012; Schlosser, 2014). These models revealed chromium delivery to the target tissue (small intestines), with higher concentrations achieved in mice than in rats and as such consistent with small intestinal tumour formation, which was observed upon chronic exposures in mice but not in rats. Exposure – tissue concentrations were linear or supra linear indicating that the exposures did not saturate gastric reducing capacity (Collins *et al*., 2010).

The model was expanded for humans orally exposed to chromium VI. Therefore information from studies and from the published literature regarding the toxicokinetics for total chromium in humans was used. The model is based on a mixed second-order, pH-dependent process and provided a good description of chromium toxicokinetics consistent with current knowledge on chromium exposure in humans. Gastric lumen pH, gastric lumen transit time, gastric lumen volumes, and gastric fluid production were identified as important sources for human variability for which data is lacking in order to further develop key assumptions made in the PBPK models and to allow improved health risk assessment (Kirman *et al*., 2013).

3.2.2. Mode of action

The weight of evidence supports the plausibility that chromium VI may act through a mutagenic and genotoxic mode of action (MOA). In addition, chromium VI has been shown to deregulate cell growth (IARC, 2012).

Chromium VI readily crosses biological membranes via sulphate transporters. Inside the cell, highly reactive chromium VI is reduced thereby producing oxidative damage to proteins, lipids and DNA. Genetic lesions include DNA adducts, DNA-strand breaks, DNA-protein crosslinks, oxidized bases, abasic sites, and DNA inter- and intrastrand crosslinks (O'Brien *et al*., 2001; Salnikow *et al*., 2008; Chun *et al*., 2010; Nickens *et al*., 2010; Sugden and Stearns, 2000). In the cell, chromium III can bind to DNA and generate DNA adducts leading to genomic instability and mutations as is observed by in vitro studies in human and bacterial cells (Quievryn *et al.,* 2003). Additionally, reduction of chromium VI can result in DNA damage from ROS (Thompson *et al*., 2011). Recent studies have

shown in vivo generation of double strand breaks in chromium VI-exposed *Drosophila larvae* (Mishra *et al*., 2013).

In vitro, low chromium VI concentrations cause persistent activation of the mitogen-activated protein kinases ERK-1, ERK-2, JNK and p38 (Chuang and Yang, 2001; Kim and Yurkow, 1996) and the phosphorylation of the mitogenic transcription factors NFκB, ATF-2 and c-Jun (Samet *et al*., 1998; Ye *et al*., 1995). As these protein kinases and transcription factors constitute important mediators in inflammatory processes and tumour growth, effects on cellular signal transduction that deregulate cell growth are also to be expected in the case of chromium VI, in addition to the direct genotoxic mechanisms involved (Hartwig, 2007, 2010).

In vivo, chromium VI has been shown to be genotoxic by all routes of administration in rodents treated with high doses of chromium VI (ATSDR, 2000b; ATSDR, 2008; OEHHA, 2011). In a 90-day animal study designed to build upon and expand the NTP's study, inflammatory effects were observed in the small intestines of mice that were orally exposed at carcinogenic doses of chromium VI. These are likely to be the consequence of oxidative damage and it has been suggested that they may precede regenerative hyperplasia and tumour formation (Thompson *et al*., 2013). Whole genome microarray analysis of duodenal epithelial samples identified changes in genes involved in oxidative stress response, cell cycle regulation, or lipid metabolism (Kopec *et al*., 2012). Occupational exposure through inhalation has been shown to cause DNA damage in circulating lymphocytes (IARC, 2012).

IARC (1990) concluded that "…relevant data support the underlying concept that chromium VI ions generated at critical sites in the target cells are responsible for the carcinogenic action observed" (IARC, 1990). Despite the overwhelming evidence of the potential of chromium VI to cause genotoxicity and mutagenicity, it is still unclear at present whether low oral exposures to chromium VI escape the reductive capacities of the stomach and will result in significant DNA damage (de Flora, 2000).

3.2.3. Effects in animals

Different studies addressed the acute toxicity of chromium VI. In summary, acute oral median lethal doses (LD50 values) in rats exposed to chromium VI compounds varied between 13 and 29 mg/kg bw depending on the compound administered and the sex of the rat (Gad *et al*., 1986). Single-dose (24-hour) dermal LD50 values in New Zealand rabbits varied between 336 and 763 mg/kg bw.

The main effects observed in animals after medium-term oral exposure to chromium compounds were decreases in body weight gain and changes in haematological and immune parameters. The most recent National Toxicology Program (NTP) study (2008) in

which rats and mice were exposed for two years to sodium dichromate administered in drinking water was used to derive tolerated daily intake levels for non-carcinogenic effects. In female rats, histiocytic infiltration of the liver was observed at the lowest dose of 0.2 mg/kg bw/d. Using the same data set, WHO/IPCS (2013) calculated a benchmark dose for a 10% response (BMD10) and identified the lowest BMD10 (0.12 mg/kg bw/d) in female mice with increased epithelial hyperplasia in the duodenum.

Exposure of rats through inhalation resulted in pulmonary inflammation and neutrophil migration (Cohn *et al*., 1998).

A number of studies have reported reproductive and developmental effects in rats and mice orally exposed to high doses of chromium VI compounds. In the NTP studies, no effects were observed on spermatogenesis or reproductive outcome in mice and rats exposed under similar conditions (NTP, 1996; NTP, 1997). For the oral route of exposure, the Murthy *et al*. (1996) study in mice provided a No Observed Adverse Effect Level (NOAEL) of 0.142 mg/kg bw/d for female reproductive toxicity.

Sensitisation has been observed in rats that were exposed for three weeks daily to K_2CrO_4 (100 mg/L) in drinking water as evidenced by increased proliferation of T and B lymphocytes in response to the mitogens concanavalin A and liposaccharide (Snyder and Valle, 1991).

Various studies showed that chromium compounds induced cancers in experimental animals following diverse exposure pathways including the oral route, inhalation, intratracheal, intrapleural, intra muscular, intraperitoneal, intravenous and subcutaneous injections (ATSDR, 2008). Carcinogenesis occurred mostly at the site of administration. Inhalation induced lung cancers in mice (Nettesheim et al., 1971) and rats (Glaser et al., 1986; Glaser et al., 1988). By repository injection several chromium compounds (calcium chromate, lead chromate, zinc chromate, strontium chromate) caused local sarcomas.Potassium chromate given orally enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects (Davidson et al., 2004).

The NTP conducted a two-year drinking-water study of sodium dichromate dihydrate in male and female B6C3F1 mice, and in male and female F344 rats (NTP, 2008). Sodium dichromate caused cancer of the oral cavity in rats and of the gastro-intestinal tract in mice. It was concluded that there is clear evidence of carcinogenic activity of orally administered sodium dichromate dihydrate in male and female F344 rats and clear evidence of carcinogenic activity in male and female B6C3F1 mice (NTP, 2008; Witt *et al*., 2013). IARC (2012) also concluded that there is sufficient evidence in experimental animals for the carcinogenicity of chromium VI compounds after oral exposure.

3.2.4. Effects in humans

In humans most data on effects are derived from reported cases of accidental exposure to very high doses and from occupational exposure by inhalation. It is mainly workers in chromate production, chromate pigment production and chromium electroplating who are exposed to chromium compounds.

Skin contact with compounds containing chromium VI causes rashes and ulcers. Dermal exposure to chromium VI has also been linked to allergic contact dermatitis. Using a patch test, 2 µg was required to evoke a positive skin reaction in hypersensitive subjects. The prevalence of chromium sensitivity in the general population has been estimated to be between 0.5% and 1.7% in studies in several European countries (Peltonen and Fräki, 1983; Hartwig, 2007; Hartwig, 2010). The North American Contact Dermatitis Group Patch-Test Results revealed that 2.8% of 3,440 patients tested between 1996 and 1998 by 12 North American dermatologists exhibited a positive allergenic reaction to 0.25% potassium dichromate solution (Marks *et al*., 2000). Virtually no response was detected at concentrations below 4 to 5 mg/kg of chromium VI. However, this 4-5 mg/kg cut-off has several associated uncertainties including individual susceptibility and the use of different compounds for testing. However, sensitising properties of chromium VI are not addressed by the SCHER in this opinion.

Inhalation in occupationally exposed workers induced effects in the airways such as nasal mucosal ulceration and septal perforation. Changes in lung function parameters were also observed. Exposure was estimated based on the exposure period (defined as the period between when a worker was hired and the time symptoms were first detected) and on the mean and median annual chromium VI concentrations likely to be experienced in the job position held when the symptoms first occurred (Gibb *et al*., 2000a; Lindberg and Hedenstierna, 1983).

Reduced sperm count and semen quality were observed in a study with 21 exposed workers in an electroplating factory in China that were compared to unexposed controls (Li *et al*., 2001). In 57 Indian welders, higher blood chromium levels but also higher blood nickel levels were found to be associated with decreased sperm vitality (Danadevi *et al*., 2003).

Chromium VI has been shown to cause DNA damage (DNA strand breaks, DNA–protein crosslinks, micronuclei, chromosomal aberrations or sister chromatid exchanges) in the lymphocytes of workers (electroplaters, welders or ferrochromium alloy foundry workers who were mainly exposed by inhalation, as reviewed in WHO/IPCS, 2013). Not all human studies showed consistent results. They were limited in several aspects: generally, the levels of exposure to chromium VI were not known and exposed and non-exposed groups were compared often based on job description. Co-exposure to other potentially active

compounds (i.e. ultraviolet irradiation and other potentially genotoxic metals) occurred in several studies. Some of the studies used groups that were too small to have the statistical power to reliably assess the cytogenetic changes in workers.

There have been at least 50 epidemiological studies in workers that could be informative about cancer risks related to chromium VI after inhalation exposure. These studies allowed IARC (2012) to conclude that chromium VI is carcinogenic for the lungs. However only two studies provided quantitative estimates of the cancer risk associated with exposure to chromium IV which are based on measured exposure data in the populations studied. Both studies were retrospective cancer mortality studies of occupationally exposed workers carried out in the US. In the Baltimore study reported by Gibb *et al*. (2000b), exposure assessment was based on 70,000 contemporary measurements of airborne chromium VI spanning the entire study period. These data were used to derive individual cumulative exposure estimates related to job titles. Also in the retrospective cohort study of former employees of a chromate production plant in Painesville, Ohio, USA, individual chromium VI exposure was estimated based on chromium VI analysis of air samples combined with information from a job exposure matrix (Luippold *et al*., 2003).

Almost all of the relative risk estimates for cancer of the lung are greater than 1.0. A recent meta-analysis estimated an overall standardised mortality ratio (SMR) of 1.41 (95% CI: 1.35–1.47) for lung cancer among 47 studies of workers with possible chromium VI exposure (Cole and Rodu, 2005). IARC concluded that there is sufficient evidence in humans for the carcinogenicity of chromium VI compounds and classified chromium VI as carcinogenic to humans (Group 1).

Regarding the effect of chromium VI on nasal and nasal sinus cancers, the epidemiological evidence remains suggestive but inconclusive (IARC, 2012).

An association between gastro-intestinal tract cancer and exposure to chromium VI in drinking water has been reported at a contaminated location in China (Zhang and Li, 1997). But there are major uncertainties regarding the study outcome, especially in the estimation of the exposure (Brandt-Rauf, 2006; Beaumont *et al*., 2008 and follow-up author correspondence; Smith, 2008). A metadata analysis did not reveal any increase in cancers of the gastro-intestinal tract in workers which were exposed mainly through inhalation (Gatto *et al*., 2010), but the individual studies were small and interpretation was hampered by lack of adequate exposure measurements and lack of information on potential confounders such as smoking, alcohol consumption, dietary factors, and socioeconomic status.

3.3. Exposure assessment

Human exposure to chromium occurs from both natural and anthropogenic sources, however, the levels of exposure for individuals vary according to geologic and geographical variations as well as to the vicinity to industrial or waste disposal sites. Exposure specifically to chromium VI is difficult to quantify because specific forms of chromium are often not identified in exposure studies. Although chromium VI in the environment may be reduced to chromium III, chromium VI can persist under specific conditions, depending on factors like the pH level, the amount of organic matter or the redox potential (Clifford and Man Chau, 1988). It was assumed that for acidic or neutral soils, sediments and waters, chromium VI will be rapidly reduced to chromium III and that 3% of the chromium III formed will be oxidised back to chromium VI. Under less favourable conditions, e.g. alkaline conditions (pH>8, e.g. in seawater) and/or neutral conditions, where low concentrations of reducing agents for chromium VI exist, the rate of reduction of chromium VI to chromium III is reported to be slow, with a half-life of around one year (ECB, 2005). In addition, chromium VI exists mainly as highly soluble oxoanions in the environment and is expected to be mobile in soils and sediments although its adsorption is pH dependent (ECB, 2005).

The general population may be exposed to chromium VI through inhalation of ambient air, ingestion of water, or skin contact with products that contain chromium VI compounds, such as leather products, products coloured with chromium pigments or pressure-treated wood.

3.3.1. Environment

In the EU risk assessment report for chromium compounds, the indirect exposure to chromium VI via the environment was calculated (ECB, 2005). The assessment focused on local impact of emissions from the production and use of five chromium VI compounds. Estimated concentrations in water and fish, for two process steps and also in the air were taken into account in order to calculate exposure values. Depending on the vicinity to emission sites of different production processes, daily exposure of adults via the environment was calculated to be in the range of 0.009 to 11 µg chromium VI/kg bw. RIVM has estimated the exposure of the general population to chromium VI via air (outdoor) at 0.0057 to 0.43 ng/kg bw/d (RIVM, 2001). Indoor chromium concentrations can be higher than outdoor concentrations, for example up to 10–400 times as a result of smoking (WHO, 2003). A 1990 study reported the average concentration of chromium VI to be 0.0012 µg/m^3 (<0.001 to 3 µg/m^3) in indoor air samples collected from residences in New Jersey (NTP, 2011).

Children may be exposed to chromium via the environment to a greater extent than adults because of higher inhalation and ingestion rates per unit of body weight. The average concentration of chromium in the urine of children at ages five and younger was reported to be significantly higher than in adults residing near industrial sites where chromium waste was used (Fagliano *et al*., 1997) although it has to be noted that urinary biomonitoring has some limitations due to minor sensitivity to detect low level exposure and due to variability of individuals (Anderson *et al*., 1993; Gargas *et al*., 1994; Finley *et al*., 1996).

The behaviour of young children to ingest soil, either intentionally through pica[8] or unintentionally through hand-to-mouth activity, may result in additional ingestion of chromium from soil and dust. In order to reduce the cancer risk to a *de minimis* level (i.e., one in a million), the State of New Jersey recommended that soil levels should not exceed 130 mg chromium VI/kg soil in residential areas and 190 mg chromium VI/kg soil in non-residential areas (NJDEP, 1995a; NJDEP, 1995b). The US EPA recommended a concentration of 270 mg chromium VI/kg soil based on cancer risk following inhalation (EPA, 1996a) and a maximum concentration of 390 mg chromium VI/kg soil based on a reference dose (RfD) of 0.005 mg/kg bw/d, calculated for children of 15 kg body weight ingesting 200 mg soil/d (EPA, 1996b).

In the UK, the average concentration of total chromium in soil, based on analysis of 6,000 samples from England and Wales, was reported to be 39 mg/kg soil (McGraw and Smith, 1990). A range from 5 to 1,500 mg/kg soil was measured in uncontaminated "background" soils (Bowen, 1979; Braithwaite, 1995). However, in some environments (e.g. serpentine rocks), mean concentrations of chromium in naturally occurring soils are higher: 2,221 mg chromium VI/kg soil (Cornwall) and 10,347 mg chromium VI/kg soil (Scotland) (Smith *et al*., 1989). Chromium VI was detected in soil from a heavily contaminated area of the UK and accounted for between 10% and 29% of the total chromium measured (9,400 to 26,150 mg total chromium/kg soil) (EHD, 1991).

Based on these data, the SCHER estimated the following exposure to chromium VI from soil for children. The amounts measured for uncontaminated soil were chosen for best, average and worst case scenarios. As it is known that 10 to 29% of the total chromium in contaminated soils is chromium VI, the SCHER calculated the exposure scenarios based on the assumption, that 20% of the total chromium would be chromium VI. An amount of 200 mg/d soil ingested by a child[9] was chosen for the assessment as well as a body

[8] Pica is an eating behaviour, typically defined as the persistent eating of non-nutritive substances like clay, sand, stones and pebbles.
[9] Default value related to EPA, 1999; EPA 2011

weight of 10 kg[10], as small children are most likely to ingest soil. The SCHER also estimated that 10% of the ingested chromium VI might be absorbed from the gut and become bioavailable, taking into account the current knowledge on kinetics of chromium VI and the fact that the gut of small children might be more permeable. The SCHER is aware of the fact that the assessment performed for the uptake of chromium VI from soil by small children is related to one data source only and may be highly variable depending on different soil compositions and geographical conditions.

Table 1: Exposure assessment for the uptake of chromium VI by children from soil

		best case	average case	worst case
Chromium total	mg/kg soil	5	39	1500
Chromium VI (20% of chromium total)	mg/kg soil	1	7.8	300
Amount of soil ingested	mg soil/d	200	200	200
Bodyweight	Kg	10	10	10
Internal exposure (10% absorption from gut)	µg/kg bw/d	0.02	0.156	6

3.3.2. Food

Chromium contents in food were reported to range from 20 to 590 µg/kg (EPA, 1985) or from 10 to 1,300 µg/kg (WHO, 2003) with the highest levels in meat, molluscs (with a bioconcentration factor of 9,100 L/kg based on mussel dry weight), crustaceans, vegetables and unrefined sugar.

Dietary intake of total chromium by humans has been estimated to range from 5 to 500 µg/d, with a typical value of approximately 100 µg/d (EPA, 1985). Analysis of samples of bread in Portugal for both total chromium and chromium VI revealed that roughly 10% of the total chromium in bread was chromium VI (Soares *et al*., 2010). Mean levels of chromium VI in bread were 3.8 and 4.6 µg/kg for white and whole bread, respectively. The authors estimated mean chromium VI intakes of 0.57 and 0.69 µg/d from bread. When evaluating chromium in food and drinking water, EFSA reported that there was a lack of data on the presence of chromium VI in food. Therefore, the EFSA Panel on Contaminants in the Food Chain decided to consider all reported analytical results in food as chromium III. This assumption was based on the fact that food is a reducing medium, and that oxidation of chromium III to chromium VI would not be favoured in such a medium. However, the Panel also noted that if even a small proportion of total chromium

[10] Default value related to ECETOC, 2001; EPA 2011

in food was in the form of chromium VI, it could contribute substantially to chromium VI exposure.

Chromium has been detected in breast milk at concentrations of 0.06-1.56 µg/L (Casey and Hambidge, 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies on mice have shown that chromium crosses the placenta and can concentrate in foetal tissue (Danielsson *et al*., 1982; Saxena *et al*., 1990a).

3.3.3. Drinking water

As far as drinking water quality and consumer protection is concerned, the World Health Organization (WHO) and the EU have established a guideline value of 50 µg/L for total chromium in drinking water (WHO, 2003; Council Directive 98/83/EC). Following a call for data on chromium levels in food and drinking water analytical results were reported to EFSA (EFSA, 2014). However, in public literature there is limited data of chromium VI concentrations in drinking water in Europe. In the Netherlands, the total chromium concentration was below 2 µg/L in 98% of the drinking water supplies investigated and below 1 µg/L in 76% (Fonds *et al*., 1987). In Germany, various types of chromium were detected in raw and drinking water samples at concentrations ranging from <0.02 to 1 µg/L. In the majority of samples, chromium VI was measured while chromium III was present only in very few samples and at very low concentrations. It could also be shown that the addition of oxidising agents such as ozone, chlorine, and chlorine dioxide to drinking water results in oxidation of chromium III to chromium VI (Sacher and Thoma, 2013).

For the determination of chromium VI in drinking water, several studies were conducted in the USA in the last years. In 2002, chromium VI was detected in 59% of 483 drinking water sources (CDHS, 2002). 38% had chromium VI levels between 1 and 5 µg/L, 13% between 6 and 10 µg/L and 6% between 11 and 20 µg/L. The California Department of Public Health (CDPH) reported 2,208 sources of drinking water with detections above 1 µg/L. Seven sources had chromium VI levels above 50 µg/L, 5 sources had levels between 41 and 50 µg/L, 14 sources had levels between 31 and 40 µg/L, and 61 sources had levels between 21 and 30 µg/L. Chromium VI levels in 456 sources were between 6 and 10 µg/L and 1,434 sources had levels between 1 and 5 µg/L (CDPH, 2010).

In the United States, the Sacramento Groundwater Authority reported the occurrence of chromium VI in groundwater at levels below 5 µg/L (126 of 206 samples), 5-10 µg/L (in 63 samples), and greater than 10 µg/L in 17 of the 206 samples (SGA, 2013).

OEHHA calculated the exposure to chromium VI from drinking water. An uptake of 0.2 µg/d chromium VI was estimated based on a concentration of 10 µg/L, 2 L ingested

drinking water and an absorption from the gut of 1%. OEHHA also considered inhalation, ingestion and dermal uptake of chromium VI during showering, which was negligible compared to drinking water exposure (OEHHA, 2011).

EFSA evaluated the risks to public health related to the presence of chromium in food and drinking water (EFSA, 2014). Based on data from 88 samples, EFSA calculated the exposure to chromium VI for different consumer groups in all types of drinking water and in bottled water. The mean chronic exposure to chromium VI from consumption of all types of drinking water ranged from 0.7 (minimum LB) to 159.1 ng/kg bw/d (maximum UB). The 95th percentile exposure ranged from 2.8 (minimum LB) to 320.2 (maximum UB) ng/kg bw/d. The highest exposure to chromium VI through the consumption of all types of drinking water was estimated for infants and toddlers. In those dietary surveys with reported data on consumption of bottled water, the highest exposure to chromium VI was also estimated in infants and toddlers, with a mean chronic exposure ranging from < 0.1 (minimum LB) to 149.8 ng/kg bw/d (maximum UB, infants). The 95th percentile exposure ranged from 0.0 (minimum LB) to 148.7 ng/kg bw/d (maximum UB, toddlers). An additional contribution to the exposure to chromium VI was considered from the water used to prepare certain foods (coffee, tea infusions, and infant dry and follow-on food mainly, but also some others such as instant soup, evaporated and dried milk, and dehydrated fruit juice). A worst-case scenario, with no reduction of the chromium VI present in water into chromium III when the foods are ingested immediately after their preparation, was assumed. This scenario led to an increase up to two-fold in the exposure levels to chromium VI, in comparison to those estimated via the consumption of drinking water only.

3.3.4. Consumer products

Contact with copper chrome arsenate (CCA)-treated wood was identified as a source of chromium VI exposure for adults and for children in the EU risk assessment report. A body burden of 1.63 µg/kg bw/d has been calculated, based on the inhalation and dermal exposure values for a typical consumer handling and sawing dry CCA treated timber. For a child playing on CCA-treated timber, a body burden of 0.1 µg/kg bw/d has been estimated for oral ingestion and dermal exposure (ECB, 2005).

For chromated end products with a layer of chromium oxide on the metal surface, up to 15% chromium VI has been measured in the coating (AFSSET, 2008).

Concerning consumer products, leather articles contribute considerably to chromium VI exposure. Surveys of chromium VI in articles of leather in Germany and Denmark have demonstrated that more than 30% of the tested articles contained chromium VI in concentrations above 3 mg/kg (Danish EPA, 2012).

In leather goods investigated in Germany between 2000 and 2006, chromium VI was detected in more than half of 850 samples; in one sixth of the samples, the levels were higher than 10 mg/kg leather (BfR, 2007). In surveys conducted in 2008 and 2009, the chromium VI concentration was above 3 mg/kg in 23% and 32%, and above 10 mg/kg in 9% and 16%, respectively. The highest chromium VI concentrations found in the 2009 survey were 141 mg/kg in work clothes, 137 mg/kg in footwear and 112 mg/kg in gloves (BVL, 2011; BVL, 2010).

In a survey of the Danish market from 2002, 35% leather products contained chromium VI in levels above the detection limit of 3 mg/kg. The concentration ranged from 3.6 to 14.7 mg/kg (analysed according to DIN 53315). The study also showed that some of the purchased baby shoes exceeded the limit for migration of chromium from toys according to European Standard EN71 (Rydin, 2002). In 2011, the Danish EPA (Johansen *et al.,* 2011) aimed to clarify whether chromium VI and chromium III compounds released from leather shoes in Denmark constitute a potential of causing allergic reactions. A screening revealed that the typical range of chromium content in leather shoes seems to be between 1 and 3%. The results indicated no correlation between content of chromium and shoe category (ladies', men's or children's shoes) or shoe type (sandals, boots or ordinary shoes). The quantitative analysis using EN ISO 17075 showed chromium VI contents higher than the quantification limit of 3 mg/kg in 44% of the shoes (8/18). The median was 6 mg/kg with a range reaching from 3 to 62 mg/kg. A sixth of the shoes contained more than 10 mg/kg chromium VI. Sandals seemed to be over-represented among the shoes with detectable chromium VI. The shoe with one of the highest levels of chromium VI content was a child's sandal. No relation was found between chromium VI and chromium III levels (Johansen *et al*., 2011).

In a worst case scenario, the dermal exposure to chromium VI from a chromium-leather tanned shoe was calculated to be 0.45 µg/cm², based on a content of 3 mg chromium VI/kg leather (Danish EPA, 2012).

Pigments based on chromium VI additionally play an important role regarding consumer exposure. Lead sulphochromate and lead chromate molybdate sulphate, for example, are produced in the EU in quantities of 30,000 tonnes (ECHA, 2011). The listed potential applications include paints and varnishes, printing inks, vinyl and cellulose acetate plastics, textile printing, leather finishing, linoleum and paper.

The EU rapid alert system (RAPEX) frequently publishes a list of consumer products exceeding the current limit value for chromium VI, demonstrating the impact of consumer products regarding the exposure of the general public to chromium VI.

3.4. Risk characterisation

In order to derive safe migration limits for chromium VI from toys, the SCHER used data from the NTP studies (NTP, 2008), which were also the basis for the health goals derived by OEHHA and also for the risk evaluation by EFSA. The SCHER is of the opinion that the general approach from OEHHA is justified in order to estimate additional cancer cases attributed to chromium VI exposure. Due to the mode of action, there is evidence that carcinogenic effects observed in experimental animals may also be of relevance for humans. Although chromium VI may be rapidly converted to chromium III in biological tissues, the reductive capacity under certain circumstances may not be sufficient to exclude carcinogenic effects.

Regarding the exposure of children to chromium VI from toys, the SCHER considered the oral exposure route as most important with respect to potential carcinogenic effects, although dermal exposure to chromium VI from toy materials is expected to contribute to the systemic exposure. However, the SCHER cannot estimate the cancer risk from dermal exposure as the SCHER is not aware of studies on cancer after dermal application of chromium VI. For proposing revised migration limits, the SCHER followed the approach used in the current Toy Safety Directive and considered the dose related to one extra-cancer case in a million after oral exposure. The SCHER is also of the opinion that children are a vulnerable subgroup and the age sensitive factor used is justified.

3.4.1. Dose response analysis

3.4.1.1. Non carcinogenic end points

The relevant study for non-carcinogenic endpoints for risk assessment of chromium VI by the oral route is the NTP 2008 study in which rats and mice were exposed for two years to sodium dichromate administered in drinking water. Histiocytic infiltration of the liver in female rats occurred at 0.2 mg/kg bw/d. This concentration was used by OEHHA to derive an acceptable daily dose (ADD) of 0.0002 mg/kg bw/d. OEHHA used an aggregated uncertainty factor of 1,000 to provide an adequate margin of safety for human exposure to chromium VI in drinking water which included 10 for using a LOAEL, 10 to extrapolate between species, and 10 to protect potentially sensitive human subpopulations (including antacid users). WHO/IPCS (2013), using the same data set, calculated a benchmark dose for a 10% response (BMD10) and identified the lowest BMD10 (0.12 mg/kg bw/d) in female mice with increased epithelial hyperplasia in the duodenum. WHO/IPCS used 0.094 mg/kg bw/d as the lower limit on the benchmark dose for a 10% response (BMDL10) for the TDI calculation and included an uncertainty factor of 100 that includes 10 for extrapolation from experimental animals to humans and 10 for human inter-individual variability. The TDI calculated by IPCS is 0.0009 mg/kg bw/d for oral exposure to chromium VI compounds. The same value was derived as the

minimal risk level (MRL) for hazardous substances by the ATSDR (2012) on the same basis using similar uncertainty factors.

3.4.1.2. Oral Potency Estimates for carcinogenicity based on Animal Studies

Given the limitation of available human studies, the derivation of the oral carcinogenic potency of chromium VI is based on the results obtained from animal studies. Although the extrapolation of the results from animal studies to low-level exposure of humans via drinking water is considered to carry uncertainties (IARC, 2012), carcinogenic effects of chromium VI might also be expected in humans due to the postulated mode of action. McCarroll *et al*. (2010) reported that the weight of evidence supports the plausibility that chromium VI may act through a mutagenic mode of action. A linear extrapolation and the application of age sensitivity factors are therefore recommended.

Four cancer bioassays, conducted in male rats, female rats, male mice, and female mice, were identified in which animals given chromium VI in drinking water displayed statistically significant increases in tumours (NTP, 2008). The mouse was the more sensitive species and data for female and male mice on occurrence of adenomas and carcinomas of the small intestine are summarised in table 2.

Table 2: Small intestine tumours in female and male mice administered chromium VI

	0 mg/L	14.3 mg/L	28.6 mg/L	57 mg/L	85.7 mg/L	172 mg/L	257.4 mg/L	516 mg/L
females	1/44	1/45	-	4/47	-	17/45**	-	22/49**
males	1/49	3/49	2/49	-	7/50*	-	20/48**	-

Number of animals with tumours/number of animals at risk (alive at the time of the first occurrence of tumour (day 451).Tumours include adenomas and carcinomas in duodenum, ileum or jejunum.

* Statistically significant ($p<0.05$) Fisher's exact test

** Statistically significant ($p<0.0001$) Fisher's exact test

(adapted from NTP, 2008; OEHHA 2011)

Different organisations (e.g. OEHHA[11], RAC[12], EFSA) modelled the data of this study using different approaches.

OEHHA derived Public Health Goals (PHG) for contaminants in drinking water. The method to estimate life-time cancer risks is based on a mutagenic mode of action for chromium VI, a linear extrapolation and the application of age sensitivity factors (U.S. EPA Cancer Guidelines, 2005). For the dose-response a lifetime time-weighted average dose was employed as the dose metric. The combined incidence data of adenomas and

[11] OEHHA derives Public Health Goals (PHG) for contaminants in drinking water. The method to estimate life time cancer risks is based on U.S. EPA Cancer Guidelines (2005), a mutagenic mode of action for chromium VI, a linear extrapolation and the application of age sensitivity factors.

[12] Committee for Risk Assessment of the European Chemicals Agency ECHA

carcinomas of the small intestine for male B6C3F1 mice and for female B6C3F1 mice were used as the outcome parameter. The mean and lower-bound estimates of the dose (ED10 and LED10) associated with a ten percent increase in tumours was obtained through a multistage model which takes into account competing risks and the age dependence of cancer rates.

The mouse dose associated with a 10-percent increase in the incidence in tumours was 1.2 mg/kg bw/d in male B6C3F1 mice. The lower bound estimate of this dose was 0.9 mg/kg bw/d. A factor of 0.164 was used to scale to a human equivalent dose based on the ratio of mouse to human body weight (a time-averaged weight of 0.050 kg was used for mice and a 70-kg adult human body weight: $(0.050 \text{ kg}/70 \text{ kg})^{0.25}$). The data from female mice only fit the model well when the high-dose group was excluded. The modelling yielded similar results in male and female mice. The potency was determined based on the slope of the exposure response relations. The slope factor is the tumour response, e.g., 10% divided by the dose associated with that response ie. 0.196 mg/kg bw/d. The multistage model yielded a slope factor of 0.1 / 0.196 mg/kg bw/d = 0.5 mg/kg bw/d based on the data of male B6C3F1 mice, which fit the data better (no discarded data points) than the data from female mice.

Table 3: Oral cancer potency estimates based on NTP data and OEHHA approach

Starting point	BMD10: 1.2 mg/kg bw/d
Allometric scaling	$(0.050 \text{ kg}/70 \text{ kg})^{1/4}$
Adjusted starting point	0.196 mg/kg bw/d
Statistical model	Multistage model Slope factor: 0.5 mg/kg bw/d
Dose corresponding with 1.00E-06 extra cancer risk	0.002 µg/kg bw/d
Age sensitive factor (children)	10
Dose corresponding with 1.00E-06 extra cancer risk for children	**0.0002 µg/kg bw/d**

According to REACH regulation for non-threshold carcinogens, a qualitative assessment must be made of the likelihood that effects are avoided when implementing the exposure scenario. In order to make this concept more precise, ECHA developed the concept of Derived Minimal Effect Levels (DMEL) based on adequate animal data using two approaches: 1) the "linearised" approach that includes a high-to-low dose extrapolation that by default is taken as linear and 2) the "large assessment factor" approach used by EFSA (see table 5). Both formats are based on similar principal elements of risk extrapolation and risk evaluation, using T25, BMD10 or BMDL10[13] as the dose-descriptor.

[13] Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health

The EFSA CONTAM Panel applied the BMD approach to analyse the data on the incidence of neoplastic effects using the default BMR of 10% extra risk for the incidence, the BMD10 and its 95% lower confidence limit. The Panel selected a lowest BMDL10 of 1.0 mg chromium VI/kg bw /d for combined adenomas and carcinomas of the small intestine in male and female mice as reference point (RP) for estimation of MOEs for neoplastic effects. The panel concluded that for substances that are both genotoxic and carcinogenic, a Margin of Exposure (MOE) of 10 000 or higher, based on a BMDL10 from an animal study, is of littleconcern from a public health point of view. This corresponds to a daily dose of 0.1 µg/kg bw (see table 4).

Using the "linearised" approach, the DMEL is calculated to be 0.002 µg/kg bw/d based on one additional cancer case in 100,000 or 0.0002 µg/kg bw/d based on one additional cancer case in 1,000,000 (see table 4), which corresponds to the value derived by OEHHA.

Table 4: Calculation of DMELs for chromium VI

	"Linearised" approach	**"Large assessment factor"**
Relevant Dose descriptor So far, for the "linearity" method it is proposed to use the BMD, while the EFSA method uses the BMDL.	1.2 mg/kg bw	1 mg/kg bw
Modification of the relevant dose descriptor For this scenario (general population, oral exposure) there is no need for a modification factor	not applied	not applied
Corrected Dose Descriptor	1.2 mg/kg bw	1 mg/kg bw
Interspecies extrapolation For the "linearity" approach only the allometric scaling factor is applied	7	10
Intraspecies extrapolation	not applied	10
Age factor	10	not applied
Nature of the carcinogenic process	not applied	10
Point of comparison	not applied	10
High to low dose extrapolation	10,000 (linearity, 1:100,000) 100,000 (linearity, 1:1.000.000)	not applied
Calculation of DMEL (corrected BMD/BMDL divided by overall assessment factor)	1.2 mg/kg/d / (7 * 10 * 10,000) = 0.000002 mg/kg/d 1.2 mg/kg/d / (7 * 10 * 100,000) = 0.0000002 mg/kg/d	1 mg/kg/d / 10,000 = 0.0001 mg/kg/d
DMEL (based on BMD/BMDL) 1:10,000 1:100,000 1:1,000,000	 - 0.002 µg/kg bw/d 0.0002 µg/kg bw/d	 0.1 µg/kg bw/d - -

3.4.2. Early life exposures

Children are generally considered to be more susceptible than adults to chemicals because of the higher exposure rates per unit of body weight and potentially higher susceptibility due to immature metabolism, immunologic response and other developmental aspects.

Physiologic differences between children and adults may result in age-related changes in pharmacokinetics and pharmacodynamics (Fernandez *et.al*. 2011) having an impact on

exposure and effects of chromium VI. Factors such as gastric pH and emptying time, intestinal transit time and immaturity of secretion among other factors may result in higher (or lower) bioavailability of chemicals entering the body. Specifically for oral exposure of chromium VI, it should be taken into account that the reductive capacity in children may be lower than in adults as a result of higher pH in the stomach. At birth, pH is practically neutral (6-8), then falls to approximately 1-3 within the first 24 h following birth, and later on gradually returns to neutrality by day 10 (Morselli *et al*., 1980, Bartelink *et al*., 2006). It slowly declines thereafter to reach adult values by the age of three years (Stewart *et al*., 1980). Changes in pH may result in a slower conversion of chromium VI to chromium III in children than in adults.

The proclivity of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, may result in additional ingestion of chromium from soil and dust.

Weighting factors are used to calculate cancer risks from exposures of infants, children and adolescents to reflect their anticipated special sensitivity to carcinogens. The OEHHA weighted cancer risks by a factor of 10 for exposures that occur from the third trimester of pregnancy to <2 years of age, and by a factor of 3 for exposures that occur from ≥2 years through <16 years of age. For OEHHA this approach applies to all carcinogens, regardless of the purported mechanism of action, unless chemical-specific data exist that could be used to make more specific adjustments to risk.

3.4.3. Migration limits for the exposure of children to chromium VI from toys

The current EU migration limits in the Toy Safety Directive 2009/48/EC have been derived on the basis of a daily virtual safe dose of 0.0053 µg/kg bw (OEHHA, 1999) and considering that 5% of this virtual safe dose is allocated to the exposure to chromium VI from toys.

The migration limits were calculated based on specific exposure scenarios and assumptions proposed by RIVM (2008) for different toy materials to include scraped-off toys, dry powder or pliable material and liquid and/or sticky material. This methodology for the assessment of the chemical safety of toys acknowledges that exposure to chemicals does not only occur from toys and that the exposure from toys only accounts for a small proportion of the overall exposure for a particular chemical. Therefore, in the current TSD, it was decided to allocate 5% of the virtual safe dose to the exposure to chromium VI from toys. Current migration limits for different toy materials are summarised in table 5.

Using the same approach but with the revised virtual safe dose for chromium VI of 0.0002 µg/kg bw/d, the maximum permissible migration limits for chromium VI would need to be lowered by a factor of 26.5. For the revised values see Table 5.

The SCHER additionally calculated migration limits using a less conservative approach (see the Annex). RIVM proposed amounts of toy materials directly ingested for scrapped-off toy material (8 mg), dry, powder-like or pliable toy materials (100 mg) and liquid or sticky toy materials (400 mg) (RIVM, 2008). While the default value for scrapped-off toy materials is recommended for all age groups, the default values for dry, powder-like or pliable toy materials as well as for sticky toy materials are proposed to apply to children under 3 years of age only, as very young children are the most likely to put toys in their mouths. For these toy materials, RIVM recommends a frequency of 1/week for the ingestion default values when the exposure is compared to a chronic health-based limit value. However, further research is needed concerning this estimation.

The SCHER calculated revised migration limits, which are proposed in table 5 and the Annex using formula 1.

$$ML = \frac{P_{VSD} \cdot VSD \cdot BW}{A_{MT} \cdot 100} \; x \; K \qquad \text{mg/kg toy material} \quad [1]$$

where:

ML	=	migration limit (mg/kg product)
P_{VSD}	=	percentage of VSD (5)
VSD	=	virtually safe dose (2.10^{-7} mg/kg bw/d)
BW	=	body weight (default 7.5 for children one year of age)
A_{MT}	=	amount of toy material (8, 100, or 400 mg)
100	=	conversion factor from percentage to fraction
K	=	conversion factor from mg/mg toy material to mg/kg toy material (10^6).

Table 5: Migration limit values for chromium VI from toys

	VSD (µg/kg/bw/d)	Migration Limit Value (mg/kg toy material) 5% VSD		
		Scraped-off toy materials	Dry, powder like or pliable toy materials	Liquid or sticky toy materials
		8 mg	100 mg	400 mg
Current VSD (OEHHA, 1999)	0.0053	0.2	0.02	0.005
Revised VSD (OEHHA, 2011)	0.0002	0.0094	0.0008	0.0002

conservative approach according to the current Toy Safety Directive, allocating 5% of VSD to toys, considering daily uptake of toy materials

(VSD = Virtual Safe Dose)

Considering the different sources for exposure to chromium VI, the SCHER is aware of a relevant background exposure. Depending on different scenarios, the virtual safe dose for children may be already reached or even exceeded via uptake of chromium VI from drinking water or through ambient air. For exposure to chromium VI via drinking water, EFSA concluded on a low concern (MOE values > 10 000) for all age groups with the exception of infants at UB exposure estimates (maximum UB - minimum LB: 6,300 – 71,000). When considering the 95th percentile exposure, MOE values below 10 000 were found at UB exposure estimates, particularly for infants (maximum UB - minimum LB: 3,100 – 21,000), toddlers (maximum UB - minimum LB: 4,200 – 62,000), and other children (maximum UB - minimum LB: 6,600 – 360,000).

For this reason, the SCHER recommends that for children any additional exposure to chromium VI from toys should be reduced to the lowest levels achievable. These levels may depend on BAT.

3.4.4. Test methods for migration of chromium from toys

The European Standard EN 71-3 (Safety of toys - Part 3: Migration of certain elements) includes methods of analysis for speciation of chromium III and VI. Detection of chromium VI, however, is greatly limited due to the high reactivity of chromium compounds. Interconversion between chromium III and chromium VI may occur during sample preparation and migration procedure. Therefore, the method developed for detection of chromium VI is not sufficiently sensitive for migration limits currently set for scrapped-off and dry, powder-like or pliable toy materials and compliance with the limits cannot be demonstrated. Limits of detection (LOD) and quantification (LOQ) are given in Table 6.

Table 6: LOD and LOQ values for chromium compounds according to EN 71-3

	LOD	LOQ
Chromium (total)	0.023	0.046
Chromium III	0.064	0.128
Chromium VI	0.026	0.053

To overcome analytical limitations, the following options are recommended in EN 71-3: (a) to determine the migration limit of total chromium (i.e. chromium III + chromium VI). If the migration of total chromium is below the maximum limit for chromium VI, it can be inferred that the material complies with the requirements for both chromium III and chromium VI; (b) to perform a safety assessment of the toy material.

The SCHER is aware that lowering the migration limits for chromium VI from toys would make it more difficult to demonstrate compliance with the legislation.

3.4.5. Uncertainties

Major uncertainties in the assessment of the potential oral cancer risk from chromium VI in toys are related to (1) the extrapolation from high-dose exposure in experimental animals to low-dose exposure by migration from toys, (2) the variability of reduction and absorption of ingested chromium VI and differences in reduction and absorption between humans and rodents as well as (3) the variability of background exposure. While uncertainties under (1) may result in over-estimation, uncertainties (2) and (3) have the potential to cause both over- as well as under-estimation of exposure and risk.

4. OPINION

The SCHER was asked:

1. ***to review the available scientific data and conclusions drawn for chromium VI in the light of the OEHHA technical support document for the Public Health Goal for hexavalent chromium in drinking water, of July 2011*****;***

The SCHER reviewed the OEHHA technical support document for the Public Health Goal for chromium VI in drinking water as well as additional recently published scientific documents on the health effects of chromium VI in order to assess the relevance of the oral cancer potency for the safety levels laid down for chromium VI in the Toy Safety Directive. The SCHER is of the opinion that the US-National Toxicology Program (NTP) study provides sound scientific evidence on the occurrence of oral and gastro-intestinal cancer after oral uptake of chromium VI in animals.

Chromium VI is well known to induce lung cancer in humans after inhalation. An impact of chromium VI after oral exposure may be expected. Although it is obvious that chromium VI is metabolised to chromium III in the gastro-intestinal tract, the SCHER is of the opinion that the reductive capacity might not be sufficient to completely convert chromium VI into chromium III and to prevent genotoxic effects.

Available studies allow the quantification of the dose response relationship both for carcinogenic and non-carcinogenic endpoints, and a virtual safe dose as well as a TDI can be derived from the data. The SCHER is of the opinion that the general approach from OEHHA is appropriate to estimate additional cancer cases attributed to chromium VI exposure. The virtual safe dose for one additional cancer case in a million derived from the approach performed by OEHHA (0.0002 µg/kg bw/d) is in the same range as a DMEL derived by the "linearised" approach used for REACH (0.0002 µg/kg bw/d).

2. ***to consider whether the migration limits for chromium VI in point 13 of section III of Annex II of the Toy Safety Directive 2009/48/EC are still appropriate to ensure the safety of toys;***

The current migration limits are based on a highly uncertain virtual safe dose of 0.0053 µg/kg bw/d associated with one additional cancer case in a million, suggested by OEHHA in 1999 in the absence of data for oral cancer potency. Based on the 2008 NTP study, OEHHA derived a daily dose of 0.0002 µg/kg bw associated with one additional cancer case in a million. The SCHER is of the opinion that the current migration limits for chromium VI from toys should be revised and based on the new, lower value for a virtual safe dose.

3. ***to propose if the current limits are no longer appropriate, new limits, clearly indicating the data on which they would be based.***

Considering a virtual safe dose of 0.0002 µg/kg bw/d based on data from the 2008 NTP study and using the current approach of the Toy Safety Directive, the SCHER proposes the following revised migration limits for chromium VI: 0.0094 mg/kg toy for scraped-off toy materials, 0.0008 mg/kg toy material for dry, (powder-like or pliable) toy materials and 0.0002 mg/kg toy material for liquid or sticky toy materials, respectively. The SCHER acknowledges that new data for the amount of toy material ingested may be discussed and may lead to different migration limits in the future (see the Annex).

The SCHER recognises that the proposed migration limits are conservative and may not be achieved for certain toy materials. The Committees, also points out that detection methods for chromium VI migration are affected by limitations and may not be sufficiently sensitive.

However, the SCHER is of the opinion that children are a vulnerable subgroup with respect to exposure to chromium VI. Considering relevant background exposure, any additional exposure to chromium VI from toys should be minimised to the lowest achievable levels using the best available technology.

5. MINORITY OPINION

None.

6. CONSIDERATION OF THE RESPONSES RECEIVED DURING THE CONSULTATION PROCESS

A public consultation on this Opinion was opened on the website of the non-food scientific committees between 06 June and 21 July 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Thirteen organisations and individuals provided total of 95 comments to different chapters and subchapters of the Opinion during the public consultation. Among the organisations participating in the consultation were institutes of public health, public authorities and private companies, notably from the toy industry.

Each contribution was carefully considered by the SCHER and the scientific opinion has been revised to take account of relevant comments. The reference list has been accordingly updated with relevant publications. The scientific rationale and the opinion section were clarified and strengthened.

The text of the comments received and the response provided by the SCHER is available here:
http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scher_consultation_09_en.htm

7. LIST OF ABBREVIATIONS

ADD	Acceptable Daily Dose
ATSDR	US Agency for Toxic Substances and Disease Registry
BAT	Best available technology
BMD10	Benchmark Dose, defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response
CCA	Copper Chrome Arsenate
CDPH	California Department of Public Health
Chromium VI	Hexavalent Chromium
CSTEE	Scientific Committee on Toxicity, Ecotoxicity, and the Environment
DMEL	Derived Minimal Effect Level
DNA	Deoxyribonucleic acid
ECB	European Chemicals Bureau
ECDC	European Centre for Disease prevention and Control
ECHA	European Chemicals Agency
ED10	The dose corresponding to a 10% increase in an adverse effect, relative to the control response
EFSA	European Food Safety Authority
EHD	Environmental Health Department, Glasgow
EMA	European Medicines Agency
EPA	United States Environmental Protection Agency
EU	European Union
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
LD50	Acute oral median lethal doses
LED10	Lower Limit on Effective Dose 10 - The 95% lower confidence limit of the dose of a chemical needed to produce an adverse effect in 10 percent of those exposed to the chemical, relative to control
LOAEL	Lowest Observed Adverse Effect Level
MOA	Mutagenic Mode of Action
MRL	Minimal risk level

NOAEL	No Observed Adverse Effect Level
NJDEP	New Jersey Department of Environmental Protection
NTP	National Toxicology Program
NOAEL	No Observed Adverse Effect Level
OEHHA	Office of Environmental Health Hazard Assessment, California
PBK	Physiologically-based kinetic
PHG	Public Health Goal
RAC	Committee for Risk Assessment, ECHA
RAPEX	European Union Rapid Alert System for non-food dangerous products
RBC	Red Blood Cells
RIVM	the Netherlands National Institute for Public Health and the Environment
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SGA	Sacramento Groundwater Authority
SMR	Standardised Mortality Ratio
TDI	Tolerable Daily Intake
TSD	Toy Safety Directive
USA	United States of America
US-NTP	United States National Toxicology Programme
VSD	Virtually Safe Dose
WHO	World Health Organization

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9. Annex

Migration limit values for chromium VI from toys based on lower amounts of toy materials ingested by children > 3 years of age as proposed by RIVM (2008)

	VSD (µg/kg/bw/d)	Migration Limit Value (mg/kg toy material) 5% VSD		
		Scraped-off toy materials	Dry, powder like or pliable toy materials	Liquid or sticky toy materials
		8 mg	14.3 mg	57.1 mg
Current VSD (OEHHA, 1999)	0.0053	0.2	0.02	0.005
Revised VSD (OEHHA, 2011)	0.0002	0.0094	0.0053	0.0013

allocating 5% of VSD to toys, approach considering daily uptake of scrapped-off toy materials and weekly uptake of dry, powder-like or pliable toy materials as well as of sticky toy materials

(VSD = Virtual Safe Dose)