Scientific Committee Health and Environmental Risks

SCHER

Preliminary opinion on chromium VI in toys

SCHER approved this opinion by written procedure on 23rd of July 2014

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SCHER

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All Declarations of Working Group members are available at the following webpage: http://ec.europa.eu/health/scientific_committees/environmental_risks/members_committee/index_en.htm

ABSTRACT

Scope of this opinion is 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 gastrointestinal cancer in animals after oral uptake of chromium VI was shown. Due to the mode of action there is evidence, that carcinogenic effects observed in experimental animals are also of relevance for humans. A virtual safe dose was derived and new values for migration limits for chromium VI from toys were recommended. 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.

Keywords: Scientific opinion, Chromium VI, toys

Opinion to be cited as:

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EXECUTIVE SUMMARY

The SCHER has evaluated recent data from animal studies on carcinogenicity after oral uptake by drinking water in order to derive safe migration limits for chromium VI from toys. Those data were used by the Californian Office of Environmental Health Hazard Assessment (OEHHA) to derive a Public Health Goal (PHG) for chromium VI in drinking water. A PHG is the level of a chemical contaminant in drinking water that does not pose a significant health risk.

The SCHER is of the opinion that the general approach of OEHHA is justified in order to estimate additional cancer cases attributed to oral chromium VI exposure from drinking water. Recently also the International Programme on Chemical Safety (IPCS) 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 are also of relevance for humans. Although chromium VI may be rapidly converted to chromium III in biological tissues, the reductive capacity 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. The SCHER is of the opinion, that children are a vulnerable subgroup and therefore an additional safety factor of 10 for an exposure at early life stages is justified. Studies available allow 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 $10^{6,}$). This dose could be considered as a virtual safe dose[1].

The current European Union (EU) migration limits have been 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. The SCHER is of the opinion, that the current migration limits for chromium VI from toys should be revised to take into account this new, lower value.

Migrations limits for chromium VI are allocated to 5% of the virtual safe dose according to the Toy Safety Directive 2009/48/EC. The SCHER proposes new migration limits of

[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),

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. However, considering the different sources for exposure to chromium VI, the SCHER is aware of a considerable background exposure. Depending on different scenarios, the virtual safe dose may be reached or even exceeded for children already via uptake of chromium VI from food and 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.

1. BACKGROUND

The Toy Safety Directive (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 behaviour of children.

The migration limits are based on a 2008 report of the Netherlands National Institute for Public Health and the Environment (RIVM)[2] and the opinion of the Scientific Committee[3]. In the 2010 SCHER opinion on the evaluation of migration limits for chemical elements in toys, 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[4] SCHER also recommended the amount allocated to exposure from toys to be limited to a maximum of 10%.

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."

Based on findings of this recent study, a Public Health Goal (PHG) of 0.02 parts per billion (ppb) for hexavalent chromium 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[5]. A final technical support document for the PHG was published in July 2011 (OEHHA, 2011).

2. TERMS OF REFERENCE

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

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2 http://www.rivm.nl/bibliotheek/rapporten/320003001.pdf
3 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
4 http://ec.europa.eu/health/archive/ph_risk/committees/sct/documents/out235_en.pdf
5 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

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 in the environment is almost totally derived from human activities (WHO, 1990). An important source is production and use of chromium compounds (mainly chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate) as well as 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 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 during 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) and *Public Health Goal for Hexavalent Chromium in Drinking Water*, California Environmental Protection Agency (OEHHA, 2011). The SCHER focused mainly on information of 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 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 within minutes (De Flora *et al*. 1997). There is a large inter- and intra-individual variability in humans since the conversion depends on the gastric content and on pH. Absorption of chromium VI in adult humans varies between 0.5% and 18% when studied in volunteer experiments. 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 (Finley *et al*. 1996; Finley *et al*. 1997; Kerger *et al*. 1996). For chromium VI administered as potassium chromate or dichromate absorption in humans after oral exposure 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 was recovered in the urine in humans with an average half-life of 39 hours (Kerger *et al*. 1996).

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 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). The half-life of chromium in various tissues of rats administered chromium VI was long and exceeded 20 days.

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 unspecific anion channels. Inside the cell, highly reactive chromium VI is thought to directly damage macromolecules or generate reactive metabolites that damage macromolecules, thereby inducing toxic effects. In the cell it is possible that chromium III also provides toxic effects, as chromium III is capable of binding to proteins and peptides (Chun *et al*. 2010; Nickens *et al*. 2010; Sugden and Stearns, 2000). *In vitro* studies have shown mutagenicity of chromium VI compounds in bacterial tests. Exposure of various types of mammalian cells demonstrated genotoxicity such as DNA interstrand crosslinks, DNA strand breaks and DNA–protein crosslinks (Cohen *et al*. 1993).

Also *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). Occupational exposure through inhalation has been shown to cause DNA damage in the lymphocytes (IARC, 2012). At present it is unclear whether significant DNA damage is likely to result from low environmental exposures to chromium VI due to

the reductive capacities of the lung for inhalation exposures or the stomach for oral exposures (de Flora, 2000).

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). 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).

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 2 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, although not given alone, enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects (Davidson *et al*. 2004). The NTP conducted a 2-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 gastrointestinal 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). 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. Mainly workers in chromate production, chromate pigment production and chromium electroplating have been 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.

Inhalation in occupationally exposed workers induced effects in the airways such as nasal mucosal ulceration and septal perforation. Also changes in lung function parameters were observed. Exposure was estimated based on exposure period as the time from hire to occurrence of the first findings, and the mean and median annual chromium VI concentrations for the job title where the clinical findings 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, 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 gastrointestinal 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 especially in the estimation of the exposure (Brandt-Rauf, 2006; Beaumont *et al*. 2008 and follow-up author correspondence; Smith, 2008).

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 geographical variations as well as 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 e.g. pH, the amount of organic matter or 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 reductants for chromium VI exist, it will be assumed that the rate of reduction of chromium VI to chromium III is slow, with a half-life of around 1 year. 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, food, 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 production and use of five chromium VI compounds. Estimated concentrations in water and fish, and for two process steps also concentrations in 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 as the average concentration of chromium in the urine of children at ages five and younger was significantly higher than in adults residing near industrial sites where chromium waste was used (Fagliano *et al*. 1997). The behaviour of young children to ingest soil, either intentionally, through pica[6] 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

[6] Pica is an eating behaviour, typically defined as the persistent eating of non-nutritive substances like clay, sand, stones and pebbles.

(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 for contaminated soils it is known that 10 to 29% of total chromium in soil were 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[7] was chosen for the assessment as well as a body weight of 10 kg[8], as mainly small children are 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 related to different soil composition 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
Uptake (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.

[7] Default value related to EPA, 1999; EPA 2011

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

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.

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). However, 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, chromium species 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. 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 levels between 41 and 50 µg/L, 14 sources levels between 31 and 40 µg/L, and 61 sources 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. A 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).

The SCHER used the reported data to estimate the exposure to chromium VI from drinking water for children. Three values for the amount of chromium VI in drinking water were chosen, 1 µg/L for the best case, 10 µg/L for the average case and 50 µg/L for the worst case scenario. The amount of drinking water used was 0.75 L/d for infants and toddlers and 1 L/d for children. Values chosen for body weight were 10 and 25 kg, respectively. Default values were chosen considering EFSA guidelines (EFSA, 2012; EFSA, 2010). 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.

Table 2: Exposure assessment for the uptake of chromium VI by children from drinking water

		best case	average case	worst case
Chromium VI	µg/L	1	10	50
Consumption infants and toddlers	L/d	0.75	0.75	0.75
Bodyweight	kg	10	10	10
Exposure (10% absorption from gut)	µg/kg bw/d	0.0075	0.075	0.375
Chromium VI	µg/L	1	10	50
Consumption children	L/d	1	1	1
Bodyweight	kg	25	25	25
Exposure (10% absorption from gut)	µg/kg bw/d	0.004	0.04	0.2

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 yellow 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. Products for children and babies (e.g. shoes, leather baby shoes, crawling shoes and wooden toys) were also reported to contain considerably high contents of 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. 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 are also of relevance for humans. Although chromium VI may be rapidly converted to chromium III in biological tissues, the reductive capacity 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. For proposing revised migration limits therefore, the SCHER 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 an additional safety factor of 10 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 2 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 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 be afflicted with 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 3.

Table 3: 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. RAC[9], OEHHA[10]) modelled the data set to derive a BMD10[11] (OEHHA) or a BMDL10 (RAC). For the dose-response a lifetime time-weighted average

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

[10] 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.

dose was employed as the dose metric. The combined incidence data of adenomas and 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 fitted the model well only 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 fitted the data better (no discarded data points) than the data from female mice.

Table 4: 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**

3.4.2. Early life exposures

Early life exposures to carcinogens may result in greater lifetime risk compared to exposures later in life (OEHHA, 2009). 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 lower pH in the stomach. Infants' stomachs are near neutral pH

[11] A BMD is defined as a statistical lower confidence limit on the dose producing a predetermined level of change in adverse response compared with the response in untreated animals (EPA, 1995) and frequently used

during the first days to weeks after birth, and stomach pH levels generally remain higher than adults during the first three months of life, leading to the assumption that conversion of chromium VI into chromium III may be less in children compared to adults (OEHHA, 2001). 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. Children may also be exposed to chromium via the environment to a greater extent than adults as the average concentration of chromium in the urine of children at ages five and younger was significantly higher than in adults residing near industrial sites where chromium waste was used (Fagliano *et al*. 1997). The behaviour 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.

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, 5% of the virtual safe dose was decided to be allocated to the exposure to chromium VI from toys. Current migration limits for the different toy materials are summarised in table 5.

Using the same approach but the new 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. The SCHER calculated revised migration limits, which are proposed in table 5 (see below) using formula 1.

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

in risk assessment.

where:

ML = migration limit (mg/kg product)

PVSD = percentage of VSD (5)

VSD = virtually safe dose (0.0000002 mg/kg bw/d)

BW = body weight (default 7.5 for children one year of age)

AMT = 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).

Considering the different sources for exposure to chromium VI, the SCHER is aware of a considerable background exposure. Depending on different scenarios, the virtual safe dose may be reached or even exceeded for children already via uptake of chromium VI from food and drinking water or through ambient air. 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.

Table 5: Migration limit values for chromium VI from toys (VSD = Virtual Safe Dose)

Chromium VI	VSD (µg/kg/bw/d)	Migration Limit Value (mg/kg toy material) 5% VSD		
		Scraped-off toy materials (8 mg)	Dry, powder like or pliable toy materials (100 mg)	Liquid or sticky toy materials (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

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 further scientific documents on 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 NTP study provides scientific evidence on the occurrence of oral and gastrointestinal cancer after oral uptake of chromium VI in animals. Chromium VI is genotoxic and the mode of action implies that carcinogenicity may occur at the sites of contact within the body.

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, the reductive capacity might not be sufficient in order to completely prevent genotoxic effects. The SCHER considered the general approach from OEHHA appropriate in order to estimate additional cancer cases attributed to chromium VI exposure. Studies available 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.

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 new 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, taking into account 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 the virtual safe dose of 0.0002 µg/kg bw/d based on new data from the NTP study, the revised migration limits for chromium VI are proposed to be 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 (see table 5). These migration limits are calculated according to the procedure recommended by RIVM (2008) and in accordance with the Toy Safety Directive.

The SCHER is also of the opinion that children are a vulnerable subgroup with respect to exposure to chromium VI and therefore supports the additional safety factor proposed by OEHHA. In the view of a considerably high background exposure, any additional exposure to chromium VI from toys should be minimised to the lowest achievable levels.

5. MINORITY OPINION

None

6. LIST OF ABBREVIATIONS

ADD	Acceptable Daily Dose
ATSDR	US Agency for Toxic Substances and Disease Registry
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
Chromium VI	Hexavalent Chromium
CSTEE	Scientific Committee on Toxicity, Ecotoxicity, and the Environment
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
EMA	European Medicines Agency
EU	European Union
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
NTP	National Toxicology Program
NOAEL	No Observed Adverse Effect Level
OEHHA	Office of Environmental Health Hazard Assessment, California
PHG	Public Health Goal
RAPEX	European Union Rapid Alert System
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
SMR	Standardised Mortality Ratio
TDI	Tolerable Daily Intake
TSD	Toy Safety Directive
USA	United States of America
US-NTP	United States National Toxicology Programme
US EPA	United States Environmental Protection Agency
VSD	Virtually Safe Dose
WHO	World Health Organization

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