Screening Assessment for the Challenge

C.I. Pigment Red 104

Chemical Abstracts Service Registry Number
12656-85-8

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of C.I. Pigment Red 104, Chemical Abstracts Service Registry Number (CAS RN) 12656-85-8. The substance C.I. Pigment Red 104 was identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. The substance was identified as a high priority because it was considered to pose greatest potential for exposure (GPE) to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity, reproductive toxicity and developmental toxicity. The substance also met the ecological categorization criteria for persistence and inherent toxicity to aquatic organisms. Therefore, this assessment of C.I. Pigment Red 104 focuses on information relevant to the evaluation of both human health and ecological risks.

In response to a notice issued under section 71 of CEPA 1999, in 2006 C.I. Pigment Red 104 was reported to be manufactured in and imported into Canada. After exports, the amount remaining for use in this country ranged between 100 000 and 1 000 000 kg. It is primarily used for plastic formulation for commercial applications and export; commercial, non-consumer paints and coatings; and commercial printing inks or coatings used for plastics and certain outdoor applications such as commercial identification decals.

There were no empirical data identified regarding measured concentrations of C.I. Pigment Red 104 in environmental media (i.e., air, water, soil and food) in Canada. Given the physical and chemical properties and sources of this substance, exposure to C.I. Pigment Red 104 is expected to be negligible via drinking water, ambient air or consumer products. Exposure to the general population in Canada is expected to be predominantly from soils, although these exposures are expected to be low due to the primarily commercial use of the substance, very limited industrial releases and the encapsulation and incorporation of the substance into a solid matrix. However, these exposures could not be quantified due to lack of measured concentrations.

The substance C.I. Pigment Red 104 is considered persistent because it contains metal ions, lead (Pb^{2+}) and the chromate (CrO_4^{2-}) ions, which are considered to be infinitely persistent. Therefore, C.I. Pigment Red 104 meets the persistence criteria as set out in the *Persistence and Bioaccumulation Regulations.* The current state of the science does not allow for the unambiguous interpretation of the bioaccumulation potential of metal-containing inorganic substances such as C.I. Pigment Red 104. Experimental toxicity studies conducted with its analogue, C.I. Pigment Red 34, suggest that C.I. Pigment Red 104 is not hazardous to aquatic organisms at a loading rate (100 mg/L) that is considered to represent a reasonable environmental worst-case scenario. Additionally, considering the low solubility of C.I. Pigment Red 104 and its analogue, C.I. Pigment Yellow 34, it is unlikely that organisms associated with other compartments would be harmed by exposure to C.I. Pigment Red 104 as well.

Based principally on the weight of evidence classification of C.I. Pigment Red 104 by the European Commission and the assessment of hexavalent chromium and inorganic lead compounds by several national and international agencies, a critical effect for the characterization of risk to human health is carcinogenicity. The substance C.I. Pigment Red 104, together with lead chromate and C.I. Pigment Yellow 34, was carcinogenic in rats after subcutaneous and intramuscular administration and these animal studies are supported by epidemiological studies that indicate an increased frequency of lung cancer in chromate pigment production workers. As well, C.I. Pigment Red 104 or its principal components were genotoxic in a limited number of *in vitro* and *in vivo* experimental systems.

On the basis of the carcinogenicity of C.I. Pigment Red 104, for which there may be a probability of harm at any level of exposure, it is concluded that C.I. Pigment Red 104 is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of ecological hazard and reported releases of C.I. Pigment Red 104, it is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. The substance C.I. Pigment Red 104 meets the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations.*

In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that C.I. Pigment Red 104 meets one or more of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999*.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance C.I. Pigment Red 104 was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity, reproductive toxicity and developmental toxicity. The Challenge for C.I. Pigment Red 104 was published in the *Canada Gazette* on May 12, 2007 (Canada 2007). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although C.I. Pigment Red 104 was determined to be a high priority for assessment with respect to risks to human health under CEPA 1999, it also met the ecological categorization criteria for persistence and inherent toxicity for aquatic organisms during the categorization of the Domestic Substances List. Therefore, this assessment focuses on information relevant to the evaluation of human health and ecological risks.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to October 2007 for the environmental section, and up to January 2008 for the health effects section of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the proposed conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Donna Vorhees (The Science Collaborative), Glenn Talaska (University of Cincinnati) and Joan Strawson (TERA). Comments on these sections were also received from Herman Gibb, Sciences International. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

Table 1. Substance identity

Chemical Abstracts Service Registry Number (CAS RN)	12656-85-8
Name on Domestic Substances List (DSL)	*C.I. Pigment Red 104*
Inventory names[1]	*C.I. Pigment Red 104* (TSCA, AICS, ECL, SWISS, PICCS, ASIA-PAC, NZIoC)*;* *Lead chromate molybdate sulfate red* (EINECS)*;* *Pigment Red 104* (ENCS)*;* *Silica Encapsulated Pigment Red 204; Molybdate Orange; Lead Chromate Molybdate* (PICCS)
Other names	*C.I. 77605; Chrome Vermilion; Horna Molybdate Orange MLH 84SQ; Krolor Orange KO 906D; Krolor Orange RKO 786D; Mineral Fire Red 5DDS; Mineral Fire Red 5GGS; Mineral Fire Red 5GS; Molybdate Orange Y 786D; Molybdate Orange YE 421D; Molybdate Orange YE 698D; Molybdate Red; Molybdate Red AA 3; Molybden Red; Molybdenum orange; Molybdenum Red; Renol; Molybdate Red RGS; Vynamon Scarlet BY; Vynamon Scarlet Y*
Chemical group (DSL stream)	UVCBs (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials) - Inorganics
Chemical sub-group	Group IVA and group VIB element compounds; chromium VI-containing; lead II-containing; molybdenum VI-containing; oxides; sulfates
Chemical formula	$PbCrO_4$ * $PbSO_4$ * $PbMoO_4$ (Solid solution crystal of $PbCrO_4$, $PbSO_4$, and $PbMoO_4$ in varying proportions) (Environment Canada 2007a)
Chemical structure	N/A
Simplified Molecular Input Line Entry System (SMILES)	N/A
Molecular mass	$PbCrO_4$ = 323.2 g/mol (main constituent); $PbSO_4$ = 303.3 g/mol; $PbMoO_4$ = 367.1 g/mol

1 **Source:** National Chemical Inventories (NCI). 2007: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Combined Inventories of Asia-Pacific Region); ECL (Korean Existing Chemicals List) EINECS (European Inventory of Existing Chemical Substances); ENCS (Existing and New Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); SWISS (Inventory of Notified New Substances); TSCA (Toxic Substances Control Act Chemical Substance Inventory).

Analogue justification for ecological purposes

C.I. Pigment Red 104 is quite similar to C.I. Pigment Yellow 34 (CAS RN 1344-37-2), another substance that has been identified as part of the Ministerial Challenge. C.I. Pigment Yellow 34 is also identified as a UVCB metal-containing substance and its chemical formula is described as $PbCrO_4$ * $PbSO_4$ (a solid solution crystal of $PbCrO_4$ and $PbSO_4$ in varying proportions)

(Environment Canada 2007a). Although Pigment Yellow 34 does not contain a molybdenum component ($PbMoO_4$) like C.I. Pigment Red 104 , it contains the same two other major components as C.I. Pigment Red 104 ($PbCrO_4$ and $PbSO_4$) in similar proportions. Additionally, the solubility of C.I. Pigment Yellow 34 is very similar to that of lead chromate alone. This suggests that C.I. Pigment Red 104 may have a similar solubility in water. Both substances have similar types of applications that require durability (through low solubility) in order to resist weathering in harsh environments. These chemicals are therefore considered to be analogues for the purposes of this assessment.

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of C.I. Pigment Red 104 that are relevant to its environmental fate.

Table 2. Physical and chemical properties for Pigment Red 104

Property	Type	Value (SI units)	Temperature (°C)	Reference
Physical state	Experimental	Solid		IUCLID 2000
Average particule size (µm)	Experimental	~ 200	-	Environment Canada 2007a
	Experimental (range)	0.1–1	-	Lewis 1988
Melting point (ºC)	Experimental	> 800	-	IUCLID 2000
Boiling point (ºC)	-	Not available	-	-
Density (kg/m^3)	Experimental	3800–6000 (3.8–6 g/cm^3)	20	IUCLID 2000
Vapour pressure (Pa)	Experimental	Negligible	Not indicated	IUCLID 2000
Henry's Law constant ($Pa\ m^3/mol$)	Calculated	Negligible	-	-
Log K_{ow} (Octanol-water partition coefficient, dimensionless)	-	Not applicable	-	-
Water solubility (mg/L)	Experimental, parent substance	< 0.01	20	IUCLID 2000
	Experimental, $PbCrO_4$ (major component)	0.058	25	Weast 1965
		0.17	20	Lide 2006
	Experimental, $PbSO_4$ (minor component)	42.5	25	NICNAS 2007
	Calculated from an analogue[2]	0.062; 0.693; 0.764	21-25;13-17;19.5-20.4	Study Submission 2006a; 2006b; 2006c

Property	Type	Value (SI units)	Temperature (°C)	Reference
Log K_{oc} (Organic carbon partition coefficient, dimensionless)	-	Not applicable	-	-
Log K_{sw} (Partition coefficient soil-water, dimensionless)[3]	Experimental	Pb(3.444-5.212) Cr(2.812-4.764)	-	Thibault et al. 1990; Janssen et al. 1997; Sauvé et al. 2000
Log K_{sdw} (Partition coefficient sediment-water, dimensionless)[3]	Experimental	Pb(4.553-6.075) Cr(4.928-5.627)	-	Smock 1983; Timmermans et al. 1989; Keenan and Alikhan 1991; Van Hattum et al. 1991; Davis et al. 1996; Besser et al. 2001; Allison and Allison 2005
Log K_{ssw} (Partition coefficient suspended sediment-water, dimensionless)[3]	Experimental	Pb(5.391-6.879) Cr(4.376-5.759)	-	Chiffoleau et al. 1994; Lofts and Tipping 2000; Roditi et al. 2000; Allison and Allison 2005; Gobeil et al. 2005

1 Values in parentheses represent the values in the original units as reported by the authors.

2 The solubility of C.I. Pigment Red 104 was estimated using the solubility of the substance analogue (CASRN 1344-37-2–C.I. Pigment Yellow 34). Solubility was back-calculated using the total-dissolved concentrations of the metals (Cr, Pb) and information on the composition of the parent substance analogue.

3 Partition coefficients apply to the dissolved metal fractions.

This substance contains several different constituents, including lead chromate ($PbCrO_4$), lead sulfate ($PbSO_4$) and lead molybdate ($PbMoO_4$). Therefore, the proportion of these constituents in the pigment must be considered when evaluating exposure for each of the metals. The *Pigment Handbook* (Lewis 1988) provides a range of composition percentages for the different constituents that are included in the second column of Table 3. Using the average composition (middle value of the range) and the molecular weight, the weight fractions of lead and the anionic moieties are calculated for each constituent. Table 4 provides the total weight composition for each moiety by summing the contributions from each constituent.

Table 3. Composition range and weight fractions for C.I. Pigment Red 104

Constituent	Composition range (%)	Average composition (%)	Molecular weight (g/mol)		Weight fraction (%)	
			Pb	Other	Pb	Other
$PbCrO_4$	69–80	75	207.2	116	48	27
$PbSO_4$	9–15	12	207.2	96	8	4
$PbMoO_4$	3–7	5	207.2	159	3	2
Other	3–13	8	--	--	--	--

Table 4. Weight fraction of specific moieties for C.I. Pigment Red 104

Moiety	Composition (%)
Pb	59
CrO_4	27
SO_4	4
MoO_4	2

Sources

C.I. Pigment Red 104 is not known to be naturally produced in the environment. The principal metallic components of this substance, lead and chromium, are naturally occurring and as such are considered infinitely persistent. Lead concentrations in the rock of the upper continental crust have been determined to range between 17 and 20 ppm; chromium concentrations have been determined to be approximately 35 ppm (Reimann and de Caritat 1998).

As indicated in Table 2, these compounds are not highly soluble. However, while lead sulfate is present in the pigment at six fold lower quantities, it is orders of magnitude more soluble. Therefore, lead sulfate may be a more significant source of dissolved lead from C.I. Pigment Red 104, despite being present in much smaller quantities. However, there are various grades of pigments including those in which the pigment is encapsulated in a dense amorphous silica coating, which significantly reduces its solubility and bioavailability (Lewis 1988).

Based on a survey conducted under section 71 of CEPA 1999, in 2006 C.I. Pigment Red 104 was both manufactured in and imported into Canada (Environment Canada 2007b). Based on an exportation rate of around 75% of all substance manufactured (Environment Canada 2007a), between 100 000 and 1 000 000 kg of this substance would be remaining for use in this country.

Uses

According to the Color Pigments Manufacturers Association, the significant applications for these pigments in Canada are plastic formulation for commercial applications and export;

commercial, non-consumer paints and coatings; and a very limited number of commercial printing inks or coatings used for plastics and certain outdoor applications such as commercial identification decals. For example, these pigments are used for applications that require safety attributes such as high visibility and so are used in traffic paint striping for highways and airports, and safety identification paints on buses, ambulances and fire trucks. Industrial paints using lead chromate pigments include automotive finishes, industrial and agricultural equipment, industrial baking enamels and air-dried finishes (Environment Canada 2007a).

The substance C.I. Pigment Red 104 is not used in consumer paints because the Canadian *Hazardous Products Act* prohibits furniture and other articles for children that are painted with a surface-coating material that contains lead compounds of which the total lead content is more than 600 mg/kg (Canada 2005a). A concentration greater than 600 mg/kg would be required technically to manufacture a paint coloured with this substance (Environment Canada 2007a). The *Hazardous Products Act* also prohibits toys, equipment and other products for use by a child in learning or play and pencils and artists' brushes that have had a surface coating material applied to them that contains more than 600 mg/kg of total lead (Canada 2005a).

The *Surface Coating Materials Regulations* of the *Hazardous Products Act* (Canada 2005b) prohibits surface coatings (paints) containing greater than 600 mg/kg of total lead except

1. as an anti-corrosive or an anti-weathering coating applied to buildings or equipment used for agricultural or industrial purposes;
2. as an anti-corrosive or an anti-weathering coating applied to any structure, other than a building, used for agricultural, industrial or public purposes;
3. as a touch-up coating for metal surfaces;
4. on traffic signs;
5. for graphic art on billboards or similar displays;
6. for identification marks in industrial buildings; and
7. material for the purposes of arts, crafts or hobbies, other than material for use by children.

These regulations do not apply in the case of a surface-coating material that is used exclusively in an industrial setting, other than for a use described [above], on surfaces where the finish is so durable and tightly adhered to the surface that it cannot be chewed or chipped under foreseeable use.

The substance C.I. Pigment Red 104 is not listed in the Food Additive Tables of Division 16 of the Food and Drug Regulations, and is therefore not permitted as a food colour in Canada. In addition, personal communication with the Health Protection and Foods Branch of Health Canada confirmed that this substance is not currently being used in food packaging material (as per email from the Food Packaging and Incidental Additives Section, Health Products and Food Branch, Health Canada, dated 2008 March 07, unreferenced).

Releases to the Environment

Submissions from a survey conducted under section 71 of CEPA 1999, in 2006 indicated that industrial releases of C.I. Pigment Red 104 to ambient air, water and soil were extremely low (i.e., less than 0.1% of the total quantity manufactured in or imported into Canada) (Environment Canada 2007b). As well, there are provincial and municipal regulations or bylaws regarding levels of acceptable releases of lead or chromium (such as *Ontario Regulation 419/05 Air Pollution – Local Air Quality* (ON 2005) and the Sewer Use By-Law (Durham 2004)).

Mass flow tool

To estimate potential release of the substance to the environment at different stages of its life cycle, a mass flow tool was used (Table 5). Empirical data concerning releases of this substance to the environment are not available. Therefore, for each identified type of use of the substance, proportion and quantity of release to the different environmental media are estimated, as is the proportion of the substance chemically transformed or sent for waste disposal. Assumptions and input parameters used in making these estimates are based on information obtained from a variety of sources including responses to regulatory surveys, Statistics Canada, manufacturers' websites and technical databases. Of particular relevance are emission factors, which are generally expressed as the fraction of a substance released to the environment, particularly during its manufacture, formulation and use associated with industrial processes. Sources of such information include emission scenario documents, often developed under the auspices of the Organisation for Economic Cooperation and Development (OECD), and default assumptions used by different international chemical regulatory agencies. It is noted that the level of uncertainty in the mass of the substance in circulation and quantity released to the environment generally increase toward the end of the life cycle.

Table 5. Estimated releases and losses of C.I. Pigment Red 104 to environmental media, transformation and distribution to management processes, based on the mass flow tool[1]

Medium or process	Proportion of the mass (%)	Major life cycle stage involved[2]
Soil	1.0	Industrial use
Air	0.5	Manufacture, waste disposal
Water	7.9	Manufacture, formulation and industrial use
Transformation	2.8	Waste disposal
Waste disposal	87.8	Waste disposal

[1] For C.I. Pigment Red 104, information from the following OECD emission scenario documents was used to estimate releases to the environment and distribution of the substance, as summarized in this table: OECD 2004; Brooke and Crookes 2007. Values presented for releases to environmental media do not account for possible mitigation measures that may be in place in some locations (e.g., partial removal by sewage treatment plants). Specific assumptions used in derivation of these estimates are summarized in Environment Canada 2007c.
[2] Applicable stage(s): production-formulation-industrial use-consumer use-service life of article/product-waste disposal.

The results suggest that the substance mainly ends up in waste management sites (87.8%). Of the substance, 2.8% is transformed, which in this case means destruction or modification of the structure of the substance during its incineration. Of the estimated releases to the environmental

media, 7.9%, 1% and 0.5% are released to water, soil and air, respectively. Although results from a survey conducted under section 71 of CEPA 1999 in 2006 (Environment Canada 2007b) indicated that releases to all media from industrial manufacture and formulation were extremely low (i.e., less than 0.1% of the total quantity manufactured in or imported into Canada),the mass flow tool results indicate that specific applications and/or post-application releases (e.g., from commercial use) that are expected to make the greatest contribution to environmental levels.

Based on the above, water is expected to be the medium receiving the greatest proportion of C.I. Pigment Red 104 emitted during product manufacturing, formulation and industrial use. It is anticipated that the majority of the substance bound in the product will be sent to landfills or incinerators for disposal. Note that the tool assumes no releases from such waste disposal sites.

Although no information is available on the quantity of importation of finished products containing C.I. Pigment Red 104, it is anticipated that if this importation were considered, the relative quantities of releases to the various environmental media would not be greatly different from those estimated here. However, it is likely that the percentage sent for waste management would be somewhat higher if importation of finished products were taken into consideration and the percentage released to water would be lower.

Given some potentially dispersive uses of this chemical in specific coloured products, it is expected that C.I. Pigment Red 104 is being released into the Canadian environment mainly as a result of industrial use of these products.

Environmental Fate

Solubility and dissociation

Inorganic metal-containing compounds often dissolve, dissociate and release ions in the solution (Environment Canada 2003). The estimated solubility in water of C.I. Pigment Red 104 is quite low, ranging from < 0.01 to 0.764 mg/L (Table 2), with geometric and arithmetic means of 0.135 and 0.382 mg/L respectively—based on data for C.I. Pigment Yellow 34. A relatively low proportion of the parent substance is thus expected to dissolve, dissociate and release the lead (Pb^{2+}) and chromate (CrO_4^{2-}) ions in typical aquatic media with a pH between 6 and 8 and under conditions that are moderately oxic (~ 0.4–0.7 V, or dissolved oxygen > 4 mg/L). These moieties, released from the parent substance, are of greatest toxicological significance and are thus the moieties of concern for this assessment (Environment Canada 2003). The molybdate (MoO_4^{-2}) ion is also released but its ecotoxicity is lower than that of chromium and lead moieties of concern, and did not meet the inherent toxicity criterion in the context of categorization (CEPA Environmental Registry 2006); therefore, it is not further evaluated in this assessment. In addition to the low solubility of the parent substance itself, its encapsulation in paints, plastics and coatings that are made to last for long periods of time and resist harsh environments further restrains the dissolution of the parent substance and therefore further limits the bioavailability of the metals contained in the substance (Environment Canada 2007a).

The total dissolved metal concentrations in experimental solutions assumed to be saturated of the analogue C.I. Pigment Yellow 34 is reported to vary from 0.012 to 0.179 mg/L for chromium and from 0.02 to 0.36 mg/L for lead (Table 2). The total dissolved metal concentrations were obtained based upon the following procedure: (1) dissolution of the parent substance C.I. Pigment Yellow 34 after 20 to 24 hours stirring in dilution test water of pH 7.1 to 8.4 at room temperature; (2) 0.2 or 0.45 µm filtration and; (3) measurement of total dissolved metals in filtrate. The loading rate was 100 or 125 mg of parent substance per litre (Study Submission 2006a; 2006b; 2006c).

Partitioning

As C.I. Pigment Red 104 is a metal-containing inorganic substance, the fate analysis based on log K_{ow} and K_{oc} is not applicable to it. Typical fugacity modelling is also not applicable to this substance or to the metal ions that are released from it on dissolution because, as for other non-volatile chemicals, these substances exert zero partial pressure and fugacity in air (Diamond et al. 1992). The fate of the dissociated metals may however be characterized by partition coefficients - namely soil, suspended particles and sediments to water partition coefficients (K_{sw}, K_{ssw} and K_{sdw}), which are presented in Table 2.

Since C.I. Pigment Red 104 is a solid and has a negligible vapour pressure, it is not expected to partition to air. The partitioning of this substance may also depend on the compartment to which it is released. Once released to surface water and moist soils, the fate of C.I. Pigment Red 104 depends upon its solubility and dissociation in water (OECD 2001) as mentioned above. The fate analysis of the dissociated Pb^{2+} and CrO_4^{2-} ions indicates that they can transform and form dissolved complexes with dissolved ligands present in the aquatic environment (Tipping 2002; Schecher and MacAvoy 1992). Information on metal binding to dissolved ligands may be obtained from thermodynamic constant databases (Smith and Martell 2004; IUPAC 2001), assuming that the metal ion and ligand in the environment are at equilibrium (Stumm and Morgan 1996). Because of the strong tendency of these metals to sorb to aquatic particles (Table 2; K_{ssw}), a significant proportion of dissolved forms of these metals will end up in sediments (Table 2; K_{sdw}) through the settling of suspended particles (Hamilton-Taylor et al. 1984). The remaining metal ions can then be taken up by aquatic organisms as assumed by models relating metal concentrations in aquatic organisms to those of their surroundings (e.g., the free ion activity model, Campbell 1995; the biotic ligand model, DiToro et al. 2001, 2005). Therefore, the moieties of concern issued from the dissolution and dissociation of C.I. Pigment Red 104, Pb^{2+} and CrO_4^{2} are expected to be found in water, sediments and soils but not in air. Note that some non-dissolved C.I. Pigment Red 104 (as parent substance) is also expected to be found in sediments and moist soils. When released to dry soils, it will mainly remain there with some of the substance leaching locally into ground and/or surface water ecosystems when the soil gets soaked by rain or melting snow/ice. The solid parent substance is not expected to be found in significant amounts in water, considering that its density is a few times greater than that of water.

According to the mass flow tool results presented in Table 5, C.I. Pigment Red 104 is mainly released to water during manufacture, formulation and industrial use (8.7%); therefore, releases

to water seem to be of greatest potential concern in Canada. As noted above, once released to water, a significant portion of the substance released will end up in sediments. Particles of traffic striping paint containing the substance may enter surface water from surface runoff from roadways into drainage ditches, watercourses or wetlands. Additionally, a very small percentage of the substance may be solubilized to release the Pb^{2+} and CrO_4^{2-} moieties of concern. If wastewaters are treated prior to release, a certain percentage of C.I. Pigment Red 104 may be removed during the sewage treatment process and later applied to soil as sludge, resulting in release to soil. Of the 87.8% that is sent to waste disposal (buried in landfills), most will remain in the soil of the landfill but some leaching (e.g., associated with the degradation of plastics, paints or coatings) might be possible. Overall, considering the information on releases and fate, water, soil and sediments are expected to be the most important receiving media for this chemical.

Data on environmental concentrations of C.I. Pigment Red 104 have not been identified. However, concentrations of lead and chromium have been measured in the Canadian environment (e.g., in surface waters, Borgmann et al. 2007).

Persistence and Bioaccumulation Potential

Environmental Persistence

A metal ion is considered infinitely persistent because it cannot degrade any further. When a metal ion is the moiety of concern, the persistence of this metal ion is attributed to the parent compound. This method is justified because even sparingly soluble compounds release a small quantity of metal ion into solution (Environment Canada 2003).

The substance C.I. Pigment Yellow 104 is considered persistent because both of its moieties of concern, the lead (Pb^{2+}) and the chromate (CrO_4^{2-}) ions, are considered infinitely persistent. Therefore, C.I. Pigment Red 104 meets the persistence criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The current state of the science does not allow for the unambiguous interpretation of the significance of various measures of bioaccumulation (e.g., BCFs, BAFs) for metal-containing inorganic substances. Therefore, such substances are evaluated only on the basis of their properties relating to toxicity and persistence (Environment Canada 2003). It is anticipated that evolution of scientific understanding will eventually allow broader interpretation of the potential for bioaccumulation for such substances.

Potential to Cause Ecological Harm

Ecological Effects Assessment

A - In the Aquatic Compartment

No experimental ecotoxicity data are available for C.I. Pigment Red 104. The aquatic acute toxicity of the chemical analogue C.I. Pigment Yellow 34 has been determined using an alga, *Scenedesmus subspicatus*, an invertebrate named *Daphnia magna* and Rainbow Trout, *Oncorhynchus mykiss* (Table 6). These results will be used to directly estimate the toxicity of C.I. Pigment Red 104.

Table 6. Empirical aquatic toxicity data from the analogue C.I. Pigment Yellow 34 to be used for C.I. Pigment Red 104

Organism	Test type	Endpoint	Duration	Value (mg/L)	Reference
Scenedesmus subspicatus (Algae)	Acute	EC_{50}[1]	72	> 100 [2]	Study Submission 2006a
Daphnia magna (Invertebrate)	Acute	EC_{50}[3]	48	> 100 [2]	Study Submission 2006b
Oncorhynchus mykiss (Rainbow Trout – Fish)	Acute	LC_{50}	96	> 100 [2]	Study Submission 2006c

[1] Effect on growth rate or development of biomass.
[2] No effect at 100 mg/L loading rate, the highest nominal concentration tested.
[3] Immobilization.

Green algae, *Scenedesmus subspicatus* cultures were exposed to C.I. Pigment Yellow 34 (Study Submission 2006a). The tests were run at a water temperature of 23ºC and a pH of 7.1 on average. The water hardness level was not mentioned. The substance C.I. Pigment Yellow 34 was added to deionized water, stirred during 20 hours and the undissolved test substance was removed by filtration (0.2 µm). Total dissolved metals (Cr, Pb) were measured in the filtrate. The highest nominal test concentration was 100 mg/L and total dissolved metal concentrations are shown in Table 2. Organisms were exposed to the full-strength filtrate (100 mg/L nominal) and subsequent dilutions of the filtrate to give nominal concentrations of 50, 25, 12.5, 6.25, 2.08, 0.69, 0.23 and 0.08 mg/L. There were no significant effects on the reduction in biomass nor on the growth rate of algae in each of the concentrations tested after 72 hours.

The substance C.I. Pigment Yellow 34 was also tested on *Daphnia magna* (Study Submission 2006b). The water temperature during the test varied between 19.5 and 20.4ºC, pH oscillated between 7.4 and 8.1 and the hardness was in between 220 and 241 mg/L as $CaCO_3$. The test substance was added to test medium, stirred during 24 hours and the undissolved test substance was removed by filtration (0.2 µm). Total dissolved metals (Cr, Pb) were measured in the filtrate. The highest nominal test concentration was 100 mg/L and total dissolved metal concentrations are shown in Table 6. Organisms were exposed to the full-strength filtrate (100 mg/L nominal) and subsequent dilutions of the filtrate to give nominal concentrations of 50, 25

and 12.5 mg/L. No effects were observed: all daphnids were mobile after 48 hours in any of the concentrations tested.

Finally, C.I. Pigment Yellow 34 was tested on fish. Juvenile Rainbow Trout, *Oncorhynchus mykiss* were exposed during 96 hours to a moderately hard groundwater containing the test substance (Study Submission 2006c). Average hardness and pH of the test water were 230 mg/L as $CaCO_3$ and 8.3, respectively. The water temperature ranged from 13 to 17ºC. Each of the test concentrations (1000; 100; 10 and 1 mg/L) were prepared as follows. All test solutions containing the various amounts of test substance were stirred overnight, followed by 2 filtrations (1 and 0.45 µm) to remove the undissolved test substance. Average total dissolved metals (Cr, Pb) were measured in the filtrate of the nominal 100 mg/L test concentration. The results are presented in Table 2. Fish were exposed to the filtrates and no mortality was observed in any of the concentrations tested after 96 hours.

All laboratory studies showed that there were no effects observed on aquatic organisms at measured concentrations resulting from a 100-mg/L loading rate of the parent substance. It should be noted that the proportion that dissolves could be higher under different environmental conditions. However, because 100 mg/L is a much higher loading rate than would be expected to occur in nature, the concentrations tested can be considered to represent a "reasonable worst-case scenario." Total dissolved metal concentrations as high as those measured in the studies are unlikely to result very often in nature from dissolution of C.I. Pigment Red 104. Based on the data extrapolated from C.I. Pigment Yellow 34, C.I. Pigment Red 104 is not considered to be highly hazardous to aquatic organisms.

B - In Other Environmental Compartments

No empirical or predicted effects data for non-aquatic non-mammalian organisms were considered for the metal moieties of concern (lead and chromium) released from the substance. Given the low solubility of C.I. Pigment Red 104, and its analogue, C.I. Pigment Yellow 34, however, exposures for such organisms through contaminated soils and/or food are not likely to be significant. Laboratory studies on mammals are discussed under the "Potential to Cause Harm to Human Health" section in this screening assessment.

Characterization of Ecological Risk

Manufacture and importation volumes of C.I. Pigment Red 104 into Canada, along with its widespread and some specific potentially dispersive uses, indicate a potential for release of this chemical into the Canadian environment. Based on the available information relating to the metal moieties released on dissolution/dissociation, C.I. Pigment Red 104 is persistent in the environment. However, once in the environment, release of bioavailable metals of concern (lead and chromium) will be limited because of its resistance to solubilization.

Although quantitative estimates of metal exposures resulting from release of C.I. Pigment Red 104 have not been made, the experimental ecotoxicological aquatic data for a chemical analogue suggest that it is not likely to cause acute harm to aquatic organisms, due to its very low water solubility. Although it is possible that dissolution of C.I. Pigment Red 104 could

result in dissolved concentrations of lead and chromium capable of causing chronic harm to sensitive aquatic biota, the likelihood of this happening is considered to be small. Information on potential impacts in other environmental compartments has not been evaluated; however, considering its low solubility, it is unlikely that organisms associated with other compartments would be harmed by exposure to this substance.

This information suggests that C.I. Pigment Red 104 has a relatively low potential to cause ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

There is uncertainty regarding metal exposures that could result from dissolution of C.I. Pigment Red 104 released into the Canadian environment. Solubility data were experimentally determined after relatively short periods of dissolution time and with neutral to slightly alkaline test water pHs. Longer periods and/or lower pHs, to be more realistic of certain environmental conditions, might have led to increased total dissolved metal concentrations in the test solutions. However, using 2 loading rates (1000 and 100 mg/L) gave similar total dissolved metals concentrations in the test solutions suggesting that solutions were near or saturated at a pH of around 8.3 (Study Submission 2006c). Solutions were assumed saturated in the experimental conditions tested.

There is also uncertainty about the acute toxicity values that were determined in water with relatively high ionic strength (e.g., high hardness) that could have mitigated metal toxicity (Study Submission 2006b; 2006c). Differences in water chemistries (e.g., hardness, DOC, major ions concentrations, etc.) could then have interfered with bioavailability of the pigment and consequently the potential for adverse effects. On the other hand, some fine particles might have passed through the filters and this might have resulted in increased metal concentrations in the filtrate. This could have resulted in an overestimate of the chemical solubility and bioavailability of the parent substance. Indeed, the particles size distribution presented in Table 2 indicates that a significant proportion of the particles of the substance are smaller than 0.45 µm and would represent the dissolved colloidal fraction.

Potential for toxicity to soil and sediment-dwelling biota was not specifically examined. However, it is assumed that the conclusion that effects to aquatic species are unlikely because of the limited solubility of the substance (leading to low bioavailable metal fractions) is applicable to other types of organisms as well.

Furthermore, no chronic toxicity tests were conducted for C.I. Pigment Red 104 and concentrations of both lead and chromium reported in Table 2 are in the range that could cause chronic effects to sensitive pelagic biota. However, concentrations as high as those measured would be unlikely to result very often in nature from dissolution of C.I. Pigment Red 104.

Finally, there is uncertainty in concluding outside a moiety-based assessment on individual substances that can contribute to the total release of bioavailable lead or chromium to the environment. In the context of this Challenge assessment, only sources of bioavailable lead and

chromium attributable to dissolution of Pigment Red 104 were considered independently of other sources of such metals to the environment. The conclusion reached in this assessment, that Pigment Red 104 has a relatively low potential to cause ecological harm in Canada, does not preclude the possible inclusion of this substance in future moiety-based assessments of lead or chromium-containing compounds.

Potential to Cause Harm to Human Health

Exposure Assessment

Measured concentrations of C.I. Pigment Red 104 in environmental media in Canada or elsewhere were not available. Submissions from a survey conducted under section 71 of CEPA 1999 in 2006 indicated that industrial releases of C.I. Pigment Red 104 to ambient air, water and soil were extremely low (i.e., less than 0.1% of the total quantity manufactured in or imported into Canada) (Environment Canada 2007b). However, the mass flow tool suggests that post-application releases of the substance may be significant.

Given its physical and chemical properties, estimations of the concentration of C.I. Pigment Red 104 in drinking water were not considered to be relevant. Its low solubility in water indicates that the majority of releases to this medium, from industrial or post-application commercial sources (e.g., deterioration of traffic striping paint and migration from landfills after waste disposal), would be in the form of suspended particulates. These particulates are highly likely to be removed via settling or filtration during wastewater treatment and/or subsequent drinking water treatment processes, and therefore the concentrations remaining in drinking water would be negligible.

Due to its negligible vapour pressure, any industrial releases of C.I. Pigment Red 104 to ambient air would be in the form of particulates. The majority of these particulates would be captured prior to release from the facility and any remaining particulates would be expected to settle before significant transport had occurred. Using the quantity of releases reported under section 71 of CEPA 1999, a dispersion model was applied using extremely conservative assumptions to estimate the ambient air concentrations downwind from pigment manufacturing facilities (the details of the model cannot be revealed due to the confidential nature of the release data used for the calculations). The maximum concentration of C.I. Pigment Red 104 predicted to be present in ambient air was 0.36 $\mu g/m^3$. This concentration is expected to be extremely conservative and would only be relevant for those living next to the facility. The general population of Canada is not expected to be exposed to C.I. Pigment Red 104 through inhalation of ambient air.

Given the physical chemical properties of C.I. Pigment Red 104, in the environment it is expected to be found primarily in soils and/or sediments. Reported industrial releases of this substance to the environment via manufacturing or formulation were extremely low and so are not expected to contribute to the overall concentrations found in soil. As the mass flow tool suggests, application and/or post-application releases (i.e., painting of buildings, vehicles, signage, and traffic striping) are likely to be a significant source of this substance to water,

sediment and soil. However, given that the substance is often directly incorporated into the matrix of the solid material and the dispersive use of these products, the availability of this substance for human exposure is expected to be minimal. Landfills and areas of high product usage may have higher concentrations of this substance in the soil; however, migration of the substance from these areas is expected to be low due to its negligible vapour pressure and low water solubility. The low solubility of this substance also indicates that bioavailable exposures through soils, suspended solids and sediment are not likely to be significant and would be further reduced by the substance being incorporated into a solid matrix or encapsulated in silica. Therefore, significant quantities of C.I. Pigment Red 104 are not expected to be found in the food chain.

The substance C.I. Pigment Red 104 is not used for the manufacture of products for use by the general population and therefore there is no direct exposure to them via this route. This substance is used in commercial settings to manufacture items that consumers may come in contact with after application, such as road paint, pigmented polymers and pigments used in wiring. As the substance is not volatile, there would be no relevant exposure through the inhalation pathway. It is possible that a consumer may have dermal contact with the pigments following application; however, the resulting dermal exposure is expected to be low for several reasons. This substance is often directly incorporated into the matrix of the solid material (i.e., polymer) and, generally, solid materials have the lowest potential for exposure by the dermal route as migration through the solid matrix and subsequent absorption through the skin would be very limited. Specifically, chromium and lead, and particularly their salts, are not known to have a high potential for systemic exposure by the dermal route as they have low skin permeability coefficients relative to other chemicals (US EPA 1992), and the silica encapsulation of this pigment would further prevent migration.
The confidence in the characterization of exposure to C.I. Pigment Red 104 is low as the concentrations of this substance in environmental media could not be quantified in Canada or elsewhere. However, given the physical and chemical properties of this substance and its commercial use and applications, it is expected that exposure to the general population of Canada is negligible. It is possible that there may be small populations of Canadians that are exposed to higher concentrations than would be expected in the general environment. This could occur in persons living near facilities that are manufacturing or using large quantities of this substance or those that are participating in activities such as automotive restoration and repair, or using artists' paints that may contain C.I. Pigment Red 104. Given the lack of data available for this substance, it is not possible to quantify the exposures from these sources.

Health Effects Assessment

The available experimental toxicological data on health effects for C.I. Pigment Red 104 and its principal components, lead chromate, lead sulfate and lead molybdate, as well as the epidemiological investigations among workers involved in lead chromate pigment production and use, are presented in Appendix 1.

The European Commission (ESIS 2007) has classified C.I. Pigment Red 104 as a Category 3 carcinogen ("causes concerns for humans owing to possible carcinogenic effects")[1]. The European Commission has concluded that C.I. Pigment Red 104, together with lead chromate and C.I. Pigment Yellow 34, "show(s) evidence for carcinogenicity in several studies with rats after subcutaneous and intramuscular administration. Lead chromate induced both benign and malignant tumours at the site of injection and, in one study, renal carcinomas. The animal studies are supported by epidemiological studies demonstrating an increased frequency of lung cancer among workers involved in production of chromate pigments. The animal studies are also supported by genotoxic(ity) studies as well as cell transformation studies. The substances show resemblance to known mutagens/carcinogens" (ECB 2003). The carcinogenicity of C.I. Pigment Red 104 has not been examined in experimental animals via oral, dermal or inhalation administration. Bronchial tumours did not develop in rats following two-year bronchial implantation with C.I. Pigment Red 104; however, squamous cell metaplasia was observed in male and female rats (Levy et al. 1986). Additionally, local benign and malignant tumours were significantly induced in male and female rats following subcutaneous or intramuscular injection of molybdenum orange or lead chromate, the principal component of C.I. Pigment Red 104 and in one study 3 of 23 male rats developed renal tumours, which were not observed in control animals (0 of 22) (Maltoni 1974, 1976; Maltoni et al. 1982; Furst et al. 1976). A number of additional studies by intratracheal, intrapleural, intrabronchial and intramuscular administration of lead chromate or its derived pigments did not significantly induce tumour incidence in various animal species (Levy et al. 1986; Hueper 1961; Furst et al. 1976; Steffee and Baetjer 1965).

In humans, epidemiological investigations have been conducted in occupational settings in various geographic locations with an attempt to identify the relationship between occupational engagement in lead chromate pigment production and cancer risk. Workers in this industry were exposed not only to the pigments themselves but also to the soluble hexavalent chromium compounds used as raw materials in the pigment production. The majority of the results showed an increased risk of lung cancer among the workers in the plants where both lead and zinc chromate pigments were produced (Sheffet et al. 1982; Hayes et al. 1989; EEH 1976; EEH 1983; Davies 1979; Davies 1984; Haguenoer et al. 1981; Deschamps et al. 1995; Fentzel-Beyme 1983; Korallus et al. 1993). The only exception is the study conducted in five chromate pigment production plants in Japan where no significantly increased mortality due to lung cancer was observed (Kano et al. 1993). The authors stated this might be because the amount of hexavalent chromium compounds in the work environment has been lowered as a result of engineering hygiene considerations such as improved ventilation, the wearing of masks, attention to work clothes and bathing after work. Two epidemiological studies conducted in the plants where only lead chromate pigments were produced reported a slightly elevated risk in respiratory tract tumour, but no statistical significance has been reached (Davies 1979; EEH 1983). The authors speculated that the numbers of observed and expected deaths were too small in these studies for definitive conclusions. With respect to lead chromate pigment use, the only available epidemiological investigation did not indicate a statistically significant association between spray painting and respiratory-cancer-caused mortality (Chiazze et al. 1980).

[1] The European Commission has proposed a reclassification for C.I. Pigment Red 104 as a Category 2 carcinogen ("should be regarded as if they are carcinogenic") (ECB 2007).

In addition to the European Commission classification, lead chromate pigments have been assessed together with hexavalent chromium (Chromium VI) compounds by other jurisdictions. The International Agency for Research on Cancer (IARC 1990) classified Chromium VI compounds as Group 1 (carcinogenic to humans). IARC concluded that there is "sufficient evidence" in humans for the carcinogenicity of Chromium VI compounds as encountered in the chromate pigment production industry and "sufficient evidence" in experimental animals for the carcinogenicity of lead chromates. The United States National Toxicological Program (NTP 2005a) concluded that Chromium VI compounds are "known to be human carcinogens based on sufficient evidence of carcinogenicity in humans" and the United States Environmental Protection Agency (US EPA 1998) has classified Chromium VI compounds as Group A— "known human carcinogen by the inhalation route of exposure." However, the US EPA concluded that carcinogenicity of Chromium VI compounds "by the oral route of exposure cannot be determined" (Group D). Environment Canada and Health Canada (Canada 1994) concluded that "the group of hexavalent chromium compounds as a whole is entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human life or health" and classified Chromium VI compounds as "carcinogenic to humans" (Group 1).

Lead chromate has also been assessed together with inorganic lead compounds. The International Agency for Research on Cancer (IARC 2006) classified inorganic lead compounds as "probably carcinogenic to humans" (Group 2A) and concluded that there is "limited evidence" in humans and "sufficient evidence" in experimental animals for the carcinogenicity of inorganic lead compounds. The United States National Toxicological Program (NTP 2005b) concluded that lead compounds are "reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals" and the US EPA (US EPA 1993) concluded that inorganic lead compounds are "probable human carcinogens" (Group 2B) based on "sufficient animal evidence" while "human evidence is inadequate." Lead is also listed on Schedule 1 (List of Toxic Substances) under the *Canadian Environmental Protection Act* in Canada (Environment Canada 2006).

The European Commission (ECB 2003) has stated that C.I. Pigment Red 104, together with C.I. Pigment Yellow 34 and lead chromate, "show(s) pronounced response in several *in vitro* assays; one positive *in vivo* bone marrow test is available. The substances show resemblance to known mutagens/carcinogens" (ECB 2003). The genotoxicity of C.I. Pigment Red 104, as well as its principal components, have been assessed in a range of assays (see Appendix 1). *In vivo*, C.I. Pigment Red 104, suspended in olive oil, did not significantly increase the frequency of micronuclei induction in mouse bone marrow cells following intraperitoneal injection; however, the authors speculated that the results may not be definitive as there was no evidence that the test material was reaching the target tissue (Odagiri et al. 1989). Additionally, lead chromate showed positive results in *in vivo* micronuclei induction when suspended in gum Arabic saline, and positive results in sex-linked recessive lethal assay when dissolved in nitrilotriacetic acid (NTA) (Watanabe et al. 1985; Costa et al. 1988). It is recognized that the *in vitro* genotoxicity of C.I. Pigment Red 104 and lead chromate are often enhanced following dissolution in acid or alkali or NTA solution. Aqueous suspensions of C.I. Pigment Red 104 did not significantly induce gene mutation in bacteria unless dissolved in NaOH or NTA (Venier et

al. 1985; De Flora 1981; Connor and Pier 1990; Pier et al. 1991). On the other hand, C.I. Pigment Red 104 (as molybdenum orange) showed clastogenic effects in mammalian cells as indicated by chromosomal aberration and sister chromatid exchange assays (Levis and Majone 1981; Venier et al. 1985). Lead chromate was also clastogenic in various tests. When suspended in water or acetone, it induced genetic damage in human and animal cells *in vitro*, including chromosomal aberration, micronuclei induction and sister chromatid exchange. It caused chromium-DNA adducts formation, DNA-protein cross-linking, DNA strand breakage, centrosome abnormalities, aneuploidy and cell transformation. Upon primary dissolution, lead chromate induced mutation in bacteria and mammalian cells and mitotic recombination in yeast (Appendix 1).

Although a thorough analysis of the mode of action is beyond the scope of this screening assessment, the European Commission has stated that a possible mode of action for the genotoxicity of C.I. Pigment Red 104 is through the reduction of insoluble $PbCrO_4$ by glutathione reductase/NADPH and the generation of OH^- radicals that cause DNA strand breakage (ECB 2003).

Limited information is available regarding non-cancer endpoints for C.I. Pigment Red 104. In the only available studies conducted in experimental animals, C.I. Pigment Red 104 preparations, with or without silica-encapsulation, were orally administrated to rats and dogs for 90 days. The lowest-observed-(adverse)-effect level (LO(A)EL) in dogs was observed at 2000 ppm administered in the diet (60 mg/kg bw/day) and was based on significantly altered haematological parameters including decreased haemoglobin and haematocrit values and altered erythrocyte morphology, significantly increased aminolevulinic acid in the urine, as well as dose-related pathological changes of the kidneys. Testicular degeneration was noted in the treated animals but not in the controls, which the authors speculated to be the result of poor nutrition or the younger age of the animals at the sacrifice time, and therefore was considered to be an indirect effect of the treatment (IBT 1975a, 1976a). Similar haematological, urinary and renal effects were observed in rats administered 2000 ppm in the diet (100 mg/kg-bw/day) (IBT 1975b, 1976b). These studies were conducted by Industrial Bio-Test Laboratories Inc. (IBT), and the abstracts of the study results were published in *Toxicology and Applied Pharmacology* (Christofano et al. 1976; Kennedy et al. 1976). No information is available as to whether these studies have been audited, reducing the confidence of the information presented.

The European Commission (ESIS 2007) has classified C.I. Pigment Red 104 as Category 1 for developmental toxicity ("known to cause developmental toxicity in humans") and as Category 3 for reproductive toxicity ("cause concern for human fertility"). The original dataset considered for these classifications is not available. A limited epidemiological investigation of a lead chromate production plant in China showed that the rates of threatened abortions were significantly higher among female workers and the wives of male workers who had been exposed to lead chromate (Wang and Zhao 1985). Effects of C.I. Pigment Red 104 on the reproductive system were also observed in the oral subchronic studies in dogs, described above, where impaired testicular degeneration was noted in the treated animals but not in the controls, although the authors considered it as an indirect effect of the treatment (Christofano et al. 1976; original data in IBT 1975a, 1976a).

The low solubility of C.I. Pigment Red 104 is indicative of limited bioavailability. The bioavailability of lead chromate and lead-chromate-derived pigments has been investigated in experimental animals. Administration of non-encapsulated or silica-encapsulated Chrome Yellow/lead chromate to rats by gavage (150 mg/kg-bw/day, five days per week, for four weeks) resulted in an increased level of lead in the blood and kidneys. No chromium could be detected in blood from exposed rats (detection limit = 10 µg/L). The kidney levels of chromium were increased significantly only in rats treated with non-encapsulated pigment. These results indicate that silica encapsulation reduces the gastrointestinal bioavailability of chromium from lead chromate pigments (Clapp et al. 1991; Pier et al. 1991). Administration of lead chromate to rats via whole body inhalation (5.3 ± 0.8 mg CrVI/m^3, 4 hours per day for 1 to 4 days) led to the accumulation of both chromium and lead chromate in the lungs. The chromium concentration in urine and feces were significantly increased following administration, whereas both chromium and lead concentrations in blood were only slightly elevated (above 5 µg/L for chromium) (Bragt et al. 1990). In addition, a short-term study in male rats showed that lead did not migrate from polypropylene plastic coloured with lead chromate-molybdate following oral administration (Gage and Litchfield 1967). Investigations employing other routes of administration, including intratracheal injection, instillation and infusion to the tracheal lobe bronchus, of lead chromate or lead paint resulted in increased lead and chromium levels in various tissues and retention in the lungs (Bragt and van Dura 1983; Perrault et al. 1995; Eaton et al. 1984).

Workers in a plastic production plant exposed to dust containing various chemicals, including lead and lead chromate, had significantly increased chromium levels in their urine samples. Their blood lead levels were also significantly increased, but not their serum chromium levels (Boscolo et al. 1997). Other occupational studies (McAughey et al. 1988; Wiegand et al. 1988) also showed that the urine and blood chromium levels in lead chromate pigment production workers were higher than those typically observed in non-occupationally exposed persons (Iyengar and Woittiez 1988). In two lead chromate-based paint factories in the United Kingdom, blood lead levels were detected in a range of 9–25 µg/L for warehouse men, a range of 10–36 µg/L for ball mill loaders, and a range of 9–15 µg/L for spray painters. The author stated that these levels were commonly found in non-lead workers (Cowley 1984).

Data from the bioavailability studies in experimental animals and observations in occupationally exposed humans suggest that lead chromate and its derived pigments have some level of bioavailability.

The confidence in the hazard characterization of neoplastic potential associated with C.I. Pigment Red 104 is considered to be moderate, as data are available from epidemiological investigations, from carcinogenicity studies in experimental animals via parenteral administration and a number of genotoxicity studies. However no long-term (> 90 days) laboratory studies conducted via conventional exposure routes (oral, dermal or inhalation) are available. The confidence in the hazard characterization of non-cancer effects associated with C.I. Pigment Red 104 is considered to be low. There is a high level of uncertainty regarding the reproductive toxicity and developmental toxicity of C.I. Pigment Red 104 due to lack of information. With respect to the repeated-dose toxicity of C.I. Pigment Red 104, characterization of potential toxicological effects is limited as experimental animal data is

available for only one route (oral) and for one duration and these studies were conducted by Industrial Bio-Test Laboratories. In addition, the oral LO(A)EL identified was the lowest exposure level tested in the studies, increasing the uncertainty as to the actual effect level at which these effects may occur.

Characterization of Risk to Human Health

Based principally on the weight of evidence classification of C.I. Pigment Red 104 by the European Commission as a Category 3 carcinogen (ESIS 2007), and the assessments of hexavalent chromium and inorganic lead compounds by several national and international agencies (US EPA 1993, 1998; IARC 1990, 2006; Canada, 1994; NTP 2005a, b), a critical effect for characterization of risk to human health for C.I. Pigment Red 104 is carcinogenicity. Although most of these classifications were based on groups of hexavalent chromium compounds or inorganic lead compounds, they, along with the information on lead chromate, support the limited data available on C.I. Pigment Red 104. As well, C.I. Pigment Red 104 or its principal components were genotoxic in a limited number of *in vitro* and *in vivo* experimental systems. Therefore, a mode of action for carcinogenicity involving direct interaction with genetic material cannot be precluded.

With respect to non-cancer effects, margins of exposure comparison were not derived due to negligible potential for exposure to the general population of Canada and the uncertainties regarding non-cancer effect levels (reproductive toxicity, developmental toxicity and repeated-dose toxicity).

Uncertainties in Evaluation of Risk to Human Health

There is uncertainty regarding the bioavailability of this substance; however, limited data indicate that there is some level of absorption of lead and chromate after exposure to lead chromate and its derived pigments. In addition, although genotoxicity of the pigment or lead chromate is generally more pronounced after dissolution in acid or base, positive results were also obtained in aqueous media. However, encapsulation of the pigment has been shown to reduce bioavailability and genotoxicity in some studies. In-depth consideration of a mode of action for carcinogenicity for this substance is beyond the scope of this screening assessment. As well, the health effects database for the C.I. Pigment Red 104 as a discrete substance is limited. There is uncertainty concerning to the actual exposure levels of the workers in some of the epidemiological investigations as workplace exposure monitoring data were not available and protective measures were sometimes implemented during the time period of studies.

The confidence in the characterization of exposure to C.I. Pigment Red 104 is low as the concentrations of this substance in environmental media could not be quantified in Canada or elsewhere leading to uncertainty in the exposure assessment. However, based on the properties and uses of the substance, there is confidence that actual environmental exposure levels are low. However, for a small population of Canadians, there is uncertainty regarding possible exposure to higher concentrations, but these could not be quantified.

Conclusion

Based on the available information, it is concluded that C.I. Pigment Red 104 is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the carcinogenicity of C.I. Pigment Red 104, for which there may be a probability of harm at any level of exposure, it is concluded that C.I. Pigment Red 104 is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed that C.I. Pigment Red 104 does not meet the criteria in paragraph 64a and 64b of CEPA 1999, but it does meet the criteria in paragraph 64c of CEPA 1999. Additionally, Pigment Red 104 meets the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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Appendix 1. Summary of health effects information for C.I. Pigment Red 104 (CASRN: 12656-85-8)[1]

Endpoint	**Lowest effect levels/Results[2]**			
CASRN	**12656-85-8 (C.I. Pigment Red 104; Molybdate chrome orange)**	**7758-97-6 (lead chromate)**	**7446-14-2 (lead sulfate)**	**10190-55-3 (lead molybdate)**
Laboratory animals and *in vitro*[3]				
Acute toxicity	**Lowest oral LD_{50}** (rat) > 5000 mg/kg-bw (NPIRI raw materials data handbook 1983). [No additional LD_{50} or LC_{50} value identified] [The skin and eye irritation tests in rabbits were negative (BASF AG 1988; Ciba-Geigy Limited 1986)]	**Lowest oral LD50** (mouse) > 12 000 mg/kg-bw (Yakuri 1968). [No additional study identified]	**Lowest oral LD_{LO}** (dog) = 2000 mg/kg-bw (equivalent to 1366 mg lead/kg-bw, Sax 1984). [Additional study in guinea pigs, Sax 1984]	No data identified.
Short-term repeated-dose toxicity	No data identified.	No data identified.	No data identified.	No data identified.
Subchronic toxicity	**Lowest oral LO(A)EL** (dog, 4/sex/group, 90 days) = 2000 ppm in diet, equivalent to 60 mg/kg-bw/day, based on significantly decreased haemoglobin and haematocrit values, altered erythrocyte morphology, pathologic changes of the kidney. Other effects and clinical signs such as impaired gonadal development, lethargy, anorexia, dehydration, emaciation, hyperirritability, disorientation, motor ataxia and	No data identified.	No data identified.	No data identified.

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	convulsions prior to death were observed (Christofano et al. 1976; original data in IBT 1975a, 1976a). [Additional studies in rats: Kennedy et al. 1976; original data in IBT 1975b, 1976b]			
Chronic toxicity/ carcinogenicity	**Carcinogenicity**: Single subcutaneous injection of 30 mg molybdenum orange to Sprague-Dawley rats (20/sex/group). Animals were maintained for 117–152 weeks. Significant increases of sarcomas at the injection sites were observed (36/40 in treated animals versus 0/60 in control animals) (Maltoni 1974, 1976; Maltoni et al. 1982). Bronchial implantation of 2 mg molybdenum chrome orange in Porton-Wistar rats (50/sex/groups). The animals were maintained for two years. No bronchial tumour was observed. Bronchial inflammation, squamous metaplasia and dysplasia were reported (Levy et al. 1986). [No additional data identified]	**Carcinogenicity**: **Positive results** Single subcutaneous injection of 30 mg lead chromate or basic lead chromate to Sprague-Dawley rats (20/sex/group). Animals were maintained for 117–152 weeks. Significant increases of sarcomas at the injection sites were observed (26/40 or 27/40 in treated animals versus 0/60 or 1/80 in control animals) (Maltoni 1974, 1976; Maltoni et al. 1982). Intramuscular injection of 8 mg lead chromate to Fisher-344 rats (25/sex/group) once a month for 9 months resulted in significant increases of local sarcomas (31/47 in treated animals versus 0/22 in control animals). In addition, renal carcinomas were observed in male rats at 24 months (3/23 in treated animals versus 0/22 in control animals) (Furst et al.	No data identified.	No data identified.

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		1976). **Negative results** After intramuscular injection of lead chromate (doses unspecified) to rats (32–34/group), 1/33 rats developed local tumours. The result was not statistically significant. No further information available (Hueper 1961). After intrapleural implantation of lead chromate (doses unspecified) in rats for 27 months, 3/34 rats developed local tumours. The result was not statistically significant (Hueper 1961). After intramuscular injection of 3 mg lead chromate to NIH-Swiss mice (25 female/group) every four months for two years, lymphonmas were observed at 16 months (2/17 in treated animals versus 1/15 in untreated control and 2/22 in vehicle-treated control), lung carcinomas were observed at 24 months (3/17 in treated animals versus 1/15 in untreated control and 1/22 in vehicle-treated control). The result was not statistically		

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		significant (Furst et al. 1976). Intra-tracheal instillation of 3 mg lead chromate preparation in guinea pigs (13/group) six times at 3-month intervals. The animals were maintained for life. No pulmonary adenoma was observed (Steffee and Baetjer 1965). Intra-tracheal instillation of 10 mg lead chromate preparation in rabbits (7/group) every 3 months for 9–15 months. The animals were maintained for 40–50 months. No pulmonary tumours observed (Steffee and Baetjer 1965). Bronchial implantation of 2 mg lead chromate in Porton-Wistar rats (50/sex/groups). The animals were maintained for two years. Bronchial tumours were observed (1/98 in treated animals versus 0/100 in control animals). The result was not statistically significant (Levy et al. 1986).		
Reproductive toxicity	No data identified.	No data identified.	No data identified.	No data identified.
Developmental toxicity	No data identified.	No data identified.	No data identified.	No data identified.
Genotoxicity and	**Mutagenicity**	**Mutagenicity**	**Mutagenicity**	No data identified.

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related endpoints: *in vitro*	**Positive** in Ames tests in *Salmonella typhimurium* TA 100 when dissolved in nitrilotriacetic acid or NaOH with or without metabolic activation. **Negative** in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA 538, with and without metabolic activation. Test material was dissolved in ether or encapsulated with high percentages of silica (for TA100) (De Flora et al. 1981; Connor and Pier 1990; Pier et al. 1991). **Sister Chromatid Exchange Positive** in CHO cells when suspended in water or dissolved in NaOH or nitrilotriacetic acid (Levis and Majone 1981; Venier et al. 1985). **Chromosomal aberration Positive** in CHO cells. Test material (molybdenum orange) was suspended in cell growth medium or dissolved in NaOH (Levis and Majone 1981).	**Ames tests** **Positive** in *Salmonella typhimurium* TA 98 and TA1538, with and without metabolic activation; **Positive** in TA 100, with metabolic activation; **Positive** in TA1537, without metabolic activation. Test material was dissolved in HCl (Nestmann et al. 1979). **Negative** in *Salmonella typhmurium* TA1535, with and without metabolic activation; **Negative** in TA1537, with metabolic activation; **Negative** in TA 100, without metabolic activation or encapsulated with high percentages of silica; **Negative** in TA102, without metabolic activation. Test material was suspended in water or oil, or dissolved in HCl or DMSO (Nestmann et al. 1979; De Flora et al. 1985; Pier et al. 1991). **Gene mutation in *Escherichia coli*** **Positive** in *E. coli* K12 WP2 *uvr*$^-$ *trp*$^+$ reversion fluctuation assay, without metabolic activation. Test material was dissolved in 0.5 N NaOH (Nestmann et al. 1979); **Positive** in *E. coli trp*$^-$ *to trp*$^+$ spot	**Negative**: Ames tests in *Salmonella typhimurium* TA98, 100, 1535, 1537, 1538 with and without activation (JETOC 1996; Connor and Pier 1990). Mutation in *E. coli wp2uvra* with and without activation (JETOC 1996). **Sister Chromatid Exchange Positive**: In human lymphocytes cells and in non-human cells (no further details) (Tucker et al. 1993 and Montaldi et al. 1985).	

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		tests and fluctuation test when dissolved in nitrilotriacetic acid, but **Negative** when suspended in water (Venier et al. 1987, cited in ECB 2003); **Negative** in *E. coli* K12 *gal*$^-$ forward mutation and *E. coli trp*$^-$ reversion plate test, without metabolic activation, when dissolved in 0.5 N NaOH (Nestmann et al. 1979). **Gene mutation in mammalian cells** **Positive** in HPRT mutation assays in CHO-K1 cells when dissolved in 1N NaOH (Yang et al. 1992, cited in ECB 2003); **Negative** in HPRT mutation assays in Chinese hamster V79 cells for 8-azagunine resistance and 6-thioguanine resistance when suspended in water or cell culture medium but **Positive** results were obtained when dissolved in NTA (Newbold et al. 1979 and Celotti et al. 1987); **Negative** in mutation assays in C3H 10T1/2 mouse cells for ouabain resistance, and in CHO cells for 6-thioguanine resistance and ouabain resistance, without metabolic activation, test material was suspended in acetone (Patierno et al. 1988; Patierno and		

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		Landolph 1989). **Chromosomal Aberration** **Positive** in CHO cells and human foreskin fibroblasts, without metabolic activation (Xu et al. 1992; Wise et al. 1992, 1994, cited in ECB 2003 and Grlickova-Duzevik et al. 2006; Savery et al. 2007); **Positive** in human primary bronchial fibroblasts (Wise et al. 2002), human lung cell line WTHBF-6 cells and human epithelial cell line BEP2D cells (Wise et al. 2004, 2006a), the test material was suspended in acetone in all the experiments; **Positive** in CHO cells when the test material was suspended in water (Koshi and Iwasaki 1983) or dissolved in NTA (Montaldi et al. 1987) and in human lymphocytes when the test material was dissolved in NaOH (Douglas et al. 1980) **Micronuclei induction** **Positive** in human peripheral blood lymphocytes. An enhanced effect was observed following addition of NTA (Montaldi et al. 1987). **Sister Chromatid Exchange**		

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		Positive in human peripherical blood lymphocytes when suspended in water or dissolved in NaOH (Tucker et al. 1993, cited in ECB 2003; Douglas et al. 1980). **Positive** in CHO cells when suspended in water or dissolved in NaOH or NTA (Loprieno et al. 1985; Montaldi et al. 1987). **DNA damage** **Positive:** DNA single strand breaks or DNA-protein cross-links in CHO cells, without metabolic activation. Test material was suspended in acetone (Xu et al. 1992). Comet assay for double strand DNA breaks in human bronchial cells. Test material was suspended in acetone (Xie et al. 2005). Apoptosis and DNA fragmentation in CHO cells. Test material was suspended in acetone (Blankenship et al. 1997). **Negative:** DNA double strand breaks or DNA-DNA cross-links. Test		

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		material was suspended in acetone (Xu et al. 1992). Differential survival tests in *E. coli* W3110 (*polA*$^+$) and P3478 (*polA*$^-$). Test material was dissolved in 0.5 N NaOH (Nestmann et al. 1979). Induction of DNA fragmentation in CHO cells. Test material was dissolved in NaOH (Douglas et al. 1980). **Cr-DNA adduct formation** **Positive** in human lung small airway epithelial cells (Singh et al. 1999). **SOS response** **Negative** in *E. coli* PQ37 when dissolved in water but **Positive** when dissolved in NTA (Vernier et al. 1989). **Cell transformation** **Positive** in the C3H 10T1/2 mouse cells and Syrian hamster embryo cells, with and without simian adenovirus SA7 viral enhancement, and without metabolic activation; **Positive** in human non-tumorigenic		

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		osteosarcoma TE85 cells, without metabolic activation. Test material was suspended in acetone or water or cell culture medium (Patierno et al., 1988; Patierno and Landolph, 1989; Schechtman et al. 1986; Elias et al. 1989; Sidhu et al. 1991); **Positive** in induction of anchorage independent colonies formation in human foreskin cells. Test material was suspended in acetone (Biedermann and Landolph 1987). **Mitotic recombination** **Positive** in *Saccharomyces cerevisiae* D5 mitotic recombination, without metabolic activation. However, S9 reduced the mutagenic potency. Test material was dissolved in 1 N HCl, (Nestmann et al. 1979). **Centrosome abnormalities and aneuploidy** **Positive** in human WTHBF-6 cells (a cloned cell line from normal human bronchial fibroblasts) when suspended in acetone (Holmes et al. 2006; Wise et al. 2006b)		
Genotoxicity and related endpoints:	**Negative** in ICR/Jcl mouse bone marrow cells following	**SLRLM** (sex-linked recessive lethal mutation)	No data identified.	No data identified.

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in vivo	intraperiotoneal injection with molybdenum-red. Test material was suspended in olive oil. The authors speculated that the results may not be definitive as there was no evidence that the test material was reaching the target tissue (Odagiri et al. 1989). [No additional study identified]	**Positive** in *Drosophila melanogaster*. Test material was dissolved in NTA (Costa et al. 1988) **Micronuclei induction** **Positive** in C57B1/6N mouse bone marrow cells following intra-peritoneal injection. Test material was suspended in 0.5% gum Arabic saline (Watanabe et al. 1985).		
Humans				
Chronic toxicity/ carcinogenicity	**Neoplastic endpoints** **Lead chromate pigment production** Historical cohort study among men employed at a lead and zinc chromate pigment production plant (lead to zinc = 9:1) in the United States during 1940–1969 for more than 1 month. 1296 whites and 650 non-whites were included in the study. A significantly increased relative risk (RR) for lung cancer (RR = 160) was observed for the white men. The RR was increased to 190 for the white men who were employed for at least 2 years and who had been exposed to 0.5 to > 2 mg of CrVI/m^3 chromates. Although RR of 200 for stomach	**Neoplastic endpoints** See data for 1344-37-2	**Neoplastic endpoints** See data for 1344-37-2	**Neoplastic endpoints** See data for 12656-85-8

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	cancer, 170 for pancreatic cancer and 290 for Hodgkin's disease were found, none of these were significant. However, further analysis revealed a significant risk for stomach cancer in the white men [standardized mortality ratio (SMR) = 230] and lung cancer in the non-white men (SMR = 200). Air monitoring at the plant in the later years were from less than 0.1 to more than 2 mg of CrVI/m^3). Workers were probably co-exposed to nickel sulfate and nickel carbonate. Smoking information was not available. 67 subjects were removed in the follow-up study conducted in 1982. The increased risk for lung cancer was observed to be associated with the years of employment and the years of exposure to chromate dusts in the factory. For the subjects who had been followed for more than 30 years and had been employed for more than ten years, the SMR for lung cancer was 190 (95% CI = 111-295) and, among this group, for those whose jobs were associated with exposure to			

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	chromate dust, the SMR was increased to 321 (95% CI = 117-698) (Sheffet et al. 1982; Hayes et al. 1989). Historical cohort study among 574 men employed at three chromate pigment production plants in the United States from the mid-1920s to the end of 1979 for at least 6 months. At plant 1 (246 workers) where lead chromate pigments (chrome yellow, chrome green and molybdata orange) were produced, the SMR for respiratory cancer was 164.4 (95% CI = 45-421); for lung cancer, it was 130 (95% CI = 27-381); for digestive system cancer, it was 120.3 (95% CI = 15-434); for all causes, it was 63.5 (95% CI = 40-97). At plants 2 (164 workers) and 3 (164 workers), both lead and zinc chromate pigments were produced. In addition, at plant 2, strontium chromate and barium chromate were produced. The workers in plant 3 were also studied by Sheffet et al. (1982) (see above). The combined SMR from plants 2 and 3 for lung			

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	cancer or for stomach cancer was significantly increased (SMR = 228 and 667, respectively). Because of the non-significant rate for respiratory cancer at plant 1 and the co-exposure to other chromates at plants 2 and 3, no definitive conclusion regarding the risk of lung cancer in lead chromate-exposed workers can be drawn from this study. In 1975, the average workroom air concentrations of chromium and lead in plant 1 were 0.05 mg total chromium/m^3 and 0.28 mg lead/m^3; in plant 2, 0.06 mg total chromium/m^3 and 0.26 mg lead/m^3; in plant 3, 0.19 mg chromium/m^3 and 0.79 mg lead/m^3 [EEH 1976, 1983]. Historical cohort study among 1152 men who worked at three chromate pigment production plants in the United Kingdom for at least 1 year from the 1930s or 1940s to 1981. Significant excesses for lung cancer mortality were observed only among the workers exposed to high and moderate levels of chromates at factories A (675			

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	men) and B (222 men) where zinc and lead chromate pigments were produced at both factories. The SMR for lung cancer was significantly increased in both factories (SMR was in the range of 222–223 in factory A; and 373–562 in factory B). The combined SMR for lung cancer in the medium- and high-exposure groups was 310 (95% CI = 160-540), 270 (95% CI = 110-560), or 388 (95% CI = 170-760) for 1 year, 5–9 years or more than 10 years employment, respectively. At factory C, 255 men were exposed only to lead chromate and experienced normal mortality. No exposure monitoring data of chromate or lead at the workplace were reported. The exposure levels of the workers were graded based on their jobs (Davies 1979, 1984). Historical cohort study among 666 men employed for at least 1 year during 1950–1975 in five Japanese chromate pigment production factories where lead chromate, zinc chromate, molybdate orange and/or			

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	strontium chromate were produced. Sodium dichromate, anhydrous chromic acid and potassium dichromate were used as the raw materials. The follow-up study was ended in 1989. Three subjects died from lung cancer, two of whom smoked. The SMR results showed no excess mortality due to lung cancer or other malignant neoplasmas among the workers engaged in the manufacture of chromate pigment in Japan (O/E = 3/2.95). The actual exposure level at the work places was unknown; however, the mean level of CrVI at the work places after 1976 was 0.003–0.019 mg/m^3 (Kano et al. 1993). Prospective cohort study among 251 men who worked at a French lead and zinc chromate pigment factory for more than 6 months from 1958–1977. The SMR for lung cancer was 461 (95% CI = 270-790). The follow-up study included 294 men who worked at this factory for at least 6 months from 1958–			

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	1987. The SMR for lung cancer was 360 (95% CI = 213-568); for digestive tract cancer was 130 (95% CI = 60-247); for brain cancer (only two cases) was 844 (95% CI = 102-3049). Atmospheric samples taken in 1981 showed the chromates level in the filtration department was in the range of 2–3 μg/m^3, in the grinding department, it was in the range of 6–165 μg/m^3, in the drying and sacking department, it was in the range of 6–178 μg/m^3 and in the sacks marking department, it was more than 2000 μg/m^3 (Haguenoer et al. 1981; Deschamps et al. 1995). Prospective cohort study among 1396 men who worked for more than 6 months during 1945–1976 at three German and two Dutch plants where zinc and lead chromate pigments were produced. The SMR for lung cancer was significantly increased in a restricted cohort with 978 men employed before 1965 (SMR= 204; 95% CI = 123-319). In the follow-up study, 1417 workers with at least			

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	1 year of exposure experience at the two German plants were followed until 1988. The work place exposure levels were reduced owing to the change of production process. The SMR for bronchial carcinoma was 227 (95% CI = 178-285) in the group of 739 workers who worked before and after the change-over periods. In the group of 678 workers who only worked after the change-over period, the SMR for lung cancer was 126 (95% CI = 58-238). The mean annual exposure level during 1977–1987 was in the range of 0.012–0.073 mg Cr/m^3 (Fentzel-Beyme 1983; Korallus et al. 1993). **Lead chromate pigment use** Historical cohort study among 226 white male spray-painters from ten US automobile assembly plants and died during 1970–1976 or 1972–1976. The proportionate mortality ratio (PMR) for respiratory cancer among the spray-painters was increased, but did not reach statistical significance when compared with the country and non-spray painter reference			

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	groups (PMR = 139 and 108, respectively). In a nested case-control study, the relative risk for lung cancer associated with spray-painting experience was analysed. 263 decedents who died from lung cancer were identified in the ten plants. 1001 controls were decedents who died from circulatory disease or accidents from the same population (matched for plant and age). Mantel-Haenszel odd ratio analysis showed the relative risk for lung cancer in the white male spray-painters was not significantly increased. The paints contained chromate pigments, no further exposure information or employment history data available (Chiazze et al. 1980). **Additional studies:** Dalager et al. 1980, Langård and Norseth 1975, and Langård and Vigander 1983: workers were mainly exposed to zinc chromate pigments. Bertazzi et al. 1981: workers were co-exposed to asbestos, zinc, barium, and strontium chromates.			

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	Chen and Seaton 1998: literature-based meta analysis among painters; workers were exposed to organic solvents, lead chromate pigment, asbestos and others.			
Reproductive and developmental toxicity	No data identified.	Retrospective survey among workers in a lead chromate production plant in China. 22 exposed female workers with 42 controls, and 19 exposed male worker's wives with 91 controls were enrolled in this study. The rates for threatened abortion were significantly increased among the female workers and the wives of male workers exposed to lead chromate (31.8% in exposed women versus 2.4 % in controls and 36.8% in exposed men's wives versus 2.2% in controls, respectively), no further information available (Wang and Zhao 1985).	No data identified.	No data identified.

1. The toxicity data for lead chromate (7758-97-6), lead sulfate (7446-12-2) and lead molybdate (10190-55-3) are included in the assessment for C.I. Pigment Red 104 (12656-85-8) as they are the principal components of latter.
2. LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LD_{LO} = lowest lethal dose; LOEC = Lowest-Observed-Effect Concentration; LOEL = Lowest-Observed-Effect Level