European Chemicals Agency (ECHA), Helsinki

Services to support the assessment of remaining cancer risks related to the use of chromium- and arsenic-containing substances in Applications for Authorisation.

Service Request
under the Multiple Framework Contract with re-opening of competition
for scientific services for ECHA

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FINAL REPORT FOR

HEXAVALENT CHROMIUM

NOVEMBER 2013

Consortium ETeSS
Expert Team providing scientific support for ECHA

CONTENTS

1 INTRODUCTION

The project specification requires a review of the relevant scientific literature related to the carcinogenicity of the chromium VI-containing compounds listed in table 1.1 below (Work Package 1-WP1) and the establishment of relevant carcinogenicity dose-response curves for each of these substances (Work Package 2-WP 2) for the purpose of Authorisation under REACH.

Table 1.1: Cr(VI) compounds considered in this project (with their chemical identifiers and carcinogenicity classification in Annex VI of CLP Regulation)

No	Name of the substance	EC no	CAS no	Carcinogenicity C&L in Annex VI of CLP Regs
1	Lead sulfochromate yellow (C.I. Pigment Yellow 34)	215-693-7	1344-37-2	Carc 1B
2	Lead chromate	231-846-0	7758-97-6	Carc 1B
3	Lead chromate molybdate sulphate red (C.I. Pigment Red 104)	235-759-9	12656-85-8	Carc 1B
4	Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid	231-801-5; 236-881-5	7738-94-5: 13530-68-2	Carc 1B
5	Ammonium dichromate	231-143-1	7789-09-5	Carc 1B
6	Chromium trioxide	215-607-8	1333-82-0	Carc 1A
7	Potassium chromate	232-140-5	7789-00-6	Carc 1B
8	Potassium dichromate	231-906-6	7778-50-9	Carc 1B
9	Sodium chromate	231-889-5	7775-11-3	Carc 1B
10	Sodium dichromate	234-190-3	7789-12-0; 10588-01-9	Carc 1B
11	Pentazinc chromate octahydroxide	256-418-0	49663-84-5	Carc 1A
12	Dichromium tris(chromate)	246-356-2	24613-89-6	Carc 1B
13	Potassium hydroxyocataoxodizincatedichromate	234-329-8	11103-86-9	Carc 1A
14	Strontium chromate	232-142-6	7789-06-2	Carc 1B

We have identified and obtained existing detailed, good-quality reviews of the carcinogenicity of hexavalent chromium (Cr(VI)) compounds, including quantitative risk assessments, published in the scientific literature or by particular authorities around the world since the year 2000. These are outlined in table 1.2 below:

Table 1.2: Outline of reviews/publications of Cr(VI) compounds used as the basis of this project

Reference/year	Title	Organisation	Content/aim of publication
SCOEL, 2004	Recommendation from SCOEL: Risk assessment of hexavalent chromium	Scientific Committee on Occupational Exposure Limits, EU DG Employment	Hazard and risk assessment of Cr(VI) compounds for the purpose of setting an Indicative Occupational Exposure Limit Value (IOELV)
OSHA, 2006	Occupational Exposure to hexavalent chromium	Occupational Safety and Health Administration, USA	Hazard and risk assessment of Cr(VI) compounds for the purpose of setting a Threshold Limit Value (TLV) for workers
Goldbohm et al., 2006	Risk estimation of carcinogens based on epidemiological data: a structured approach, illustrated by an example on chromium	n.a.	Methodology for quantitative cancer risk assessment on the basis of epidemiological data – Cr(VI) compounds used as a case study
Draft USEPA, 2010*	Toxicology review of hexavalent chromium. In support of summary information on IRIS	Environmental Protection Agency, USA	Hazard and risk assessment of Cr(VI) compounds for the purpose of establishing oral standards for the general population
ATSDR, 2012	Toxicological profile for chromium	Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services	Hazard assessment of Cr(VI) compounds aimed at health care providers
IARC, 2012	Chromium (VI) compounds. Monograph on the evaluation of carcinogenic risks to humans	International Agency for Research on Cancer, Lyon, France	Cancer hazard assessment of Cr(VI) compounds for categorisation purposes
TERA, 2012	ITER (International Toxicity Estimates for Risk) White Paper – In support of the inhalation cancer risk assessment of hexavalent chromium	Toxicity Excellence for Risk Assessment, Cincinnati, USA	Cancer hazard assessment of Cr(VI) in support of inhalation quantitative risk evaluation
Seidler et al., 2012	Systematic review and	n.a.	Inhalation cancer risk assessment of Cr(VI)

	quantification of respiratory cancer risk for occupational exposure to hexavalent chromium		for workers

n.a. = not applicable
*This document is still a draft – however, the contractor has obtained permission from the USEPA to cite and use it

In addition, we have identified and obtained individual studies cited in these reviews that have been crucial to the overall position developed by each review; and any other more recent relevant studies not included in these reviews.

Our approach has been to build on these reviews by adding new evidence that has become available in more recent years and by identifying the studies key to cancer dose-response analysis and risk estimation.

As the focus of the project is cancer risk assessment of Cr(VI) compounds, attention has been given mainly to carcinogenicity data by the inhalation, oral and dermal routes of exposure. In addition, toxicokinetic data and Mode-of-action (MoA) information, including genotoxicity data have been considered, as this information is relevant to the characterisation of cancer risks.

Cr(VI) compounds have been classified as human carcinogens by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) and by authorities of most industrialized nations. This classification is based mainly on the results of epidemiological studies linking Cr(VI) to lung cancer. Under the CLP (classification, labelling and packaging) Regulations of the European Union, Cr(VI) trioxide, pentazinc chromate octahydroxide and potassium hydroxyocataoxodizincatedichromate are classified as human carcinogens (Category 1A). The chromates of potassium, sodium, calcium, strontium and lead and all other not-specified Cr(VI) compounds are classified as carcinogenic to animals (Category 1B).

2 PHYSICAL-CHEMICAL PROPERTIES

Cr(VI) compounds represent one of a number of oxidation states in which chromium occurs. Chromates and dichromates exist as a wide variety of compounds with 20 to 30 being of major industrial importance. These include ammonium chromate and dichromate, barium chromate, calcium chromate and dihydrate, chromic chromate, chromium chloride, chromium trioxide (chromic acid), chromyl dichloride, lead chromates, potassium chromate and dichromate, sodium chromate and dichromate and zinc chromates. The solubility of chromates varies widely and ranges from virtually insoluble to highly soluble. The various uses of the term solubility have caused much confusion and to harmonise discussions and classification it has been proposed (Cross et al., 1997) that the water solubility of Cr(VI) compounds can be defined as: poorly soluble (<1 g/L), sparingly soluble (1 - 100 g/L); highly soluble (>100 g/L). Thus, poorly soluble includes lead and barium chromate, sparingly soluble includes strontium, calcium and zinc chromate and highly soluble would include sodium and potassium chromates and dichromate (SCOEL, 2004).

In the United States of America, the Occupational Safety and Health Administration (OSHA) has divided Cr(VI) compounds and mixtures into the following three categories: water-insoluble (solubility < 0.01 g/L), slightly soluble (solubility 0.01 g/L – 500 g/L), and highly water-soluble (solubility ≥ 500 g/L) (OSHA, 2006).

Fitting the water solubility data of the 14 Cr(VI) compounds under consideration to both schemes gives very comparable results. Results are presented in table 2.1 below. Only pentazinc chromate octahydroxide is considered to be insoluble according to the SCOEL scheme and sparingly soluble according to the OSHA scheme.

Table 2.1: Solubility classification of the 14 Cr(VI) compounds considered in this project according to SCOEL and OSHA schemes

Name of the substance	EC no	Water solubility (g/L)	SCOEL solubility classification scheme	OSHA solubility classification scheme
Lead sulfochromate yellow (C.I. Pigment Yellow 34)	215-693-7	$1.4x10^{-4}$ - $3.8x10^{-4}$		
Lead chromate	231-846-0	$5.8x10^{-5}$ - $5.8x10^{-4}$		
Lead chromate molybdate sulphate red (C.I. Pigment Red 104)	235-759-9	$< 10^{-5}$		
Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid	231-801-5; 236-881-5	617-1000 (chromic acid)		

Ammonium dichromate	231-143-1	308-890		
Chromium trioxide	215-607-8	617-1668		
Potassium chromate	232-140-5	394-792		
Potassium dichromate	231-906-6	49-1020		
Sodium chromate	231-889-5	873		
Sodium dichromate	234-190-3	2300-5080		
Pentazinc chromate octahydroxide	256-418-0	< 0.5 and < 0.02		worst case
Dichromium tris(chromate)	246-356-2	31 (CrVI)		
Potassium hydroxyocataoxodizincatedichromate	234-329-8	0.5-1.5 g/l		
Strontium chromate	232-142-6	1.2-30		

Horizontal lines = insoluble; Clear = highly soluble; Black = sparingly/slightly soluble

Therefore, in order to classify the 14 Cr(VI) compounds concerned in relation to their solubility, we would give preference to the scheme used by OSHA (2006), because the domain of the sparingly soluble substances, which might have a higher carcinogenic potency than insoluble and highly soluble Cr(VI) compounds (see later in the document), covers a wider range of solubilities (0.01 - 500 g/L) than the scheme used by SCOEL (1 - 100 g/L). Table 2.2 below shows the categorization of the 14 Cr(VI) compounds of interest according to the solubility scheme proposed by OSHA (2006).

Table 2.2: Solubility categorization of the 14 Cr(VI) compounds under consideration

Highly soluble Cr(VI) compounds according to OSHA (2006) scheme (water solubility > 500 g/L)	**Sparingly/slightly soluble** Cr(VI) compounds according to OSHA (2006) scheme (water solubility 0.01 – 500 g/L)	**Insoluble** Cr(VI) compounds according to OSHA (2006) scheme (water solubility < 0.01 g/L)
Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid; Ammonium dichromate; Chromium trioxide; Potassium chromate; Potassium dichromate; Sodium chromate; Sodium dichromate	Pentazinc chromate octahydroxide; Dichromium tris (chromate); Potassium hydroxyocataoxodizincatedichromate; Strontium chromate	Lead sulfochromate yellow (C.I. pigment yellow 34); Lead chromate; Lead chromate molybdate sulphate red (C.I. Pigment Red 104);

Cr(VI) compounds are mostly lemon-yellow to orange to dark red in colour. They are typically solid (i.e. crystalline, granular, or powdery) although one

compound (chromyl chloride) is a dark red liquid that decomposes into chromate ion and hydrochloric acid in water (OSHA, 2006).

The molecular entity that drives the carcinogenicity of these Cr(VI) compounds is the Cr(VI) ion, which is released when these substances solubilise and dissociate in biological fluids. Therefore, this document, similarly to other international reviews of Cr(VI) compounds, will use Cr(VI) as the relevant dose metric. Table 2.3 below shows for each of the 14 Cr(VI) compounds under consideration, which percentage of the total mass constitutes Cr(VI). For the three substances containing lead (i.e. lead sulfochromate yellow, lead chromate and lead chromate molybdate sulphate red), it is also possible that the Pb ion could contribute to their toxicity. However, there is no evidence that lead has caused cancer in humans, leading to the conclusion that Cr(VI) is also the relevant dose metric for the carcinogenicity of these lead chromates.

Table 2.3: Cr(VI) content of the 14 Cr(VI) substances under consideration

No	Name of the substance	Percentage of Cr(VI)*
1	Lead sulfochromate yellow (C.I. Pigment Yellow 34)	10.94%
2	Lead chromate	16.09%
3	Lead chromate molybdate sulphate red (C.I. Pigment Red 104)	11.52%
4	Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid	47.70% (dichromic acid) 44.06% (chromic acid)
5	Ammonium dichromate	41.26%
6	Chromium trioxide	52.0%
7	Potassium chromate	26.78%
8	Potassium dichromate	35.35%
9	Sodium chromate	32.10%
10	Sodium dichromate	39.70%
11	Pentazinc chromate octahydroxide	8.98%
12	Dichromium tris(chromate)	57.52%
13	Potassium hydroxyocataoxodizincatedichromate	24.82%
14	Strontium chromate	25.54%

*for the most typical composition (where this varies) of each substance

3 CANCER HAZARD ASSESSMENT (WP 1)

3.1 Cancer hazard identification

3.1.1 Carcinogenicity

3.1.1.1 Inhalation

3.1.1.1.1 Human data

A large number of case reports dating to the late 19th and early-to-mid-20th centuries raised suspicions that workers in various industries with exposure to Cr(VI) compounds, including chromate production, production of chromate pigments and chromium plating may be at risk of developing various cancers (Newman, 1890; Pfeil, 1935; Teleky, 1936; IARC, 1990 cited in IARC, 2012). Beginning in the mid-20th century, cohort mortality studies were undertaken in these industries as well as in some other occupations and industries with potential exposure to chromium compounds, such as ferrochromium or stainless steel production, welding, leather tanning, and some others. These studies aimed at investigating associations between exposure to Cr(VI) and mortality by varying diseases (assessed from the underlying cause of death on the death certificates of the cohort members). By the 1980s considerable evidence had accumulated on cancer risks of Cr(VI)-exposed workers leading to the identification of Cr(VI) compounds as human carcinogens (IARC, 1990).

IARC (2012) concluded that the large majority of the informative cohort studies indicate that there is an excess risk of lung cancer (type and site not further specified) among workers exposed to Cr(VI), particularly in chromate production (Mancuso 1975; Mancuso, 1997; Hayes et al., 1979; Gibb et al., 2000; Luippold et al., 2003, Crump et al., 2003; Proctor et al., 2003, 2004; Park et al., 2004, Park & Stayner, 2006 cited in IARC, 2012), chromate pigment production (Davies, 1979; Davies 1984a and b, Hayes et al., 1989 cited in IARC, 2012), and chromium electroplating (Sorahan et al., 1987 cited in IARC, 2012, Hara et al., 2010 cited in ATSDR, 2012). It is unlikely that any biases or chance can explain these findings (see table 3.1 below for more details of studies).

Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered (Luippold et al., 2005 cited in IARC, 2012), but these latter analyses had few subjects and low power (IARC, 2012). These studies in chromate production workers provide the strongest dose-response relationships between lung cancer mortality and cumulative exposure to Cr(VI) (ATSDR, 2012).

Studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and sub-cohorts reported, though not every relative risk estimate was statistically significant. Also, among chromium electroplating workers, there was a clear pattern of excess risks in

most cohorts (IARC, 2012). These studies found significant elevations in lung cancer risk in association with surrogate indicators of Cr(VI) exposure, such as duration of employment at jobs in which exposure to Cr(VI) occurred; however, estimates of risks attributable specifically to Cr(VI) exposure were not reported (ATSDR, 2012).

Workers in other industries (stainless steel welding, ferrochromium production, leather tanning) who may have had somewhat lower levels of Cr(VI) exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates (IARC, 2012). Results from these studies remain inconclusive with respect to work-associated elevations in lung cancer rates (ATSDR, 2012).

A few of the cohort studies in chromate production, pigment production and electroplating collected high-quality smoking histories, and incorporated these into nested case–control analyses; these tended to show elevated risks independent of smoking. Several other studies had collected partial or representative smoking frequencies among their workers, and for most of these studies, the main results were unlikely to have been meaningfully confounded by smoking patterns in the workers.

A review of 10 cohort studies of chromate production workers, chromate pigment production workers and chromium platers estimated a mean standardized mortality ratio (SMR) for lung cancer of 278 (Steenland et al., 1996 cited in SCOEL, 2004). A recent meta-analysis estimated an overall SMR of 141 (95%CI: 135–147) for lung cancer among 47 studies of workers with possible Cr(VI) exposure (Cole & Rodu, 2005 cited in IARC, 2012).

Very few of the available epidemiological studies provided results relating to specific Cr(VI) compounds. Workers in chromate production were likely to have been exposed to mixtures of sodium, potassium, calcium and ammonium chromates and dichromates; the highest and most consistent excess risks were observed in these cohorts. Workers in chromate pigment production and spray painting were likely to have been exposed to zinc and/or lead chromates, also resulting in high risks. Steel smelting and welding probably resulted in exposure to alkaline chromates, and risks reported in these cohorts tended to be less clear than among the chromate producers and the chromate pigment producers (IARC, 2012).

Table 3.1: Cohort studies of Cr(VI) and lung and respiratory cancer (from IARC, 2012)

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
Chromate production								
Brinton et al (1952) US	5522 person-years in 7 chromate production plants: employed 1940-50, followed 1946-50			All workers	26	28.9	[18.87-42.35]	SMR ref US
Enterline (1974) US	1200 workers in 3 chromate production plants employed 1937-40, followed 1941-60		All respiratory cancers	All workers	69	9.43	[7.34-11.93]	SMR ref US
Satoh et al (1981) Tokyo	896 chromium compound production workers employed 1918-75, followed 1918-78			All workers	26	9.5	[6.20-13.92]	SMR ref Japan
Korallus et al (1982) Germany	1140 workers in 2 chromate production plants employed >1 year 1934-79			All workers	51	2.1	[1.56-2.76]	SMR ref North Rhine Westphalia
De Marco et al (1988) Italy	540 chromate production workers employed 10 years or more, employed and			All workers	14	2.17	1.18-3.63	SMR ref Italy
				High* exposure to Cr VI	6	4.2	[1.53-9.14]	SMR ref Italy

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
	following during 1948-85							
Davies et al (1991) United Kingdom	2298 workers in 3 chromate production factories; exposed before 1976, followed-up 1950-88			All workers	175	1.97	[1.69-2.28]	SMR ref national
				High chromate exposure jobs	151	2.45	[2.07-2.87]	SMR ref national
				Post-process change	14	1.02	0.56-1.71	SMR ref national
Korallus et al (1993) Germany	2 chromate-producing factories; 1417 workers with ≥1 year of exposure. Exposure and follow-up periods 1948-88	Not used here[2]	Overlap with Birk *et al* cohort. Includes both pre- and post-process change workers	All pre-process change workers	66	2.27	1.78-2.85	SMR ref North Rhine Westphalia
Rosenman and Stanbury (1996) New Jersey, US	3408 workers in 4 chromate production facilities, employed during 1937-71			All white males	170	1.95	1.67-2.27	PMR ref US
				All black males	54	1.88	1.41-2.45	PMR ref US
				White males, 20+ years duration	18	2.83	1.68-4.47	PMR ref US
				Black males, 20+ years duration	6	6.30	2.30-13.71	PMR ref US
Gibb et al (2000) Baltimore, US	2357 male workers at a chromium production plant, excluding those	Exposure estimated for each worker;	Smoking status available for most workers	All workers	122	1.80	1.49-2.14	SMR ref Maryland

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
	who began work before 1950; followed 1950-92	estimates assigned by job title, and JEM based on air measurements						
				Cumulative exposure: 0.077-5.25mg Cr03.yrs/m3	38	2.24	1.60-3.03	SMR ref Maryland
Luippold et al (2003)	482 chromate production workers employed ≥1 year 1940-72 and followed 1941-97	JEM developed from hygiene surveys, used to derive cumulative exposure estimates		All workers	51	2.41	1.80-3.17	SMR ref Ohio
				Cumulative exposure: 2.70-23mg.yr/m3	20	4.63	2.83-7.16	SMR ref Ohio
				Hired after 1959	6	0.92	0.34-2.01	SMR ref Ohio
Luippold et al (2005) US	Two plants producing chromates; both using low exposure process; 430 men in Plant 1 employed 1971-98 and followed 1979-98, 187 men in Plant 2 employed 1979-98 and followed 1980-98	Not used here[2]		All workers	3	0.84	0.17-2.44	SMR ref state

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
Birk et al (2006) Germany	901 workers with >1 year exposure at 2 low exposure chromate-production plants. Exposure period approximately 1960-98, followed for same period	Detailed employment histories reconstructed for each cohort member; industrial hygiene survey; more than 12000 urinary chromium results collected during routine medical examinations	A subset of workers in the Korallus study – those exposed post-change in process. Smoking status available for most workers	All workers	22	1.48	0.93-.2.25	SMR ref North Rhine Westphalia
				Cumulative exposure based on urine levels: >200ug.yr/1	12	2.09	1.08-3.65	SMR ref North Rhine Westphalia
Chromate paints and pigments								
Dalager et al (1980) US	977 spray painters using zinc chromate paints in aircraft		All respiratory cancers	All workers	21	1.84	[1.14-2.81]	PMR ref US

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
	maintenance at 2 US military bases, employed to 1959, followed 1959-77							
Bertazzi et al (1981) Italy	427 workers in a plant manufacturing paint and coatings, employed 1946-77, followed 1954-78	Major exposure was chromate pigments	Documented co-exposure to asbestos	All workers	8	2.27	[0.98-4.47]	SMR ref local rates
Frentzel-Beyme (1983) Germany and Holland	978 workers in 5 plants manufacturing zinc and lead chromates, 15076 person-years		Dates of employment and follow-up unclear	All workers	19	2.0	[1.20-3.12]	SMR ref national rates
Langård and Vigander (1983) Norway	133 workers in a zinc chromate pigment production plant employed 1948-72, followed 1948-80	Not used here[2]		>3 years' employment	6	44	[16.07-95.77]	SIR ref Norway
Davies (1984a & b) United Kingdom	1152 male workers in 3 lead and/or zinc chromate pigment factories employed 1930s to 1981, followed to 1981	Jobs were allocated to exposure grades high, medium and low, based on discussion with		All workers	28	3.59	2.4-5.2	SMR ref England and Wales
				High exposure	12	4.00	2.1-7.0	SMR ref England and Wales

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
		management						
Hayes et al (1989) New Jersey, US	1879 lead and zinc chromate pigment production workers employed 1940-69, followed to 1982	Not used here[2]	Lung and pleura	All workers	41	1.16	0.83-1.58	SMR ref US
				10+ years duration	8	1.94	0.83-3.83	SMR ref US
Deschamps et al (1995) France	294 men in a chromate pigment production plant, employed and followed 1958-87			All workers	18	3.6	2.13-5.68	SMR ref local region
				Duration 20+ years	6	3.77	1.38-8.21	SMR ref local region
Chromium electro-plating								
Silverstein et al (1981) US	238 workers in automotive diecasting and Ni-Cr plating plant employed before 1978, followed 1974-78			Men	28	1.9	[1.26-2.75]	PMR ref US
				Women	10	3.7	[1.77-6.80]	PMR ref US
Franchini et al (1983) Parma, Italy	116 “thick” platers in nine plants employed and followed 1951-81			All workers, latency >10 yrs	3	5.0	[1.03-14.61]	SMR ref Italy
Itoh et al (1996) Japan	1193 platers from 415 small-scale chrome plating plants employed			All workers	14	1.81	0.99-3.04	SMR ref Japan

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
	1970-76, followed 1976-92							
Sorahan et al (1998) Midlands, United Kingdom	1762 workers in a large chrome plating plant employed 1946-76, followed 1946-95	List of jobs in cohort assessed for chrome exposure	All workers exposed to chromic acid mists	All male platers	49	1.25	0.93-1.66	SMR ref England and Wales
				All female platers	16	1.24	0.71-2.01	SMR ref England and Wales
				Duration 5+ years, males	10	4.25	1.83-9.87	OR based on nested case-control
Sorahan and Harrington (2000) Yorkshire, United Kingdom	920 male chrome platers from 54 plants in Yorkshire. Employed before 1972, followed 1972-97	Industrial hygiene surveys carried out at 42 plants		All workers	60	1.85	1.41-2.38	SMR ref England and Wales
				Duration ≥5 years	19	1.41	0.85-2.20	SMR ref England and Wales
				Chrome platers	-	1.39	0.96-2.00	OR internal analysis includes an unexposed work group, adjusted for smoking

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
Roberti et al (2006) Italy	226 platers in a "bright" electroplating plant employed 1968-94, followed 1968-2003	Not used here[2]		All males	7	3.13	1.23-6.44	SMR ref Venice
Cohorts in other industries								
Axelsson et al (1980) Sweden	1876 workers in ferro-chromium plant employed >1 year 1930-75 followed 1951-75			All workers	7	1.2	[0.48-2.47]	SIR ref county
Langård et al (1990) Norway	1235 ferro-chromium and ferro-silicon male workers employed 1928-65, followed 1953-85		Lung and pleura	All ferro-chromium workers	10	1.5	[0.72-2.76]	SMR ref Norway
Moulin et al (1990) France	2269 workers in a ferro-alloy and SS production plant employed and followed 1952-82. Nested case-control based on 12 cases and 58 controls	Job histories; expert assessment for PAH, Cr, Ni	Uncertain exposure to Cr VI	All workers >1 year duration	11	2.04	1.02-3.64	SMR ref France
				Exposed to Cr and/or NI	4	2.75	0.29-26.30	OR from nested case-control
Simonato et al (1991)	11092 male welders from 135 companies in	Not used here[2]	Results for mild steel welders	Predominantly stainless steel welders	20	1.23	0.75-1.90	SMR ref national rates

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
9 European countries	9 European countries, variable periods of employment and follow-up across countries		showed excess risk of lung cancer	Duration 20+ years' predominantly stainless steel welding	13	1.74	0.93-2.97	SMR ref national rates
Gérin et al (1993) 9 European countries	JEM was applied to welders in the Simonato et al cohort	JEM for exposure to Ni and Cr VI derived from measurements and expert opinion	All results shown are for Ever SS welders for >5yrs, analysed with 20yrs latency	Cumulative Cr VI exposure 0.05-0.5 mg.yrs/m3	7	1.30	0.52-2.68	SMR ref national rates
				Cumulative exposure to Cr VI 0.5 1.5mg.yrs/m3	9	1.93	0.88-3.66	SMR ref national rates
				Cumulative exposure to CrVI 1.5+mg.yrs/m3	5	1.41	0.46-3.29	SMR ref national rates
Hansen et al (1996) Denmark	10059 welders, stainless steel grinders, and other metal workers from 79 welding companies, employed 1964-84; followed 1968-86	Mailed questionnaire on lifetime occupation, and smoking/drinking habits. 83% response	Cohort partly included in Simonato study. Results for mild steel welders showed similar excess risk of lung	All SS welders	23	1.19	0.75-1.79	SMR ref Denmark

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
			cancer					
Lauritson and Hansen (1996) Denmark	Nested case-control within cohort of 8372 respondents of the Hansen et al 1996 cohort; 94 lung cancer deaths occurring 1946-86, 439 controls	Occupation and smoking history based on mailed questionnaires	Overlap with Hansen et al 1996 and with Simonato et al 1991. Results for mild steel welders showed similar excess risk of lung cancer	All SS welders	20	1.5	0.8-2.6	OR adjusted for smoking
Alexander et al (1996) Washington state	2429 aerospace workers with >6 months exposure to Cr VI, employed 1940-94 and followed 1974-94	Industrial hygiene data and work history records; available for all years of the study		All workers	15	0.8	0.4-1.3	SIR ref Puget Sound
				49.3-184.7 chromate-years	5	1.1	0.3-2.5	SIR ref Puget Sound
Milatou-Smith et al (1997) Sweden	233 stainless steel welders from 8 different companies employed >5 years 1950-65, followed 1955-92	Air measurement for Cr VI		High exposure to CrVI	6	1.64	0.60-3.58	SMR ref Sweden
Rafnsson et al (1997) Iceland	1172 licensed stone masons, born after 1880 and alive in 1955; followed 1955-93		It was shown that Icelandic cement dust contains Cr VI and that masons	All workers	25	1.69	1.09-2.49	SIR ref Iceland

Author date/place	Characteristics of cohort	Exposure assessment	Comments	Exposure category	n[1]	Relative risk	95% CI	Type of estimate and reference population
			have measurable Cr VI in urine					
Boice et al (1999) California	3634 workers who were exposed to chromates at an aircraft manufacturing plant employed >1 year since 1960, followed 1960-96	Not used here[2]		All workers	87	1.02	0.82-1.26	SMR ref California for white workers and US general population for non-white workers
Moulin et al (1990) France	4288 male workers in a SS and metallic alloy production plant employed >1 year from before 1968 to 1991, followed 1968-92	No airborne measurements were available; exposure estimates were based on experts' JEM	Uncertain exposure to Cr VI	All workers	54	1.2	0.90-1.57	SMR ref region
				Exposed to chromium and/or nickel	33	0.72	0.32-1.62	OR based on internal analyses
Halasová et al (2005) Istbene, Slovak Republic	Workers in ferro-chromium plant followed 1985-99		Uncertain exposure to Cr VI. Number of workers unclear	Workers exposed to Cr	59	4.04	[3.08-5.21]	Ratio of directly standardised rates using local area rates

[1] n Number of exposed cases

* High – Not further defined

[2] Not used here: This signifies that the study did involve an exposure assessment protocol of some sort, but that the result presented in this table does not depend on that exposure assessment

There are some case reports, cohort studies and case–control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to Cr(VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports (IARC, 2012).

3.1.1.1.2 Animal data

Cr(VI) compounds have been tested for carcinogenicity in several animal species and strains. None of the available studies meets current standards. Calcium chromate induced lung tumours in mice (males and females combined) when given by inhalation (Nettesheim et al., 1971 cited in IARC, 2012). In rats, it caused lung tumours (adenoma, squamous cell carcinoma, or adenocarcinoma) when given by intratracheal administration (Steinhoff et al., 1986 cited in IARC, 2012) or intrabronchial administration (Levy & Venitt, 1986 cited in IARC, 2012) and bronchial carcinomas (or squamous cell carcinomas) when administered by intrabronchial administration (Levy et al., 1986 cited in IARC 2012).

Zinc and strontium chromates caused bronchial carcinomas in rats when administered by intrabronchial implantation (Levy et al., 1986 cited in IARC 2012).

Chromium trioxide when tested as a mist by inhalation caused nasal papillomas in mice (Adachi & Takemoto, 1987 cited in IARC 2012). A low incidence of lung adenocarcinomas was induced after inhalation of chromium trioxide, and some lung tumours were observed in rats exposed by intrabronchial administration but neither were statistically significant (Adachi et al., 1986; Levy et al., 1985; Levy & Venitt, 1986 cited in IARC 2012).

Sodium dichromate (when given by inhalation or intratracheal administration) caused lung tumours (benign and malignant) (Glaser et al., 1985; Steinhoff et al., 1986 cited in IARC 2012) in rats.

Overall, the administration of calcium chromate in mice and sodium dichromate in rats by inhalation caused lung cancer. Calcium chromate and sodium dichromate administered by intratracheal instillation caused lung cancer in rats. Intratracheal administration of calcium chromate, zinc chromate, and strontium chromate caused lung cancer in rats (IARC, 2012).

Some studies provide valuable insight on the lung carcinogenic potency of Cr(VI) compounds in laboratory animals. Total dose administered, dose rate, amount of dosage, dose per administration, number of times administered, exposure duration and the type of Cr(VI) compound are major influences on the observed tumor incidence in animals. It was found that slightly water-soluble calcium, strontium, and zinc chromates showed the highest incidence of lung tumors, as indicated in the results of the Steinhoff and Levy studies, even when compared to similar doses of the more water soluble sodium chromates and chromic acid compounds. The highly insoluble lead chromates

did not produce lung tumors by the intrabronchial implantation procedure. No information on particle size was available in these studies (OSHA, 2006).

3.1.1.2 Dermal

3.1.1.2.1 Human data

There is no evidence that dermal exposure to Cr(VI) compounds has caused skin or other tumors in humans. Some of the early epidemiology studies included investigations of ill health and all tumors. Hence, it would be anticipated that had there been any significant increases in skin tumors, these would have been recorded.

3.1.1.2.2 Animal data

Dermal cancer bioassays with Cr(VI) compounds alone are not available.

3.1.1.3 Oral

3.1.1.3.1 Human data

According to IARC (2012), there is little evidence that oral exposure to Cr(VI) has caused stomach or other cancers in humans. There are as many relative risk point estimates above 1.0 as there are below. There has been concern about possible hazards related to the ingestion of Cr(VI) in drinking-water, and one study in the People's Republic of China (Zhang & Li, 1987 cited in IARC, 2012) and a subsequent reanalysis of the Chinese data (Beaumont et al., 2008 cited in IARC, 2012) seem to indicate a somewhat elevated risk of stomach cancer when drinking-water was heavily polluted by a ferrochromium plant. However, results from a single study do not constitute rigorous evidence of an association between oral exposure to Cr(VI) and cancer of the stomach (IARC 2012).

A similar conclusion was reached by the USEPA (Draft USEPA, 2010). This draft document states that human studies in which health outcomes (primarily cancer) were evaluated among populations that resided near sources of industrial waste containing Cr(VI) compounds and unknowingly consumed Cr(VI) in drinking water provide some evidence of possible associations between oral exposure to Cr(VI) and cancer. These epidemiological studies evaluated populations in Liaoning Province, China (Kerger et al., 2009; Beaumont et al., 2008; Zhang and Li, 1997, 1987), Kings County/San Bernardino County, California (Fryzek et al., 2001), Nebraska (Bednar and Kies, 1991), and Glasgow, United Kingdom (Eizaguirre-Garcia et al., 2000, 1999) that unknowingly were exposed to Cr(VI) over some time period. Of these studies, the most detailed analyses were of data collected from the JinZhou area of Liaoning Province, China, where groundwater, surface water, and agricultural soils were contaminated with chromium derived from Cr(VI) production (e.g., 0.001–20 mg chromium/L in residential well water). This

study found evidence of an excess risk of mortality from stomach cancer from 1970 to 1978 in residents of the area, relative to the reference populations (four other areas in Liaoning Province, and the total population of the province) (Beaumont et al., 2008).

Studies of chromium-exposed populations in California and Nebraska (Fryzek et al., 2001; Bednar and Kies, 1991) found no significant correlation between cancer mortality and drinking water concentration, and the study of the population in Glasgow (Eizaguirre-Garcia et al., 2000, 1999) found no correlation between leukemia risk and distance from a former chromium processing facility (where elevated soil concentrations for Cr(VI) were measured).

Overall, a moderately elevated risk of stomach cancer mortality was seen in JinZhou (Liaoning Province, China), but this risk was not established in other populations exposed to drinking water contaminated with Cr(VI). The epidemiologic data are not sufficient to establish a causal association between exposure to Cr(VI) by ingestion and cancer (Draft USEPA, 2010).

There is also no evidence that inhalation exposure to Cr(VI) in occupational cohorts has caused cancer of the gastro-intestinal tract.

3.1.1.3.2 Animal data

The National Toxicology Program (NTP) conducted 2-year drinking-water studies of sodium dichromate dihydrate in male and female B6C3F1 mice, and in male and female F344 rats. In rats, sodium dichromate dihydrate significantly increased the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/L) of males and females. Trend analysis indicated a dose–response relationship in both males and females. In mice, sodium dichromate dihydrate significantly increased tumours (adenomas or carcinomas) of the small intestine (duodenum, jejunum, or ileum) in the two-highest dose groups of males (85.7 and 257.4 mg/L) and females (172 and 516 mg/L). Dose–response relationships were observed in both sexes (NTP, 2008, cited in IARC 2012).

Overall, oral administration of sodium dichromate to rats and mice caused cancer of the oral cavity and of the gastrointestinal tract.

3.1.1.4 Summary of carcinogenicity

Overall, Cr(VI) compounds cause lung cancer in humans and animals by the inhalation route and tumours of the gastrointestinal tract in rodents by the oral route.

3.1.2 Other relevant information

3.1.2.1 Toxicokinetics

3.1.2.1.1 Deposition and Absorption

3.1.2.1.1.1 Inhalation

The amount and location of deposition of inhaled Cr(VI) compounds will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. These factors include air-flow velocities, which are affected by breathing rate and tidal volume; airway geometry; and aerosol particle size. In general, deposition in the thoracic and pulmonary regions of the respiratory tract increases (as a fraction of the total deposited dose) as particle sizes decrease. Larger particles (e.g., >10 µm in diameter) deposit in the extra-thoracic region. In general, less water-soluble Cr(VI) compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms (ATSDR, 2012).

Cr(VI) can be systemically absorbed by the respiratory tract. This has been shown by both human and animal data. The absorption of inhaled Cr(VI) compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, and solubility), the reduction capacity of the ELF (epithelial lining fluid) and alveolar macrophages and clearance by the muco-ciliary escalator and phagocytosis. Highly water soluble Cr(VI) compounds (e.g. sodium chromate) enter the bloodstream more readily than highly insoluble Cr(VI) compounds (e.g. lead chromate). However, insoluble compounds may have longer residence time in the lung. The chromate $(CrO_4)^{2-}$ anion enters cells via facilitated diffusion through non-specific anion channels (similar to phosphate and sulfate anions) (OSHA, 2006).

Inhaled Cr(VI) is reduced to Cr(III) in the epithelial lining fluid of the lungs by a variety of reducing agents. This serves to limit uptake into lung cells and absorption into the bloodstream as Cr(III) ions do not readily cross cellular membranes. Cr(V) and Cr(IV) are transient intermediates in this reduction process (OSHA, 2006).

Ascorbate and glutathione in the ELF and macrophages have been shown to reduce Cr(VI) to Cr(III) in the lungs (Suzuki, 1988 cited in OSHA, 2006). A study by Suzuki and Fukuda (1990) showed that the reduction of Cr(VI) by glutathione is slower than the reduction by ascorbate. Another study has reported the reduction of Cr(VI) to Cr(III) by ELF obtained from the lungs of 15 individuals by bronchial lavage and has estimated that the mean daily extracellular lung Cr(VI) reductive capacity of an individual is approximately 137 mg (De Flora et al., 1997 cited in OSHA, 2006).

3.1.2.1.1.2 Dermal

Absorption of Cr(VI) can also take place after dermal exposure, particularly if the exposures are high and the skin is damaged. Dermal absorption percentages up to 4% are reported from studies in guinea-pigs with soluble Cr(VI) compounds in aqueous solutions. Dermal absorption rates in humans vary from 0.03 ng/cm^2/h to 10 µg/cm^2/h dependent on solvent, exposure

condition and the concentration of Cr(VI) (Corbett et al., 1997; Cross et al., 1997 cited in OSHA, 2006).

3.1.2.1.1.3 Oral

After oral exposure up to 10% of ingested Cr(VI) is absorbed from the gastrointestinal tract (generally in the upper small intestine) in humans. In general, the absorption fraction of soluble Cr(VI) compounds is higher than that of insoluble forms (e.g., $CrCO_3$). Much of the ingested Cr(VI) is reduced by the gastric juices to Cr(III) before absorption, limiting the bioavailability of Cr(VI) by the oral route. Oral absorption of Cr(VI) is also affected by the nutritional status of Cr(III); the absorption fraction is higher when dietary intakes of Cr(III) are lower (OSHA, 2006).

3.1.2.1.2 Distribution, Metabolism and Elimination

Following absorption of Cr(VI) compounds from various exposure routes, chromium is taken up by the blood cells and is widely distributed in tissues as Cr(VI). Inside blood cells and tissues, Cr(VI) is rapidly reduced to lower oxidation states and bound to macromolecules which may result in genotoxic or cytotoxic effects. In blood a substantial proportion of Cr(VI) is taken up into erythrocytes, where it is reduced to Cr(III) and becomes bound to haemoglobin and other proteins (OSHA, 2006).

Absorbed chromium is excreted from the body in a rapid phase, representing clearance from blood and in two slower phases, representing clearance from tissues. Urinary excretion is the primary route of elimination, accounting for over 50% of eliminated chromium. Although chromium is excreted in urine and faeces, the intestine plays only a minor part in chromium elimination representing only about 5% of elimination from blood (OSHA, 2006).

3.1.2.2 Genotoxicity

A large number of studies have examined multiple types of genotoxicity in a wide range of experimental test systems. The body of evidence establishes that both soluble and insoluble forms of Cr(VI) cause structural DNA damage that can lead to genotoxic events such as mutagenisis, clastogenisis, inhibition of DNA replication and transcription, and altered gene expression, all of which probably play a role in neoplastic transformation. The reactive intermediates and products that occur from intracellular reduction of Cr(VI) cause a wide variety of DNA lesions. The type(s) of DNA damage that are most critical to the carcinogenic process is an area of active investigation (OSHA, 2006).

3.1.2.2.1 Human data

Studies of chromosomal and DNA damage in workers exposed to Cr(VI) vary in their findings. Some studies reported higher levels of chromosomal aberrations, sister chromatid exchanges, or DNA strand breaks in peripheral

lymphocytes of stainless steel welders and electroplaters. Other studies were not able to find excess damage in DNA from the blood lymphocytes of workers exposed to Cr(VI). These reports are difficult to interpret since co-exposure to other genotoxic agents (e.g., other metals, cigarette smoke) is likely to have occurred and the extent of Cr(VI) exposures was not known (OSHA, 2006).

3.1.2.2.2 In vitro data

Many Cr(VI) compounds are mutagenic in bacterial and mammalian test systems *in vitro*. In bacterial Salmonella typhimurium strains, soluble Cr(VI) caused base pair substitutions at A-T sites as well as frame shift mutations. Several Cr(VI) compounds have produced mutagenic responses at various genetic loci in mammalian cells. Clastogenic damage, such as sister chromatid exchange and chromosomal aberrations, have also been reported for insoluble Cr(VI) and soluble Cr(VI) (OSHA, 2006). Induction of micronuclei *in vitro* has been described by Thompson et al (2012) but only at concentrations of Cr(VI) that reduced significantly cell viability (TERA, 2012). In contrast to Cr(VI) compounds, Cr(III) does not cause genotoxicity in intact cellular systems, presumably due to the inability of Cr(III) to penetrate cell membranes.

3.1.2.2.3 Animal data

Genotoxicity has been reported following Cr(VI) administration to animals *in vivo.* Soluble Cr(VI) at high doses induced micronucleated erythrocytes in mice following intraperitoneal (IP) administration (Itoh and Shimada, 1998; Knudsen, 1980 cited in OSHA, 2006). Soluble Cr(VI) also increased the mutation frequency in liver and bone marrow following IP administration to lacZ transgenic mice. The physiological relevance of this route of exposure is questionable.

Intratracheal instillation of soluble Cr(VI) produced a time- and dose-dependant elevation in mutant frequency in the lung of Big Blue transgenic mice (Cheng et al., 2000 cited in OSHA, 2006). However, there are several caveats to this study, and the applicability of these results is highly uncertain. In this investigation, Cr(VI) was instilled surgically at high concentrations and administered doses were highly toxic or lethal to the animals. Izzotti et al. (1998) reported DNA damage (fragmentation, crosslinks and 8-OHdG) in the lungs of rats exposed to soluble sodium dichromate by intratracheal instillation. The authors concluded that the nucleotide modifications observed were consistent with oxidative DNA damage. Oral administration of soluble Cr(VI) in animals did not produce genotoxicity in several studies probably due to route-specific differences in absorption (Shindo et al., 1989; Mirsalis et al., 1996 cited in ATSDR, 2012; De Flora et al., 2006; 2008; NTP, 2007 cited in TERA, 2012). Overall, therefore, although it is well accepted that Cr(VI) can be genotoxic and mutagenic, the evidence for such conclusion is primarily derived from *in vitro* data at cytotoxic exposures and from *in vivo* data by artificial routes of administration (TERA, 2012).

3.1.2.2.4 Mechanisms of Cr(VI) genotoxicity

There has been a great deal of research to identify the types of damage to DNA caused by Cr(VI), the reactive intermediates that are responsible for the damage, and the specific genetic lesions critical to carcinogenesis. It has been shown that Cr(VI) is inactive in DNA binding assays with isolated nuclei or purified DNA. However, Cr(III) is able to produce DNA protein cross-links, sister chromatid exchanges, and chromosomal aberrations in an acellular system. Zhitkovich et al. (2001) showed that incubation of Chinese hamster ovary cells with soluble Cr(VI) produced ternary complexes of Cr(III) cross-linked to cysteine, other amino acids, or glutathione and the DNA phosphate backbone. Utilizing the pSP189 shuttle vector plasmid, they showed these DNA-Cr(III)-aminoacid cross-links were mutagenic when introduced in human fibroblasts (OSHA, 2006).

Cr(VI) undergoes a series of reduction steps in cells, to form the thermodynamically stable Cr(III). Intracellular reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols, such as glutathione and cysteine. During the reduction process, variable amounts of Cr(V) and Cr(IV) as well as organic radical species are generated; their exact nature, however, depends largely on the reducing species (Wetterhahn & Hamilton, 1989, cited in IARC, 2012). Furthermore, comparative *in-vivo* and *in-vitro* studies reveal a major impact of the intracellular reductants on the nature and biological consequences of the resultant DNA lesions. The major intracellular reductant under physiological conditions appears to be ascorbate, reaching millimolar concentrations in human tissues, and accounting for about 90% of Cr(VI) reduction reactions *in vivo* (Standeven et al., 1992 cited in IARC 2012). In contrast, only micromolar concentrations of ascorbate are usually present in cell cultures (Quievryn et al., 2002 cited in IARC, 2012), which leads to an increase in thiol-mediated chromate reduction. When ascorbate is the reductant, two electrons are transferred, and Cr(IV) but not Cr(V) is generated as the first intermediate, whereas with cysteine as a reductant, predominantly Cr(V) is formed due to one-electron transfers (Stearns & Wetterhahn, 1994 cited in IARC, 2012). In both cases, the final product is Cr(III), which reacts to produce different types of DNA lesions (IARC, 2012).

DNA lesions generated after exposure to Cr(VI) include Cr(III)–DNA adducts, DNA–protein and DNA–DNA interstrand crosslinks, DNA breaks as well as several oxidative DNA–base modifications. The predominant form of Cr(III)–DNA adducts are ternary adducts, where chromium forms a link between DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed chromium–ligand complexes during the reduction process. These adducts are formed primarily at phosphate groups, but the subsequent partial formation of chelates involving the phosphate group and the *N*7-position of the guanine have been suggested. Chelates formed from chromium–ascorbate are premutagenic DNA lesions (Zhitkovich et al., 2001 cited in IARC, 2012).

The formation of DNA–protein crosslinks after chromate exposure is well established, but is estimated to account for less than 1% of Cr–DNA adducts. Biological consequences are likely to be disturbances of DNA replication and transcription. The formation of DNA–DNA crosslinks appears to be restricted to certain *in-vitro* conditions, due to severe steric hindrance upon intercalation of octahedral Cr(III) complexes (Zhitkovich, 2005 cited in IARC, 2012). DNA single-strand breaks may arise due to the reaction of Cr(V) with hydrogen peroxide, forming hydroxyl radicals. Nevertheless, if ascorbate is the predominant reductant under *in-vivo* conditions, the generation of Cr(V) and thus, single-strand breaks, appears to be of minor importance (Quievryn et al., 2003 cited in IARC 2012).

Cytogenetic alterations in Cr(VI)-exposed cells in culture and *in vivo*, such as increased frequencies of chromosomal breaks and micronuclei, are suggested to be due to DNA double-strand breaks, produced by a cell replication-dependent mechanism in the G2 phase of the cell cycle. Recent evidence suggests the involvement of mismatch repair in the formation of double-strand breaks. Thus, the mutagenic ascorbate–Cr–DNA adducts lead to the error-prone repair of double strand breaks through non-homologous end-joining. Furthermore, these adducts induce mismatches during replication, leading to aberrant mismatch repair and genomic instability (Reynolds et al., 2007; Salnikow & Zhitkovich, 2008 cited in IARC 2012). This is supported by evidence that Cr(VI)-induced cancers in exposed workers were associated with microsatellite instability and exhibited the loss of expression of MLH1, which is one of the essential mismatch-repair proteins (Takahashi et al., 2005 cited in IARC, 2012).

In the reduction of Cr(VI) to Cr(III) by cellular reductants, potentially toxic intermediates (oxygen radicals, sulphur radicals, and chromium radicals) are generated (Yao et al., 2008 cited in IARC 2012). In a cell-free system, Cr(VI) reacted with glutathione to form chromium (V) and thiyl radicals (Wetterhahn et al., 1989 cited in IARC 2012). Furthermore, after reduction of Cr(VI) by glutathione, Cr(V) can undergo Fenton-type reactions, producing hydroxyl radicals (Shi et al., 1994 cited in IARC 2012), and 8-oxoguanine in isolated DNA (Faux et al., 1992 cited in IARC 2012). In cultured mammalian cells, Cr(VI) induces the formation of superoxide and nitric oxide (Hassoun & Stohs, 1995 cited in IARC 2012). The administration of Cr(VI) to animals, which have higher tissue levels of ascorbate compared with cultured cells, did not result in the formation of 8-oxoguanine (Yuann et al., 1999 cited in IARC 2012). This may be due to the lack of Cr(V) formation when ascorbate is the predominant reducing agent (IARC 2012).

Overall, studies of the different types of DNA damage caused by Cr(VI) demonstrate that Cr(VI) itself is not biologically active. Cr(VI) must undergo intracellular reduction to Cr(V), Cr(IV), and Cr(III) before the damage to DNA can occur. The evidence suggests that Cr(III) can cause DNA-Cr-aminoacid, DNA-Cr-DNA crosslinks and Cr-DNA mono-adducts. In addition, ROS (reactive oxygen species) generated during intracellular reduction of Cr(VI) lead to oxidative DNA damage. However, the specific DNA lesions

responsible for neoplastic transformation have yet to be firmly established (OSHA, 2006).

3.1.2.2.5 Conclusions

In conclusion, the overall body of evidence indicates that Cr(VI) is genotoxic *in vivo*, resulting in the formation of DNA adducts and oxidative DNA damage. However, clear evidence of mutagenicity *in vivo* in the target tissues (lung and intestine) by relevant routes of exposure is lacking. This supports the contention that Cr(VI) is only weakly mutagenic *in vivo* and that its mutagenicity is most likely to be only a contributory factor in the carcinogenic process (TERA, 2012).

3.1.2.3 Irritation and inflammation

It is well recognised that at least some hexavalent chromium compounds have irritative/corrosive properties. Sustained tissue inflammation can play an important role in the process by which some substances can give rise to cancer, including substances such as formaldehyde that can also damage DNA. Hence the potential contribution of tissue irritation/inflammation to the carcinogenicity of Cr(VI) compounds merits exploration. This is important in relation to dose-response considerations.

3.1.2.3.1 Animal data

There are two informative studies of the carcinogenicity of Cr(VI) in rodent lung (Glaser et al., 1985; Steinhoff et al., 1986 cited in TERA, 2012). Steinhoff et al. (1986) reported that repeated intratracheal administration of Cr(VI) up to 0.25 mg/kg bw five times per week for 30 months did not increase lung tumours. In contrast, a single intratracheal administration of 1.25 mg/kg bw per week for 30 months induced lung tumours in 17.5% of the rats. At this dose, there were signs of chronic inflammation, including the presence of alveolar macrophages, proliferation of bronchiolar epithelium, and chronic inflammatory thickening of alveolar septa. These lesions were much milder in rats exposed to the same weekly dose but in five instillations of 0.25 mg/kg bw, as well as in rats receiving five instillations of 0.05 or 0.01 mg/kg bw, or single instillations of 0.5 or 0.05 mg/kg bw/week for 30 months. Steinhoff et al. concluded that the Cr VI concentration (rather than total dose) delivered to the respiratory tract epithelium and the consequent tissue irritancy/inflammation were important in tumour formation. Similar results were seen with lung tumours induced by calcium chromate (Steinhoff et al., 1986).

Glaser et al. (1985) conducted an inhalation study with Cr(VI) as sodium dichromate, and as a chromium oxide mixture of 3 Cr(VI):2Cr(III) (Cr_5O_{12}). Rats were exposed to 25, 50 or 100 µg/m^3 dichromate, or 100 µg/m^3 Cr_5O_{12} for 18 months, followed by a 12-month observation period. The incidence of lung tumour formation was 16% (3/19) in the 100 µg/m^3 dichromate group, but no tumours were observed in the 50 µg/m^3, 25 µg/m^3, or control groups. Exposure to Cr_5O_{12} at 100 µg/m^3 (~63 µg/m^3 Cr(VI)) also increased lung

tumour incidence from 0 to 6% (1/18). Accumulation of macrophages in lungs, eosinophilic substances inside the alveolar lumens, focal thickened septa, and fibrosis were seen, only in animals exposed to 100 µg/m^3 $Cr_5O_{12.}$ In these Cr_5O_{12}–treated animals the chromium lung burden, measured 12 months after termination of exposure, was 10-fold higher than in rats exposed to 100 µg/m^3 dichromate The inflammatory response was attributed by the authors to the less soluble Cr_5O_{12} being more slowly cleared from the lung than the more soluble sodium dichromate. In this study, however, there seems to be no clear relationship between Cr(VI) lung burden, inflammation and tumour incidence.

Over two decades later, the potential role of inflammation in the carcinogenicity of Cr(VI) has been explored in a series of studies conducted by Beaver and colleagues. Mice exposed to 0.6 mg/ml zinc chromate via intranasal instillation, either once or repeatedly (every 14 days for 64 days) exhibited clear signs of peribronchiolar, alveolar, and interstitial inflammation, as well as elevated and aberrant cell proliferation in the airway lining, indicative of an emerging tumourigenic process (Beaver et al., 2009 cited in TERA, 2012). Beaver et al. concluded that Cr(VI)-induced inflammation could make an important contribution to the initiation and promotion of neoplastic growth in the lung.

Recent oral studies indicate that Cr(VI) can induce oxidative stress and proliferative responses in the mouse small intestine (Kopec et al., 2012; Thompson et al., 2011 cited in TERA, 2012). Toxicogenomic profiling suggests that gene changes induced at this site by Cr(VI) are more consistent with those caused by other non-genotoxic carcinogens than genotoxic carcinogens (Thompson et al., 2012 cited in TERA, 2012). The data suggest that oxidative stress and regenerative hyperplasia might be contributory factors in the carcinogenicity of Cr(VI) towards the gastrointestinal tract.

3.1.2.3.2 Human data

Results from the key occupational epidemiology studies provide some support for the notion that irritation and inflammation might play an important role in the carcinogenicity of Cr(VI). In the Baltimore cohort, there was clear evidence of widespread irritation effects of Cr(VI), manifest in clinical findings such as nasal septum perforation and bleeding, irritated or ulcerated skin, and nasal irritation and ulceration, identified in routine examinations of the cohort members (Gibb et al., 2000b cited in TERA, 2012). Nasal irritation and ulceration were the most common clinical findings, occurring in more than 60% of the cohort. Given these findings, it would seem likely that there would also have been epithelial inflammation further along the respiratory tract, in areas less easily observed in routine clinical checks. Average time (and exposure) from the start of employment to first occurrence of these findings was less than 3 months. The median and mean exposure concentration of Cr(VI) at the time of their occurrence was approximately 10 µg Cr(VI)/m^3 and 25 µg Cr(VI)/m^3 respectively.

Similarly, for the early Painesville cohort, TERA (2012) mentions that among 100 randomly chosen workers, 92% had nasal septum ulceration and 65% had nasal septum perforation. Further, 98% and 93% of the workers respectively, had engorgement and hypertrophy of the nasal turbinates. Again, it would seem likely that there would also have been epithelial inflammation further along the respiratory tract, in areas less easily observed in routine clinical examinations. An increased incidence of lung cancer was observed in these workers (e.g. SMR of 365 from the Luippold et al. (2003) cohort exposed during the 1940s). It is reasonable to hypothesise that respiratory tract epithelial inflammation resulting from Cr(VI) exposures might have played a role in the lung cancer observed.

Three studies on chrome-platers also provide some information on upper respiratory irritation with exposure to Cr(VI) as chromic acid. In the study of Cohen et al. (1974, cited in USEPA, 1998), nasal ulcers and perforations were associated with Cr(VI) concentrations of 0.09 to 9.1 μg/m^3, averaging 2.9 μg/m^3. Ninety-five percent of the 37 workers studied exhibited pathologic changes in nasal mucosa in a concentration-duration response. More than half of the workers employed less than 1 year had nasal pathology that was more severe than simple redness of the nasal mucosa. Almost all the workers (35 of 37) employed longer than 1 year had nasal tissue damage. The authors noted the lack of good industrial hygiene practices and implied that direct contact, such as touching of the nose with chromium-contaminated hands, was a potentially important source of exposure. A subsequent study by Lucas and Kramkowski (1975, cited in USEPA, 1998) revealed similar results. Cr(VI) concentrations ranged from 1 to 20 μg/m^3, averaging 4 μg/m^3 Again, the authors considered that direct hand-to-nose contact was a significant contributory factor.

Lindberg and Hedenstierna (1983, cited in USEPA, 1998) also found similar effects on nasal pathology and subjective symptoms. They reported reddening of the nasal mucosa at 1 to 2 μg Cr(VI)/m^3, and nasal irritation (chronic and nasal septal ulceration and perforation) in two-thirds of the subjects exposed to concentrations of 2 to 20 μg Cr(VI)/m^3. All workers with nasal ulceration had been exposed to chrome acid mist, which contained Cr(VI) at 20 μg/m^3, or greater than 20 μg/m^3 near the baths. An important additional observation was a reduction in pulmonary function (vital capacity and forced expiratory volume), with Cr(VI) exposures greater than 2 μg/m^3.

These human data indicate that airborne Cr(VI) can be damaging to the respiratory tract epithelium. Interpretation of the dose-response characteristics is confounded by the evident occurrence of contaminating hand-to-nose contact, but the available data suggest that airborne concentrations of 1-10 μg Cr(VI)/m^3 and above cause irritation of the upper respiratory tract epithelium. There is also some evidence for irritation of lower regions and it would be reasonable to expect this; such effects would be less immediately observable, clinically. The available dose-response evidence is not strong, but suggests that a no-effect concentration for irritation of the respiratory tract might lie below 1 μg Cr(VI)/m^3.

3.1.2.4 MoA considerations for Cr(VI)-induced cancer

Most assessments and authorities have considered that genotoxicity is a major, if not the sole mode-of-action (MoA) by which Cr(VI) compounds give rise to cancer. There has been more in-depth probing of the potentially important contributory components of this MoA.

In 2006, OSHA concluded that on the basis of the available evidence, the most plausible MoA underlying the lung carcinogenicity of Cr(VI) compounds was genotoxicity. In this MoA, the Cr(VI) ion is taken up by epithelial cells in the bronchoalveolar region of the lung. Cr(VI) in solution can be taken up via facilitated diffusion mediated by sulphate/phosphate anion transport channels. This is because Cr(VI) exists in a tetrahedral configuration as a chromate oxyanion similar to the physiological anions, sulphate and phosphate.

Once inside the cell, the Cr(VI) ion is rapidly reduced, non-enzymatically, by several reducing agents, producing chromium in the intermediate oxidation states Cr(V) and Cr(IV), and the more chemically stable Cr(III). Unlike Cr(VI), these other chromium forms are able to react with DNA and protein to generate a variety of adducts and complexes. In addition, reactive oxygen species (ROS) are produced from these reduction reactions. The most plentiful reducing factors in the cell are ascorbate and thiols such as glutathione (GSH) and cysteine. Depletion of cellular GSH and other thiols is believed to retard the complete reduction of Cr(VI) to Cr(III), allowing build-up of intermediates Cr(V) and Cr(IV) (OSHA, 2006).

These reactive intermediates, and not Cr(VI) itself, are considered to be the ultimate genotoxic agents that initiate the carcinogenic process (OSHA, 2006).

IARC (2012) concluded that several genotoxic processes are involved in the carcinogenesis induced by Cr(VI) that include the induction of DNA damage, the generation of oxidative stress and aneuploidy, leading to cell transformation. With respect to DNA damage, the spectrum of induced lesions appears to depend strongly on the cellular reductant involved.

Although such uptake might appear not to apply as readily to less water-soluble compounds, OSHA (2006) concluded that both water soluble and insoluble Cr(VI) compounds can deliver Cr(VI) into the cell. In fact, cell surface interactions with slightly water-soluble chromates may create a concentrated microenvironment of chromate ion in close proximity to the lung cells, which might result in higher intracellular Cr(VI) than would occur from highly water-soluble chromates that dissolve and diffuse rapidly in the aqueous fluid lining the epithelia of the lung and are cleared more quickly from the respiratory tract. This is consistent with the studies of respiratory tract carcinogenesis in animals, which indicate that the most tumourigenic chromates have sparing-to-moderate water solubility.

Water-insoluble Cr(VI) particulates are also able to come in close contact with the lung cell surface. Even if they release little readily absorbable chromate ions by simple water dissolution, studies have shown that, for example, lead chromate particles adhere to the surface of cells in culture, causing cell-enhanced dissolution and also phagocytic uptake of the particles into the cell, where further solubilisation can occur.

An important consideration in this MoA is the propensity for Cr(Vi) reduction to take place outside the cell, thereby preventing Cr(VI) uptake. In the epithelial lining fluid of the lungs (and in the gastrointestinal tract), Cr(VI) can be reduced to the poorly-permeating Cr(III). This will have a limiting effect on cellular uptake of Cr(VI). Ascorbic acid and glutathione (GSH) are believed to be the key molecules responsible for the extracellular reduction of Cr(VI). The available evidence indicates that the speed and extent of extracellular reduction depends on the concentration and nature of the reductants in the extracellular fluid. At present, there is no information on the relative comparison of the rate of extracellular reduction of Cr(VI) with the rate of its cell uptake under physiological conditions *in vivo*. Thus, the extent to which extracellular reduction of Cr(VI) is a limiting factor in Cr(VI)-induced carcinogenesis is unclear. However, extracellular reduction could impart a non-linear characteristic to the cancer dose-response relationship of Cr(VI) (De Flora, 2000 cited in SCOEL, 2004; OSHA, 2006). With a finite concentration of reductant lying outside the cell, much of a relatively low concentration of extracellular Cr(VI) would be reduced and therefore not enter the cell, but the impact would be much less for relatively high concentrations; on this basis one would predict sub-linearity at the lower end of the dose-response curve.

Despite the attractiveness of the proposed genotoxic MoA, there are aspects of the database for Cr(VI) carcinogenicity that pose interpretational problems. It is noteworthy that although Cr(VI) inhalation exposure has been associated with increased risk of lung cancer among workers in certain industries - specifically chromate production, pigment production, and chrome plating - there is little or no evidence that inhaled Cr(VI) has caused cancer in other industries with significant potential for Cr(VI) exposure (welding, aerospace, ferrochrome, tanning, glassware cleaning) (IARC, 2012).

In addition. several recent review articles have concluded that Cr(VI) has only weak mutagenic potential, and have suggested that other MoAs may be operational in Cr(VI)-induced lung cancer (Holmes et al., 2008; Nickens et al., 2010 cited in TERA, 2012).

Prefacing such thinking, SCOEL (2004) stated that it should be recognised that the irritant and inflammatory properties of Cr(VI) compounds may also contribute to the carcinogenic process; and importantly, for dose-response characterisation and risk assessment, for these effects there will be dose thresholds. SCOEL commented that it is not known to what extent irritancy may contribute towards carcinogenicity, but that it is quite plausible that linear

extrapolation at low doses, below those applying to existing studies and at which irritancy does not occur, may overestimate the true cancer risk.

More recently, TERA (2012) has reviewed both the animal and human evidence in support of the role played by tissue irritation in Cr(VI)-induced carcinogenicity and has argued for a non-mutagenic MoA for Cr(VI)-induced tumours, involving tissue irritation and inflammation.

The contractor observes that although it is well accepted that Cr(VI) can be genotoxic, the evidence for such a conclusion is primarily derived from *in vitro* data at cytotoxic concentrations and from *in vivo* data by routes of administration not reflecting real-life human exposure. Although this evident genotoxicity has been generally taken to indicate that Cr(VI) acts by a genotoxic MoA, there is a body of evidence supporting the conclusion that Cr(VI) is weakly mutagenic and other factors, particularly tissue inflammation, could play an important role in tumour formation.

The possibilities of extracellular reduction of Cr(VI) and a significant contribution of irritancy and inflammation to the carcinogenic process would suggest non-linearity, and even a dose threshold, for cancer at the lower end of the dose-response curve. However, the available epidemiological and experimental animal data are of insufficient statistical power in the low dose range to permit elucidation of the dose-response curve (Crump et al., 2003; Proctor et al., 2004; Park et al., 2004; Park and Stayner, 2006 cited in TERA, 2012). Further, the epidemiological studies—with the exception of the Painesville study— use cumulative exposure as the dose-metric; a measure of exposure intensity might be more appropriate in examining these additional considerations.

3.1.2.5 Specific consideration of toxicokinetics and physical-chemical properties of Cr(VI) compounds in lung cancer assessment

Cr(VI)-induced pulmonary carcinogenesis generally involves localized tissue regions sustaining high Cr(VI) exposure and chronic cellular toxicity, primarily in bronchial bifurcations of the lung where particles predominantly deposit (Nickens et al., 2010; Ishikawa et al., 1994 in TERA, 2012). Further, animal research demonstrates that sparingly soluble forms of Cr(VI), which have a longer residence time in the lung than soluble forms, have greater carcinogenic potential (Steinhoff et al., 1986; Levy et al., 1986 in TERA, 2012). This is consistent with the observation that Cr(VI) carcinogenicity is most pronounced in the chromate production and chromate pigment production industries, where workers are exposed to sparingly soluble chromates, including calcium, zinc, strontium and lead chromates (OSHA 2006; Proctor et al., 2003; 2004; IARC, 1990 in TERA, 2012). Further, when lime was removed from the chromate production process in the mid to late 1950s, which resulted in decreased exposure to calcium chromate in this industry, cancer risks were also significantly reduced (Davies et al., 1991; Luippold et al., 2003; 2005; Birk et al., 2006, in TERA, 2012).

Thus, both the animal and human data indicate that the forms of Cr(VI) with the longest residency time in the lung, i.e., the sparingly soluble forms, pose the more significant cancer hazard. This information indicates that the lung tissue dose (i.e. the sum of inhaled and retained dose less eliminated dose) is the dose metric most predictive of lung cancer risk (TERA, 2012).

3.1.2.5.1 Particle Size

While only very limited data are available on the particle size of airborne Cr(VI) in the historical chromate production industry, the data that do exist from the Luippold et al., (2003) cohort (Painesville plant) indicate that the aerodynamic equivalent diameter (AED) of the dust was 1.7 µm (Proctor et al., 2003 in TERA 2012). Also, the U.S Public Health Service (PHS) conducted an evaluation of worker health in the early 1950s in the chromate production industry (PHS, 1953). This survey included workers of both the Painesville (cohort examined originally by Mancuso, 1975; 1997 and updated by Luippold et al., 2003) and Baltimore (cohort examined initially by Hayes et al., 1975 and updated by Gibb et al., 2000) chromate production plants. Similar to the particle size reported for the Painesville plant, PHS (1953) reported median particle sizes in the range of 1.0 µm. In addition, evidence from the chromate production industry suggests that the particle sizes of the Cr(VI) exposures must have been in the range that affects the tracheo-bronchial and alveolar regions of the lung, in that these cohorts experienced high rates of lung cancer (TERA, 2012).

Large particle size may be at least partially responsible for the lack of increased lung cancer risk in the aerospace industry. Although Cr(VI) exposures in the aerospace industry have been comparable (high) with those of chromate production workers in terms of total airborne Cr(VI) concentration, and aerospace painters are exposed to sparingly soluble forms of Cr(VI), no increased lung cancer risk has been reported in the vast majority of studies. This is likely to be due to the larger particle sizes to which these workers are exposed (TERA, 2012) – see below.

Sabty-Daily et al. (2005 - cited in TERA, 2012) evaluated the size distribution of paint spray aerosol particles containing Cr(VI) at an aerospace facility. The sampled paint products consisted of strontium chromate in an epoxy resin matrix. In paint aerosol, particles containing total chromium had a mass median aerodynamic diameter (MMAD) of 7.5 µm; for particles containing Cr(VI), MMAD was 8.5 µm. On average, 62% of the Cr(VI) mass of the paint aerosol had particles >10 µm. In this study, the investigators also reported that about 72% of the Cr(VI) mass inhaled by a painter as particles from paint aerosol was deposited in the head airways region and about 1.4% of the Cr(VI) mass had the potential to deposit in the tracheo-bronchial region. This is an important consideration because lung cancer among Cr(VI)-exposed workers is most typically a bronchogenic carcinoma. Only 2% of the Cr(VI) mass had the potential to deposit in the alveolar region (Sabty-Daily et al., 2005 - cited in TERA, 2012).

Further, LaPuma et al. (2001; 2002 cited in TERA, 2012) quantified the Cr(VI) content and mass of dry chromate paint particles of varying sizes. The particles were found to range from 0.7 to 34.1 µm, Particles less than 7 µm in size had disproportionately less Cr(VI) per mass of dry paint compared to larger particles. The chromium content per mass of dry paint decreased substantially with decreasing particle size. The smallest particles, which were about 0.7 µm in size, contained about 10% of the chromium content per mass of dry paint as the larger particles. Therefore, the smaller particles contained less chromium compared to larger particles, due to their smaller size (mass varies with the cube of the radius, i.e. if the radius is reduced to one-tenth, mass reduces to one-thousandth), and they also had less chromium content per mass of dry paint. These findings indicated that exposure to Cr(VI) may differ between the painters and workers exposed to chromate pigments in other industries (TERA, 2012).

3.1.2.5.2 Solubility

It has been recognized for decades that the toxicity of Cr(VI) compounds can vary depending on the solubility of the salt. Strontium chromate is sparingly soluble in water at 1,200 mg/L at 25℃. Barium chro mate and lead chromate, on the other hand, are even less soluble (barium, 4.4 mg/L; lead, 0.58 mg/L), and although calcium chromate is much more soluble (163,000 mg/L) than the strontium salt, the forms of calcium chromate in the chromate production industry are not simple salts but complex molecules of sparing solubility (Proctor et al., 2003, in TERA, 2012). Thus, the calcium chromate compounds to which the workers of the historical chromate production industry were exposed from kiln dust and roast were likely far less soluble than pure calcium chromate.

The studies by Levy & Venitt and Levy et al. (1986 in TERA, 2012) found high incidences of 43% and 62% bronchial carcinomas in rats treated with two different samples of strontium chromate, which is sparingly soluble. By comparison, sodium dichromate, a highly water-soluble compound, did not cause a significant increase in tumor incidence. These studies were performed using an intrabronchial pellet implantation system whereby pellets loaded with the test compound were surgically implanted into the bronchi of the animals. Implanting a pellet creates a high level of the compound in a small, localized area, which is more likely to overwhelm the body’s defense mechanisms and to result in tissue irritation and inflammation, as well as genetic damage (TERA, 2012).

Finally, it is important to note that the historical chromate production workers were exposed to a wide range of Cr(VI) particulates and aerosols of varying solubility. These included sparingly soluble forms of calcium chromate that were generated in the production kilns and the highly water soluble chromates and dichromates which were produced in the production process of this industry (Proctor et al., 2003; 2004 cited in TERA, 2012). Further, both the Baltimore (Gibb et al., 2000) and Painesville plants (Luippold et al., 2003) operated chromic acid production processes, and in Baltimore, the plant also produced Cr(VI)-containing pigments such as zinc and lead chromate.

Several studies of chromate production worker cohorts have demonstrated that the excess cancer risk is reduced when less lime is added to the roast mixture, reducing worker exposure to the sparingly soluble calcium chromate compounds (Luippold et al., 2003 cited in TERA, 2012). Unfortunately, the analytical procedures used to characterize exposure for most of the time periods during which both the Painesville and Baltimore cohorts members worked involved a water extraction of Cr(VI). Thus, exposure to sparingly soluble forms of Cr(VI) may not have been accurately characterized. Rather the measured concentrations were mostly of Cr(VI) as a soluble salt. Although the carcinogenicity of sparingly soluble forms is greater than that of soluble forms or that of insoluble forms in animal models, the dose-response between water-soluble Cr(VI) measured in the Painesville and Baltimore chromate production plants and increased lung cancer risk or between insoluble Cr(VI) in chromate pigment production plants and increased lung cancer risk is nonetheless positive (TERA, 2012).

In summary, lung carcinogenic potency of Cr(VI) compounds is expected to be greater for respirable-sized particles, moderate/slight solubility, and increased residence time in the lung. However, quantifying carcinogenic potency for different Cr(VI) compounds is not possible with the currently available information.

3.1.3 Conclusion of cancer hazard identification

Overall, Cr(VI) causes lung tumours in humans and animals by the inhalation route and tumours of the gastrointestinal tract in animals by the oral route. These are both local, site-of-contact tumours – there is no evidence that Cr(VI) causes tumours elsewhere in the body. A clear MoA for these tumours has not been established; however, the weak *in vivo* mutagenicity of Cr(VI) and its irritative properties point towards non-linearity and the possible existence of a dose threshold. Notwithstanding this, at the present time, the available evidence is insufficient to determine where this threshold may lie on the dose-response curve. In addition, it is possible that both the mutagenicity and irritative/inflammatory properties of Cr(VI) contribute to its carcinogenicity.

Lung carcinogenic potency of Cr(VI) compounds is expected to be greater for respirable particles, moderate/slight solubility, and increased residence time in the lung. However, quantifying carcinogenic potency for Cr(VI) compounds of different solubility is not possible with the currently available information.

3.2 Cancer hazard characterisation

3.2.1 Key studies for quantitative cancer risk assessment

3.2.1.1 Inhalation

It is generally recognized that human data from epidemiological studies, if available, are preferred as the starting point for quantitative risk analysis of carcinogens above the use of data from experimental animal studies. This is, because effects observed in animal species have to be translated into effects expected in humans, i.e., an extrapolation step is needed that not only is substantially uncertain, but also, from a precautionary principle approach, has to be conservative in nature. Besides the advantage that epidemiological data relate to the same species (i.e., man), the most important other advantages of epidemiological data over animal data are that exposure conditions and other circumstances that may modify the risk are usually much more comparable to those in the target population than those simulated in an animal experiment. Quantitative risk assessment based on epidemiological studies entails therefore substantially less uncertainty than if based on animal models, irrespective of some inherent uncertainties introduced by the epidemiological design itself.

Therefore, for inhaled Cr(VI) compounds for which lung tumours were observed in both epidemiological and animal studies, it is the human data that is generally used for quantitative cancer risk analysis.

For inhaled Cr(VI), the epidemiological studies that provide adequate exposure-response relationships for risk estimation (i.e. risk levels at multiple exposure categories of airborne Cr(VI)) are not many. These include Hayes et al. (1975), Mancuso (1997), Gerin et al. (1993), Alexander et al. (1996), Gibb et al. (2000), Crump et al. (2003), Luippold et al. (2003), Park et al. (2004) and Park & Steyner (2006). In addition, when taking into account methodological quality, consideration of confounding by smoking, size of cohort, length of follow-up and exposure measurement methods, the studies that provide adequate data are only five: Gibb et al. (2000), Crump et al. (2003), Luippold et al. (2003), Park et al. (2004) and Park & Steyner (2006). These five studies relate to two cohorts only: the Baltimore (Gibb et al., 2000; Park et al., 2004 and Park & Steyner, 2006) and the Painesville chromate production cohorts (Luippold et al., 2003; Crump et al., 2003).

3.2.1.1.1 Baltimore cohort

First described by Hayes et al. (1975), Gibb et al. (2000) updated the cohort study of a Baltimore, Maryland, chrome production plant. The cohort included 2357 male workers (white and non-white) first employed between 1950 and 1974. Follow-up was through the end of 1992 for a total of 70,736 person-years and an average length of 30 years per cohort member. A strength of this study was the availability of ambient Cr(VI) measurements from personal and area sampling and from a variety of locations and job titles. Ambient levels of Cr(VI) were monitored throughout the entire study period. Using

these concentration estimates, a job exposure matrix was constructed giving annual average exposures by job title. Mean cumulative Cr(VI) exposure in the cohort was 134 µg/m^3-yr (range 0 – 5300 µg/m^3-yr). Based on the job exposure matrix and work histories for the cohort members, Gibb et al. computed the person-years of observation, the observed numbers of lung cancer deaths, and the expected numbers of lung cancer deaths categorized by cumulative Cr(VI) exposure and age of death. They found that cumulative Cr(VI) exposure was a significant predictor of lung cancer risk over the exposure range of 0 to 2760 µg/m^3-yr. They reported a RR (Relative Risk) of 1.42 for a cumulative CrO^3 exposure of 1.5 – 8.9 µg/m^3-yr, a RR of 1.57 for a cumulative CrO^3 exposure of 9 – 76.9 µg/m^3-yr and a RR of 2.24 for a cumulative CrO^3 exposure of 77 – 5250 µg/m^3-yr. Analysis of lung cancer mortality by cumulative Cr(VI) exposure indicated that risks were not significantly increased at exposure levels around 0.045 mg/m^3-years (equivalent to 1.2 µg/m^3 for 40 years) (OSHA, 2006).

Another advantageous characteristic of this study was that information was available for smoking status from the employee records. Smoking status (yes/no) at the beginning of employment was known for over 90 % of the study subjects and was included in the statistical analysis. Smoking was found to be strongly associated with lung cancer mortality. Cumulative Cr(VI) exposure was significantly associated with lung cancer mortality, even after adjustment for smoking. However, this study also included workers who were employed for a short period of time (less than 90 days). While the authors justify the inclusion of these short-term workers for their contribution to the low cumulative dose range, little is known about the remaining work lives of these employees. These employees may have been exposed to carcinogenic substances at other plants or through other work. Based on data from Gibb et al. (2000), an excess lifetime risk of lung cancer resulting from Cr(VI) exposure was analysed by means of Poisson regression models (Park et al. 2004). From a linear relationship, a RR of 2.44 (95 % CI 1.54–3.83) for 1 mg CrO_3 m^{-3}-year was estimated. The Baltimore cohort data also served as the basis for model calculations by Park and Stayner (2006) who examined the existence of non-linearities (from Seidler et al., 2012).

3.2.1.1.2 Painesville cohort

Luippold et al. (2003) and Crump et al. (2003) studied a cohort of 482 predominantly white, male employees who started work between 1940 and 1972 at the same Painesville, Ohio, chromate production plant studied earlier by Mancuso (1977). Mortality status was followed through 1997 for a total of 14,048 person-years. The average worker had 30 years of follow-up. This more recent investigation improved on the Mancuso study by considering smoking status. However, data regarding smoking status were available only for 41 % of the workers; the prevalence of smoking in the cohort was high (78 %). The distribution of smoking status across all of the cumulative exposure categories was reported to be comparable, suggesting that the SMRs for the different exposure categories were not confounded (OSHA, 2006).

The exposure measurements for this study were taken from 21 industrial hygiene surveys of ambient Cr(VI) levels and extrapolated to estimate the levels over the entire exposure period (1940–1972). Exposure information was then linked to the employees using job-exposure matrices (JEM) to calculate each individual's cumulative occupational Cr(VI) exposure. Mean cumulative Cr(VI) exposure in the cohort was 1580 µg/m^3-yr (range 3 – 23000 µg/m^3-yr). The workers included in the study had to have worked for at least 1 year, and workers who were transferred to another chrome plant where no exposure information was available were excluded from the study (from Seidler et al., 2012).

Luippold et al. (2003) and Crump et al. (2003) found significant dose-related trends for lung cancer SMRs as a function of year of hire, duration of employment and cumulative Cr(VI) exposure. Lung cancer mortality was increased for the two highest cumulative Cr(VI) exposure categories (≥ 1.05 to < 2.70 mg/m^3-years, SMR = 365; ≥ 2.70 to 23 mg/m^3-years, SMR = 463), but not for the first three exposure groups. Stratified analysis of lung cancer mortality by cumulative Cr(VI) exposure indicated that risks were significantly increased only at exposure levels over 1.05 mg/m^3-years (equivalent to 25 µg/m^3 for 40 years).

3.2.1.1.3 Comparison of the two cohorts

While the Luippold/Crump cohort was smaller and less racially diverse than the Gibb cohort, the workforce contained fewer transient, short-term employees. The Luippold/Crump cohort consisted entirely of workers employed over one year. Fifty-five percent had worked for more than five years. In comparison, 65% of the Gibb cohort had worked for less than a year and 15% for more than five years at the Baltimore plant. There was less information about the smoking behaviour (smoking status available for only 35% of members) of the Luippold/Crump cohort compared to that of the Gibb cohort. One aspect that the Luippold/Crump cohort had in common with the Gibb cohort was extensive and well-documented air monitoring of Cr(VI). The cumulative Cr(VI) exposures for the Luippold/Crump cohort, which ranged from 0.003 to 23 mg/m^3-yr, were generally higher but overlapped those of the Gibb cohort (OSHA, 2006).

There is no information in these papers about which Cr(VI) compounds the workers were exposed to and the particle size of such exposures. However, it is well established that the historical chromate production workers were exposed to a wide range of Cr(VI) particulates (some data on particle size are presented in section 3.1.2.4.1) and aerosols of varying solubility These included sparingly soluble forms of calcium chromate that were generated in the production kilns and the highly water soluble chromates and dichromates which were produced in the production process of this industry (Proctor et al., 2003; 2004 cited in TERA, 2012). Further, both the Baltimore (Gibb et al., 2000) and Painesville plants (Luippold et al., 2003) operated chromic acid production processes, and in Baltimore, the plant also produced Cr(VI)-containing pigments such as zinc and lead chromate.

While only very limited data are available on the particle size of airborne Cr(VI) in the historical chromate production industry, the data that do exist from the Painesville plant indicate that the aerodynamic equivalent diameter (AED) of the dust was 1.7 μm (Proctor et al., 2003 in TERA, 2012). Also, median particle sizes in the range of 1.0 μm were reported by a survey which included workers of both the Painesville and Baltimore plants (PHS, 1953 cited in TERA, 2012).

It is noted that the Baltimore (Gibb et al., 2000; Park et al., 2004) and Painesville (Luippold et al., 2003; Crump et al., 2003) cohort studies have been the basis of the majority of the quantitative cancer risk assessments of inhaled Cr(VI) that in recent years have been produced by other organisations around the world (OSHA, 2006) or published in the open literature (Goldbohm et al., 2006; Seidler et al., 2012). The only exception is the risk evaluation performed by SCOEL (2004), which was based on a meta-analysis of 10 studies by Steenland et al. (1996). As this meta-analysis lacked information on exposure intensity and duration, SCOEL assumed that the overall SMR of 266 derived from these 10 studies was associated with an average exposure duration of 15 years at three possible Cr(VI) exposures of 500, 1000 or 2000 µg/m^3.

3.2.1.2 Oral

Oral administration of sodium dichromate to rats and mice causes cancer of the oral cavity and of the gastrointestinal tract (NTP, 2008 cited in Draft USEPA, 2010).

3.2.1.2.1 Rat

NTP (2008) conducted a 2-year chronic and carcinogenicity study of sodium dichromate dihydrate in drinking water in rats and mice. Groups of F344/N rats (“core” study animals; 50/sex/group) were exposed to sodium dichromate dihydrate in drinking water at concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L (equivalent to 0, 5, 20, 60, or 180 mg Cr(VI)/L, respectively). Based on water consumption measured throughout the study, NTP (2008) calculated average daily doses over the 2-year treatment duration of approximately 0, 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg bw/day for males (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg Cr(VI)/kg bw/day, respectively) and 0.7, 2.7, 7, and 20 mg sodium dichromate dihydrate/kg bw/day for females (equivalent to 0, 0.24, 0.94, 2.4, or 7.0 mg Cr(VI)/kg bw/day, respectively) (Draft USEPA, 2010).

Animals were observed twice daily for mortality and clinical signs of toxicity; after 5 weeks of treatment, clinical signs were recorded at 4-week intervals. Body weights were recorded weekly for the first 13 weeks, and then at 4-week intervals for the duration of the study. Water consumption was recorded weekly for the first 13 weeks of treatment and then every 4 weeks. At the end of the 2-year treatment period, complete necropsies and microscopic examinations of comprehensive tissues were performed on all “core” study

animals. An additional “special study” group of male rats (10/group) was exposed to the same drinking water concentrations as the “core” animals for up to 53 weeks. For the “special study” only, blood was collected on days 4 and 22 and at 3, 6 and 12 months for haematology (i.e., Hct; Hb concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; mean cell hemoglobin concentration [MCHC]; and leukocyte count and differentials) and clinical chemistry (i.e., urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, sorbitol dehydrogenase, bile acids) analyses. At the end of the 53-week treatment period, the “special study” animals were evaluated for chromium tissue distribution (Draft USEPA 2010).

Survival rates of exposed “core” study rats were similar to controls. Throughout the study, water consumption was decreased in the two highest dose groups compared to controls. During the second year of the study, water consumption in the two highest dose groups in males was decreased by 15 and 22%, respectively, and by 15 and 27%, respectively, in females (statistical significance not reported). No data on food consumption were reported. At the end of the 2-year treatment period, body weight was decreased in males and females in the highest dose group by 12 and 11%, respectively, compared with controls (statistical significance not reported). NTP (2008) suggested that decreased body weights in the highest dose group may have been partially due to decreased water consumption (due to decreased palatability), rather than being an adverse effect of sodium dichromate dihydrate. No treatment-related signs of clinical toxicity were observed throughout the study (Draft USEPA, 2010).

Gross and microscopic examinations of “core” study rats exposed to sodium dichromate dihydrate in drinking water for 2 years showed non-neoplastic lesions of the small intestine (duodenum), liver, and lymph nodes in both sexes, non-neoplastic lesions of the salivary gland in females, and neoplastic lesions of the oral cavity in both sexes (NTP, 2008). The incidence of minimal-to-mild cellular histiocytic infiltration of the duodenum was significantly increased in males and females at ≥ 0.77 and ≥ 2.4 mg Cr(VI)/kg bw/day, respectively, compared with controls; increases in both sexes were dose-related. Duodenal histiocytic infiltrate was characterized by single or clusters of macrophages in the lamina propria of the duodenal villi. Based on incidence data, males appeared more sensitive than females to Cr(VI)-induced non-neoplastic changes of the small intestine (Draft USEPA, 2010).

Incidence data for neoplastic lesions of the oral cavity in male and female rats exposed to sodium dichromate dihydrate in drinking water for 2 years are summarized in the table below. Neoplasms observed in the oral cavity of treated rats were squamous cell carcinoma of the oral mucosa (both sexes), squamous cell papilloma of the oral mucosa (males only), squamous cell carcinoma of the tongue (both sexes), and squamous cell papilloma and carcinoma of the tongue (both sexes). The incidences of squamous cell carcinoma of the oral mucosa (13.6%) and of combined squamous cell papilloma or carcinoma (15.7%) of the oral mucosa were significantly increased in male rats treated with 5.9 mg Cr(VI)/kg bw/day, compared with

controls. The incidences of squamous cell carcinoma of the oral mucosa (23.9%) and of combined squamous cell carcinoma of the oral mucosa or tongue (23.9%) were significantly increased in females treated with 7.0 mg Cr(VI)/kg bw/day, compared with controls. The incidences of other neoplastic lesions of the oral cavity were not significantly increased in any treatment group in males or females compared with controls, although the incidence of squamous cell carcinoma of the oral mucosa in female rats in the 2.4 mg Cr(VI)/kg bw/day group (4.6%) exceeded that of historical controls (0/300 in drinking water studies; 5/1,400 by all routes) (Draft USEPA, 2010).

Other neoplasms observed in treated rats included pancreatic acinar adenoma and benign pheochromocytomas in males and mononuclear cell leukemia in females. However, the incidence of these neoplasms did not exhibit dose-dependence. Thus, NTP (2008) concluded that the relationship of neoplastic changes in other tissues (e.g., not of the oral cavity) to exposure to sodium dichromate dihydrate was uncertain (Draft USEPA, 2010).

Table 3.2: Incidence of neoplastic lesions observed in the oral cavity of male and female F344/N rats exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Neoplasm type	**Treatment group (mg Cr(VI)/kg bw/day)**				
	0	**0.21**	**0.77**	**2.1**	**5.9**
Males					
Oral mucosa, squamous cell papilloma					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	1/49 (2%)
Oral mucosa, squamous cell carcinoma					
Overall rate[a]	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	6/49 (12%) [543]
Adjusted rate[c]	0% *p < 0.001*	0%	0%	0%	13.6% *p = 0.015*
Tongue, squamous cell papilloma					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	1/49 (2%)
Tongue, squamous cell carcinoma					
Overall rate[a]	0/50 (0%)	1/50 (2%)	0/49 (0%)	0/50 (0%)	0/49 (0%)
Oral mucosa or tongue, squamous cell papilloma or carcinoma					
Overall rate[a]	0/50 (0%)	1/50 (2%) [729]	0/49 (0%)	0/50 (0%)	7/49 (14.5%) [543]
Adjusted rate[c]	0% $p < 0.001$	2.4%	0%	0%	15.7% $p = 0.007$
Neoplasm	**Treatment group (mg Cr(VI)/kg bw/day)**				

type					
	0	**0.24**	**0.94**	**2.4**	**7.0**
Females					
Oral mucosa, squamous cell carcinoma					
Overall rate[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%) [646]	11/50 (22%) [506]
Adjusted rate[c]	0% *p < 0.001*	0%	0%	4.6%	23.9% *p < 0.001*
Tongue, squamous cell papilloma					
Overall rate[a,b]	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Tongue, squamous cell carcinoma					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Oral mucosa or tongue, squamous cell papilloma or carcinoma					
Overall rate[a]	1/50 (2%) [618]	1/50 (2%) [729T]	0/50 (0%)	2/50 (4%) [646]	11/50 (22%) [506]
Adjusted rate[c]	2.2% *p* < 0.001	2.3%	0%	4.6%	23.9% *p* = 0.002

[a] Overall rate: number of animals with lesion/number of animals examined; parenthesis are the percent of animals examined with lesion; brackets are days to first incidence; T: observed at terminal sacrifice. *p*-Value under treatment group incidence data indicates statistically significant Poly-3 test for pairwise comparison between control and exposed group. Statistical analysis using overall rates was only conducted if adjusted rates were not determined.
[b] Adjusted rate not reported.
[c] Adjusted rate: Poly-3 estimated neoplasm incidence (expressed as percent of animals with neoplasm) adjusted for intercurrent mortality. *p*-Value under control group indicates statistically significant positive Poly-3 trend test. *p*-Value under treatment group incidence data indicates statistically significant Poly-3 test for pairwise comparison between control and exposed groups, using adjusted rates.

In conclusion, exposure of rats to sodium dichromate dihydrate in drinking water for 2 years resulted in a significant increase in squamous epithelial neoplasms of the oral mucosa and tongue in both sexes at the highest exposure level (average daily doses of 5.9 and 7.0 mg Cr(VI)/kg bw/day in males and females, respectively), but not at the three lower exposure levels. NTP (2008) concluded that the results from this study provided clear evidence of carcinogenic activity of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous cell neoplasms of the oral cavity (Draft USEPA, 2010). A NOAEL of 2.1 mg Cr(VI)/kg bw/day could be identified for non-neoplastic lesions of the intestine (minimal-to-mild cellular histiocytic infiltration of the duodenum) from this study.

3.2.1.2.2 Mouse

B6C3F1 mice were exposed to sodium dichromate dihydrate in drinking water for up to 2 years (NTP, 2008). Groups of 50 male mice (male “core” study animals) were exposed to sodium dichromate dihydrate in drinking water at concentrations of 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L (equivalent to 0, 5, 10, 30, or 90 mg Cr(VI)/L, respectively). Based on water consumption measured throughout the study, NTP (2008) calculated average daily doses for males over the 2-year treatment duration of

approximately 0, 1.1, 2.6, 7, or 17 mg sodium dichromate dihydrate/kg bw/day (equivalent to 0, 0.38, 0.91, 2.4, or 5.9 mg Cr(VI)/kg bw/day, respectively). Groups of 50 female mice (female “core” study animals) were exposed to sodium dichromate dihydrate in drinking water at concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L (equivalent to 0, 5, 20, 50, or 190 mg Cr(VI)/L, respectively). Based on water consumption measured throughout the study, NTP (2008) calculated average daily doses for females over the 2-year treatment duration of approximately 0, 1.1, 3.9, 9, or 25 mg sodium dichromate dihydrate/kg bw/day (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg Cr(VI)/kg bw/day, respectively). “Core” study mice were subjected to the same evaluations and procedures as those described above for the “core” study rats (NTP, 2008). An additional “special study” group of female mice (10/group) were exposed to the same drinking water concentrations of sodium dichromate dihydrate as the “core” animals for up to 53 weeks. For the “special study” animals only, blood was collected on day 22 and at 3, 6, and 12 months for haematologic analyses (i.e., Hct; Hb concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials). At the end of the 53-week treatment period, the “special study” animals were evaluated for chromium tissue distribution (Draft USEPA, 2010).

Survival rates of the “core” study mice exposed to sodium dichromate dihydrate were similar to controls (NTP, 2008). Throughout the study, water consumption by males and females was decreased in the two highest dose groups compared with controls. During the second year of the study, water consumption in the two highest dose groups was decreased by 15 and 35%, respectively, in males and by 25 and 32%, respectively, in females (statistical significance not reported). No data on food consumption were reported. At the end of the 2-year treatment period, body weight in males in the highest dose group was decreased by 6% compared with controls (statistical significance not reported), and body weight in females in the two highest dose groups was decreased by 8 and 15%, respectively. NTP (2008) suggested that decreased body weights in the highest dose groups may have been partially due to reduced water consumption because of poor drinking water palatability, rather than being an adverse effect of sodium dichromate dihydrate exposure. No treatment-related signs of clinical toxicity were observed throughout the study (Draft USEPA, 2010).

Gross and microscopic examinations of the “core” study mice exposed to sodium dichromate dihydrate in drinking water for 2 years showed non-neoplastic lesions of the small intestine, liver, lymph nodes, and pancreas, and neoplastic lesions of the small intestine (NTP, 2008). In the small intestine, statistically significant increases in the incidences of minimal-to-mild diffuse epithelial hyperplasia of the duodenum were observed in male and female mice in all treatment groups and of the jejunum in females at 8.7 mg Cr(VI)/kg bw/day, compared with controls. NTP (2008) noted that diffuse epithelial hyperplasia was consistent with tissue regeneration following epithelial cell damage. Incidences of minimal-to-mild histiocytic cellular infiltration of the duodenum were increased at ≥ 2.4 and ≥ 3.1 mg Cr(VI)/kg bw/day in males and females, respectively, and of the jejunum at 8.7 mg

Cr(VI)/kg bw/day in females, compared with controls. Moderate-to-severe focal epithelial hyperplasia was also observed in the duodenum in males and females, although incidences were not significantly different from controls (the incidence did not exceed 2/50 rats in any dose group) and did not exhibit dose-dependence. Due to its morphological similarity to adenoma, focal epithelial hyperplasia was classified as a pre-neoplastic lesion by NTP (2008) (Draft USEPA, 2010).

Incidence data for neoplastic lesions of the small intestine in male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years are summarized in the tables below. In male mice, incidences of combined small intestine (duodenum, jejunum, and ileum) adenoma or carcinoma were significantly increased at ≥ 2.4 mg Cr(VI)/kg bw/day and incidences of duodenal adenoma, small intestine adenoma, and small intestine carcinoma were significantly increased at 5.9 mg Cr(VI)/kg bw/day. In addition, significant positive dose-related trends were observed for the incidences of duodenal adenoma, duodenal carcinoma, jejunal adenoma, small intestine adenoma, small intestine carcinoma, and combined small intestine adenoma or carcinoma. In female mice, significant increases in the incidences of duodenal adenoma, small intestine adenoma, and combined small intestine adenoma or carcinoma were observed at ≥ 3.1 mg Cr(VI)/kg bw/day and incidences of duodenal carcinoma, jejunal adenoma, and small intestine carcinoma were significantly increased at 8.7 mg Cr(VI)/kg bw/day. Significant positive dose-related trends were observed for duodenal adenoma, duodenal carcinoma, jejunal adenoma, small intestine adenoma, small intestine carcinoma, and combined small intestine adenoma or carcinoma. No other statistically or biologically significant neoplasms were observed in other tissues.

Table 3.3: Incidence of neoplastic lesions observed in the small intestine of <u>male</u> B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Tissue and lesion type	**Treatment group (mg Cr(VI)/kg bw/day)**				
	0	**0.38**	**0.91**	**2.4**	**5.9**
<u>Males</u>					
<u>Duodenum, adenoma</u>					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	6/50 (12%) *p* ≤ 0.05
<u>Duodenum, all adenoma (includes multiple adenomas)</u>					
Overall rate[a]	1/50 (2%) [665]	0/50 (0%)	1/50 (2%) [729]	5/50 (10%) [729]	15/50 (30%) [451]
Adjusted rate[c]	2.2% *p < 0.001*	0%	2.3%	10.8%	32.9% *p < 0.001*
<u>Duodenum, carcinoma</u>					

Overall rate[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%) [729]	3/50 (6%) [729]
Adjusted rate[c]	0% *p < 0.011*	0%	0%	4.3%	6.8%
Jejunum, adenoma					
Overall rate[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%) [714]
Adjusted rate[c]	0% *p* = 0.002	0%	0%	0%	6.8%
Jejunum, multiple carcinoma					
Overall rate[a,b]	0/50	1/50	0/50	0/50	0/50
Jejunum, all carcinoma (includes multiple)					
Overall rate[a,b]	0/50	2/50	0/50	1/50	2/50
All small intestine[d], adenoma					
Overall rate[a]	1/50 (2%) [665]	1/50 (2%) [729]	1/50 (2%) [729]	5/50 (10%) [729]	17/50 (34%) [451]
Adjusted rate[c]	2.2% *p < 0.001*	2.3%	2.3%	10.8%	37.2% *p < 0.001*
All small intestine[d], carcinoma					
Overall rate[a]	0/50 (0%)	2/50 (4%) [729]	1/50 (2%) [729T]	3/50 (6%) [729]	5/50 (10%) [729]
Adjusted rate[c]	0% *p* = 0.014	4.5%	2.3%	6.5%	11.4% *p* = 0.028
All small intestine[d], adenoma or carcinoma					
Overall rate[a]	1/50 (2%) [665]	3/50 (6%) [729]	2/50 (4%) [729]	7/50 (14%) [729]	20/50 (40%) [451]
Adjusted rate[c]	2.2% *p < 0.001*	6.8%	4.6%	15.1% *p = 0.032*	43.8% *p < 0.001*

Table 3.4: Incidence of neoplastic lesions observed in the small intestine of female B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Tissue and lesion type	**Treatment group (mg Cr(VI)/kg bw/day)**				
	0	**0.38**	**1.4**	**3.1**	**8.7**
			Females		
Duodenum, multiple adenoma					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%) *p* ≤ 0.05
Duodenum, all adenoma (includes multiple)					
Overall rate[a]	0/50	0/50	2/50	13/50	12/50

	(0%)	(0%)	(4%) [729]	(25%) [729]	(24%) [693]
Adjusted rate[c]	0% *p < 0.001*	0%	4.2%	27.8% *p < 0.001*	25.2% *p < 0.001*
Duodenum, carcinoma					
Overall rate[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%) [729]	6/50 (12%) [625]
Adjusted rate[c]	0% *p < 0.001*	0%	0%	2.1%	12.6% *p = 0.019*
Jejunum, multiple adenomas					
Overall rate[a,b]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Jejunum, all adenomas (including multiple)					
Overall rate[a]	0/50 (0%)	1/50 (2%) [729]	0/50 (0%)	2/50 (4%) [729]	5/50 (10%) [729]
Adjusted rate[c]	0% *p = 0.002*	2.2%	0%	4.3%	10.6% *p = 0.035*
Jejunum, carcinoma					
Overall rate[a,b]	1/50 (2%)	0/50 (0%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
All small intestine[d], adenoma					
Overall rate[a]	0/50 (0%)	1/50 (2%) [729]	2/50 (4%) [729]	15/50 (30%) [729]	16/50 (32%) [693]
Adjusted rate[c]	0% *p < 0.001*	2.2%	4.2%	32.0% *p < 0.001*	33.7% *p < 0.001*
All small intestine[d], carcinoma					
Overall rate[a]	1/50 (2%) [729]	0/50 (0%)	2/50 (4%) [729]	3/50 (6%) [729]	7/50 (14%) [625]
Adjusted rate[c]	2.2% *p* < 0.001	0%	4.2%	6.4%	14.7% *p* = 0.037

[a] Overall rate: number of animals with lesion/number of animals examined; parentheses are the percent of animals examined with lesion; brackets indicate the days to first incidence; T: observed at terminal sacrifice.
p-Value under treatment group incidence data indicates statistically significant Poly-3 test for pairwise comparison between control and exposed group. Statistical analysis using overall rates were only conducted if adjusted rates were not determined.
[b] Adjusted rate not reported.
[c] Adjusted rate: Poly-3 estimated neoplasm incidence (expressed as % of animals with neoplasm) adjusted for intercurrent mortality. *p*-Value under control group indicates statistically significant positive Poly-3 trend test.
p-Value under treatment group incidence data indicates statistically significant Poly-3 test for pairwise comparison between control and exposed groups, using adjusted rates.
[d] Duodenum, jejunum, or ileum.

In conclusion, exposure of B6C3F1 mice to sodium dichromate dihydrate in drinking water for 2 years resulted in significant increases in the incidences of neoplasms of the small intestine in males and females at doses ≥ 2.4 and ≥ 3.1 mg Cr(VI)/kg bw/day, respectively. NTP (2008) concluded that the results of this study provided clear evidence of carcinogenic activity of sodium dichromate dihydrate in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine. Although water consumption was reduced in both male and female rats and mice at the two highest doses, the NTP concluded that the animals in this two-year bioassay were not suffering from dehydration, and thus this reduced water consumption had little impact on the study results (Draft USEPA, 2010). A LOAEL of 0.38 mg

Cr(VI)/kg bw/day could be identified for non-neoplastic lesions of the intestine (minimal-to-mild diffuse epithelial hyperplasia of the duodenum) from this study.

4 DOSE-RESPONSE ANALYSIS AND QUANTITATIVE CANCER RISK ASSESSMENT (WP2)

4.1 Other quantitative cancer risk assessments of Cr(VI)

4.1.1 Inhalation, workers

It is well established that Cr(VI) compounds cause lung cancer in humans and animals by the inhalation route. Quantitative cancer risk assessments of Cr(VI) for the inhalation route in workers have been published by several authorities around the world and in the scientific literature. The most recent ones are presented and discussed below.

4.1.1.1 SCOEL, 2004

SCOEL (Scientific Committee on Occupational Exposure Limits, 2004) proposed to derive cancer risk estimates from more than one study as under- or over-estimation of exposure conditions in individual studies could have had dramatic effects on any quantitative risk estimation derived from such epidemiological findings. SCOEL (2004) used summary epidemiological findings from ten published cohort studies reviewed by Steenland et al (1996), involving chromate production workers, chromate pigment production workers and chromium platers (see table 4.1 below). An overall lung cancer SMR of 266 was calculated.

Table 4.1: Selected studies of Cr(VI)-exposed workers (from Steenland et al., 1996)

Study	Industry type	Lung cancer SMR	95% CI
Enterline (1974)	Chromate production	943	(733 – 1193)
Hayes *et al* (1979)	Chromate production	203	(155 – 263)
Alderson *et al* (1981)	Chromate production	242	(200 – 290)
Satoh *et al* (1981)	Chromate production	923	(627 – 1310)
Korallus *et al* (1982)	Chromate production	210	(156 – 276)
Frentzel-Beyme (1983)	Chromate pigment production	204	(123 – 319)
Davies (1984a&b)	Chromate pigment production	182	(137 – 243)
Sorohan *et al* (1987)	Chromium electroplaters	150	(117 – 189)
Hayes *et al* (1989)	Chromate pigment production	143	(93 – 213)
Takahashi *et al* (1990)	Chromium electroplaters	187	(81 – 369)
Overall		**266**	**(243 – 292)**

Measured exposure data were not available in the meta-analysis by Steenland et al. (1996), resulting in a number of assumptions being made. It was assumed that the mean length of employment of all study subjects included in the ten selected studies was 15 years. Three separate series of calculations were then made, in which the typical TWA (time-weighted average) occupational exposure of these study subjects was assumed to be (based on expert judgement) either 500 μg/m^3, 1000 μg/m^3 or 2000 μg/m^3. Consequently, the mean cumulative exposure to Cr(VI) of the study subjects was assumed to be either 7500 μg/m^3-yr (assumption 1),15000 μg/m^3-yr (assumption 2) or 30000 μg/m^3-yr (assumption 3). For each of these assumptions, three further scenarios were considered. Firstly, all the excess SMR was considered to be due to Cr(VI) exposure (the SMR of 266 represented an excess SMR of 166, or excess relative risk of 1.666) (scenario a). Secondly, confounding by smoking or other occupational exposures meant that the baseline SMR was 130 and not 100 (i.e. in the absence of Cr(VI) exposure the overall SMR in the selected cohorts was 130, with smoking + other exposures accounted for 30% of the lung cancer mortality risk above the baseline SMR); the overall relative excess risk was thus 1.36 (scenario b). Thirdly, confounding by smoking or other occupational exposures meant that the baseline SMR was 160 and not 100 (i.e. smoking + other exposures accounted for 60% of the lung cancer mortality risk above the baseline SMR); the overall excess relative risk was thus 1.06 (scenario c).

A linear relationship between relative risk (RR) of lung cancer mortality and cumulative Cr(VI) exposure was assumed according to the formula:

$RR = 1 + \beta X \quad or \quad RR - 1 = \beta X$

where

RR = risk of dying from lung cancer at a given exposure X relative to risk of dying from lung cancer if unexposed;

1 = relative risk of the unexposed

RR – 1 = excess RR

β = risk coefficient

X = cumulative Cr(VI) exposure in μg/m^3-yr

For each set of assumptions, an estimate of the risk coefficient (β) – the excess relative risk due to 1 μg/m^3-yr of exposure – was obtained by dividing the total estimated excess relative risk by the estimated mean individual cumulative exposure. For example, a risk coefficient of 0.0002213 was calculated for scenario (a) (excess SMR = 166; excess RR = 1.66) at a TWA of 500 μg Cr(VI)/m^3 for 15 years (assumption 1), equivalent to a cumulative exposure of 7500 μg Cr(VI)/m^3-yr (1.66/7500 μg/m^3-yr = 0.0002213 excess relative risk at 1 μg/m^3-yr). These risk coefficients were then applied to life-table calculations in which a population of 1000 male workers aged 20 years

was assumed to be exposed to different TWA Cr(VI) concentrations over a working lifetime (40 years) and followed up to the age of 85 years. The risk coefficient (a measure of relative risk and not of absolute risk) was assumed to be constant at all ages and periods of follow-up. The life-table analysis was considered to provide a theoretical attenuation of the risk estimates as a result of the age-specific lung cancer mortality rates. The 1981 life-table for England and Wales lung cancer mortality was used. This life-table predicted a background incidence of lung cancer mortality of 84.74 cases (before the age of 85 years) among 1,000 UK males followed from the age of 20 years.

For scenario (a) and assumption 1 (cumulative exposure of 7500 µg Cr(VI)/m^3-yr), the life-table calculations predicted a total of 113.18 lung cancers among 1,000 UK males before the age of 85 years. The number of excess cancers was thus predicted to be 28.4 (113.18 – 84.74) in 1,000 males.

The life-table calculations were then repeated for a number of TWA values (50, 25, 10, 5, and 1µg/m^3) and then each set of TWA values was considered in conjunction with alternative assumptions about the magnitude of the overall excess risk which could be attributed to Cr(VI) exposure. Numbers of excess lung cancers in 1,000 male workers exposed for a working lifetime (40 years) to 50 µg/m^3 of Cr(VI) and followed to age 85 were predicted to be in the range 5 - 28 (depending on different scenarios and assumptions). The corresponding number of excess lung cancers was estimated to be about 2 - 14 x 10^{-3} for an exposure level of 25 µg/m^3, 1 - 6 x 10^{-3} for an exposure level of 10 µg/m^3, 0.5 - 3 x 10^{-3} for an exposure level of 5 µg/m^3 and 0.1 - 0.6 x 10^{-3} for an exposure level of 1 µg/m^3. At each exposure concentration, the lower risk estimate of the range was derived from the assumptions of scenario (c) (excess RR = 1.06) with the highest Cr(VI) concentration of 2000 µg/m^3; the higher risk estimate of the range was derived from the assumptions of scenario (a) (excess RR = 1.66) with the lowest Cr(VI) concentration of 500 µg/m^3.

Table 4.2: SCOEL (2004) excess lifetime lung cancer risk estimates for male UK workers at different Cr(VI) exposure concentrations by applying a life-table analysis up to age 85

TWA Cr(VI) exposure concentration (µg/m^3)	Cumulative Cr(VI) exposure over 40 years (µg/m^3-yr)	Excess lung cancer risk in male UK workers
50	2000	5 - 28 x10^{-3}
25	1000	2 - 14 x10^{-3}
10	400	1 - 6 x10^{-3}
5	200	0.5 - 3 x10^{-3}
1	**40**	**0.1 - 0.6 x10^{-3}**
0.5	20	0.5 - 3 x10^{-4}
0.25	10	0.2 - 1.4 x10^{-4}
0.1	4	0.1 - 0.6 x10^{-4}
0.01	0.4	0.1 - 0.6 x10^{-5}

Unit (at 1 µg/m^3) excess risk is highlighted in bold

Overall, a **unit excess lifetime lung cancer risk of 0.1 - 0.6x10^{-3}** was estimated by SCOEL (2004) for male UK workers at an exposure

concentration of 1 µg/m^3 Cr(VI) for a working life (40 years) by applying a life-table analysis up to age 85. As a linear relationship was assumed, this unit risk can be easily used to calculate excess lung cancer risks at other exposure levels.

It is noted that although this risk estimate derives from a large meta-analysis of 10 studies involving chromate production workers, chromate pigment production workers and chromium platers, such review paper lacked information on exposure intensity and duration. Thus, SCOEL assumed that the overall SMR of 266 (RR = 2.66) derived from these 10 studies was associated with an average exposure duration of 15 years at three possible (but relatively high) Cr(VI) exposure concentrations of 500, 1000 or 2000 µg/m^3 (equivalent to cumulative Cr(VI) exposures of 7500, 15000 and 30000 µg/m^3–yr). These exposure assumptions might explain why lower risk estimates were calculated by SCOEL in comparison to other risk evaluations of Cr(VI) that are publically available (see below). It is also noted that the Luippold et al. (2003) cohort study used together with the Gibb et al. (2000) study by other regulatory bodies or publications to estimate Cr(VI) cancer risks was not available at the time SCOEL performed its assessment. The contractor believes that these shortcomings, especially the exposure estimates, restrict the applicability of the SCOEL assessment.

4.1.1.2 OSHA (2006)

OSHA (2006) considered that two recently studied occupational cohorts, those by Gibb et al. (2000) and Luippold et al. (2003) had the strongest data sets on which to quantify lung cancer risks from cumulative Cr(VI) exposure (i.e. air concentration x exposure duration). Of the various available studies, these two had the most extensive and best documented Cr(VI) exposures spanning three or four decades. Both cohort studies characterized observed and expected lung cancer mortality and reported a statistically significant positive association between lung cancer risk and cumulative Cr(VI) exposure. Both studies accounted for confounding by smoking, were large and had extensive follow-up.

A variety of exposure-response models were fitted to these data, including linear relative risk, quadratic relative risk, log-linear relative risk, additive risk, and Cox proportional hazards models. The linear relative risk models generally provided a superior fit to the data when compared to other relative risk models and hence, estimates from these linear models were selected. To calculate excess cancer risks for a working life of 45 years (from 20 to 65 years) at specific Cr(VI) exposure concentrations, life-table analyses were made of the number of extra lung cancers per 1,000 workers exposed to Cr(VI) based on the linear relative risk estimates. The life-table accounted for both lung cancer risk and competing mortality through age 100. Rates of lung cancer for the life-table calculations were based on the 2000 U.S. lung cancer mortality rates for both sexes and all races. In addition to the maximum likelihood estimates, 95% confidence intervals (CI) for the excess (work) lifetime risks were derived.

As it can be seen from table 4.3 below, the maximum likelihood estimates from the linear relative risk model fitted to the Gibb et al. (2000) data were three- to five-fold higher than the estimates based on the Luippold et al. (2003) data at equivalent cumulative Cr(VI) exposures and the confidence limits around the projected risks from the two data sets did not overlap. This indicated that the maximum likelihood estimates derived from one data set were unlikely to describe the lung cancer mortality observed in the other data set. Despite this statistical inconsistency between the risk estimates, the differences between them were not considered to be unreasonably great given the potential uncertainties involved in estimating cancer risks from the data. Since the analyses based on these two cohorts were each of high quality and their projected risks were reasonably close (well within an order of magnitude), OSHA (2006) considered the excess lifetime risk of lung cancer from occupational exposure to Cr(VI) to be best represented by the range of risks that lie between the maximum likelihood estimates of the Gibb et al. (2000) and Luippold et al. (2003) data sets.

Table 4.3: OSHA (2006) excess lifetime lung cancer risk estimates for male US workers at different Cr(VI) exposure concentrations by applying a life-table analysis up to age 100

TWA Cr(VI) exposure concentration ($\mu g/m^3$)	**Cumulative Cr(VI) exposure over 45 years ($\mu g/m^3$-yr)**	**OSHA best estimates of excess lung cancer risk in workers**	**Maximum likelihood estimates and 95% CI of excess lung cancer risk in workers based on the Gibb et al. (2000) cohort**	**Maximum likelihood estimates and 95% CI of excess lung cancer risk in workers based on the Luippold et al. (2003) cohort**
52	2340	$101 - 351 \times 10^{-3}$	351×10^{-3} ($181 \times 10^{-3} - 493 \times 10^{-3}$)	101×10^{-3} ($62 \times 10^{-3} - 147 \times 10^{-3}$)
20	900	$41 - 164 \times 10^{-3}$	164×10^{-3} ($76 \times 10^{-3} - 256 \times 10^{-3}$)	41×10^{-3} ($21 \times 10^{-3} – 60 \times 10^{-3}$)
10	450	$21 - 86 \times 10^{-3}$	86×10^{-3} ($39 \times 10^{-3} - 142 \times 10^{-3}$)	21×10^{-3} ($12 \times 10^{-3} - 31 \times 10^{-3}$)
5	225	$10 - 45 \times 10^{-3}$	45×10^{-3} ($20 \times 10^{-3} – 75 \times 10^{-3}$)	10×10^{-3} ($6.2 \times 10^{-3} – 15 \times 10^{-3}$)
1	**45**	**$2.1 - 9.1 \times 10^{-3}$**	**9.1×10^{-3}** ($4 \times 10^{-3} – 16 \times 10^{-3}$)	**2.1×10^{-3}** ($1.2 \times 10^{-3} – 3.1 \times 10^{-3}$)
0.5	22.5	$1.0 - 4.6 \times 10^{-3}$	4.6×10^{-3} ($2 \times 10^{-3} – 7.8 \times 10^{-3}$)	1.0×10^{-3} ($0.62 \times 10^{-3} – 1.6 \times 10^{-3}$)
0.25	11.25	$0.52 - 2.3 \times 10^{-3}$	2.3×10^{-3} ($1 \times 10^{-3} – 3.9 \times 10^{-3}$)	0.52×10^{-3} ($0.31 \times 10^{-3} – 0.79 \times 10^{-3}$)
0.1	4.5	$0.21 - 0.91 \times 10^{-3*}$		
0.01	0.45	$0.21 - 0.91 \times 10^{-4*}$		

* extrapolated values

OSHA (2006) best estimates of numbers of excess lung cancers in 1000 workers exposed for a working lifetime (45 years) to 52 µg/m^3 of Cr(VI) and followed up to age 100 were in the range 101 - 351. The corresponding number of excess lung cancers was estimated to be about 41 - 164 x 10^{-3} for an exposure level of 20 µg/m^3, 21 - 86 x 10^{-3} for an exposure level of 10 µg/m^3, 10 - 45 x 10^{-3} for an exposure level of 5 µg/m^3 and 2.1 – 9.1 x 10^{-3} for an exposure level of 1 µg/m^3.

Overall, a **unit excess lifetime lung cancer risk of 2.1 – 9.1 x10^{-3}** was estimated by OSHA (2006) for male US workers at an exposure concentration of 1 µg/m^3 Cr(VI) for a working life (45 years) by applying a life-table analysis up to age 100. As a linear relationship was assumed, this unit risk can be easily used to calculate excess lung cancer risks at other exposure concentrations.

It is noted that OSHA (2006) risk estimates are much higher (more than one order of magnitude) than those calculated and proposed by SCOEL (2004). This is explained by the fact that the reconstructed cumulative Cr(VI) exposures in the Gibb et al. (2000) and Luippold et al. (2003) cohort studies, on which the OSHA risk estimates are based, were much lower (mean Cr(VI) cumulative exposure was 134 µg/m^3-yr in the Gibb cohort and 1580 µg/m^3-yr in the Luippold cohort) than the cumulative Cr(VI) exposures assumed by SCOEL for the Steenland meta-analysis (7500, 15000 or 30000 µg/m^3-yr) on which the SCOEL risk estimates are based. It is important to point out that there is great uncertainty in both the exposure assumptions made by SCOEL and the reconstructed exposure values from the Gibb et al. (2000) and Luippold et al. (2003) cohort studies.

In addition, OSHA (2006) concluded that the slightly soluble Cr(VI) compounds produced a higher incidence of respiratory tract tumors than highly water soluble or highly water insoluble Cr(VI) compounds in animal studies using similar experimental conditions. This is likely to reflect the greater tendency for chromates of intermediate water solubility to provide a persistent high local concentration of solubilized Cr(VI) in close proximity to the target cell. Highly soluble chromates dissolve and diffuse rapidly in the aqueous fluid lining the epithelia of the lung and are cleared more quickly from the respiratory tract. Thus, these chromates are less able to achieve the higher and more persistent local concentrations within close proximity of the lung cell surface than the slightly water soluble chromates. Water insoluble Cr(VI) particulates are also able to come in close contact with the lung cell surface but do not release readily absorbable chromate ions into the biological environment as rapidly.

Thus, OSHA concluded that slightly soluble Cr(VI) compounds are likely to exhibit a greater degree of carcinogenicity than highly water soluble or water insoluble Cr(VI) when the same dose is delivered to critical target cells in the respiratory tract of the exposed worker. OSHA also believed it reasonable to regard water insoluble Cr(VI) to be of similar carcinogenic potency to highly

water soluble Cr(VI) compounds in the absence of convincing scientific evidence to indicate otherwise.

After evaluating lung cancer rates in other occupational cohort studies with respect to the forms of Cr(VI) in the workplace, reliability in the Cr(VI) exposure data, and the presence of potentially confounding influences (e.g. smoking) and bias (e.g. healthy worker survivor bias) as well as information on solubility, particle size, cell uptake, and other factors influencing delivery of Cr(VI) to lung cells, OSHA considered the risks estimated from the Gibb and Luippold cohorts to represent adequately risks to workers exposed to equivalent levels of Cr(VI) compounds in other industries.

OSHA (2006) considered that, as with any risk assessment, there is some degree of uncertainty in the projection of risks as a result of the data, assumptions, and methodology used in the analysis. The exposure estimates in the Gibb et al. and Luippold et al. data sets relied, to some extent, on a paucity of air measurements using less desirable sampling techniques to reconstruct Cr(VI) exposures, particularly in the 1940s and 1950s. Additional uncertainty is introduced when extrapolating from the cohort exposures, which usually involved exposures to higher Cr(VI) levels for shorter periods of time to an equivalent cumulative exposure involving a lower level of exposure for a working lifetime. The study cohorts consisted mostly of smokers, but detailed information on their smoking behaviour was unavailable. While the risk assessments make some adjustments for the confounding effects of smoking, it is unknown whether the assessments fully account for any interactive effects that smoking and Cr(VI) exposure may have on carcinogenic action. However, OSHA did not have reason to believe that the above uncertainties had introduced errors that had resulted in serious over-prediction or under-prediction of risk.

4.1.1.3 Goldbhom et al., 2006

In this publication, the authors selected the three cohort studies by Mancuso (1997), Gibb et al. (2000), and Luippold et al. (2003)/Crump et al. (2003) for quantitative cancer risk estimation of Cr(VI). All three publications included the minimal data rerquired for an independent assessment, had quantified exposure (based on airborne concentrations of Cr(VI)), and used several exposure categories to enable exposure–response modelling. The study by Mancuso et al. (1997) was used in the risk assessment conducted by the EPA (U.S. Environmental Protection Agency, 1998) as the best study before the much larger study by Gibb et al. (2000) became available.

The Mancuso study was the smallest, with the exposure assessment being based on one industrial hygiene survey only. However, exposure levels and contrast in exposure were high. No information on smoking status of the cohort was available. A dose-related increase in lung cancer mortality was reported in association with cumulative exposure to Cr(VI) (RR = 5.1 at 0.25 – 0.49 mg/m^3-yr; RR = 6.1 at 0.5 – 0.99 mg/m^3-yr; RR = 8.0 at 1.0 – 1.99 mg/m^3-yr; RR = 13.2 at 2.0 – 3.99 mg/m^3-yr).

The Gibb study was by far the largest study; exposure assessment was based on frequent industrial hygiene surveys, and data on smoking status were available for 93% of the cohort, which is important, as smoking is a strong determinant of lung cancer and therefore a serious potential confounder. The exposure levels and contrast in exposure were, however, low (for more details of the study, see above).

The Luippold/Crump study, conducted in cohorts from the same Ohio plant but from a more recent generation than the Mancuso study, was much smaller, but had extensive exposure information and relatively high exposure levels. Smoking status was known for part of the cohort (for more details of the study, see above).

The authors decided to estimate the lifetime risk of cancer for all three studies separately and not to use a combined estimate of the RR to get better insight into the differences and similarities between the estimates. The authors fitted to the three datasets a linear relative risk model [RR = 1+ β(exposure)] and a log-linear model [RR = $e^{\beta(exposure)}$)] through Poisson regression. As the linear Poisson regression model failed to converge for the Mancuso data, the authors used linear regression (least squares) with the reported age-adjusted lung cancer mortality rates instead.

The highest RR per unit of exposure was estimated from the Gibb study, followed by the Mancuso cohort and the Luippold/Crump study. The results did not differ very much between the linear and log-linear model for the Mancuso and Crump data, in contrast to the Gibb dataset, which resulted in very high RRs for the log-linear model.

The linear relative risk function of cumulative Cr(VI) exposure derived from each dataset was then used to estimate the Excess Lifetime Risk (ELR) for a worker population during a working life of 40 years using the age-specific lung cancer death rates of the Dutch general male population (121- 834 per 100,000 from age 58 yr to 89 yr, Visser et al., 2001). ELRs were calculated using both the life-table analysis (which takes into account that a cohort is dying out from other causes of death than just lung cancer) and the conditional method. It is well established that the conditional method results in overestimation of risks especially with increasing old age when all-cause mortality has a stronger impact.

The ELRs for lung cancer deaths up to age 89 for occupational exposure to 1 µg/m^3 Cr(VI) for 40 years as calculated from the life tables, ranged between 3 and 16 x 10^{-3} for the three datasets. If based on the conditional method up to age 89, the ELRs were almost twice as high. If the background lung cancer mortality rate was that of a non-smoking population, the ELRs were 10 times smaller.

Table 4.4: Excess Lifetime Risks of lung cancer death for male Dutch workers exposed to 1 µg/m^3 Cr(VI) for 40 years based on 3 different datasets and the linear relative risk model

Data set	Mancuso (1997)	Gibb et al. (2000)	Luippold/Crump et al. (2003)
Life table method Up to age 89	**5.9×10^{-3}**	**16.4×10^{-3}**	**3.0×10^{-3}**
Estimate based on low background lung cancer mortality risk of never smokers	0.6×10^{-3}	1.7×10^{-3}	0.3×10^{-3}
Conditional method Up to age 89	10.5×10^{-3}	29.7×10^{-3}	5.2×10^{-3}

Overall, a **unit excess lifetime lung cancer risk of 3 – 16 $x10^{-3}$** was estimated by Goldbohm et al. (2006) for male Dutch workers at an exposure concentration of 1 µg/m^3 Cr(VI) for a working life (40 years) by applying a life-table analysis up to age 89. As a linear relationship was assumed, this unit risk can be easily used to calculate excess lung cancer risks at other exposure concentrations.

The authors commented that the results (point estimates) of the risk estimation based on the three studies (with the application of a linear relative risk model) were all within a relatively small range, i.e., 3 – $16x10^{-3}$ excess lung cancer deaths up to age 89 at 1 µg/m^3 Cr(VI) for a working life (40 years). The Gibb study resulted in the highest estimates, because it had the steepest slope; the difference between this and the other two studies was that the average exposure was lower and the exposure range much smaller in the Gibb study. This might indicate that the true shape of the exposure–response relation is more like a square root, where the curve begins steep but levels off at higher exposures. Such a shape has been observed for many other substances as well, but it is speculated that it is due to bias (Stayner et al., 2003). On the other hand, it might indicate that the Gibb study, although by far the largest, is hampered by the small range of exposures resulting in a less robust estimate of the slope, due to a low signal-to-noise ratio.

The authors also commented that the evaluation illustrated that the outcome of the risk assessment process as quantified by the ELR relies heavily on the background rates of specific cancers in the population of interest, since relative risk is used as input. If this background rate is strongly influenced by other environmental or lifestyle risk factors, such as smoking on lung cancer, the derived excess lifetime risk may vary with a factor of up to 10 depending on the proportion of smokers in the population. This is true even if the epidemiological data may have shown that no interaction between the two risk factors was present. In other words, the RR for exposure to a certain substance can be the same for smokers as for non-smokers, but the ELR shows a difference up to one order of magnitude depending on the proportion of smokers in the population. This is because the effect of exposure multiplies the background risk in relative risk models.

4.1.1.4 Seidler et al., 2012

In this publication, the authors systematically searched the open literature for studies reporting on occupational Cr(VI) exposure and cancers of the respiratory tract. To be included, studies needed to provide data for more than one level of occupational Cr(VI) exposure, adequately consider the confounding effects of smoking and be of adequate methodological quality.

Six articles were found to provide potentially relevant data for establishing an exposure-risk relationship (Crump et al., 2003; Gibb et al., 2000; Gerin et al., 1993; Park et al., 2004; Park and Stayner, 2006; Luippold et al., 2003). These studies were based on the data from three retrospective cohorts. The study authors combined the information concerning the same cohort and considered data from one cohort published in separate papers as one dataset for the further phases of the evaluation. Only studies on two of the cohorts were considered to be of acceptable methodological quality, so that they could be included in the derivation of the exposure–response relationship; these were studies on the Baltimore cohort (Gibb et al., 2000; Park et al., 2004; Park and Stayner, 2006) and the Painesville cohort (Crump et al., 2003; Luippold et al., 2003). Another study (Gerin et al., 1993) did not consider smoking sufficiently and lacked a detailed description of exposure measurement methods. It was therefore given a low-quality assessment score and not considered for the derivation of exposure-risk relationships.

A linear model

$$SMR = \beta \times Cr(VI)\text{-}years + SMR_0$$

was applied to the datasets from the two cohorts (Gibb et al., 2000/Park et al., 2004 for the Baltimore cohort and Luippold et al., 2003/Crump et al., 2003 for the Painesville cohort), where β is the estimate of exposure effect and SMR_0 is the calculated standardized mortality ratio (SMR) for the cohort in the absence of any occupational Cr(VI) exposure. The least square approach was used to fit the linear model to the crude extracted data with Cr(VI)-years as the explanatory (independent) variable and SMR as the response (dependent) variable. The equivalent linear model for relative risks (RRs) was

$$RR = \beta \times Cr(VI)\text{-}years + 1$$

Both Gibb et al. (2000) and Park et al. (2004) analysed data obtained from the Baltimore cohort. However, these studies used different exposure categories to calculate the SMRs. Whereas the evaluation by Gibb et al. (2000) was based on four categories where the number of observed deaths was approximately evenly distributed, Park et al. (2004) divided the data into five categories, placing 60 % (N = 72) of the observed deaths into the lowest exposure category and further sub-categorizing the higher exposures. By fitting a linear model to the data provided by Gibb et al. (2000), an estimate of exposure effect (slope) β of 4.52 was obtained. The estimate of the exposure effect β obtained by fitting the linear model to the Park et al. (2004) data was lower (2.82), but appeared to be better suited to the linear model. In addition, the correlation coefficient of the linear model's fit to the Park data was significant.

The Cr(VI) exposure range examined for the Painesville cohort was considerably wider than that of the Baltimore cohort. The highest reported cumulative exposure given for the Painesville cohort (Luippold et al., 2003, Crump et al., 2003) was 29 mg/m^3-years. By fitting a linear model to the data provided by Luippold et al. (2003) and Crump et al. (2003), an estimate of exposure effect (slope) β of 0.68 was obtained.

For aggregating the studies, a mean β value was calculated from the individual estimates β derived from Luippold et al. (2003)/Crump et al. (2003) and Park et al. (2004). The results from Gibb et al. (2000) were not taken into account as the Park et al. (2004) evaluation of the Baltimore cohort provided a more detailed representation of the higher cumulative Cr(VI) exposures levels, potentially reducing the effect of the inclusion of workers with short-term Cr(VI) exposure and improving comparability to the exposure categories in the studies by Luippold et al. (2003)/Crump et al. (2003). A mean β of 1.75 was thus obtained ([0.68 + 2.82]/2).

The excess lifetime (absolute) risk associated with a defined cumulative occupational exposure to Cr(VI), ELR(x) was then estimated by subtracting the background lung cancer risk found in the general population. As the epidemiological studies of Cr(VI) exposure reported the cancer risk only for male workers, a male reference population was used. In the case of a linear dose–response relationship, the ELR(x) is calculated by multiplying the lifetime risk in the reference population ($LR_{nonexposed}$) by the excess relative risk due to a given cumulative Cr(VI) exposure (conditional method):

$$ELR(x) = RR \times LR_{nonexposed}$$
$$= (\beta \times Cr(VI)\text{-}years + 1)\, LR_{nonexposed}$$

The cumulative lifetime risks of dying from lung cancer for males between ages 0 and 74 ($LR_{nonexposed}$ = 48/1000) were obtained from the Globocan project for the 27 EU member states (Globocan, 2008). A lifetime working time of 40 years (age 20 to 60) was assumed. In addition, as the conditional method had a tendency to overestimate excess risks especially at older ages, ELRs for 1 µg/m^3 Cr(VI) workplace air concentration were calculated for a German male population ($LR_{nonexposed}$ = 41/1000) by applying both the conditional method up to age 74 and the life-table method up to age 74, 80, or 89.

Table 4.5: Excess Lifetime Risks of lung cancer death for male <u>European</u> workers exposed to different concentrations of Cr(VI) for 40 years based on 3 datasets and applying the conditional method

Cr(VI) exposure concentration (µg/m^3)	Cumulative Cr(VI) exposure over 40 years (µg/m^3-yr)	ELR of lung cancer based on <u>Luippold/Crump et al. (2003) and Park et al. (2004)</u> β = 1.75	ELR of lung cancer based on <u>Luippold/Crump et al. (2003)</u> β = 0.68	ELR of lung cancer based on <u>Park et al. (2004)</u> β = 2.82	ELR of lung cancer based on <u>Gibb et al. (2000)</u> β = 4.52

50	2000	168×10^{-3}	65.3×10^{-3}	270.7×10^{-3}	413.9×10^{-3}
25	1000	84×10^{-3}	32.6×10^{-3}	135.4×10^{-3}	217.0×10^{-3}
10	400	33.6×10^{-3}	13.1×10^{-3}	54.1×10^{-3}	86.8×10^{-3}
5	200	16.8×10^{-3}	6.53×10^{-3}	27.1×10^{-3}	43.4×10^{-3}
2.5	100	8.4×10^{-3}	3.26×10^{-3}	13.5×10^{-3}	21.7×10^{-3}
1	**40**	**3.36×10^{-3}**	**1.31×10^{-3}**	**5.41×10^{-3}**	**8.68×10^{-3}**
0.5	20	1.68×10^{-3}	0.65×10^{-3}	2.71×10^{-3}	4.34×10^{-3}
0.25	10	0.84×10^{-3}	0.33×10^{-3}	1.35×10^{-3}	2.17×10^{-3}
0.1	4	0.34×10^{-3}	0.13×10^{-3}	0.54×10^{-3}	0.87×10^{-3}
0.01	0.4	0.34×10^{-4}	0.13×10^{-4}	0.54×10^{-4}	0.87×10^{-4}

Overall, based on relative risk calculations from the pooled mean of β (1.75) from the Luippold/Crump et al. (2003) and Park et al. (2004) studies, a **unit excess lifetime lung cancer risk of 3.36×10^{-3}** was estimated for male European workers by Seidler et al. (2012) at an exposure concentration of 1 µg/m^3 Cr(VI) for a working life (40 years) by applying the conditional method. As a linear relationship was assumed, this unit risk can be easily used to calculate excess lung cancer risks at other exposure concentrations.

Table 4.6: Excess Lifetime Risks of lung cancer death for male German workers exposed to 1 µg/m^3 Cr(VI) for 40 years based on the combined Luippold/Crump et al. (2003) and Park et al. (2004) studies and applying both the conditional method and the life-table analysis

Cr(VI) exposure concentration (µg/m^3)	Cumulative Cr(VI) exposure over 40 years (µg/m^3-yr)	Method	Up to age (yr)	ELR of lung cancer based on Luippold/Crump et al 2003 and Park et al 2004 β = 1.75
1	40	Conditional	74	2.9
1	40	Life-table	74	2.3
1	40	Life-table	80	3.2
1	**40**	**Life-table**	**89**	**4.1**

Lung cancer mortality is slightly lower for the German population (41/1,000) compared to the European population (48/1,000). Therefore, the excess absolute risk for 1 µg/m^3 workplace air concentration of Cr(VI) decreased from 3.3 per 1,000 for the European population to 2.9 per 1,000 for the German

population (based on the conditional method up to age 74). Additionally, excess risks were calculated by a life-table analysis up to ages 74, 80, or 89 years. When the life-table analysis was applied, the excess absolute risk slightly diminished from 2.9 per 1,000 to 2.3 per 1,000 for the German population (up to age 74). However, the excess absolute risk rose to 4.1 per 1,000 when mortality was followed up to age 89 (life-table method).

Overall, based on relative risk calculations from the pooled mean of β (1.75) from the Luippold/Crump et al. (2003) and Park et al. (2004) studies, a **unit excess lifetime lung cancer risk of 4.1 x10^{-3}** was estimated for male German workers by Seidler et al. (2012) at an exposure concentration of 1 µg/m^3 Cr(VI) for a working life (40 years) by applying a life-table analysis up to age 89.

The authors commented that these risk estimates needed to be seen in the context of the limitations of the analysis being performed; these limitations arose from uncertainties in the exposure measurements conducted in the studies selected, from deficiencies in the assessment of possible co-exposures to other lung carcinogens, and from the lack of complete assessment of confounding factors, especially smoking. All these limitations implied that there is considerable uncertainty in the risk calculations presented. Another important limitation concerned transferability of the risk estimates derived from the Baltimore and Painesville cohorts (exposed to relatively small particles of soluble and sparingly soluble Cr(VI) compounds) to workplaces outside chromate production. Transferability to other workplaces may be limited by different physical forms, particle sizes and solubilities of the Cr(VI) compounds present in these other occupational scenarios.

The authors also commented that there were remarkable differences in the excess risk estimates derived from the Baltimore (higher risks) and Painesville cohorts (lower risks). The authors discussed several factors, which could have explained these differences. The employment period of the Painesville cohort began a decade earlier than that of the Baltimore cohort (1940 compared to 1950). The working conditions changed over these years causing a decrease in airborne Cr(VI) concentrations. Smoking status was known for only 41 % of the Painesville cohort. The inclusion of very short-term employees (working less than 90 days) in the Baltimore cohort could also have led to an increased SMR in the low exposure range for this cohort.

4.1.2 Inhalation, general population

It is well established that Cr(VI) compounds cause lung cancer in humans and animals by the inhalation route.

There is only a small number of quantitative cancer risk assessments of Cr(VI) for the inhalation route in the general population. These are briefly presented below.

An unit excess lifetime lung cancer risk of 1.2 $x10^{-2}$ at an environmental exposure concentration of 1 µg Cr(VI)/m^3 for 70 years was established by the USEPA (1998). This unit risk resulted in an excess lifetime risk of 10^{-6} at an exposure concentration of 0.08 ng Cr(VI)/m^3 for 70 years.

An unit excess lifetime lung cancer risk of 4 $x10^{-2}$ at an environmental exposure concentration of 1 µg Cr(VI)/m^3 for 70 years was established by WHO (Air Quality Guidelines, 2000). This unit risk resulted in an excess lifetime risk of 10^{-6} at an exposure concentration of 0.025 ng Cr(VI)/m^3 for 70 years.

These risk estimates were derived by applying linear models to various occupational epidemiology datasets (published in the 70s and 80s) and by extrapolating risks from occupational exposure durations (8h/day, 5 days/week for 40 years) to average lifetime exposures (24h/day, 7 days/week for 70 years).

A cancer-based chronic inhalation reference value for the general population of 0.24 µg Cr(VI)/m^3 has been recently established by Haney et al. (2012) using a nonlinear, threshold approach. This value was derived from a NOAEC in workers of 19.9 µg Cr(VI)/m^3 estimated on the basis of a lack of a statistically significant increase in lung cancer in humans from the epidemiological study conducted by Birk et al. (2006) in the German chromate production industry. This NOAEC was equivalent to a cumulative no effect exposure level of 0.195 mg Cr(VI)/m^3-yr and a mean exposure duration of 9.8 years. This was the lowest point of departure (PoD) that could be estimated from those human carcinogenicity dose-response studies considered by the authors to be of high methodological quality. A NOAEC of 83.9 µg Cr(VI)/m^3 (equivalent to a cumulative no effect exposure level of 0.26 mg Cr(VI)/m^3-yr and a mean exposure duration of 3.1 years) was calculated from the study conducted by Park and Steyner (2006) in the Baltimore chromate production cohort and a NOAEC of 88.8 µg Cr(VI)/m^3 (equivalent to a cumulative no effect exposure level of 0.817 mg Cr(VI)/m^3-yr and a mean exposure duration of 9.2 years) was estimated from the study conducted by Luippold et al. (2003) in the Painesville chromate production cohort.

In the study by Birk et al. (2006), the mortality of 901 male workers from two German chromate production plants employed since each plant converted to a no-lime production process, was followed-up through 1998. More than 12,000 urine samples and 450 air samples were available to characterise Cr(VI) exposure, and smoking status was available for 93% of cohort members. The mean duration of Cr(VI) exposure was 10 years and the mean time since first exposure was 17 years. The cohort lacked sufficient job history information and air monitoring data to estimate individual airborne Cr(VI) exposures. Instead, it was possible to derive individual cumulative urinary chromium estimates as an exposure surrogate. The approximate geometric average of urinary chromium measurements from 1960 to 1998 was 7-8 µg/L. Overall, the SMR for lung cancer mortality appeared to be increased (SMR = 148; 95%CI: 93-225) in comparison to the German population rate. No clear dose-response was found in stratified analyses by duration of employment

and time since hire. However, on the basis of urinary chromium data, lung cancer risk was elevated only in the highest cumulative exposure group (SMR = 209; 95%CI: 1.08-3.65 at > 200 µg Cr/L urine-yr, equivalent to > 0.26 mg Cr(VI)/m^3-yr on the basis of a biological exposure index-type conversion). There was no increase in lung cancer mortality in the lower exposure groups, but the number of lung cancer deaths was small in these groups.

The worker NOAEC of 19.9 µg Cr(VI)/m^3 was subsequently adjusted to an environmental NOAEC applicable to the general population of 7.1 µg Cr(VI)/m^3 using the following dosimetric adjustment:

19.9 µg Cr(VI)/m^3 x (10/20) x (5/7) = 7.1 µg Cr(VI)/m^3

The adjustment took into account a non-occupational ventilation volume of 20 m^3 in 24 hours compared to an occupational ventilation volume of 10 m^3 in 8 hours and an exposure frequency of 7 days/wk for the general population compared to an exposure frequency of 5 days/wk for workers.

The environmental NOAEC of 7.1 µg Cr(VI)/m^3 was finally divided by an overall assessment factor of 30 to obtain a reference value of 0.24 µg Cr(VI)/m^3. The overall factor of 30 was obtained by multiplying a factor of 10 for intrahuman variability by a factor of 3 for uncertainties in the database (limited statistical power of epidemiological studies to detect increased risk at low exposure levels). The authors stated that this reference value was 3000 times higher than the 10^{-6} excess cancer risk air concentration of 0.08 ng Cr(VI)/m^3 established for the general population by the USEPA in 1998 (see above) using a linear approach.

The authors adopted a threshold approach on the basis that the considerable and rapid extracellular reduction of Cr(VI) to C(III) occurring in the lungs, which significantly minimises absorption of Cr(VI) into the lung epithelium at low exposures, imparts non-linearity to the cancer dose-response relationship of Cr(VI) in the low-dose region. The authors calculated that at the selected NOAEC of 19.9 µg Cr(VI)/m^3 only a fraction (up to a worst-case of 53%) of the lung extracellular reductive capacity of an individual (as estimated by De Flora et al., 1997 from *ex-vivo* samples – see toxicokinetic section of this document) had been consumed. The authors therefore concluded that the extracellular reduction of Cr(VI) imparts a sufficiently low slope at low exposures of Cr(VI) such that any residual cancer risk at the proposed reference value is considered to be negligible.

The contractor considers that the adoption of a threshold approach at low exposures has merit. However, there are serious flaws in using the stated human NOAEC for lung cancer as starting point. The robustness of this NOAEC is hampered by the low statistical power of epidemiological studies to detect an increased risk of lung cancer at low exposures, and cannot represent a reliable dose threshold for lung cancer.

4.1.3 Oral, general population and workers

According to IARC (2012), there is inadequate evidence that oral exposure to Cr(VI) has caused stomach or other cancers in humans. There is also no evidence that inhalation exposure to Cr(VI) in occupational cohorts has caused cancer of the gastro-intestinal tract. However, it is well established that Cr(VI) compounds cause tumours of the gastrointestinal tract in rodents by the oral route.

There are fewer quantitative cancer risk assessments of Cr(VI) for the oral route compared to the inhalation route. A recent evaluation has been produced by the USEPA in 2010 (Draft USEPA, 2010). This is presented and discussed below.

4.1.3.1 Draft USEPA, 2010 (permission to cite obtained from USEPA)

The USEPA selected the NTP bioassay in rats and mice (NTP, 2008) for dose-response assessment because it was a well-conducted lifetime animal study of Cr(VI) carcinogenicity via ingestion, and no other adequate studies of Cr(VI) carcinogenicity by the oral route were available.

In the rat study, exposure to sodium dichromate dihydrate in drinking water for 2 years resulted in a significant increase in squamous epithelial neoplasms of the oral mucosa and tongue in both sexes at the highest exposure level (average daily doses of 5.9 and 7.0 mg Cr(VI)/kg bw/day in males and females, respectively), but not at the three lower exposure levels.

Table 4.7: Incidences of squamous cell papillomas or carcinomas in the oral cavity of male F344/N rats exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Sodium dichromate dihydrate concentration (mg/L)	Estimated daily intake of Cr(VI) (mg/kg bw/day)	Incidence of squamous cell papillomas or carcinomas in examined animals
0	0	0/50 (0%)
14.3	0.21	1/50 (2%)
57.3	0.77	0/49 (0%)
172	2.1	0/50 (0%)
516	5.9	7/49 (14.5%)[a]

[a] Statistically significantly elevated above control at $p < 0.05$ using Fisher's exact test.

Table 4.8: Incidences of squamous cell papillomas or carcinomas in the oral cavity of female F344/N rats exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Sodium dichromate dihydrate concentration (mg/L)	Estimated daily intake of Cr(VI) (mg/kg bw/day)	Incidence of squamous cell papillomas or carcinomas in examined animals
0	0	1/50 (2%)
14.3	0.24	1/50 (2%)
57.3	0.94	0/50 (0%)

172	2.4	2/50 (4%)
516	7.0	11/50 (22%)[a]

[a] Statistically significantly elevated above control at $p < 0.05$ using Fisher's exact test.

In the mouse study, exposure to sodium dichromate dihydrate in drinking water for 2 years resulted in significant increases in the incidences of neoplasms of the small intestine in males and females at doses ≥ 2.4 and ≥ 3.1 mg Cr(VI)/kg bw/day, respectively.

Table 4.9: Incidences of adenomas and carcinomas combined in the small intestine of male B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Sodium dichromate dihydrate concentration (mg/L)	Estimated daily intake of Cr(VI) (mg/kg bw/day)	Incidence of adenomas or carcinomas in examined animals
0	0	1/49 (2%)
14.3	0.38	3/49 (6.1%)
28.6	0.91	2/49 (4.1%)
85.7	2.4	7/50 (14%)[a]
257.4	5.9	20/48 (41.7%)[a]

[a] Statistically significantly elevated above control at $p < 0.05$ using Fisher's exact test.

Table 4.10: Incidences of adenomas and carcinomas combined in the small intestine of female B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 2 years (from Draft USEPA, 2010)

Sodium dichromate dihydrate concentration (mg/L)	Estimated daily intake of Cr(VI) (mg/kg bw/day)	Incidence of adenomas or carcinomas in examined animals
0	0	1/49 (2%)
14.3	0.38	1/50 (2%)
57.3	1.4	4/49 (8.2%)
172	3.1	17/49 (34.7%)[a]
516	8.7	22/49 (44.9%)[a]

[a] Statistically significantly elevated above control at $p < 0.05$ using Fisher's exact test.

Of the two species, the mouse was determined to be the most sensitive because tumor incidences were statistically significantly elevated at lower doses and a greater response was exhibited by the mice at the two highest doses. Therefore, the mouse tumor incidence data were used as the basis for the derivation of the oral cancer slope factor (CSF). The CSF represents the excess cancer risk at a dose of 1 mg/kg bw/d.

In order to derive the oral CSF, BMD (benchmark dose) modelling was carried out using USEPA's BMDS (USEPA, 2000). The multistage model was fitted to the data and the $BMDL_{10}$ (lower 95% confidence bound of the dose corresponding to a BMR of 10% extra risk) was estimated. The CSF was then calculated by dividing the BMR_{10} (0.1) by the $BMDL_{10}$ and then converting this slope value to human equivalents.

A **$BMDL_{10}$ of 0.9 mg/kg bw/day** was identified in males and a $BMDL_{10}$ of 1 mg/kg bw/day was identified in females, leading to a CSF of 0.09 (mg/kg bw/day)$^{-1}$ in males and a CSF of 0.1 (mg/kg bw/day)$^{-1}$ in females. The animal CSF values were then converted in human CSF values by multiplying them for the mouse allometric scaling factor (~ 6). Human oral CSF values for tumours of the small intestine caused by Cr(VI) of 0.5 and 0.6 (mg/kg bw/day)$^{-1}$ in males and females, respectively, were calculated.

The human CSF values based on the incidence of small intestine tumors in male and female mice were very similar. Given the poorer fit of the multistage model to the female mouse data, a CSF estimate based on the male mouse data was considered to be associated with less uncertainty. Therefore, the human CSF of 0.5 (mg/kg bw/day)$^{-1}$, based on the incidence of neoplasms in the small intestine of male mice, was selected as the most appropriate CSF for Cr(VI). A human oral CSF of 0.5 (mg/kg bw/day)$^{-1}$ implies that at an oral dose of 1 mg/kg bw/d of Cr(VI) there is an excess risk of tumors of the small intestine in adults of 5 x10^{-1}.

The human oral CSF (for adults) was then extrapolated linearly to lower dose levels of Cr(VI) as a mutagenic MoA for Cr(VI) carcinogenicity could not be excluded. In addition, in the absence of chemical-specific data to evaluate differences in age-specific susceptibility, increased early-life susceptibility to Cr(VI) was assumed and ADAFs (age-derived assessment factors) were applied. Partial excess risks for each age group at a specified dose level were then calculated by multiplying the human CSF for the age-specific ADAF, the specified average daily dose and the fraction of the exposure duration (e.g., a partial risk of 0.0001 = 10 × 0.5 × 0.001 × 2/70 for exposures to 1 µg Cr(VI)/kg bw/day from age 0 to <2 years, as shown in the table below), and the total (lifetime) excess risk was estimated from adding together the partial risks.

A **unit lifetime (70 yr) excess small intestine cancer risk of 8 x10^{-4}** at a constant average oral daily dose of **1 µg/kg bw/day Cr(VI)** from birth was estimated.

For workers exposed to Cr(VI) (via the gastro-intestinal tract) 5 days/week for 40 years, a unit (at 1 µg/kg bw/day Cr(VI)) excess (working) lifetime cancer risk of the small intestine could be calculated by multiplying the human CSF of 0.5 for an age-specific ADAF of 1, a dose of 0.001 mg Cr(VI)/kg bw/day and relevant general population-workers duration adjustment factors (5/7 x 40/70). A **unit ELR** of small intestine cancer of **2 x10^{-4} for workers exposed to 1 µg/kg bw/day Cr(VI) via the gastro-intestinal tract for 40 years** was derived.

Table 4.11: Application of ADAFs for a 70-year exposure to 1 µg/kg bw/day Cr(VI) from ages 0 to 70 (from Draft USEPA, 2010)

Age group	ADAF	Slope factor (per mg/kg bw/d)	Average daily dose (mg/kg bw/day)	Duration adjustment	Partial risk
0–<2 yrs	10	0.5	0.001	2 yrs/70 yrs	1 × 10^{-4}

2–<16 yrs	3	0.5	0.001	14 yrs/70 yrs	3×10^{-4}
≥16 yrs	1	0.5	0.001	54 yrs/70 yrs	4×10^{-4}
				Total risk	**8×10^{-4}**

As a linear relationship was assumed, these unit lifetime risks can be easily used to calculate excess small intestine cancer risks for the general population and workers at other oral doses of Cr(VI), as shown in table 4.12 below.

Table 4.12: Excess lifetime small intestine cancer risk estimates for the general population (70 years) and workers (40 years) exposed to different oral daily doses of Cr(VI) as proposed by USEPA (Draft USEPA, 2010)

Constant average oral daily dose of Cr(VI) (µg/kg bw/day)	Excess small intestine cancer risk in the general population ($x10^{-4}$)	Excess small intestine cancer risk in workers ($x10^{-4}$)
10	80	20
5	40	10
2.5	20	5
1	8	2
0.5	4	1
0.25	2	0.5
0.1	0.8	0.2
0.01	0.08	0.02

It should be noted that there is significant uncertainty around these risk estimates, in particular because extensive linear extrapolation (already 3 orders of magnitude at an oral dose of 2.5 µg/kg bw/day) beyond the experimental range was performed. It is also noted that there is significant extracellular reduction of oral Cr(VI) to Cr(III) by saliva, gastric juices and intestinal bacteria (De Flora et al., 1997 in Draft USEPA, 2010). De Flora and collaborators (1997) estimated that the reducing capability of these fluids in humans amounts to 0.7-2.1, 84-88 and 11-24 mg Cr(VI)/day for saliva, gastric juices and intestinal bacteria respectively. Extracellular reduction minimises the bioaccessibility/bioavailability of Cr(VI) to the target tissues of the gastro-intestinal tract at low dose levels, imparting non-linearity to the dose-response relationship. There is also considerable evidence showing that although Cr(VI) causes DNA damage *in vivo* under conditions that by-pass the normal physiological defence mechanisms of the body (e.g. intraperitoneal administration or direct contact at high doses), in general, it tends to be not mutagenic in animals when administered by the oral route (De Flora et al., 2006; Mirsalis et al., 1996; NTP, 2008 in ATSDR, 2012). Furthermore, recently, it has been argued that the irritative properties of Cr(VI) (involving tissue injury/irritation/inflammation and cell proliferation) could be more crucial than genotoxicity to its carcinogenicity. By taking all of these factors into account, the above risk estimates (based or extrapolated from Draft USEPA, 2010) are likely to be highly conservative at low exposures.

4.2 Contractor's proposed options and recommendations

4.2.1 Inhalation, workers

A summary of the quantitative cancer risk assessments of Cr(VI) for the inhalation route in workers, published by several authorities around the world and in the scientific literature in recent years (see table 4.13 below), shows that with the exception of the SCOEL (2004) evaluation, similar risk estimates were obtained. This is not surprising because, again, with the exception of the SCOEL (2004) assessment, the same datasets (those from the chromate production plants in Baltimore and Painesville) were used as the basis for risk estimation. Instead, SCOEL used a meta-analysis of 10 studies involving chromate production workers, chromate pigment production workers and chromium platers (Steenland et al., 1996). In all the assessments, the output from the application of a linear risk function/model to the observed data was used for subsequent linear extrapolation, with the underlying assumption of a genotoxic, non-threshold MoA. In some cases (SCOEL, 2004 and Seidler et al., 2012), only a linear model was fitted to the observed data. Where different models were applied, the output from the linear function was selected because of a superior fit (OSHA, 2006) or because no significant differences in fit between different models were noted (Goldbohm et al., 2006).

The contractor notes that the observed data covered by these studies fit a linear dose-response relationship better than, or at least as well as any other relationship. Hence, just below the exposure range covered by the observed data, there is no biological or mathematical basis for not continuing with assumed linearity (instead of applying any of a substantial number of other possible mathematical constructs). A more debatable and important issue is whether or not the underlying biology means that the dose-response relationship departs from linearity at a point further outside the observed range; and particularly whether or not threshold conditions apply in this region of the dose-response relationship.

Table 4.13: Unit occupational excess lifetime risks of lung cancer death determined by different authorities or publications

Source	8h-TWA Cr(VI) concentration ($\mu g/m^3$)	Cumulative Cr(VI) exposure ($\mu g/m^3$-yr)	Models fitted to the observed data*	Method of ELR estimation	Reference population	Underlying studies	Unit ELR of lung cancer ($x10^{-3}$)
SCOEL (2004)	1	40	Linear	Life-table up to age 85	UK	Steenland et al. (1996) meta-analysis	0.1-0.6
OSHA (2006)	1	45	Linear Quadratic Log-linear Additive Cox-proportional	Life-table up to age 100	US	Gibb et al. (2000) & Luippold et al. (2003)	2.1-9.1
Goldbohm et al. (2006)	1	40	Linear Log-linear	Life-table up to age 89	NL	Mancuso (1997) & Gibb et al. (2000) & Luippold/Crump et al. (2003)	3-16
Seidler et al. (2012)	1	40	Linear	Conditional & Life-table up to age 89	EU & DE	Park et al. (2004) & Luippold/Crump et al. (2003)	3.4-4.1

*Output from underlined model is that selected for subsequent linear extrapolation

As it can be seen from the table, the unit risk estimates (at 1 $\mu g/m^3$ 8h-TWA for a working life) from OSHA (2006), Goldbohm et al. (2006) and Seidler et al. (2012) are all in the same order of magnitude, ranging from $2.1x10^{-3}$ (OSHA, 2006) to $16x10^{-3}$ (Goldbohm et al., 2006). The relatively small differences are mainly due to differences in the reference population used, method of ELR estimation, averaging of estimates from datasets, length of work exposure considered, length of follow-up and exclusion of some subsets of data.

The unit risk estimates derived by SCOEL (2004) are more than one order of magnitude lower, ranging from 0.1 to $0.6x10^{-3}$. These estimates derive from a meta-analysis of 10 studies (Steenland et al., 1996) which lacked information on exposure intensity and duration. Thus, SCOEL assumed that the overall SMR of 266 (RR = 2.66) derived from these 10 studies was associated with an average exposure duration of 15 years at three possible (but relatively high) Cr(VI) exposure concentrations of 500, 1000 or 2000 $\mu g/m^3$ (equivalent to cumulative Cr(VI) exposures of 7500, 15000 and 30000 $\mu g/m^3$–yr). These exposure assumptions are significantly higher than those measured in the US plants and might explain why lower risk estimates were calculated by SCOEL in comparison to the other risk evaluations of Cr(VI) considered in this document. It is the contractor's view that the SCOEL (2004) risk estimates are less reliable: are not consistent with the other available estimates; are less conservative; are based on exposure assumptions rather than actual

exposure data; and did not include the more recent epidemiological studies providing exposure-response relationships between Cr(VI) and lung cancer mortality (Gibb et al., 2000; Park et al., 2004, Luippold et al., 2003; Crump et al., 2003). These limitations restrict the value of the SCOEL assessment.

It is noted that the remaining three risk estimates (OSHA, 2006; Goldbohm et al., 2006; and Seidler et al., 2012) are all based on the same datasets from the chromate production plants in Baltimore and Painesville (Gibb et al., 2000; Park et al., 2004; Mancuso, 1997; Luippold et al., 2003; and Crump et al., 2003). The workers in these plants were exposed to respirable-sized particles (AED of 1.7 µm and median particle size of 1.0 µm, respectively) of soluble and sparingly soluble Cr(VI) compounds (ammonium, potassium and sodium chromates and dichromates, calcium, zinc and strontium chromates). These three reviews offer cancer risk estimates for exposure to Cr(VI) delivered to the lung from any of a range of different Cr(VI)-containing compounds with widely varying water solubility, from “sparingly” to “highly” soluble. The epidemiological data are insufficiently discriminatory to allow one to distinguish between the contributions to cancer production made by individual Cr(VI) compounds.

It is the contractor’s view that the US datasets represent the best available studies of the dose-response relationship between Cr(VI) and lung cancer in terms of methodological quality, accounting for confounding by smoking and quantitative exposure-response information. No new epidemiological study on occupational Cr(VI) exposure and lung cancer meeting these criteria has been published in recent years or since these three assessments were completed. Therefore, it is the contractor’s view that the same studies underpinning these evaluations of Cr(VI) carcinogenicity should constitute the basis of the quantitative cancer risk assessment presented in this document.

The risk estimates by OSHA (2006), Goldbohm et al. (2006) and Seidler et al. (2012) were derived by linear extrapolation of the output obtained by the application of linear models to the observed data, with the underlying assumption of a genotoxic non-threshold MoA. It is the contractor’s view that, at present, there is insufficient evidence to deviate from linearity. A clear MoA for the carcinogenicity of Cr(VI) has not been established. The Cr(VI) ion expresses genotoxicity in many different assays and therefore it has been the conventional wisdom that genotoxicity is key to its MoA. However, recently it has been argued that *in vivo,* Cr(VI) is only weakly mutagenic and its irritative properties (involving oxidative stress, oxidative DNA damage, tissue injury/irritation/inflammation and cell proliferation) could be crucial to its carcinogenicity.

Overall, therefore, it is the contractor’s view that the same studies and the same methodology used by the other three evaluations of Cr(VI) carcinogenicity should be employed here for the purpose of this assessment. It is also the contractor’s view that repeating such analyses would produce very similar, if not, the same results. Considering the large uncertainties that still surround the resulting estimates, there would be no significant additional benefit in replicating such analyses.

It is the view of the contractor that of the three risk estimates (OSHA, 2006; Goldbohm et al., 2006; and Seidler et al., 2012) considered more reliable, those (unit risk of 3.4 – 4.1x10^{-3} with its linear function) derived by Seidler et al. (2012) represent the most relevant for this project for the following reasons. The Seidler et al. (2012) risk estimates were calculated on the basis of the European or German background rate of lung cancer. Such reference populations are the most relevant to the authorisation of Cr(VI) compounds under REACH in the EU. The range of the estimates is quite tight, facilitating their more straightforward interpretation and application. Highly uncertain subsets of data from the Gibb et al. (2000) study in the Baltimore plant were excluded from the analysis, improving comparability to the risk estimates obtained by Luippold et al. (2003)/Crump et al. (2003) from the Painesville plant. Also, both the conditional method and the life-table analysis were applied in deriving the ELRs, increasing precision and robustness.

Overall, therefore, for occupational inhalation exposure to all Cr(VI)-containing substances of slight to high water solubility, an **excess lifetime (up to age 89) lung cancer risk of 4 x10^{-3}** for workers exposed to an 8h-TWA concentration of **1 µg Cr(VI)/m^3 for 40 years** is recommended as a key reference point for regulatory purposes. It is also suggested that, at least for exposures down to 1 µg Cr(VI)/m^3 for 40 years, a linear dose-response with unit (i.e. per 1 µg Cr(VI)/m^3) risk of 4 x10^{-3} is applied. The derived risk estimates for different levels of exposure above 1 µg Cr(VI)/m^3 are shown in table 4.14 below.

It is possible that airway epithelium irritation/inflammation caused by Cr(VI) could be a substantial contributing factor to the carcinogenic process. If so, and with an apparent threshold for such irritative response in humans just below 1 µg Cr(VI)/m^3, it could be that at lower, sub-irritant exposure levels, the risk of cancer falls away more steeply than a linear relation would suggest. Hence, it is the contractor's view that the lower the exposure (certainly below 1 µg/m^3), the more likely it is that the linear relationship overestimates the cancer risk.

Therefore, while table 4.14 below also presents risk estimates for a linear dose-response curve applying to exposures below 1 µg Cr(VI)/m^3, we have less confidence in the robustness of these low-exposure risk estimates. In addition, as discussed by Haney et al. (2012) in their proposal for an inhalation cancer reference value for the general population based on a threshold approach, considerable and rapid extracellular reduction of Cr(VI) to C(III) occurs in the lungs. It is likely that this will lessen significantly the absorption of Cr(VI) into the lung epithelium at low exposures, imparting non-linearity to the cancer dose-response relationship of Cr(VI) in the low-dose region. Haney et al. (2012) consider that any residual cancer risk at the proposed reference value of 0.24 µg Cr(VI)/m^3 is negligible.

Overall, it is the contractor's view that the risk estimates in the table below for exposures lower than 1 µg Cr(VI)/m^3 might well greatly overestimate the real cancer risks. It is also considered that at progressively lower Cr(VI) air

concentrations (from about 0.1 µg/m^3 downwards), cancer risks may be negligible.

Finally, notwithstanding the lack of reliability and biological plausibility of the low-exposure risk estimates produced by "long-distance" linear extrapolation, their worth is further diminished by the fact that such low exposure concentrations cannot be measured reliably and are unlikely to occur in the workplaces that are the main focus of consideration for Cr(VI)-related Authorisations.

Table 4.14: Proposed excess lifetime (up to age 89) lung[$] cancer risk estimates for workers exposed at different 8h-TWA concentrations of Cr(VI) (respirable fraction) for 40 years

TWA Cr(VI) exposure concentration –respirable fraction (µg/m^3)	Excess lung cancer risk in EU workers (x10^{-3})
25	100
12.5	50
10	40
5	20
2.5	10
1	**4**
0.5	2(?)
0.25	1(?)
0.1	0.4(?)
0.01	0.04(?)

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)

Although this is the best dose-response relationship that can be derived by linear extrapolation from the available data, it should be acknowledged that there are still considerable uncertainties surrounding it and the risk estimates derived from it. These arise from limitations in the exposure measurements conducted in the studies selected, from deficiencies in the assessment of possible co-exposures to other lung carcinogens, from the lack of complete assessment of confounding factors, especially smoking and from extrapolating linearly from a fitted model outside the range of observation (already 10-20 times lower at 1 µg/m^3), especially when mechanistic evidence is suggestive of non-linearity at low exposure levels. Still, it is believed that these uncertainties are not so large to have introduced errors resulting in serious over-prediction or under-prediction of risk, at least for exposures above1 µg Cr(VI)/m^3.

Another important limitation concerns the applicability of such risk estimate derived from the Baltimore and Painesville cohorts (exposed to relatively small particles of soluble and sparingly soluble Cr(VI) compounds) to workplaces outside chromate production. The available evidence shows that the proposed risk estimates are applicable to exposures to aerosols of "soluble" and "sparingly soluble" Cr(VI) compounds (i.e. acids generated from chromium trioxide and its oligomers, ammonium dichromate, chromium

trioxide, potassium chromate, potassium dichromate, sodium chromate, sodium dichromate, pentazinc chromate octahydroxide, dichromium tris chromate, potassium hydroxyoctaoxodizincatedichromate and strontium chromate from the 14 Cr(VI) substances considered within this project).

Similar levels of exposure to particles of "insoluble" Cr(VI) compounds are expected to pose a lower risk, because of decreased bioavailability of Cr(VI). However, even with such compounds, *some* Cr(VI) becomes bioavailable; and unfortunately there is insufficient evidence to quantify these differences in carcinogenic potency between Cr(VI) substances of different solubilities. Therefore, one could either apply the proposed risk estimates also to particles of insoluble Cr(VI) compounds (i.e. lead sulfochromate yellow, lead chromate and lead chromate molybdate sulphate red), accepting that they will perhaps overestimate the risks, or apply an arbitrary adjustment factor (e.g. reduce the risk estimates by 5, or 10, etc). The contractor advocates the former approach as being more solidly based on the currently available scientific data.

The risk of lung cancer will be reduced if the particle size of the material in air is such that a proportion at least cannot enter the lower respiratory tract. Although the epidemiology studies contain insufficient information to determine the exact location of the observed tumours, these occurred in the lung and not higher up in the respiratory tract. It is also noted that the workers in the cohort studies from which the lung cancer risk estimates have been derived were exposed to respirable-sized particles (AED of 1.7 µm in the Baltimore cohort and median particle size of 1.0 µm in the Painesville cohort). Therefore, it seems reasonable to associate the above lung cancer risk estimates with material in air of "respirable" particle size. The Organisation for Standardization (ISO) and the Comite Europeen de Normalisation (CEN) have developed an internationally accepted definition of "respirable fraction", which relates to specific air sampling criteria. The "respirable fraction" is defined as the portion of inhalable particles that enter the deepest part of the lung, the non-ciliated alveoli. For this fraction, the particle diameter corresponding to 50% sampling efficiency (D_{50}) is given as 4 µm (CEN, 1993).

Having concluded that only the "respirable fraction" of the inhalation Cr(VI) exposure would be associated with an increased risk of lung cancer, the question arises of whether the inhalable[1], non-respirable particles of different Cr(VI) compounds (i.e. the airborne particles that enter the respiratory system via the nose or mouth but are too big to penetrate the gas exchange region of the lungs) would be harmless or would pose a different threat. It is well-established that inhaled larger particles that deposit in the upper respiratory tract are cleared by the mucociliary escalator and swallowed in the gastro-intestinal tract.

According to IARC (2012), there is "inadequate" evidence that oral exposure to Cr(VI) has caused stomach or other cancers in humans. There is no evidence that inhalation exposure to Cr(VI) in occupational cohorts has

[1] The "inhalable fraction" is defined as the portion of airborne material that enters the nose and mouth during breathing. For this fraction, the particle diameter corresponding to 50% sampling efficiency (D_{50}) is given as 100 µm (CEN, 1993).

caused cancer of the gastro-intestinal tract. However, it is well established that some Cr(VI) compounds have caused tumours of the gastrointestinal tract (in particular of the small intestine) in rodents by the oral route.

Therefore, it seems reasonable to associate the "inhalable, non-respirable fraction" of Cr(VI) inhalation exposure with the potential for an increased risk of cancer of the small intestine. It is proposed that the intestine cancer dose-response and risk estimates established for the oral route in workers (see section "Oral, general population and workers") by linear extrapolation of mouse data are applied here to workers exposed by the inhalation route, as shown in table 4.15 below. Obviously, inhalation exposures to these inhalable, non-respirable particles of Cr(VI) compounds will have to be converted first into doses by applying the standard worker breathing rate of 1.25 m^3/hr and the standard worker body weight default value of 70 kg.

Table 4.15: Proposed excess lifetime small intestine[$] cancer risk estimates for workers exposed to different daily doses of Cr(VI) arising from inhalation exposure to inhalable, non-respirable particles for 40 years

Constant average daily dose of Cr(VI) (µg/kg bw/day) arising from inhalation exposure to inhalable, non-respirable particles (5 d/wk for 40 years)	Excess small intestine cancer risk in workers ($x10^{-4}$)
10	20
5	10
2.5	5(?)
1	2(?)
0.5	1(?)
0.25	0.5(?)
0.1	0.2(?)
0.01	0.02(?)

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

4.2.2 Inhalation, general population

There is only a small number of quantitative cancer risk assessments of Cr(VI) for the inhalation route in the general population. A unit excess lifetime lung cancer risk of 1.2 $x10^{-2}$ at an environmental exposure concentration of 1 µg Cr(VI)/m^3 for 70 years, with its associated linear function, was established by the USEPA (1998). This unit risk resulted in an excess lifetime risk of 10^{-6} at an exposure concentration of 0.08 ng Cr(VI)/m^3 for 70 years.

A unit excess lifetime lung cancer risk of 4 $x10^{-2}$ at an environmental exposure concentration of 1 µg Cr(VI)/m^3 for 70 years, with its associated linear function, was established by WHO (Air Quality Guidelines, 2000). This unit risk resulted in an excess lifetime risk of 10^{-6} at an exposure concentration of 0.025 ng Cr(VI)/m^3 for 70 years.

These risk estimates were derived by applying linear models to various occupational epidemiology datasets (published in the 1970s and 1980s) and by extrapolating risks from occupational exposure durations to average lifetime exposures.

It is the view of the contractor that, as these unit risks are based on relatively old worker cohort studies, it would be more appropriate to extrapolate (to the general population) the occupational risk estimates proposed by Seidler et al. (2012) which are based on the most recent studies of the dose-response relationship between Cr(VI) exposure and lung cancer.

A unit excess lifetime (up to age 89) lung cancer risk (with its linear function) of 4 $x10^{-3}$ for workers exposed to an 8h-TWA concentration of 1 µg Cr(VI)/m^3 for 40 years was estimated by Seidler et al. (2012). Extrapolation of this estimate to continuous lifetime exposure (4 $x10^{-3}$ x 24/8 x 7/5 x 70/40) results in a **unit excess lifetime lung cancer risk for the general population** of **2.9 x 10^{-2}** at an ambient exposure concentration of **1 µg Cr(VI)/m^3 for 70 years**, equivalent to an excess lifetime risk of 10^{-6} at an ambient exposure concentration of 0.034 ng Cr(VI)/m^3 for 70 years.

In contrast to these risk estimates derived by the application of linear, non-threshold methodologies, there is also a recent cancer-based chronic inhalation “reference value” (at which the cancer risk is considered to be negligible) established by Haney et al. (2012) using a nonlinear, threshold approach. Haney et al. have proposed such a value of 0.24 µg Cr(VI)/m^3 by applying assessment factors to a human NOAEC (19.9 µg Cr(VI)/m^3) based on the lack of statistically significant increases in lung cancer from occupational cohort studies. A threshold approach was adopted on the basis that there is considerable and rapid extracellular reduction of Cr(VI) to C(III) occurring in the lungs. It is likely that this will lessen significantly the absorption of Cr(VI) into the lung epithelium at low exposures, imparting non-linearity to the cancer dose-response relationship of Cr(VI) in the low-dose region. Haney et al. (2012) consider that any residual cancer risk at the proposed “reference value” will be negligible.

It is the view of the contractor that the adoption of a threshold approach at low exposures has merit. However, there are serious flaws in using the stated human NOAEC for lung cancer as starting point. The robustness of this NOAEC is hampered by the low statistical power of epidemiological studies to detect an increased risk of lung cancer at low exposures, and cannot represent a reliable dose threshold for lung cancer.

It is noted that this reference value is 7000 times higher than the 10^{-6} excess lifetime cancer risk air concentration of 0.034 ng Cr(VI)/m^3 extrapolated from the occupational risk estimates proposed by Seidler et al. (2012). Although this threshold-based value is not fully supported by the contractor, the comparison above highlights the inherent problems of estimating risks at low exposures by extensive linear extrapolation, especially when mechanistic considerations suggest that non-linearity might well apply at low concentrations.

Therefore, as for the proposed occupational risk estimates, it is suggested that for environmental exposures of the general population down to 1 µg Cr(VI)/m^3 for 70 years, a linear dose-response relationship with unit (i.e. per 1 µg Cr(VI)/m^3) risk of 2.9 x10^{-2} is applied. However, for environmental exposures below 1 µg Cr(VI)/m^3 the risk estimates derived linearly from the proposed unit risk should be considered to overestimate significantly the real cancer risks. It is also proposed that at progressively lower ambient Cr(VI) concentrations (from about 0.1 µg/m^3 downwards), cancer risks should be regarded as negligible. The cancer risk estimates for different levels of environmental exposure above and below 1 µg Cr(VI)/m^3 derived linearly from the proposed unit risk are shown in table 4.16 below.

Table 4.16: Proposed excess lifetime lung[$] cancer risk estimates for the general population exposed at different ambient concentrations of Cr(VI) (respirable fraction) for 70 years

Ambient Cr(VI) exposure concentration –respirable fraction (µg/m^3)	Excess lung cancer risk in the general population (x10^{-3})
10	290
5	145
2.5	72
1	**29**
0.5	14(?)
0.25*	7(?)
0.1	2.9(?)
0.01	0.29(?)
0.001	0.029(?)
0.0001	0.0029(?)

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)
*Threshold-based reference value at which cancer risks are considered to be negligible (by Haney et al., 2012)

In addition, as for the proposed occupational risk estimates, these risk values should be associated with exposure to Cr(VI) arising from the "respirable fraction" of "soluble", "sparingly soluble" or "insoluble" Cr(VI) compounds.

However, as for workers, inhalation exposure to inhalable, non-respirable particles of Cr(VI) compounds should be associated with the potential for an increased risk of cancer of the small intestine, given that such particles are cleared by the mucociliary escalator into the gastro-intestinal tract.

It is proposed that the small intestine cancer dose-response and risk estimates established for the oral route in the general population (see section "Oral, general population and workers") by linear extrapolation of mouse data are applied here to the general population exposed by the inhalation route, as shown in table 4.17 below. Obviously, inhalation exposures to these inhalable, non-respirable particles of Cr(VI) compounds will have to be converted first into doses by applying the standard human resting breathing rate of 0.8 m^3/hr and the standard average human body weight default value of 60 kg.

Table 4.17: Proposed excess lifetime (70 yr) small intestine[$] cancer risk estimates for the general population exposed to different daily doses of Cr(VI) arising from inhalation exposure to inhalable, non-respirable particles

Constant average daily dose of Cr(VI) (µg/kg bw/day) arising from inhalation exposure to inhalable, non-respirable particles	Excess small intestine cancer risk in the general population ($x10^{-4}$)
10	80
5	40
2.5	20(?)
1	8(?)
0.5	4(?)
0.25	2(?)
0.1	0.8(?)
0.01	0.08(?)

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

4.2.3 Dermal, workers

There is no evidence that dermal exposure to Cr(VI) compounds has caused skin or other tumors in humans. Some of the early epidemiology studies included investigations of ill health and all tumors. Hence, it would be anticipated that had there been any significant increases in skin tumors, these would have been recorded. Dermal cancer bioassays in animals with Cr(VI) compounds alone are not available. As the tumors induced by Cr(VI) by both the inhalation and oral routes are of a local nature, route-to-route extrapolation to assess dermal cancer risks is not appropriate. Overall, therefore, the available evidence indicates that Cr(VI) compounds do not pose cancer risks by the dermal route.

4.2.4 Oral, general population and workers

There are fewer quantitative cancer risk assessments of Cr(VI) for the oral route compared to the inhalation route. A recent draft evaluation produced by the USEPA in 2010 estimated a **unit lifetime (70 yr) excess intestine cancer risk of 8 x10^{-4}** at a constant average oral daily dose of **1 µg/kg bw/day Cr(VI)** from birth, with its associated linear function (Draft USEPA, 2010 – see table 4.18 below). An extrapolation of this unit ELR in the general population to **workers** exposed (5 days/week for 40 years) to Cr(VI) via the gastro-intestinal tract produced a **unit intestine cancer ELR of 2 x10^{-4}** at a daily dose of **1 µg/kg bw/day Cr(VI**), with its associated linear function.These estimates were derived by linear extrapolation of tumor incidence data in mice. It is the contractor's view that given the uncertainties in the role played by Cr(VI) genotoxicity in the carcinogenic process, it is difficult to move away from linearity in a regulatory context. Therefore, it is proposed that the oral cancer risk values estimated by the USEPA (2010) for the general population or extrapolated by the contractor for workers are adopted here, as shown in table 4.18 below.

Table 4.18: Proposed excess lifetime small intestine[$] cancer risk estimates for the general population (70 years) and workers (40 years) exposed to different oral daily doses of Cr(VI)

Constant average oral daily dose of Cr(VI) (µg/kg bw/day)	Excess small intestine cancer risk in the general population (x10^{-4})	Excess small intestine cancer risk in workers (x10^{-4})
10	80	20
5	40	10
2.5	20(?)	5(?)
1	8(?)	2(?)
0.5	4(?)	1(?)
0.25	2(?)	0.5(?)
0.1	0.8(?)	0.2(?)
0.01	0.08(?)	0.02(?)

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

It should also be noted that the above risk estimates are applicable to "soluble" Cr(VI) substances (as they were derived from testing the soluble sodium dichromate) but they might be conservative for the "slightly soluble" and "insoluble" chromates as these substances are expected to be less bioavailable. In the absence of further information on how solubility affects oral carcinogenic potency of different Cr(VI) compounds, one could either

apply the risk estimates in table 4.18 also to “slightly soluble” and “insoluble” Cr(VI) compounds accepting that they will perhaps overestimate the risks, or apply an arbitrary adjustment factor (e.g. reduce the risk estimates by 5, or 10, etc). The contractor advocates the former approach as being more solidly based on the currently available scientific data.

5 OVERALL CONCLUSIONS

The project specification required a review of the relevant scientific literature related to the carcinogenicity of the Cr(VI)-containing compounds listed in table 5.1 below and the establishment of relevant carcinogenicity dose-response curves for each of these substances for the purpose of Authorisation under REACH.

Table 5.1: Cr(VI) compounds considered in this project (with their chemical identifiers, solubility considerations and carcinogenicity classification in Annex VI of CLP Regulation)

No	Name of the substance	EC no	CAS no	Carcinogenicity C&L in Annex VI of CLP Regs
1	Lead sulfochromate yellow (C.I. Pigment Yellow 34) insoluble	215-693-7	1344-37-2	Carc 1B
2	Lead chromate insoluble	231-846-0	7758-97-6	Carc 1B
3	Lead chromate molybdate sulphate red (C.I. Pigment Red 104) insoluble	235-759-9	12656-85-8	Carc 1B
4	Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid highly soluble	231-801-5; 236-881-5	7738-94-5: 13530-68-2	Carc 1B
5	Ammonium dichromate highly soluble	231-143-1	7789-09-5	Carc 1B
6	Chromium trioxide highly soluble	215-607-8	1333-82-0	Carc 1A
7	Potassium chromate highly soluble	232-140-5	7789-00-6	Carc 1B
8	Potassium dichromate highly soluble	231-906-6	7778-50-9	Carc 1B
9	Sodium chromate highly soluble	231-889-5	7775-11-3	Carc 1B
10	Sodium dichromate highly soluble	234-190-3	7789-12-0; 10588-01-9	Carc 1B
11	Pentazinc chromate octahydroxide slightly soluble	256-418-0	49663-84-5	Carc 1A
12	Dichromium tris(chromate) slightly soluble	246-356-2	24613-89-6	Carc 1B
13	Potassium hydroxyocataoxodizincatedichromate slightly soluble	234-329-8	11103-86-9	Carc 1A
14	Strontium chromate slightly soluble	232-142-6	7789-06-2	Carc 1B

The contractor identified and obtained existing detailed, good-quality reviews of the carcinogenicity of Cr(VI) compounds, including quantitative risk assessments, published in the scientific literature or by particular authorities around the world since the year 2000. In addition, the contractor identified and obtained individual studies cited in these reviews that have been crucial to the

overall position developed by each review; and any other more recent relevant studies not included in these reviews.

The molecular entity that drives the carcinogenicity of these Cr(VI) compounds is the Cr(VI) ion, which is released when these substances solubilise and dissociate in biological fluids. Therefore, this document, similarly to other international reviews of Cr(VI) compounds, uses Cr(VI) as the relevant dose metric. For the three substances containing lead (i.e. lead sulfochromate yellow, lead chromate and lead chromate molybdate sulphate red), it is also possible that the Pb ion could contribute to their toxicity. However, there is no evidence that lead has caused cancer in humans, leading to the conclusion that Cr(VI) is also the relevant dose metric for the carcinogenicity of these lead chromates.

This document also considers the impact of particle size (for the inhalation route only) and solubility (and therefore bioaccessibility /bioavailability) on the expression of carcinogenicity. A table summarising information on the solubility and particle size distribution of the 14 Cr(VI) compounds under consideration is presented in Appendix 1.

Cr(VI) causes lung tumours in humans and animals by the inhalation route and tumours of the gastrointestinal tract in animals by the oral route. These are both local, site-of-contact tumours – there is no evidence that Cr(VI) causes tumours elsewhere in the body. A clear MoA for these tumours has not been established. The Cr(VI) ion expresses genotoxicity in many different assays and therefore it has been the conventional wisdom that genotoxicity is key to its MoA. However, recently, it has been argued that *in vivo,* Cr(VI) is only weakly mutagenic and its irritative properties (involving oxidative stress, oxidative DNA damage, tissue injury/irritation/inflammation and cell proliferation) could be crucial to its carcinogenicity.

Lung carcinogenic potency of Cr(VI) compounds is expected to be greater for respirable particles, moderate/slight solubility, and longer residence time in the lung. However, quantifying any differences in carcinogenic potency for Cr(VI) compounds of different solubility is not possible with the currently available information.

5.1 Inhalation, workers

A summary of the quantitative cancer risk assessments of Cr(VI) for the inhalation route in workers, published by several authorities around the world and in the scientific literature in recent years, is given in table 5.2 below. In all the assessments, the output from the application of a linear risk function/model to the observed data was used for subsequent linear extrapolation, with the underlying assumption of a genotoxic non-threshold MoA. The contractor notes that the observed data covered by these studies fit a linear dose-response relationship better than, or at least as well as any other relationship. Hence in *beginning* to extrapolate outside of the exposure range covered by the observed data there is no biological or mathematical

basis for not continuing with assumed linearity (instead of applying any of a substantial number of other possible mathematical constructs). A more debatable and important issue is whether or not the underlying biology means that the dose-response relationship departs from linearity at a point further outside the observed range; and partially whether or not threshold conditions apply in this region of the dose-response relationship (see below).

Three of these assessments (OSHA, 2006; Goldbohm et al., 2006; and Seidler et al., 2012) were based on the same datasets from the chromate production plants in Baltimore and Painesville, USA (Gibb et al., 2000; Park et al., 2004; Mancuso, 1997; Luippold et al., 2003; and Crump et al., 2003).

The workers in these plants were exposed to respirable-sized particles (aerodynamic equivalent diameter of 1.7 µm and median particle size of 1.0 µm) of soluble (ammonium, potassium and sodium chromates/dichromates) and sparingly soluble Cr(VI) compounds (calcium, zinc and strontium chromates). The epidemiological data are insufficiently discriminatory to allow one to distinguish between the contributions to cancer production made by individual substances.

Table 5.2: Unit occupational excess lifetime risks of lung cancer death determined by different authorities or publications

Source	8h-TWA Cr(VI) concentration (µg/m^3)	Cumulative Cr(VI) exposure (µg/m^3-yr)	Models fitted to the observed data*	Method of ELR estimation	Reference population	Underlying studies	Unit ELR of lung cancer (x10^{-3})
SCOEL (2004)	1	40	Linear	Life-table up to age 85	UK	Steenland et al. (1996) meta-analysis	0.1-0.6
OSHA (2006)	1	45	Linear Quadratic Log-linear Additive Cox-proportional	Life-table up to age 100	US	Gibb et al. (2000) & Luippold et al. (2003)	2.1-9.1
Goldbohm et al. (2006)	1	40	Linear Log-linear	Life-table up to age 89	NL	Mancuso (1997) & Gibb et al. (2000) & Luippold/Crump et al. (2003)	3-16
Seidler et al. (2012)	1	40	Linear	Conditional & Life-table up to age 89	EU & DE	Park et al. (2004) & Luippold/Crump et al. (2003)	3.4-4.1

*Output from underlined model is that selected for subsequent linear extrapolation

As it can be seen from the table, the unit risk estimates (at 1 µg/m^3 8h-TWA for a working life) from OSHA (2006), Goldbohm et al. (2006) and Seidler et

al. (2012) are all in the same order of magnitude, ranging from $2.1x10^{-3}$ (OSHA, 2006) to $16x10^{-3}$ (Goldbohm et al., 2006). The relatively small differences are mainly due to differences in the reference population used, method of ELR estimation, averaging of estimates from datasets, length of work exposure considered, length of follow-up and exclusion of some subsets of data.

The risk estimates obtained at Cr(VI) exposures down to about 1 µg/m^3 seem reasonable, given that lung cancer was directly observed in the epidemiological data to correlate linearly with Cr(VI) exposures from a level only 10-20 times higher.

It is the contractor's view that the US datasets represent the best available studies of the dose-response relationship between Cr(VI) and lung cancer in terms of methodological quality, accounting for confounding by smoking and quantitative exposure-response information.

In contrast, SCOEL used a meta-analysis of 10 studies involving chromate production workers, chromate pigment production workers and chromium platers (Steenland et al., 1996) which did not include actual exposure measurements. It is the contractor's view that the SCOEL (2004) lower risk estimates are less reliable: are not consistent with the other available estimates; are based on exposure assumptions rather than actual exposure data; and did not include the more recent epidemiological studies providing exposure-response relationships between Cr(VI) and lung cancer mortality (Gibb et al., 2000; Park et al., 2004, Luippold et al., 2003; Crump et al., 2003).

Of the three risk estimates (OSHA, 2006; Goldbohm et al., 2006; and Seidler et al., 2012) considered more reliable, those derived by Seidler et al. (2012) represent the most relevant for this project, for the following reasons. The Seidler et al. (2012) risk estimates were calculated on the basis of the European or German background rate of lung cancer. Such reference populations are the most relevant to the authorisation of Cr(VI) compounds under REACH in the EU. The range of the estimates is quite tight, facilitating their more straightforward interpretation and application. Highly uncertain subsets of data from the Gibb et al. (2000) study in the Baltimore plant were excluded from the analysis, improving comparability to the risk estimates obtained by Luippold et al. (2003)/Crump et al. (2003) from the Painesville plant. Also, both the conditional method and the life-table analysis were applied in deriving the ELRs, increasing precision and robustness.

Overall, using the Seidler analyses, for occupational inhalation exposure to all Cr(VI)-containing substances of slight to high water solubility (see table 5.1), an **excess lifetime (up to age 89) lung cancer risk of $4 x10^{-3}$ for workers exposed to an 8h-TWA concentration of 1 µg Cr(VI)/m^3 for 40 years** is recommended as a key reference point for regulatory purposes. It is also suggested that, at least for exposures down to 1 µg Cr(VI)/m^3 for 40 years, a linear dose-response relationship with unit (i.e. per 1 µg Cr(VI)/m^3) risk of 4 $x10^{-3}$ is applied. The derived risk estimates for different levels of exposure above 1 µg Cr(VI)/m^3 are shown in table 5.3 below.

It is possible that airway epithelium irritation/inflammation caused by Cr(VI) could be a substantial contributing factor to the carcinogenic process. If so, and with an apparent threshold for such an irritation response in humans just below 1 µg Cr(VI)/m^3, it could be that at lower, sub-irritant exposure levels, the risk of cancer falls away more steeply than a linear relation would suggest. Hence, it is the contractor's view that the lower the exposure (certainly below 1 µg/m^3), the more likely it is that the linear relationship overestimates the cancer risk. Therefore, while table 5.3 also presents risk estimates for a linear dose-response curve applying to exposures below 1 µg Cr(VI)/m^3, the contractor has less confidence in the robustness of these low-exposure risk estimates.

In addition, as discussed by Haney et al. (2012) in their proposal for an inhalation cancer "reference value" for the general population based on a threshold approach, considerable and rapid extracellular reduction of Cr(VI) to C(III) occurs in the lungs. It is likely that this will lessen significantly the absorption of Cr(VI) into the lung epithelium at low exposures, imparting non-linearity to the cancer dose-response relationship of Cr(VI) in the low-dose region.

Overall, it is the contractor's view that the risk estimates in table 5.3 for exposures below 1 µg Cr(VI)/m^3 might well greatly overestimate the real cancer risks. It is also considered that at progressively lower Cr(VI) air concentrations (from about 0.1 µg/m^3 downwards), cancer risks may be negligible.

Table 5.3: Proposed excess lifetime (up to age 89) lung[$] cancer risk estimates for workers exposed at different 8h-TWA concentrations of Cr(VI) (respirable fraction) for 40 years

TWA Cr(VI) exposure concentration – respirable fraction (µg/m^3)	Excess lung cancer risk in EU workers (x10^{-3})
25	100
12.5	50
10	40
5	20
2.5	10
1	**4**
0.5	2(?)
0.25	1(?)
0.1	0.4(?)
0.01	0.04(?)

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)

The available evidence shows that the proposed risk estimates are applicable to exposures to aerosols of the highly soluble and slightly soluble Cr(VI) compounds in table 5.1.

Similar levels of exposure to “insoluble” Cr(VI) compounds (see table 5.1) are expected to pose a lower risk, because of decreased bioavailability of Cr(VI). However, even with such compounds, *some* Cr(VI) becomes bioavailable; and currently there is insufficient evidence to quantify these differences in carcinogenic potency between Cr(VI) substances of different solubility. Therefore, one could either apply the risk estimates in table 5.3 also to particles of insoluble Cr(VI) compounds (i.e. lead sulfochromate yellow, lead chromate and lead chromate molybdate sulphate red), accepting that they will perhaps overestimate the risks, or apply an arbitrary adjustment factor (e.g. reduce the risk estimates by 5, or 10, etc). The contractor advocates the former approach as being more solidly based on the currently available scientific data.

The risk of lung cancer will be reduced if the particle size of the material in air is such that a proportion at least cannot enter the lower respiratory tract. It is noted that the workers in the cohort studies from which the lung cancer risk estimates have been derived were exposed to respirable-sized particles (AED of 1.7 µm in the Baltimore cohort and median particle size of 1.0 µm in the Painesville cohort). Therefore, it seems reasonable to associate the above lung cancer risk estimates with material in air of “respirable” particle size.

Having concluded that only the “respirable fraction” of the inhalation Cr(VI) exposure would be associated with an increased risk of lung cancer, the question arises of whether the inhalable, non-respirable particles of different Cr(VI) compounds would be harmless or would pose a different threat. It is well established that inhaled larger particles that deposit in the upper respiratory tract are cleared by the mucociliary escalator and swallowed in the gastro-intestinal tract. It is also well established that some Cr(VI) compounds have caused tumours of the gastrointestinal tract (in particular of the small intestine) in rodents by the oral route.

Therefore, it seems reasonable to associate the “inhalable, non-respirable fraction” of Cr(VI) inhalation exposure with the potential for an increased risk of cancer of the small intestine. It is proposed that the intestine cancer dose-response and risk estimates established for the oral route in workers (see section “Oral, general population and workers”) by linear extrapolation of mouse data are applied here to workers exposed by the inhalation route, as shown in table 5.4 below. Obviously, inhalation exposures to these inhalable, non-respirable particles of Cr(VI) compounds will have to be converted first into doses by applying the standard worker breathing rate of 1.25 m^3/hr and the standard worker body weight default value of 70 kg.

Table 5.4: Proposed excess lifetime small intestine[$] cancer risk estimates for workers exposed to different daily doses of Cr(VI) arising from inhalation exposure to inhalable, non-respirable particles for 40 years

Constant average daily dose of Cr(VI) (µg/kg bw/day) arising from inhalation exposure to inhalable, non-respirable particles (5 d/wk for 40 years)	Excess small intestine cancer risk in workers ($x10^{-4}$)

10	20
5	10
2.5	5(?)
1	2(?)
0.5	1(?)
0.25	0.5(?)
0.1	0.2(?)
0.01	0.02(?)

[$] Background cumulative lifetime risk of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

5.2 Inhalation, general population

There is only a small number of quantitative cancer risk assessments of Cr(VI) for the inhalation route in the general population (USEPA, 1998; WHO, 2000). These risk estimates were derived by applying linear models to various occupational epidemiology datasets (published in the 1970s and 1980s) and by extrapolating risks from occupational exposure durations to average lifetime exposures.

It is the view of the contractor that, as these unit risks are based on relatively old worker cohort studies, it would be more appropriate to extrapolate (to the general population) the occupational risk estimates proposed by Seidler et al. (2012) which are based on the most recent studies of the dose-response relationship between Cr(VI) exposure and lung cancer.

A unit excess lifetime (up to age 89) lung cancer risk (with its linear function) of 4×10^{-3} for workers exposed to an 8h-TWA concentration of 1 µg Cr(VI)/m^3 for 40 years was estimated by Seidler et al. (2012). Extrapolation of this estimate to continuous lifetime exposure ($4 \times 10^{-3} \times 24/8 \times 7/5 \times 70/40$) results in a **unit excess lifetime lung cancer risk for the general population** of **2.9×10^{-2}** at an ambient exposure concentration of **1 µg Cr(VI)/m^3 for 70 years**, equivalent to an excess lifetime risk of 10^{-6} at an ambient exposure concentration of 0.034 ng Cr(VI)/m^3 for 70 years.

In contrast to these risk estimates derived by the application of linear, non-threshold methodologies, there is also a recent cancer-based chronic inhalation “reference value” (at which the cancer risk is considered to be negligible) established by Haney et al. (2012) using a nonlinear, threshold approach. Haney et al. have proposed such a value of 0.24 µg Cr(VI)/m^3 by applying assessment factors to a human NOAEC (19.9 µg Cr(VI)/m^3) based

on the lack of statistically significant increases in lung cancer from occupational cohort studies. The contractor considers that the adoption of a threshold approach at low exposures has merit. However, there are serious flaws in using the stated human NOAEC for lung cancer as starting point.

It is noted that this reference value is 7000 times higher than the 10^{-6} excess lifetime cancer risk air concentration of 0.034 ng Cr(VI)/m^3 extrapolated from the occupational risk estimates proposed by Seidler et al. (2012). Although this threshold-based value is not fully supported by the contractor, the comparison above highlights the inherent problems of estimating risks at low exposures by extensive linear extrapolation, especially when mechanistic considerations suggest that non-linearity might well apply at low concentrations.

Therefore, as for the proposed occupational risk estimates, it is suggested that for environmental exposures of the general population down to 1 µg Cr(VI)/m^3 for 70 years, a linear dose-response relationship with unit (i.e. per 1 µg Cr(VI)/m^3) risk of 2.9 x10^{-2} is applied. However, for environmental exposures below 1 µg Cr(VI)/m^3 the risk estimates derived linearly from the proposed unit risk should be considered to overestimate significantly the real cancer risks. It is also proposed that at progressively lower ambient Cr(VI) concentrations (from about 0.1 µg/m^3 downwards), cancer risks should be regarded as negligible. The cancer risk estimates for different levels of environmental exposure above and below 1 µg Cr(VI)/m^3 derived linearly from the proposed unit risk are shown in table 5.5 below.

Table 5.5: Proposed excess lifetime lung[$] cancer risk estimates for the general population exposed at different ambient concentrations of Cr(VI) (respirable fraction) for 70 years

Ambient Cr(VI) exposure concentration – respirable fraction (µg/m^3)	**Excess lung cancer risk in the general population (x10^{-3})**
10	290
5	145
2.5	72
1	**29**
0.5	14(?)
0.25*	7(?)
0.1	2.9(?)
0.01	0.29(?)
0.001	0.029(?)
0.0001	0.0029(?)

[$] Background cumulative lifetime risk of dying from lung cancer between ages 0 and 74 in EU males is 48/1000 (Globocan, 2008)
*Threshold-based reference value at which cancer risks are considered to be negligible (by Haney et al., 2012)

In addition, as for the proposed occupational risk estimates, these risk values should be associated with exposure to Cr(VI) arising from the “respirable fraction” of “soluble”, “sparingly soluble” or “insoluble” Cr(VI) compounds.

However, as for workers, inhalation exposure to inhalable, non-respirable particles of Cr(VI) compounds should be associated with the potential for an increased risk of cancer of the small intestine, given that such particles are cleared by the mucociliary escalator into the gastro-intestinal tract.

It is proposed that the intestine cancer dose-response and risk estimates established for the oral route in the general population (see section "Oral, general population and workers") by linear extrapolation of mouse data are applied here to the general population exposed by the inhalation route, as shown in table 5.6 below. Obviously, inhalation exposures to these inhalable, non-respirable particles of Cr(VI) compounds will have to be converted first into doses by applying the standard human resting breathing rate of 0.8 m^3/hr and the standard average human body weight default value of 60 kg.

Table 5.6: Proposed excess lifetime (70 yr) small intestine[$] cancer risk estimates for the general population exposed to different daily doses of Cr(VI) arising from inhalation exposure to inhalable, non-respirable particles

Constant average daily dose of Cr(VI) (µg/kg bw/day) arising from inhalation exposure to inhalable, non-respirable particles	Excess small intestine cancer risk in the general population ($x10^{-4}$)
10	80
5	40
2.5	20(?)
1	8(?)
0.5	4(?)
0.25	2(?)
0.1	0.8(?)
0.01	0.08(?)

[$] Background cumulative lifetime risks of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

5.3 Dermal, workers

There are no data to indicate that dermal exposure to Cr(VI) compounds presents a cancer risk to humans.

5.4 Oral, general population and workers

There are fewer quantitative cancer risk assessments of Cr(VI) for the oral route compared to the inhalation route. A recent draft evaluation produced by

the USEPA in 2010 estimated a **unit lifetime (70 yr) excess intestine cancer risk of 8 x10^{-4}** at a constant average oral daily dose of **1 µg Cr(VI)/kg bw/day** from birth, with its associated linear function (Draft USEPA, 2010 – see table 5.7 below). An extrapolation of this unit ELR in the general population to **workers** exposed (5 days/week for 40 years) to Cr(VI) via the gastro-intestinal tract produced a **unit intestine cancer ELR of 2 x10^{-4}** at a daily dose of **1 µg/kg bw/day Cr(VI**), with its associated linear function. These estimates were derived by linear extrapolation of tumour incidence data in mice. It is the contractor's view that given the uncertainties in the role played by Cr(VI) genotoxicity in the carcinogenic process, it is difficult to move away from linearity in a regulatory context. Therefore, it is proposed that the oral cancer risk values estimated by the USEPA (2010) for the general population or extrapolated by the contractor for workers are adopted here, as shown in table 5.7 below.

Table 5.7: Proposed excess lifetime small intestine[$] cancer risk estimates for the general population (70 years) and workers (40 years) exposed to different oral daily doses of Cr(VI)

Constant average oral daily dose of Cr(VI) (µg/kg bw/day)	Excess small intestine cancer risk in the general population (x10^{-4})	Excess small intestine cancer risk in workers (x10^{-4})
10	80	20
5	40	10
2.5	20(?)	5(?)
1	8(?)	2(?)
0.5	4(?)	1(?)
0.25	2(?)	0.5(?)
0.1	0.8(?)	0.2(?)
0.01	0.08(?)	0.02(?)

[$] Background cumulative lifetime risks of dying from intestine cancer between ages 0 and 74 in Germany is 9/1000 in females and 16/1000 in males (IARC, 2008)

However, it should be noted that due to a number of reasons (extensive linear extrapolation from mouse data beyond the experimental range; non-linearity at low doses arising from the extracellular reduction of Cr(VI) in the gastro-intestinal tract; weak and inconsistent mutagenic response of Cr(VI) by the oral route; and contribution to the carcinogenic process of gastric epithelium irritation/inflammation from a dose of 0.38 mg/kg bw/day in the mouse), the lower-dose risk estimates proposed above are likely to be unreliable and highly conservative.

It should also be noted that the above risk estimates are applicable to "soluble" Cr(VI) substances (as they were derived from testing the soluble sodium dichromate) but they might be conservative for the "slightly soluble" and "insoluble" chromates as these substances are expected to be less bioavailable. In the absence of further information on how solubility affects oral carcinogenic potency of different Cr(VI) compounds, one could either apply the risk estimates in table 5.7 also to "slightly soluble" and "insoluble" Cr(VI) compounds accepting that they will perhaps overestimate the risks, or apply an arbitrary adjustment factor (e.g. reduce the risk estimates by 5, or

10, etc). The contractor advocates the former approach as being more solidly based on the currently available scientific data.

5.5 Appendix 1

Table 5.8: Solubility and particle size information of the 14 Cr(VI) compounds under consideration in this project

Cr(VI) compound	Solubility classification (based on OSHA, 2006 scheme)	Particle size distribution of substance as manufactured
lead sulfochromate yellow	insoluble	pigment yellow / volumetric distribution D10 – 0.36 µm D50 – 0.67 µm D98 – 1.55 µm 0.1 µm – 0.23 % 0.5 µm – 26.67 % 1 µm – 83.03 % 2 µm – 100 %
lead chromate	insoluble	
lead chromate molybdate sulphate	insoluble	pigment red / volumetric distribution D10 – 0.1 µm D50 – 0.47 µm D98 – 3.08 µm 0.1 µm – 10.13 % 0.5 µm – 53 % 1 µm – 83.85 % 2 µm – 99.56 % 6 µm – 100 %
acids generated from chromium trioxide and their oligomers	highly soluble	
ammonium dichromate	highly soluble	
chromium trioxide	highly soluble	> 1 mm (94.5%) 0.1 - < 1 mm (5.5%) < 0.1 mm (< 0.01%)
		> 1 mm (98.8%) 0.1 - < 1 mm (1.1%) < 0.1 mm (< 0.01%)
		> 1 mm (99.2%) 0.1 - < 1 mm (0.8%) < 0.1 mm (< 0.01%)
potassium chromate	highly soluble	
potassium dichromate	highly soluble	> 1 mm (< 0.01 %) 0.1 - < 1 mm (99.3 %) < 100 µm (0.5 %) < 10 µm (0.003 %) < 1 µm (not detectable)
sodium chromate	highly soluble	
sodium dichromate	highly soluble	> 1 mm (0.6 %) 0.1 - < 1 mm (94.7 %) < 100 µm (5.2 %)
		> 1 mm (39.2 %) 0.1 - < 1 mm (60.8 %) < 100 µm (0.04 %)
pentazinc chromate octahydroxide	slightly soluble	number count 4.83 µm (MMD) 2.69 µm (± 2.08) (10^{th} P) 7.98 µm (± 2.08) (90^{th} P)
		volumetric distribution

		4.31 µm (MMD) D10 – 0.83 µm D50 – 2.41 µm D90 – 10.82 µm D99 – 23.83 µm 0.25 – 40 µm (range)
dichromium tris(chromate)	slightly soluble	
potassium hydroxyocataoxodizincatedichromate	slightly soluble	2.41 µm (MMD) 0.22 µm (10^{th} P) 1.61 µm (50^{th} P) 5.83 µm (90^{th} P) 11.06 µm (99^{th} P) 0.06 (0.18 %) – 25 (100 %) µm
strontium chromate	slightly soluble	paint spray aerosol particles (epoxy resin matrix) 8.5 µm (MMAD) 62 % (> 10 µm)
		volumetric distribution 3.64 µm (MMD) 0.37 µm (10^{th} P) 2.73 µm (50^{th} P) 7.55 µm (90^{th} P) 16.43 µm (99^{th} P) 0.06 (0.07 %) – 50 (100 %) µm

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7 GLOSSARY

ELR (Excess Lifetime Risk) is the risk attributable to the exposure of interest (i.e. risk in the exposed group minus risk in the unexposed group). It is also defined as the additional or extra risk of developing the disease due to exposure to a toxic substance incurred over the lifetime of an individual.

JEM (Job-Exposure Matrix) comprises a list of levels of exposure to an agent for selected occupational titles.

Rate is the frequency of occurrence of disease in a population. It can be directly observed by the number of subjects developing disease divided by the total time experienced for the subjects followed. This parameter is applicable to incidence (number of new cases of the disease detected) or mortality (number of cases died as a result of the disease).

RR (Relative Risk) is the ratio of two rates (e.g., rate among exposed group divided by rate among unexposed group). The standardized ratio, such as standardized mortality ratio (SMR) or standardized incidence ratio (SIR), which are used in cohort studies if the unexposed reference group is the general population, is also a measure of relative risk as is the *odds ratio* (OR), which is derived from case-control studies.

Risk is measured as the number of subjects developing disease during a time period divided by the number of subjects followed for the time period and represents the average risk of disease in the population. It is a proportion.

SMR (Standardized Mortality Ratio) is a quantity, expressed as either a ratio or percentage quantifying the increase or decrease in mortality of a study cohort with respect to the general population.

Unit risk is an excess lifetime risk per unit of exposure.

8 LITERATURE SEARCH STRATEGY

Reviews were identified by google search using the following key terms: “chromium VI”, “risk assessment”, “review”, “evaluation”.

New publications not included in the reviews were identified by searching PubMed for the period 2012 – present (24 May 2013) using the following key terms: “chromium VI”, “carcinogenicity”, “risk assessment”, “genotoxicity”, “mutagenicity”, “mode of action”, “mechanism”.