CHROMIUM AND CHROMIUM COMPOUNDS

Chromium and chromium compounds were considered by previous IARC Working Groups, in 1972, 1979, 1982 and 1987 (IARC, 1973, 1979, 1980a, 1982, 1987a). Since that time, new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Chemical and Physical Data

The list of chromium alloys and compounds given in Table 1 is not exhaustive, nor does it necessarily reflect the commercial importance of the various chromium-containing substances, but it is indicative of the range of chromium alloys and compounds available.

1.1 Synonyms, trade names and molecular formulae of chromium and selected chromium-containing compounds

Table 1. Synonyms (Chemical Abstracts Service names are given in bold), trade names and atomic or molecular formulae of chromium and selected chromium compounds

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Metallic chromium [0] and chromium [0] alloys			
Chromium	7440-47-3	**Chrome**	Cr
Cobalt-chromium alloy[c]	11114-92-4 (91700-55-9)	**Chromium alloy (nonbase), Co, Cr**; cobalt alloy (nonbase), Co, Cr	-
Cobalt-chromium-molybdenum alloy[c]	12629-02-6 (8064-15-1; 11068-92-1; 12618-69-8; 55345-18-1;	**Cobalt alloy (base), Co 56-68, Cr 25-29, Mo 5-6, Ni 1.8-3.8, Fe 0-3, Mn 0-1, Si 0-1, C 0.2-0.3 (ASTM A567-1)**	

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
	60382-64-1; 83272-15-5; 85131-98-2; 94076-26-3)	Akrit CoMo35; AMS 5385D; Celsit 290; F 75; HS 21; Protasul-2; Stellite 21; Vinertia; Vitallium; X25CoCr-Mo62 28 5; Zimalloy	
Chromium-containing stainless steels[c]	71631-40-8 (51204-69-4, 59601-19-3, 84723-14-8, 94197-89-4, 98286-69-2)	**Iron alloy (base), Fe 64-72, Cr 21-23, Ni 4.5-6.5, Mo 2.5-3.5, Mn 0-2, Si 0-1, N 0.1-0.2 (ASTM A276-S31803)** AF 22; AF 22-130; AISI 318L; Alloy 2205; Arosta 4462; AST 2205; Avesta 2205; Avesta 223FAL; CR22; 22Cr; 22Cr5Ni; CrNiMoN22-5-3; DIN 1.4462; ES 2205; FAL 223; 744LN; Mann AF-22; Nirosta 4462; NKK-Cr22; Novonox FALC 223; NU 744 LN; NU stainless 744LN; Remanit 4462; SAF 2205; Sandvik SAF 2205; SS 2377; Stainless steel 2205; Uddeholm Nu744LN; UHB 744LN; UNS S31803; Uranus 45N; UR45N; Vallourec VS22; VEW A903; VLX 562; VS 22; X2CrNiMoN2253; Z2 CND 22.5 AZ	-
Ferro-chrome[d]	11114-46-8 (11133-75-8, 11143-43-4, 12604-52-3)	**Chromium alloy (base), Cr, C, Fe, N, Si; ferrochromium**; carbon ferrochromium; chrome ferroalloy; chromium ferroalloy	-
Iron-nickel-chromium alloy	11121-96-3	**Iron alloy (base), Fe 39-47, Ni 30-35, Cr 19-23, Mn 0-1.5, Si 0-1, Cu 0-0.8, Al 0-0.6, Ti O-0.6, C 0-0.1 (ASTM B163-800)** AFNOR ZFeNC45-36; AISI 332; Alloy 800; Alloy 800NG; Cr20Ni32TiAl; 20Cr32NiTiAl; DIN 1.4876; FeCr21Ni32TiAl; IN 800; Incoloy 800; JIS NCF800; N800; NCF800; NCF 800 HTB; NCF steel; Nickel 800; Nicrofer 3220; Ni33Cr21TiAl; POLDI AKR 17; Pyro-met 800; Sanicro 31; Thermax 4876; TIG N800	-
Nickel-chromium alloy	12605-70-8	Nichrome; **Nickel alloy (base), Ni 57-62, Fe 22-28, Cr 14-18, Si 0.8-1.6, Mn 0-1, C 0-0.2 (ASTM B344-60 Ni, 16 Cr)** Chromel C; Kh15N60N; NiCr6015; PNKh; Tophet C	-
Chromium [III] compounds			
Basic chromic sulfate	12336-95-7 (39380-78-4)	Basic chromium sulfate; **chromium hydroxide sulfate ($Cr(OH)(SO_4)$)**; chromium sulfate; monobasic chromium sulfate; sulfuric acid, chromium salt, basic Chromedol; Chrometan; Chrome tan; Peachrome	$Cr(OH)SO_4$
	64093-79-4	**Neochromium**	$Cr(OH)SO_4.Na_2SO_4.H_2O$

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Chromic acetate	1066-30-4	**Acetic acid, chromium (3+) salt**; chromium acetate; chromium [III] acetate; chromium triacetate	$Cr(OCOCH_3)_3$
Chromic chloride	10025-73-7	**Chromium chloride ($CrCl_3$)**; chromium [III] chloride; chromium trichloride; C.I. 77295; trichlorochromium	$CrCl_3$
Chromic hydroxide	1308-14-1	Chromic acid (H_3CrO_3); **chromium hydroxide ($Cr(OH)_3$)**; chromium [III] hydroxide; chromium (3+) hydroxide; chromium trihydroxide	$Cr(OH)_3$
Chromic nitrate	13548-38-4 (20249-21-2)	Chromium nitrate; chromium [III] nitrate; chromium (3+) nitrate; chromium trinitrate; **nitric acid, chromium (3+) salt**	$Cr(NO_3)_3$
Chromic oxide	1308-38-9	Chrome oxide; chromia; **chromium oxide (Cr_2O_3)**; chromium [III] oxide; chromium sesquioxide; chromium (3+) trioxide; C.I. 77288; C.I. Pigment Green 17; dichromium trioxide	Cr_2O_3
		Anadonis Green; Casalis Green; Chrome Green; Chrome Ochre; Chrome Oxide Green BX; Chrome Oxide Green GN-M; Chromium Oxide Pigment; Chromium 111 Oxide; Chromium Oxide Green; Chromium Oxide X1134; 11661 Green; Green Chrome Oxide; Green Chromic Oxide; Green Chromium Oxide; Green Cinnabar; Green Oxide of Chromium; Green Oxide of Chromium OC-31; Green Rouge; Guignet's Green; Leaf Green; Levanox Green GA (hydrated chromic oxide); Oil Green; Oxide of Chromium; P-106F10; Pure Chromium Oxide Green 59; Ultramarine Green	
Chromic perchlorate	13537-21-8	Chromium perchlorate; chromium triperchlorate; **perchloric acid, chromium (3+) salt**	$Cr(ClO_4)_3$
Chromic phosphate	7789-04-0	Chromium monophosphate; chromium orthophosphate; chromium phosphate; **phosphoric acid, chromium (3+) salt (1:1)**; phosphoric acid, chromium [III] salt	$CrPO_4$
		Arnaudon's Green (hemiheptahydrate); Plessy's Green (hemiheptahydrate)	
Chromic sulfate	10101-53-8 (39378-25-1)	Chromium sulfate (2:3); chromium [III] sulfate; dichromium sulfate; dichromium tris(sulfate); dichromium trisulfate; **sulfuric acid, chromium (3+) salt (3:2)**; C.I. 77305	$Cr_2(SO_4)_3$
		Baychrom A; Baychrom F; Chromitan B; Chromitan MS; Chromitan NA; Cromitan B; Koreon	
Chromite ore	1308-31-2 (61026-56-0)	Chrome ore; **chromite (Cr_2FeO_4)**; chromite mineral; iron chromite	$Cr_2O_3.FeO$
Nickel chromate	12018-18-7	**Chromic acid (H_2CrO_4), nickel salt (1:1)**	$NiCrO_4$

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Potassium chromic sulfate	10141-00-1 (14766-82-6; 81827-72-7; 81827-73-8)	Chrome alum; chrome potash alum; chromic potassium sulfate; chromium potassium sulfate; potassium chromium alum; potassium chromium sulfate; potassium disulfatochromate [III]; **sulfuric acid, chromium (3+) potassium salt (2:1:1)** Chrome Alum 0% Basicity; Crystal Chrome Alum	$KCr(SO_4)_2$
Chromium[VI] compounds			
Ammonium chromate	7788-98-9	Chromic acid, ammonium salt; **chromic acid (H_2CrO_4), diammonium salt**; diammonium chromate; neutral ammonium chromate	$(NH_4)_2CrO_4$
Ammonium dichromate	7789-09-5	Ammonium bichromate; ammonium chromate; **chromic acid ($H_2Cr_2O_7$), diammonium salt**; diammonium dichromate; dichromic acid, diammonium salt	$(NH_4)_2Cr_2O_7$
Barium chromate	10294-40-3 (12000-34-9; 12231-18-4)	Barium chromate (VI); barium chromate (1:1); barium chromate oxide; **chromic acid (H_2CrO_4), barium salt (1:1)**; C.I. 77103; C.I. Pigment Yellow 31 Baryta Yellow; Lemon Chrome; Lemon Yellow; Permanent Yellow; Steinbuhl Yellow; Ultramarine Yellow	$BaCrO_4$
Basic lead chromate	1344-38-3 (54692-53-4)	C.I. 77601; **C.I. Pigment Orange 21**; C.I. Pigment Red; lead chromate oxide Arancio Cromo; Austrian Cinnabar; Basic Lead Chromate Orange; Chinese Red; Chrome Orange; Chrome Orange 54; Chrome Orange 56; Chrome Orange 57; Chrome Orange 58; Chrome Orange Dark; Chrome Orange Extra Light; Chrome Orange G; Chrome Orange Medium; Chrome Orange NC-22; Chrome Orange R; Chrome Orange 5R; Chrome Orange RF; Chrome Orange XL; Chrome Red; C.P. Chrome Orange Dark 2030; C.P. Chrome Orange Extra Dark 2040; C.P. Chrome Orange Light 2010; C.P. Chrome Orange Medium 2020; Dainichi Chrome Orange R; Dainichi Chrome Orange 5R; Genuine Acetate Orange Chrome; Genuine Orange Chrome; Indian Red; International Orange 2221; Irgachrome Orange OS; Light Orange Chrome; No. 156 Orange Chrome; Orange Chrome; Orange Nitrate Chrome; Pale Orange Chrome; Persian Red; Pigment Orange 21; Pure Orange Chrome M; Pure Orange Chrome Y; Red Lead Chromate; Vynamon Orange CR	$PbO.PbCrO_4$
Calcium chromate	13765-19-0	Calcium chromium oxide; calcium monochromate; **chromic acid (H_2CrO_4), calcium salt (1:1)**; C.I. 77223; C.I. Pigment Yellow 33 Calcium Chrome Yellow; Gelbin; Yellow Ultramarine	$CaCrO_4$

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Chromium [VI] chloride	14986-48-2	Chromium hexachloride; **(OC-6-11)-chromium chloride ($CrCl_6$)**	$CrCl_6$
Chromium trioxide	1333-82-0 (12324-05-9; 12324-08-2)	Chromia; chromic acid; chromic [VI] acid; chromic acid, solid; chromic anhydride; chromic trioxide; **chromium oxide (CrO_3)**; chromium [VI] oxide; chromium (6+) trioxide; monochromium trioxide	CrO_3
Chromyl chloride	14977-61-8	Chlorochromic anhydride; chromium chloride oxide; chromium dichloride dioxide; **chromium, dichlorodioxo-(T-4)**; chromium dioxide dichloride; chromium dioxychloride; chromium oxychloride; dichlorodioxochromium	CrO_2Cl_2
Lead chromate	7758-97-6 (8049-64-7)	**Chromic acid (H_2CrO_4), lead (2+) salt (1:1)**; C.I. 77600; C.I. Pigment Yellow 34; crocoite; lead chromium oxide; phoenicochroite; plumbous chromate Canary Chrome Yellow 40-2250; Chrome Green; Chrome Green UC61; Chrome Green UC74; Chrome Green UC76; Chrome Lemon; Chrome Yellow; Chrome Yellow 5G; Chrome Yellow GF; Chrome Yellow LF; Chrome Yellow Light 1066; Chrome Yellow Light 1075; Chrome Yellow Medium 1074; Chrome Yellow Medium 1085; Chrome Yellow Medium 1295; Chrome Yellow Medium 1298; Chrome Yellow Primrose 1010; Chrome Yellow Primrose 1015; Cologne Yellow; Dainichi Chrome Yellow G; LD Chrome Yellow Supra 70 FS; Leipzig Yellow; Paris Yellow; Pigment Green 15; Primrose Chrome Yellow; Pure Lemon Chrome L3GS	$PbCrO_4$
Molybdenum orange	12656-85-8	**C.I. Pigment Red 104** Chrome Vermilion; Krolor Orange RKO 786D; Lead chromate molybdate sulfate red; Mineral Fire Red 5DDS; Mineral Fire Red 5GGS; Mineral Fire Red 5GS; Molybdate Orange; Molybdate Orange Y 786D; Molybdate Orange YE 421D; Molybdate Orange YE 698D; Molybdate Red; Molybdate Red AA 3; Molybden Red; Molybdenum Red; Renol Molybdate Red RGS; Vynamon Scarlet BY; Vynamon Scarlet Y	$PbMoO_4 \cdot PbCrO_4 \cdot PbSO_4$
Potassium chromate	7789-00-6	Bipotassium chromate; **chromic acid (H_2CrO_4), dipotassium salt**; dipotassium chromate; dipotassium monochromate; neutral potassium chromate; potassium chromate [VI]	K_2CrO_4

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Potassium dichromate	7778-50-9	**Chromic acid ($H_2Cr_2O_7$), dipotassium salt**; dichromic acid, dipotassium salt; dipotassium bichromate; dipotassium dichromate; potassium bichromate; potassium dichromate [VI]	$K_2Cr_2O_7$
Sodium chromate	7775-11-3	**Chromic acid (H_2CrO_4), disodium salt**; chromium disodium oxide; chromium sodium oxide; disodium chromate; neutral sodium chromate; sodium chromium oxide	Na_2CrO_4
Sodium dichromate	10588-01-9 (12018-32-5)	Bichromate of soda; **chromic acid ($H_2Cr_2O_7$), disodium salt**; chromium sodium oxide; dichromic acid, disodium salt; disodium dichromate; sodium bichromate; sodium dichromate [VI]	$Na_2Cr_2O_7$
Strontium chromate	7789-06-2 (54322-60-0)	**Chromic acid (H_2CrO_4), strontium salt (1:1)**; C.I. Pigment Yellow 32; strontium chromate [VI]; strontium chromate (1:1) Deep Lemon Yellow; Strontium Chromate 12170; Strontium Chromate A; Strontium Chromate X-2396; Strontium Yellow; Sutokuro T	$SrCrO_4$
Zinc chromate[e]	13530-65-9 (1308-13-0; 1328-67-2; 14675-41-3)	**Chromic acid (H_2CrO_4), zinc salt (1:1)**; chromium zinc oxide; zinc chromium oxide; zinc tetraoxychromate; zinc tetroxychromate Buttercup Yellow	$ZnCrO_4$
Zinc chromate hydroxides	15930-94-6 (12206-12-1; 66516-58-3)	Basic zinc chromate; chromic acid (H_6CrO_6), zinc salt (1:2); chromic acid (H_4CrO_5), zinc salt (1:2), monohydrate; chromium zinc hydroxide oxide; zinc chromate hydroxide; zinc chromate [VI] hydroxide; **zinc chromate oxide ($Zn_2(CrO_4)O$), monohydrate**; zinc hydroxychromate; zinc tetrahydroxychromate; zinc yellow[f]	$Zn_2CrO_4(OH)_2$ and others
Zinc potassium chromates (hydroxides)	11103-86-9 (12527-08-1; 37809-34-0)	Basic zinc potassium chromate; chromic acid ($H_6Cr_2O_9$), potassium zinc salt (1:1:2); **potassium hydroxyoctaoxodizincatedichromate(1-)**; potassium zinc chromate hydroxide; zinc yellow[f]	$KZn_2(CrO_4)_2(OH)$ and others
Other chromium compounds			
Chromium carbonyl	13007-92-6 (13930-94-4)	**Chromium carbonyl ($Cr(CO)_6$)**; chromium hexacarbonyl; hexacarbonyl chromium	$Cr(CO)_6$
Chromic chromate	24613-89-6	**Chromic acid (H_2CrO_4), chromium (3+) salt (3:2)**; chromium chromate	$Cr_2(CrO_4)_3$
Chromium [II] chloride	10049-05-5	**Chromium chloride ($CrCl_2$)**; chromium dichloride; chromous chloride	$CrCl_2$

Table 1 (contd)

Chemical name	Chem. Abstr. Services Reg. No.[a]	Synonyms and trade names	Formula[b]
Chromium [IV] dioxide	12018-01-8	Chromium dioxide; **chromium oxide (CrO_2)**; chromium [IV] oxide	CrO_2

[a] Replaced CAS Registry numbers are given in parentheses.

[b] Compounds with the same synonym or trade name can have different formulae.

[c] Thousands of alloys of chromium with other metals are listed by the Chemical Abstracts Registry Service; approximately 1300 contain cobalt, over 400 also contain molybdenum and nearly 100 are chromium-containing stainless steels. An example of each is listed here.

[d] Chemical Abstracts Registry Service lists several ferrochromium alloys; one example is given.

[e] The term 'zinc chromate' is also used to refer to a wide range of commercial zinc and zinc potassium chromates.

[f] 'Zinc yellow' can refer to several zinc chromate pigments; it has the CAS No. 37300-23-5.

1.2 Chemical and physical properties of pure substances

Known physical properties of some of the chromium compounds considered in this monograph are given in Table 2. Data on solubility refer to saturated solutions in water or other specified solvents. Hexavalent chromium compounds are customarily classed as soluble or insoluble in water; such a classification is useful in industry but might not be relevant to determining the biological properties of a compound. There is thus no general agreement on the definition of solubility: in practice, the aqueous solubility of Cr[VI] compounds has been classified as prompt (1 min) and short-term (30 min) (Van Bemst *et al.*, 1983). In laboratory studies, solubilization depends on, e.g., the medium used in in-vitro tests; for human exposures, solubility is related to the chemical environment in the respiratory tract. Examples of soluble hexavalent chromium compounds are sodium chromate (873 g/l at 30 °C) and potassium chromate (629 g/l at 20 °C). Hexavalent chromium compounds classed as insoluble include barium chromate (4.4 mg/l at 28 °C) and lead chromate (0.58 mg/l at 25 °C) (Windholz, 1983; Weast, 1985). Compounds with solubilities towards the middle of this range are not easily classified, and technical-grade compounds, such as the various zinc chromates, can have a wide range of solubilities.

1.3 Technical products and impurities

(*a*) *Chromite ore*

Chromite ore consists of varying percentages of chromium, iron, aluminium and magnesium oxides as the major components. It has been classified into three

Table 2. Physical properties of chromium and chromium compounds[a]

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Metallic chromium [0]					
Chromium	51.996	1900	2642	Steel-grey, lustrous metal or powder	Insoluble in water; soluble in dilute hydrochloric acid and sulfuric acid; insoluble in nitric acid or nitrohydrochloric acid
Chromium[III] compounds					
Basic chromic sulfate[b]	165.06	--	--	Green powder	Soluble in water (approximately 700 g/l at 35°C[b])
Chromic acetate (hydrate)	229.14 (247.15)	--	--	Grey-green powder (blue-violet needles)	Slightly soluble in water; insoluble in ethanol; soluble in cold water, acetone (2 g/l at 15°C) and methanol (45.4 g/l at 15°C)
Chromic chloride (hexahydrate)	158.36 (266.45)	1150 (83)	Sublimes at 1300	Violet crystalline scales	Anhydrous form is insoluble in cold water, slightly soluble in hot water, but insoluble in ethanol, acetone, methanol and diethyl ether. The hydrated form is very soluble in water (585 g/l), soluble in ethanol, slightly soluble in acetone and insoluble in diethyl ether.
Chromic nitrate (7.5 hydrate) (nonahydrate)	238.03 (373.13) (400.15)	- (100) (60)	- Decomposes Decomposes at 100	Pale-green powder (brown crystals) (deep-violet crystals)	Soluble in water. Both hydrated forms soluble in water; the nonahydrate is soluble in acids, alkali, ethanol and acetone
Chromic oxide	151.99	2435	4000	Light to dark-green, fine crystals	Insoluble in water, acids, alkali and ethanol
Chromic phosphate (dihydrate)	147 (183.00)	> 1800°C	--	Violet crystalline solid	Insoluble in water. Hydrated form is slightly soluble in cold water; soluble in most acids and alkali but not in acetic acid

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Chromic sulfate	392.16	—	—	Violet or red powder	Insoluble in water; slightly soluble in ethanol; insoluble in acids
Potassium chromic sulfate (dodecahydrate)	283.23 (499.39)	(89)	(400)	(Violet ruby-red to black crystals)	Hydrated form is soluble in water (243.9 g/l at 25°C; 500 g/l in hot water); slightly soluble in dilute acids; insoluble in ethanol
Chromium[VI] compounds					
Ammonium chromate	152.07	180	—	Yellow acicular crystals	Soluble in water (405 g/l); insoluble in ethanol, slightly soluble in ammonia, acetone and methanol
Ammonium dichromate	252.06	170 (dec)[c]	—	Orange-red crystals	Soluble in water (308 g/l at 15°C; 890 g/l at 30°C) and ethanol; insoluble in acetone
Barium chromate	253.33	—	—	Yellow crystals	Very slightly soluble in water (4.4 mg/l at 28°C); soluble in mineral acids
Basic lead chromate	546.37	—	—	Red crystalline powder	Insoluble in water; soluble in acids and alkali
Calcium chromate (dihydrate)	156.09 (192.10)	(200)	—	Yellow crystalline powder	Slightly soluble in water and ethanol; soluble in acids. Hydrated form is soluble in water (163 g/l at 20°C; 182 g/l at 45°C), acids and ethanol
Chromium trioxide	99.99	196	Decomposes at 250[c]	Dark-red crystals, flakes or granular powder	Soluble in water (625 g/l at 20°C; 674.5 g/l at 100°C), ethanol, diethyl ether and sulfuric and nitric acids
Chromyl chloride	154.90	-96.5	117	Dark-red volatile liquid	Decomposes in water and ethanol; soluble in ether, acetic acid, carbon tetrachloride, carbon disulfide, benzene, nitrobenzene, chloroform and phosphorous oxychloride

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Lead chromate	323.18	844	Decomposes	Yellow to orange-yellow crystalline powder	Very slightly soluble in water (0.58 mg/l at 25°C); soluble in most acids and alkali but not in acetic acid or ammonia
Nickel chromate	174.71	—	—	—	Insoluble in water; soluble in nitric acid and hydrogen peroxide
Potassium chromate	194.20	968.3	Decomposes[c]	Lemon-yellow crystals	Soluble in water (629 g/l at 20°C; 792 g/l at 100°C); insoluble in ethanol
Potassium dichromate	294.19	398	Decomposes at 500	Bright orange-red crystals	Soluble in water (49 g/l at 0°C; 1020 g/l at 100°C); insoluble in ethanol
Sodium chromate	161.97	792	Decomposes[c]	Yellow crystals	Soluble in water (873 g/l at 30°C) and methanol (3.44 g/l at 25°C); slightly soluble in ethanol
Sodium dichromate (dihydrate)	262.00 (298.00)	356.7	Decomposes at 400[c]	Reddish to bright-orange crystals	Soluble in water (2380 g/l at 0°C; 5080 g/l at 80°C); and methanol (513.2 g/l at 19.4°C); insoluble in ethanol
Strontium chromate	203.61	Decomposes[d]	—	Yellow crystalline powder	Slightly soluble in water (1.2 g/l at 15°C; 30 g/l at 100°C); soluble in hydrochloric, nitric and acetic acids and ammonium salts
Zinc chromate	181.37	—	—	Lemon-yellow crystals	Insoluble in cold water; decomposes in hot water; soluble in acids and liquid ammonia
Zinc chromate hydroxide	280.74	—	—	Fine yellow powder	Slightly soluble in water; soluble in dilute acids, including acetic acid
Other chromium compounds					
Chromium carbonyl	220.06	Decomposes at 110	Explodes at 210	Colourless crystals or white solid	Insoluble in water; slightly soluble in carbon tetrachloride and iodoform; insoluble in ethanol, diethyl ether and acetic acid

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Chromium [II] chloride	122.90	824	--	White lustrous needles or fused fibrous mass	Soluble in water; insoluble in ethanol and diethyl ether
Chromium dioxide	83.99	300	--	Brown-black crystalline powder	Insoluble in water; soluble in nitric acid

[a]From Windholz (1983) and Weast (1985), unless otherwise specified

[b]From British Chrome & Chemical Ltd (1988)

[c]From Udy (1956)

[d]From Hartford (1979)

general grades associated with their use and chromic oxide content: metallurgical (greater than 46%), chemical (40-46%) and refractory (less than 40%) grades (Papp, 1985). During the past two decades, technological advances have allowed considerable interchangeability among the various grades, particularly the so-called chemical grade which can be utilized in all three industries. A more definitive classification is: (i) 'high-chromium' chromite (metallurgical-grade), containing a minimum of 46% chromic oxide and a chromium:iron ratio greater than 2:1; (ii) 'high-iron' chromite (chemical-grade), with 40-46% chromic oxide and a chromium:iron ratio of 1.5:1 to 2:1; and (iii) 'high-aluminium' chromite (refractory-grade), containing more than 20% aluminium oxide and more than 60% aluminium oxide plus chromic oxide (Papp, 1983).

Chromite from one US processor had the following typical analysis: chromium (as chromic oxide), 45.57%; iron (as ferric oxide), 29.80%; aluminium (as aluminium oxide), 13.80%; magnesium (as magnesium oxide), 9.28%; silicon (as silicon dioxide), 1.13%; and calcium (as calcium oxide), 0.40% (Cyprus Specialty Metals, 1988).

(*b*) *Metallic chromium and chromium alloys*

Chromium (pure) metal is a minor product of the metallurgical processing of chromium. It is available as electrolytic chromium (98.7-99.5% Cr; Elkem Metals Co., 1986), aluminothermic chromium (98.3% Cr (Morning, 1975) and 99.0-99.8% Cr (Delachaux, 1989)) and vacuum aluminothermic chromium (99.5-99.8% Cr; Delachaux, 1989). Electrolytic chromium and aluminothermic chromium typically contain traces of silicon, carbon, phosphorus, sulfur, iron, aluminium, nitrogen, oxygen and hydrogen (Elkem Metals Co., 1986; Belmont Metals, 1989). Chromium metal rapidly forms an oxide layer at the surface in air; such oxidation of finely divided chromium powder can result in the conversion of a large fraction of the metal to metal oxide upon prolonged storage (Sunderman *et al.*, 1974).

Ferrochromiums are the main intermediates in the metallurgical processing of chromium. There are three categories: high-carbon, low-carbon and ferrochromium silicon. The compositions of typical ferrochromiums are given in Table 3 (Morning, 1975).

Chromium-containing steels are usually stainless steels and are iron-base alloys. Some representative analyses of various grades are given in Table 4.

Chromium alloys can be categorized as nickel-chromium, cobalt-chromium and iron-nickel-chromium alloys. Some representative analyses are given in Table 5.

A range of chromium-containing alloys is used for surgical implants. Specifications of the American Society for Testing and Materials for such alloys are given in Table 6.

Table 3. Composition of typical ferrochromium and chromium metals[a]

Grade	Chromium	Silicon	Carbon	Sulfur (max)	Phosphorus (max)
High-carbon	65-70	1-2	5-6.5	0.04	0.03
Charge chromium:					
50-55% chromium	50-55	3-6	6-8	0.04	0.03
66-70% chromium	66-70	3	5-6.5	0.04	0.03
Low-carbon:					
0.025% carbon	67-75	1	0.025	0.025	0.03
0.05% carbon	67-75	1	0.05	0.025	0.03
Ferrochromium-silicon					
36/40 grade	35-37	39-41	0.05	-	-
40/43 grade	39-41	42-45	0.05	-	-

[a]From Morning (1975)

Table 4. Elemental analysis of representative grades of stainless steel[a]

Grade of steel	Elements in presence of iron (weight %)								
	Cr	Ni	Mn	Mo	C	Si	S	P	N
Austenitic									
AISI-201	16.0-18.0	3.5-5.5	5.5-7.5	-	0.15	1.0	0.03	0.06	0.25
AISI-302	17.0-19.0	8.0-10.0	2.0	-	0.15	1.0	0.03	0.05	-
AISI-304	18.0-20.0	8.0-10.5	2.0	-	0.08	1.0	0.03	0.05	-
AISI-316	16.0-18.0	10.0-14.0	2.0	2.0-3.0	0.08	1.0	0.03	0.05	-
Ferritic									
AISI-405	11.5-14.5	-	1.0	-	0.08	1.0	0.03	0.04	-
AISI-430	16.0-18.0	-	1.0	-	0.12	1.0	0.03	0.04	-
AISI-442	18.0-23.0	-	1.0	-	0.20	1.0	0.03	0.04	-
Martensitic									
AISI-403	11.5-13.0	-	1.0	-	0.15	0.50	0.03	0.04	-
AISI-440 A	16.0-18.0	-	1.0	0.75	0.60-0.75	1.0	0.03	0.04	-

[a]From Nickel Development Institute (1987a)

Table 5. Elemental analyses of representative chromium alloys (weight %)

Alloy	Cr	Ni	Co	Fe	Mo	W	Ta	Nb	Al	Ti	Mn	Si	C	B	Zr
Nickel base															
Cast alloys															
Cast alloy 625	21.6	63.0	–	2.0	8.7	–	–	3.9	0.2	0.2	0.06	0.20	0.20	–	–
Nimocast alloy 263	20.0	55.0	20.0	0.5	5.8	–	–	–	0.5	2.2	0.50	–	0.06	0.008	0.04
Udimet 500	18.0	52.0	19.0	–	4.2	–	–	–	3.0	3.0	–	–	0.07	0.007	0.05
Wrought alloys															
Hastelloy alloy X	22.0	47.0	1.5	18.5	9.0	0.6	–	–	–	–	0.50	0.50	0.10	–	–
Inconel alloy 617	22.0	54.0	12.5	–	9.0	–	–	–	1.0	–	–	–	0.07	–	–
Nimonic alloy PE 16	16.5	43.5	–	34.4	3.2	–	–	–	1.2	1.2	–	–	0.05	0.003	0.04
Cobalt base															
Cast alloys															
Haynes alloy 1002	22.0	16.0	Bal.	1.5	–	7.0	3.8	–	0.3	0.2	0.70	0.40	0.60	–	0.30
WI-52	21.0	–	63.0	2.0	–	11.0	–	2.0	–	–	0.25	0.25	0.45	–	–
Wrought alloy															
Haynes alloy 188	22.0	22.0	39.0	3.0 (max)	–	14.0	–	–	–	–	1.25 (max)	0.40	0.10	–	–
Iron–nickel base															
Wrought alloys															
Haynes alloy 556	22.0	20.0	20.0	29.0	3.0	2.5	0.9	0.1	0.3	–	1.50	0.40	0.10	–	–
Incoloy alloy 800	21.0	32.5	–	46.0	–	–	–	–	0.4	0.4	0.80	0.50	0.05	–	–

[a]From Nickel Development Institute (1987b); Bal, balance

Table 6. Composition specifications for four representative chromium–containing alloys used in surgical implants (weight %)[a]

Alloy	Cr	Mo	Ni	Fe	C	Si	Mn	N	P	S	Ti	W	Co
A	27.0–30.0	5.0–7.0	1.0 max	0.75 max	0.35 max	1.0 max	1.0 max	NA	NA	NA	NA	NA	Balance
B	19.0–21.0	9.0–10.5	33.0–37.0	1.0 max	0.025 max	0.15 max	0.15 max	NA	0.015 max	0.01 max	1.0 max	NA	Balance
C	18.0–22.0	3.0–4.0	15.0–25.0	4.0–6.0	0.05 max	0.50 max	1.0 max	NA	NA	0.01 max	0.5–3.5	3.0–4.0	Balance
D	26.0–30.0	5.0–7.0	1.0 max	0.75 max	0.35 max	1.0 max	1.0 max	0.25 max	NA	NA	NA	NA	Balance

[a]From American Society for Testing and Materials (1984a, 1987a,b, 1988a)

NA, not applicable

(*c*) *Chromium [III] compounds*

Basic chromic sulfate is produced by one company in the UK, as 67% basic chromic sulfate and 25-37% sodium sulfate (British Chrome & Chemical Ltd, 1988).

Chromic acetate is available as a 50% green aqueous solution with the following typical analysis; chromium, 11.4%; sulfate, less than 0.2%; chloride, less than 0.1% (McGean-Rohco, 1984).

Chromic chloride hexahydrate is available as a 62% green aqueous solution, typically containing 12% chromium and less than 0.2% sulfate (McGean-Rohco, 1984).

Chromic nitrate is available as a hydrate ($Cr(NO_3)_3.7.5\text{-}9H_2O$) in granules; 12.5-13.5% chromium and as the nonahydrate in liquid form (6.5-10.9% chromium) (McGean-Rohco, 1984).

Chromic oxide is available in several grades depending on its use in metallurgical and refractory industries. A typical analysis of a metallurgical grade is 99.4% chromium (as chromic oxide) and less than 0.1% moisture. A typical analysis of a refractory grade is 98.5-99.4% chromium (as chromic oxide), 0.1% alkali metals (as sodium oxide), 0.1% other metal oxides (mainly aluminium, iron and magnesium), and average particle size, 0.5-3.5 μm (American Chrome & Chemicals, undated a,b,c,d). Chromic oxide pigment (dark chromium oxide) typically contains > 99.0% chromium as chromic oxide (Mineral Pigments Corp., undated a).

Chrome base spinels are part of the family of mixed metal oxide organic coloured pigments. Two such pigments are (i) chromium iron nickel black spinel, the composition of which may include any one or a combination of cupric oxide, manganese oxide and manganese sesquioxide as modifiers, and (ii) chrome manganese zinc brown spinel, which may contain any one or a combination of aluminium oxide, nickel monoxide, silicon dioxide, stannous oxide and titanium dioxide as modifiers (Dry Color Manufacturers' Association, 1982).

Chromic phosphate tetrahydrate is available with a purity of 99.9% (National Chemical Co., undated a).

Analytical reagent-grade *chromium sulfate* hydrate is available with the following impurities: ammonium, 0.01% max; chloride, 0.002% max; insoluble matter, 0.01% max; and iron, 0.01% max. Analytical reagent-grade *potassium chromic sulfate* dodecahydrate is available at a purity greater than 98.0%. Potassium chromic sulfate with various degrees of hydration is available commercially as Chrome Alum Crystal (violet crystals) containing 10% chromium and Chrome Alum 0% Basicity (green powder) containing 15.4% chromium (McGean-Rohco, 1984).

(*d*) *Chromium[VI] compounds*

Ammonium dichromate is available as analytical reagent-grade crystals (99.5%) and as purified-grade crystals and granules with the following impurities: chloride, 0.005% max; fixed alkalis (as sulfate), 0.1-0.2% max; insoluble matter, 0.005% max; and sulfate, 0.005% max.

Calcium chromate is available at a purity of 96% min (Barium & Chemicals, 1988a). When used as a pigment for primer applications, it has the following typical analysis: chromium oxide, 45%; calcium oxide, 44%; chloride, less than 0.001%; sulfate, less than 0.001%; and moisture, 0.01% (National Chemical Co., undated b).

Chromium trioxide is available commercially at a purity of 99.9% (McGean-Rohco, 1984; Occidental Chemical Corp., 1987a; American Chrome & Chemicals, undated e). Two grades available from one company in Europe contain maxima of 20 and 100 mg/kg metallic impurities.

Analytical reagent-grade *potassium chromate* (crystals) is available at a purity of 99.0%. *Potassium dichromate* is available at a purity of 99.8% (Occidental Chemical Corp., 1987b).

Technical-grade anhydrous *sodium chromate* is available at a purity of 99.5% (Occidental Chemical Corp., 1987c). *Sodium dichromate* dihydrate is available at a purity of 100.0% (American Chrome & Chemicals, undated f). Anhydrous sodium dichromate is available at a purity of 99.70% (American Chrome & Chemicals, undated g).

Barium chromate is available at a purity of 98.5-99% (Atomergic Chemetals Corp., 1980; Barium & Chemicals, 1988b; National Chemical Co., undated c).

The term '*zinc chromate*' is a generic term for a series of commercial products with three kinds of molecular structure: (i) 'zinc chromate' type (like $ZnCrO_4$); (ii) 'basic zinc chromate' type (like zinc tetrahydroxychromate ($ZnCrO_4.4Zn(OH)_2$); and (iii) '(basic) zinc potassium chromate' type (like $3ZnCrO_4.Zn(OH)_2.K_2CrO_4.2H_2O$). Several different commercial 'zinc chromates' are also referred to as 'zinc yellow'.

Analytical reagent-grade *lead chromate* powder is available at a purity of >98%. The commercial lead chromate pigments, Primrose Chrome Yellow, Light Chrome Yellow and Medium Chrome Yellow, contain 65-89% lead chromate (Mineral Pigments Corp., undated b,c; National Chemical Co., undated d).

Molybdenum orange is described as a complex of lead molybdate, lead chromate and lead sulfate (National Chemical Co., undated e). One composition comprises 65% lead, 12% chromium and 3% molybdenum (Wayne Pigment Corp., 1985a,b).

Strontium chromate is available at a purity of 99% (National Chemical Co., undated f). A strontium chromate pigment is available with a typical analysis of 41.4% strontium and 46.7-47.3% chromium (Mineral Pigments Corp., undated d).

2. Production, Use, Occurrence and Analysis

The early history of chromium compounds, including synthetic methods used in their preparation, has been reviewed (Mellor, 1931).

2.1 Production

Chromium was first isolated and identified as a metal by the French chemist, Vauquelin, in 1798, working with a rare mineral, Siberian red lead (crocoite, $PbCrO_4$).

A generalized flow diagram for the production processes used now to lead from chromite ore to the major products containing chromium is shown in Figure 1.

(*a*) *Chromite ore*

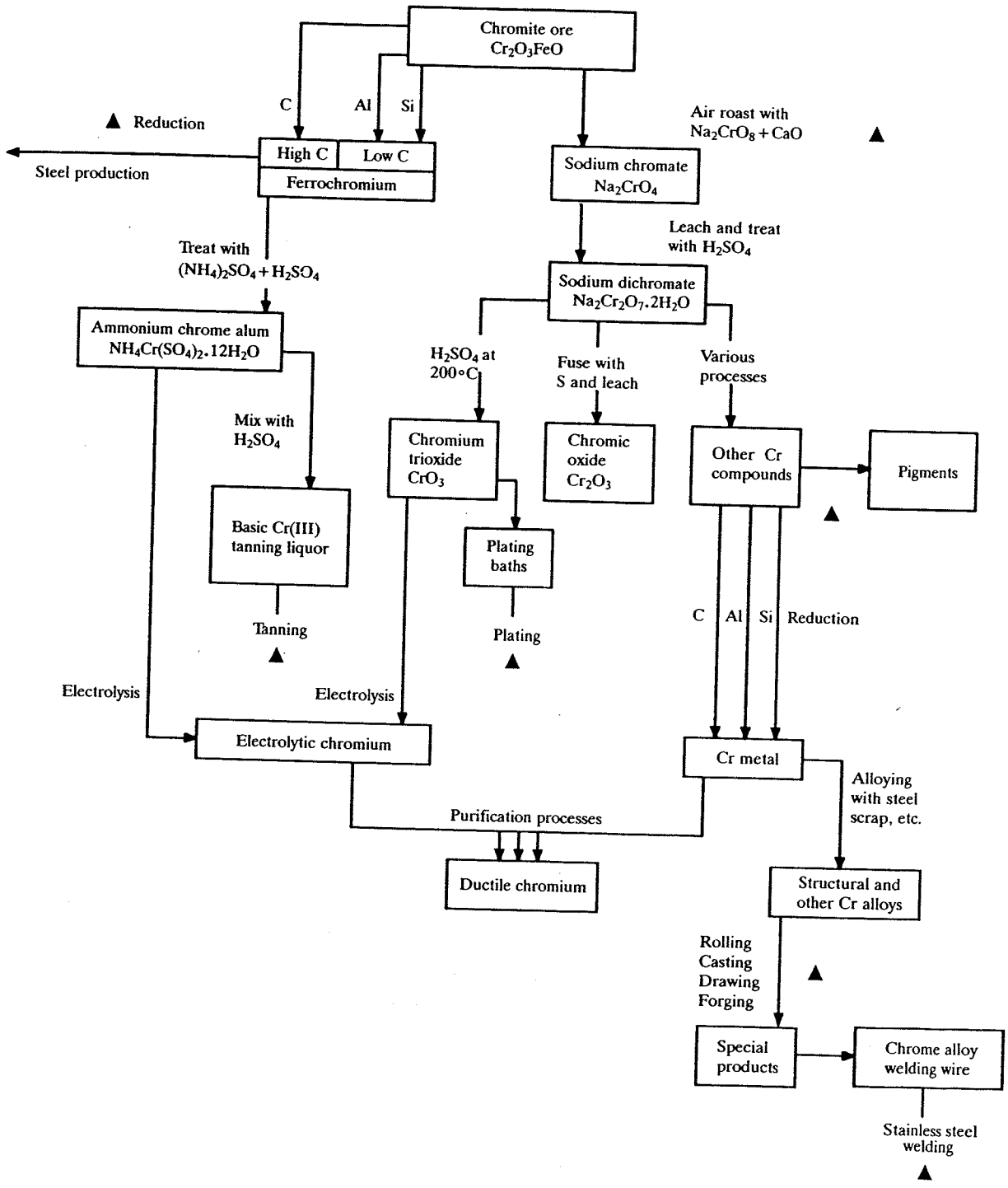
Although chromium is found in various minerals, chromite is the sole source of chromium used commercially (Stern, 1982). From 1797 until 1827, chromite from the Ural Mountains of Russia was the principal source of world supply, primarily for chemical use. After chromite ore was discovered in the USA in 1827, that country became the principal source for the limited world demand; it no longer produces it. Large Turkish deposits were developed in 1860 to supply the world market. Table 7 presents world production figures by region in 1976, 1982 and 1987.

(*b*) *Metallic chromium and chromium alloys*

Chromium metal is made commercially in the USA by two processes: (i) an electrolytic method in which a chromium-containing electrolyte, prepared by dissolving a high-carbon ferrochromium in a solution of sulfuric acid and chromium potassium sulfate, is subjected to electrolysis; and (ii) an aluminothermic reduction method in which chromic oxide is reduced with finely divided aluminium (Bacon, 1964; Papp, 1983).

In 1970, US production of chromium metal and metal alloys, other than ferrochromium alloys, was 14 thousand tonnes (about 75% by the electrolytic method; IARC, 1980a); this had increased to 18 thousand tonnes by 1976 (Morning, 1978). Production included chromium briquets, exothermic chromium additives and miscellaneous chromium alloys, in addition to chromium metal. By 1987, US production of chromium metal and ferrochromium-silicon (including exothermic chro-

Fig. 1. Simplified flow chart for the production of metallic chromium, chromium compounds and selected products from chromite ore. Processes for which occupational exposure levels to chromium are available are indicated by ▲[a]



[a]From Stern (1982)

mium additives and other miscellaneous chromium alloys) had dropped to 1900 tonnes (Papp, 1988).

Table 7. World mine production of chromite ore by region (thousand tonnes)[a]

Region[b]	1976	1982	1987
Albania	794	675	830
Brazil	172	276	227
Cuba	32	27	122
Cyprus	9	3	0
Egypt	1	0	0
Finland	414	345	712
France (New Caledonia)	10	50	62
Greece	27	29	64
India	401	364	522
Iran	160	41	56
Japan	22	11	12
Madagascar	221	44	100
Oman	0	0	6
Pakistan	11	4	8
Philippines	427	322	172
South Africa	2409	2431[c]	3787[c]
Sudan	22	19	8
Turkey	740	453	599
USSR	2120	2939	3148
Viet Nam	9	16	15
Yugoslavia	2	0	0
Zimbabwe	608	432	540
Total	8611	8481	10 990

[a]From Morning (1978); Papp (1987, 1988)

[b]In addition to the regions listed, Argentina, Bulgaria, China, Colombia, the Democratic Republic of Korea and Thailand may also have produced chromite ore, but output was not reported quantitatively and available general information was inadequate for formulation of reliable estimates of production.

[c]Includes production by Bophuthatswana

Chromium metal has been produced in Japan since 1956, where it is manufactured by two companies by electrolysis of an ammonium chromic sulfate solution. About 9000 tonnes were produced in 1977; there were no reported imports or exports (IARC, 1980a).

Ferrochromium is produced by treatment of chromite ore in electric furnaces using coke as a reducing agent. Worldwide production figures for all grades of ferrochromium are summarized in Table 8.

Table 8. World production of ferrochromium (all grades, in thousands of metric tonnes)[a]

Country	1983	1985	1987
Albania	35	13	35
Brazil	80	136.2	113.5
Finland	58.7	133	143
France	18.1	0	0
Germany, Federal Republic of	45	70	23
Greece	18.5	45	45
India	53.5	78.5	122.1
Italy	45.4	57.6	59
Japan	329.1	379.7	291
Philippines	27	51	59
South Africa	699.5	851	948
Spain	18	30	17.6
Sweden	119.4	135	110
Turkey	30.1	53.3	54
USA[b]	33	99.7	106.7
USSR	634	415	NA
Yugoslavia	68	73	80
Zimbabwe	140	180	185

[a]From Chromium Association (1989)
[b]Includes L and HC ferrochromium, FeSiCr, Cr metal and other miscellaneous alloys
NA, not available

Chromium-containing steels (stainless steels and others) are produced by melting cast iron and adding ferrochromium and/or steel scraps in large electric furnaces. The melt is transferred to a refining vessel to adjust the carbon content and impurity levels and is then cast into ingots or continuously into casting shapes. Defects in the cast steel are repaired by cutting or scarfing or by chipping or grinding. The desired shapes are produced primarily by rolling, and their surfaces are conditioned by a variety of operations, including grinding, polishing and pickling (Warner, 1984).

Production figures are given in Table 9.

Chromium alloys are produced by technology very similar to that used for steel production, except that the melting and decarburizing units are generally smaller

and greater use is made of vacuum melting and remelting (Warner, 1984). No data were available on production volumes of these alloys.

Table 9. Stainless-steel production in selected countries[a] (in thousands of metric tonnes)

Country	1987	1988
Austria	54	67
Belgium	182	254
Finland	189	206
France	720	784
Germany, Federal Republic of	957	1186
Italy	550	623
Japan	2722	3161
Spain	327	426
Sweden	457	482
UK	393	427
USA	1840	1995
Yugoslavia	30	30

[a]From ERAMET-SLN (1989)

Cobalt-chromium alloys were first made in 1907 by fusion of cobalt with 10-60% chromium (Haynes, 1907). Commercial production began shortly thereafter, and since 1920 more than 75% of the cobalt used in the USA has been for the manufacture of alloys with chromium (Sibley, 1976).

Eight US companies produced chromium alloys in 1975, but separate data on the quantity of cobalt-chromium alloys produced were not available (Morning, 1978). Stellite (usually 53% Co, 35% Cr and the remainder tungsten) has been produced by one company in the UK (Roskill Information Services, 1974).

(c) *Chromium [III] compounds*

Solutions of *chromic acetate* are produced by dissolving freshly prepared hydrous chromic oxide in acetic acid (IARC, 1980a). Commercial mixtures of chromic acetate with sodium acetate have been prepared by reduction of sodium dichromate with glucose or corn sugar in the presence of acetic acid (Copson, 1956).

Chromic acetate was produced by five companies in the USA, but no data on volumes were available (IARC, 1980a); it is now produced by one company (Chemical Information Services Ltd, 1988). Annual production in Japan has been about 30 tonnes (IARC, 1980a). Chromic acetate is currently produced by two companies each in Japan and the UK and one each in Australia, Canada and Italy (Chemical Information Services Ltd, 1988).

Chromic chloride hexahydrate is prepared by dissolving freshly prepared chromium hydroxide in hydrochloric acid. Anhydrous chromic chloride can be produced by passing chlorine over a mixture of chromic oxide and carbon (Sax & Lewis, 1987). Chromic chloride has been produced by two companies in the USA, but no data on volumes were available.

In Japan, chromic chloride has been produced from chromic sulfate by converting it to purified chromic carbonate, which is treated with hydrochloric acid. About 100 tonnes of chromic chloride were produced by one Japanese company in 1977; there were no reported imports or exports. Four companies currently produce chromic chloride in Japan (Chemical Information Services Ltd, 1988).

Chromic chloride is also produced by three companies in the UK, two in the Federal Republic of Germany and one each in Australia and the German Democratic Republic (Chemical Information Services Ltd, 1988).

Chromic hydroxide is produced by adding a solution of ammonium hydroxide to the solution of a chromium salt (Sax & Lewis, 1987). It is produced by one company each in Argentina, Brazil, France, Japan and Turkey, two each in Austria, Spain, the UK and the USA and four in India (Chemical Information Services Ltd, 1988).

Chromic nitrate may be produced by the action of nitric acid on chromium hydroxide (Sax & Lewis, 1987). It is produced by three companies each in Japan, the UK and the USA, two each in Italy and Spain and one in the Federal Republic of Germany (Chemical Information Services Ltd, 1988).

Anhydrous *chromic oxide* is produced commercially by heating chromic hydroxide, by heating dry ammonium dichromate, or by heating sodium dichromate with sulfur and washing out the sodium sulfate (Sax & Lewis, 1987). The hydrated material is made commercially by calcining sodium dichromate with boric acid and hydrolysing chromic borate (IARC, 1980a).

Chromic oxide was produced by six companies in the USA in 1977. US production of the most important type of chromic oxide, chromic oxide green, was reported to be about 6000 tonnes in 1971 (IARC, 1980a), about 3700 tonnes in 1976 and 2700 tonnes in 1977 (Hartford, 1979). It is now produced by one company in the USA (Chemical Information Services Ltd, 1988). Chromic oxide has been produced in Japan by two companies, either by heating hydrous chromic oxide or chromium trioxide or by reducing sodium dichromate with carbon. An estimated 2700 tonnes were produced in 1977 (IARC, 1980a). It is also produced by two companies each in the Federal Republic of Germany and the UK and one each in France, India, Italy, Spain and Switzerland (Chemical Information Services Ltd, 1988).

A violet hexahydrate form of *chromic phosphate* is formed by mixing cold solutions of potassium chromium sulfate (chrome alum) with disodium phosphate. A

green crystalline dihydrate is obtained by boiling the violet hexahydrate with acetic anhydride or by heating it in dry air (Udy, 1956).

Chromic phosphate is produced by two companies in the USA and one each in Australia, Austria, the Federal Republic of Germany, India, Japan and the UK (Chemical Information Services Ltd, 1988).

Solutions of mixed hydrated *chromic sulfates* are obtained by dissolving chromic oxide in concentrated sulfuric acid and allowing it to stand until crystals of the hydrated chromic sulfate separate. The anhydrous form is produced by heating any of the hydrates to 400°C in air or to 280°C in a stream of carbon dioxide (IARC, 1980a). Mixtures of *basic chromic sulfates* (containing mainly $Cr(OH)SO_4$) with sodium sulfate are produced commercially by the organic reduction (with such substances as molasses) of a solution of sodium dichromate in the presence of sulfuric acid or by reduction of dichromate solutions with sulfur dioxide (Copson, 1956).

Two companies in the USA produce chromium sulfate and one produces basic chromic sulfate, but no data on volumes were available (Chemical Information Services Ltd, 1988).

Both chromium sulfate and basic chromic sulfate have been produced in Japan since about 1950, by reduction of sodium dichromate with glucose. The combined production of the two producers in 1977 (which are still operating) was about 2000 tonnes basic chromic sulfate and about 120 tonnes chromium sulfate (IARC, 1980a).

Chromium sulfate is also produced by one company each in Brazil, France, India and New Zealand, two each in the Federal Republic of Germany and Spain and three in the UK. Basic chromic sulfate is also produced by one company each in Australia, Brazil, Colombia, Italy, Mexico, Pakistan, Turkey and the USSR, two each in China and India and three in the UK (Chemical Information Services Ltd, 1988).

Potassium chromic sulfate dodecahydrate (potassium chrome alum) is produced commercially by the reduction of potassium dichromate with sulfur dioxide (Copson, 1956). One company in the USA currently produces potassium chromic sulfate, but no data on volumes were available (Chemical Information Services Ltd, 1988). It was produced commercially in Japan before 1940. Production reached about 20-30 tonnes in 1970; subsequently, the annual quantity produced decreased rapidly, and only about one tonne was produced in 1977 (IARC, 1980a).

Potassium chromic sulfate is also produced by one company in Brazil and one company in Czechoslovakia (Chemical Information Services Ltd, 1988).

(*d*) *Chromium[VI] compounds*

Hexavalent chromium compounds that are commonly manufactured include sodium chromate, potassium chromate, potassium dichromate, ammonium di-

chromate and chromium trioxide. Other materials that contain chromium[VI] are paint and primer pigments, graphic art supplies, fungicides, wood preservatives and corrosion inhibitors (National Institute for Occupational Safety and Health, 1975). Each chromate-producing process involves the roasting of chromite ore with soda and lime at about 1100°C in a furnace or rotary kiln (Gafafer, 1953). Water-soluble hexavalent chromium compounds do not occur in the ore but comprise part of roast, residue and product materials (Kuschner & Laskin, 1971). The presence of lime ensures that aluminium and silicon oxides in the ore are converted to insoluble compounds, the soluble sodium chromate being recovered by a leaching and crystallization process (National Institute for Occupational Safety and Health, 1975). Chromium trioxide is produced by acidifying the leachate solution with sulfuric acid (Gafafer, 1953). In the manufacture of pigments, chromium trioxide or alkali chromates are reacted with soluble compounds of zinc, lead, iron, molybdenum, strontium and other metals (Stern, 1982). The insoluble precipitates are washed, filtered and dried in the wet department of the processing plant and then ground, blended and packed in the dry departments, where conditions are often dustiest (Gafafer, 1953).

Ammonium dichromate is produced by a crystallization process involving equivalent amounts of sodium dichromate and ammonium sulfate. When low alkali salt content is required, it can be prepared by the reaction of ammonia with chromium trioxide (Hartford, 1979).

Ammonium dichromate is produced by one company each in Argentina, Australia, Brazil, France, Japan, Spain and Switzerland, by two each in the Federal Republic of Germany and India, by four in the USA, and by five in the UK (Chemical Information Services Ltd, 1988).

Calcium chromate is produced commercially by the reaction of calcium chloride with sodium chromate. Hydrated forms can be made, but the anhydrous salt is the only product of commercial significance (IARC, 1980a).

Calcium chromate is currently produced by three companies in the USA, but no data on volumes were available (Chemical Information Services Ltd, 1988). Calcium chromate was formerly produced in Japan at an annual rate of about 100 tonnes, but it has been produced recently in only small amounts for reagent use (IARC, 1980a). It is also produced by one company each in Australia and the UK and two in France (Chemical Information Services Ltd, 1988).

Chromium trioxide is produced commercially by the reaction of sodium dichromate with concentrated sulfuric acid (Hartford, 1979). In 1978, there were two US producers of chromium trioxide, each with a capacity to produce 18 thousand tonnes per year (Anon., 1978). Annual US production in 1977 was in the range of 26 thousand tonnes (Hartford, 1979). In 1988, there were six US producers (Chemical

Information Services Ltd, 1988) with a combined capacity of 52 thousand tonnes per year (Anon., 1988a).

Commercial production in Japan was started before 1940. In 1977, three companies produced a total of 8300 tonnes, of which 1200 tonnes were exported; there were no reported imports (IARC, 1980a). Four companies currently produce chromium trioxide in Japan (Chemical Information Services Ltd, 1988).

Chromium trioxide is also produced by four companies each in the Federal Republic of Germany, India and the UK, three in China, two each in Argentina, Brazil and Mexico and one each in France, Italy, Pakistan, Poland and the USSR (Chemical Information Services Ltd, 1988).

Potassium chromate is produced by the reaction of potassium dichromate with potassium hydroxide or potassium carbonate (Hartford, 1979).

There was one US producer in 1977, but no data on volumes were available; combined US imports of potassium chromate and potassium dichromate in that year were 2.7 tonnes (US Department of Commerce, 1978). There are currently two US producers, but no data on volumes were available (Chemical Information Services Ltd, 1988). Combined US imports of the two compounds in 1985, 1986 and 1987, respectively, were 580, 750 and 1000 tonnes from the UK (52%), the USSR (22%), the Federal Republic of Germany (13%) and Canada (11%); combined US exports for the same years were 64, 19 and 9 tonnes to the Philippines (40%), the Republic of Korea (30%) and Panama (30%) (Papp, 1988).

The two Japanese producers made about one tonne in 1977 for reagent uses; there were no reported imports or exports (IARC, 1980a). One company currently produces potassium chromate in Japan (Chemical Information Services Ltd, 1988). It is also produced by five companies in the UK, four in Brazil, three each in India and Italy, and one each in Argentina, Canada, the Federal Republic of Germany, Spain and Switzerland (Chemical Information Services Ltd, 1988).

Potassium dichromate is produced industrially by roasting chrome ore with potassium carbonate (IARC, 1980a), or, preferably, by reacting sodium dichromate with potassium chloride (Hartford, 1979). Combined US production of potassium dichromate and potassium chromate in 1966 was estimated to be 2600-3800 tonnes, the potassium dichromate believed to be the more important industrially (IARC, 1980a).

Three companies in the USA produce potassium dichromate (Chemical Information Services Ltd, 1988). Current information on imports/exports is given above. Potassium dichromate was first produced commercially in Japan before 1940. Production by two companies in 1978 amounted to about 1000 tonnes, well below the 3200 tonnes level of 1972 and below the 1977 level of 1400 tonnes. Exports are believed to be minor (IARC, 1980a).

Potassium dichromate is also produced by six companies in India, five in the UK, four in Brazil, two each in the Federal Republic of Germany and Italy, and one each in Argentina, Romania, Spain, Switzerland, Turkey, Yugoslavia and the USSR (Chemical Information Services Ltd, 1988).

Sodium chromate is produced commercially by roasting chromite ore with sodium carbonate, or with sodium carbonate and calcium oxide, and leaching to dissolve the sodium chromate. After treatment to remove hydrated alumina, the sodium chromate solution is either marketed directly or evaporated to produce hydrated or anhydrous crystals (Hartford & Copson, 1964). Sodium chromate may also be produced from sodium dichromate by treatment with sodium hydroxide.

Two companies produced sodium chromate in the USA in 1978. The combined US production of sodium chromate and sodium dichromate increased from 123 thousand tonnes in 1967 to 144 thousand tonnes in 1977 (Hartford, 1979), and was 159 thousand tonnes in 1978. Currently, three companies in the USA have been reported to produce sodium chromate, but data on production volumes were not available (Chemical Information Services Ltd, 1988).

Commercial production in Japan started before 1940. Production in 1977 by the two producing companies was less than 10 tonnes (IARC, 1980a); two companies currently produce this compound (Chemical Information Services Ltd, 1988). It is also produced by five companies in India, four in Brazil, three in the UK, two in the Federal Republic of Germany and one in Spain (Chemical Information Services Ltd, 1988).

Sodium dichromate is produced commercially by the reaction of sulfuric acid with sodium chromate (Hartford, 1979). Three companies in the USA produced this compound in 1976. In 1988, two of five companies that produced it (Chemical Information Sciences Ltd, 1988) had a combined capacity of 144 thousand tonnes per year (Anon., 1988b).

Sodium dichromate was first produced commercially in Japan in about 1908. In 1978, the combined production of two companies was estimated to be 20.7 thousand tonnes, slightly below the 1977 level of 21 thousand tonnes (IARC, 1980a). Three companies currently produce it in that country (Chemical Information Services Ltd, 1988).

Sodium dichromate is also produced by five companies in India, four each in Brazil and the UK, three in China, two each in the Federal Republic of Germany and Turkey, and one each in Argentina, Czechoslovakia, Italy, Mexico, Pakistan, Poland, Romania, Spain, Switzerland and the USSR (Chemical Information Services Ltd, 1988).

Barium chromate is produced commercially by the reaction of barium chloride with sodium chromate (Copson, 1956). Five companies in the USA produced this

chemical in 1977 (IARC, 1980a), and now there are four (Chemical Information Services Ltd, 1988), but no data on volumes were available. Barium chromate is produced by one company in Japan (Chemical Information Services Ltd, 1988). Production in 1977 was estimated to have been less than 50 tonnes; there were no reported imports or exports (IARC, 1980a). It is also produced by four companies in France, two in the UK, and one each in Australia, Austria, Belgium, the Federal Republic of Germany, India, Italy and Spain (Chemical Information Services Ltd, 1988).

Basic lead chromate (Chrome Orange) is produced by the reaction of lead oxide with sodium dichromate in the presence of acetic acid or by the reaction of lead nitrate with sodium chromate in the presence of sodium carbonate (Chalupski, 1956). No information on production of this compound in the USA was available, but combined production of Chrome Yellow and Chrome Orange, containing various proportions of basic lead chromate, amounted to 32.1 thousand tonnes in 1976 and 28.2 thousand tonnes in 1977 (Hartford, 1979). Basic lead chromate is also produced by one company each in Argentina, Colombia, the Federal Republic of Germany, Italy, Japan, Poland and Spain (Chemical Information Services Ltd, 1988).

Lead chromate (Chrome Yellow) can be produced by reacting sodium chromate with lead nitrate, or by reacting lead monoxide with chromic acid solution. By varying the proportion of reactants, either lead chromate ($PbCrO_4$) or lead chromate oxide (basic lead chromate; $PbO.PbCrO_4$) can be produced. High lead chromate content is associated with yellow pigments; increasing the lead chromate oxide content gives orange colours; and mixing with lead molybdate gives red pigments (Chalupski, 1956).

No information on production of this compound in the USA was available, but combined production of Chrome Yellow and Chrome Orange pigments was 32.1 thousand tonnes in 1976 and 28.2 thousand tonnes in 1977 (Hartford, 1979). Assuming an average of 70% lead chromate in these pigments, about 20 thousand tonnes of lead chromate were produced in the USA or imported for use in these pigments in that year. Lead chromate is currently produced by five companies in the USA (Chemical Information Services Ltd, 1988).

Commercial production in Japan was started in about 1910, and there were three major producers and one minor producer in 1977. Production in 1977 was 10.8 thousand tonnes and exports were 1800 tonnes. Six companies currently produce lead chromate in Japan (Chemical Information Services Ltd, 1988). Production of Chrome Yellow in 1984, 1985 and 1986, respectively, was 9900, 8500 and 7900 tonnes (Sasaki, 1985, 1986, 1987).

Lead chromate is also produced by six companies in Spain, five in Italy, three in Belgium, two each in Argentina, Austria, Canada, China, the Federal Republic of

Germany, France, the Netherlands and Turkey, and one each in Australia, Colombia, Mexico, Poland, Taiwan and the UK (Chemical Information Services Ltd, 1988).

Molybdenum orange pigments are variable complexes of lead sulfate, lead chromate and lead molybdate, made by pouring sodium dichromate, sulfuric acid and sodium molybdate into excess lead nitrate, preferably cold, at pH3. An ageing step is required in precipitation to permit development of the orange tetragonal form (Hartford, 1979).

Molybdenum orange is currently produced by four companies in the USA (Chemical Information Services Ltd, 1988). US imports for 1985, 1986 and 1987, respectively, were 980, 750 and 1100 tonnes from Canada (78%), the Federal Republic of Germany (16%) and Japan (6%) (Papp, 1988). Four companies currently produce molybdenum orange and molybdenum red in Japan (Chemical Information Services Ltd, 1988), and production of molybdenum red in 1984, 1985 and 1986, respectively, was 2900, 2600 and 2200 tonnes (Sasaki, 1985, 1986, 1987).

Molybdenum orange (including molybdenum red) is also produced by one company each in Australia, Austria, Canada, Colombia, India, Italy, Mexico and Taiwan, two each in Belgium, the Federal Republic of Germany, France and the Netherlands and four in Spain (Chemical Information Services Ltd, 1988).

Strontium chromate is prepared by adding a solution of a strontium salt to a solution of sodium chromate (Lalor, 1973).

Production of strontium chromate by three companies in the USA in 1970 was estimated to be 680 tonnes (Lalor, 1973). US imports in 1977 were 242 tonnes, mostly from Canada (US Department of Commerce, 1978). It is currently produced by five companies in the USA, but no data on volumes are available (Chemical Information Services Ltd, 1988). US imports for 1985, 1986 and 1987, respectively, were 390, 120 and 120 tonnes from France (61%), the Federal Republic of Germany (15%) and Canada (11%) (Papp, 1988).

Production in Japan began after 1940. The combined production of three companies in 1977 was about 600 tonnes, comparable with that of the previous seven years; there were no reported imports or exports (IARC, 1980a). Two companies currently produce strontium chromate in that country (Chemical Information Services Ltd, 1988).

Strontium chromate is also produced by four companies in France, two each in Australia, Italy, Spain and the UK and one each in Austria, Belgium, Brazil and the Federal Republic of Germany (Chemical Information Services Ltd, 1988).

Zinc chromates have been produced commercially since about 1940. Basic zinc chromates (including 'zinc chromates') are prepared by reaction between a solution of chromium trioxide and a slurry of zinc oxide. Zinc potassium chromates are pre-

pared by a reaction between a solution of sodium dichromate, a slurry of zinc oxide and a solution of potassium chloride (Lalor, 1973).

Zinc chromate (zinc tetroxychromate) is currently produced by three companies each in Belgium, France, Italy, Japan, Spain and the USA, two each in Argentina and Austria, and one each in Australia, Canada, Colombia, India, the Netherlands, Norway, Poland, Taiwan, Turkey and the UK. Zinc potassium chromate is produced by two companies in Austria, one each in Belgium, France, Italy, Norway, Turkey and the USA (Chemical Information Services Ltd, 1988), and probably elsewhere. Production of 'zinc chromate' in Japan in 1984, 1985 and 1986 was 1530, 1280 and 1000 tonnes, respectively (Sasaki, 1985, 1986, 1987).

(*e*) *Other chromium compounds*

Chromium carbonyl is produced by the reaction of carbon monoxide with chromic chloride and aluminium metal (IARC, 1980a). Two companies in the USA produce this chemical, but no data on volumes are available. Chromium carbonyl is also produced by one company in the Federal Republic of Germany (Chemical Information Services Ltd, 1988).

2.2 Use

An early use of chromium compounds was as pigments, particularly chrome yellow. Basic chromic sulfate was used in tanning hides, as the reaction of chromium with collagen raises the hydrothermal stability of the leather and renders it resistant to bacterial attack. The most important use of chromium, namely as an alloying element, developed gradually during the nineteenth century and led to the introduction of chromium steels (Westbrook, 1979).

Chromium is currently used in such widely diversified products as stainless, tool and alloy steels, heat- and corrosion-resistant materials, special purpose alloys, alloy cast iron, pigments, metal plating, leather tanning, chemicals, and refractory materials for metallurgical furnaces. It is used in the metallurgical industry to enhance such properties as hardenability (response to quenching), creep (unit stress that will produce plastic deformation at a specified rate and temperature), strength and impact strength and resistance to corrosion, oxidation, wear and galling; its major use is in the production of stainless steel. Chromium pigments represent the largest use of chromium in the chemical industry (Papp, 1983).

(*a*) *Chromite ore*

Use of chromite ore in the USA decreased from 1.3 million tonnes in 1974 to 912 thousand tonnes in 1976, when utilization by the three consuming industries was as follows: metallurgical, 59.3%; refractory, 20.1%; and chemical, 20.6% (Morning, 1978). US consumption of chromite ore (and concentrate) was 504 thousand tonnes

in 1987, 91% of which was used by the chemical and metallurgical industries and 9% by the refractory industry (Papp, 1988).

The metallurgical grade is used primarily to produce ferrochromium alloys, which are used in the production of stainless and other special steels (Bacon, 1964). The major use of chromite refractory materials in 1974 was in iron and steel processing, nonferrous alloy refining, glass making and cement processing (Morning, 1975); in 1987, the primary use was in refractory bricks to line metallurgical furnaces (Papp, 1988). Chemical-grade chromite ore is converted (by a series of operations involving roasting with soda ash and/or lime and leaching, with appropriate control of acidity) to sodium dichromate, used as such and in the production of many other chromium chemicals (Copson, 1956).

The major use of chromite ore in Japan has been in the production of ferrochromium (90%), the balance being used in the manufacture of refractory materials (6%), chromium compounds (3%) and chromium metal (1%) (IARC, 1980a).

(*b*) *Metallic chromium and chromium alloys*

Chromium metal (pure) is used to prepare alloys with high purity specifications. Chromium is thus an important and widely used alloying element in ferrous and nonferrous alloys, including those based on nickel, iron-nickel, cobalt, aluminium, titanium and copper. In alloys based on nickel, iron-nickel and cobalt, chromium is used primarily to confer oxidation and corrosion resistance. In alloys of aluminium, titanium and copper, chromium is used to control microstructure. Stainless steel contains at least 12% and may contain up to 36% chromium. Chromium-containing tool steels contain 1-12% chromium. Most full alloy steels contain 0.5-9% chromium, but some grades contain up to 28%. Cast irons contain 0.5-30% chromium (Papp, 1983).

In 1976, 70% (170 thousand tonnes) of all US chromium metal and metal alloys were used in the production of stainless steel. Of the total of chromium metal and alloys used in the production of commercial alloys, about 60% was in high-carbon ferrochromium, 11% in low-carbon ferrochromium, 21% in ferrochromium-silicon and 7.4% in other alloys, chromium briquets, exothermic additives and chromium metal (Morning, 1978). In 1987, 82% (330 thousand tonnes) of all US chromium ferroalloys, metal and other chromium-containing materials were used in the production of stainless steel. Of the total of chromium metal and alloys used in the production of commercial alloys, about 88% was in high-carbon ferrochromium, 6.5% in low-carbon ferrochromium, 4% in ferrochromium-silicon, 0.5% in other alloys and 1% in chromium metal (Papp, 1988).

Chromium-containing steels are widely used in, for instance, general engineering, architectural panels and fasteners, pollution control equipment, chemical

equipment, cryogenic uses, hospital equipment, domestic equipment, automotive parts, engine components and food processing (Eurométaux, 1986).

Chromium alloys are used in a large variety of applications, including jet engine parts, nuclear plants, high-temperature reaction vessels, chemical industry equipment, high temperature-resistant equipments, coinage, desalinization plants, ships' propellers, acid-resistant equipment, cutting tools and implants (National Research Council, 1974).

Cobalt-chromium alloys were originally developed for use in cutting tools. Subsequently, because of their corrosion resistance, they were also used for equipment in contact with acids and other chemicals. They are used for facing valves and seats in internal combustion engines; wearing surfaces or cutting edges of hot shears, trimming dies, cam gauges, punches and turbine blades; pipeline linings; and pumps for corrosive liquids (Cobalt Development Institute, 1985). Stellite alloys are used in high-temperature applications. The superalloys are used for turbine discs and blades and nozzle vanes in jet engines; grates and quenching baskets in furnaces; and high-temperature springs and fasteners (Roskill Information Services, 1974). Vitallium alloy (27 wt% Cr, 5% Mo, 0.5% C, balance Co) is most commonly used as a denture alloy (Sullivan *et al.*, 1970).

(c) *Chromium[III] compounds*

Chromic acetate is used in printing and tanning, as a textile mordant, a polymerization and oxidation catalyst, and an emulsion hardener (Hartford, 1979; Sax & Lewis, 1987). Most of the chromic acetate produced in Japan has been used in dyeing processes (IARC, 1980a).

Chromic chloride is used for the production of commercial solutions of the basic chlorides ($Cr(OH)_2Cl$) by reaction with sodium hydroxide. These solutions have been reported to have minor special applications, such as use as a mordant for alizarin dyes on cotton yarn and certain cyamine dyes on silk. In Japan, they are also used for decorative chromium plating (IARC, 1980a).

Anhydrous chromic chloride has been used as a catalyst for polymerizing olefins, for chromium plating (including vapour plating), for preparing sponge chromium and other chromium salts, as an intermediate, and for waterproofing (Sax & Lewis, 1987).

Chromic hydroxide has been used as a catalyst, a tanning agent, a mordant, and in the preparation of Guignet's green (hydrated chromic oxide green) (Sax & Lewis, 1987).

Chromic nitrate has been used as a catalyst and a corrosion inhibitor (Sax & Lewis, 1987). It has also been used in textiles and in the manufacture of chromium dioxide (Hartford, 1979).

Most *chromic oxide* (anhydrous and hydrated) is used as a pigment. A substantial portion is also used in metallurgy in the manufacture of chromium metal and aluminium-chromium master alloys and, to a lesser extent, as a catalyst, in refractory brick, and as a chemical intermediate (IARC, 1980a; Sax & Lewis, 1987).

Anhydrous chromic oxide is the most stable green pigment known and is used in applications requiring resistance to heat, light and chemicals (e.g., in glass and ceramics). It is used in dyeing polymers, and its resistance to alkali makes it a valuable colourant for latex paints. It has special use in colouring cement and granules for asphalt roofing and in camouflage paints. Metallurgical-grade anhydrous chromic oxide is used in the manufacture of chromium metal and aluminium-chromium master alloys. It is used as a catalyst in the preparation of methanol, butadiene and high-density polyethylene. Chromic oxide is also used in refractory brick as a minor component to improve performance. When used as a mild abrasive for polishing jewellery and fine metal parts, it is known as 'green rouge' (IARC, 1980a).

Hydrated chromic oxide is also used as a green pigment, especially for automotive finishes (IARC, 1980a).

In Japan, chromic oxide has been used for the production of refractory materials (36%), pigments (35%), abrasives (15%) and other uses, such as glaze for glass (14%) (IARC, 1980a).

Chromic phosphate is used in pigments, phosphate coatings and wash primers, and as a catalyst (Hartford, 1979; Sax & Lewis, 1987).

Chromic sulfate is used in chrome plating, chromium alloys, green paints and varnishes, green inks, ceramic glazes, and as a mordant for textile dyeing. Basic chromic sulfate is the principal chemical used in leather tanning (Sax & Lewis, 1987).

Potassium chromic sulfate (chrome alum) has been reported to be used as a mordant prior to application of mordant dyes. It is also used to treat cotton that has been dyed with certain direct cotton dyes and sulfur dyes, rendering the dyed textile faster to washing. Another important application is in the preparation of hydrous chromic oxide, which, in turn, is used to make many of the trivalent chromium mordants (Howarth, 1956). It has also been used in chrome-tan liquors for tanning, in photographic fixing baths, and in ceramics (Sax & Lewis, 1987).

(*d*) *Chromium[VI] compounds*

Ammonium dichromate has a variety of uses, including a mordant for dyeing; in pigments; in the manufacture of alizarin, potassium chromic sulfate and catalysts; in oil purification; in pickling; in leather tanning; in synthetic perfumes; in photography; in process engraving and lithography; and in pyrotechnics (Sax & Lewis, 1987).

Calcium chromate is largely used as a corrosion inhibitor and as a depolarizer in batteries (Hartford, 1979). Its addition to protective coatings for steel and light metals is sometimes reported as a pigment use, but its primary function in these products is to inhibit corrosion. It is also used in ceramics and in paint pigments (Barium & Chemicals, undated). The use of calcium chromate as a pigment was discontinued in Japan some years ago (IARC, 1980a).

A major use of *chromium trioxide* has been in chromium plating, particularly in the production of automobiles. Uses in other metal-finishing operations include aluminium anodizing, particularly on military aircraft; chemical conversion coatings, which provide both decoration and corrosion protection; and the production of phosphate films on galvanized iron or steel (IARC, 1980a). Other uses of chromium trioxide are as a wood preservative (Anon., 1988a), as a corrosion inhibitor for ferrous alloys in recirculating water systems, as an oxidant in organic synthesis and in catalyst manufacture. Small amounts are used to modify the properties of basic magnesite refractories (IARC, 1980a).

US demand for chromium trioxide was 31.5 thousand tonnes in 1978 (Anon., 1978) and 57 thousand tonnes in 1988 (Anon., 1988a). The pattern of use in the USA in 1978 was as follows: metal treating and plating, 80%; wood treatment, 10%; chemical manufacturing, 5%; and other, 5% (Anon., 1978). The pattern of use in the USA in 1988 was: wood treatment, 63%; metal finishing, 22%; other (including water treatment, magnetic particles and catalysts), 7% (Anon., 1988a).

In Japan, the major use of chromium trioxide (90%) has been in chromium plating; 3% is used in pigments and 7% in other uses such as abrasives. The total used in Japan dropped from 11 800 tonnes in 1972 to 8300 tonnes in 1977 (IARC, 1980a).

Potassium chromate has limited applications in the textile industry — when a potassium rather than a sodium salt is essential or when differences in solubility or other physical properties make its use desirable (Howarth, 1956). Among these uses are as a mordant for wool, in dyeing nylon and wool with mordant acid dyes, in oxidizing vat dyes and indigosol dyes on wool, in dyeing with chromate colours, in treating direct dyes and some sulfur dyes on cotton to render them faster to washing, in oxidizing aniline black, and in stripping dyed wool (IARC, 1980a).

Potassium dichromate was once the most important commercial chromium compound, but it has largely been replaced in many applications by sodium dichromate. It is used in many small-volume applications such as photomechanical processing, chrome-pigment production and wool preservative formulations. The major use for potassium dichromate in Japan has been pigment production (54%); dye manufacture consumes an estimated 22%, with the remaining 24% used as an oxi-

dizing agent in miscellaneous uses (as a catalyst and in other applications) (IARC, 1980a).

Sodium chromate is used in inks, leather tanning, wood preservation, corrosion inhibition, as a pigment in paint, water treatment, drilling muds, textile dyeing, cutting oils, catalysts, and as a raw material for the production of other chromium compounds (Sax & Lewis, 1987; American Chrome & Chemicals, undated h,i). In Japan, its principal use is as a mordant in dyeing operations (IARC, 1980a).

Sodium dichromate is the primary base material for the manufacture of chromium chemicals, which are used in leather tanning, metal treatment, drilling muds, textile dyes, catalysts, and wood and water treatment (Papp, 1983).

Demand for sodium dichromate in the USA was 146 thousand tonnes in 1978 (Anon., 1979) and 149 thousand tonnes in 1988 (Anon., 1988b). The pattern of use in 1978 was as follows: manufacture of chromium trioxide, 28%; manufacture of pigments, 24%; manufacture of leather tanning chemicals, 17%; corrosion control, 7%; metal treatment, drilling muds and textiles, 8%; and other (including chemical manufacture, catalysts, and wood preservation), 8% (Anon., 1979). The pattern of use in the USA in 1988 was as follows: manufacture of chromium trioxide, 54%; leather tanning, 9%; manufacture of chromium oxide, 9%; manufacture of pigments, 8%; wood preservation, 5%; and other (including drilling muds, catalysts, water treatment and metal finishing), 5% (Anon., 1988b).

Barium chromate is used in pyrotechnics, in high-temperature batteries, in safety matches, as a corrosion inhibitor in metal-joining compounds, as a pigment in paints, in ceramics, in fuses, in metal primers, and in ignition control devices (Hartford, 1979; Sax & Lewis, 1987). In Japan, the principal use was reported to be in explosive fuses (IARC, 1980a).

Chrome orange pigments, consisting largely of basic lead chromate, have been widely used in paints, metal protective primers and linoleum (Chalupski, 1956). In the early 1970s, use of chrome oranges in the USA was decreasing, although they were still being used in tints and rust-inhibiting paints (Schiek, 1973).

Lead chromate is used to make pigments for paints to be applied to both wood and metal. Chrome yellows (containing 52-98% lead chromate) are considered to be the most versatile of the inorganic pigments and are therefore found in many formulations designed for a wide spectrum of uses. The largest use of chrome yellows in the early 1970s was in paint for automotive finishes, farm machinery, architectural and air-dried finishes, and water-thinned coatings for exterior and interior use. Medium chrome yellow paints make up about 30% of the paint used for traffic control. Chrome yellows are also used as colourants in vinyls, rubber and paper. The second largest use of chrome yellows is in printing inks (Schiek, 1973).

The major use for lead chromate in Japan is in the production of pigments for paint and inks (85%); other uses are as a colourant for synthetic resins (14%) and miscellaneous applications (1%) (IARC, 1980a).

Molybdenum orange pigments are used in coatings, inks and plastics (National Chemical Company, undated e).

Strontium chromate was first used commercially (near the end of the nineteenth century) as a colourant in artists' paints, under the name 'citron yellow'. It was replaced for this use by organic pigments in 1936, at which time it was also being used for corrosion resistance on aluminium and magnesium alloys. Later, it was used in chemical-resistant coatings because of its low reactivity, and in epoxy polyamide vehicles and vinyl sheeting because of its heat-resistant properties. In 1973, some strontium chromate was still being used in vinyl sheeting and chemical-resistant coatings and in primer coatings for water tanks, but most of it was used, either alone or in combination with basic zinc chromate, in wash primers or in aluminium flake coatings (Lalor, 1973). Strontium chromate has also been used as an additive to control the sulfate content of solutions in electrochemical processes (Hartford & Copson, 1964). In Japan, the only known use has been as a corrosion inhibitor (IARC, 1980a).

Zinc chromates are used as pigments in paints, varnishes and oil colours. Many of them are used as a corrosion-resisting primer coatings and in metal conditioners (wash primers) applied before priming; in this case, they are used more for their chemical characteristics than their hue (Lalor, 1973; Windholz, 1983).

(*e*) *Other chromium compounds*

Chromium carbonyl has reportedly been used as an isomerization and polymerization catalyst, as a gasoline additive, and as a chemical intermediate (Sax & Lewis, 1987). It has also been used in the synthesis of 'sandwich' compounds (Hartford, 1979) from aromatic hydrocarbons, such as dibenzene(chromium) from benzene. Some of these compounds have been investigated as possible sources of vapour-deposited chromium and for the production of carbides.

2.3 Occurrence

The occurrence and distribution of chromium in the environment has been reviewed (Sayato & Nakamuro, 1980; Sequi, 1980; Balsberg-Påhlsson *et al.*, 1982; Cary, 1982; Filiberti *et al.*, 1983; Fishbein, 1984; Gauglhofer, 1984; Jin & Hou, 1984; Barceló *et al.*, 1986; Poschenrieder *et al.*, 1986; Camusso & Montesissa, 1988; Nriagu & Nieboer, 1988).

(*a*) *Natural occurrence*

Chromium is widely distributed in the earth's crust but is concentrated in the ultrabasic rocks. At an overall crust concentration of 125 mg/kg Cr (National Re-

search Council, 1974), it is the twentieth most abundant element, ranking with vanadium, zinc, nickel, copper and tungsten (Westbrook, 1979). Only the trivalent and hexavalent compounds are detected in the environment in significant quantities (Fishbein, 1976). In reducing environments, chromium[VI] is unstable relative to chromium[III]. The average concentration of chromium in basalt, shale and granite has been reported to be 200, 100 and 20 ppm (mg/kg), respectively. The world average concentration of chromium in ultramafic, mafic, intermediate and felsic rock has been reported to be 2000, 200, 50 and 25 ppm (mg/kg), respectively. Concentrations in rock samples from Hawaiian lavas, from the Skaergaard intrusion in Greenland and from tertiary lavas of northeastern Ireland ranged from less than 1 ppm to 1750 ppm (mg/kg) chromium (Cary, 1982).

Chromium is found in nature only in the combined state and not as the free metal. It exists mainly as chromite, which has the idealized composition $FeO.Cr_2O_3$, although this composition has been found in nature only in meteorites. Chromite is a mixed metal oxide spinel containing iron, chromium, magnesium and aluminium in various proportions (Hartford, 1963) and as such is found in considerable quantities in Zimbabwe, the USSR, South Africa, New Caledonia and the Philippines (National Research Council, 1974; World Health Organization, 1988); it contains 40-50% chromium (Bidstrup & Case, 1956).

Of the chromium chemicals (other than chromite ore) included in this monograph, only two are known to occur in nature in mineral form: lead chromate as crocoite and potassium dichromate as lopezite (Hartford, 1963).

(*b*) *Occupational exposures*

Occupational exposures to a number of specific chromium compounds have been reported. With respect to hexavalent compounds, the most important exposures are to sodium, potassium, calcium and ammonium chromates and dichromates during chromate production, to chromium trioxide during chrome plating, to insoluble chromates of zinc and lead during pigment production and spray painting, to water-soluble alkaline chromates during steel smelting and welding and to other chromates during cement production and use. Trivalent compounds that are common in work place air include chromite ore during chromate production and in the ferrochromium industry, chromic oxide during pigment production and use, and chromic sulfate during leather tanning. In addition, occupational exposures to airborne dusts containing chromium metal may occur during production, welding, cutting and grinding of chromium alloys (Stern, 1982; Nieboer *et al.*, 1984; World Health Organization, 1988; see the monograph on welding, pp. 463-474). A schematic diagram of the production processes for some important commercial chromium compounds was given in Figure 1, on which those operations for which exposure data are available are indicated.

Potential occupational exposure to chromium occurs through inhalation, ingestion or skin contact (National Research Council, 1974). The US National Institute for Occupational Safety and Health (1977) estimated that about two million workers are exposed to chromium and chromium compounds. Chromium ulcers or chromate dermatitis, which are indicative of occupational exposure, have been reported in numerous occupations, involving manual handling of cement, leather, plastics, dyes, textiles, paints, printing inks, cutting oils, photographic materials, detergents, wood preservatives, anticorrosion agents and welding rods (Pedersen, 1982; Burrows, 1983; Polak, 1983; Nieboer *et al.*, 1984; Table 10; see also section 3.3(*b*), p. 182).

Table 10. Occupations with potential exposure to chromium[a]

Abrasives manufacturers	Jewellers
Acetylene purifiers	Laboratory workers
Adhesives workers	Leather finishers
Aircraft sprayers	Linoleum workers
Alizarin manufacturers	Lithographers
Alloy manufacturers	Magnesium treaters
Aluminium anodizers	Match manufacturers
Anodizers	Metal cleaners
Battery manufacturers	Metal workers
Biologists	Milk preservers
Blueprint manufacturers	Oil drillers
Boiler scalers	Oil purifiers
Candle manufacturers	Painters
Cement workers	Palm-oil bleachers
Ceramic workers	Paper waterproofers
Chemical workers	Pencil manufacturers
Chromate workers	Perfume manufacturers
Chromium-alloy workers	Photoengravers
Chromium-alum workers	Photographers
Chromium platers	Platinum polishers
Copper etchers	Porcelain decorators
Copper-plate strippers	Pottery frosters
Corrosion-inhibitor workers	Pottery glazers
Crayon manufacturers	Printers
Diesel locomotive repairmen	Railroad engineers
Drug manufacturers	Refractory-brick manufacturers
Dye manufacturers	Rubber manufacturers
Dyers	Shingle manufacturers
Electroplaters	Silk-screen manufacturers
Enamel workers	Smokeless-powder manufacturers
Explosives manufacturers	Soap manufacturers

Table 10 (contd)

Fat purifiers	Sponge bleachers
Fireworks manufacturers	Steel workers
Flypaper manufacturers	Tanners
Furniture polishers	Textile workers
Fur processors	Wallpaper printers
Glass-fibre manufacturers	Wax workers
Glass frosters	Welders
Glass manufacturers	Wood-preservative workers
Glue manufacturers	Wood stainers
Histology technicians	

[a]From National Research Council (1974)

This section summarizes data on exposure to chromium in air and the results of biological monitoring in various industries and occupations. The biological indicator levels are influenced by the solubility of chromium compounds and by the time of sampling. It should be noted that the chromium compounds, the timing of collection of biological samples (normally at the end of a shift) and the analytical methods used differ from study to study, and elevated levels of chromium in biological fluids and tissue samples are mentioned only as indications of uptake of chromium. (See also section 3.3(*b*) and the monographs on nickel and nickel compounds, and on welding.)

(i) *Ferrochromium steel and high chromium alloy production*

During the electrothermal reduction of chromite ore with coke for the production of ferrochromium, workers in the area near the furnaces are exposed to fumes containing 0.1-10% chromium (Stern, 1982).

In 1959, an industrial hygiene survey was carried out in a US plant producing ferrochromium, ferrosilicon and chromium alloys in electric furnaces. The mean concentrations of chromium trioxide [values for chromium calculated by the Working Group in square brackets] in the air were 1 [<1] μg/m³ in the maintenance shop, 266 [140] μg/m³ in the charging area, 317 [160] μg/m³ in the casting area and 2470 [1300] μg/m³ in the finishing area. The overall mean of 127 samples was 452 μg/m³ chromium trioxide [230 μg/m³ chromium] (Princi *et al.*, 1962).

In 1973, workplace concentrations of hexavalent chromium were reported to be 30-60 μg/m³ during the production of ferrochromium in the USSR (World Health Organization, 1988).

Concentrations of total dust and chromium in 1975 in a Norwegian ferrochromium plant are shown in Table 11. In various occupations, the mean level of total

Table 11. Air concentrations of total dust and chromium in a Norwegian ferrochromium plant[a]

Occupation or area	No. of samples	Mean and range of dust concentration (mg/m^3)	Mean and range of chromium concentration ($\mu g/m^3$)
Potmen	20	6.3 (4.0-15.7)	40 (20-70)
Cleaner-balers	5	18.2 (10.5-23.9)	90 (50-130)
Crane drivers	10	4.6 (3.1-7.6)	40 (10-50)
Packers	10	4.9 (2.3-8.3)	290 (50-1300)
Maintenance workers	9	15.6 (4.0-46.0)	90 (20-370)
Transport workers	9	12.8 (5.6-30.1)	10 (10-30)
Charge floor	5	4.8 (2.8-8.4)	50 (30-70)
Top electrode	3	15.5 (13.9-17.8)	170 (150-190)
Packing area	18	1.9 (0.3-5.5)	190 (10-1340)

[a]From Langård *et al.* (1980)

chromium was 10-290 $\mu g/m^3$, about 11-13% of which was water-soluble (Langård *et al.*, 1980).

Among Swedish ferrochromium workers, exposure to hexavalent chromium was estimated at 250 $\mu g/m^3$ during arc-furnace operations and 10-50 $\mu g/m^3$ during transport, metal grinding, maintenance and sample preparation. The total concentration of metallic and trivalent chromium at the work sites was 500-2500 $\mu g/m^3$ (Axelsson *et al.*, 1980).

In an Italian ferrochromium plant, dust samples contained 0.9-3.8% chromium, and airborne levels of total chromium were 20-158 $\mu g/m^3$. The concentration of hexavalent chromium was below 1 $\mu g/m^3$. Levels of urinary chromium measured at the beginning and end of a work shift were low (less than 5 $\mu g/g$ creatinine), although the results indicated absorption of chromium in some groups of workers (Foa *et al.*, 1988).

In ten steel, 15 iron and 11 copper alloy foundries in Finland in 1973 and 1974, furnacemen and casters were exposed to a mean level of 1-6 $\mu g/m^3$ acid-soluble chromium (Tossavainen, 1976).

During the production of chromium carbide powder in the USSR, dust concentrations were 11-20 mg/m^3 during weighing of chromium[III] oxide, 260-640 mg/m^3 during milling and 24-200 mg/m^3 during loading, screening and packing of the product (Brakhnova, 1975). In open-hearth steel works, concentrations of chromium trioxide in work place air were 13-37 $\mu g/m^3$ [7-20 $\mu g/m^3$ chromium] (Belitskaya, 1981).

In Sweden, the tissue concentrations of chromium in the lungs of 20 deceased smelter workers were three to four times higher than those of eight control subjects (median level, 0.29 and 0.08 μg/g wet tissue, respectively) (Brune *et al.*, 1980).

In Finland, fumes and dusts contained 6-15% chromium during ferrochromium smelting, 1.5-5% during stainless-steel smelting, 0.2-0.3% during continuous casting and 1.6-13% during grinding of stainless steel (Koponen *et al.*, 1981). Air concentrations of total chromium were 200 μg/m³ during ferrochrome smelting and 10 μg/m³ during continuous casting of stainless steel. The mean concentration of hexavalent chromium during the production of stainless steel was 1.5 μg/m³ (Koponen, 1985).

In France, air concentrations of total chromium ranged from 15 to 300 μg/m³ in a steel production plant (Klein, 1985).

Triebig *et al.* (1987) measured the exposure of 230 workers in high-alloy steel plants to chromium in the Federal Republic of Germany. Levels of chromium trioxide [chromium] in the air were 10-2280 [5-1200] μg/m³. Urinary levels of chromium were 0.1-79 μg/g creatinine, indicating some exposure to metal fumes and dusts in steel smelting, cutting and grinding.

(ii) *Production of chromates and of chromate pigments*

Airborne concentrations of chromates [chromium] in four US chromate plants over the period 1941-47 were 10-4600 [5-2300 μg/m³] at kilns and mills, 40-340 [20-170] μg/m³ at dryers, 200-21 000 [100-11 000] μg/m³ in packing areas and 3-2170 [2-1100] μg/m³ in other parts of the factories (Machle & Gregorius, 1948). Workplace air concentrations of chromium[III], chromium[VI] and total chromium during various operations in chromite ore processing were reported for a plant in Ohio (USA) which produced sodium dichromate (Bourne & Yee, 1950) and for a chromate production plant in the UK (Buckell & Harvey, 1951; see Table 12).

Table 12. Air concentrations of chromium[III] and chromium[VI] in US[a] and UK[b] chromate factories

Operation	Chromium[III] (mg/m³)		Chromium[VI] (mg/m³)	
	USA	UK	USA	UK
Chromite and lime mixing	1.52	2.14	0.03	0.005
Roasting	0.39	0.17	0.26	0.029
Filtering	0.12	0.037	0.08	0.52
Shipping	0.30	0.005	0.2	0.88

[a]From Bourne & Yee (1950)
[b]From Buckell & Harvey (1951)

In a chromate production plant in the USA, the levels of water-soluble hexavalent chromium were 100-900 μg/m³ in 1945-49 and 5-100 μg/m³ in 1950-59 (Braver *et al.*, 1985). In 1953, the US Public Health Service studied the health hazards associated with the chromate-producing industry. Six plants were directly involved in the production of alkaline chromates and dichromates from chromite ore. One of the plants also manufactured chromium pigments. In about 1600 air samples, the weighted average exposures by occupational groups were 7-890 μg/m³ insoluble chromium as chromite, 5-170 μg/m³ water-soluble chromium[VI] and 10-470 μg/m³ acid-soluble, water-insoluble chromium (Gafafer, 1953).

Concentrations of soluble and acid-insoluble chromium in lung tissues of 16 chromate manufacturing workers in the USA ranged from 3 to 161 μg/g dry tissue and 5 to 402 μg/g dry tissue, respectively; the workers had been exposed to chromite ore, sodium chromate, potassium dichromate and various intermediate chromium compounds for 1.5-42 years (Baetjer *et al.*, 1959a).

In Italy, chromic acid and alkaline chromate production workers were exposed to mean levels of 110-150 μg/m³ chromates [60-80 μg/m³ hexavalent chromium] (Vigliani & Zurlo, 1955). More recently, dust exposures and urinary excretion of chromium were studied in another Italian factory that produces potassium dichromate and chromic sulfate. A group of 22 potassium dichromate workers was exposed to levels of 10-100 μg/m³ chromium[III] and 8-212 μg/m³ water-soluble chromium[VI] (Mutti *et al.*, 1984), and their mean urinary concentration of total chromium was 31.5 μg/l (Cavalleri & Minoia, 1985). A group of 15 chromic sulphate workers were exposed to levels of 46-1689 μg/m3 chromium[III] and 2-23 μg/m³ chromium[VI] (Mutti *et al.*, 1984); their urinary chromium concentrations averaged 24.7 μg/l. Chromium levels in serum and erythrocytes were also increased among exposed workers (Cavalleri & Minoia, 1985).

In Japan, air concentrations of total chromium during sodium and potassium dichromate and chromium trioxide production in one plant ranged from 19 to 219 μg/m³; in 1960, levels of chromium trioxide [chromium] were 390-20 170 [180-10 000] μg/m³ in this factory, where enclosures and local exhausts were not properly used. Chromium content was measured in several organs of six chromate workers who had been exposed for over ten years and had died of lung cancer; the chromium concentration in the lungs averaged 51.1 μg/g wet weight, while in unexposed controls it averaged 0.31 μg/g wet weight (Kishi *et al.*, 1987). In six Japanese studies, the chromium contents of the lungs of chromate workers were 0.5-132 μg/g wet weight and 14-2368 μg/g dry weight, as compared to 0.05-3.72 μg/g wet weight and 0.47-5.14 μg/g dry weight in men without occupational exposure (Adachi, 1987). High concentrations of chromium were found in the respiratory organs of chromate workers who had died of cancer, and in the spleen, liver, kidney, brain, heart, bone marrow

and skin (Hyodo *et al.*, 1980; Teraoka, 1987). In 1957, chromium trioxide [chromium] concentrations in the plant ranged from 40-8430 [20 to 4300] μg/m³, with a mean of 520 [260] μg/m³ (Hyodo *et al.*, 1980).

Chromate pigment workers are exposed primarily to zinc and lead chromates although they may also be exposed to other compounds, such as chromium trioxide, sodium chromate and dichromate and zinc oxide (Davies, 1984a).

In three Norwegian pigment plants producing zinc and lead chromates, workers mixing raw materials and filling sacks were exposed to mean concentrations of 1.2-9.8 mg/m³ total dust and 10-1350 μg/m³ chromium. The chromium levels to which foremen are exposed were taken as a measure of general exposure in the plants; in one plant it was 40 μg/m³, in another it was 190 μg/m³ (Langård & Norseth, 1975).

In India, the concentration of chromium in the urine of workers exposed to chromates in two paint manufacturing factories was about ten fold that of unexposed persons (Tandon *et al.*, 1977).

In almost all positions at a US chromate pigment plant, production workers were exposed to hexavalent chromium in the form of zinc and lead chromates. Concentrations of airborne chromium were estimated to be more than 2 mg/m³ for highly exposed workers, between 0.5 and 2 mg/m³ for moderately exposed workers and less than 0.1 mg/m³ for the low-exposure category (Sheffet *et al.*, 1982).

(iii) *Leather tanning* (see also IARC, 1981)

The most common tanning process involves the use of basic chromic sulfate liquor. Tanning is accomplished in large vats where the hides are soaked with dehairing, neutralizing, pickling, colouring and finishing chemicals. In the two-bath method, the hides are first immersed in a bath of hexavalent chromium salts (potassium or sodium dichromate), sodium chloride and sulfuric acid, and then removed and placed in a reduction bath to reduce the dichromate to trivalent chromic sulfate. An exothermic reaction takes place with a reduction agent such as sugar, starch or sulfur dioxide. The majority of tanneries do not produce their own tanning liquors, and a large number of proprietary products are available for direct use. Occupational exposure to chromium in the tanning industry may occur through contact with the trivalent chromium solutions. Wet, freshly tanned skins contain 1-2% chromium by weight, and dry leather powder contains 2-6% depending on the method and degree of tanning (Stern, 1982; Stern *et al.*, 1987).

Airborne levels of 20-50 μg/m³ trivalent chromium were measured in 1975 in an Italian tannery when tanning baths were emptied (IARC, 1980a).

Air concentrations of trivalent chromium in a Finnish tannery were 1-29 μg/m³ (personal samples). Two press operators were exposed to a mean level of 13 μg/m³, and their urinary chromium excretion varied during one working week from 5 to 62

μg/l. A diurnal variation was evident, with the highest values occurring in post-shift samples. Blood samples contained 10-22 μg/l chromium in the plasma and 4.7-11 μg/l in whole blood; plasma levels were < 1 μg/l in workers who were less exposed to tanning liquors. During press operations, splashes are common, and absorption from the gastrointestinal tract was suggested to be the main route of exposure (Aitio *et al.*, 1984).

Urine samples were collected from 34 male tannery workers in Turkey. The mean urinary concentration of chromium was 6.6 μg/l (5.6 μg/g creatinine) in tannery workers, 2.3 μg/l (1.9 μg/g creatinine) in office and kitchen workers at the same factory and 0.22 μg/l (0.26 μg/g creatinine) in unexposed controls (Saner *et al.*, 1984).

In two leather tanning facilities in the USA, the total concentration of chromium in work place air was 0.2-54 μg/m^3, with a mean of 39 μg/m^3 (Stern *et al.*, 1987).

(iv) *Chromium plating*

There are two types of chromium electroplating: decorative ('bright') and hard chromium plating. In decorative plating, a thin (0.5-1 μm) layer of chromium is deposited over nickel or nickel-type coatings to provide protective, durable, non-tarnishable surface finishes. Hard chromium plating produces a thicker (5-10 μm) coating, usually directly on the base metal, to increase its heat, wear and corrosion resistance. Plating baths contain chromium trioxide (250-350 g/l) and sulfuric acid (2.5-3.5 g/l) or a mixture of sulfuric acid and fluoride or fluorosilicate, as well as various organic additives. Electrolysis emits bubbles of oxygen and hydrogen that generate chromium trioxide mist by bursting at the liquid surface. Surfactants and floating balls may be used to control the mist emission (Guillemin & Berode, 1978; Stern, 1982; Sheehy *et al.*, 1984). Exposure to substances other than chromium occurs in a number of pretreatment and finishing operations: acid and alkali mists, nitrogen oxides, cyanide and solvents may be released during pickling, acid dipping, stripping and degreasing processes, and metal and abrasive dusts are released from grinding and polishing. In some plants, decorative-chrome platers also perform nickel plating (Sheehy *et al.*, 1984).

Air measurements made in metal plating plants since 1928 are summarized in Table 13. It is apparent that exposures to chromium have been markedly reduced with modern technology. In most studies, the levels were measured as total water-soluble chromium or hexavalent chromium and reported as a chromium trioxide concentration.

Table 13. Workplace levels of hexavalent chromium during metal plating

Reference and country	Process and sampling data	Chromium oxide (chromium VI) concentration ($\mu g/m^3$)
Bloomfield & Blum (1928) USA	Chromium plating 6 plants, 19 samples	120-6900 [60-3800]
Riley & Goldman (1937) USA	Chromium plating	
	with no local exhaust	2780-3680 [1440-1910]
	with low local exhaust	11 200 [580]
	with high local exhaust	340 [180]
Gresh (1944) USA	Chromium plating 7 samples	90-1200 [45-600]
Molos (1947) USA	Chromium plating	
	with local exhaust	4500-5000 [2300-2500]
	with plastic beads on the bath	1900-3000 [950-1500]
	with plastic beads and local exhaust	20-50 [10-25]
Sheehy *et al.* (1984) USA	Chromium plating	
	with no local exhaust	[140-2960]
	with local exhaust	[0.5-270]
	with local exhaust and plastic beads on the bath	[0.5-5]
Lumio (1953) Finland	Chromium plating 16 plants	< 3 [< 1.5]
Hama *et al.* (1954) USA	Decorative chromium plating 4 plants	2-60 [1-30]
Kleinfeld & Rosso (1965) USA	Decorative chromium plating	
	with no local exhaust	180-1400 [90-730]
	with local exhaust	2-9 [2-5]
Hanslian *et al.* (1967) Czechoslovakia	Chromium plating 8 plants	23-681 [12-330]
Mitchell (1969) UK	Chromium plating (stripping)	
	with no local exhaust	240-21 300 [120-10 600]
	with local exhaust	10-30 [5-15]
Gomes (1972) Brazil	Chromium plating	
	8 hard chromium plants	< 100-1400 [< 50-700]
	63 decorative chromium plants	< 100-700 [< 50-350]

Table 13 (contd)

Reference and country	Process and sampling data	Chromium oxide (chromium VI) concentration ($\mu g/m^3$)
National Institute for Occupational Safety and Health (1973-81) (reviewed by Sheehy *et al.*, 1984) USA	Hard chromium plating	
	plant 1	[1.1-48.6]
	plant 2	[0.8-9.6]
	plant 3	[3.6-66.0]
	plant 4	[3-6]
	Decorative chromium plating	
	plant 5	[< 0.5-3]
	plant 6	[0.2-5.9]
	plant 7	[0.2-9.0]
	plant 8	[< 3]
	Nickel-chromium plating	
	plant 9	[2.9]
	Zinc plating	
	plant 10	[< 1.2-3.6]
	plant 11	[0.3]
Royle (1975a) UK	Chromium plating	
	40 plants	< 30 [< 15]
	2 plants	> 30 [> 15]
Yunusova & Pavlovskaya (1975) [quoted by the World Health Organization, 1988] USSR	Chromium plating	
	8 plants	[40-400]
Michel-Briand & Simonin (1977) France	Chromium plating	5-15 [2.5-7.5]
Guillemin & Berode (1978) Switzerland	Hard chromium plating	
	6 plants, 23 samples	2-655 [1-330]
	Bright chromium plating	
	6 plants, 11 samples	2-26 [1-13]
Ekholm *et al.* (1983) Sweden	Hard chromium plating	
	4 plants	< 1-46
	Decorative chromium plating	
	9 plants	< 1-2
Mutti *et al.* (1984) Italy	Chromium plating	
	24 hard chromium platers	[4-146]
	16 bright chromium platers	[0-31]

Table 13 (contd)

Reference and country	Process and sampling data	Chromium oxide (chromium VI) concentration ($\mu g/m^3$)
Sheehy *et al.* (1984) USA	Chromium, nickel, zinc, copper, cadmium and silver plating, 8 plants	
	53 personal samples	[< 1-14]
	293 tank area samples	[< 1-11 000]
	39 general area samples	[< 1-31]
Sorahan *et al.* (1987) UK	Decorative chromium plating	
	60 samples before 1973	0-8000 [0-4000]
	numerous samples after 1973	< 50 [< 25]

Typical levels of chromium in post-shift urine samples from electroplaters are given in Table 14. In one study of 21 electroplaters, chromium levels in serum were 0.2-1.3 µg/l (Verschoor *et al.*, 1988). High concentrations of chromium were found in the respiratory organs of two chromium platers as well as in the spleen, liver, kidney and heart (Teraoka, 1987).

Table 14. Urinary concentrations of chromium in electroplaters

Reference and country	Type of workers (no.)	Mean and range of chromium concentrations in urine (µg/l or µg/g creatinine)
Franzen *et al.* (1970) Federal Republic of Germany	Chromium platers (133)	< 4-32 µg/l
Schaller *et al.* (1972) Federal Republic of Germany	Chromium platers (12)	9.7 (1.4-24.6) µg/l
Guillemin & Berode (1978) Switzerland	Hard chromium platers[a] (21)	23 µg/l (18 µg/g)
	Bright chromium platers[a] (16)	5.6 µg/l (5.3 µg/g)
Sarto *et al.* (1982) Italy	Bright chromium platers (17)	6.1 µg/g
	Hard chromium platers (21)	10.0 µg/g
Lindberg & Vesterberg (1983) Sweden	Chromium platers (90)	[< 0.3-98 µg/l] Calculated by the Working Group from plots

Table 14 (contd)

Reference and country	Type of workers (no.)	Mean and range of chromium concentrations in urine (μg/l or μg/g creatinine)
Mutti *et al.* (1984) Italy	Hard chromium platers[a] (24)	15.3 μg/g
	Bright chromium platers[a] (16)	5.8 μg/g
Verschoor *et al.* (1988) Netherlands	Chromium platers (21)	9 (1-34) μg/g
Nagaya *et al.* (1989) Japan	Chromium platers (44)	0.25 (0.05-1.54 μmol/l) [13 (3-80) μg/l]

[a]Corresponding air concentrations can be found in Table 13.

(v) *Welding*

Welding produces particulate fumes that have a chemical composition reflecting the elemental content of the consumable used. For each couple of process/material of application, there is a wide range of concentrations of the elements present in the fume. Chromium and nickel are found in significant concentrations in fumes from welding by manual metal arc, metal inert gas and tungsten inert gas processes on stainless and alloy steels. Typical ranges of total fume, total chromium and hexavalent chromium found in the breathing zone of welders are presented in Table 15. Certain special process applications not listed can also produce high chromium and nickel concentrations, and welding in confined spaces produces significantly higher concentrations of total fume and elemental constituents. Exposure to welding fumes that contain nickel and chromium can lead to elevated levels of these elements in tissues, blood and urine (see monograph on welding for details).

(vi) *Other occupations*

During the production of trivalent chromium compounds (chromic oxide and chromic sulfate) in the Federal Republic of Germany, work place air contained 180-13 200 μg/m^3 chromic oxide and 850-2700 μg/m^3 chromic sulfate during filtering, drying and unloading operations (Korallus *et al.*, 1974a).

Exposures of spray painters to solvents and paint mists have been measured in a variety of industries by the US National Institute for Occupational Safety and Health. Air concentrations of total chromium in breathing zone samples were 1600 μg/m^3 during aircraft painting, 220 μg/m^3 during railroad car painting and 5-9 μg/m^3 during metal furniture painting (O'Brien & Hurley, 1981). At a US plant manu-

Table 15. Total fume and chromium concentrations found in the breathing zone of welders[a]

Process[b]	Total fume[c] (mg/m³)	Total Cr (μg/m³)	Cr(VI) (μg/m³)
MMA/SS	2-40	30-1600	25-1500[d]
MIG/SS	2-3	60	< 1
TIG/SS	1-3	10-55	< 1

[a]From van der Wal (1985)

[b]MMA, manual metal arc; SS, stainless steel; MIG, metal inert gas; TIG, tungsten inert gas

[c]50%-90% range

[d]50%-90% Cr(VI) from MMA/SS is soluble in water (Stern, 1982).

facturing truck bodies and refuse handling equipment, breathing zone concentrations of paint mists ranged from 4.8 to 47 mg/m³ total dust and 10 to 400 μg/m³ chromium (Vandervort & Cromer, 1975). Personal air samples had concentrations of hexavalent chromium ranging from 30 to 450 μg/m³ with a mean of 230 μg/m³ during spray painting of buses (Zey & Aw, 1984), 13 to 2900 μg/m³ with a mean of 607 μg/m³ during spray painting of aircraft wheels (Kominsky *et al.*, 1978) and 10 to 40 μg/m³ with a mean of 20 μg/m³ during spray painting of bridge girders (Rosensteel, 1974).

Breathing zone samples were also taken in a small automotive body repair workshop in the USA. One of the eight samples contained 490 μg/m³ chromium; the others were below the detection limit (Jayjock & Levin, 1984).

In a Swedish study, mean chromium levels of 1300 μg/m³ were measured during car painting and 500 μg/m³ during industrial painting, while work place levels averaged 300 μg/m³ during grinding activities (Elofsson *et al.*, 1980). Low overall levels were found for spray painters working in a fireplace manufacturing plant; the concentrations of total dust and chromium oxide [unspecified] were 1700 and 5-8 μg/m³ [chromium, 3-4 μg/m³], respectively (Hellquist *et al.*, 1983).

In Italy, 12 spray painters using lead and zinc chromate paints were exposed to levels of 450-1450 μg/m³ insoluble hexavalent chromium, and their mean urinary excretion was 13.2 μg/g creatinine at the end of a work shift (Mutti *et al.*, 1984).

At the largest wood treatment plant in Hawaii, air concentrations of 2-9 μg/m³ chromium were measured. Urinary excretion of 89 workers using chromated copper arsenate wood preservatives did not differ from that of controls (Takahashi *et al.*, 1983).

In a cement-producing factory in the USSR, concentrations of hexavalent chromium in work place air varied from 5 to 8 μg/m³, measured as chromium trioxide (Retnev, 1960). Hexavalent chromium was found in 18 of 42 US cement samples at concentrations ranging from 0.1 to 5.4 μg/g, with a total chromium content of 5-124 μg/g (Perone *et al.*, 1974). Portland cement contains 41.2 ppm (mg/kg) chromium (range, 27.5-60), due to the presence of chromium in limestone. Soluble chromium in cement averaged 4.1 mg/kg (range, 1.6-8.8), of which 2.9 mg/kg (range, 0.03-7.8) was hexavalent chromium (Fishbein, 1976). Analysis of 59 samples of Portland cement from nine European countries showed concentrations of 1-83 μg/g hexavalent chromium and 35-173 μg/g total chromium (Fregert & Gruvberger, 1972). In France and Belgium, cements manufactured in 11 plants contained 8-49 μg/g total chromium, originating from limestone, clay, gypsum, fly ash and slag used in the manufacture as well as from the refractory kiln materials (Haguenoer *et al.*, 1982). Cement in Iceland contained 5.8-9.5 mg/kg hexavalent chromium (Rafnsson & Jóhannesdóttir, 1986).

In open-cast chromium mining in the USSR, concentrations of total airborne dust ranged from 1.3 to 16.9 mg/m³; in the crushing and sorting plant, dust levels were 6.1-188 mg/m³. The chromium content of settled dust varied from 3.6 to 48% (calculated as chromic oxide). No hexavalent chromium was found in the dust (Pokrovskaya *et al.*, 1976; World Health Organization, 1988).

During the manufacture of chromium[III] lignosulfonate in Finland, five packing workers were exposed to dust containing about 2% trivalent chromium. The product contained 6% trivalent chromium attached to wood lignin. In personal samples, the concentration of chromium in the air was 2-230 μg/m³, and three-day averages ranged from 11 to 80 μg/m³. Urinary levels in samples from workers were 0.01-0.59 μmol/l (0.5-30 μg/l), and mean excretion was 0.02-0.23 μmol/l (1-12 μg/l). It was concluded that chromium occurred exclusively in a trivalent state in both dust and urine (Kiilunen *et al.*, 1983).

(*c*) *Air*

Chromium is generally associated with particulates in ambient air at concentrations of 0.001-0.1 μg/m³ (Fishbein, 1976; O'Neill *et al.*, 1986). In the USA in 1966, only seven of 58 cities in the National Air Sampling Network had annual average chromium levels of 0.01 μg/m³ or more, and only 16 had maximal single values above that level. In approximately 200 urban stations in the USA during 1960-69, annual mean concentrations were 0.01-0.03 μg/m³ (minimal level detectable, 0.01 μg/m³). In nonurban areas, the level of chromium was less than 0.01 μg/m³. Levels of 0.9-21.5 μg/m³ were reported in 23 localities in northern England and Wales in 1956-58 (Fishbein, 1976). In 1957-74, the amount of chromium in the atmospheric

aerosol at a rural site in the UK declined at an average yearly rate of 11.3% (Salmon *et al.*, 1977).

During the period May 1972-April 1975, the range of average levels of chromium determined at 15 stations in Belgium was 0.01-0.04 μg/m³ (maximal value, 0.54 μg/m³). The values were stated to reflect background pollution and levels representative of those in air inhaled by the majority of the population. Sampling station locations were selected to avoid, as much as possible, a direct influence of local sources (Kretzschmar *et al.*, 1977).

Coal from many sources can contain as much chromium as soils and rocks, i.e., up to 54 ppm (mg/kg); consequently, the burning of coal can contribute to chromium levels in air, particularly in cities (Fishbein, 1976; Merian, 1984). Particulates emitted from coal-fired power plants contained 2.3-31 ppm (mg/kg) chromium, depending on the type of boiler firing; the emitted gases contained 0.22-2.2 mg/m³. These concentrations were reduced by fly ash collection to 0.19-6.6 ppm (mg/kg) and 0.018-0.5 mg/m³, respectively (Fishbein, 1976). Fly ash has been shown to contain 1.4-6.1 ppm (mg/kg) chromium[VI] (Stern *et al.*, 1984).

Mean concentrations in the air of US cities with metallurgical chromium or chromium chemical producers or with refractories were 0.012-0.016 μg/m³, all of which were higher than the US national average. Cement-producing plants are probably an additional source of chromium in the air. When chromate chemicals are used as rust inhibitors in cooling towers, they are dissolved in recirculating water systems, which continually discharge about 1% of their flow to waste. Additionally, chromate and water are lost to the atmosphere (Fishbein, 1976).

The concentration of chromium in the air at the South Pole was reported to be 0.005 ng/m³. Concentrations in samples taken over the Atlantic Ocean ranged from 0.007 to 1.1 ng/m³. Airborne chromium concentrations were reported to be 0.7 ng/m³ in the Shetland Islands and Norway, 0.6 in northwestern Canada, 1-140 in Europe, 1-300 in North America, 20-70 in Japan and 45-67 in Hawaii, USA (Cary, 1982).

(*d*) *Water*

Naturally occurring chromium concentrations in water arise from mineral weathering processes, soluble organic chromium, sediment load and precipitation (Cary, 1982).

Concentrations of chromium in rivers have been found to be 1-10 μg/l. Chromium (both hexavalent and trivalent) is generally found at lower concentrations in seawater (well below 1 μg/l) than in rivers and wells. It has been estimated that 6.7 million kg of chromium are added to the oceans every year. As a result, much of the chromium lost from the land by erosion and mining is eventually deposited on the ocean floor (Fishbein, 1976).

The mean chromium concentration in ocean water in 1979 was 0.3 μg/l, with a range of 0.2-50 μg/l. Samples taken from the first 100 m of water from several areas of the Pacific Ocean contained about 0.12 μg/l chromium, about 83% being hexavalent chromium; below 100 m, total chromium increased to about 0.16 μg/l, with hexavalent chromium accounting for 90%. In saline waters of Australia, 62-87% of the labile chromium present (< 1 μg/l) was hexavalent (Cary, 1982).

Of 1500 samples of US surface waters taken between 1960 and about 1968, 24.5% contained chromium detectable spectrographically; the maximal and mean levels observed were 112 and 9.7 μg/l, respectively (Kroner, 1973). A survey of chromium content of 15 North American rivers showed levels of 0.7-84 μg/l, with most in the range of 1-10 μg/l (Hartford, 1979). Levels in 3834 samples of tap water taken from 35 regions of the USA in 1974-75 ranged from 0.4 to 8 μg/l chromium, with the median 1.8 μg/l (US Environmental Protection Agency, 1984).

Of 170 samples taken from lakes in the higher Sierra Mountains of California, USA, in 1968, only two contained as much as 5 μg/l chromium. Chromium concentrations in 1977 in the Amazon (Brazil) and Yukon (USA) Rivers were 2.0 and 2.3 ppb (μg/l), respectively; the two rivers were considered to represent unpolluted systems draining watersheds of a wide variety of mineral types from extremely different climates. The concentration of chromium in 96% of the 4342 samples of stream- and river-water in Canada was less than 10 μg/l; about 2% of the samples contained 15-500 μg/l chromium (Cary, 1982).

The mean concentration of dissolved chromium compounds in the Rhine River during 1975 was 6.5 μg/l with a range of 3.7-11.4 μg/l; the concentration in drinking-water was 0.29 μg/l (Nissing, 1975). The concentration of chromium compounds in Austrian medicinal and table waters was determined as 1.2-4.2 μg/l (Sontag *et al.*, 1977). The average levels of chromium in three tributaries of the Han River in the Republic of Korea were found to be 96, 106 and 65 μg/l (Min, 1976).

Municipal sewage sludge can contain chromium at levels up to 30 000 mg per kg dry sludge (Pacyna & Nriagu, 1988).

Surface waters and groundwaters contaminated with wastewaters from electroplating operations, leather tanning and textile manufacturing, or through deposition of airborne chromium, may also be sources of chromium exposure. Other sources are solid wastes resulting from the roasting and leaching steps of chromate manufacture and improper disposal of municipal incineration wastes in landfill sites (Beszedits, 1988; Calder, 1988; Handa, 1988).

(e) *Soil and plants*

Chromium is present in the soil at levels which vary from traces to 250 mg/kg (as chromic[III] oxide) (Davis, 1956) and is particularly prevalent in soil derived from basalt or serpentine (US Environmental Protection Agency, 1984).

Virtually all plants contain detectable levels of chromium, taken up by the roots or through the leaves. Vegetables from 25 botanical families were found to contain chromium in amounts varying from 10-1000 μg/kg of dry matter, with most samples in the range of 100-500 μg/kg (Davis, 1956). Strong seasonal variations in chromium levels were found in three kinds of grass (World Health Organization, 1988).

The chromium content of mosses and liverworts collected in 1951 in a remote rural area in Denmark was compared with that in the same plants collected in 1975: an increase of about 62% was observed, which coincided with increases in industrial activity and fossil fuel combustion (Rasmussen, 1977).

The chromium content of cigarette tobacco from different sources has been reported as follows: Iraq, 8.6-14.6 mg/kg (two varieties); Iran, 4.3-6.2 mg/kg (two brands); and the USA, 0.24-6.3 mg/kg (Al Badri *et al.*, 1977).

(f) *Food*

The chromium content of most foods is extremely low; small amounts were found in vegetables (20-50 μg/kg), fruits (20 μg/kg) and grains and cereals (excluding fats, 40 μg/kg). The mean daily intakes of chromium from food, water and air have been estimated to be 280, 4 and 0.28 μg, respectively (Fishbein, 1976). Hartford (1979) indicated that nearly all foodstuffs contain chromium in the range of 20-590 μg/kg, resulting in a daily intake for humans of 10-400 μg, with an average of about 80 μg. In a more recent study, the mean daily intake of chromium for 22 healthy subjects was about 24.5 μg (Bunker *et al.*, 1984).

(g) *Animal tissues*

Table 16 summarizes data on chromium levels in tissues from various food and feral animals.

The report of the US National Status and Trends Program for Marine Environmental Quality, conducted by the National Oceanic and Atmospheric Administration (1987), gave concentrations of chromium at 0.1-11.0 μg/g (dry weight) in mussels and oysters collected in 1986 at East, West, and Gulf Coast sites, and 0.02-1.4 μg/g (dry weight) in livers of ten species of fish collected in 1984 throughout the USA.

Table 16. Chromium levels found in food and feral animals

Animal	Tissue	Range (mean) (μg/kg)	Comments	Reference
Largemouth bass	Muscle	1-2	Collected near Savannah River, SC, USA, nuclear plant	Koli & Whitmore (1983)
Bluegill		1		
Catfish		1		
Redbreast sunfish		1		
Crappie, American eel		2		
Spotted sunfish		1-2		
American shad	Gonad	ND-180	Collected in 1979, USA	Eisenberg & Topping (1986)
	Flesh	ND		
Finfish	Flesh	ND-1900	Collected in 1978-79	
Striped bass	Gonad	ND	Collected in 1978-79	
	Liver	ND	Collected in 1978-79	
	Flesh	ND	Collected in 1978-79	
Striped bass	Liver	2600-9800 (6000)	Collected from Chesapeake Bay, MD, USA	Heit (1979)
	Muscle	2700-9500 (5000)		
Cattle	Blood	(25/10)	Grazed on pasture treated/untreated with sludge (from Chicago, IL, USA)	Fitzgerald *et al.* (1985)
	Bone	(614/934)		
	Brain	(209/306)		
	Diaphragm	(206/215)		
	Heart	(172/434)		
	Kidney	(231/390)		
	Liver	(186/365)		
	Milk	(248/160)		
Cattle	Liver	200-3000		Stowe *et al.* (1985)
Cattle	Kidney	< 10-30	Collected from slaughter-houses in Queensland, Australia	Kramer *et al.* (1983)
	Liver	< 10-910 (10)		
	Muscle	< 10-100		
Cattle			Oklahoma, USA	Kerr & Edwards (1981)
	Blood	6-66 (22)	Unexposed animals	
		1080	Animal found dead near an oil-well drilling site	
	Kidney	500-6200 (2970)	Unexposed animals	
		15 800	Animal found dead near a recently completed oil well	

Table 16 (contd)

Animal	Tissue	Range (mean) (μg/kg)	Comments	Reference
Clam American oyster	Body	(2100-3800) (1300)	Collected from Lake Pontchartrain, LA, USA	Byrne & DeLeon (1986)
Pike-perch	Body	10-20 (10)	The Netherlands Hollands Diep	Vos *et al.* (1986)
Cod Baltic herring Sole Eel Pike-perch Blue mussel Shrimp		10-20 (10) 10-70 (20) 10-20 (20) 20-340 (80) 10-70 (20) 210-810 (430) 100-710 (260)	Collected near the coast Collected from Lake Ijssel Collected from Eastern Scheldt Collected from Western Wadden Sea	
Killifish Common tern	Body Liver	(3600-7600) ND-18 310	Collected near electroplating industry, RI, USA	Custer *et al.* (1986)
Cape oyster	Body	< 100-4600	Collected along the coast of South Africa	Watling & Watling (1982)
Sponge	Body	1 000 000-2 000 000 (1 520 000)	Collected near the Tarapur coast, India	Patel *et al.* (1985)
Snapping turtle	Kidney Liver	(930-1260) (100-1970)	Collected from uncontaminated areas of MD, USA	Albers *et al.* (1986)
	Kidney Liver	(1130-2970) (360-600)	Collected from contaminated areas of NJ, USA	
Crab Shrimp	Body	40-200 (120) 29-133 (59)	Collected in sewage outfall area of the Arabian Gulf, Saudi Arabia	Sadiq *et al.* (1982)
Pacific oyster	Body Gills Intestine Mantle Muscle	(93 000, 113 000) (40 000, 170 000) (42 000, 106 000) (47 000, 188 000) (35 000, 111 000)	Collected from two culture beds in Deep Bay, Hong Kong	Wong *et al.* (1981)

ND, none detected

(*h*) *Human tissues and secretions*

As with most metals that occur in trace quantities, the normal concentrations of chromium in human tissues are usually reported wrongly because of extraneous additions during sampling and analysis. However, recent developments in the analytical chemistry of chromium permit the reliable routine determination of nanogram quantities in biological samples (Nieboer & Jusys, 1988). Selected current reference values for chromium concentrations in a few biological materials are presented in Table 17.

Table 17. Chromium concentrations in specimens from non-occupationally exposed persons[a]

Sample	Median	Range
Serum	0.19 µg/l	0.12-2.1 µg/l
Blood	< 0.5 µg/l	-
Urine	0.4 µg/l	0.24-1.8 µg/l
Liver	[c]	8-72 ng/g wet weight
Lung[b]	204 ng/g wet weight	29-898 ng/g wet weight

[a]From Iyengar & Woittiez (1988), except when noted
[b]From Raithel *et al.* (1987)
[c]Too few measurements to determine median values

(*i*) *Regulatory status and guidelines*

The 1970 WHO European and 1978 Japanese standard for chromium[VI] in drinking-water (World Health Organization, 1970; Ministry of Health & Welfare, 1978) and the European standard for total chromium in surface water intended for the abstraction of drinking-water (Commission of the European Communities, 1975) are 0.05 mg/l. The US Environmental Protection Agency (1988) has established the same maximal contaminant level for chromium in drinking-water, as the maximal permissible level in water delivered to any user of a public water system.

The US Environmental Protection Agency (1979) also established pretreatment standards that limit the concentration of chromium that may be introduced into a publicly owned wastewater treatment facility by leather tanning and finishing plants. The maximal total chromium permitted in existing sources on any one day is 6 mg/l, and the average daily values for 30 consecutive days must not exceed 3 mg/l.

Table 18 gives occupational exposure limits for airborne chromium in various forms.

Table 18. Occupational exposure limits for airborne chromium in various forms[a]

Country or region	Year	Form of chromium	Concentration (mg/m^3)	Interpretation[b]
Austria	1987	Cr, soluble compounds (as Cr)	0.1	TWA
Belgium	1987	Cr, compounds (as Cr)	0.05	TWA
		Cr, soluble compounds (as Cr)	0.1	TWA
Brazil	1987	Cr, compounds (as Cr)	0.04	TWA
Bulgaria	1987	Cr, compounds (as Cr)	0.1	TWA
Chile	1987	Cr, compounds (as Cr)	0.04	TWA
China	1987	Cr, compounds (as CrO_3), chromium trioxide, chromates, dichromates (as CrO_3)	0.5	TWA
Czechoslovakia	1987	Cr, compounds (as Cr)	0.05	Average
		Cr, compounds (as Cr)	0.1	Maximum
Denmark	1988	Cr and inorganic Cr compounds, except those mentioned below	0.5	TWA
		Chromates, chromium trioxide (as Cr)	0.02	TWA
Egypt	1987	Cr, compounds (as Cr)	0.1	TWA
Finland	1987	Cr, Cr[II] and Cr[III] compounds (as Cr)	0.5	TWA
		Cr[VI] compounds (as Cr)	0.05	TWA
France	1986	Cr[VI] and derivatives	0.05	TWA
German Democratic Republic	1987	Cr, compounds, except those mentioned below	0.5	TWA
			1.0	STEL
		Chromium trioxide, chromates, dichromates (as CrO_3)	0.1	TWA
			0.1	STEL
Hungary	1987	Cr, compounds (as Cr)	0.05	TWA
			0.1	STEL
India	1987	Cr, compounds (as Cr)	0.05	TWA
		Cr, soluble compounds (as Cr)	0.5	TWA
Indonesia	1987	Cr, compounds (as Cr)	0.1	TWA
Italy	1987	Cr, compounds (as Cr)	0.05	TWA
		Cr, soluble compounds (as Cr)	0.5	TWA
Japan	1987	Cr, compounds (as Cr)	0.1	TWA
Korea, Republic of	1987	Cr, compounds (as Cr)	0.05	TWA
Mexico	1987	Chromite ore (as Cr)	0.05	TWA
		Cr, compounds (as Cr); insoluble, soluble Cr[II], Cr[III], Cr[VI] compounds (as Cr)	0.5	TWA

Table 18 (contd)

Country or region	Year	Form of chromium	Concentration (mg/m^3)	Interpretation[b]
Netherlands	1986	Cr, soluble compounds (as Cr)	0.5	TWA
		Chromyl chloride	0.15	TWA
		Cr, insoluble compounds; chromium trioxide (as Cr)	0.05	TWA
Norway	1981	Cr, Cr[II] and Cr[III] compounds (as Cr)	0.5	TWA
		Chromates, chromium trioxide (as Cr)	0.02	TWA
Sweden	1987	Cr and inorganic Cr compounds, except those mentioned below	0.5	TWA
		Chromates, chromium trioxide (as Cr)	0.02	TWA
Switzerland	1987	Cr, compounds (as Cr); Cr, soluble compounds (as Cr)	0.5	TWA
		Cr[II] and Cr[III] soluble compounds; chromium oxychloride dust (as Cr)	0.05	TWA
Taiwan	1987	Cr and compounds (as Cr)	0.1	TWA
UK	1987	Cr, Cr[II] and Cr[III] compounds (as Cr)	0.5	TWA
		Cr[VI] compounds (as Cr)	0.05	TWA
USA[c]				
ACGIH	1988	Zinc chromates (as Cr)	0.01	TWA
		Chromite ore (chromate) (as Cr); water-soluble and certain (confirmed human carcinogens) water-insoluble Cr[VI] compounds (as Cr); lead chromate (as Cr)	0.05	TWA
		Chromium metal, Cr[II] and Cr[III] compounds (as Cr)	0.5	TWA
NIOSH	1988	Carcinogenic Cr[VI]	0.001	TWA
		Other Cr[VI]; chromic acid	0.025	TWA
		(as noncarcinogenic Cr[VI])	0.05	Ceiling (15 min)
OSHA	1987	Soluble chromium, chromic and chromous salts	0.5	TWA
		Chromium metal and insoluble salts	1.0	TWA
USSR	1987	Cr and compounds (as Cr)	0.01	MAC
		Chromium phosphate uni-substituted (as Cr[III])	0.02	MAC

Table 18 (contd)

Country or region	Year	Form of chromium	Concentration (mg/m³)	Interpretation[b]
Yugoslavia	1987	Cr and compounds (as Cr)	0.1	TWA

[a]From Arbeidsinspectie (1986); Institut National de Recherche et de Sécurité (1986); Arbetarskyddsstyrelsens (1987); Cook (1987); Health and Safety Executive (1987); US Occupational Safety and Health Administration (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); National Institute for Occupational Safety and Health (1988)

[b]TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

[c]ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration

2.4 Analysis

Numerous analytical methods have been developed for the qualitative and quantitative determination of chromium in a wide variety of matrices. Methods for analysing urban, industrial and work-place air, fresh water, sea-water, sewage effluents, sediments, soil, foodstuffs, crops, plants and biological materials such as human milk, blood, serum, urine and faeces and human and animal tissues, have been reviewed (National Research Council, 1974; Whitney & Risby, 1975; US Environmental Protection Agency, 1977, 1978; Slavin, 1981; Torgrimsen, 1982; Love, 1983; Nieboer *et al.*, 1984; US Environmental Protection Agency, 1984; O'Neill *et al.*, 1986; Harzdorf, 1987; Cornelis, 1988; World Health Organization, 1988).

Typical methods for the analysis of chromium are summarized in Table 19.

Most instrumental procedures are not specific for the oxidation states of chromium and are suitable for total chromium determinations only, unless accompanied by prior separations or supportive qualitative analyses. The reagent *sym*-diphenylcarbazide forms a violet complex with chromium[VI] but not with other chromium compounds, and the stability of the colour contributes to the high sensitivity of the analysis of soluble chromate in aerosols, water, cement and other materials. Interfering, reducing or oxidizing substances, if present in the sample, must be taken into account, since they tend to cause erroneous results during sampling, sample storage and preparation and spectrometric measurement (National Institute for Occupational Safety and Health, 1975). The chromium content of single particles can be determined by electron microscopy combined with X-ray microanalysis. Electron spectroscopy can be used to measure the valency state of chromium in thin surface layers of solid samples (Lautner *et al.*, 1978).

Table 19. Analytical methods for chromium and chromium compounds

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Formulations				
Tanning liquors (trivalent chromium)	Oxidize to Cr[VI] (dichromate) with ammonium persulfate (oxidant) and cupric sulfate-cobaltous nitrate mixture (catalyst)	IT	NR	Makarov-Zemlyanskii *et al.* (1978)
Pigments	Dissolve in hydrofluoric acid	EAAS	0.1 mg/kg	Kolihova *et al.* (1978)
Air				
Total chromium	Collect particulate sample on polystyrene filter; irradiate for 5 min at a flux of 2×10^{12} neutrons/ $cm^2 \times sec$; count with a Ge(Li) detector	NAA	0.02 μg	Dams *et al.* (1970)
Total chromium	Extract collection filter with mixture of hot hydrochloric and nitric acids; concentrate extraction liquid; hold overnight; dilute	AAS	NR	Smith *et al.* (1976)
Total chromium	Collect particulate sample on acetate fibre superfilter; use filter as thin target sample and bombard in a proton beam for 10 min	X-REA	0.01 μg	Li *et al.* (1979)
Total chromium	Collect particulate sample on 0.8 μm cellulose ester membrane; extract with hydrochloric and nitric acids; dilute	AAS	0.06 μg	National Institute for Occupational Safety and Health (1984a); Eller (1984) [Method 7024]
Total chromium	Extract collection filter with mixture of concentrated nitric and perchloric acids; evaporate to dryness; redissolve in dilute nitric/perchloric acid mixture	ICP/AES	1 μg	Eller (1984) [Method 7300]; O'Neill *et al.* (1986)

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Total chromium	Collect particulate sample on cellulose nitrate membrane; extract with nitric acid; dilute	EAAS	0.09 μg	Kettrup *et al.* (1985)
Hexavalent chromium	Extract collection filter with 0.5 N sulfuric acid; filter to remove suspended dust; add *sym*-diphenylcarbazide	VIS	0.05 μg	Eller (1984) [Method 7600]; O'Neill *et al.* (1986)
Hexavalent chromium	Extract collection filter with hot 2% sodium hydroxide/3% sodium carbonate solution; add 6 N sulfuric acid and *sym*-diphenylcarbazide	VIS	0.05 μg	Eller (1984) [Method 7600]; O'Neill *et al.* (1986)
Hexavalent chromium	Collect particulate sample on 5.0-μm polyvinylchloride membrane; extract with sulfuric acid or with sodium hydroxide-sodium carbonate solution; add *sym*-diphenylcarbazide; measure absorption at 540 nm	VIS	0.05 μg	Abell & Carlberg (1974); Carelli *et al.* (1981); Bhargava *et al.* (1983); National Institute for Occupational Safety and Health (1984b)
Soluble chromium compounds	Collect aerosol sample compounds in sodium hydroxide solution with a midget impinger; oxidize Cr[III] compounds with bromine; add *sym*-diphenylcarbazide; measure absorption at 540 nm	VIS	2.3 μg/m³	Kettrup *et al.* (1985)
Chromic acid	Collect aerosol sample on a cellulose ester membrane; chelate Cr[VI] with ammonium pyrrolidine dithiocarbamate; extract with methyl isobutyl ketone	EAAS	0.2 μg	National Institute for Occupational Safety and Health (1973)

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Water				
Wastewaters Total chromium Hexavalent chromium	–	PP	 0.04 mg/l 0.01 mg/l	Heigl (1978)
River water	Separate suspended particles by centrifugation; add diethyldithiocarbamate; filter through acetate superfilter; use filter as thin target sample and bombard in a proton beam for 10 min	X-REA	NR	Li *et al.* (1979)
Seawater Hexavalent and total chromium	Extract with ammonium pyrrolidine dithiocarbamate into chloroform at pH 2	IDMS	0.001 µg/l	Osaki *et al.* (1976)
Hexavalent and trivalent chromium, selective	Extract hexavalent chromium with Aliquat-336 (a mixture of methyl tri-*n*-alkyl ammonium chlorides) at pH 2; extract trivalent chromium by adding thiocyanate to at least 1M; adjust pH to 6-8	EAAS	0.01 µg/l [VI] 0.03 µg/l [III]	de Jong & Brinkman (1978)
Drinking-water, surface water, groundwater, domestic and industrial wastewaters Total chromium	Various acidification/evaporation/dilution steps, depending on specific matrix and method	AAS	0.05 mg/l	US Environmental Protection Agency (1983, 1986) [Methods 218.1, 218.3, 3005, 3010, 7190]
		ICP/AES	7 µg/l	[Methods 200.7, 6010]
		EAAS	1 µg/l	[Methods 218.2, 3020, 7191]
Hexavalent chromium	Acidify to pH 3.5 with acetic acid; add lead nitrate, glacial acetic acid and ammonium sulfate; centrifuge and discard supernatant; dissolve precipitate in concentrated nitric acid	EAAS	2 µg/l	US Environmental Protection Agency (1983, 1986) [Methods 218.5, 7195]

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Hexavalent chromium	Chelate with ammonium pyrrolidine dithiocarbamate or pyrrolidine dithiocarbamic acid in chloroform; extract with methyl isobutyl ketone	AAS	NR	US Environmental Protection Agency (1983, 1986) [Methods 218.4, 7197]
Hexavalent chromium	Use ammonium hydroxide/ammonium chloride as supporting electrolyte	DPP	10 µg/l	US Environmental Protection Agency (1986) [Method 7198]
Hexavalent chromium	Remove interfering metals by adding aluminium sulfate; filter; add sodium hypochlorite solution; add phosphoric acid solution and sodium chloride; add *sym*-diphenylcarbazide	VIS	NR	Deutsches Institut für Normung (1987) [DIN 38405]; (see also US Environmental Protection Agency (1986) [Method 7196]
Oily waste samples: oils, greases, waxes, crude oil (soluble chromium)	Dissolve in xylene or methyl isobutyl ketone	AAS	0.05 mg/l	US Environmental Protection Agency (1986) [Methods 3040, 7190]
		ICP	7 µg/l	[Method 6010]
Sediments, sludges, soils and solid wastes (total chromium)	Digest with nitric acid and hydrogen peroxide; dilute with dilute hydrochloric or nitric acid	AAS	0.05 mg/l	US Environmental Protection Agency (1986) [Methods 3050, 7190]
		ICP	7 µg/l	[Method 6010]
		EAAS	1 µg/l	[Methods 3050, 7191]
Sediments	Activate with neutrons for 6 h	NAA	1.5 mg/kg	Ackermann (1977)
Food				
Tinned foods	Oxidize to hexavalent chromium with hydrogen peroxide; treat with *sym*-diphenylcarbazide	VIS	0.05 mg/kg	Il'inykh (1977)

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Biological samples				
SRM 1569 brewers' yeast; SRM 1577 bovine liver; SRM 1570 spinach; human hair and nails	Chemical procedures developed for digestion of biological matrices and separation of chromium without large analytical blanks or significant losses by volatilization	IDMS	1 μg	Dunstan & Garner (1977)
Blood, plasma, urine	Dilute with Triton X100 solution; standard addition method	EAAS	NR	Morris *et al.* (1989)
Tissue	Digest sample with nitric and sulfuric acids with a defined time-temperature programme; dilute with water; standard addition method	EAAS	0.3 μg/g wet wt	Raithel *et al.* (1987)
Serum	-	NAA	NR	Versieck *et al.* (1978)
Serum, human milk, urine	Dilute with water	EAAS	0.05 ng/ml (urine, serum) 0.1 ng/ml (milk)	Kumpulainen *et al.* (1983)
Blood or tissue	Digest with mixture of nitric, perchloric and sulfuric acids; heat for 4-5 h; cool; dilute with deionized water or add yttrium internal standard	ICP/AES	0.01 μg/g blood 0.2 μg/g tissue	Eller (1985) [Method 8005]
Blood erythrocytes	Wash with isotonic saline; dilute with Triton X100 solution	EAAS	1 μg/l	Lewalter *et al.* (1985)
Human urine Total chromium	Adjust pH to 2.0 with sodium hydroxide; add polydithiocarbamate resin; filter, saving filtrate and resin; adjust filtrate to pH 8.0 and add more resin; ash filters and resins; add nitric/perchloric acid mixture and warm	ICP/AES	0.1 μg	Eller (1984) [Method 8310]

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Total chromium	Dilute and acidify with nitric acid	EAAS	0.1-0.5 µg/l	Nise & Vesterberg (1979); Kiilunen *et al.* (1987); Angerer & Schaller (1988)
Plant materials	Dry in an oven at 120°C for 2-4 h; ash in a muffle furnace at 550°C for 6 h	ES	2 mg/kg	Dixit *et al.* (1976)
Airborne chromium				
Welding fumes Hexavalent chromium	Extract with sodium carbonate; remove precipitate by filtration; add *sym*-diphenylcarbazide; measure absorption at 540 nm	EAAS	0.8 µg	Thomsen & Stern (1979)
Total and hexavalent chromium	Extract with sodium hydroxide and carbonate or fuse with sodium carbonate; remove precipitate by filtration; acidify with sulfuric acid; add *sym*-diphenylcarbazide; measure absorption at 540 nm	VIS	1 µg/m³	Moreton *et al.* (1983)
Hexavalent and trivalent chromium	Collect on polycarbonate membranes	ESCA, NAA	0.001 µg	Lautner *et al.* (1978)
Total, hexavalent and trivalent chromium	Collect on cellulose ester membranes	PIXE, ESCA, TEM, EDXA	0.0001-0.01 µg	Bohgard *et al.* (1979)
Welding fumes; complex matrices with redox systems				
Insoluble and total hexavalent chromium	Add sodium carbonate; warm; remove precipitate by filtration	AAS	1 µg/m³	Thomsen & Stern (1979)
Total chromium	Add phosphoric acid:sulfuric acid (3:1)	AAS	1 µg/m³	Pedersen *et al.* (1987)
Welding and brazing fumes	Sample on cellulose ester membrane filter; load sample and irradiate	XRF	2 µg	Eller (1984) [Method 7200]

Table 19 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Cement (hexavalent chromium)	Extract with water; add ammonium acetate and ethylene diamine	DPP	0.3 μg/g	Vandenbalck & Patriarche (1987)
Grinding dusts	Collect particulate sample on polycarbonate membrane	SEM, EDXA	NR	Koponen (1985)
Paint aerosols (hexavalent chromium)	Extract with a sodium hydroxide—sodium carbonate solution; dilute with buffer solution	IC	0.003 μg	Molina & Abell (1987)

[a]Abbreviations: IT, iodometric titration; EAAS, electrothermal atomic absorption spectrometry; NAA, neutron activation analysis; AAS, atomic adsorption spectrometry; X-REA, X-ray emission analysis; ICP/AES, inductively coupled argon/plasma/atomic emission spectroscopy; VIS, visible absorption spectrometry; PP, pulse polarography; IDMS, isotope dilution mass spectrometry; DPP, differential pulse polarography; ES, emission spectrography; ESCA, electron spectroscopy for chemical analysis; PIXE, proton induced X-ray emission; TEM, transmission electron microscopy; EDXA, energy dispersive X-ray analysis; XRF, X-ray fluorescence; SEM, scanning electron microscopy; IC, ion chromatography

[b]NR, not reported

The American Society for Testing and Materials (ASTM) has established standard methods for determining the chromium (or chromium compound) content of various commercial products. These include methods for the chemical analysis of chromium-containing refractory materials and chromium ore (ASTM C572-81), for chromium in water (ASTM D1687-86), for strontium chromate pigment (ASTM D1845-86) and for chromic oxide in leather that has been partly or completely tanned with chromium compounds (ASTM D2807-78); a colorimetric method for the determination of soluble chromium (trivalent and hexavalent chromium) in workplace atmospheres (ASTM D3586-85); methods for the determination of chromium (including chromium oxide) in the solids of liquid coatings (paint) or in dried films obtained from previously coated substrates (ASTM D3718-85a), for chromium in residues obtained by air sampling of dusts of lead chromate and lead silicochromate-type pigments (ASTM D4358-84), for chromium and ferrochromium (ASTM E363-83), for chromium oxide in chromium ores (ASTM E342-71), for yellow, orange and green pigments containing lead chromate and chromium oxide green (ASTM D126-87) and for zinc yellow pigment (zinc chromate yellow) (ASTM D444-88) (American Society for Testing and Materials, 1971, 1978, 1981, 1983, 1984b, 1985a,b, 1986a,b, 1987c, 1988b).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

The carcinogenicity of chromium and chromium-containing compounds in experimental animals has been reviewed recently (Yassi & Nieboer, 1988; Fairhurst & Minty, 1990).

The description and evaluation of the available carcinogenicity studies in experimental animals have been subdivided into four subsections, mainly according to the chemical and physical properties of different chromium-containing materials: (*a*) Metallic chromium; (*b*) chromium [III] compounds; (*c*) chromium [VI] compounds; and (*d*) other chromium compounds. Chromium-containing alloys used in implants will be considered in a subsequent volume of *IARC Monographs* (Volume 52), in a monograph on cobalt and cobalt compounds.

(*a*) *Metallic chromium*

(i) *Intrapleural administration*

Mouse: No tumour was observed after 14 months in a group of 50 male C57Bl mice, approximately six weeks of age, that received six intrapleural injections of 10 µg chromium powder in 0.2 ml of a 2.5% gelatin-saline solution every other week. A total of 32 mice lived for up to 14 months (Hueper, 1955).

Rat: Groups of 17 female and eight male Osborne-Mendel rats, approximately four months old, were given six monthly intrapleural injections of 16.8 mg chromium powder in 50 µl lanolin; and 25 male Wistar rats, of approximately the same age, received six weekly intrapleural injections of 0.5 mg chromium powder suspended in 0.1 ml of a 2.5% gelatin-saline solution. Six Osborne-Mendel rats survived up to 19-24 months and 12 Wistar rats up to 25-30 months. Three female Osborne-Mendel rats developed adenofibromas of the thoracic wall; in addition, one rat also had a retroperitoneal haemangioma. Two other rats [group unspecified] had a haemangioma and an angiosarcoma, and another rat [group unspecified] had an intra-abdominal round-cell sarcoma. Of 12 male Wistar rats receiving gelatin alone, three developed intra-abdominal round-cell sarcomas (Hueper, 1955).

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[1]The Working Group was aware of carcinogenicity studies in progress with sodium chromate by intraperitoneal administration in mice and rats, with calcium chromate and chromite ore residue by inhalation in rats and with chromium by intratracheal administration in hamsters (IARC, 1988).

(ii) *Intramuscular administration*

Rat: A group of 24 male Fischer rats, eight weeks of age, received a single intramuscular injection of 2 mg chromium dust (elemental Cr, 65%, chromium oxides as Cr_2O_3, 35%; Ni, Al, Cu, Mn and Co, < 0.1%; mean particle diameter, 1.6 μm) suspended in 0.5 ml penicillin G procaine. No local tumour was reported in the 22 survivors at 24 months (Sunderman *et al.*, 1974). [The Working Group noted that only a single low dose was given.]

Two groups of 18 and 20 male Fischer-344 rats, aged eight weeks, received a single intramuscular injection of 4.4 mg chromium dust (Cr, 76%; O_2, 24%; Mn, 0.2%; median particle diameter, 1.4 μm) suspended in 0.2 ml penicillin G procaine. The study was terminated at two years, when 13/18 and 0/20 were still alive in the two groups, respectively; the low survival in the second group was due to an epidemic of pulmonary pneumonia. No local tumour developed in either group (Sunderman *et al.*, 1980). [The Working Group noted that only a single dose was given.]

A group of 25 male and 25 female weanling Fischer-344 rats received monthly intramuscular injections of 100 mg chromium powder (99.9% pure) in 0.2 ml tricaprylin. Treatment was continued until definite nodules appeared at the injection site in more than one animal [time unspecified]. The study was terminated at 644 days [survival figures not given]. A single injection-site fibrosarcoma was reported in a male rat. No local tumour was seen in 50 vehicle-control rats (Furst, 1971).

(iii) *Intraperitoneal administration*

Mouse: A group of 50 male C57Bl mice, approximately six weeks old, was given weekly intraperitoneal injections for four consecutive weeks of 10 μg chromium powder (diameter, > 100 μm to colloidal particle size) suspended in 0.2 ml of a 2.5% gelatin-saline solution. Forty mice survived up to 21 months, at which time the experiment was terminated. One mouse developed a myeloid leukaemia; no other tumour was noted (Hueper, 1955). [The Working Group noted the low dose given.]

Rat: A group of 25 male Wistar rats, three to four months old, was given weekly intraperitoneal injections for six consecutive weeks of 50 μg chromium powder in 0.1 ml of a 2.5% gelatin-saline solution. One rat developed a scirrhous carcinoma of the caecal submucosa, two rats developed intra-abdominal round-cell sarcomas, one rat had both a sarcoma of the leg of cartilaginous osteoid origin and an insulinoma of the pancreas, and one rat had an insulinoma (Hueper, 1955). [The Working Group noted that no vehicle control group was reported and that the authors stated that, although round-cell sarcomas also occurred in controls, insulinomas were found only in treated rats.]

(iv) *Intravenous administration*

Mouse: A group of 25 C57Bl mice [sex unspecified], about eight weeks of age, received six weekly injections into the tail vein of 2.5 μg chromium powder (particle size, ≤4 μm) in 0.05 ml of a gelatin-saline solution. Six animals lived up to 12 months, but none to 18 months. No tumour was observed (Hueper, 1955).

Rat: A group of 25 male Wistar rats, approximately seven months of age, was given six weekly injections of 90 μg chromium powder in 0.18 ml of a 2.5% gelatin-saline solution into the left vena saphena. Fifteen were still alive at one year and 13 at two years, at which time the study was terminated. Round-cell sarcomas were observed in four rats - three in the ileocaecal region and one in the intrathoracic region. One rat had a haemangioma of the renal medulla, and two rats had papillary adenomas of the lungs, one of which showed extensive squamous-cell carcinomatous changes. Use of vehicle-treated controls was not reported. The author stated that, although round-cell sarcomas also occurred in groups of control rats in this series of studies, lung adenomas were found only in treated rats (Hueper, 1955).

Rabbit: Eight albino rabbits [sex unspecified], approximately six months of age, received six weekly intravenous injections of 25 mg/kg bw chromium powder in 0.5 ml of a 2.5% gelatin-saline solution into the ear vein; the same course of treatment was given four months later; and, three years after the first injection, a third series of injections was given to the three surviving rabbits. Four rabbits given intravenous injections of the vehicle alone served as controls. One of three rabbits that survived six months after the last injection developed a tumour of uncertain origin (apparently an immature carcinoma) involving various lymph nodes, but no tumour occurred in controls (Hueper, 1955).

(v) *Intrafemoral administration*

Rat: A group of 25 male Wistar rats, approximately five months old, received an injection into the femur of 0.2 ml of a 50% (by weight) suspension of chromium powder (approximately 45 mg) in 20% gelatin-saline and was observed for 24 months; 19 survived over one year. No tumour developed at the injection site. Similarly, a group 25 male Osborne-Mendel rats, approximately five months of age, was injected in the femur with a similar dose of chromium powder in 0.2 ml lanolin and observed for 24 months; 14 survived for one year, and one rat developed a fibroma at the injection site (Hueper, 1955).

[The Working Group noted that many of the above studies suffered from various limitations, including the use of low doses, low effective numbers of animals and inadequate reporting.]

(vi) *Administration with known carcinogens*

Rat: Groups of 35-62 female Wistar rats, four to six weeks old, were given one intratracheal instillation of 10 mg powdered chromium (purity, 99.4%; diameter, 1-3 μm) in combination with 1 or 5 mg 20-methylcholanthrene (MC) or MC alone in saline and were killed at various intervals up to 12 weeks. Squamous-cell carcinomas of the lung developed 12 weeks after treatment in 7/12 (58%) rats given Cr + 5 mg MC, in 3/12 (25%) given Cr + 1 mg MC, in 3/7 (43%) given 5 mg MC alone, in 1/8 (12.5%) given 1 mg MC alone and in 0/12 given Cr alone (Mukubo, 1978.) [The Working Group noted the short duration of the study.]

(*b*) *Chromium[III] compounds*

(i) *Intratracheal instillation*

Rat: Random-bred and Wistar rats [age, sex and distribution unspecified] were given single intratracheal instillations of 50 and 20 mg chromic oxide, respectively. Malignant lung tumours developed in 7/34 and 6/18 animals; and four and five of these, respectively, were lung sarcomas, which appeared between 11 and 22 months after treatment (Dvizhkov & Fedorova, 1967). [The Working Group noted that use of controls was not reported and other details were not given.]

(ii) *Intrabronchial administration*

Rat: A group of 98 rats [strain, age and sex unspecified] received implants of intrabronchial stainless-steel mesh pellets (5 × 1 mm) loaded with 3-5 mg of a 50:50 mixture of chromic oxide with a cholesterol binder. Animals were observed up to 136 weeks. No lung tumour was found in treated or in 24 cholesterol binder-treated controls (Laskin *et al.*, 1970).

Groups of 100 male and female Porton-Wistar rats received intrabronchial pellets loaded with 2 mg chromite ore [purity not given], 2 mg chromic oxide (metallurgical-grade, 99-100% pure), 2 mg chromic chloride hexahydrate (95% pure) or 2 mg chrome tan ($Cr_2(OH)_2(SO_4)_2Na_2SO_4 \cdot xH_2O$ [purity not given]) suspended 50:50 in cholesterol. The incidence of squamous metaplasia in the left bronchus of treated animals was similar to that in controls. An increased incidence was seen with all five Cr[VI] compounds examined in the same study (see p. 125; Levy & Venitt, 1986).

In a second study using the same technique, no lung tumour was seen in a group of 101 rats treated with high silica chrome ore (TSS 695, containing 46.1% chromic oxide) (Levy *et al.*, 1986).

(iii) *Oral administration*

Mouse: Groups of 54 male and 54 female weanling Swiss mice received 5 mg/l chromic acetate in drinking-water for life. No difference was found in the survival

of treated females compared with controls, but treated males died earlier than control males (mean survival, 831 *versus* 957 days); only 60% of males survived 18 months. The incidence of tumours in treated animals was no greater than that in controls (Schroeder *et al.*, 1964).

Rat: Chromic acetate was given in drinking-water at a level of 5 mg/l to 46 male and 50 female weanling Long Evans rats for life. At least 70% of the animals survived for up to two years; treated females lived as long as control females, but treated males lived up to 100 days longer than control males. The incidences of tumours at various sites in rats of either sex were not significantly different from those in controls. The total numbers of autopsied animals with tumours were: 16/39 treated males, 18/35 treated females, 9/35 male controls and 15/35 female controls (Schroeder *et al.*, 1965).

Chromic oxide (green) obtained by the reduction of chromate at 600°C was baked in bread with other nutrients at levels of 1, 2 and 5%, and the bread was fed to groups of 60 male and female inbred BD rats, 100 days of age, on five days per week for two years. At the high-dose level, the total dose consumed was about 1800 g/kg bw. Average survival times were 860-880 days. Mammary fibroadenomas were found in three rats given 1%, in one given 2% and in three given 5%. One mammary carcinoma and two fibroadenomas were detected in controls (Ivankovic & Preussmann, 1975).

(iv) *Intrapleural administration*

Mouse: Only granulomas were produced when 10 mg chromite ore dust [$FeO(CrAl)_2O_3$] particles (average diameter, 1 μm; range, 0.1-5 μm) were injected intrapleurally in 0.5 ml distilled water into 25 Balb/c mice [sex and age unspecified]. Animals were killed at intervals from two weeks to 18 months after the injection (Davis, 1972). [The Working Group noted the lack of detailed reporting.]

Rat: A group of 14 male and 11 female Osborne-Mendel rats, four months of age, received six monthly intrapleural injections of 37 mg chromite ore suspended in 0.05 ml lanolin. Thirteen survived one year and all animals were dead at 24 months. One thoracic tumour (fibrosarcoma) was found in a treated animal but none in 25 controls (Hueper, 1955).

A group of 34 rats [strain, sex and age unspecified] received intrapleural implantations of chromic acetate [dose unspecified] in sheep fat. Eighteen rats were still alive at 15 months and 15 at 21 months. One implantation-site tumour [type unspecified] was seen. Of 34 control rats administered sheep fat alone, 30 were alive at one year and 11 at 21 months; none developed a tumour (Hueper, 1961).

A group of 42 Bethesda Black [NIH Black] rats [sex unspecified], approximately three months of age, received eight intrapleural implantations over 13 months of 25 mg chromic acetate in gelatin capsules. No implantation-site tumour

was seen after two years (Hueper & Payne, 1962). [The Working Group noted the lack of controls.]

(v) *Intramuscular administration*

Rat: A group of 34 rats [sex, age and strain unspecified] received intramuscular implantations of chromic acetate [dose unspecified]. Thirty were still alive at one year and 17 at 21 months. One animal developed an injection-site tumour [type unspecified]. Of 32 controls given implants of sheep fat alone 30 were alive at one year and ten at 21 months. None developed a local tumour (Hueper, 1961).

A group of 35 Bethesda Black [NIH Black] rats [sex unspecified], approximately three months of age, received an intramuscular implantation of 25 mg chromic acetate in a gelatin capsule; a further seven intramuscular implantions were made over a period of 24 months, at which time the rats were sacrificed. One spindle-cell sarcoma was observed at the site of implantation (Hueper & Payne, 1962). [The Working Group noted that no control group was reported.]

(vi) *Intraperitoneal administration*

Mouse: In a strain A mouse assay for lung adenomas, three groups of ten male and ten female strain A/Strong mice, six to ten weeks of age, were given intraperitoneal injections of chromic sulfate suspended in tricaprylin three times a week for eight weeks (total doses, 480, 1200 and 2400 mg/kg bw). Animals were killed 30 weeks after the first injection. No significant increase in the incidences of pulmonary adenomas over those in 20 vehicle-treated or 20 untreated control mice of each sex was observed (Stoner *et al.*, 1976; Shimkin *et al.*, 1977). [The Working Group noted the small number of animals used.]

Rat: In experiments with Wistar and random-bred rats [sex, age and distribution unspecified], 4/20 animals developed lung sarcomas 16-19 months after a single intraperitoneal injection of 20 mg chromic oxide (Dvizhkov & Fedorova, 1967). [The Working Group noted that no control group was reported.]

(vii) *Intravenous administration*

Mouse: Strain A mice in a group of 25 males and 25 females [age unspecified] were each given an intravenous injection into the tail vein of 5 mg chromite ore (39-60% chromic oxide; particle size, 1.6 μm) suspended in saline. The animals were killed at three, 4.5 and six months. There was no difference in the incidence of pulmonary adenomas between treated mice and 75 untreated controls (Shimkin & Leiter, 1940; Shimkin *et al.*, 1977).

Rabbit: A group of six female albino rabbits, six months of age, received six weekly intravenous injections of 25 mg chromite ore suspended in 5 ml of a 2.5% gelatin-saline solution; treatment was repeated in four of the six rabbits nine months later. The six rabbits died or were killed at 13, 20, 22, 22, 48 and 48 months.

No tumour was observed during these periods (Hueper, 1955). [The Working Group noted the small number of animals used and the lack of controls.]

(viii) *Intrafemoral administration*

Rat: A group of 15 male and 10 female Osborne-Mendel rats, five months of age, each received an injection into the femur of 0.05 ml of a 50% (by volume) suspension containing about 58 mg chromite ore (44% chromic oxide) in lanolin; 13 survived one year. No tumour developed at the injection site (Hueper, 1955).

(ix) *Administration with known carcinogens*

Rat: Groups of 15 male Fischer 344 rats, seven weeks of age, received drinking-water (distilled) containing 0 or 500 mg/l *N*-nitrosoethylhydroxyethylamine (NEHEA) for two weeks. Thereafter, rats received drinking-water alone or drinking-water containing 600 mg/l chromic chloride hexahydrate (98% pure) for 25 weeks, when the study was terminated. There was no significant increase in the incidence of renal-cell tumours in the group receiving NEHEA and chromic chloride (6/15) over that in the group given NEHEA alone (2/15). No renal tumour was reported in the group receiving chromic chloride alone (Kurokawa *et al.*, 1985). [The Working Group noted that the experiment was not intended as a test for the overall carcinogenicity of chromic chloride.]

(c) Chromium[VI] compounds

(i) *Inhalation*

Mouse: Groups of 136 C57Bl/6 mice of each sex, eight weeks old, were exposed by inhalation to calcium chromate dust (reagent grade; particle size, 99.9% < 1.0 μm) at 13 mg/m^3 for 5 h per day on five days per week over their lifespan. The median survival time was 93 weeks for treated and 80 weeks for control mice. Six lung adenomas appeared in treated males and eight in females, compared with three and two in the 136 respective controls [$p = 0.04$ for males and females combined]. No carcinoma was seen; no information was given on the occurrence of tumours at other sites (Nettesheim *et al.*, 1971).

A group of 50 female ICR/JcI mice [age unspecified] was exposed by inhalation to chromic acid (chromium trioxide) mist (particle size, 84.5% > 5 μm) generated by a miniaturized electroplating system at a chromium concentration of 3.63 mg/m^3 for 30 min per day on two days per week for up to 12 months. Mice surviving at that time were maintained for a further six months; two groups of ten mice killed at 12 and 18 months served as controls. A single lung adenoma was reported in 1/15 mice that died or were killed between six and nine months; lung adenomas occurred in 3/14 mice that died between ten and 14 months; and 1/19 adenoma and 2/19 adenocarcinomas in mice that died at 15-18 months. In the control groups, no lung

tumour was reported in ten mice killed at 12 months, but 2/10 adenomas occurred in those killed at 18 months. The authors observed nasal perforations in six mice exposed for more than ten months and time-related inflammatory changes, including squamous metaplasia, in the trachea and bronchus of exposed mice (Adachi *et al.*, 1986). [The Working Group noted the incomplete reporting of lesions.]

A group of 43 female C57Bl mice [age unspecified] was exposed by inhalation to chromic acid (chromium trioxide) mist (85% of particles > 5 μm) generated by a miniaturized electroplating system at a chromium concentration of 1.81 mg/m³ for 120 min twice a week for 12 months, at which time 23 mice were killed. The remaining 20 were killed six months after the last exposure. Nasal perforation was seen in 3/23 and 3/20 mice killed at 12 and 18 months, respectively; 0/23 and 6/20 nasal papillomas occurred in these groups. A single lung adenoma was reported in the group killed at 18 months. No nasal inflammatory change or lung tumour was seen in a group of 20 untreated control mice (Adachi, 1987). [The Working Group noted the inadequate reporting of lesions.]

Rat: Groups of 20 male TNO-W74 Wistar rats, six weeks of age, were exposed by inhalation to sodium dichromate at 25, 50 or 100 μg/m³ Cr (average mass median diameter, 0.36 μm), produced from an aqueous sodium dichromate solution, for 22-23 h per day on seven days per week for 18 months. The rats were then held for a further 12 months, at which time the study was terminated. A control group consisted of 40 untreated male rats. Survival was about 90% at 24 months; at termination at 30 months, survival was 65, 55, 75 and 57.5% in the 25, 50, 100 μg/m³ and control groups respectively. In rats that survived 24 or more months, lung tumours occurred in 0/37, 0/18, 0/18 and 3/19 in the control, 25, 50 and 100 μg/m³ groups, respectively. The three lung tumours were two adenomas and an adenocarcinoma; a squamous carcinoma of the pharynx was also reported in this group. The incidence of treatment-related tumours was not increased at other sites (Glaser *et al.*, 1986). [The Working Group noted the small number of animals used.]

(ii) *Intratracheal instillation*

Mouse: A group of 62 strain A mice [sex unspecified], ten to 11 weeks of age, received six intratracheal injections of 0.03 ml of a 0.2% saline suspension of zinc chromate [basic potassium zinc chromate, $K_2O.4ZnO.4CrO_3.3H_2O$ (Baetjer *et al.*, 1959b)] at six-week intervals and were observed until death. No pulmonary carcinoma was found; pulmonary adenomas occurred in 31/62 exposed, in 7/18 untreated control and 3/12 zinc carbonate-treated control animals (Steffee & Baetjer, 1965).

Groups of 40 male and 40 female Sprague-Dawley rats, ten weeks of age, received intratracheal instillations of 1 ml/kg bw sodium dichromate (99.95% pure) or calcium chromate (chemically pure) in 0.9% sodium chloride solution once a week or five times a week. Equal numbers of male and female rats were used as vehicle

and untreated controls. Administered doses and schedules are given in Table 20. Treatment and study of all groups was continued for 30 months; median survival was approximately 800 days in the sodium dichromate-treated groups. [The Working Group noted that survival was not reported for the calcium chromate-treated groups.] No lung tumour was reported in the groups treated five times weekly with sodium dichromate. Among animals treated weekly with sodium dichromate, 14/80, 1/80 and 0/80 animals developed lung tumours in the groups receiving 1.25, 0.25 and 0.05 mg/kg bw, respectively, with 0/80 in controls [$p < 0.001$, Cochran-Armitage test for trend]. Of the 14 animals that developed lung tumours after receiving 1.25 mg/kg bw sodium dichromate weekly 12 had adenomas and eight had malignant lung tumours, described as two adenocarcinomas (bronchioalveolar) and six squamous-cell carcinomas. The authors noted that two of the tumours were questionable and that the majority of the observed lung tumours were small, non-metastasizing, non-fatal and co-existed with scarring and other treatment-related inflammatory changes not seen in animals treated five times a week with lower doses. In the groups receiving calcium chromate, similar findings were made, with a total of six lung tumour-bearing rats (five adenomas ($p < 0.01$) and one squamous-cell carcinoma) in the group receiving 0.25 mg/kg bw five times a week, and 13 lung-tumour-bearing rats (11 adenomas ($p < 0.01$) and three with two squamous-cell carcinomas and one adenocarcinoma ($p < 0.01$)) in the group receiving 1.25 mg/kg bw once a week. [The Working Group assumed that one rat had both an adenoma and a squamous-cell carcinoma.] The authors noted that one of the squamous-cell carcinomas may have been a metastasis from a primary tumour of the jaw (Steinhoff *et al.*, 1986).

Hamster: Groups of 35 male Syrian golden hamsters, about six weeks old, received weekly intratracheal instillations of 0.1 mg calcium chromate in 0.2 ml saline for 56 weeks and were maintained for a further 44 weeks. No lung tumour was reported (Reuzel *et al.*, 1986).

Guinea-pig: Groups of 21 or 13 guinea-pigs [sex and strain unspecified], three months of age, received six intratracheal instillations of 0.3 ml of a 1% suspension in saline of 3 mg zinc chromate as basic potassium zinc chromate (Baetjer *et al.*, 1959b) or 3 mg lead chromate, at three-monthly intervals. The animals were observed until death. A single pulmonary adenoma was seen in the group given zinc chromate, but no pulmonary carcinoma. No pulmonary adenoma was seen in the lead chromate group or in 18 vehicle controls (Steffee & Baetjer, 1965). [The Working Group noted the limited reporting of the study.]

Rabbit: Groups of seven rabbits [sex and strain unspecified], four months of age, received three to five intratracheal instillations of 1 ml of a suspension in saline of 1% (10 mg) zinc chromate (basic potassium zinc chromate, Baetjer *et al.*, 1959b) or lead chromate at three-monthly intervals. No lung tumour was reported in

Table 20. Protocol and results of test by intratracheal instillation of various chromium[VI] compounds to rats[a]

Compound	No. of animals		Dose (mg/kg bw)	Schedule	No. of lung tumours		Total no. of tumour-bearing animals
	Males	Females[b]			Benign	Malignant	
Sodium dichromate	40	50	0.25	5 × weekly	–	–	–
Sodium dichromate	40	45	0.05	5 × weekly	–	–	–
Sodium dichromate	40	45	0.01	5 × weekly	–	–	–
Sodium dichromate	40	40	1.25	1 × weekly	12*	8*	14
Sodium dichromate	40	40	0.25	1 × weekly	–	1	1
Sodium dichromate	40	40	0.05	1 × weekly	–	–	–
Calcium chromate	40	50	0.25	5 × weekly	5*	1	6
Calcium chromate	40	40	1.25	1 × weekly	11*	3*	13
Benzo[*a*]pyrene	0	10	5.0	1 × weekly			
Dimethyl carbamoyl chloride	10	10	1.0	1 × weekly			
Sodium chloride (0.9%)	40	50	1 ml/kg	5 × weekly	–	–	–
Sodium chloride (0.9%)	40	40	1 ml/kg	1 × weekly	–	–	–
Untreated	40	50	–	–	–	–	–

[a]From Steinhoff *et al.* (1986)

[b]Only 40 females used for carcinogenicity tests (five to ten extra in test groups)

*Significant at $p < 0.01$

treated animals or in five saline-treated controls (Steffee & Baetjer, 1965). [The Working Group noted the limited reporting of the study.]

(iii) *Intrabronchial administration*

Rat: A group of 100 rats [strain, sex and age unspecified] received intrabronchial implantations of stainless-steel mesh pellets (5 × 1 mm) loaded with 3-5 mg of a 50:50 mixture of calcium chromate with a cholesterol binder. Six squamous-cell carcinomas and two adenocarcinomas of the lung were found in animals observed up to 136 weeks. The median time to appearance of tumours was 540 days. A group of 100 rats similarly treated with chromium trioxide and observed up to 136 weeks had no such tumour, nor did 24 controls treated with cholesterol binder (Laskin *et al.*, 1970). [Although the incidence of lung tumours was not statistically significant, the Working Group noted the probable biological significance of these tumours.]

Groups of approximately 50 male and 50 female Porton-Wistar rats, six to eight weeks old, received intrabronchial implantations into the left lung of stainless-steel mesh pellets (5 × 1 mm) loaded with about 2 mg of a series of chromium-containing test materials suspended 50:50 in cholesterol. Groups of approximately 75 male and 75 female rats receiving blank pellets or pellets loaded with cholesterol alone acted as negative controls. Animals were maintained for 24 months, at which time the study was terminated and all lungs and abnormal tissues examined. [The Working Group noted that survival was not reported]. No lung tumour was seen in either control group or among rats receiving pellets loaded with sodium dichromate (99-100% pure) or sodium chromate (98-99% pure); a single squamous-cell carcinoma of the left lung was seen in the group treated with chromic acid (chromium trioxide; 99-100% pure) and eight squamous-cell carcinomas ($p < 0.05$) of the left lung in the group treated with calcium chromate (95% pure). There was a significant increase in the incidence of bronchial squamous metaplasia of the left lung in rats without lung tumours in all treatment groups when compared to the groups receiving cholesterol or a blank pellet. Of animals that received intrabronchial pellets loaded with zinc potassium chromate ($K_2CrO_4.3ZnCrO_4.Zn(OH)_2$, 99-100% pure) suspended in cholesterol, 3/61 developed squamous-cell carcinomas of the left lung (Levy & Venitt, 1986).

In a second study using the techniques and protocol described above, the incidences of squamous-cell carcinomas of the left lung in groups of animals given a range of lead chromates, zinc chromates and strontium chromates were as shown in Table 21. Significance was calculated by comparing the incidence of bronchial carcinomas in each test group with that in a reference group comprising the two negative control groups and all groups treated with chromium-containing materials. Survival was 96% at 400 days and 54% at 700 days. Calcium chromate (96.7% pure), included as a positive control, induced 25/100 left-lung bronchial carcinomas

(24 squamous-cell carcinomas and one adenocarcinoma); chromium trioxide (99.9% pure) induced 2/100 left-lung bronchial carcinomas (one squamous-cell carcinoma and one anaplastic carcinoma); sodium dichromate dihydrate (TSS 612; 99.7% pure) gave 1/100 left-lung squamous-cell carcinoma; and a residue material (vanadium solids) from the bichromate production process, containing 5.3% calcium chromate and 17.2% sodium dichromate, induced 1/100 squamous-cell carcinoma of the left lung. No bronchial carcinoma was seen in the 100 rats given cholesterol alone; and 22/48 bronchial carcinomas (21 squamous-cell carcinomas and one anaplastic carcinoma) were seen in a positive control group receiving 20-methylcholanthrene (Levy *et al.*, 1986).

Table 21. Incidence of bronchial carcinomas in rats administered various chromium[VI] compounds by intrabronchial implantation into the left lung[a]

Compound	Composition	Incidence of bronchial carcinomas
Lead chromates		
Lead chromate (99.8% pure)	Pb, 64%; CrO_4, 35.8%	1/98
Primrose chrome yellow	Pb, 62.1%; Cr, 12.6%	1/100
Molybdate chrome orange[b]		0/100
Light chrome yellow	Pb, 62.1%; Cr, 12.5%	0/100
Supra (70 FS) LD chrome yellow	PbO, 61.5%; CrO_3, 26.9%	1/100
Medium chrome yellow	Pb, 60.2%; Cr, 16.3%	1/100
Silica encapsulated medium chrome yellow	Pb, 40.4%; Cr, 10.5%	0/100
Barium chromate (98% pure)	Ba, 54.1%; CrO_4, 42.1%	0/101
Zinc chromate IW (low water solubility)	ZnO, 39.4%; CrO_3, 40.8%	5/100[c] [p = 0.004]
Zinc chromate (Norge composition)	ZnO, 39.2%; CrO_3, 43.5%	3/100[c] [p = 0.068]
Zinc tetroxychromate	Zn, 56.6%; Cr, 8.8%	1/100
Strontium chromate	Sr, 42.2%; CrO_4, 54.1%	43/99
Strontium chromate	Sr, 43.0%; Cr, 24.3%	62/99
Cholesterol control		0/100
20-Methylcholanthrene control		22/48

[a]From Levy *et al.* (1986)

[b]Composition incompletely described by Levy *et al.* (1986); it is a mixture of lead chromate, lead sulfate and lead molybdate (Pb, 62.9%; Cr, 12.9%; Mo, 4.2%).

[c]Significance for each treatment group based on a reference group composed of a combination of the negative control group and all groups treated with chromate-containing materials, except those treated with calcium or strontium chromate

(iv) *Intrapleural administration*

Rat: A number of chromium[VI] compounds [doses unspecified] administered to rats [sex, age and strain unspecified] by intrapleural implantation in experiments lasting 27 months gave the following numbers of implantation-site tumours [type unspecified]: strontium chromate, 17/28 (nine alive at one year); barium chromate, 1/31 (30 alive at one year); lead chromate, 3/34 (32 alive at one year); zinc yellow [unspecified composition], 22/33 (11 alive at one year); calcium chromate, 20/32 (none alive at one year); sintered calcium chromate, 17/33 (nine alive at one year, one alive at 21 months); and sodium dichromate, 0/26 (20 alive at one year, none alive at 18 months). None of 34 control rats had tumours (30 alive at one year, five alive at two years) (Hueper, 1961).

Groups of 20 male and 19 female Bethesda Black [NIH Black] rats, three months of age, received 16 monthly intrapleural injections of 2 mg sodium dichromate in gelatin and were observed for up to two years. One adenocarcinoma of the lung was observed; no tumour at the injection site was observed in 60 control rats treated with gelatin solution. After intrapleural implantation of 12.5 mg calcium chromate in a gelatin capsule to 14 rats, eight developed malignant tumours [type unspecified] at the site of implantation after two years compared with none in 35 controls (Hueper & Payne, 1962).

(v) *Subcutaneous administration*

Mouse: A group of 26 female and 26 male C57Bl mice received calcium chromate or sintered calcium chromate (prepared by heating calcium chromate with less than 1% impurities to about 1100 °C for about 1 h) by subcutaneous injection of 10 mg chromium compound in tricaprylin, and the animals were observed for 18-26 months. One sarcoma was observed in 13 mice treated with calcium chromate that lived longer than six months, but none was seen at the injection site in the other treated groups or in vehicle controls. Histologically, the injection-site tumours were spindle-cell sarcomas or fibrosarcomas (Payne, 1960a).

Rat: Groups of 40 male and female Sprague-Dawley rats, 13 weeks of age, received a single subcutaneous injection of 30 mg lead chromate (chromium yellow) or basic lead chromate (chromium orange) in water. Sarcomas (rhabdomyosarcomas and fibrosarcomas) developed at the injection site in 26/40 and 27/40 animals, respectively, within 117-150 weeks. No local tumour occurred in 60 vehicle-control rats, and a single local sarcoma occurred in 80 control rats that received comparable subcutaneous injections of iron yellow or iron red (Maltoni, 1974, 1976; Maltoni *et al.*, 1982).

Groups of 20 male and 20 female Sprague-Dawley rats, 13 weeks of age, received single subcutaneous injections of 30 mg zinc yellow (basic zinc chromate) at 20% or 40% CrO_3 in 1 ml saline. Local sarcomas (rhabdomyosarcomas and fibrosarcomas) were seen in 6/40 and 7/40 rats given 20% and 40% CrO_3 at 110 and 137 weeks, respectively. No local tumour had occurred in the 40 control animals by 136 weeks (Maltoni *et al.*, 1982).

A further group of 20 male and 20 female Sprague-Dawley rats received single subcutaneous injections of 30 mg molybdenum orange (described as a mixture of lead chromate, sulfate and molybdate) in 1 ml saline. At termination of the study at 117 weeks, 36/40 rats had injection-site sarcomas; no local tumour occurred in 45 male and 15 female untreated controls (Maltoni, 1974; Maltoni *et al.*, 1982).

(vi) *Intramuscular administration*

Mouse: Groups of 26 female and 26 male C57Bl mice [age unspecified] received calcium chromate or sintered calcium chromate (prepared by heating calcium chromate with less than 1% impurities to about 1100 °C for about 1 h) by intramuscular implantation of 10 mg of the chromium compound mixed with 20 mg sheep fat. Animals were observed for a total of 14 months. Nine implantation-site sarcomas were observed among 46 mice given sintered calcium chromate that lived longer than six months; one sarcoma was observed in 50 mice given non-sintered calcium chromate; and no sarcoma was found among 50 control mice that lived six months or more (Payne, 1960a).

A group of 25 female NIH-Swiss weanling mice was given intramuscular injections of 3 mg lead chromate in trioctanoin every four months. Two lymphomas were seen within 16 months and three lung adenocarcinomas within 24 months among 17 mice that were necropsied. The incidences of these tumours were 1/15 and 1/15 in untreated control mice and 2/22 and 1/22 among vehicle-injected control mice (Furst *et al.*, 1976).

Rat: Groups of 35 Bethesda Black [NIH Black] male and female rats, approximately three months of age, received an intramuscular implantation of pellets containing 25 mg calcium chromate (99% pure), 25 mg sintered calcium chromate or 25 mg sintered chromium trioxide, all in 50 mg sheep fat. Sarcomas (spindle-cell sarcomas and fibrosarcomas) at the implantation site were seen after 12-14 months in 8/35 rats given calcium chromate, 8/35 given sintered calcium chromate and 15/35 given sintered chromium trioxide. No local tumour was seen in 35 controls or in groups of 20 males and 15 females given implants of 25 mg barium chromate (99% pure) in 50 mg sheep fat (Hueper & Payne, 1959). [The Working Group noted that sintered chromium trioxide at 1100 °C would contain appreciable amounts of chromic chromate; it also noted the short duration of the experiment.]

In groups of 32-34 rats [sex, strain and age unspecified] that received intramuscular implantation of various chromium compounds in sheep fat [doses unspecified], the following incidences of implantation-site tumours [type unspecified] were recorded after 27 months: calcium chromate, 9/32 (22 alive at one year, seven alive at two years); sodium dichromate, 0/33 (25 alive at one year, 16 alive at 18 months); sintered calcium chromate, 12/34 (22 alive at one year, none alive at two years); strontium chromate, 15/33 (20 alive at one year); barium chromate, 0/34 (30 alive at one year); lead chromate, 1/33 (28 alive at one year); and zinc yellow [composition unspecified], 16/34 (22 alive at one year). None of 32 control rats given implants of sheep fat alone developed local tumours (30 alive at one year, six alive at two years) (Hueper, 1961).

A group of 20 male and 19 female Bethesda Black [NIH Black] rats, three months of age, was given 16 intramuscular injections of 2 mg sodium dichromate in gelatin at monthly intervals and observed for two years (17 alive at 16 months). No tumour appeared at the injection site. After intramuscular implantation of 12.5 mg calcium chromate in a gelatin capsule to eight rats, four malignant tumours developed at the implantation site in animals observed for two years; compared with none in 35 controls (Hueper & Payne, 1962).

Each of a group of 24 male CB stock rats, five to six weeks of age, was given an intramuscular injection of calcium chromate in arachis oil (total dose, 19 mg) once a week for 20 weeks. Eighteen developed spindle-cell or pleomorphic-cell sarcomas at the injection site, none of which metastasized [$p < 0.01$]. The mean time to tumour appearance was 323 days (duration of experiment, 440 days). No tumour developed in 15 control rats given arachis oil only that were alive at 150 days (Roe & Carter, 1969).

Groups of 25 male and 25 female weanling Fischer-344 rats received intramuscular injections of 8 mg lead chromate suspended in trioctanoin once a month for nine months or 4 mg calcium chromate in the same vehicle once a month for 12 months. Lead chromate induced 14 fibrosarcomas and 17 rhabdomyosarcomas at the site of injection in 31/47 rats. In addition, renal carcinomas were observed in 3/23 male rats at 24 months. Calcium chromate induced tumours (three fibrosarcomas, two rhabdomyosarcomas) in 5/45 animals. No such tumour appeared in a group of 22 controls injected with the vehicle (Furst *et al.*, 1976). [The Working Group noted that the renal tumours might be attributable to the lead content of the compound (IARC, 1980b)].

(*d*) *Other chromium compounds*

(i) *Inhalation*

Mouse: Groups of mice, eight to ten weeks of age, were exposed in dust chambers for 4 h per day on five days per week to a mixed chromium dust[1] containing 1-2 mg/m^3 soluble chromium (as chromium trioxide) until they died or were killed (total dose of chromium trioxide inhaled, 272-1330 mg-h): 127 Swiss females were exposed for up to 58 weeks, ten Swiss males and 11 Swiss females for up to 39 weeks, 34 strain A females for 16 weeks, 45 strain A females for 24 weeks, 110 strain A females for 38 weeks, 52 strain A males for 46 weeks, 50 C57Bl males for 42 weeks and 61 C57Bl females for 41 weeks. No lung carcinoma was observed, and the incidence of lung adenomas did not significantly exceed that in control mice in any strain. The experiment lasted for up to 101 weeks (Baetjer *et al.*, 1959b). [The Working Group noted the low doses and the small numbers of animals used.]

Rat: A group of 78 Wistar rats [sex unspecified], six to eight weeks of age, was exposed by inhalation to a mixed chromium dust[1] for 4-5 h per day on four days a week for life, to give an average chromium trioxide concentration of 3-4 mg/m^3. No significant difference in tumour incidence was observed between treated and control groups. A group of 38 Sherman rats [sex unspecified], six to eight weeks of age, received 16 monthly intratracheal injections of 0.1 ml of a suspension consisting of 0.5% mixed chromium dust plus 0.6% potassium dichromate, equivalent to 0.07 mg chromium/dose. No lung tumour occurred (Steffee & Baetjer, 1965).

A group of 20 male TNO-W74 Wistar rats, six weeks of age, was exposed by inhalation to 100 μg/m^3 pyrolysed Cr[VI]/Cr[III] oxides (3:2; average mass median diameter, 0.39 μm) for 22-23 h per day on seven days a week for 18 months. The rats were then held for a further 12 months. A control group consisted of 40 untreated male rats. Survival was over 90% at 24 months and at 30 months was 50% and 42% in treated and controls, respectively. A single lung adenoma was found in the treated group and none in the controls (Glaser *et al.*, 1986). [The Working Group noted the small number of animals used].

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[1]The Working Group noted that, in the publications of Baetjer *et al.*, the mixed chromium dust used was prepared by grinding to a fine powder the roast that is produced when chromite ore is heated at a high temperature with sodium carbonate and calcium hydroxide. The mixture contained approximately 12% chromium, consisting of water-soluble sodium chromate (chromium[VI]), water-insoluble but acid-soluble chromium[VI] and [III] chemicals and some unchanged chromite ore; to this mixture was added 1% potassium bichhromate. The final analysis of the dust gave 13.7% chromium trioxide and 6.9% chromic oxide. The Working Group commented that this roasted mixture, known as 'frit', is the product of the first stage of the bichromate production process prior to leaching. This first-stage process may or may not involve the addition of calcium hydroxide or limestone.

Groups of 120 male and 120 female Sprague-Dawley rats, six to seven weeks of age, were exposed by inhalation to 0.5 mg/m^3 'unstabilized', 0.5 or 25 mg/m^3 'stabilized' chromium[IV] dioxide particles (mass median aerodynamic diameter, 2.6-2.8 μm) for 6 h a day on five days per week for two years. Ten rats from each group were killed at 12 months for interim observation. Between 101 and 108 lungs were examined for each group exposed up to 24 months. [The Working Group noted that no survival data were reported.] In the 25 mg/m^3 stabilized group, there was treatment-related alveolar bronchiolization. In addition, lung adenomas occurred in 1/106 males and 1/108 females in this group, and keratin cysts and 'cystic keratinized squamous-cell carcinomas' in 108 females. The authors considered that the cystic keratinized squamous-cell carcinomas were related to a dust reaction alone and were not true malignant tumours (Lee *et al.*, 1988). [The Working Group noted that similar lesions of the lung were described in a previous *IARC Monograph* on titanium dioxide (IARC, 1989).]

Guinea-pig: Three-month-old guinea-pigs [sex unspecified] were exposed by inhalation to a combination of mixed chromium dust[1] for 4-5 h per day on four days per week for lifespan (average dose, 3-4 mg/m^3 chromic trioxide); 3/50 developed pulmonary adenomas. No pulmonary adenoma occurred in 44 controls (Steffee & Baetjer, 1965).

Rabbit: Eight rabbits [sex and strain unspecified], four months of age, were exposed by inhalation for 4-5 h per day on four days per week for up to 50 months to mixed chromium dust[1] according to a complex dosage schedule (average dose, 3-4 mg/m^3 chromium trioxide). No pulmonary tumour was seen (Steffee & Baetjer, 1965).

(ii) *Intratracheal instillation*

Mouse: Five to six intratracheal instillations of a mixed chromium dust[1], equivalent to 0.04 mg chromium trioxide per instillation, were given either to 14 and 20 Swiss males, which were then observed for 26 and 32 weeks, respectively; to 45 and 110 Swiss females, observed for up to 32 and 48 weeks, respectively; to 28, 52, 77 and 48 strain A females observed for up to 31, 37, 43 and 52 weeks respectively; to 17 strain A males observed for up to 52 weeks; or to 48 C57Bl males and 47 C57Bl females observed for up to 32 weeks. Treated animals developed no more lung tumours than did untreated control animals (Baetjer *et al.*, 1959b).

Guinea-pig: Groups of 19 guinea-pigs [sex unspecified], three months old, were given six intratracheal instillations of 0.3 ml of a 1% suspension in saline of a mixed chromium dust[1] or a pulverized residue dust (roast material from which solu-

[1]See footnote on p. 130

ble chromates had been leached) at intervals of three months. The animals were observed until they died. No pulmonary carcinoma developed in any experimental group or in 18 vehicle controls (Steffee & Baetjer, 1965).

Rabbit: Groups of rabbits received three to five intratracheal injections of 1 ml of a 1% suspension in saline of mixed chromium dust (ten rabbits) or 'pulverized residue dust' (roast material from which soluble chromates had been leached) (seven rabbits) at intervals of three months. No pulmonary tumour was seen in either group (Steffee & Baetjer, 1965).

(iii) *Intrabronchial administration*

Rat: A group of 100 rats [strain, sex and age unspecified] received intrabronchial implants of stainless-steel mesh pellets (5 × 1 mm) loaded with 3-5 mg of a 50:50 mixture of a chromate process residue (an intermediate process residue from the bichromate-producing industry, which may have contained up to 3% calcium) with a cholesterol binder. Animals were observed up to 136 weeks. One squamous-cell carcinoma was observed after 594 days in 1/93 rats that lived more than 150 days. No lung tumour was seen in 24 cholesterol binder-treated controls (Laskin *et al.*, 1970).

In a study using intrabronchial implantation, described previously (p. 125), no bronchial tumour was seen in five groups of 100 Porton-Wistar rats that received pellets loaded with five residues from bichromate production: Bolton high lime residue, residue after alumina precipitation, residue from slurry tank (free of soluble chromium), residue from vanadium filter and residue from slurry disposal tank. All five materials contained less than 5% hexavalent chromium (Levy & Venitt, 1986; Levy *et al.*, 1986).

In a second study using the technique described above, but examining bichromate production residues containing lime, the following incidences of squamous-cell carcinomas of the left lung were seen: high lime residue from old tip (TSS 643D; Cr_2O_3, 2.4%; $CaCrO_4$, 2.7%; Na_2CrO_4, 1.0%), 1/99; kiln frit (TSS 643B, with 2% limestone added to feedmix; Cr_2O_3, 13.0%; Na_2CrO_4, 29.0%), 2/100; and recycled residue (TSS 643C, with 2% limestone added to feedmix; Cr_2O_3, 20.4%; Na_2CrO_4, 2.2%), 0/100 (Levy *et al.*, 1986).

(iv) *Intrapleural administration*

Mouse: Groups of 30 male and 25 female strain A mice, eight to ten weeks of age, were given four intrapleural injections of 0.05 ml of a 2 or 4% suspension of mixed chromium dust[1] in olive oil at intervals of four to six weeks. The incidence of

[1]See footnote on p. 130.

lung tumours during an observation period of 38 weeks was similar to that in a control group of 23 males and 18 females (Baetjer *et al.*, 1959b).

Rat: A group of 25 male Bethesda Black [NIH Black] rats, three months of age, received sheep-fat cubes containign 25 mg roasted chromite ore implanted into the pleural cavity. Squamous-cell carcinomas of the lungs were observed in 2/24 rats that survived 19-24 months. One lung adenoma occurred in the 4/15 female controls given an implant of sheep fat that survived this period (Hueper, 1958). [The Working Group noted that the roasted chromite ore tested in this study was a process-derived material that contained unspeciated chromium compounds formed during oxidative heating of a chromium ore that had been subjected to alkaline leaching. Hueper sometimes referred to this material as 'chromate' and sometimes as 'chromite'.]

Of a group of 32 rats [age, sex and strain unspecified] that received intrapleural implantations of chromite roast residue [amount unspecified], 5/32 (28 alive at one year, ten alive at 24 months) developed malignant tumours at the implantation site. In a group of 34 rats given chromic chromate [precise chemical nature unspecified], 25 tumours developed at the implantation site. None of 34 control rats had a tumour (30 alive at one year, five alive at 24 months) (Hueper, 1961).

When 25 mg roasted chromite ore in 50 mg sheep fat (equivalent to 2 mg Cr) were implanted intrapleurally into 15 male and 20 female Bethesda Black rats [age unspecified], implantation-site sarcomas occurred in three rats over 17 months. No tumour was seen in 35 rats injected intrapleurally with the sheep-fat vehicle only (Payne, 1960b)

(v) *Intramuscular administration*

Mouse: A group of 26 male and 26 female C57Bl mice [age unspecified] was given intramuscular implantations of 10 mg roasted chromite ore (equivalent to 0.79 mg chromium) in sheep fat. None developed tumours at the implantation site within 22 months. No local tumour developed in 52 controls treated with sheep fat alone (Payne, 1960b). [The Working Group noted that no data on survival were reported.]

Rat: A group of 31 female Bethesda Black [NIH Black] rats, approximately three months old, was given intramuscular implants of small cubes composed of 25 mg roasted chromite ore suspended in 75 mg sheep fat. Three rats developed fibrosarcomas at the site of implantation within 24 months. No implantation-site tumour occurred in 15 vehicle-treated controls (Hueper, 1958).

In a group of 34 rats [age, sex and strain unspecified] that received intramuscular implantations of chromite roast residue, 1/34 (32 alive at one year, two alive at 27 months) developed a malignant tumour at the injection site [type unspecified]. In a further group of 22 rats given intramuscular implantations of chromic chromate [precise chemical nature unspecified], 24 local tumours were observed after 24

months. None of 32 controls given implants of sheep fat alone developed local tumours (30 alive at one year, six alive at 24 months) (Hueper, 1961).

(vi) *Injections into subcutaneously implanted tracheal grafts*

Rat: Seventy-two tracheal rings excised from female Wistar-Lewis rats were implanted subcutaneously into the backs of 13 rats of the same strain (weighing 100-150 g at the start of the experiment). Two weeks later, the grafts were filled by injection with 0.05 ml of an agar suspension of 2.5 mg chromium carbonyl with or without 2.5 mg benzo[*a*]pyrene. Biopsies were performed at intervals. Ten squamous-cell carcinomas developed in 24 tracheas that received the mixture, and two carcinomas developed in 22 tracheas treated with chromium carbonyl alone. Three of the tracheal carcinomas produced by the mixture metastasized within nine months. The time to appearance of the tumours was four to 14 months. No tumour occurred in the four trachea that received the vehicle only (Lane & Mass, 1977).

The experiments described in section 3.1 are summarized in Table 22, by compound.

Table 22. Summary of studies used to evaluate the carcinogenicity to experimental animals of metallic chromium and chromium compounds

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Metallic chromium				
Chromium	Intratracheal	Rat (53)	0/12	Mukubo (1978)
Chromium	Intrapleural	Mouse (50)	0/50	Hueper (1955)
Chromium	Intrapleural	Rat/2 groups (25; 25)	A few tumours, also in controls	Hueper (1955)
Chromium	Intramuscular	Rat (24)	0/22 local tumour	Sunderman *et al.* (1974)
Chromium	Intramuscular	Rat (38)	0/38 local tumour	Sunderman *et al.* (1980)
Chromium	Intramuscular	Rat (50)	1/50 *vs* 0/50	Furst (1971)
Chromium	Intraperitoneal	Mouse (50)	0/50 local tumour	Hueper (1955)
Chromium	Intraperitoneal	Rat (25)	5/25 (mixed)	Hueper (1955)
Chromium	Intravenous	Mouse (25)	0/25	Hueper (1955)
Chromium	Intravenous	Rat (25)	6/25 (mixed)	Hueper (1955)
Chromium	Intravenous	Rabbit (8)	1/3 *vs* 0/4	Hueper (1955)
Chromium	Intrafemoral	Rat/2 groups (25; 25)	0/25; 1/25 local tumour	Hueper (1955)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Chromium[III] compounds				
Chromic acetate	Drinking-water	Mouse (108)	M 6/39 *vs* 11/44 F 9/29 *vs* 22/60	Schroeder *et al.* (1964)
Chromic acetate	Drinking-water	Rat (96)	M 16/39 *vs* 9/35 F 18/35 *vs* 15/35	Schroeder *et al.* (1965)
Chromic acetate	Intrapleural	Rat (34)	1/34 *vs* 0/34	Hueper (1961)
Chromic acetate	Intrapleural	Rat	0/42 local tumour	Hueper & Payne (1962)
Chromic acetate	Intramuscular	Rat (34)	1/34 *vs* 0/32 local tumour	Hueper (1961)
Chromic acetate	Intramuscular	Rat (35)	1/35 local tumour	Hueper & Payne (1962)
Chromic oxide	Oral (in bread)	Rat (3 groups of 60)	As controls	Ivankovic & Preussman (1975)
Chromic oxide	Intratracheal	Rat (?)	Malignant lung tumours 7/34 (50 mg) and 6/18 (20 mg)	Dvizhkov & Fedorova (1967)
Chromic oxide	Intrabronchial	Rat (98)	0/98 *vs* 0/24	Laskin *et al.* (1970)
Chromic oxide	Intrabronchial	Rat (100)	0/100 *vs* reference[b]	Levy & Venitt (1986)
Chromic oxide	Intraperitoneal	Rat (?)	Lung sarcomas 4/20	Dvizhkov & Fedorova (1967)
Chromic chloride hexahydrate	Intrabronchial	Rat (100)	0/100 *vs* reference[b]	Levy & Venitt (1986)
Chromic chloride	Drinking-water	Rat (15)	0/15	Kurokawa *et al.* (1985)
Chrome tan	Intrabronchial	Rat (100)	0/100 *vs* reference[b]	Levy & Venitt (1986)
Chromic sulfate	Intraperitoneal	Mouse (10 per group; 3 dose levels)	As controls	Stoner *et al.* (1976)
Chromite	Intrabronchial	Rat (100)	0/100 *vs* reference[b]	Levy & Venitt (1986)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Chromite (high silica chrome ore TSS 645)	Intrabronchial	Rat	0/99 *vs* reference[b]	Levy *et al.* (1986)
Chromite	Intrapleural	Mouse (25)	0/25	Davis (1972)
Chromite	Intrapleural	Rat (25)	1/25 *vs* 0/25	Hueper (1955)
Chromite	Intravenous	Mouse (50)	As controls	Shimkin & Leiter (1940)
Chromite	Intravenous	Rabbit (6)	0/6	Hueper (1955)
Chromite	Intrafemoral	Rat (25)	0/25 local tumour	Hueper (1955)
Chromium[VI] compounds				
Calcium chromate	Inhalation	Mouse (136)	Lung adenomas M 6/136 *vs* 3/136 F 8/136 *vs* 2/136	Nettesheim *et al.* (1971)
Calcium chromate	Intrabronchial	Rat (100)	Bronchial carcinomas 8/100 *vs* 0/24 (NS)	Laskin *et al.* (1970)
Calcium chromate	Intrabronchial	Rat (100)	Squamous-cell carcinomas 8/84 *vs* reference[b] $p < 0.05$	Levy & Venitt (1986)
Calcium chromate	Intrabronchial	Rat (100)	Bronchial carcinomas 25/100 ($p < 0.01$) positive control	Levy *et al.* (1986)
Calcium chromate	Intratracheal	Rat (80)	Lung: 5 x weekly; 0.25 mg/kg 6/80 *vs* 0/80 ($p < 0.01$) Lung: 1 x weekly; 1.25 mg/kg 13/80 *vs* 0/80[c] ($p < 0.01$)	Steinhoff *et al.* (1986)
Calcium chromate	Intratracheal	Hamster (35)	No lung tumour	Reuzel *et al.* (1986)
Calcium chromate	Intramuscular	Mouse (52)	1/50 *vs* 0/50 local tumour (NS)	Payne (1960a)
Calcium chromate sintered	Intramuscular	Mouse (52)	9/46 *vs* 0/50 local tumours [$p < 0.01$)]	Payne (1960a)
Calcium chromate	Intramuscular	Rat	9/32 *vs* 0.32 local tumours [$p < 0.01$]	Hueper (1961)
Calcium chromate sintered	Intramuscular	Rat	12/34 *vs* 0/32 local tumours [$p < 0.01$]	Hueper (1961)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Calcium chromate	Intramuscular	Rat (50)	5/45 *vs* 0/22 local tumours (NS)	Furst *et al.* (1976)
Calcium chromate	Intramuscular	Rat (8)	4/8 *vs* 0/35 local tumours	Hueper & Payne (1962)
Calcium chromate	Intramuscular	Rat (24)	18/24 *vs* 0/15 local tumours [$p < 0.01$]	Roe & Carter (1969)
Calcium chromate	Intramuscular	Rat (35)	8/35 *vs* 0/35 [$p < 0.01$]	Hueper & Payne (1959)
Calcium chromate sintered	Intramuscular	Rat (35)	8/35 *vs* 0/35 [$p < 0.01$]	Hueper & Payne (1959)
Calcium chromate	Intraperitoneal	Rat (14)	8/14 *vs* 0/35 local tumours	Hueper & Payne (1962)
Calcium chromate	Intraperitoneal	Rat (?)	20/32 *vs* 0/34 [$p < 0.01$]	Hueper (1961)
Calcium chromate sintered	Intraperitoneal	Rat (?)	17/33 *vs* 0/34 [$p < 0.01$]	Hueper (1961)
Calcium chromate	Subcutanous	Mouse (52)	1/13 *vs* 0/52 (NS)	Payne (1960a)
Calcium chromate sintered	Subcutaneous	Mouse (52)	0/31 *vs* 0/52	Payne (1960a)
Chromic acid (chromium trioxide)	Inhalation	Mouse (50)	Lung adenomas, 10-14 months: 3/14 *vs* 0/10 (NS) Adenomas, 15-18 months: 1/19 *vs* 2/10 Adenocarcinoma: 2/19 *vs* 0/10 (NS)	Adachi *et al.* (1986)
Chromic acid (chromium trioxide)	Inhalation	Mouse (43)	Nasal papilloma, 18 months: 6/20 *vs* 0/20 ($p < 0.05$); 1/20 adenoma of lung	Adachi (1987)
Chromic acid (chromium trioxide)	Intrabronchial	Rat (100)	Squamous-cell carcinoma: *vs* reference[b] (NS)	Levy & Venitt (1986)
Chromic acid (chromium trioxide)	Intrabronchial	Rat (100)	Bronchial carcinoma: 2/100 *vs* 0/100 (NS)	Levy *et al.* (1986)
Chromic acid (chromium trioxide)	Intrabronchial	Rat (100)	Lung: 0/100 *vs* 0/24	Laskin *et al.* (1970)
Chromic oxide sintered	Intramuscular	Rat (35)	15/35 local tumours	Hueper & Payne (1959)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Sodium dichromate	Inhalation	Rat (20 per group)	Lung tumours: controls, 0/37 25 μg, 0/18 50 μg, 0/18 100 μg, 3/19 (2 adenomas) 1 adenocarcinoma + 1 squamous-cell carcinoma of pharynx	Glaser *et al.* (1986)
Sodium dichromate	Intrabronchial	Rat (100)	0/89 *vs* reference[b]	Levy & Venitt (1986)
Sodium dichromate	Intrabronchial	Rat (100)	Bronchial carcinoma: 1/100 *vs* 0/100 (NS)	Levy *et al.* (1986)
Sodium dichromate	Intratracheal	Rat (80)	5 × weekly: 0/80 in all groups 1 × weekly: control, 0/80; 0.05 mg/kg, 0/80; 0.25 mg/kg, 1/80; 1.25 mg/kg, 14/80[c] ($p < 0.01$)	Steinhoff *et al.* (1986)
Sodium dichromate	Intrapleural	Rat (39)	Lung adenocarcinoma: 1/34	Hueper & Payne (1962)
Sodium dichromate	Intrapleural	Rat (?)	0/26 *vs* 0/34 local tumour	Hueper (1961)
Sodium dichromate	Intramuscular	Rat (39)	0/39 local tumour	Hueper & Payne (1962)
Sodium dichromate	Intramuscular	Rat	0/33 *vs* 0/32 local tumour	Hueper (1961)
Sodium chromate	Intrabronchial	Rat (100)	Lung: 0/89 *vs* reference[b]	Levy & Venitt (1986)
Bichromate residue (vanadium solids)	Intrabronchial	Rat (100)	Bronchial carcinoma: 1/100 *vs* reference[b]	Levy *et al.* (1986)
Zinc chromates				
Basic potassium zinc chromate	Intratracheal	Mouse (62)	Pulmonary adenomas: 31/62 *vs* 7/18	Steffee & Baetjer (1965)
Basic potassium zinc chromate	Intratracheal	Guinea-pig (21)	Pulmonary adenomas: 1/21 *vs* 0/18	Steffee & Baetjer (1965)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Basic potassium zinc chromate	Intratracheal	Rabbit (7)	0/7 *vs* 0/5	Steffee & Baetjer (1965)
Zinc potassium chromate	Intrabronchial	Rat (100)	Squamous-cell carcinoma: 3/61 *vs* reference ($p < 0.05$)	Levy & Venitt (1986)
Zinc chromate (IW)	Intrabronchial	Rat (100)	Lung: 5/100 *vs* reference[b] [$p = 0.004$]	Levy *et al.* (1986)
Zinc chromate (Norge)	Intrabronchial	Rat (100)	3/100 *vs* reference[b] [p = 0.068] NS according to authors	Levy *et al.* (1986)
Zinc tetroxychromate	Intrabronchial	Rat (100)	1/100 *vs* reference[b] (NS)	Levy *et al.* (1986)
Zinc yellow	Intrapleural	Rat	22/33 *vs* 0/34	Hueper (1961)
Zinc yellow	Subcutaneous	Rat (40)	Local tumours: control, 0/40 20% CrO_3, 6/40 40% CrO_3, 7/40	Maltoni *et al.* (1982)
Zinc yellow	Intramuscular	Rat	16/34 *vs* 0/32	Hueper (1961)
Lead chromates				
Lead chromate	Intrabronchial	Rat (100)	Bronchial carcinoma: 1/98 *vs* 0/100 (NS)	Levy *et al.* (1986)
Primrose chrome yellow	Intrabronchial	Rat (100)	1/100 *vs* reference[b] (NS)	Levy *et al.* (1986)
Molybdate chrome orange	Intrabronchial	Rat (100)	0/100	Levy *et al.* (1986)
Molybdenum orange	Subcutaneous	Rat (40)	36/40 *vs* 0/60	Maltoni (1974); Maltoni *et al.* (1982)
Light chrome yellow	Intrabronchial	Rat (100)	0/100	Levy *et al.* (1986)
Supra LC chrome yellow	Intrabronchial	Rat (100)	1/100 *vs* reference[b] (NS)	Levy *et al.* (1986)
Medium chrome yellow	Intrabronchial	Rat (100)	1/100 *vs* reference[b]	Levy *et al.* (1986)
Silica encapsulated	Intrabronchial	Rat (100)	0/100 (NS)	Levy *et al.* (1986)
Lead chromate	Intratracheal	Guinea-pig (13)	0/13	Steffee & Baetjer (1965)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Lead chromate	Intrapleural	Rat	3/34 *vs* 0/34	Hueper (1961)
Lead chromate	Intramuscular	Mouse (25)	Lymphoma, lung adenocarcinoma: not different from controls	Furst *et al.* (1976)
Lead chromate	Subcutaneous	Rat (40)	26/40 *vs* 0/60 and 1/80 local tumours	Maltoni (1974, 1976); Maltoni *et al.* (1982)
Basic lead chromate	Subcutaneous	Rat (40)	27/40 *vs* 0/60 and 1/80 local tumours	Maltoni (1974, 1976); Maltoni *et al.* (1982)
Lead chromate	Intramuscular	Rat (50)	31/47 *vs* 0/22 local tumours and 3/23 M *vs* 0/22 renal carcinomas	Furst *et al.* (1976)
Lead chromate	Intramuscular	Rat	1/33 *vs* 0/32 local tumour	Hueper (1961)
Barium chromate	Intrabronchial	Rat (101)	0/101	Levy *et al.* (1986)
Barium chromate	Intrapleural	Rat (?)	1/31 *vs* 0/34	Hueper (1961)
Barium chromate	Intramuscular	Rat (?)	0/34 *vs* 0/32 local tumour	Hueper (1961)
Barium chromate	Intramuscular	Rat (35)	0/35	Hueper & Payne (1959)
Strontium chromate	Intrabronchial	Rat (100)	Bronchial carcinoma: 43/99 *vs* reference[b]	Levy *et al.* (1986)
Strontium chromate	Intrabronchial	Rat (100)	Bronchial carcinoma: 64/99 *vs* reference[b]	Levy *et al.* (1986)
Strontium chromate	Intrapleural	Rat (?)	17/28 *vs* 0/34	Hueper (1961)
Strontium chromate	Intramuscular	Rat	15/33 *vs* 0/32 local tumour	Hueper (1961)
Other chromium compounds and chromium-containing mixtures				
Mixed chromium dust	Inhalation	Mouse (500)	As controls	Baetjer *et al.* (1959b)
Mixed chromium dust	Inhalation	Rat (78)	As controls	Steffee & Baetjer (1965)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Mixed chromium dust	Inhalation	Guinea-pig (50)	Pulmonary adenomas: 3/50 *vs* 0/44	Steffee & Baetjer (1965)
Mixed chromium dust	Inhalation	Rabbit (8)	0/8 local tumour	Steffee & Baetjer (1965)
Mixed chromium dust	Intratracheal	Mouse (506)	As controls	Baetjer *et al.* (1959b)
Mixed chromium dust	Intratracheal	Guinea-pig (19)	0/19 *vs* 0/18	Steffee & Baetjer (1965)
Mixed chromium dust plus $K_2Cr_2O_4$	Intratracheal	Rat (38)	0/38 local tumour	Steffee & Baetjer (1965)
Mixed chromium dust	Intratracheal	Rabbit (10)	0/10 local tumour	Steffee & Baetjer (1965)
Mixed chromium dust	Intrapleural	Mouse (55)	As controls	Baetjer *et al.* (1959b)
Residue dust	Intratracheal	Guinea-pig (19)	0/19 *vs* 0/18	Steffee & Baetjer (1965)
Residue dust	Intratracheal	Rabbit (7)	0/7 local tumour	Steffee & Baetjer (1965)
Roasted chromite ore	Intrapleural	Rat (25)	Bronchial carcinoma: 2/24	Hueper (1958)
Roasted chromite ore	Intrapleural	Rat (35)	3/35 *vs* 0/35	Payne (1960b)
Roasted chromite ore	Intramuscular	Mouse (52)	0/52 local tumour	Payne (1960b)
Roasted chromite ore	Intramuscular	Rat (31)	3/31 *vs* 0/15	Hueper (1958)
Roasted chromite residue	Intrapleural	Rat (32)	5/32 *vs* 0/34	Hueper (1961)
Roasted chromite residue	Intramuscular	Rat (34)	1/34 vs 0/32	Hueper (1961)
Chromate process residue	Intrabronchial	Rat (100)	1/93 *vs* 0/24	Laskin *et al.* (1970)

Table 22 (contd)

Compound	Route	Species (No. at start)	Tumour incidence[a]	Reference
Bichromate production residues (all with < 5% Cr[VI])	Intrabronchial			Levy & Venitt (1986); Levy *et al.* (1986)
Bolton high lime residue		Rat (100)	0/100	
Alumina precipitation residue		Rat (100)	0/100	
Slurry tank residue		Rat (100)	0/100	
Vanadium filter residue		Rat (100)	0/100	
Slurry disposal residue tank		Rat (100)	0/100	
Bichromate production residues with lime				
High lime residue (TSS 643D)	Intrabronchial	Rat (99)	Bronchial carcinoma: 1/99 (NS)	Levy *et al.* (1986)
Kiln frit (CTSS 643B) + 2% limestone	Intrabronchial	Rat (100)	2/100 (NS)	Levy *et al.* (1986)
Recycled residue (CTSS 643C) + 2% limestone	Intrabronchial	Rat (100)	0/100	Levy *et al.* (1986)
Pyrolysed Cr[VI]/Cr[III] 3:2 oxide	Inhalation	Rat (20)	Lung adenoma: 1/20 *vs* 0/40	Glaser *et al.* (1986)
Chromium[IV] dioxide	Inhalation	Rat		
Unstabilized (0.5 mg/m³)		(240)	0/240 *vs* 0/240	Lee *et al.* (1988)
Stabilized (0.5 and 25 mg/m³)		(480)	2/210 adenomas 6/108 keratin cysts 2/108 cystic keratin squamous lesions	

[a]NS, not significant

[b]*p*-Value calculated by comparing the incidence of bronchial carcinomas in each test group with that in a reference group comprising the two negative control groups and all the groups receiving chromium-containing materials

[c]No. of tumour-bearing animals

3.2 Other relevant data in experimental systems

(a) *Absorption, distribution, excretion and metabolism*

The metabolism of chromium has been reviewed (Aitio *et al.*, 1988; Nieboer & Jusys, 1988; World Health Organization, 1988). De Flora and Wetterhahn (1990) have specifically reviewed the redox chemistry of chromium[VI] with respect to cellular metabolism; a metabolic model has been suggested by Elinder *et al.* (1988).

(i) *Metallic chromium and chromium alloys*

Chromium-cobalt alloys appear to release chromium[VI] after intramuscular implantations in rats (Wapner *et al.*, 1986). Chromium metal powder released chromium[VI] when incubated in aerated phosphate buffer, Ringer's solution, phosphate buffer with added bicarbonate and Locke's physiological buffer (Grogan, 1957).

(ii) *Chromium[III] compounds*

In contrast to chromium[VI] compounds, less than 1% of chromium[III] is absorbed from the gastrointestinal tract of animals (Mertz, 1969).

Four hours after intratracheal instillation of chromic chloride in rabbits, 85% of the chromium remained in the lungs and 8% was found in the urine; after uptake, chromium was confined mainly to plasma, and the peak concentration was reached after 20 min (Wiegand *et al.*, 1984a).

After exposure of rats by inhalation to chromic chloride particles (mass median aerodynamic diameter (MMAD), 1.8 and 1.5 μm; 19 and 27% less than 1 μm; 8-10.7 mg chromium/m^3), only one clearance phase was demonstrated, with a half-time of about 160 h (Suzuki *et al.*, 1984). As with chromium[VI] compounds, the highest organ concentrations in both rats and rabbits were found in the kidney and liver after exposure to chromic chloride by the pulmonary route, although the concentrations found were lower than those after a corresponding exposure to chromium[VI] (Suzuki *et al.*, 1984; Wiegand *et al.*, 1984a).

Chromium (especially trivalent chromium) strongly accumulated in the interstitial tissues of the gonads of male mice, but not in seminiferous epithelium (Danielsson *et al.*, 1984).

Little chromium[III] is taken up by cells (Aaseth *et al.*, 1982; Nieboer & Jusys, 1988), but more of some organic chromium[III] complexes may be taken up (Yamamoto *et al.*, 1981; Norseth *et al.*, 1982).

After parenteral administration of chromium[III] to rats (as with chromium[VI]), chromium is excreted predominantly in the urine (National Research Council, 1974; Langård, 1980, 1982). Less than 2% of an intravenous dose of chromic chloride was found in the faeces of rats 8 h after injection (Hopkins, 1965). In a

subsequent study, seven days after intraperitoneal injection of chromic chloride to mice, the cumulated amounts excreted in faeces and urine were about equal (Bryson & Goodall, 1983).

Studies on the mechanism of excretion of chromium[III] by the kidneys indicate that glomerular filtration is the major mechanism (Donaldson *et al.*, 1986).

As with chromium[VI], biliary excretion of chromic chloride has been demonstrated in rats (Cikrt & Bencko, 1979; Norseth *et al.*, 1982); less than 1% of an intravenously injected dose of chromic chloride was excreted in 5 h (Norseth *et al.*, 1982).

The elimination curve for chromium, as measured by whole-body determination, has an exponential form. In rats, three different components of the curve have been identified, with half-times of 0.5, 5.9 and 83.4 days after intravenous injection of chromic chloride at 1 μg/kg bw Cr (Mertz *et al.*, 1965).

In contrast to results with hexavalent chromium, a single intraperitoneal injection of chromic chloride to mice resulted in 45% retention of chromium three weeks after the injection (Bryson & Goodall, 1983).

In mice administered sodium dichromate, chromium was shown to cross the placenta throughout gestation; transfer was more effective than with chromic chloride, which was not detectably transferred during early gestation, although placental transfer of chromium[III] did occur during late gestation (Danielsson *et al.*, 1982).

A total of 25-30% of chromium administered as chromic chloride to pregnant rats on days 17-20 of gestation was transferred to the placental-fetal unit (Wallach & Verch, 1984). Groups of ICR mice were given a single intraperitoneal injection of [^{51}Cr]chromic chloride on day 8 of gestation and were sacrificed 4, 8 and 12 h after injection. The radioactivity in the fetus increased with time since injection, whereas maternal blood levels decreased (Iijima *et al.*, 1983a).

(iii) *Chromium[VI] compounds*

Gastrointestinal absorption of chromates has been reported. In a review, 3-6% of an administered dose was reported to appear in the urine of rats; this may be an underestimate of the absorption from the gastrointestinal tract, which also takes part in chromium excretion (Mertz, 1969). The absorption of chromates depends on the degree of reduction of chromium[VI] to chromium[III], which is poorly absorbed from the gastrointestinal tract (Donaldson & Barreras, 1966; De Flora *et al.*, 1987a).

Following intratracheal administration of sodium chromate solution to rabbits, about 45% (as Cr) remained in the lungs 4 h after instillation; 15% was excreted in urine. The highest concentration of chromium[VI] was reached in red cells after about 3 h, and the corresponding plasma concentration at that time was about one-third of that in red cells (Wiegand *et al.*, 1984a). Absorption from the lungs may be decreased by extracellular reduction of the hexavalent form (Suzuki, 1988).

Zinc chromate was absorbed in rats exposed to known atmospheric concentrations (6.3-10.7 mg/m^3, equivalent to 1.3-2.2 mg/m^3 Cr) in an inhalation chamber: a five-fold increase in the blood chromium level was observed after 100 min of exposure by inhalation, and this level increased at a similar rate during the next 150 min (Langård *et al.*, 1978).

Suzuki *et al.* (1984) exposed rats by inhalation to potassium dichromate particles (MMAD, 1.6-2.0 μm: 12-25% of particles < 1 μm; determined by multistage impactor (Andersen Sampler) and controlled by electron microscopy). A two-phase clearance pattern for chromium was demonstrated, the smaller particles having half-times of 30 h and 700 h; for larger particles, a single phase with a half-time of 160 h was demonstrated. [The Working Group noted that no statistical evaluation of the differences is given in the paper.] The authors stated that there might also be an undetected rapid component for the larger particles and noted that reduction of the hexavalent form may explain the two-phase clearance from the respiratory tract after exposure to chromium[VI]. This reduction was demonstrated by Suzuki (1988).

Sodium chromate (69 μg Cr), zinc chromate (66 μg Cr) and lead chromate (38 μg Cr), all at 20 μl, were injected intratracheally into Wistar rats; 30 min later, 36, 25 and 81% of the doses, respectively, were still present in the lungs. From 30 min and up to six days, lung clearance followed first-order kinetics, with half-times of 2.4 days for sodium chromate, 1.9 days for zinc chromate and 1.8 days for lead chromate. Limited amounts of chromium were found in blood and organs after exposure to lead chromate; the concentrations found were similar with sodium and zinc chromates. At ten days, 20% of the dose of sodium and zinc chromates had been excreted in the urine; negligible amounts of lead chromate were found. After exposure to lead chromate, about 80% of the chromium was excreted in faeces during the same interval (Bragt & van Dura, 1983).

Percutaneous absorption of labelled sodium chromate occurred in guinea-pigs (Wahlberg & Skog, 1963): a maximum of 4% of the dose applied on the skin disappeared within 5 h, and labelled chromium was detected in a number of organs.

Following administration of chromium[VI], most of the chromium found in the blood is bound to red blood cells (Mutti *et al.*, 1979; Suzuki *et al.*, 1984; Wiegand *et al.*, 1984a). After exposure of rats by inhalation to potassium dichromate or of rabbits by inhalation to sodium dichromate, the highest concentrations were found in the kidney and liver (Suzuki *et al.*, 1984; Wiegand *et al.*, 1984a). The spleen also contained high concentrations of chromium after subcutaneous administration of potassium dichromate to rats (Mutti *et al.*, 1979). The organ concentrations after exposure to chromium[VI] were always much higher than after a corresponding exposure to chromium[III] (Suzuki *et al.*, 1984; Wiegand *et al.*, 1984a).

After parenteral administration of chromium[VI] to rats, chromium was excreted predominantly in the urine (National Research Council, 1974; Langård, 1980, 1982). Seven days after intraperitoneal injection of potassium chromate to mice, urinary excretion was twice as high as faecal excretion; following administration of chromium[III], faecal excretion was three times as high as urinary excretion (Bryson & Goodall, 1983).

Subcutaneous injections of 3 mg/kg bw potassium dichromate were given to rats every other day for eight weeks. Urinary elimination of chromium increased steadily during the experiment and was correlated with the concentration of chromium in the renal cortex (Franchini *et al.*, 1978).

Elimination of chromium from the blood of rats exposed by inhalation to zinc chromate was slow: the blood chromium level fell by less than 50% during the first three days after exposure; and after 18 and 37 days 20% and 9% of the initial concentration, respectively, remained. Excretion occurred mainly *via* the urine (Langård *et al.*, 1978).

Biliary excretion of chromium following administration of sodium dichromate has been demonstrated in rats (Cikrt & Bencko, 1979; Norseth *et al.*, 1982); 6-8% of an intravenous dose of sodium dichromate was excreted in 5 h (Norseth *et al.*, 1982).

Three weeks after a single intraperitoneal injection of potassium dichromate to mice, 7.5% chromium was retained. After repeated weekly intraperitoneal injections of potassium dichromate, about 3% of chromium was retained eight weeks after the first injection. In both cases, this level is about one-sixth of that observed after administration of chromium[III] (Bryson & Goodall, 1983).

Chromium[VI] (tested as sodium dichromate and as an unspecified chromate *in vitro*) was transported effectively through mammalian cell membranes by the carboxylate, sulfate and phosphate carrier systems; the kinetics of uptake also involve intracellular reduction to the trivalent form (Sanderson, 1976; Wetterhahn-Jennette, 1981; Aaseth *et al.*, 1982; Alexander *et al.*, 1982). Chromium[VI] (tested as sodium dichromate) was rapidly reduced to chromium[III] after cellular uptake, but such reduction may also take place outside the cell, with decreased uptake as a result (De Flora *et al.*, 1987a; Suzuki, 1988). Glutathione seems to be the most important factor for intracellular reduction of chromium[VI], but ascorbic acid, microsomes in the presence of NAD/NADH microsomal cytochrome P450, mitochondria and proteins such as haemoglobin and glutathione reductase in red blood cells may also be active in the reduction process (Connett & Wetterhahn, 1983; Ryberg & Alexander, 1984; Wiegand *et al.*, 1984b; Connett & Wetterhahn, 1985; De Flora & Wetterhahn, 1990). Once absorbed and retained in biological tissue, chromium compounds occur in the trivalent form (Mertz, 1969). Initial binding may involve the pentavalent form (Rossi & Wetterhahn, 1989). When the reducing

capacity of liver cells is decreased, the hexavalent form may be found in bile (Norseth *et al.*, 1982).

After treatment of rats with sodium dichromate at 20 mg/kg bw intraperitoneally (134 μmol/kg bw Cr), more of the chromium associated with chromatin was bound to DNA than was the case after chromic chloride treatment (Cupo & Wetterhahn, 1985a).

The intracellular reduction of hexavalent chromium implies the generation of short-lived species of pentavalent and tetravalent chromium with affinities that differ from that of the trivalent form (Connett & Wetterhahn, 1983). The pentavalent form is stabilized by increased amounts of glutathione (Kitagawa *et al.*, 1988). The reduction process thus serves as a detoxification process even intracellularly, when it takes place at a distance from the target site for toxic or genotoxic effect; it serves to activate if it takes place near the cell nucleus, presumably of target organs (De Flora & Wetterhahn, 1990). It has been suggested that phagocytosis may be important for the uptake of hexavalent compounds — in particular soluble forms — as it would allow the slow intracellular release of chromate ions over a long time (Norseth, 1986).

(*b*) *Toxic effects*

As a general rule, chromium[VI] is much more toxic than chromium[III] when administered to animals, and very marked differences in the cytotoxicity of compounds of the two oxidation states have been observed *in vitro*. Effects on the kidney and the respiratory organs are the most important (for reviews, see Nieboer & Jusys, 1988; World Health Organization, 1988).

The mean intravenous lethal dose in mice is 85 mg/kg bw chromic sulfate, 400-800 mg/kg bw chromic chloride and 2290 mg/kg bw chromic acetate (National Research Council, 1974). The LD_{50} in rats for potassium dichromate administered by stomach tube was reported to be 177 mg/kg for males and 149 mg/kg for females (World Health Organization, 1988).

(i) *Chromium[III] compounds*

Morphological changes in rabbit alveolar macrophages occurred after exposure by inhalation to chromic nitrate (0.6 mg/m^3 Cr) for four to six weeks. Fewer macrophages were obtained by lavage than with chromium[VI], but only chromium[III] caused functional changes in macrophages, measured by increased metabolic activity and reduced phagocytotic activity. The authors speculated that these effects may be due to the release of chromium[III] ions from phagocytized particles, with subsequent binding to macromolecules in the cell. Such particles were not seen after exposure to chromium[VI] (Johansson *et al.*, 1986).

Chromium[III] has been found in ribonucleic acids from all sources examined. It is possible that chromium helps stabilize the structure of RNA (Wacker & Vallee,

1959). Chromium bound to only a limited extent to chromatin and DNA from the liver and kidney of rats treated intraperitoneally with chromic chloride at 80 mg/kg bw (290 μmol/kg bw Cr), as indicated in a study by Tsapakos *et al.* (1983a); DNA damage, as measured by alkaline elution, was not demonstrable in kidney after injection of chromium[III]. The binding of chromic nitrate to denatured or native DNA was limited and relatively unaffected by the presence of microsomes and NADPH (Tsapakos & Wetterhahn, 1983).

Chromic chloride was 100 times less effective than chromium[VI] in inhibiting DNA synthesis (Levis *et al.*, 1978a). A large difference in cytotoxic activity between chromium[VI] and chromium[III] was also noted when the effects of 11 water-soluble chromium compounds on BHK cells were compared: of the chromium[III] compounds, only chromic nitrate appeared to be cytotoxic, but it was contaminated with chromium[VI] at about 0.2% (Levis & Majone, 1979).

Chromic chloride inhibited the uptake of ribo- and deoxyribonucleosides by BHK cells (Levis *et al.*, 1978a). In contrast to chromium[VI], chromic chloride inhibited the plasma membrane Mg^{2+}-ATPase activity of BHK cells only when it was present in the incubation medium and not when cells were pretreated with it (Luciani *et al.*, 1979).

Chromic oxide particles are taken up by cells by phagocytosis; chromium[III] may thus reach its target sites even if it is not derived from intracellular chromate ion. An inhibitory effect on cell cycle progression in Chinese hamster cells was demonstrated after exposure to crystalline chromic oxide (particle size, 91% < 1 μm; purity, 99.8%) at concentrations ranging from 50 to 200 μg/ml (Elias *et al.*, 1986). Chromic chloride does, however, stimulate RNA synthesis both *in vitro* and *in vivo* in mouse liver and in regenerating rat liver (Okada *et al.*, 1981, 1983, 1984).

(ii) *Chromium[VI] compounds*

Renal lesions in animals are confined to the proximal convoluted tubules (for review, see National Research Council, 1974; Aitio *et al.*, 1988; World Health Organization, 1988). In rats exposed to a single subcutaneous dose of 15 mg/kg bw potassium dichromate, increases in urinary β-glucuronidase, lysozyme, glucose and protein as well as morphological changes in renal tubules were observed, although the glomerular filtration rate was unchanged (Franchini *et al.*, 1978).

Ngaha (1981) demonstrated that urinary volume was increased with increased amounts of acid and alkaline phosphatases in the urine in rats after subcutaneous injection of potassium dichromate at 25 mg/kg. The concentrations of the phosphatases and of lactate dehydrogenase in kidney tissue decreased. No significant change in the levels of these enzymes in liver tissue was demonstrated.

Morphological changes occurred in rabbit alveolar macrophages after exposure by inhalation to sodium chromate (0.9 mg/m^3 Cr) for four to six weeks. Significantly more macrophages were present in the lavage fluid from the chromium[VI]-exposed animals than in those exposed to chromium[III], but functional changes in macrophages were observed after exposure to chromium[III] and not after exposure to chromium[VI] (Johansson *et al.*, 1986). Activation of phagocytosis was demonstrated in rat alveolar macrophages after exposure to 25-50 μg/m^3 sodium dichromate by inhalation for 28 days; exposure to 200 μg/m^3 for the same interval inhibited phagocytotic function. Lung clearance of inhaled [^{59}Fe] iron oxide was significantly decreased after exposure to the high dose of sodium dichromate. The antibody response to sheep red blood cells and the mitogen-stimulated T-lymphocyte response were stimulated at the low doses but inhibited at the high dose (Glaser *et al.*, 1985).

Exposure of cats by inhalation to 11-23 mg/m^3 chromium[VI] as dichromate for 2-3 h/day during five days caused bronchitis and pneumonia. In rabbits exposed similarly, no effect was observed. Mixed dusts containing chromates (7 mg/m^3 as chromium trioxide) were fatal to mice when inhaled for 37 h over ten days; whereas no marked effect was noted in rabbits or guinea-pigs that inhaled 5 mg/m^3 (as chromium trioxide) for 4 h/day on five days/week for one year (National Research Council, 1974). Increased subepithelial connective tissue and flattened epithelium in the large bronchi were observed in mice exposed to chromate (Nettesheim *et al.*, 1971).

In chronically treated cell cultures, chromium[VI] was much more active than chromium[III] in reducing cell growth and survival, independently of the particular compound used (Bianchi *et al.*, 1980). Chromium bound to chromatin and DNA from liver and kidney of rats treated intraperitoneally with sodium dichromate (140 μmol [7.2 mg]/kg as Cr) (Tsapakos *et al.*, 1983a) Binding of chromium to nucleic acids *in vitro* depends on the reduction of the chromium[VI] to chromium[III]. In contrast to chromium[III], binding to denaturated or native DNA was demonstrated with potassium dichromate only in the presence of the complete microsomal reducing system (Tsapakos & Wetterhahn, 1983).

Potassium dichromate induced a rapid blockage of DNA replication in Syrian hamster fibroblasts (BHK line), whereas RNA and protein synthesis were inhibited secondarily (Levis *et al.*, 1978b). It also reduced the colony-forming ability of BHK cells at 10^{-7}-10^{-4}M. It facilitated the uptake of ribo- and deoxyribonucleosides in BHK cells (Levis *et al.*, 1978a). The effect of potassium dichromate on the nucleoside pool in BHK cells could not be explained solely by changes in transport (Bianchi *et al.*, 1979). Plasma membrane Mg^{2+}-ATPase activity of BHK cells was inhibited when the cells were pretreated with potassium dichromate, even when chromate was absent from the assay medium (Luciani *et al.*, 1979). Mitochondrial

respiration was inhibited by about 50% by the addition of 25 μM [1.3 mg] sodium chromate in rat liver (Ryberg & Alexander, 1984).

(*c*) *Effects on reproduction and prenatal toxicity*

(i) *Chromium[III] compounds*

Treatment of sea-urchin sperm with potassium chromic sulfate or chromic nitrate (5×10^{-5}-5×10^{-4} M [2.6-26 mg]) before fertilization failed to induce larval malformation (Pagano *et al.*, 1983).

In cultured mouse embryos, chromium nitrate (0.02-2 μg/ml Cr) caused less impairment of blastocyst formation and inhibition of hatching from the zona pellucida to the formation of the inner cell mass than the chromium[VI] salts tested (Jacquet & Draye, 1982).

In contrast to chromium[VI], chromic chloride showed no overt cytotoxicity in chick limb bud mesenchymal cells *in vitro* (Danielsson *et al.*, 1982).

Groups of 30 pregnant ICR mice were given a single intraperitoneal injection of [^{51}Cr]chromic chloride (19.5 mg/kg bw Cr) on day 8 of gestation and were sacrificed at intervals of 4-192 h after injection. More pyknotic cells were observed in the neural plate of experimental embryos than controls [percentages not given], especially by 8 h after injection (Iijima *et al.*, 1983a).

A dose-dependent increase in the frequency of rib fusion in fetuses (6-16%, depending on dose) and exencephaly and anencephaly were seen occasionally at higher dose levels following intraperitoneal injection of 9.8-24.4 mg/kg bw chromic chloride to mice on day 8 of gestation. Maternal effects were not described (Matsumoto *et al.*, 1976).

(ii) *Chromium[VI] compounds*

Treatment of sea-urchin sperm with sodium chromate before fertilization resulted in a number of abnormal larvae, depending on length of exposure and concentration. Sea-urchin embryos reared in the presence of chromate at 5×10^{-5}-5×10^{-4} M had retarded differentiation of the gut and skeleton (Pagano *et al.*, 1983).

Cultured mouse embryos at the two-cell stage were incubated in Brinster's medium with potassium chromate or calcium chromate (0.02-2 μg/ml Cr). Blastocyst formation was damaged, and hatching of the blastocyst from the zona pellucida to the formation of the inner cell mass was inhibited (Jacquet & Draye, 1982).

As reported in an abstract, male mice were administered 3×10^{-3} M [882 mg] potassium bichromate by either intratesticular or intraperitoneal injection, then mated weekly. A decrease in the number of sperm was seen after three weeks of treatment, and abnormalities in shape reached about 50% of the total sperm after four weeks of treatment. Decreases in the number of implantation sites, in litter size and in fetal body weight were observed. No conspicuous malformation of fetuses

was detected. None of the females became pregnant after three weeks of treatment of males (Yasuda, 1980).

Sodium chromate inhibited chondrogenesis in chick limb bud mesenchymal cells *in vitro* at concentrations of about 0.1 μg/ml Cr (Danielsson *et al.*, 1982).

Chromium trioxide dissolved in saline was injected into the air sacs of embryonated chicken eggs at doses of 0.002-0.05 mg/egg on days 0-4 of incubation. Control eggs were injected with a comparable volume of saline. All embryos were examined on day 8, and malformations, such as short and twisted limbs, microphthalmia, exencephaly, short and twisted neck, everted viscera, oedema and reduced body size, were observed in treated eggs. Most embryos showed unilateral or bilateral limb defects (Gilani & Marano, 1979).

Chromium trioxide was administered intravenously at doses of 5, 7.5, 10 or 15 mg/kg bw to groups of ten pregnant golden hamsters early on day 8 of gestation. Fetuses were collected on gestation days 12, 14 and 15 and were examined for frequency and types of malformations. In the different dose groups, 6-40% of the fetuses were resorbed and 1-100% of fetuses had growth retardation; 2% of control fetuses were resorbed. Maternal toxicity (mortality, decreased weight gain, kidney tubular necrosis) was seen in treated animals. Cleft palate occurred in 34-85% of exposed fetuses (2% in controls) and defects in skeletal ossification in up to 96% (Gale, 1978). On comparing five strains of hamsters (ten animals per group, exposure to 8 mg/kg bw on day 8), different susceptibilities were observed: three strains were very susceptible to the embryotoxic effects, while the others were more resistant. In the more susceptible strains, the percentage of resorption sites was 13-28%, whereas in the less susceptible strains it was 7-11%. External abnormalities observed were cleft palate (0-30%) and hydrocephalus. Maternal toxicity (decreased weight gain) was seen in all groups. The time of administration of the chromium trioxide was important: cleft palate was induced only when chromium was administered on day 7, 8 or 9 of gestation and not when it was given on day 10 or 11 (Gale & Bunch, 1979; Gale, 1982).

(*d*) *Genetic and related effects*

The activity of chromium and chromium compounds in tests for genetic and related effects was evaluated in previous *IARC Monographs* (1980a, 1982, 1987a,b). Moreover, a number of reviews on this subject are available in the literature (e.g., Heck & Costa, 1982a,b; Léonard & Lauwerys, 1980; Petrilli & De Flora, 1980; Paschin & Kozachenko, 1981; Levis & Bianchi, 1982; Petrilli & De Flora, 1982; Baker, 1984; Bianchi & Levis, 1984; Hansen & Stern, 1984; Bianchi & Levis, 1985; Petrilli *et al.*, 1986a,b; Sunderman, 1986; Venitt, 1986; Bianchi & Levis, 1987, 1988; Nieboer & Shaw, 1988; World Health Organization, 1988; De Flora *et al.*, 1990).

Over 600 reports have been published on 32 chromium compounds of various oxidation states and solubilities, and the data base covers 125 experimental systems with different endpoints and/or targets. The studies described below are summarized in Appendix 1 to this volume.

(i) *Metallic chromium*

Metallic chromium was assayed for the ability to induce cell transformation (anchorage-independent growth) in Syrian hamster BHK fibroblasts. Although chromium particles were phagocytized by cells, no significant increase in the number of cell foci growing in soft agar was observed (Hansen & Stern, 1985). [See General Remarks, p. 44, for concerns about this assay.]

As reported in an abstract, male Sprague-Dawley rats were exposed to chromium fumes generated from powders of chromium metal by a plasma flame sprayer at concentrations of 1.84 ± 0.55 mg/m^3 or 0.55 ± 0.07 mg/m^3 fume for 5 h/day on five days a week for one week or two months. Significant increases in the frequencies of sister chromatid exchange and of chromosomal aberrations were observed in peripheral blood lymphocytes, whereas chromosomal aberration frequencies in bone-marrow cells were unchanged (Koshi *et al.*, 1987). [The Working Group noted that some oxidation of metallic chromium may have occurred during generation of the fumes.]

(ii) *Chromium[III] compounds*

Twelve chromium[III] compounds of various water solubilities were assayed in a number of short-term tests, often at the same time as chromium compounds of other oxidation states. They included: (a) highly soluble compounds, such as chromic chloride, chromic acetate, chromic nitrate, chromic sulfate and chromic potassium sulfate; (b) sparingly soluble products, such as basic chromic sulfate or neochromium, chromium alum and chromic phosphate; and (c) almost insoluble compounds, such as chromic hydroxide, chromic oxide, chromite ore and cupric chromite. In addition, several reports dealt with the activity of chromium[III] tannins and of chromium[III] compounds bound to organic ligands, as described below. In evaluating the results, summarized in Appendix 1, it should be noted that some of the positive results, obtained with both pure laboratory compounds and industrial products, might be due to contamination by traces of chromium[VI] (indicated as [+] in Appendix 1); therefore, reported positive results with chromium[III] compounds should be interpreted with caution, particularly for those studies in which the purity of test compounds was not checked.

In several studies, the activity of chromic chloride in acellular (i.e., purified nucleic acids) or subcellular (i.e., cell nuclei) systems was investigated. Depurination of calf thymus DNA did not occur, as shown by the unchanged release of adenine detectable by thin-layer chromatography. In addition, it did not induce

mutation of single-stranded ϕ X 174 *am*3 DNA, transfected into *Escherichia coli* spheroplasts and then tested for reversion in a progeny phage assay (Schaaper *et al.*, 1987). As reported previously, chromium[VI] trioxide was also inactive in this system; chromic chloride, however, induced *lacZ*α forward mutation in double-stranded M13mp2 DNA, transfected into JM101 *E. coli* (Snow & Xu, 1989). Moreover, chromic chloride suppressed the infectivity of tobacco mosaic virus RNA, probably by nonenzymic cleavage of internucleotide phosphodiester bonds (Huff *et al.*, 1964). Assessments of viscosity, ultraviolet absorption spectra and thermal denaturation of purified DNA and RNA showed that, at variance with chromium[VI] which (as an oxidizing agent) breaks the polynucleotide chain (see potassium dichromate), chromium[III] is responsible for physicochemical alterations of nucleic acids by interacting with the phosphate groups and nitrogen bases (Tamino & Peretta, 1980; Tamino *et al.*, 1981). As evaluated by nucleotide incorporation into calf thymus DNA in the presence of *E. coli* DNA polymerase, chromic chloride inhibited DNA synthesis more potently than chromium[VI] (potassium dichromate); however, at levels below the inhibitory concentration, it enhanced nucleotide incorporation (Nishio & Uyeki, 1985). Like chromium[VI] (potassium dichromate), chromic chloride increased misincorporation of nucleotide bases into daughter DNA strands synthesized from a synthetic polynucleotide template, poly[d(A-T)], in the presence of avian myeloblastosis virus or *E. coli* DNA polymerases (Sirover & Loeb, 1976; Tkeshelashvili *et al.*, 1980). The misincorporated bases were present as single-base substitutions (Tkeshelashvili *et al.*, 1980). In contrast to chromium[VI] salts (potassium chromate and potassium dichromate), chromic chloride favoured cross-links between *E. coli* DNA and bovine serum albumin, as assessed by checking ^{3}H-DNA-bovine serum albumin binding in a filtration assay (Fornace *et al.*, 1981). The same chromium[III] compound produced DNA fragmentation (alkaline elution technique), as determined by single-strand breaks and cross-links in isolated calf thymus nuclei (Beyersmann & Köster, 1987) and in purified DNA from V79 cells (Bianchi *et al.*, 1983). DNA-protein cross-links were also detected by exposing nuclei of mouse leukaemia L1210 cells to chromic chloride; chromium[VI] (potassium chromate) was inactive (Fornace *et al.*, 1981).

Most studies in which the activity of chromium[III] compounds was evaluated in prokaryotes yielded negative results. Chromic chloride did not induce λ prophage in *E. coli* WP2$_{s}$(λ) (Rossman *et al.*, 1984) after overnight incubation at concentrations near the growth inhibitory concentration of the compound. No SOS response was induced in *E. coli* GC2375, UA4202 or PQ30 by chromic chloride, chromic nitrate or chromic acetate (Llagostera *et al.*, 1986), or in strain PQ37 by chromic potassium sulfate (De Flora *et al.*, 1985a) or chromic chloride (Olivier & Marzin, 1987). Chromic nitrate, chromic chloride and chromic potassium sulfate

were confirmed to be inactive in strain PQ37, whereas chromic acetate produced a low but significant increase in SOS-inducing activity (Venier *et al.*, 1989).

In differential killing assays with *E. coli*, chromic chloride was equally toxic in the wild strain AB1157 and in the repair-deficient strains AB1886 (*uvrA6*$^-$), GW801 (*recA56*$^-$), GW802 (*recA56*$^-$*uvrA6*$^-$), PAM AA34 (*recA56*$^-$*lexA2*$^-$) and PAM5717 (*lexA2*$^-$) (Warren *et al.*, 1981).

Chromic chloride, chromic phosphate and chromic oxide (spotted in powder form) were equally toxic in *E. coli* WP2 (wild strain) and in the repair-deficient strains WP2 *uvrA* (*uvrA*$^-$), CM571 (*rec A*$^-$) and WP100 (*uvrA*$^-$ *rec A*$^-$), as assessed by the streak method on agar and, in the case of chromic phosphate, by means of a test-tube assay (Yagi & Nishioka, 1977).

Chromic chloride and chromic acetate were equally toxic to WP2 and to the repair-deficient strains WP67 (*uvrA*$^-$*polA*$^-$) and CM871 (*uvrA*$^-$*recA*$^-$*lexA*$^-$) when assayed in the treat-and-plate test, but these compounds, chromic nitrate and chromic potassium sulfate were more toxic in the repair-deficient strains when assayed by a liquid micromethod (De Flora *et al.*, 1984a). Four conditions were required to elicit this unusual positivity of chromium[III] in this system: (a) performance of the test in a liquid medium, (b) long contact between chromium[III] and bacteria (at least 6-8 h), (c) a physiological pH (7.0-7.4) and (d) the presence of high, subtoxic concentrations (0.2-0.3 M) of phosphate (De Flora *et al.*, 1990). Chromic chloride, chromic sulfate and chromic potassium sulfate did not induce differential killing of *S. typhimurium* TA1978 (wild strain) or TA1538 (*rec*$^-$) (Gentile *et al.*, 1981). In the *rec* assay in *Bacillus subtilis* H17 (wild strain) and M45 (*rec*$^-$), negative results were obtained with chromic chloride (Nishioka, 1975; Nakamuro *et al.*, 1978; Matsui, 1980; Gentile *et al.*, 1981), chromic sulfate and chromic potassium sulfate (Kada *et al.*, 1980; Kanematsu *et al.*, 1980; Gentile *et al.*, 1981). Positive results were obtained in this system, using the spot test procedure, with chromic acetate and chromic nitrate. Chromic acetate also gave positive results in the *arg*$^-$ → *arg*$^+$ reversion test in *E. coli* Hs30R (Nakamuro *et al.*, 1978).

No reversion of *trp*$^-$ → *trp*$^+$ was produced in *E. coli* by chromic chloride or chromic acetate (strains WP2 and WP2*uvrA*) (Petrilli & De Flora, 1982) or by chromic sulfate (strain DG1153) (Arlauskas *et al.*, 1985). In a *lacI*$^+$/*lacI*$^-$ forward mutation assay in *E. coli* KMBL3835, chromic chloride yielded unclear results (Zakour & Glickman, 1984).

In more than 30 reports (see Appendix 2), highly soluble or sparingly soluble chromium[III] compounds were inactive in the *his*$^-$ → *his*$^+$ reversion test in several strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA92, TA94, TA97, TA98, TA100 and TA102) in the absence of exogenous metabolic systems (Tamaro *et al.*, 1975; Petrilli & De Flora, 1977, 1978a; De Flora, 1981a; Tso & Fung, 1981; Venier *et al.*, 1982; Bennicelli *et al.*, 1983; Bianchi *et al.*, 1983; De Flora *et al.*, 1984a,b;

Arlauskas *et al.*, 1985; Langerwerf *et al.*, 1985; Loprieno *et al.*, 1985; Marzin & Phi, 1985; Petrilli *et al.*, 1985). Chromic chloride, chromic nitrate, chromic potassium sulfate, chromium alum and neochromium were still not mutagenic in the presence of metabolic systems, including post-mitochondrial supernatants of rat liver, lung or muscle, rat muscle mitochondria (with or without ATP), human erythrocyte lysates and oxidized glutathione. Mutagenic effects were produced by all these compounds only in the presence of a strong oxidizing agent, such as potassium permanganate (Petrilli & De Flora, 1978a). The inactivity of chromic sulfate was unaffected by the presence of nitrilotriacetic acid (NTA) (Loprieno *et al.*, 1985). Surprisingly, high amounts of chromic chloride [unspecified source and purity] were reported to be weakly mutagenic to strains TA98 and TA94 in one study (Langerwerf *et al.*, 1985). Other positive results can be ascribed to contamination with traces of chromium[VI], in a chromic nitrate sample (Venier *et al.*, 1982; Bianchi *et al.*, 1983) and in an industrial chromite sample (Petrilli & De Flora, 1978a; De Flora, 1981a; Venier *et al.*, 1982; Bianchi *et al.*, 1983).

Chromic chloride was reported to induce mitotic gene conversion at the *trp5* locus and point reverse mutation at the *ilv* locus in strain D7 of *Saccharomyces cerevisiae*. Such activity, usually detected when the yeast was in the logarithmic growth phase, was very weak, was obtained only with high doses of chromium[III] and occurred only in the presence of 0.1 M phosphate; no activity was seen when 0.05 M Tris-hydrochloric acid was used as the buffer (Galli *et al.*, 1985; Bronzetti *et al.*, 1986).

Chromic potassium sulfate gave weakly positive results in an unscheduled DNA synthesis assay in mature pollen of *Petunia hybrida* (W166K) (Jackson & Linskens, 1982). [The Working Group noted that the effect was very weak and that the existence of a dose-response relationship was not investigated.] Chromic nitrate induced chromosomal aberrations in the root tips of *Vicia faba* (Gläss, 1955).

A study of the cytotoxic effects produced in Syrian hamster BHK monolayers and of mitotic cycle alterations in human epithelial-like heteroploid HEp2 cells produced by chromic chloride, chromic sulfate, chromium alum, neochromium and chromium[VI]-contaminated chromite provided evidence that chromium[III] is far less active than chromium[VI] (Levis & Majone, 1981). Chromic chloride did not induce unscheduled DNA synthesis in mouse kidney A18BcR cells (Raffetto *et al.*, 1977) or human heteroploid EUE cells (Bianchi *et al.*, 1983). It did not inhibit DNA synthesis in Syrian hamster BHK fibroblasts, even when the cells were reversibly permeabilized in hypertonic medium (Bianchi *et al.*, 1984), or in mouse L cells unless they were permeabilized with detergents (Nishio & Uyeki, 1985).

Chromic chloride did not induce DNA fragmentation in mouse leukaemia 1210 cells (Fornace *et al.*, 1981), in Chinese hamster V79 cells (Bianchi *et al.*, 1983) or in human embryo lung IMR-90 fibroblasts (Fornace *et al.*, 1981), as assessed by al-

kaline elution, or in human white blood cells, as assessed by the alkaline unwinding technique (McLean *et al.*, 1982). Similarly, chromic nitrate, even at concentrations up to 25 times those of chromium[VI] compounds needed to damage DNA, did not produce DNA fragmentation (alkaline elution) in chicken embryo hepatocytes (Tsapakos *et al.*, 1983b). In contrast, a sample of cupric chromite induced DNA-protein cross-links in Novikoff ascites hepatoma cells, as evaluated by high-speed centrifugation of detergent-treated cells followed by polyacrylamide gel electrophoresis; chromous chloride was inactive in this test (Wedrychowski *et al.*, 1986a).

Using the *hprt* forward mutation assay, negative results were obtained with chromic sulfate in mouse mammary carcinoma Fm3A cells (8-azaguanine resistance) (Nishimura & Umeda, 1978 [Abstract]), with chromic acetate in Chinese hamster V79/4 cells (8-azaguanine resistance) (Newbold *et al.*, 1979) and in CHO cells (6-thioguanine resistance) (Bianchi *et al.*, 1983). In V79 cells, a sample of chromic oxide, uncontaminated with chromium[VI] was phagocytized, as shown by electron microscopic detection of intracytoplasmic vacuoles containing crystalline chromic oxide particles, after an 18-h exposure of cells; it also induced 6-thioguanine resistance (Elias *et al.*, 1986).

Mostly negative results have been reported with regard to the induction of sister chromatid exchange by chromium[III] compounds in various types of cultured mammalian cells (Table 23). Both positive and negative results have been reported in the literature concerning the ability of these compounds to induce chromosomal aberrations in mammalian cells (Table 24). In parallel assays, aberrations were induced more frequently than sister chromatid exchange by chromium[III] compounds, but much higher concentrations of chromium[III] than chromium[VI] were generally needed to induce chromosomal aberrations, due perhaps to an indirect effect of high doses, such as the release of lysosomal nucleases (Levis & Majone, 1981). The decreased frequency of chromium[III]-induced chromosomal aberrations in the presence of superoxide dismutase, copper (salicylate), copper (tyrosine), catalase and mannitol suggests the involvement of active oxygen species (Friedman *et al.*, 1987). The occasional finding of both sister chromatid exchange and chromosomal aberrations in CHO cells was ascribed by the authors to contamination of their chromium[III] samples with traces of chromium[VI] (Levis & Majone, 1979; Bianchi *et al.*, 1980; Venier *et al.*, 1982).

Chromic chloride inhibited spindle formation in human skin fibroblasts, but only at the highest concentration tested (100 μM), which was several orders of magnitude higher than the concentration required for chromium[VI] compounds (sodium chromate and calcium chromate) to produce the same effect (Nijs & Kirsch-Volders, 1986).

Table 23. Induction of sister chromatid exchange by chromium[III] compounds in cultured mammalian cells

Chromium compound	Cell line	Result and comments	Reference
Chromic acetate	Chinese hamster CHO	-	Levis & Majone (1979)
		-	Bianchi *et al.* (1980)
	Mouse macrophage P388D$_1$	+	Andersen (1983)
	Human peripheral lymphocytes	+	Andersen (1983)
Chromic chloride	Mouse primary lymphocytes (BALB/c)	-	Venier *et al.* (1982)
		-	Majone *et al.* (1983)
		-	Bianchi *et al.* (1983)
	Mouse primary lymphocytes (BALB/Mo)	-	Venier *et al.* (1982)
		-	Majone *et al.* (1983)
		-	Bianchi *et al.* (1983)
	Mouse LSTRA lymphocytes	-	Bianchi *et al.* (1983)
	Syrian hamster embryo primary	-	Tsuda & Kato (1977)
	Chinese hamster CHO	-	Macrae *et al.* (1979)
		-	Levis & Majone (1979)
		-	Levis & Majone (1981)
		-	Majone & Rensi (1979)
		-	Bianchi *et al.* (1980)
		-	Bianchi *et al.* (1983)
		-	Venier *et al.* (1982)
		-	Uyeki & Nishio (1983)
		+ (48-h incubation)	Venier *et al.* (1985a)
	Chinese hamster lung Don	-	Koshi (1979)
		+	Ohno *et al.* (1982)
	BHK fibroblasts	-	Bianchi *et al.* (1984)
	BHK fibroblasts (permeabilized)	-	Bianchi *et al.* (1984)
	Human peripheral lymphocytes	-	Ogawa *et al.* (1978)
		-	Stella *et al.* (1982)
	Chinese hamster V79	+ (300 × dose needed for Cr[VI])	Elias *et al.* (1983)
Chromic nitrate	Chinese hamster CHO	-	Levis & Majone (1979)
		-	Bianchi *et al.* (1980)
		-	Venier *et al.* (1982)

Table 23 (contd)

Chromium compound	Cell line	Result and comments	Reference
Chromic potassium sulfate	Chinese hamster CHO	-	Levis & Majone (1979)
		-	Bianchi *et al.* (1980)
Chromic sulfate	Chinese hamster CHO	-	Levis & Majone (1981)
		-	Loprieno *et al.* (1985)
	Chinese hamster lung Don	-	Ohno *et al.* (1982)
Chromium alum	Chinese hamster CHO	-	Levis & Majone (1981)
		-	Venier *et al.* (1982)
Neochromium	Chinese hamster CHO	-	Levis & Majone (1981)
Chromic oxide	Mouse macrophage P388D$_1$	- (taken up by cells after 48 h)	Andersen (1983)
	Chinese hamster V79	+ (1000 × dose needed for Cr[VI])	Elias *et al.* (1983)

Chromic chloride (Bianchi *et al.*, 1983; Hansen & Stern, 1985) and chromic oxide (Hansen & Stern, 1985) did not induce anchorage-independent growth in Syrian hamster BHK fibroblasts (see General Remarks, p. 44, for concern about this assay). Chromic chloride was reported to produce morphological transformation of mouse fetal cells (Raffetto *et al.*, 1977), but it did not transform Syrian hamster embryo primary cells nor, in contrast to chromium[VI] (potassium chromate), did it affect the transforming capacity of benzo[*a*]pyrene (Rivedal & Sanner, 1981).

In vivo, intraperitoneal injection of chromic chloride did not induce DNA fragmentation in rat liver or kidney cells (Tsapakos *et al.*, 1983b; Cupo & Wetterhahn, 1985a), as assessed by the alkaline elution technique in the same laboratory from which positive results were reported with chromium[VI] (see sodium dichromate). The number of micronucleated erythrocytes in bone-marrow cells of BALB/c mice was not increased after intraperitoneal injection of 250-500 mg/kg bw chromic nitrate, which contrasts with the positive result recorded with a soluble chromium[VI] compound (potassium dichromate) at ten-fold lower doses (Fabry, 1980).

Table 24. Induction of chromosomal aberrations by chromium[III] compounds in cultured mammalian cells

Chromium compound	Cell line	Result	Reference
Chromic acetate	Chinese hamster CHO	+	Levis & Majone (1979)
		+	Bianchi *et al.* (1980)
	Human peripheral lymphocytes	+	Nakamuro *et al.* (1978)
Chromic chloride	Mouse fetal	+	Raffetto *et al.* (1977)
	Syrian hamster embryo	-	Tsuda & Kato (1977)
	Chinese hamster CHO	+	Levis & Majone (1979)
		+	Levis & Majone (1981)
		+	Majone & Rensi (1979)
		+	Bianchi *et al.* (1980)
		+	Venier *et al.* (1982)
	Human peripheral lymphocytes	-	Nakamuro *et al.* (1978)
		-	Sarto *et al.* (1980)
		+	Kaneko (1976)
		+	Stella *et al.* (1982)
Chromic nitrate	Chinese hamster CHO	-	Levis & Majone (1979)
		-	Bianchi *et al.* (1980)
		-	Venier *et al.* (1982)
	Human peripheral lymphocytes	-	Nakamuro *et al.* (1978)
Chromic potassium sulfate	Chinese hamster CHO	+	Levis & Majone (1979)
		+	Bianchi *et al.* (1980)
Chromic sulfate	Mouse mammary carcinoma Fm3A	-	Umeda & Nishimura (1979)
	Syrian hamster embryo primary	-	Tsuda & Kato (1977)
	Chinese hamster CHO	+	Levis & Majone (1981)
	Chinese hamster 237-2a	+	Rössner *et al.* (1981)
Chromium alum	Chinese hamster CHO	+	Levis & Majone (1981)
Neochromium	Chinese hamster CHO	+	Levis & Majone (1981)
Chromic oxide	Chinese hamster CHO	[+]	Levis & Majone (1981)
		[+]	Venier *et al.* (1982)

The results of these studies with pure and industrial chromium[III] products are summarized in Appendix 1. Data on the genotoxicity of chromium tanning liquors used in the hide and leather industry, most of which are composed of almost insoluble sulfates, are also available. None of 17 tanning liquors, dissolved in water, acids or alkali, reverted *his*$^-$ *S. typhimurium* strains; however, the frequency of sister chromatid exchange was increased by eight (including chromium alum) of 13

tannins tested in Chinese hamster CHO cells. Contamination with chromium[VI] was detected in four of the active compounds (Venier *et al.*, 1982, 1985a).

The marked differences in potency seen in parallel assays with chromium[III] and chromium[VI] compounds have already been commented upon. The positive results sometimes obtained with chromium[III] compounds (46 positive and 141 negative results) can be ascribed to a variety of factors, which emerged from analyses of the literature (Levis *et al.*, 1978b; Levis & Bianchi, 1982). These include unquantified contamination with trace amounts of chromium[VI], nonspecific effects of very high doses, and penetration of chromium[III] by endocytosis following long exposure *in vitro* or under special treatment conditions, such as exposure to detergents or to subtoxic concentrations of phosphate. In addition, a technical artefact may result from interaction of chromium[III] with DNA released from disrupted cells during extraction procedures.

Chromium[III] complexes

Unlike chromium[VI] (potassium chromate), a chromic glycine complex did not produce unscheduled DNA synthesis in cultured human skin fibroblasts (Whiting *et al.*, 1979). In a differential killing assay with *E. coli* AB1157 (wild strain) and various repair-deficient strains and in the *S. typhimurium his*$^-$ reversion test, four of 17 hexacoordinate chromium[III] compounds gave positive results only in the DNA repair test and four in both tests (Warren *et al.*, 1981). The most active complexes were those containing aromatic amine ligands, like 2,2′-bipyridine and 1,10-phenanthroline. [The Working Group noted that the genotoxicity of these ligands was not checked.] Complexation with salicylate and citrate (but not with NTA, ethylenediaminetetraacetic acid, Tiron, glucose, glycine, pyrophosphate or acetate) rendered chromic chloride weakly active in the *rec* assay with *B. subtilis* (Gentile *et al.*, 1981). The mutagenicity of $[Cr(bipy)_2Cl_2]Cl$ and $[Cr(phen)_2Cl_2]Cl$ was confirmed in *S. typhimurium* TA100 (Beyersmann *et al.*, 1984). Water-soluble complexes of chromium[III] (chromic sulfate and chromic chloride) with five amino acids (arginine, aspartic acid, glycine, hydroxyproline and lysine) or with salicylic acid or ascorbic acid did not revert various *his*$^-$ *S. typhimurium* strains (Langerwerf *et al.*, 1985). Initial observations were reported in an abstract concerning the ability of $[Cr(bipy)_2Cl_2]Cl$ to induce predominantly extragenic suppressors in TA103 (Vieux *et al.*, 1986). This complex was shown in the same laboratory to revert *his*$^-$ *S. typhimurium* TA92, TA100 and TA98 (Warren *et al.*, 1981). In a further abstract (Rogers *et al.*, 1987), the same compound was reported to revert TA102 and TA104, with an appreciable reduction of activity under anaerobiosis and in the presence of the hydroxyl ion scavenger mannitol. Exposure of calf thymus nuclei to $Cr(glycine)_3$ produced DNA-protein cross-links as well as DNA strand-breaks, i.e., the same type of lesions caused by hexahydrated chromic chloride (Beyersmann & Köster,

1987). In the same study, $[Cr(phen)_2Cl_2]Cl$ also produced DNA fragmentation, but with a lower fraction of cross-links, when applied to intact Chinese hamster V79 cells; this phenanthroline complex, in contrast to $Cr(glycine)_3$, also induced 6-thioguanine resistance. No mutagenic effect was detected in *his⁻ S. typhimurium* with a commercial preparation of glucose tolerance factor, a yeast-extracted natural complex of chromium[III] with nicotinic acid, glycine, glutamic acid and cysteine, which is prescribed as a dietary supplement in cases of deficient chromium[III] intake with food and impaired glucose tolerance (De Flora *et al.*, 1989a). $Cr(maltolate)_3$, a chromium[III] complex with a low lipophilic ligand, did not induce gene mutations in *S. typhimurium* TA92, TA98, TA100 or TA104 nor sister chromatid exchange in mammalian cell culture (CHO line), whereas a complex with a high lipophilic ligand, $Cr(acetyl\ acetonate)_3$, although inactive to TA92, TA98 and TA100 strains, was clearly mutagenic to strain TA104 and increased the frequency of sister chromatid exchange (Gava *et al.*, 1989a).

(iii) *Chromium[VI] compounds*

Potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate and chromium trioxide

Highly soluble chromium[VI] compounds were assayed in several acellular systems. Potassium dichromate did not induce cross-links of *E. coli* [^{3}H]DNA to bovine serum albumin (Fornace *et al.*, 1981). It inhibited DNA synthesis by decreasing nucleotide incorporation into calf thymus DNA in the presence of *E. coli* DNA polymerase (Nishio & Uyeki, 1985). Potassium dichromate (Sponza & Levis, 1980 [Abstract]; Bianchi *et al.*, 1983) and chromium trioxide (Sirover & Loeb, 1976; Tkeshelashvili *et al.*, 1980) decreased the fidelity of DNA synthesis by altering the ratio of incorporation of radiolabelled complementary to noncomplementary nucleotides. In these studies, the synthetic polynucleotide poly[d(A-T)] was used as a template in the presence of viral (avian myeloblastosis virus), bacterial (*E. coli*) and mammalian (calf thymus) DNA polymerase (Miyaki *et al.*, 1977). Chromium trioxide induced depurination in calf thymus DNA by enhancing the release of guanine, whereas no effect was produced on the release of adenine (Schaaper *et al.*, 1987). Potassium dichromate induced breakage in the polynucleotide chain of purified DNA and RNA, as inferred from studies of viscosity, ultraviolet absorption spectra and thermal denaturation patterns (Tamino & Peretta, 1980; Tamino *et al.*, 1981). Sodium chromate induced single-strand breaks in supercoiled circular DNA of the bacterial phage PM2, but only when combined with glutathione. Of two purified reaction products, the chromium[V] complex $Na_4(glutathione)_4CrV.8H_2O$ cleared supercoiled PM2 DNA, whereas the final product, the chromium[III]-glutathione complex was inactive (Kortenkamp *et al.*, 1989). A positive (Tkeshelashvili *et al.*, 1980) and a negative result (Schaaper *et al.*, 1987) were reported for the

recovery of viral infectivity of single-stranded ϕX174 DNA which, following treatment with chromium trioxide, was transfected into *E. coli* spheroplasts (*am3* reversion). Potassium chromate induced *lacZα* forward mutation in double-stranded M13mp2 DNA transfected into JM101 *E. coli* (Snow & Xu, 1989). Gel electrophoresis analysis demonstrated production of oligonucleotides from [^{32}P-5′]-end-labelled DNA fragments treated with sodium chromate only in the presence of hydrogen peroxide (Kawanishi *et al.*, 1986). Several of these studies showed that chromium[VI] compounds are less active than chromium[III] compounds in simplified systems (See General Remarks, p. 43, for a discussion of the biological activity of chromium[VI] and chromium[III] compounds.)

DNA-damaging effects were observed by treating bacteria with highly soluble chromium[VI] compounds. Thus, potassium dichromate produced DNA fragmentation in strain WP2 of *E. coli*; this effect, detected by alkaline sucrose gradient sedimentation, was attenuated by α-tocopherol (Kalinina & Minseitova, 1983a,b). λ Prophage was induced by potassium chromate in *E. coli* $WP2_s$ (Rossman *et al.*, 1984). An SOS response, inferred from induction of an SOS operator gene coupled with a gene coding for β-galactosidase in *E. coli*, was elicited by sodium dichromate in strain PQ37 (De Flora *et al.*, 1985a), by potassium dichromate, potassium chromate and chromium trioxide in strains GC2375, UA4202 and PQ30 (Llagostera *et al.*, 1986), and by potassium dichromate and potassium chromate in strain PQ37 (Venier *et al.*, 1989) and in strains PQ35 and PQ37 (Olivier & Marzin, 1987). Potassium dichromate also showed SOS-inducing activity in strain TA1535/pSK1002 of *S. typhimurium* (Nakamura *et al.*, 1987).

As shown by means of various techniques (spot test, streak method, treat-and-plate test, liquid test), soluble chromium[VI] compounds induce nonreparable DNA damage in repair-deficient bacteria. In particular, potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate and chromium trioxide were active in the *rec* assay in *B. subtilis* in strains H17 (wild-type) and M45 (*rec*$^-$) (Nishioka, 1975; Nakamuro *et al.*, 1978; Kada *et al.*, 1980; Kanematsu *et al.*, 1980; Matsui, 1980; Gentile *et al.*, 1981). Potassium dichromate, sodium dichromate, ammonium dichromate, sodium chromate and chromium trioxide were more toxic in strain TA1538 (*rec*$^-$) than in the parental strain (TA1978) of *S. typhimurium* (Gentile *et al.*, 1981). Potassium dichromate, ammonium dichromate and potassium chromate were equally toxic in wild strain WP2 and in WP2*uvrA* (*uvrA*-) but more toxic in CM571 (*recA*$^-$) and in WP100 (*uvrA*$^-$*recA*$^-$) than in WP2 (Yagi & Nishioka, 1977). Sodium dichromate was more toxic in TM1080 (*polA*$^-$ *lexA*$^-$ R factor) and CM871 (*uvrA*$^-$*recA*$^-$*lexA*$^-$) than in the *E. coli* wild strain (WP2). No lethality was observed in WP2*uvrA* (*uvrA*$^-$) or WP67 (*uvrA*$^-$*polA*$^-$) (Petrilli & De Flora, 1982). The lethality of sodium dichromate,

potassium chromate, ammonium chromate and chromium trioxide to the triple mutant CM871 (*uvrA⁻recA⁻lexA⁻*) was greater than to WP2; this was not the case for WP67 (*uvrA⁻polA⁻*) (De Flora *et al.*, 1984a). [The Working Group noted that these results indicate the importance of the *rec* and *lex* SOS functions, rather than of the polymerase mechanism and *uvr* excision repair system, in repairing DNA damage produced by chromium[VI] in bacteria.]

Reversion to luminescence (bioluminescence test) was induced by potassium dichromate in strain Pf-13 of *Photobacterium fischeri* (Ulitzur & Barak, 1988). Reversion to *arg* autotrophy was induced by potassium dichromate and potassium chromate in *E. coli* strain Hs30R (Nakamuro *et al.*, 1978), and by sodium chromate in K12-343-113(λ) (Mohn & Ellenberger, 1977). The ability of soluble chromium[VI] compounds to revert *E. coli* to *trp* auxotrophy was reported by Venitt and Levy (1974) for sodium chromate (strains WP2 and WP2*uvrA*) and potassium chromate (WP2, WP2*uvrA* and WP2*exrA*), by Nishioka (1975) for potassium dichromate (WP2 and WP2*uvrA*, CM871 being insensitive), by Green *et al.* (1976) for potassium chromate (WP2), by Nestmann *et al.* (1979) for chromium trioxide (WP2*uvrA*, but only in a fluctuation test), by Petrilli and De Flora (1982) for sodium dichromate (WP2 and WP2*uvrA*), by Venitt and Bosworth (1983) for potassium dichromate (WP2*uvrA*, further increased under anaerobic growth conditions) and by Venier *et al.* (1987) for potassium dichromate (WP2*uvrA*, further increased by NTA). The only negative result was reported by Kanematsu *et al.* (1980), who identified potassium dichromate as a mutagen (in WP2*hcr⁻* only, WP2 *try⁻* being insensitive) but failed to detect the mutagenicity of chromium trioxide (in either WP2 or WP2*hcr⁻*). Potassium chromate had no effect on ultraviolet-induced mutagenesis in WP2 (Rossman & Molina, 1986).

The mutagenicity of soluble chromium[VI] compounds in *his- S. typhimurium* and its modulation were investigated in a large number of laboratories, using various techniques (spot test, spiral test, plate test and preincubation test). A number of studies yielded positive results (Tamaro *et al.*, 1975; Petrilli & De Flora, 1977; De Flora, 1978; Petrilli & De Flora, 1978b; Nestmann *et al.*, 1979; De Flora, 1981a,b; Tso & Fung, 1981; Petrilli & De Flora, 1982; Venier *et al.*, 1982; Bennicelli *et al.*, 1983; Bianchi *et al.*, 1983; Beyersmann *et al.*, 1984; De Flora *et al.*, 1984a,b; Arlauskas *et al.*, 1985; Langerwerf *et al.*, 1985; Loprieno *et al.*, 1985; Marzin & Phi, 1985; LaVelle, 1986a,b; Vieux *et al.*, 1986 [Abstract]; Farrell *et al.*, 1989). Negative results were reported in all the strains tested in one study only (Kanematsu *et al.*, 1980) [doses were not reported]. Using the replicate plate technique, Pedersen *et al.* (1983) claimed that a high proportion of *S. typhimurium his⁺* revertant colonies were false, but this conclusion was criticized by Baker *et al.* (1984), using the same technique. In general, with the exception of TA1535, all *his S. typhimurium* strains tested were reverted by chromium[VI]. The following ranking of sensitivity was reported:

TA102 > TA100 > TA97 > TA92 > TA1978 > TA98 > TA1538 > TA1537 (Bennicelli *et al.*, 1983). Other sensitive strains included TA103 (Gava *et al.*, 1989b), TA104 (De Flora *et al.*, 1988; Gava *et al.*, 1989b), TA94 (Langerwerf *et al.*, 1985), TS26 (LaVelle, 1986a) and GV19 (LaVelle, 1986b). The nitroreductase-deficient derivative strain TA100NR was even more sensitive than TA100, which suggests a diminution of the mutagenicity of chromium[VI] by bacterial nitroreductases (De Flora *et al.*, 1989b). Reversion patterns indicate that chromium[VI] induces frameshift errors in bacterial DNA and, to a greater extent, base-pair substitution at both GC base-pairs (TA100) and AT base-pairs (TA102, TA104). The latter two strains are known to be sensitive to oxidative mutagens. In any case, the presence of plasmid pKM101 in the most sensitive strains indicates that the mutagenicity of chromium[VI] is amplified through error-prone DNA repair pathways, which is consistent with the results of the DNA-repair tests reported above. The potency of chromium[VI] compounds correlated with their chromium[VI] content, being in the range of a few revertants per nanomole chromium[VI] in TA100 and TA102 (De-Flora, 1981a; De Flora *et al.*, 1984a,b). Since the potency of mutagens of various chemical classes tested in the same laboratory varied between 2×10^{-6} and 1.4×10^{4} revertants/nmol (6.8×10^{9}-fold range), chromium[VI] compounds can be classified as mutagens of medium potency in this test system (De Flora *et al.*, 1984b).

The bacterial mutagenicity of potassium dichromate was also confirmed in forward mutation assay in *E. coli*, testing acquired resistance to rifampicin in AB1157 and derived *recA*$^-$, *recB*$^-$, *recC*$^-$, *recF*$^-$ and *sbc*$^-$ strains (Kalinina & Minseitowa, 1983b,c), *lacI*$^+$/*lacI*$^-$ mutation in strain KMBL3835 (Zakour & Glickman, 1984), and replication of integrated λ genes in strain CHY832 (RK test) (Hayes *et al.*, 1984). Chromium trioxide induced Ara^r forward mutation in strains BA9 and BA13 of *S. typhimurium* (Ruiz-Rubio *et al.*, 1985). Potassium chromate did not induce forward or back mutations in a fluctuation test with K-12-derived *E. coli* strains but enhanced the frameshift mutagenicity of 9-aminoacridine (LaVelle, 1986a).

Reducing chemicals (ascorbic acid and sodium sulfite) and glutathione, NADH and NADPH decreased the bacterial mutagenicity of various chromium[VI] compounds (Petrilli & De Flora, 1978b; De Flora *et al.*, 1985b; Petrilli *et al.*, 1986a). A similar reducing effect was induced by other sulfur compounds, such as *N*-acetylcysteine (De Flora *et al.*, 1984c), cysteine (Petrilli *et al.*, 1986a) and dithiothreitol (Rogers *et al.*, 1987 [Abstract]). The mutagenicity of potassium dichromate was also considerably decreased by anaerobic growth conditions, but not by addition of the hydroxyl ion scavenger mannitol (Rogers *et al.*, 1987 [Abstract]). The mutagenicity of soluble chromium[VI] compounds was not affected or was poorly affected by addition of soda ash, diethyl ether, prostaglandin or ethylenediaminetetraacetic acid (Petrilli & De Flora, 1982; Petrilli *et al.*, 1986a) or complex mixtures

(crude oil, oil dispersants) (Petrilli *et al.*, 1980; De Flora *et al.*, 1985a), whereas it was inhibited by other metals (Sokolowska & Jongen, 1984 [Abstract]). Sodium dichromate and unfractionated cigarette smoke condensate had antagonistic mutagenic effects (Petrilli & De Flora, 1982). The mutagenicity of potassium dichromate was increased by nitrilotriacetic acid (Gava *et al.*, 1989a). Potassium chromate decreased the mutagenicity of ethyl methanesulfonate and increased that of sodium azide (LaVelle & Witmer, 1984) and of its metabolite azidoalanine (LaVelle, 1986b); more than additive effects were observed with 9-aminoacridine (LaVelle, 1986a).

The mutagenicity of soluble chromium[VI] compounds in *S. typhimurium* was consistently decreased by rat liver post-mitochondrial supernatant in all studies in which this aspect was evaluated (De Flora, 1978; Löfroth, 1978; Petrilli & De Flora, 1978b; Nestmann *et al.*, 1979; Petrilli & De Flora, 1980; De Flora, 1981a; Petrilli & De Flora, 1982; Venier *et al.*, 1982; Bianchi *et al.*, 1983; De Flora *et al.*, 1984a; Loprieno *et al.*, 1985; Petrilli *et al.*, 1986b). The polychlorinated biphenyl Aroclor 1254 was the most efficient inducer of this effect, followed in activity by phenobarbital and 3-methylcholanthrene (Petrilli *et al.*, 1985). Pretreatment of rats with *N*-acetylcysteine also stimulated reduction of chromium[VI] by liver and lung post-mitochondrial supernatant (De Flora *et al.*, 1985c). The effect of the rat liver fraction on the mutagenicity of various chromium[VI] compounds was inhibited by dicoumarol, a specific inhibitor of the cytosolic enzyme DT diaphorase (De Flora *et al.*, 1987b); purified DT diaphorase itself decreased the mutagenicity of sodium dichromate (De Flora *et al.*, 1988). The mutagenicity of sodium dichromate was also decreased by liver preparations from other animal species, including fish (*Salmo gairdneri*) (De Flora *et al.*, 1982), chicken, hamster (De Flora *et al.*, 1985d), Pekin duck (De Flora *et al.*, 1989a), mouse (De Flora, 1982), woodchuck (De Flora *et al.*, 1987c, 1989c) and humans (De Flora, 1982). Moreover, mutagenicity was decreased by thermostable components of human gastric juice (De Flora & Boido, 1980; De Flora *et al.*, 1987a), with peaks of reducing activity during post-meal periods following stimulation of gastric secretion (De Flora *et al.*, 1987a). Human erythrocyte lysates decreased the mutagenicity of chromium[VI] (Petrilli & De Flora, 1978b); human and rat pulmonary alveolar macrophages were particularly efficient (Petrilli *et al.*, 1986c). Human peripheral lung parenchyma decreased the mutagenicity of chromium[VI] more efficiently than a post-mitochondrial supernatant of bronchial tree (Petruzzelli *et al.*, 1989); as assessed from 71 surgical specimens from cancer and noncancer patients, the ability of lung parenchyma to decrease the mutagenicity of chromium[VI] was significantly enhanced in cigarette smokers (De Flora *et al.*, 1987d). In rats, the inhibitory effect of lung was autoinduced by repeated intratracheal instillations of sodium dichromate (Petrilli *et al.*, 1985). Comparative assays provided evidence that the reducing capacity of rat tissue post-mitochondrial supernatant ranked as follows: liver > adrenal > kidney >

testis > stomach and lung; preparations of skeletal muscle, spleen and intestine had no effect on the mutagenicity of chromium[VI] (Petrilli & De Flora, 1978b, 1980, 1982). Further assays confirmed the negligible effect of rat muscle (which is a typical target of the carcinogenicity of chromium[VI] in bioassays) in decreasing the mutagenicity of chromium[VI], as compared to liver and, to a lesser extent, to cutis and subcutis (De Flora *et al.*, 1989a). The selective loss of chromium[VI] mutagenicity was accompanied by the disappearance of measurable chromium[VI] in the presence of various body fluids and cell and tissue preparations. [The Working Group interpreted these findings as indicating mechanisms that limit the activity of chromium[VI] compounds *in vivo*.]

Forward mutation and mitotic gene conversion were induced by potassium dichromate in the yeast *Schizosaccharomyces pombe* (Bonatti *et al.*, 1976). The same compound induced reversion ($ilv^- \rightarrow ilv^+$) and mitotic gene conversion in strain D7 of *Saccharomyces cerevisiae* (Singh, 1983; Galli *et al.*, 1985; Kharab & Singh, 1985). Conversely, chromium trioxide elicited gene conversion and mitotic crossing-over but failed to revert the same yeast strain (Fukunaga *et al.*, 1982). Potassium dichromate slightly enhanced recombination frequency in strain D1513 of *Saccharomyces cerevisiae* and produced disomic and diploid gametes (Sora *et al.*, 1986), but it did not induce mitochondrial 'petite' mutants in strain D7 (Kharab & Singh, 1987).

Neither potassium chromate nor chromium trioxide induced micronuclei in pollen mother cells of *Tradescantia paludosa* (Ma *et al.*, 1984). In contrast, further studies indicated a dose-dependent increase in the induction of micronuclei by chromium trioxide, which was significantly inhibited by cysteine (Zhang *et al.*, 1984).

In *Drosophila melanogaster*, sodium dichromate gave positive results in a somatic eye-colour test (*zeste* mutation) (Rasmuson, 1985). Both potassium dichromate and chromium trioxide induced sex-linked recessive lethal mutations, but only potassium dichromate induced non-disjunction and X-Y chromosome loss at a dose corresponding to the LD_{50} (Rodriguez-Arnaiz & Molina Martinez, 1986). The induction of sex-linked recessive lethal mutations by potassium dichromate was enhanced by NTA (Gava *et al.*, 1989b).

A variety of genetic and related endpoints were explored in cultured mammalian cells. Potassium dichromate produced alterations of the mitotic index and of mitotic phases in human epithelial-like heteroploid HEp-2 cells (Majone, 1977; Levis & Majone, 1981) and NHIK 3025 cervix tissue cells (Bakke *et al.*, 1984), and imbalance of the endogenous adenylate pool in Syrian hamster BHK fibroblasts (Levis *et al.*, 1978b; Bianchi *et al.*, 1982a). It inhibited DNA synthesis, as evaluated by ^{3}H-thymidine incorporation, in mouse L cells (Nishio & Uyeki, 1985), in BHK fibroblasts and in HEp-2 cells (Levis *et al.*, 1977, 1978a,b), in which a secondary inhibition of RNA and protein syntheses was also observed (Levis *et al.*, 1978b).

Inhibition of DNA synthesis was further enhanced following reversible permeabilization of cells in hypertonic medium (Bianchi *et al.*, 1984). Potassium dichromate also reduced the colony-forming ability of BHK cells by a multi-hit mechanism of cell inactivation (Levis *et al.*, 1978a). Unscheduled DNA synthesis was induced by potassium dichromate in mouse kidney A18BcR cells (Raffetto *et al.*, 1977) but not in human EUE heteroploid cells (Bianchi *et al.*, 1982b, 1983); potassium chromate induced unscheduled DNA synthesis in human skin fibroblasts (Whiting *et al.*, 1979). Chromium trioxide inhibited repair of γ-ray-induced chromosome breaks in human peripheral blood lymphocytes (Morimoto & Koizumi, 1981).

DNA fragmentation and cross-links were produced by soluble chromium[VI] compounds in a number of cultured mammalian cell lines, as assessed by various techniques, including alkaline elution, alkaline sucrose gradient, nucleoid sedimentation, alkaline unwinding, the nick translation assay, and polyacrylamide gel electrophoresis (Table 25). An exception was a study by alkaline elution in Chinese hamster V79 cells with potassium dichromate (Bianchi *et al.*, 1983).

In the *hprt* forward mutation assay, potassium chromate did not induce 8-azaguanidine–resistant mutants in mouse mammary carcinoma FM3A cells, in contrast to the activity of potassium dichromate and chromium trioxide in the same system (Nishimura & Umeda, 1978 [Abstract]). An unspecified chromate induced 6-thioguanine resistance in Chinese hamster V79 cells (Beyersmann & Köster, 1987). Potassium dichromate induced 8-azaguanidine resistance and 6-thioguanidine resistance in Chinese hamster V79 cells (Newbold *et al.*, 1979; Rainaldi *et al.*, 1982; Paschin *et al.*, 1981; Bianchi *et al.*, 1983); its mutagenic activity was decreased by thiotepa (Paschin & Kozachenko, 1982), unaffected by nitrilotriacetic acid (Celotti *et al.*, 1987) and enhanced by nickel[II] (Hartwig & Beyersmann, 1987). In comparative assays, Chinese hamster V79 cells were found to be more sensitive to chromium[VI] than Chinese hamster CHO cells (Paschin *et al.*, 1983). The combined use of selective 8-azaguanidine-resistant and ouabain-resistant systems showed that potassium dichromate can also induce base-pair substitutions in the DNA of V79 cells (Rainaldi *et al.*, 1982). Potassium dichromate and potassium chromate induced forward mutation at the thymidine kinase locus in mouse lymphoma L5178Y cells (Oberly *et al.*, 1982). As assessed in an assay for the synthesis of P-100$^{gag\text{-}mos}$ viral proteins, sodium chromate induced expression of the *v-mos* gene in MuSVts110-infected rat kidney 6m2 cells (Biggart & Murphy, 1988).

Soluble chromium[VI] compounds consistently increased the frequency of sister chromatid exchange (Table 26). The highest frequency of induction was observed in the early S-phase of the human lymphocyte cycle (Stella *et al.*, 1982).

Table 25. Studies in which DNA fragmentation and DNA–DNA and DNA–protein cross-linking were induced in cultured mammalian cells by soluble chromium[VI] compounds

Chromium compound	Cell line	Comment	Reference
Potassium dichromate	Mouse L1210 leukaemia		Fornace *et al.* (1981)
	Novikoff ascitic hepatoma		Wedrychowski *et al.* (1986a)
	Chinese hamster CHO		Brambilla *et al.* (1980) [Abstract]; Hamilton-Koch *et al.* (1986)
	Human foreskin HSBP fibroblasts	Detected by alkaline sucrose gradient but not nick translation, nucleoid sedimentation or alkaline unwinding	Hamilton-Koch *et al.* (1986); Snyder (1988)
		Enhanced by glutathione, unaffected by hydroxyl radical scavengers (mannitol, iodine), diminished by superoxide dismutase and catalase	
	Human white blood		McLean *et al.* (1982)
Sodium dichromate	Rat primary hepatocytes		Sina *et al.* (1983)
Potassium chromate	Mouse L1210 leukaemia		Fornace *et al.* (1981)
	Chinese hamster CHO fibroblasts	DNA-protein cross-linkage, probably due to chromium[III]	Miller & Costa (1988, 1989)
	Human embryo lung IMR-90 fibroblasts		Fornace *et al.* (1981)
	Human skin fibroblasts	At 7th–8th passage	Whiting *et al.* (1979)
	Human CRL1223 fibroblasts		Fornace (1982)
	Human AG1522 fibroblasts		Fornace (1982)
	Human XP12BE fibroblasts	Similar effect in normal xeroderma pigmentosum cells	Fornace (1982)
	Novikoff ascitic hepatoma		Wedrychowski *et al.* (1986b)
	Human bronchial epithelium		Fornace *et al.* (1981)

Table 25 (contd)

Chromium compound	Cell line	Comment	Reference
Sodium chromate	Chick embryo hepatocytes	Related to glutathione and cytochrome P450 metabolism	Tsapakos *et al.* (1983b); Cupo & Wetterhahn (1984, 1985b)
	Chinese hamster V79	Decreased by α-tocopherol; increased by riboflavin and sodium sulfite; DNA-protein breaks recognized by poly(ADT-ribose)polymerase	Sugiyama *et al.* (1987, 1988)
Chromium trioxide	Novikoff ascitic hepatoma		Wedrychowski *et al.* (1986a)

Table 26. Studies in which sister chromatid exchange was induced in cultured mammalian cells by chromium[VI] compounds

Chromium compound	Cell line	Comment[a]	Reference
Potassium dichromate	Mouse lymphocytes LSTRA		Bianchi *et al.* (1983)
	BALB mouse primary lymphocytes	BALB cells carrying endogenized Moloney leukaemia virus more sensitive than uninfected cells	Bianchi *et al.* (1983); Majone *et al.* (1983)
	Mouse macrophage P388D$_1$		Andersen (1983)
	Mouse embryo blastocytes		Iijima *et al.* (1983b)
	Chinese hamster CHO		Levis & Majone (1979); Majone & Levis (1979); Bianchi *et al.* (1980); Levis & Majone (1981); Majone *et al.* (1982); Venier *et al.* (1982); Bianchi *et al.* (1983); Uyeki & Nishio (1983); Loprieno *et al.* (1985); Montaldi *et al.* (1987b)
	Chinese hamster V79		Rainaldi *et al.* (1982)
	Chinese hamster lung Don		Ohno *et al.* (1982)
	Syrian hamster BHK fibroblasts	Increased in permeabilized cells	Bianchi *et al.* (1984)
	Human peripheral blood lymphocytes		Ogawa *et al.* (1978); Gómez-Arroyo *et al.* (1981); Imreh & Radulescu (1982 [Abstract]); Stella *et al.* (1982); Andersen (1983)
	Human skin fibroblasts		Macrae *et al.* (1979)
Sodium dichromate	Chinese hamster CHO		Levis & Majone (1979); Majone & Levis (1979); Bianchi *et al.* (1980)
	Chinese hamster V79		Elias *et al.* (1983)
Potassium chromate	Chinese hamster CHO		Levis & Majone (1979); Macrae *et al.* (1979); Majone & Rensi (1979); Bianchi *et al.* (1980); Majone *et al.* (1982)
	Chinese hamster V79		Price-Jones *et al.* (1980); Elias *et al.* (1983)

Table 26 (contd)

Chromium compound	Cell line	Comment[a]	Reference
Potassium chromate (contd)	Chinese hamster lung Don		Ohno *et al.* (1982)
	Human skin fibroblasts		Macrae *et al.* (1979)
	Human peripheral blood lymphocytes		Douglas *et al.* (1980)
Sodium chromate	Chinese hamster CHO		Levis & Majone (1979); Bianchi *et al.* (1980)
	Chinese hamster V79		Elias *et al.* (1983)
Chromium trioxide	Chinese hamster CHO		Levis & Majone (1979); Bianchi *et al.* (1980)
	Chinese hamster lung Don		Koshi (1979); Ohno *et al.* (1982)
	Human peripheral blood lymphocytes		Gómez-Arroyo *et al.* (1981)
Calcium chromate	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b); Sen & Costa (1986)
Lead chromate	Human peripheral blood lymphocytes	Dissolved in NaOH	Douglas *et al.* (1980)
Strontium chromate	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b)
Zinc chromates	Chinese hamster CHO	Increased in presence of NaOH or NTA	Levis & Majone (1981); Venier *et al.* (1985b)
	Chinese hamster V79		Elias *et al.* (1983)
Basic zinc chromates	Chinese hamster CHO	Increased in presence of NaOH or NTA	Levis & Majone (1981); Venier *et al.* (1985b)
Zinc chromate	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b)
Barium chromate	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b)

Table 26 (contd)

Chromium compound	Cell line	Comment[a]	Reference
Lead chromate	Chinese hamster CHO	Increased in presence of NTA	Montaldi *et al.* (1987a,b)
	Chinese hamster CHO	Increased in presence of NTA	Loprieno *et al.* (1985)
	Human peripheral blood lymphocytes	Dissolved in NaOH	Douglas *et al.* (1980)
Chromium yellow	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b)
	Chinese hamster CHO	Increased in presence of NaOH	Levis & Majone (1981)
Chromium orange	Chinese hamster CHO	Increased in presence of NaOH	Levis & Majone (1981)
	Chinese hamster CHO		Loprieno *et al.* (1985)
Molybdenum orange	Chinese hamster CHO	Increased in presence of NTA	Venier *et al.* (1985b)
	Chinese hamster CHO	Increased in presence of NaOH	Levis & Majone (1981)

[a]NTA, nitrilotriacetic acid

As reported in an abstract, potassium dichromate also increased the frequency of micronucleated cells in human lymphocytes cultured *in vitro* (Imreh & Radulescu, 1982).

In many studies, the induction of chromosomal aberrations was investigated, often in parallel with assessments of the frequency of sister chromatid exchange; all of them gave positive results (Table 27). Chromatid-type aberrations, mainly gaps, breaks and chromatid exchanges, were the most frequently reported aberrations (Levis & Bianchi, 1982).

Two studies dealt with the induction of aneuploidy by soluble chromium[VI] salts in cultured mammalian cells: no increase in the number of aneuploids or polyploids was detected following treatment of Chinese hamster V79 cells with potassium chromate (Price-Jones *et al.*, 1980). Sodium chromate, however, exhibited spindle-modifying properties in human skin fibroblasts, as assessed by means of a differential staining technique for chromosomes and spindles, alterations in which may represent one of the major causes of aneuploidy (Nijs & Kirsch-Volders, 1986).

The majority of studies provided evidence that soluble chromium[VI] salts can induce cell transformation in different experimental systems. In particular, as evaluated by means of the soft agar assay, potassium dichromate produced anchorage-independent growth of Syrian hamster BHK fibroblasts (Bianchi *et al.*, 1983; Hansen & Stern, 1985), which was further enhanced in the presence of NTA (Lanfranchi *et al.*, 1988). [See General Remarks, p. 44, for concern about this assay.] The same compound induced morphological transformation of Syrian hamster embryo (SHE) primary cells (Tsuda & Kato, 1977; Hansen & Stern, 1985) and of mouse fetal cells at the third passage (Raffetto *et al.*, 1977), whereas a negative result was reported in mouse embryo C3H10T1/2 cells (Patierno *et al.*, 1988). [See General Remarks, p. 44, for concerns about this assay.] Sodium chromate also induced morphological transformation of SHE primary cells (DiPaolo & Casto, 1979), but potassium chromate did not, although it potentiated the transforming capacity of benzo[*a*]pyrene (Rivedal & Sanner, 1981); it also enhanced the morphological transformation induced by the simian adenovirus SA7 in SHE primary cells (Casto *et al.*, 1979).

Several studies were also carried out with soluble chromium[VI] compounds *in vivo*. Following intraperitoneal injection to Sprague-Dawley rats, sodium dichromate induced a selective DNA fragmentation in different tissues, as assessed by means of the alkaline elution technique. In particular, liver nuclei contained protein-associated DNA single-strand breaks as well as DNA-protein cross-links, whereas kidney nuclei contained mainly DNA-protein cross-links (Tsapakos *et al.*, 1981) and lung nuclei contained both DNA interstrand and DNA-protein cross-links (Tsapakos *et al.*, 1983a). These lesions were repaired most rapidly in the liver, which may provide a partial explanation of the differential toxicity of

Table 27. Studies in which chromosomal aberrations were induced in cultured mammalian cells by chromium[VI] compounds

Chromium compound	Cell line	Comment[a]	Reference
Potassium dichromate	Mouse tertiary fetal		Raffetto *et al.* (1977)
	Mouse mammary carcinoma Fm3A		Umeda & Nishimura (1979)
	Rat peripheral blood lymphocytes		Newton & Lilly (1986)
	Rat embryo fibroblasts		Bigaliev *et al.* (1977a)
	Syrian hamster embryo primary	Inhibited by sodium sulfite	Tsuda & Kato (1977)
	Chinese hamster CHO		Levis & Majone (1979); Majone & Levis (1979); Bianchi *et al.* (1980); Levis & Majone (1981); Venier *et al.* (1982)
	Chinese hamster V79		Newbold *et al.* (1979)
	Human peripheral blood lymphocytes		Nakamuro *et al.* (1978); Imreh & Radulescu (1982 [Abstract]); Stella *et al.* (1982)
Sodium dichromate	Chinese hamster CHO		Levis & Majone (1979); Majone & Levis (1979); Bianchi *et al.* (1980)
	Human peripheral blood lymphocytes		Sarto *et al.* (1980)
Potassium chromate	Mouse mammary carcinoma Fm3A		Umeda & Nishimura (1979)
	Chinese hamster CHO		Levis & Majone (1979); Majone & Rensi (1979); Bianchi *et al.* (1980)
	Chinese hamster lung Don		Koshi & Iwasaki (1983)
	Human skin fibroblasts		Macrae *et al.* (1979)
	Human peripheral blood lymphocytes		Nakamuro *et al.* (1978); Douglas *et al.* (1980)
Sodium chromate	Chinese hamster CHO		Levis & Majone (1979); Bianchi *et al.* (1980)

Table 27 (contd)

Chromium compound	Cell line	Comment[a]	Reference
Chromium trioxide	Mouse mammary carcinoma Fm3A		Umeda & Nishimura (1979)
	Syrian hamster embryo primary		Tsuda & Kato (1977)
	Chinese hamster CHO		Levis & Majone (1979); Bianchi *et al.* (1980)
	Chinese hamster lung Don		Koshi (1979)
	Human peripheral blood lymphocytes		Kaneko (1976)
Calcium chromate	Mouse embryo C3H10T1/2	Random damage	Sen *et al.* (1987)
	Chinese hamster CHO	Random damage	Levis & Majone (1979); Sen *et al.* (1987)
	Chinese hamster lung Don		Koshi & Iwasaki (1983)
Basic zinc chromates	Chinese hamster CHO	Increased in presence of NaOH	Levis & Majone (1981)
Zinc chromate	Chinese hamster lung Don		Koshi & Iwasaki (1983)
Lead chromate	Chinese hamster CHO	Increased in presence of NaOH or NTA	Levis & Majone (1981); Montaldi *et al.* (1987b)
	Chinese hamster lung Don		Koshi & Iwasaki (1983)
	Human peripheral blood lymphocytes	Increased in presence of NaOH	Douglas *et al.* (1980)

[a]NTA, nitrilotriacetic acid

chromium[VI] in these organs (Tsapakos *et al.*, 1983a). Following its injection onto the inner shell membrane of eggs, sodium dichromate produced single-strand breaks in blood cells and DNA cross-links in liver cells of chicken embryos (Hamilton & Wetterhahn, 1986). Intraperitoneally injected potassium dichromate inhibited DNA repair synthesis in rat lymphocytes (Rudnykh & Saichenko, 1985); it was active in a mammalian spot test in C57Bl/6J/BOM mice, but only when administered at 10 mg/kg and not at 20 mg/kg (Knudsen, 1980).

Intraperitoneal injection of potassium dichromate or potassium chromate to Chinese hamsters induced sister chromatid exchange in bone-marrow cells and an increased frequency of micronucleated polychromatic erythrocytes (Kaths, 1981). Micronucleated polychromatic erythrocytes were also enhanced by potassium dichromate in BALB/c mice (Fabry, 1980) and in CBA × C57Bl/6J mice (Paschin & Toropsev, 1982, 1983) and by potassium chromate in NMRI mice (Wild, 1978), ms and ddY mice, the former strain being more sensitive (Hayashi *et al.*, 1982). Comparative trials in various mouse strains showed no important sex-related variation in induction of micronucleated cells by chromium[VI] and confirmed the different susceptibilities of different strains (rank of sensitivity: ms > BDF1 > CD-1 > ddY) (Collaborative Study Group for the Micronucleus Test, 1986, 1988).

Chromosomal aberrations were induced in gill tissue cells of *Boleophthalmus dussumieri* fish by intramuscular injection or addition to water of sodium dichromate (Krishnaja & Rege, 1982). Potassium dichromate induced chromosomal rearrangements and aneuploidy in rat bone-marrow cells when given orally or intratracheally (Bigaliev *et al.*, 1977b). Following intraperitoneal or intravenous injection, it produced chromosomal aberrations in lymphocytes and bone-marrow cells (Newton & Lilly, 1986). Intraperitoneal injection of potassium dichromate was also clastogenic to bone-marrow cells of BALB/c mice (Léonard & Deknudt, 1981 [Abstract]), but no increase in chromosomal aberrations was observed in CBA × C57Bl/6J hybrid mice (Paschin *et al.*, 1981). In the same animals, dominant lethal effects were produced at 2 mg/kg bw (21 doses) and 20 mg/kg bw (single dose) (Paschin *et al.*, 1982) but not at 0.5-1.5 mg/kg bw (single dose) (Paschin *et al.*, 1981). At 20 mg/kg bw, potassium dichromate reduced the rate of pregnancies in BALB/c mice (Léonard & Deknudt, 1981 [Abstract]; Deknudt, 1982 [Abstract]) but failed to produce dominant lethal effects (Léonard & Deknudt, 1981 [Abstract]).

Calcium chromate, strontium chromate, basic zinc chromate

Calcium chromate, strontium chromate and the industrial product, basic zinc chromate or zinc yellow [$ZnCrO_4.Zn(OH)_2$ plus 10% CrO_3], are generally completely dissolved in the media used in short-term tests. The results obtained in a variety of experimental systems thus virtually overlap with those reported for highly soluble chromium[VI] compounds.

Calcium chromate failed to induce an SOS response in strain PQ37 of *E. coli* (Brams *et al.*, 1987). In contrast, it was active in a differential killing assay in *E. coli* WP2, using the triple mutant CM871 (*uvrA*$^-$ *recA*$^-$ *lexA*$^-$) (De Flora *et al.*, 1984a), and in the *trp*$^-$ → *trp*$^+$ reversion test with strains WP2 (Venitt & Levy, 1974) and WP2*uvrA* (Dunkel *et al.*, 1984). In the *his*$^-$ → *his*$^+$ reversion test in *S. typhimurium*, positive results were reported with calcium chromate (Petrilli & De Flora, 1977; De Flora, 1981a; Bennicelli *et al.*, 1983; Haworth *et al.*, 1983; De Flora *et al.*, 1984a, 1987b; Dunkel *et al.*, 1984; Petrilli *et al.*, 1985; Venier *et al.*, 1985b), strontium chromate (Venier *et al.*, 1985b) and zinc yellow (Petrilli & De Flora, 1978b; De Flora, 1981a). The potency, spectrum of sensitivity of *S. typhimurium* strains and behaviour in the presence of in-vitro metabolic systems were comparable to those reported for highly soluble chromium[VI] compounds. However, toxic effects of calcium chromate hampered the detection of forward and back mutations in the DNA of phage T4 grown in *E. coli* BB (Corbett *et al.*, 1970).

Calcium chromate induced 'petite' mutants in mitochondria of 19 haploid strains of *Saccharomyces cerevisiae* (Egilsson *et al.*, 1979) and produced differential chromosome breakage in excision-repair-deficient females of *Drosophila melanogaster* (*mei-9*^{a} test), with complete loss of the X or Y and partial loss of the Y chromosome (Zimmering, 1983).

Zinc yellow produced alterations of the mitotic cycle in human epithelial-like heteroploid HEp-2 cells (Levis & Majone, 1981). Calcium chromate stimulated DNA repair replication in Syrian hamster embryo primary cells, as evaluated by caesium chloride gradient density sedimentation (Robison *et al.*, 1984). It also produced DNA single-strand breaks, DNA interstrand and DNA-protein cross-links (alkaline elution technique) in mouse embryo C3H10T1/2 cells, Chinese hamster CHO cells and human osteosarcoma cells, the maximal sensitivity being recorded in early S-phase (Sugiyama *et al.*, 1986a,b); human cells were more sensitive than mouse or hamster cells (Sugiyama *et al.*, 1986b). In Chinese hamster CHO cells, calcium chromate produced single-strand breaks, induced alkali-labile sites (Cantoni & Costa, 1984) and, as assessed by alkaline sucrose gradient, decreased the DNA molecular weight (Robison *et al.*, 1982). DNA cross-links were more pronounced and only partially repaired in a repair-deficient line (EM9) as compared with CHO wild-type cells (AA8). Conversely, repair of single-strand breaks was similar in the two cell lines (Christie *et al.*, 1984). Calcium chromate produced strand breaks, detected by nucleoid gradient sedimentation, when applied to intact cells, but no breakage was observed when nucleoids were exposed directly to chromium[VI] (Robison *et al.*, 1984).

Calcium chromate induced forward mutation at the thymidine kinase locus in mouse lymphoma L5178Y cells, with no change (Myhr & Caspary, 1988) or decreased activity (McGregor *et al.*, 1987; Mitchell *et al.*, 1988) in the presence of rat

liver post-mitochondrial supernatant. This salt induced dose-dependent cytotoxicity and forward mutation to 6-thioguanine resistance in Chinese hamster CHO cells but no mutation to ouabain resistance in the same cells or in mouse embryo C3H10T1/2 cells (Patierno *et al.*, 1988).

The frequency of sister chromatid exchange was increased in Chinese hamster CHO cells by all three compounds (Table 26). In contrast to nickel, no predominance of sister chromatid exchange was observed in heterochromatic regions (Sen & Costa, 1986). Chromosomal aberrations, with a random distribution of chromosomal damage, were produced by calcium chromate and zinc yellow (Table 27). Aberrant division patterns and spindle modifications were also caused by calcium chromate in human skin fibroblasts (Nijs & Kirsch-Volders, 1986).

Several authors reported that calcium chromate could determine cell transformation *in vitro* in different systems: anchorage-independent growth of Syrian hamster BHK fibroblasts in carboxymethylcellulose, after several passages of treated cells (Fradkin *et al.*, 1975) or in soft agar (Bianchi *et al.*, 1983; Hansen & Stern, 1985), with an enhancing effect in the presence of NTA (Lanfranchi *et al.*, 1988), attachment-independence of virus-infected rat embryo 2 FR_4 50 cells (Traul *et al.*, 1981) [see General Remarks for concern about this assay], morphological transformation of mouse BALB/3T3 cells, R-MulV-infected rat embryo cells and Syrian hamster embryo primary cells (Dunkel *et al.*, 1981); and enhancement of morphological transformation in the same cells by the simian adenovirus SA7 (Casto *et al.*, 1979). As reported for potassium dichromate, calcium chromate did not induce morphological transformation in mouse embryo C3H10T1/2 cells (Patierno *et al.*, 1988).

Conflicting results were reported in studies *in vivo* with calcium chromate. It increased the frequency of sister chromatid exchange in bone-marrow cells of intraperitoneally injected Chinese hamsters (Kaths, 1981), whereas it failed to increase micronuclei in bone-marrow polychromatic erythrocytes of intraperitoneally injected BALB/c mice (Fabry, 1980) or Chinese hamsters (Kaths, 1981), and did not induce dominant lethal mutations in BALB/c mice (Léonard & Deknudt, 1981 [Abstract]).

Zinc chromate, barium chromate, lead chromate and derived pigments (chromium orange, chromium yellow and molybdenum orange)

An extensive data base is available concerning chromium[VI] compounds with poor solubility under the conditions used in experimental systems. These are zinc chromate, chromium orange or basic lead chromate [($PbCrO_4$.PbO)], molybdenum orange ($PbCrO_4.PbSO_4.PbMoO_4$), barium chromate, chromium yellow ($PbCrO_4.PbSO_4.SiO_2.Al_2O_3$) and lead chromate, which is one of the most insoluble salts. As is to be expected, their activity in short-term tests was related to the availability of chromate to target cells, which was often achieved by artificial solubiliza-

tion in acids or alkali, except in mammalian cells, where some penetration of insoluble compounds is likely to occur by phagocytosis.

Lead chromate did not induce differential killing in *E. coli* W3110 or P3478 (*polA*$^-$), even when dissolved in sodium hydroxide (Nestmann *et al.*, 1979); this result parallels those reported with soluble chromium[VI] compounds in *polA*$^-$ strains. It was equally toxic in WP2 and in CM871 (*uvrA*$^-$ *recA*$^-$ *lexA*$^-$), unless dissolved in NTA (Venier *et al.*, 1987). Lead chromate did not elicit the SOS response in *E. coli* PQ37, unless it was solubilized by NTA (Venier *et al.*, 1989).

Lead chromate reverted *E. coli* (*trp*$^-$ → *trp*$^+$), when assayed in a fluctuation test after preliminary solubilization in sodium hydroxide (Nestmann *et al.*, 1979) and in both the spot test and a fluctuation test when dissolved in NTA (Venier *et al.*, 1987). In the *his*$^-$ → *his*$^+$ reversion test in *S. typhimurium*, zinc chromate was active in aqueous medium, and its mutagenicity was increased in the presence of sodium hydroxide or NTA (Venier *et al.*, 1985b). Chromium orange was mutagenic when spotted directly on the centre of agar plates and also became active in the plate test when dissolved in sodium hydroxide (Petrilli & De Flora, 1978b; De Flora, 1981a) or in NTA (Venier *et al.*, 1985b; Loprieno *et al.*, 1985). Likewise, molybdenum orange was mutagenic when spotted in solid form and in the plate test when dissolved in sodium hydroxide (De Flora, 1981a). Barium chromate was inactive unless dissolved in NTA (Venier *et al.*, 1985b). Lead chromate, tested following solubilization in acid or alkali, was mutagenic to the same strains that are sensitive to soluble chromium[VI] compounds (Nestmann *et al.*, 1979; Petrilli & De Flora, 1982). When tested in aqueous suspension, it was not mutagenic, but mutagenic chromate was released when it was dissolved in sodium hydroxide or NTA (Loprieno *et al.*, 1985; Venier *et al.*, 1985b, 1987). Its inactivity in strain TA102 was unaffected by the presence of oil dispersants (De Flora *et al.*, 1985a). Highly insoluble chromium yellow was inactive even when spotted in solid form; it became mutagenic in the plate test only when dissolved in sodium hydroxide (De Flora, 1981a; Petrilli & De Flora, 1982). In the *gal*$^+$/*gal*$^-$ forward mutation test in strain K-12/343/113 (λ) of *E. coli*, lead chromate was inactive even when dissolved in sodium hydroxide (Nestmann *et al.*, 1979).

Lead chromate, dissolved in hydrochloric acid, induced mitotic recombination in strain D5 of *Saccharomyces cerevisiae*; the effect was decreased in the presence of rat liver post-mitochondrial supernatant (Nestmann *et al.*, 1979). It induced sex-linked recessive lethal mutations in *Drosophila melanogaster* only when dissolved in NTA (Costa *et al.*, 1988).

Alterations in the mitotic cycle were induced by the lead chromate-containing pigments, chromium orange, molybdenum orange and chromium yellow, in human epithelial-like heteroploid HEp-2 cells following a 48-h incubation in cell growth medium (Levis & Majone, 1981). Lead chromate, even when dissolved in sodium

hydroxide, did not induce DNA fragmentation in Chinese hamster CHO cells, as evaluated by alkaline sucrose gradient (Douglas *et al.*, 1980), and it was not mutagenic in these cells, as evaluated in both 6-thioguanine- and ouabain-resistant systems; it did not induce ouabain or 6-thioguanine resistance in mouse embryo C3H10T1/2 cells (Patierno *et al.*, 1988). In the *hprt* assay in Chinese hamster V79 cells, lead chromate gave negative results both for 8-azaguanine resistance (Newbold *et al.*, 1979) and 6-thioguanine resistance, unless it was dissolved in NTA (Celotti *et al.*, 1987).

In aqueous suspension, all of these poorly soluble chromium[VI] compounds induced sister chromatid exchange in mammalian cells (Table 26). In human peripheral blood lymphocytes, lead chromate also induced micronuclei, with an enhancing effect following addition of an equimolar concentration of NTA (Montaldi *et al.*, 1987b). Aqueous suspensions of lead chromate, of all three derived pigments and of zinc chromate were clastogenic in mammalian cells (Table 27).

Zinc chromate and lead chromate induced anchorage-independent growth of Chinese hamster BHK fibroblasts in the soft agar assay (Hansen & Stern, 1985). [See General Remarks, p. 44, for concern about this assay.] Only lead chromate (which was phagocytized) induced morphological transformation in mouse embryo C3H10T1/2 cells, which contrasted with the lack of transforming ability of potassium dichromate, calcium chromate and strontium chromate observed in the same study (Patierno *et al.*, 1988). Both lead chromate (Casto *et al.*, 1979; Hatch & Anderson, 1986) and zinc chromate (Casto *et al.*, 1979) enhanced viral transformation in Syrian hamster embryo primary cells.

Lead chromate increased the frequency of micronuclei in polychromatic erythrocytes and decreased the polychromatic/normochromatic erythrocyte ratio in bone-marrow cells of intraperitoneally treated C57Bl/6N mice (Watanabe *et al.*, 1985).

Chromyl chloride

Chromyl chloride [Cl_2CrO_2], a volatile liquid chromium[VI] compound, reverted *his*$^-$ *S. typhimurium* in the plate test; its potency, the spectrum of sensitivity of bacterial strains and the attenuating effect of rat liver post-mitochondrial supernatant were similar to those seen for soluble chromium[VI] compounds. Moreover, as assessed by suitable modifications of the standard *Salmonella* test, its vapours were also mutagenic (De Flora *et al.*, 1980; De Flora, 1981a).

(iv) *Other chromium compounds*

The water-soluble chromium[II] salt, chromous chloride [$CrCl_2$], which readily oxidizes to chromium[III] in contact with air, induced infidelity of DNA synthesis, with poly[d(A-T)] as a template in the presence of avian myeloblastosis virus DNA polymerase (Sirover & Loeb, 1976). Chromium[II] was inactive, however, in

all assays with cellular systems, including production of DNA fragmentation in Novikoff ascites hepatoma cells (Wedrychowski *et al.*, 1986a), of chromosomal aberrations and sister chromatid exchange in Syrian hamster embryo primary cells (Tsuda & Kato, 1977), and of aneuploidy in human skin fibroblasts (Nijs & Kirsch-Volders, 1986).

Chromium carbonyl [$Cr(CO)_6$], a hexacoordinated compound with oxidation state 0 (dissolved in ether due to its insolubility in water), was inactive in a differential killing test in *E. coli* (WP2 *vs.* WP67 and CM871) (De Flora *et al.*, 1984a) and in the reversion test in various *his*⁻ *S. typhimurium* strains (De Flora, 1981a; De Flora *et al.*, 1984a).

In contrast to a purple, anionic chromium[III]-glutathione complex, a green sodium chromium[V]-glutathione complex ($Na_4(GSH)_4Cr(V).8H_2O$) cleaved super-coiled DNA of the bacteriophage PM_2 (Kortenkamp *et al.*, 1989). Similarly, in contrast to chromium[VI] and [III], the chromium[V] complex *trans*-bis[2-ethyl-2-hydroxybutanoato(2-)]oxochromate[V] cleaved covalently closed, circular plasmid puc9 DNA. In addition, it reverted strain TA100 of *S. typhimurium* with a potency comparable to that of potassium dichromate (Farrell *et al.*, 1989).

3.3 Other relevant data in humans

(*a*) *Absorption, distribution, excretion and metabolism*

(i) *Chromium[III] compounds*

More than 99% of administered chromium was recovered in faeces following oral administration of chromic chloride to humans; about 94% was recovered after duodenal administration. In both cases, about 0.5% was excreted in urine (Donaldson & Barreras, 1966). After exposure to chromium[III] by inhalation, urinary concentrations of chromium were somewhat increased, indicating respiratory absorption (Aitio *et al.*, 1984; Foa *et al.*, 1988). Pulmonary uptake of chromium[III] is influenced by the nature of the compound; uptake and excretion of chromium[III] lignosulfonate dust by industrial workers was similar to that of water-soluble chromium[VI] (Kiilunen *et al.*, 1983). A study of tannery workers indicated two half-times — one in the order of hours, the other in the order of several days — for urinary excretion of chromium[III] (Aitio *et al.*, 1988).

After one volunteer had immersed his hand in tanning liquor for 1 h, monitoring of blood and urine for 24 h failed to detect dermal absorption of chromic sulfate (Aitio *et al.*, 1984). However, a fatal chromium intoxication, due to skin absorption, was described after accidental submersion of a worker in hot (70°C) chromic sulfate tanning liquor (Kelly *et al.*, 1982).

(ii) *Chromium[VI] compounds*

Following oral administration of sodium chromate in tracer doses to humans, faecal excretion of chromium indicated that about 10% of the administered dose had been absorbed from the gastrointestinal tract. After duodenal administration, approximately half of the administered radioactivity appeared to have been absorbed on the basis of faecal excretion, while 10% appeared in the urine during the first 24 h. Reduction of chromium[VI] to the trivalent form was demonstrated (Donaldson & Barreras, 1966). Circadian monitoring showed post-meal peaks of chromium[VI] reducing activity that may correspond to several tens of milligrams per day (De Flora *et al.*, 1987a).

Correlation between respiratory exposure to chromium[VI] and urinary excretion of chromium has been demonstrated in welders and in workers in the plating industry (Lindberg & Vesterberg, 1983; Aitio *et al.*, 1988). The respiratory uptake rate is unknown, but it depends on the solubility of the chromium compound (for review, see Aitio *et al.*, 1988). Chromium[VI] is reduced in the lower respiratory tract by the epithelial lining fluid and by pulmonary alveolar macrophages. At equivalent numbers of cells, the reducing efficiency of alveolar macrophages by biochemical mechanisms was significantly greater in smokers than in nonsmokers (Petrilli *et al.*, 1986c).

In contrast to chromium[III], which is bound to plasma proteins such as transferrin, chromium[VI] entering the blood stream is taken up selectively by erythrocytes, reduced, and bound predominantly to haemoglobin (Gray & Sterling, 1950; Aaseth *et al.*, 1982; Kitagawa *et al.*, 1988; see also the section on genetic and related effects). Reduction of chromium[VI] during transport in the blood is consistent with the finding that chromium is present in urine only in its reduced form (Mertz, 1969; Nomiyama *et al.*, 1980).

Aitio *et al.* (1988) reviewed the results of biological monitoring of chromium exposure to estimate biological half-times for excretion; the most data were available for manual metal arc stainless-steel welders exposed to soluble chromium[VI]. Three half-times — 7 h, 15-30 days and three to five years — were identified. The best estimates for the sizes of the different compartments are 40%, 50% and 10%, respectively. Lindberg and Vesterberg (1983) also found a correlation between exposure and urinary excretion of chromium in platers.

Retention of chromium on the skin was observed following topical application of sodium chromate (Baranowska-Dutkiewicz, 1981).

(*b*) *Toxic effects*

In adults, the lethal oral dose of chromates is considered to be 50-70 mg/kg bw. The clinical features of acute poisoning are vomiting, diarrhoea, haemorrhagic diathesis and blood loss into the gastrointestinal tract, causing cardiovascular shock

(Sharma *et al.*, 1978; World Health Organization, 1988). If the patient survives for more than about eight days, the major effects are liver necrosis and tubular necrosis of the kidneys (World Health Organization, 1988).

Chronic ulcers of the skin and acute irritative dermatitis have been reported consistently in workers exposed to chromium-containing materials (World Health Organization, 1988). Chromates and chromium[VI] released from alloys and chromium-plated objects have been associated with the induction of allergic contact dermatitis. It is generally assumed that chromium[VI] is necessary for the sensitization, while both chromium[VI] and chromium[III] may cause dermatitis in sensitized individuals (see review by Haines & Nieboer, 1988). Intracellular reduction of chromium[VI] to the trivalent form seems to be a prerequisite for the effect (Polak *et al.*, 1973). In a study conducted in Finland, 2% of men and 1.5% of women showed a positive patch-test reaction to potassium dichromate (Pelkonen & Fräki, 1983). Chromium ulcers and chromate dermatitis have been reported in people in numerous occupations that involve manual handling of products containing chromium (Pedersen, 1982; Burrows, 1983; Polak, 1983; Nieboer *et al.*, 1984). The role of chromium[III] compounds in causing skin ulcers and acute irritative dermatitis is unclear (World Health Organization, 1988).

Inhalation of chromium[VI] compounds may give rise to necrosis in the nasal septum, leading to perforation. Lindberg and Hedenstierna (1983) found nasal irritation in chrome plating workers exposed by inhalation to chromium trioxide (> 1 $\mu g/m^3$ Cr) and nasal perforation in two-thirds of workers with exposure to peak levels above 20 $\mu g/m^3$ Cr. Decreased respiratory function has been reported in platers exposed to chromates (Bovet *et al.*, 1977; Lindberg & Hedenstierna, 1983). Similar effects have been observed in welders and ferrochromium workers, although the role of chromium is uncertain as such persons have mixed exposures (World Health Organization, 1988).

Bronchial asthma may occur as a result of inhalation of chromate dust or chromium trioxide fumes (Meyers, 1950). Asthma among chromium platers, welders and ferrochromium workers has been reported to be due to exposure to chromates, among other compounds (Haines & Nieboer, 1988).

Franchini *et al.* (1978) reported on the excretion of β-glucuronidase, protein and lysozyme in the urine of 99 workers exposed to chromium compounds. No abnormal level was found among 39 stainless-steel welders; eight of 36 workers using special electrodes when welding on armoured steel had increased urinary levels of β-glucuronidase, and three of these workers had proteinuria. Among 24 workers engaged in chrome plating, nine had increased β-glucuronidase levels and four had elevated levels of protein in urine. The increased excretion of enzymes found in these workers was corroborated by exposing rats to potassium dichromate by sub-

cutaneous injection (1.5 mg/kg bw as a single injection or 0.3 mg/kg bw every other day for two weeks); furthermore, a correlation between chromium in the renal cortex and an increase in chromium clearance was reported. Verschoor *et al.* (1988) investigated a number of parameters of kidney function in chrome platers, welders, boiler-makers and an unexposed reference group. Urinary chromium values ranged from 0.3 to 62 μg/g creatinine (0.1-2 μg/g among controls). Renal function was not related to urinary chromium or to chromium clearance, but chromium clearance was increased in the two groups with the highest exposure (platers and welders).

(*c*) *Effects on reproduction and prenatal toxicity*

In a review, Clarkson *et al.* (1985) found no report in the literature of an effect of any chromium compound on reproduction or prenatal development in humans.

(*d*) *Genetic and related effects*

The studies described below are summarized in Appendix 1 to this volume.

(i) *Chromium[III] compounds*

In a comparison of 17 healthy tannery workers with continuous exposure for 13.4 ± 8.2 years to chrome alum and 13 external employees matched for social status, age, sex and years of service, no increase in the frequency of chromosomal aberrations was seen (Hamamy *et al.*, 1987). Average chromium levels of exposed persons were 0.12 μg/l plasma and 0.14 μg/l urine; these values were not considered to be different from those of controls. The level of chromium in air ranged from 15 (day) to 47 (night) μg/m³. [The Working Group noted that exposure was estimated by correlation with a parallel study.] When the data were analysed according to smoking habit, workers who smoked had higher frequencies of chromosome-type aberrations per cell (0.035) than either nonsmoking workers (0.011; $p < 0.01$) or control smokers (0.016; $p < 0.05$). The authors commented that the values for controls were relatively high in comparison with those in other cytogenetic studies reported in the literature.

In the study described below, enhanced levels of chromosomal aberrations, correlated with exposure duration, were observed in workers exposed to 'chromoxide' (Bigaliev *et al.*, 1977a). [The Working Group was unclear whether or not this was a chromium[III] compound.]

(ii) *Chromium[VI] compounds*

Bigaliev *et al.* (1977a) examined peripheral lymphocytes from 132 workers in chromium production who were exposed to one of five chromium compounds and compared them with 37 healthy, unexposed workers. Significant increases in the

frequency of chromosomal aberrations over control values of 1.88 ± 0.74% metaphases with aberrations were observed, as follows: monochromate (sodium chromate), with a dose-related trend (correlation with exposure duration) ranging from 3.6 to 8.2% aberrant metaphases; sodium chrompik (sodium dichromate), with a dose-related trend ranging from 4.5 to 5.7% aberrant metaphases; potassium dichromate, with a dose-related trend ranging from 3.6 to 9.0%; chromoxide (as reported in the preceding section), with a dose-related trend ranging from 4.5 to 7.2%; and chromanhydride (chromium trioxide), with a dose-effect trend ranging from 5.4 to 9.4%. [The Working Group noted that no information was provided on exposure levels or on selection criteria, but the overall sample size was large.] When chromosomal aberrations were examined in detail (Bigaliev *et al.*, 1977b,c; Bigaliev, 1981), increased frequencies were found for single and double fragments, for translocations and for aneuploidy, consisting mainly of chromosome loss. Dose-responses were observed overall, and for each type of damage. In a later study (Bigaliev *et al.*, 1979), elongated cell-cycle times were seen for cultured peripheral lymphocytes from a group of chromium workers with five or more years' exposure, compared with a control group registered at the city blood transfusion station. An effect of duration of exposure was reported in a further analysis (Bigaliev *et al.*, 1977c; Bigaliev, 1981).

Several studies have been carried out on chromium platers. Increased frequencies of sister chromatid exchange were found in a study of male chromium platers exposed to chromium trioxide fumes (Stella *et al.*, 1982). Mean sister chromatid exchange values of 8.08 ± 2.67 ($p < 0.001$) were observed in exposed workers *versus* 6.31 ± 1.56 in ten healthy male donors aged 20-35 who had not been exposed to ionizing radiation. The authors noted particularly that the seven youngest workers, although the most recently engaged in chromium plating, showed significantly increased sister chromatid exchange frequencies. An effect of age on the induction of sister chromatid exchange was noted in the control group. [The Working Group noted that details were not provided on exposure, or on confounding factors].

Sarto *et al.* (1982) analysed sister chromatid exchange and chromosomal aberrations in peripheral blood lymphocytes of chrome platers in four factories in the same region, grouped by type of exposure and factory: groups 1 (eight persons) and 2 (nine persons) used a 'bright plating' process and were exposed to chromium trioxide and nickel; groups 3 (12 persons) and 4 (nine persons) used a 'hard plating' process and were exposed only to chromium trioxide. Controls were 35 healthy male sanitary workers who had not been exposed to occupational or diagnostic ionizing radiation for at least five years and had not knowingly been exposed to either occupational mutagens or mutagenic drugs. Their mean ages and smoking habits were similar to those of the exposed workers. The average ages in the four exposed groups were 39, 42, 24 and 34 years, respectively; urinary chromium levels (μg/g

creatinine) in the four groups were 5.1 ± 1.8, 7.1 ± 3.3, 11.8 ± 8.7 and 6.8 ± 3.7, respectively, *versus* 1.9 + 1.4 for controls. Sister chromatid exchange frequencies in the 'hard plating' groups were increased ($p < 0.001$) from 6.60 ± 0.80% in controls to 8.30 ± 1.80%; however, when the values were analysed by age, a significant increase in sister chromatid exchange was observed only in the group of younger workers (group 3). A correlation was observed between sister chromatid exchange frequency and both age and urinary chromium levels (more sister chromatid exchange in younger workers with higher levels of chromium). A significant increase in the frequency of chromosomal aberrations, mostly of the chromosome type, was observed, from 1.7% of metaphases in controls to 3.8 ($p < 0.001$) in 'bright' platers and 2.8 ($p < 0.01$) in 'hard' platers. Chromatid-type aberrations were observed only in the 'bright' platers. The correlation between urinary chromium levels and chromosomal aberrations was poor.

No increase in the frequency of sister chromatid exchange was observed in a group of 24 male chromium platers exposed to chromium in air for 0.5-30.5 (mean, 11.6 ± 7.5) years, when compared with a group of office workers matched for sex, age and smoking habit (Nagaya, 1986). Smokers and nonsmokers were analysed separately for each group, and a smoking-related increase in the frequency of sister chromatid exchange was observed for both exposed (smokers, 10.7 ± 1.7%; nonsmokers, 9.0 ± 1.0%) persons and controls (smokers, 10.6 ± 2%; nonsmokers, 8.9 ± 1.2%). No correlation was seen between sister chromatid exchange frequencies and urinary chromium levels (13.1 ± 16.7 µg/l for exposed persons, none detected for controls). In a further study of a larger group (Nagaya *et al.*, 1989), essentially the same results were obtained. The authors speculated that the chromium exposure may have been too low to affect circulating lymphocytes. [The Working Group noted that high control values were observed in both studies.]

Choi *et al.* (1987) compared two groups of metal platers, consisting of seven workers in chromium surface treatment (group 1) and 25 workers in chromium plating (group 2), with 15 non-plating workers matched for age, sex and length of career. Exposures to chromium in air and urine were 0.027 (0.021-0.034) mg/m^3 and 24.0 ± 7.8 µg/l, respectively, for group 1, and 0.008 (0.005-0.012) mg/m^3 and 15.2 ± 5.9 µg/l, respectively, for group 2. Sister chromatid exchange frequency was increased from 3.6 ± 1.5 (controls) to 6.9 ± 1.8 ($p < 0.05$) in group 1 and to 5.4 ± 2.1 ($p < 0.05$) in group 2. A dose-effect relationship was observed with urinary chromium levels ($p < 0.01$). No effect of smoking was observed in exposed workers or controls.

Deng *et al.* (1983, 1988) observed significant increases in the frequencies of sister chromatid exchange and of chromosomal aberrations (gaps, breaks, fragments; 5.7% *versus* 0.8% in controls) in lymphocytes of seven chromium platers. Details of the study are provided in the monograph on nickel and nickel compounds, p. 389.

Several studies of occupational exposures to chromium during welding are described in the monograph on welding, pp. 487-489. Both enhancement (Koshi *et al.*, 1984) and lack of enhancement (Husgafvel-Pursiainen *et al.*, 1982; Littorin *et al.*, 1983) of sister chromatid exchange and chromosomal aberrations were reported in exposed workers.

As reported in an abstract (Imreh & Radulescu, 1982), 18 workers in a bichromate producing plant with a mean duration of exposure of 21.3 years (19-26 years) showed significantly elevated frequencies of chromosomal and chromatid-type aberrations and micronuclei when compared with eight mechanics from the same plant and with 34 healthy external controls. Sister chromatid exchange frequencies were not significantly greater than in the mechanics.

3.4 Case reports and epidemiological studies of carcinogenicity to humans

Epidemiological studies on chromium have been reviewed extensively (see, e.g., Sunderman, 1976; Norseth, 1980; Anon., 1981; Norseth, 1981; Sunderman, 1984, 1986; Adachi & Takemoto, 1987; Fan & Harding-Barlow, 1987; Hayes, 1988; World Health Organization, 1988; Yassi & Nieboer, 1988). Epidemiological studies on welders exposed to chromium and its compounds are summarized in the monograph on welding (see pp. 489-505).

Epidemiological studies of cancer in workers in industries in which exposure to chromium compounds could occur are summarized in Tables 28-31. Standardized mortality ratios (SMRs) and confidence intervals (CIs), assuming Poisson distribution, are given in square brackets when they were calculated by the Working Group.

(*a*) *Chromate production*

(i) *Case reports*

Many case reports of lung cancer have been published in relation to work in chromate production. Many of these were reviewed by a Working Group for the IARC (1980a); further case reports were made by Pfeil (1935), Alwens and Jonas (1938), Zober (1979), Hyodo *et al.* (1980), Abe *et al.* (1982), Tsuneta (1982) and Nishiyama *et al.* (1985, 1988). After having seen five cases of gastrointestinal cancer among 44 deceased chromate workers, Teleky (1936) drew attention to the possibility that chromate exposure could also be associated with an increased risk for cancer of the gastrointestinal tract.

(ii) *Epidemiological studies*

The Working Group considered six studies covering several partially overlapping populations in seven plants producing chromate from chemical-grade chromite ore (Brinton *et al.*, 1952) in the USA; the degree of overlap could not be ascertained.

Table 28. Epidemiological studies of cancer in workers in chromate-producing industries

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
Seven US chromate plants; active employees 1930–47; 193 deaths	Male oil refinery workers, 1933–38	Respiratory system	42	20.7	Digestive system Oral region (also included in respiratory system)	13 3	2.0 5.4*	Machle & Gregorius (1948)
Seven US chromium plants; active employees 1940–50; 5522 person-years	US male white, non-white	Respiratory system, except larynx	10 white 16 non-white	14.3* 80.0*	Other sites	6 (whole cohort)	1.0 ns	Brinton *et al.* (1952); Gafafer (1953)
Health survey, 897 workers	Boston X-ray survey	Bronchogenic/lung	10	53.6 (prevalence ratio)				Gafafer (1953)
Three US plants; men employed 1937–40, surveyed 1941–60	Cancer mortality; US males 1950, 1953, 1958	Respiratory (160–164)	69 (2 maxillary sinus)	9.4*	Digestive system	16	1.5 ns	Taylor (1966); Enterline (1974)
290 cases near US chromium plant	Random sample of hospital admissions	Lung	11[a]	∞				Baetjer (1950)
US chromate plant; employed one or more years 1931–37; all jobs related to exposure to soluble and insoluble chromium; lifetime exposure in months calculated	No independent comparison group	Lung	41					Mancuso & Hueper (1951); Mancuso (1975)

Table 28 (contd)

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
US chromate plant; 2101 (restricted to 1803) workers initially employed three or more months 1945–74; status 1977 (88.5% complete); population working in new and/or old production sites	Baltimore City; mortality	Lung	59	2.0*	Digestive system Other	13 14	0.60 0.40	Hayes *et al.* (1979)
Three UK chromate factories; men employed 1949–55	Cancer mortality, England and Wales	Lung	12	3.6*	All other sites	No increase		Bidstrup & Case (1956)
Same UK factories as studied by Bidstrup & Case (1956); 1948–77; 2715 males	Cancer mortality, England, Wales and Scotland	Lung	116	2.4*	Other sites Nasal cancer	80 2	1.2 ns 7.1*	Alderson *et al.* (1981)
Two FRG chromate plants; 1140 male workers employed more than one year 1934–79	Mortality, North Rhine Westphalen	Lung	51	2.1*	Stomach	12	0.94 ns	Korallus *et al.* (1982)
Tokyo chromium manufacture; 896 production workers, 1918–78	Age–, cause–specific mortality, Japanese males	Respiratory cancers	31 (6 sinonasal)	9.2*	Stomach	11	1.0	Satoh *et al.* (1981)
		1–10 years' exposure	5	4.2*				
		11–20 years' exposure	9	7.5*				
		≥21 years' exposure	17	17.5*				

Table 28 (contd)

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
273 chromate producers in Japan; 1947–73; observed 1960–82	Age-, cause-specific mortality, Japanese males	Lung	25 (plus 1 maxillary sinus)	18.3*	Digestive system	6	0.9	Watanabe & Fukuchi (1984)
540 Italian chromate producers employed 10 years or more, 1948–85	Italian cause-specific death rates	Lung Highly exposed	14 6	2.2* 4.2*	Larynx Pleura	3 3	2.9 30*	De Marco *et al.* (1988)

[a]In comparison with internal reference population

*Significant at 95% level

ns Nonsignificant

Table 29. Epidemiological studies of cancer in workers in chromate–pigment industries

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
Norwegian chromium pigment production since 1948; 133 workers of whom 24 over 3 years' employment to 1972	Cancer incidence, Norway 1955–76	Lung	6 (one case with < 3 years' employment)	44 67 (10 years' latency)	Gastrointestinal Nasal cavity	3 1	6.4 –	Langård & Norseth (1975, 1979); Langård & Vigander (1983)
UK chromate pigment factories: A, lead & zinc chromate; B, lead & zinc chromate; C, lead chromate; followed up to 1981	Mortality, England and Wales	Lung A (1932–54) B (1948–67) C (1946–60)	 21 11 7	 2.2* 4.4* 1.1 ns				Davies (1978, 1979, 1984a)
French lead and zinc chromate manufacturers; 251 males employed 6 months or more, 1958–77	Standard death rates, northern France 1958–77	Lung	11	4.6*				Haguenoer *et al.* (1981)
German and Dutch manufacturers of zinc and lead chromates; 978 workers followed up for 15 076 person-years	Local death rates, FRG and the Netherlands	Lung	19	2.0*				Frentzel-Beyme (1983)

Table 29 (contd)

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
US lead and zinc chromate production workers employed ≥1 month 1940–69; 1181 white, 698 non-white; followed up to end of 1982	Mortality, US whites and non-whites	Lung (30-year latency)	24	1.4 ns	Stomach	6	1.8 ns	Sheffet *et al.* (1982); Hayes *et al.* (1989)
		< 1 year exposure	3	1.4**				
		1–9 years' exposure	3	2.0**				
		≥10 years' exposure	6	3.2**				

** p for trend < 0.01

ns Nonsignificant

Table 30. Epidemiological studies of cancer in workers in chromium-plating industries

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
54 UK chromium-plating plants; 1056 male platers	1099 non-exposed males in plants and in two nonplating industries	Lung	24	1.4 ns	All sites Gastrointestinal Other sites	44 8 12	1.7* 1.5 ns 1.9 ns	Royle (1975a,b)
Japanese chromium platers; 952 workers with >6 months' exposure	Platers not exposed to chromium and clerical workers	Lung	0	-	All sites	5	0.5 ns	Okubo & Tsuchiya (1977, 1979, 1987)
US workers in diecasting and Ni-Cr-plating plant, 1974–78	US national mortality statistics	Lung men women	 28 10	 1.9* 3.7*	Stomach Larynx Lymphosarcoma	4 2 2	2.5 ns 3.3 ns 2.9 ns	Silverstein *et al.* (1981)
Nine plants, Parma, Italy, 116 'thick' and 62 'thin' platers; employed more than 1 year 1951–81	Mortality, Italy	Lung	3	3.3* (4.3* for 'thick' platers)	All sites	8	1.9	Franchini *et al.* (1983)
UK chromium platers; 2689 (1288 men, 1401 women) first employed 1946–75; observed 1946–83	Mortality, England and Wales	Lung men women Nasal cavity (men and women) Larynx men women	 63 9 3 3 0	 1.6* 1.1 ns 10* 3.0 ns -	Stomach (men and women) Liver men women	25 4 0	1.5 ns 6.7* -	Sorahan *et al.* (1987)

* Significant at 95% level
ns Nonsignificant

Table 31. Epidemiological studies of cancer in workers in ferrochromium industries

Study population	Reference population	Cancer of respiratory organs			Cancer at other sites			Reference
		Site	Number	Estimated relative risk	Site	Number	Estimated relative risk	
USSR ferrochromium alloy industry; 1955–69	Mortality, general population of municipality	Lung (men)	Not given	4.4–6.6* by age	All sites (men) Oesophagus (men)	Not given Not given	0.5–3.3* 2.0*–11.3*	Pokrovskaya & Shabynina (1973)
Swedish ferrochromium plant; ferroalloy; 1876 workers for 1 or more years 1930–75; traced by parish lists and cancer registry	County or national statistics; classification of work areas by Cr[III] and Cr[VI]	Lung All workers Maintenance workers Arc workers	 7 4 (2 mesotheliomas) 2 (1 mesothelioma)	 1.2 ns 4.0* 1.0 ns	Prostate (all workers)	23	1.2 ns	Axelsson *et al.* (1980)
Norwegian ferrochromium and ferrosilicon; 1235 male workers employed 1928–65	General population; internal comparison with unexposed	Lung (ferrochromium workers)	10	1.5 ns	All sites Kidney Prostate Stomach (ferrochromium workers)	132 5 12 7	0.8 ns 2.7 ns 1.5 ns 1.4 ns	Langård *et al.* (1980, 1989)

*Significant at 95% level

ns, Nonsignificant

Machle and Gregorius (1948) reported high proportionate mortality from respiratory cancer among male workers at the seven chromate-producing plants in the USA: between 1930 and 1947, the annual death rate from respiratory cancer was 2.63/1000, as compared with a frequency of 0.09/1000 in a comparison group from an oil refinery in 1933-38. [The Working Group noted that the age structures of the two populations were not given.]

Brinton *et al.* (1952) and Gafafer (1953) conducted a mortality study (a US Public Health Service study) of male workers in the seven chromate manufacturing plants during 1940-50 with 5522 person-years of membership in sick-benefit associations for persons 15-74 years old, not including workers who had terminated employment with the chromate industry and those who had died more than one year after the onset of disability. Comparison was made to age- and race-specific US male mortality rates during 1940-48. Ten deaths from cancer of the respiratory system (except larynx) were observed among white employees (SMR, 1429 [95% CI, 685-2627]). Among non-white employees, 16 deaths from cancer at this site were found (SMR, 8000 [95% CI, 4573-12 991]). For the entire study group, six deaths from cancers at all other sites were observed [SMR, 95.2; 95% CI, 35-207]. [The Working Group noted that the SMR for lung cancer may have been biased, because of the exclusion of terminated and retired workers and of those who did not belong to the sick-benefit plan.] A health survey of 897 workers gave a prevalence ratio of 53.6 for bronchogenic cancer in chromate workers compared to persons who had undergone a chest X-ray survey for lung cancer (Gafafer, 1953).

Enterline (1974) reanalysed data from a study by Taylor (1966) of 1212 male workers who had been employed in three of the US plants for three months or longer for the period 1937-60. The study cohort, constructed from earnings reports in old age and survivors disability insurance records, was restricted to men born after 1889. Vital status was ascertained through 1960 by searching the death claim files of the records; death certificates were subsequently obtained for workers for whom death claims had been filed. Age-specific mortality figures for US males in the calendar years 1950, 1953 and 1958 were used as reference. A total of 69 deaths from cancers of the respiratory system (ICD codes 160-164) was observed (SMR, 943 [95% CI, 733-1193]), two of which were from maxillary sinus cancer; the author regarded this rate as greatly elevated. Furthermore, a small excess of deaths from cancer of the digestive system was observed (16 deaths; SMR, 153 [95% CI, 88-249]).

In a study of medical records from two hospitals in Baltimore, MD, USA, near a chromate-producing plant, Baetjer (1950) found that 11 (3.8%) of 290 male lung cancer patients admitted in 1925-48 had had exposure to chromates, whereas no chromate-exposed worker was found among a 'random' sample of 725 other hospital admissions. Ten of the 11 cases had worked in the local chromate production

plant and one in an electrical company. Occupational history was derived only from records.

Mancuso (1975) reported on a cohort recruited from a US chromate-producing plant that had been investigated earlier (Mancuso & Hueper, 1951). In the earlier report, six lung cancer deaths were observed, giving a relative risk of 15; using hygiene data collected in 1949, cumulative exposures to soluble, insoluble and total chromium, combined with length of exposure, were computed for each worker in the cohort. The second analysis was confined to the 41 deaths from lung cancer that occurred in persons first employed between 1931 when the plant started operation and 1937 and followed through 1974, and rates were computed using direct standardization, with the entire plant population as the standard. Mortality from lung cancer was associated with cumulative exposure to insoluble chromium, to soluble chromium and to total chromium. [The Working Group noted that the three classes of exposure were highly correlated and the risks of exposure to soluble and insoluble chromium could not be distinguished.]

Hayes *et al.* (1979) studied workers at a chromate production plant in Baltimore, MD, USA, which had been partly renovated in 1950-51 and 1960 to reduce exposure to chromium dusts. The study cohort consisted of 2101 workers with more than 90 days of work experience, first employed between 1945 and 1974, and followed through July 1977; vital status was ascertained for 75% on an individual basis and for another 14% on a group basis. SMRs for 1803 hourly employees were calculated on the basis of expected values derived from the age-, race- and time-specific mortality rates for Baltimore City males. There were 404 deaths from all causes (SMR, 92). The overall SMR for cancer of the trachea, bronchus and lung (ICD code 162) was 202, based on 59 observed deaths (95% CI, 155-263). Workers hired between 1945 and 1949, before the plant was renovated, who had been employed for fewer than three years, had an SMR for lung cancer of 180 (95% CI, 110-270), based on 20 observed deaths, whereas workers with three or more years of employment hired in that period had an SMR of 300 (95% CI, 160-520), based on 13 observed deaths. For workers hired in 1950-59, when part of the plant had better environmental controls, similarly elevated risks were seen, based on 12 and nine cases for short-term and long-term employment, respectively. No case of lung cancer was detected in 1960-74 after the plant had been renovated, but, as the authors noted, the latent period is too short for an adequate assessment of risk for cancer at this site. Additional case-control analyses were performed to determine whether specific work areas were associated with lung cancer hazard. Controls who had died from causes other than cancer were matched individually by race, date of hire, age at initial employment and duration of employment to the 66 hourly or salaried employees who had died from lung cancer. A significant ($p < 0.05$) elevation in risk for lung cancer was found for employees who had worked in the 'special products' and dich-

romate areas, where soluble chromium[VI] compounds were produced and packaged (relative risks, 2.6 and 3.3, respectively).

On the basis of data from the previous study and the results of 555 air samples analysed in 1945-50, Braver *et al.* (1985) studied the relationship between exposure to chromium[VI] and occurrence of lung cancer. The authors reported a dose-response relationship with cumulative exposure. [The Working Group noted that the association appeared to be due predominantly to duration of exposure and not to estimated level of exposure, which did not vary substantially.]

A total of 723 chromate production workers from three factories in the UK who were interviewed and radiographed were followed up in 1949-55 by Bidstrup and Case (1956), who reported significantly higher than expected lung cancer mortality: 12 deaths [SMR, 364; 95% CI, 188-635] (based on age-adjusted rates for England and Wales). The average duration of exposure was 12.2 years; 165 (22.8%) persons had worked for more than 20 years (Bidstrup, 1951). For cancers at other sites, the observed and expected numbers of deaths did not differ significantly.

Alderson *et al.* (1981) studied 2715 chromate production workers with more than one year of work experience between 1948 and 1977 and who had undergone at least one X-ray of the lungs, 79 (2.9%) of whom were lost to follow-up, at the same three UK factories studied by Bidstrup and Case (1956). The percentage of heavy smokers was reported to be lower among the workers than among males in England and Wales [numbers not given]. During the study period, 602 deaths occurred (SMR, 135 [95% CI, 125-146]), 116 of which were from lung cancer (SMR, 242 [95% CI, 200-290]). Two deaths from nasal cancer were observed in one factory; 0.28 would have been expected for the whole cohort (SMR, 714 [95% CI, 87-2580]).

Korallus *et al.* (1982) identified 1140 workers who had been employed for one year or more at two chromate-producing plants in the Federal Republic of Germany. The study subjects were active workers and pensioners who had been hired before 1948 or workers hired thereafter. Vital status was ascertained from personnel documents and from population registries until 1979. Cause of death was determined from medical records and, in some cases, from death certificates. The SMR for respiratory cancer (ICD 8, 160-163) was 210 [95% CI, 156-276]. A total of 20 deaths from bronchial carcinomas (and one laryngeal carcinoma) was seen in one factory (SMR, 192 [95% CI, 119-294], and 30 deaths, all from bronchial carcinoma, in the second (SMR, 224 [95% CI, 151-319]). The author noted difficulties in the ascertainment of cause of death and of comparability with the standard population.

Satoh *et al.* (1981) studied 896 men who had been engaged in manufacturing chromium compounds for one or more years in a factory in the Tokyo, Japan, area between 1918 and 1975. The workers were observed from 1918 through 1978 or to death; vital status could not be ascertained for an additional 165 retired workers. The authors stated that 84% of the chromium compounds manufactured between

1934 and 1975 were hexavalent compounds and 16% trivalent compounds. The expected numbers of deaths were based on age- and cause-specific mortality rates for Japanese males. Between 1950 and 1978, 120 deaths (SMR, 90) were observed, 31 of which were from respiratory cancer [SMR, 923; 95% CI, 627-1310]; 25 of these were from lung cancer and six from sinonasal cancer. No other cancer occurred in excess. When the population was subdivided by duration of work, there were five cases of respiratory cancer in the group with one to ten years of exposure [SMR, 423; 95% CI, 138-989], nine in the group with 11-20 years' exposure [SMR, 748; 95% CI, 343-1424] and 17 in the group with more than 21 years of exposure [SMR, 1747; 95% CI, 1021-2806].

Watanabe and Fukuchi (1984) reported in an abstract a mortality study of 273 workers employed in 1947 or later at a chromate-producing factory in Japan for at least five years until 1973, previously studied by Ohsaki *et al.* (1974, 1978). The population was observed from January 1960 to December 1982. Expected numbers of deaths were based on age-, year- and cause-specific deaths rates for the Japanese male population. Sixty deaths from all causes were observed; 33 from all cancers, of which 25 were from lung cancer (SMR, 1832 [95% CI, 1190-2714]) and six from cancer of the digestive organs [SMR, 88; 95% CI, 32-192]; one cancer of the maxillary sinus was seen.

In an Italian cohort study of 981 chromate production workers employed for one year or more in 1948-85 (De Marco *et al.*, 1988), analysis was limited to the 540 workers followed up for ten years or more. Cause-specific death rates in Italy were used as a reference level. The SMR for lung cancer was 217 (14 deaths; 95% CI, 118-363), and there were three deaths each from cancers of the pleura and larynx. Among a subgroup of workers with heavy exposure to hexavalent chromium compounds (on the basis of job histories), the SMR for lung cancer was 420 (six deaths [95% CI, 154-193]).

(*b*) *Production of chromate pigments*

(i) *Case reports*

Newman (1890) reported the first case of cancer in a 'chrome worker', which was an adenocarcinoma of the anterior half of the left nostril in a 47-year-old male worker who had had perforation of his nasal septum for 20 years; the patient had been exposed to chrome pigments. Since that time, there have been a number of case reports of lung cancer in workers involved in production of chromate pigments (Gross & Kölsch, 1943; Letterer *et al.*, 1944; Langård & Kommedal, 1975; Zober, 1979; Rivolta *et al.*, 1982).

(ii) *Epidemiological studies*

Langård and Vigander (1983) followed up 133 workers for 1953-80, who had been employed in a small Norwegian company producing chromate pigments in

1948-72, previously studied by Langård and Norseth (1975). The work force was exposed to zinc chromate from 1951; a small number of workers had also been exposed to lead chromate between 1948 and 1956. While past levels of exposure to hexavalent chromium are unknown, exposures to chromates as chromium measured in 1973 ranged from 0.01 to 1.35 mg/m^3 (Langård & Norseth, 1979). One case of lung cancer occurred among 109 workers with less than three years of employment prior to 1972. Six cases of lung cancer occurred in a subpopulation of 24 workers with more than three years of work experience prior to 1972 [giving a standardized incidence ratio (SIR) of 4444 (95% CI, 1631-9674) on the basis of national incidence rates among males]. More than ten years after first exposure, the SIR was 6667 [95% CI, 2447-14 510] on the basis of national reference rates. Only 18 workers had worked at the plant for more than five years, and all six cases belonged to this subgroup. One of the cases had worked in the production of zinc chromate as well as lead chromate, while five cases had worked in the production of zinc chromate only. A previous follow-up had found one case of cancer of the nasal cavity, one of cancer of the prostate and three of cancer of the gastrointestinal tract (one cancer of the pancreas, one stomach cancer and one cancer of the large intestine) (Langård & Norseth, 1979). The three latter cases occurred in the subgroup of 24 workers employed for more than three years before 1972 [SMR, 638; 95% CI, 0.6-8.8].

Davies (1978, 1979, 1984a) studied mortality among 1002 male workers at three factories in the UK where chromate pigments were manufactured. Production of lead chromate[VI] occurred in all factories; workers in two of the factories (A and B) were additionally involved in manufacturing zinc chromate[VI] until 1964 and 1976, respectively. Small amounts of barium chromate were produced in factory A from 1942, and small amounts of strontium chromate were produced in factory B from the early 1950s to 1968. Factory A closed in 1982 and factory B in 1978. Exposure levels were classified only as high, medium or low. The 1984 report extended the follow-up from the 1930s or 1940s to the end of 1981. The expected numbers were based on calendar time period-, sex- and age-specific mortality rates for England and Wales. An excess of lung cancer appeared in two groups of workers assigned to high and medium exposure: factory A, those entering before 1955 (21 cases; SMR, 222 [95% CI, 138-340]) and factory B, those entering before 1968 (11 cases; SMR, 440 [95% CI, 220-787]). In workers with low exposure to zinc and lead chromates in factories A and B, seven lung cancer deaths were observed [SMR, 101; 95% CI, 41-208]. In factory C, where only lead chromate was produced, seven lung cancer deaths were observed [SMR, 109; 95% CI, 44-224], and the highest ratio was found for one to 29 years of follow-up of a group of 33 men among early entrants with high and medium exposure (three cases [SMR, 357; 95% CI, 74-1044]). The author indicated that moderate or heavy exposure to zinc chromate may give rise to

a high risk for developing lung cancer, and that relatively mild or short-term exposure may not constitute a measurable lung cancer hazard.

Davies (1984b) also studied a subgroup of 57 workers involved in the production of lead chromate pigments from lead nitrate in the same three factories, who had been reported to the work inspectorate to have lead poisoning, mostly between 1930 and 1945. Mortality was observed through 1981, giving 1585 person-years of observation. Four deaths from lung cancer (SMR, 145 [95% CI, 40-370]) were observed. [The Working Group noted that this small sample of workers might have been highly selected.]

Haguenoer *et al.* (1981) reported deaths among a cohort of 251 workers in a factory manufacturing zinc and lead chromate pigments in France who had been employed for more than six months between 1 January 1958 and 31 December 1977. Fifty deaths occurred, the specific cause of which was known from medical records for 30. Expected numbers were derived from death certificates. Among the 30 deaths, there were 11 confirmed lung cancer deaths (SMR, 461; 95% CI, 270-790). The mean time from first employment until detection of cancer was 17 years, and the mean duration of employment among cases was 15.3 years. [The Working Group noted that cause of death was ascertained from different sources for observed and expected cases.]

Frentzel-Beyme (1983) studied mortality among men employed for more than six months in three factories in the Federal Republic of Germany and two factories in the Netherlands that produced lead and zinc chromate pigments. The total number of study participants was 1396. Regional death rates in the two countries were used to estimate expected figures. In an analysis of 978 men with exposure beginning before 1965, 117 deaths were observed [SMR, 96], of which 19 were from lung cancer [SMR, 204; 95% CI, 123-319].

Hayes *et al.* (1989) followed-up a cohort studied by Sheffet *et al.* (1982) consisting of 1879 male employees of a New Jersey (USA) lead and zinc chromate pigment production factory who had been employed for at least one month between January 1940 and December 1969; they were observed from 1940 to 1982. US age- and calendar-specific death rates for white and nonwhite men were used as reference. Vital status was ascertained for 1737 workers (92%). Airborne chromium concentrations were measured during later years, giving estimates of > 0.5 mg/m^3 for exposed jobs and of > 2 mg/m^3 for highly exposed jobs; the ratio of lead chromate:zinc chromate in the working atmosphere was reported to be about 9:1, and low levels of nickel may have been present. The SMR for all cancers was 93 (101 deaths; 95% CI, 76-113). Among a total of 41 lung cancer deaths (SMR, 116; 95% CI, 83-158), 24 occurred among workers exposed to chromate dusts (SMR, 143). The SMR for lung cancer among men who had not worked in chromium-exposed jobs was 92 (17 deaths; 95% CI, 53-147), and that for men who had worked for less than one year was 93 (seven

deaths; 95% CI, 37-192). For those with cumulative exposure to chromate dusts of one to nine years, the SMR was 176 (nine deaths; 95% CI, 80-334), and for ten or more years, 194 (eight deaths; 95% CI, 83-383). When accounting for 30 years since first employment among men with more than ten years' exposure, the SMR rose to 321 (95% CI, 117-698), based on six cases. In jobs with exposure to chromate dusts, a nonsignificant excess of cancer of the digestive tract was found; for stomach cancer, the SMRs were 149, 185 and 214 for those with less than one, one to nine and more than ten years' exposure, respectively.

(*c*) *Chromium plating*

(i) *Case reports*

Cases of lung cancer have also been reported among chromium platers (Barbořík *et al.*, 1958; Kleisbauer *et al.*, 1972; Korallus *et al.*, 1974b,c; Michel-Briand & Simonin, 1977; Takemoto *et al.*, 1977; Sano, 1978; Zober, 1979; Brochard *et al.*, 1983; Kim *et al.*, 1985).

(ii) *Epidemiological studies*

Royle (1975b) conducted a mortality study among past and current workers with three months or more of consecutive employment in 54 chromium-plating plants in Yorkshire, UK. The study covered 1238 chromium-plating workers (1056 men, 182 women), 142 of whom had died by 31 May 1974. A control population of 1284 manual workers (1099 men, 185 women) was drawn from non-chromium-plating departments of the largest firms and from the past and current work force of two industrial companies located in the same geographic region. The control subjects were matched individually to the platers by sex, age, date when last known to be alive and, for current workers, smoking habits. The study population represented 91% of the total exposed population and 93% of the eligible controls. Compared with the controls, chromium platers experienced a significant excess proportion of deaths from total cancer: 51/142 *versus* 24/104 in men and women combined ($p < 0.01$). The excess was statistically significant only for individuals who had been platers for more than one year. In male chromium platers, 24 lung cancer deaths (ICD codes 162, 163) out of a total of 130 deaths were observed *versus* 13/96 among controls (nonsignificant). Cancer of the gastrointestinal tract and of 'all other sites' also occurred in excess in men, but the differences were not significant: 8/130 deaths from gastrointestinal cancers among exposed *versus* 4/96 in controls; 12/130 deaths from cancers of 'all other sites' in exposed *versus* 5/96 in controls. The smoking habits of platers and controls were similar. A higher proportion of controls had worked in asbestos processing (8.3% of controls *versus* 3.6% of platers); more platers had worked in coal mines, foundries, potteries, cotton manufacture and flax and hemp mills (Royle, 1975a). [The Working Group noted that past exposure to asbestos among the controls might have led to some underestimation of the lung cancer risk

in the exposed group, and that the method of analysis used made the study difficult to interpret.]

Okubo and Tsuchiya (1977, 1979) reported results from a mortality study among 952 chromium platers in Tokyo, Japan. The cohort was constructed from records for 1970-76 of the Tokyo Health Insurance Society of the Plating Industry, and consisted of chromium platers (889 men, 63 women) who were born prior to 31 May 1937, had more than six months of work experience in chromium plating and had a work history record. Vital status was ascertained from a questionnaire sent to the management of the plating firms and, for retired workers, by contacting family registers; persons whose vital status was unknown were assumed to be alive. The expected number of deaths was derived from age-, sex- and year-specific death rates for the Tokyo general population. Twenty-one deaths from all causes were observed in chromium platers [SMR, 55; 95% CI, 34-83]. No case of lung cancer occurred, although 1.2 would have been expected in men. These results were reiterated in a 99% follow-up of a subgroup reported in an abstract (Okubo & Tsuchiya, 1987). [The Working Group questioned the completeness of assembling the cohort, the low age structure of the population and the limited period of follow-up.]

Silverstein *et al.* (1981) performed a proportionate mortality study in a group of hourly employees and retirees with at least ten years of service in a die-casting and nickel- and chromium-electroplating plant in the USA. The 238 subjects who had died between January 1974 and December 1978 were included in the study. Causes of death as stated on death certificates were compared with US national mortality rates. A total of 53 deaths from cancer were observed (proportionate mortality ratio (PMR), 135 [95% CI, 101-176]) among white men and 23 among white women (PMR, 127 [95% CI, 81-191)]. The study revealed 28 lung cancer deaths (PMR, 191 [95% CI, 127-276]) in white men and ten among white women (PMR, 370 [95% CI, 178-681]). Smoking habits were not known. Four deaths from stomach cancer (PMR, 254 [95% CI, 69-648]), two from laryngeal cancer (PMR, 330 [95% CI, 40-1184] and two from lymphosarcoma and reticulosarcoma (PMR, 285 [95% CI, 35-1032]) occurred in white men. A case-control analysis of the lung cancer deaths, using deaths from cardiovascular disease as controls, tested the association of cancer with duration of work in different work sites, without considering possible confounders. An association was seen (odds ratio, 9.2; $p = 0.04$) for white men with more than five years' work in a department which, prior to 1971, was one of the major die-casting and plating areas in the plant. The authors noted that, although the population had been exposed primarily to chromium[VI], they had also been exposed to nickel compounds and may have been exposed to polycyclic aromatic hydrocarbons and metal fumes during die-casting.

Franchini *et al.* (1983) reported cancer mortality in a group of 178 Italian chromium electroplaters, 62 of whom were 'bright' (thin plating) and 116 of whom were

'hard' (thick plating) platers, and who had worked for at least one year in one of nine plants between 1951 and 1981. In 1980, exposure to chromium averaged 7 μg/m³ air as chromium trioxide near the plating baths and 3 μg/m³ in the middle of the room; measurements of urinary chromium showed that hard platers were more heavily exposed than bright platers: the median level of chromium in the urine of hard platers was 23.1 μg/g creatinine in 1974-76 and 5.7 μg/g creatinine in 1980-81. The SMR for deaths from all causes was 97 (15 deaths [95% CI, 55-163]); there were eight deaths from malignant tumours (SMR, 191; [95% CI, 82-375]) and three from lung cancer [SMR, 333; 95% CI, 69-974]. Seven of the cancer deaths occurred among hard platers [SMR, 259; 95% CI, 105-534] as did all three of the lung cancers [SMR, 429; 95% CI, 88-1252].

Sorahan *et al.* (1987) reported the mortality experience of 2689 chromium platers (1288 men, 1401 women) in the UK observed from January 1946 to December 1983 who were involved mainly in 'bright' (thin) plating of bumpers and overriders, initially reported by Waterhouse (1975). Scattered sampling of exposure had taken place before 1973, showing air concentrations of chromium trioxide up to 8.0 mg/m³, while the median values were 'nondetectable' or 'trace'; after 1973, measurements generally showed levels of chromium below 50 μg/m³. The cohort comprised workers employed in 1946-75 with more than six months' employment as a (chromium) electroplater. Death rates were compared with those of the general population of England and Wales. All members of the cohort had had at least some exposure to chromium but also some exposure to nickel chloride and nickel sulfate. A total of 213 cancer deaths (SMR, 130 [95% CI, 113-148]) and 72 lung cancer deaths (SMR, 150 [95% CI, 117-189]) were observed in men and women combined; 63 lung cancer deaths occurred in men (SMR, 158 [95% CI, 121-202]) and nine in women (SMR, 111 [95% CI, 46-261]). When the figures for each sex were combined and account was taken of time from first employment, the highest SMRs were 342 [95% CI, 182-585] after ten to 14 years and 245 [95% CI, 127-428] after 15-19 years of work at the chromium baths. Overall, three deaths (two in men, one in women) from cancer of the nose and nasal cavities occurred (SMR, 1000 [95% CI, 206-2922]); all three persons had been exposed to chromium for one to two years, while the third had also worked for 13 years plating nickel. There were 25 deaths from stomach cancer (SMR, 154 [95% CI, 100-228]), but this excess occurred only in men. Four deaths from cancer of the liver were observed in men (SMR, 667 [95% CI, 182-1707]) but none in women. In an analysis of data on first job held, the SMR for lung cancer was 199 (46 deaths [95% CI, 146-266] for men first employed as chrome bath workers and 101 (17 deaths [95% CI, 59-161]) for chromium workers who were first employed at other work sites. The authors reported that only 11% of workers had had periods of work at both the chrome baths and other chrome work. Although a

significant association was found between work at chrome baths and death from lung cancer, no such association was found with work at nickel baths (Burges, 1980).

In a case-control study in Denmark of 326 cases of laryngeal cancer and 1134 controls (Olsen & Sabroe, 1984), two of the cases occurred among male chromium platers, yielding a standardized incidence odds ratio of 110 (95% CI, 30-360).

(d) Production of ferrochromium alloys

Pokrovskaya and Shabynina (1973) studied a cohort of male and female factory workers engaged in chromium ferroalloy production between 1955 and 1969 in the USSR. Workers were reported to be exposed to chromium[VI] and chromium[III] compounds as well as benzo[*a*]pyrene. Death certificates were obtained from the municipal vital statistics office, and comparison was made with city mortality rates by sex and by ten-year age group. Access to complete work histories made it possible to exclude from the control cohort subjects who had been exposed to chromium in other plants. Male chromium workers aged 50-59 experienced significant [$p = 0.001$] increases in death rates from all malignancies, from lung cancer and from oesophageal cancer, as compared with deaths rates in the municipal population. The relative risk for lung cancer in men was reported to range from 4.4 in the 30-39-year age group to 6.6 ($p = 0.001$) in the 50-59-year age group. A large proportion of the cases of lung cancer among workers exposed to high concentrations of dust (cinder pit workers, metal crushers, smelter workers), including workers who were not exposed to benzo[*a*]pyrene in areas of furnace charge and finished products preparation. [The Working Group noted that the numbers of workers and the numbers of cancers by specific site were not reported.]

Axelsson *et al.* (1980) studied employees at a ferrochromium plant in Sweden producing ferrochromium alloys by furnace reduction of chromite ore, quartz, lime and coke; the study was restricted to all 1876 men employed for at least one year during the period 1 January 1930 to 31 December 1975 and alive in 1951. Records were available for all employees who had worked since 1913. Individuals were categorized according to length and place of work in the factory. Death certificates (1951-75) were obtained from the national Central Bureau of Statistics and incident cancer cases (1958-75) from a manual search of Cancer Registry files. Expected numbers of cancer deaths and incident cases were calculated assuming a 15-year latent period from onset of employment. The estimated levels of chromium metal plus chromium[III] in the work atmosphere ranged from 0 to 2.5 mg/m^3, and those for chromium[VI] from 0 to 0.25 mg/m^3. There were 87 cases of cancer in the period 1958-75 [SIR, 101; 95% CI, 81-125], of which seven were cancers of the trachea, bronchus, lung and pleura [SIR, 119; 95% CI, 48-245]. Among 641 arc furnace workers, who were considered as being most likely to have encountered exposure to chromium[III] and [VI], there were two cases of cancer at these sites [SIR, 95; 95%

CI, 12-344], one of which was a pleural mesothelioma. Among 326 maintenance workers, there were four cases of cancer at these sites [SIR, 400; 95% CI, 109-1024], two of which were mesotheliomas. Asbestos had been used in the factory.

Langård *et al.* (1980, 1990) studied male workers at a ferrochromium and ferrosilicon production plant in Norway, primarily to explore the hypothesis that chromium[III] might be carcinogenic to humans. Workers with one year or more of work were included. Hygiene studies in the plant in 1975 indicated the presence of chromium[III] and [VI] in the work environment; the atmosphere contained a mean of 0.01-0.29 mg/m^3 chromium, 11-33% of which was water-soluble chromium[VI]. The 1980 study comprised 976 workers with first employment before 1960 and alive in 1953; in the 1990 report, the cohort also included those with first employment before 1965 (to make a total of 1235 workers). In the latter report, 357 deaths from all causes were observed (SMR, 81 [95% CI, 73-90]). The SIR for all cancers was 84 (132 observed; 95% CI, 70-100); the total number of lung cancers was 17 (SIR, 88 [95% CI, 56-123]). Among the 379 ferrochromium workers, there were ten cases of lung cancer [SIR, 154; 95% CI, 74-283], 12 of the prostate [SIR, 151 [95% CI, 78-262] and five of the kidney [SIR, 273; 95% CI, 89-638]. The excess of lung cancer in ferrochromium workers was higher in the 1980 study (seven cases; SMR, 226 [95% CI, 91-466]).

(*e*) *Other industrial exposures to chromium*

In an exploratory proportionate mortality study, Tsuchiya (1965) investigated the occurrence of cancer in 1957-59 in about 200 Japanese companies with more than 1000 employees each. A total of 492 cancer deaths occurred among 1 200 000 workers during that period. The 22 lung cancer deaths that occurred among workers in industries handling chromium compounds were compared with the Japanese mortality rate for 1958 [SMR, 220; 95% CI, 138-333]. The author pointed out that because a person had handled chromium or nickel in a factory did not necessarily imply that he had been exposed to these elements. [The Working Group noted that the design of the study did not exclude selection bias, and that exposures to chromium and a variety of carcinogens were not mutually exclusive.]

Dalager *et al.* (1980) carried out a proportionate mortality study on a group of spray painters using zinc chromate primer paints in the maintenance of aircraft at two US military bases. Spray painting was carried out mainly in air-conditioned booths, but without respirators. The study cohort consisted of 977 white male workers who had spray painted for at least three months and who had terminated employment within a ten-year period prior to 31 July 1959. The relative 'frequency' of causes of death through 1977 was generated by comparing the observed number of cases with the expected relative frequency in the white US male population. There were 202 deaths among the spray painters; 50 had died of cancer (PMR, 136 [95%

CI, 101-179]), 21 of whom had respiratory cancer (ICD 160-164; PMR, 184 [95% CI, 114-282]). The proportionate cancer mortality rate for respiratory cancer was 146 (not significant).

Bertazzi *et al.* (1981) studied the causes of death in 1954-78 for 427 workers who had been employed for at least six months between 1946 and 1977 in a plant producing paints and coatings, including chromate[VI] pigments. They found 18 deaths due to cancer *versus* 9.8 expected on the basis of national rates; there were eight lung cancer deaths, giving SMRs of 227 [95% CI, 156-633] based on local rates and 334 [95% CI, 106-434] on the basis of national rates. The authors were unable to differentiate between exposures to different paints and coatings; they stated that the primary exposure was to chromate[VI] pigments but that there was low exposure to asbestos.

Cornell and Landis (1984) studied the causes of death for 851 men who had worked in 26 US nickel/chromium foundries between 1968 and 1979 and compared them with the mortality experience of US males and of a control group of foundry workers not exposed to nickel/chromium. Sixty deaths were from lung cancer *versus* 56.9 expected in the general population; a total of 103 deaths from all other neoplasms was observed with 118.0 expected. No death from nasal cancer was observed.

Stern *et al.* (1987) followed up 9365 workers from two chrome leather tanneries in Minnesota and Wisconsin, USA, from identification of the cohort in 1940 through to December 1982. Follow-up was 95% complete. By that time, 1582 deaths had occurred, giving a SMR of 89. The SMRs for cancer of the lung, trachea and bronchus (ICD 162-163) were low in both tanneries (18 deaths; SMR, 67; 95% CI, 40-106 and 42 deaths; SMR, 93; 95% CI, 67-126) in comparison with expected rates in the respective states. [The Working Group noted that exposure to chromium was low and occurred in only a small subgroup of the workers.]

Hernberg *et al.* (1983a,b) conducted a joint Danish-Finnish-Swedish case-control study among 167 living cases of cancer of the nasal or paranasal sinuses diagnosed between 1 July 1977 and 31 December 1980, who were individually matched for country, age and sex with patients with colonic or rectal cancer. Cases and controls were interviewed by telephone. Patients who had had work-related exposures during the ten years before occurrence of the illness were excluded. Sixteen patients, many of whom were included within the category 'stainless steel welding' and 'nickel', *versus* six controls reported exposure to chromium (odds ratio, 2.7; 95% CI, 1.1-6.6). Among 21 cases categorized as having been exposed to nickel and/or chromium, including the above cases, only two had been exposed to chromium only: one spray painter (chromates) and one steel worker.

In a case-control study in North Carolina and Virginia, USA, of 160 patients (93 men, 67 women) with cancers of the nasal cavity and paranasal sinuses diag-

nosed between 1970 and 1980, Brinton *et al.* (1984) found chromium/chromate exposure to be 5.1 times more frequent among male cases than among 290 hospital controls, based on five exposed male cases. The authors stated that the excess was associated mainly with use of chromate products in the building industry and in painting.

A hospital-based case-control study in Norway of 176 incident male lung cancer cases was performed by Kjuus *et al.* (1986). Cases were recruited between 1979 and 1983, and 176 age- and sex-matched control subjects were recruited from the same hospitals. Seven cases and six controls had been exposed to chromium and nickel compounds (welding excluded) for more than three years. The risk ratio, adjusted for smoking, was 1.4 (95% CI, 0.4-4.4).

Rafnsson and Jóhannesdóttir (1986) followed up 450 Icelandic men born between 1905 and 1945 who were licensed as masons (cement finishers). Nine deaths from cancer of the lung, trachea and bronchus (ICD 162, 163) were found (SMR, 314; 95% CI, 143-595). The eight men who had been licensed for 20 years had a SMR of 365 (95% CI, 158-720). The concentration of chromium[VI] in Icelandic cement in 1983 was 5.8-9.5 mg/kg; however, masons also work with other substances. [The Working Group noted that respiratory exposure to chromates would have been very low, suggesting that the excess may have been due to other factors.]

In an extended case-control study, Claude *et al.* (1988) further examined the possible relationship between work-related exposure and bladder cancer proposed by Claude *et al.* (1986). A total of 531 male cases were recruited from hospitals in the Federal Republic of Germany between 1977 and 1985 and were compared with sex- and age-matched controls recruited mainly from urological hospital wards. Exposure to chromium/chromate was reported for 52 cases *versus* 24 controls (odds ratio, 2.2; 95% CI, 1.4-3.5). The corresponding figures for spray painting were 49 *versus* 17 (odds ratio, 2.9; 95% CI, 1.7-4.9). Details were not given on the extent to which spray painting included exposure to chromium-containing paints. After adjustment for smoking, the rate ratio estimates for duration of exposure to chromium/chromate were (number of cases/controls in parentheses); one to nine years, 1.2 (10/8); ten to 19 years, 1.0 (9/7); 20-29 years, 2.0 (11/5); and $\geq$30 years, 3.0 (26/8), which gives a *p*-value for trend of 0.009. The corresponding rate ratios for spray painting were: 4.7 (13/2), 8.4 (8/1), 2.0 (14/9) and 2.4 (17/8). [The Working Group noted that the possibility of recall bias was high, since the risk ratios for 24/25 exposures exceeded unity.]

(f) *Environmental exposure to chromium*

The possible relation between environmental exposure to chromium and mortality from lung cancer was studied by Axelsson and Rylander (1980) in a population-based study among people living close to two Swedish ferrochromium smelt-

ers. Air concentrations of chromium near the smelter were 100-400 ng/m^3. The lung cancer mortality rates in the two communities where the smelters were located were 253 per million ($p < 0.05$) and 161 per million, respectively, as compared with the county rate of 194 per million during the entire period studied (1961-75).

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chromium in the form of various alloys and compounds has been in widespread commercial use for over 100 years. Early applications included chrome pigments and tanning liquors. In recent decades, chromium has also been widely used in chromium alloys and chrome plating.

Several million workers worldwide are exposed to airborne fumes, mists and dust containing chromium or its compounds. Of the occupational situations in which exposure to chromium occurs, highest exposures to chromium[VI] may occur during chromate production, welding, chrome pigment manufacture, chrome plating and spray painting; highest exposures to other forms of chromium occur during mining, ferrochromium and steel production, welding and cutting and grinding of chromium alloys.

Data on exposure levels are available for several specific industries and job categories covering several decades. In the past, exposures to chromium[VI] in excess of 1 mg/m^3 were found repeatedly in some processes, including chromium plating, chromate production and certain welding operations; exposures to total chromium have been even higher. Modern control technologies have markedly reduced exposures in some processes, such as electroplating, in recent years.

Occupational exposure has been shown to give rise to elevated levels of chromium in blood, urine and some body tissues, inhalation being the main route.

Nonoccupational sources of exposure to chromium include food, air and water, but the levels are usually several orders of magnitude lower than those typically encountered in occupational situations.

4.2 Experimental carcinogenicity data

Chromium[0]

Studies in rats by intratracheal, intramuscular and intrafemoral administration, in mice and rats by intrapleural and intraperitoneal administration and in mice, rats and rabbits by intravenous injections were inadequate to evaluate the carcinogenicity of *chromium metal* as a powder.

Chromium[III]

In studies in which *chromic acetate* was administered by the oral route to mice and rats and by intrapleural and intramuscular administration to rats, the incidence of tumours was not increased. In studies in which rats were administered *chromic oxide* by intrabronchial or oral routes, no increase in the incidence of tumours was observed. In experiments by intrabronchial implantation of *chromic chloride* or *chrome tan* (a basic chromic sulfate) in rats and by intraperitoneal administration of *chromic sulfate* in mice, the incidence of tumours was not increased. Many of these studies suffered from certain limitations. *Chromite ore* has been extensively tested in rats by intrabronchial, intrapleural and intrafemoral administration; no increase in the incidence of tumours was seen.

Chromium[VI]

Calcium chromate has been tested by inhalation in mice, by intratracheal administration in rats and hamsters, by intrabronchial administration and intrapleural administration in rats, by subcutaneous administration in mice, and by intramuscular administration in mice and rats. In the one study by inhalation in mice, there was an increase in the incidence of lung adenomas which was of borderline significance; in the single study by intratracheal administration and in the three studies by intrabronchial administration in rats, lung tumours were induced. No lung tumour was seen in hamsters after intratracheal instillation. Local tumours were produced in rats by intrapleural and in rats and mice by intramuscular administration of calcium chromate. *Chromium trioxide* (chromic acid) has been tested as a mist by inhalation at two dose levels in mice and as a solid by intrabronchial implantation in three studies in rats. In mice, a low incidence of lung adenocarcinomas was observed at the higher dose and of nasal papillomas at the lower dose; perforation of the nasal septum was observed at both dose levels. A few lung tumours were seen in two of the studies by intrabronchial administration in rats. *Sodium dichromate* has been tested in rats by inhalation, intratracheal, intrabronchial, intrapleural and intramuscular administration. Lung tumours, benign and malignant, were observed in the studies by inhalation and by intratracheal administration. No increase in the occurrence of local tumours was seen after intrabronchial, intrapleural or intramuscular administration. *Barium chromate* has been tested in rats by intrabronchial, intrapleural and intramuscular implantation. No increase in the occurrence of tumours was seen following intrabronchial implantation; the other studies were inadequate to allow an evaluation of the carcinogenicity of this compound. *Lead chromate* and derived pigments have been tested by intrabronchial implantation in rats without producing a significant increase in the incidence of tumours. Lead chromate and derived pigments have also been tested in rats by subcutaneous and intramuscular injection, producing malignant tumours at the site of injection

and, in one study, renal carcinomas. A study by intrapleural administration to rats could not be evaluated. No increase in tumour incidence was observed when lead chromate was administered intramuscularly to mice. A single subcutaneous injection of *basic lead chromate* produced a high incidence of local sarcomas in rats. *Zinc chromates* have been tested in rats by intrabronchial implantation, producing bronchial carcinomas, by intrapleural administration, producing local tumours, and by subcutaneous and intramuscular injection, producing local sarcomas. Two samples of *strontium chromate* were tested in rats by intrabronchial implantation, producing a high incidence of bronchial carcinomas; intrapleural and intramuscular injection of strontium chromate produced local sarcomas.

Other forms of chromium

A range of *roasted chromite ores* (Cr[III/VI]), often described as mixed chromium dust, and other residue materials encountered in the early stages of bichromate production have been tested extensively in mice, rats, guinea-pigs and rabbits by inhalation and by intratracheal, intrabronchial, intrapleural and intramuscular administration. The results of these tests were generally negative, although a low incidence of local tumours was observed in rats following intrapleural or intramuscular implantation of roasted chromite ore. The studies were considered to suffer from certain inadequacies. *Chromium[IV] dioxide* was tested by inhalation in rats, producing a few lung lesions of questionable nature; the study had a number of limitations.

4.3 Human carcinogenicity data

Epidemiological studies carried out in the Federal Republic of Germany, Italy, Japan, the UK and the USA of workers in the chromate production industry have consistently shown excess risks for lung cancer. The workers in this industry may be exposed to a variety of forms of chromium, including chromium[VI] and [III] compounds.

Similarly, studies carried out in the Federal Republic of Germany, France, the Netherlands, Norway, the UK and the USA of workers in the production of chromate pigments have also consistently shown excess risks for lung cancer. Workers in this industry are exposed to chromates, not only in the pigments themselves but also from soluble chromium[VI] compounds in the raw materials used in their production. Excess risk for lung cancer has been clearly established in facilities where zinc chromate was produced, although other chromium pigments were also generally made in these plants. A small study in the UK of workers producing lead chromate pigments showed no overall excess risk for lung cancer, but a nonsignificant excess risk was seen in a subgroup of workers with lead poisoning. No data were

available on risk associated with exposure to strontium chromate or to other specific chromate pigments.

In two limited reports from the UK and in a small Italian study, excesses of lung cancer were reported in workers in the chromium plating industry. In a group of persons working in die-casting and plating in the USA, similar results were seen. These findings were confirmed in a large study of chromium platers in the UK, which demonstrated an excess risk for lung cancer in platers, particularly among those with at least ten years of employment at chrome baths. Workers in this industry have been exposed to soluble chromium[VI] compounds and possibly also to nickel.

In three reports, from Norway, Sweden and the USSR, in which ferrochromium workers were studied, the overall results with regard to lung cancer were inconclusive. The major exposure in this industry is to chromium[III] compounds and to metallic chromium, although exposure to chromium[VI] may also occur.

Cases of sinonasal cancer were reported in epidemiological studies of primary chromate production workers in Japan, the UK and the USA, of chromate pigment production workers in Norway and of chromium platers in the UK, indicating a pattern of excess risk for these rare tumours.

For cancers other than of the lung and sinonasal cavity, no consistent pattern of cancer risk has been shown among workers exposed to chromium compounds.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to chromium[VI], but they do not contribute independently to the evaluation of chromium since welders are also exposed to other compounds. (See also the monograph on welding.)

No epidemiological study addressed the risk of cancer from exposure to metallic chromium alone.

4.4 Other relevant data

Inhaled chromium[VI] from welding and chrome-plating aerosols is readily absorbed from the respiratory tract. The degree of absorption depends on the extent of reduction of the hexavalent form to chromium[III], which is absorbed to a much lesser extent. The same factors apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less than that from the respiratory tract.

Chromium[VI] compounds may cause adverse effects to the skin, the respiratory tract and, to a lesser degree, the kidneys in humans, while chromium[III] is less toxic.

Elevated levels of sister chromatid exchange were observed in workers exposed to chromium[VI] compounds in electroplating factories in four out of six studies.

Chromosomal aberrations were found in all three studies of exposed workers; an increased frequency of aneuploidy was reported in one of these studies. The two available studies on chromium[III] were inadequate to evaluate its cytogenetic effect in humans.

Chromates enter cells more readily than chromium[III] compounds and are reduced ultimately to chromium[III]. The reduction process and the subsequent intracellular activity of reduced chromium species are important for the mechanism of toxicity and carcinogenicity of chromium[VI]. Particulate chromium[III] compounds can also enter cells by phagocytosis.

Chromium[VI] compounds cross the placental barrier in greater amounts than chromium[III] compounds. Chromium trioxide increased fetal death rate, caused growth retardation and increased the frequency of skeletal deformities and of cleft palate in rodents. Developmental effects have also been reported in mice exposed to chromic chloride.

Chromium[VI] compounds of various solubilities in water were consistently active in numerous studies covering a wide range of tests for genetic and related effects. In particular, potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate, chromium trioxide, calcium chromate, strontium chromate and zinc yellow induced a variety of effects (including DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation and dominant lethal mutation) in a number of targets, including animal cells *in vivo* and animal and human cells *in vitro*. Potassium chromate induced aneuploidy in insects, while chromium trioxide did not; various compounds induced gene mutation in insects. Potassium dichromate produced recombination, gene mutation and aneuploidy in fungi. All of these chromium[VI] compounds induced DNA damage and gene mutation in bacteria. Similar patterns were observed with zinc chromate, barium chromate, lead chromate and the derived pigments chromium orange, chromium yellow and molybdenum orange, which, however, often required preliminary dissolution in alkali or acids. A liquid chromium[VI] compound (chromyl chloride) and its vapours induced gene mutation in bacteria.

Although chromium[III] compounds were generally even more reactive than chromium[VI] compounds with purified DNA and isolated nuclei, 12 compounds of various solubilities (chromic chloride, chromic acetate, chromic nitrate, chromic sulfate, chromic potassium sulfate, chromium alum, neochromium, chromic hydroxide, chromic phosphate, chromic oxide, chromite ore and cupric chromite) gave positive results in only a minority of studies using cellular test systems, often under particular treatment conditions or at very high concentrations, which were generally orders of magnitude higher than those needed to obtain the same effects with chromium[VI] compounds. Some of the positive results could be ascribed to

contamination with traces of chromium[VI] compounds. In particular, no DNA damage was observed in cells of animals treated *in vivo* with chromic chloride, and no micronuclei were seen in cells of animals given chromic nitrate. The chromium[III] compounds tested generally did not produce DNA damage, gene mutation, sister chromatid exchange or cell transformation in cultured animal and human cells. Chromosomal aberrations were often observed with high concentrations of chromium[III] compounds. Weak effects on gene mutation and mitotic gene conversion were observed in fungi. Negative results were obtained in the large majority of tests for DNA damage and gene mutation in bacteria. Certain complexes of chromium[III] with organic ligands, which favour the penetration of chromium[III] into cells, were reported to induce DNA damage and gene mutation in bacteria and in cultured mammalian cells.

A chromium[II] compound (chromous chloride) gave negative results in in-vitro tests with animal cells (DNA damage, chromosomal aberrations and aneuploidy). A water-insoluble chromium[0] compound (chromium carbonyl) did not induce DNA damage in bacteria.

No relevant study on the genetic and related effects of metallic chromium was available to the Working Group.

4.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of chromium[VI] compounds as encountered in the chromate production, chromate pigment production and chromium plating industries.

There is *inadequate evidence* in humans for the carcinogenicity of metallic chromium and of chromium[III] compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate and lead chromates.

There is *limited evidence* in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium[III] compounds.

The Working Group made the overall evaluation on chromium[VI] compounds on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data which support the underlying concept that chromium[VI] ions generated at critical sites in the target cells are responsible for the carcinogenic action observed.

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[1]For definitions of the italicized terms, see Preamble, pp. 33–37

Overall evaluation

Chromium[VI] *is carcinogenic to humans* (Group 1).

Metallic chromium and chromium[III] compounds *are not classifiable as to their carcinogenicity to humans* (Group 3).

5. References

Aaseth, J., Alexander, J. & Norseth, T. (1982) Uptake of ^{51}Cr-chromate by human erythrocytes—a role of glutathione. *Acta pharmacol. toxicol., 50*, 310-315

Abe, S., Ohsaki, Y., Kimura, K., Tsuneta, Y., Mikami, H. & Murao, M. (1982) Chromate lung cancer with special reference to its cell type and relation to the manufacturing process. *Cancer, 49*, 783-787

Abell, M.T. & Carlberg, J.R. (1974) A simple reliable method for the determination of airborne hexavalent chromium. *Am. ind. Hyg. Assoc. J., 35*, 229-233

Ackermann, F. (1977) Method of instrumental neutron activation analysis and its application for the determination of trace metals in sediments (Ger.). *Dtsch. Gewaesserkd. Mitt., 21*, 53-60 [*Chem. Abstr., 88*, 15489g]

Adachi, S. (1987) Effects of chromium compounds on the respiratory system. Part 5. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation on our experimental studies (Jpn.). *Jpn. J. ind. Health, 29*, 17-33

Adachi, S. & Takemoto, K. (1987) Occupational lung cancer. A comparison between humans and experimental animals (Jpn.). *Jpn. J. ind. Health, 29*, 345-357

Adachi, S., Yoshimura, H., Katayama, H. & Takemoto, K. (1986) Effects of chromium compounds on the respiratory system. Part 4. Long term inhalation of chromic acid mist in electroplating to ICR female mice (Jpn.). *Jpn. J. ind. Health, 28*, 283-287

Aitio, A., Järvisalo, J., Kiilunen, M., Tossavainen, A. & Vaittinen, P. (1984) Urinary excretion of chromium as an indicator of exposure to trivalent chromium sulphate in leather tanning. *Int. Arch. occup. environ. Health, 54*, 241-249

Aitio, A., Jarvisalo, J., Kiilunen, M., Kalliomaki, P.L. & Kalliomaki, K. (1988) Chromium. In: Clarkson, T.W., Friberg, L., Nordberg, G.F. & Sager, P.R., eds, *Biological Monitoring of Toxic Metals*, New York, Plenum, pp. 369-382

Al-Badri, J.S., Sabir, S.M., Shehab, K.M., Jalil, M. & Al-Rawi, H. (1977) Determination of inorganic elements in Iraqi tobacco leaves and cigarettes by neutron activation analysis. *Iraqi J. Sci., 18*, 34-44

Albers, P.H., Sileo, L. & Mulhern, B.M. (1986) Effects of environmental contaminants on snapping turtles of a tidal wetland. *Arch. environ. Contam. Toxicol., 15*, 39-49

Alderson, M.R., Rattan, N.S. & Bidstrup, L. (1981) Health of workmen in the chromate-producing industry in Britain. *Br. J. ind. Med., 38*, 117-124

Alexander, J., Aaseth, J. & Norseth, T. (1982) Uptake of chromium by rat liver mitochondria. *Toxicology, 24*, 115-122

Alwens, W. & Jonas, W. (1938) The chromate lung cancer (Ger.). *Unio int. contra cancrum, 3*, 103-118

American Chrome & Chemicals (undated a) *Product Data Sheet: Chromium Oxide Metallurgical (Cr_2O_3)*, Corpus Christi, TX

American Chrome & Chemicals (undated b) *Product Data Sheet: Accrox C (Cr_2O_3)*, Corpus Christi, TX

American Chrome & Chemicals (undated c) *Product Data Sheet: Accrox R (Cr_2O_3)*, Corpus Christi, TX

American Chrome & Chemicals (undated d) *Product Data Sheet: Accrox S (Cr_2O_3)*, Corpus Christi, TX

American Chrome & Chemicals (undated e) *Product Data Sheet: Chromic Acid (CrO_3)*, Corpus Christi, TX

American Chrome & Chemicals (undated f) *Product Data Sheet: Sodium Bichromate ($Na_2Cr_2O_7.2H_2O$)*, Corpus Christi, TX

American Chrome & Chemicals (undated g) *Product Data Sheet: Sodium Bichromate Anhydrous ($Na_2Cr_2O_7$)*, Corpus Christi, TX

American Chrome & Chemicals (undated h) *Product Data Sheet: Sodium Chromate Anhydrous (Na_2CrO_4)*, Corpus Christi, TX

American Chrome & Chemicals (undated i) *Product Data Sheet: Sodium Chromate Tetrahydrate ($Na_2CrO_4.4H_2O$)*, Corpus Christi, TX

American Conference of Governmental Industrial Hygienists (1988) *TLVs Threshold Limit Values and Biological Exposure Indices for 1988-89*, Cincinnati, OH, pp. 15-16, 24, 38

American Society for Testing and Materials (1971) *Standard Test Method for Chromium Oxide in Chrome Ores (ASTM E342-71 (Reapproved 1985))*, Philadelphia, PA, pp. 1-3

American Society for Testing and Materials (1978) *Standard Test Method for Chromic Oxide in Leather (Perchloric Acid Oxidation) (ASTM D2807-78)*, Philadelphia, PA, pp. 1-4

American Society for Testing and Materials (1981) *Standard Methods for Chemical Analysis of Chrome-containing Refractories and Chrome Ore (ASTM C572-81)*, Philadelphia, PA, pp. 1-9

American Society for Testing and Materials (1983) *Standard Methods for Chemical Analysis of Chromium and Ferrochromium (ASTM E363-83)*, Philadelphia, PA, pp. 1-6

American Society for Testing and Materials (1984a) *Standard Specification for Wrought Cobalt-Nickel-Chromium Molybdenum Alloy for Surgical Implant Applications (ASTM F562-84)*, Philadelphia, PA, pp. 1-4

American Society for Testing and Materials (1984b) *Standard Test Method for Lead and Chromium in Air Particulate Filter Samples of Lead Chromate Type Pigment Dusts by Atomic Absorption Spectroscopy (ASTM D4358-84)*, Philadelphia, PA, pp. 1-5

American Society for Testing and Materials (1985a) *Standard Test Method for Chromium in Workplace Atmospheres (Colorimetric Method) (ASTM D3586-85)*, Philadelphia, PA, pp. 1-6

American Society for Testing and Materials (1985b) *Standard Test Method for Low Concentrations of Chromium in Paint by Atomic Absorption Spectrocopy (ASTM D3718-85a)*, Philadelphia, PA, pp. 1-4

American Society for Testing and Materials (1986a) *Standard Test Method for Chromium in Water* (*ASTM D1687-86*), Philadelphia, PA, pp. 1-9

American Society for Testing and Materials (1986b) *Standard Test Method for Chemical Analysis of Strontium Chromate Pigment* (*ASTM D1845-86*), Philadelphia, PA, pp. 1-3

American Society for Testing and Materials (1987a) *Standard Specification for Cast Cobalt-Chromium-Molybdenum Alloy for Surgical Implant Applications* (*ASTM F75-87*), Philadelphia, PA, pp. 1-2

American Society for Testing and Materials (1987b) *Standard Specification for Thermomechanically Processed Cobalt-Chromium-Molybdenum Alloy for Surgical Implant Applications* (*ASTM F799-87*), Philadelphia, PA, pp. 1-3

American Society for Testing and Materials (1987c) *Standard Test Method for Analysis of Yellow, Orange, and Green Pigments Containing Lead Chromate and Chromium Oxide Green* (*ASTM D126-87*), Philadelphia, PA, pp. 1-7

American Society for Testing and Materials (1988a) *Standard Specification for Wrought Cobalt-Nickel-Chromium-Molybdenum-Tungsten-Iron Alloy for Surgical Implant Applications* (*ASTM F563-88*), Philadelphia, PA, pp. 1-3

American Society for Testing and Materials (1988b) *Standard Test Method for Chemical Analysis of Zinc Yellow Pigment (Zinc Chromate Yellow)* (*ASTM D44-88*), Philadelphia, PA, pp. 1-5

Andersen, O. (1983) Effects of coal combustion products and metal compounds on sister chromatid exchange (SCE) in a macrophage-like cell line. *Environ. Health Perspect.*, *47*, 239-253

Angerer, J. & Schaller, K.H. (1988) *Analysen in biologischem Material* (Analysis in Biological Material), Weinheim, Deutsche Forschungsgemeinschaft, pp. 1-16

Anon. (1978) Chromic acid. *Chem. Mark. Rep.*, *213*, 9

Anon. (1979) Sodium bichromate. *Chem. Mark. Rep.*, *216*, 9

Anon. (1981) Problems of epidemiological evidence. *Environ. Health Perspect.*, *40*, 11-20

Anon. (1988a) Chemical profile: chromic acid. *Chem. Mark. Rep.*, *234*, 54

Anon. (1988b) Chemical profile: sodium bichromate. *Chem. Mark. Rep.*, *234*, 82

Arbeidsinspectie (Labour Inspection) (1986) *De Nationale MAC–Lijst 1986* (National MAC-List 1986), Voorburg, p. 10

Arbejdstilsynet (Labour Inspection) (1988) *Graensevaerdier for Stoffer og Materialer* (Limit Values for Compounds and Materials) (No 3.1.0.2), Copenhagen, p. 14

Arbetarskyddsstyrelsens (National Board of Occupational Safety and Health) (1987) *Hygieniska Gränsvärden* (Hygienic Limit Values), Stockholm, p. 28

Arlauskas, A., Baker, R.S.U., Bonin, A.M., Tandon, R.K., Crisp, P.T. & Ellis, J. (1985) Mutagenicity of metal ions in bacteria. *Environ. Res.*, *36*, 379-388

Atomergic Chemetals Corp. (1980) *Specification Sheet: Barium Chromate*, Farmingdale, NY

Axelsson, G. & Rylander, R. (1980) Environmental chromium dust and lung cancer mortality. *Environ. Res.*, *23*, 469-476

Axelsson, G., Rylander, R. & Schmidt, A. (1980) Mortality and incidence of tumours among ferrochromium workers. *Br. J. ind. Med.*, *37*, 121-127

Bacon, F.E. (1964) Chromium and chromium alloys. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 2nd ed., Vol. 5, New York, John Wiley & Sons, pp. 453-464

Baetjer, A.M. (1950) Pulmonary carcinoma in chromate workers. II. Incidence on basis of hospital records. *Arch. ind. Hyg. occup. Med.*, *2*, 505-516

Baetjer, A.M., Damron, C. & Budacz, V. (1959a) The distribution and retention of chromium in men and animals. *Arch. ind. Health*, *20*, 136-150

Baetjer, A.M., Lowney, J.F., Steffee, H. & Budacz, V. (1959b) Effect of chromium on incidence of lung tumors in mice and rats. *Arch. ind. Health*, *20*, 124-135

Baker, R.S.U. (1984) Evaluation of metals in in vitro assays, interpretation of data and possible mechanisms of action. *Toxicol. environ. Chem.*, *7*, 191-212

Baker, R.S.U., Bonin, A.M., Arlauskas, A., Tandon, R.K., Crisp, P.T. & Ellis, J. (1984) Chromium(VI) and apparent phenotypic reversion in *Salmonella* TA100. *Mutat. Res.*, *138*, 127-132

Bakke, O., Jakobsen, K. & Eik-Nes, K.B. (1984) Concentration-dependent effects of potassium dichromate on the cell cycle. *Cytometry*, *5*, 482-486

Balsberg-Påhlsson, A.-M., Lithner, G. & Tyler, G. (1982) *Krom i Miljön* (Chromium in the Environment), Solna, Statens Naturvårdsverk

Baranowska-Dutkiewicz, B. (1981) Absorption of hexavalent chromium by skin in man. *Arch. Toxicol.*, *47*, 47-50

Barbořík, M., Hanslian, L., Oral, L., Sehnalová, H. & Holuša, R. (1958) Carcinoma of the lungs in personnel working at electrolytic chromium plating (Czech). *Prac. Lek.*, *10*, 413-417

Barceló, J., Poschenrieder, C. & Gunsé, B. (1986) Impact of chromium on the environment. II. Chromium in living organisms (Sp.). *Circ. Farm.*, *293*, 31-48

Barium & Chemicals (1988a) *MSDS and Data Sheet: Calcium Chromate*, Steubenville, OH

Barium & Chemicals (1988b) *Military Specification: Barium Chromate (MIL-B-55A)*, Steubenville, OH

Barium & Chemicals (undated) *Barium, Strontium, Calcium ... and Other Chemical Products*, Steubenville, OH

Belitskaya, E.N. (1981) Physiologic and hygienic characterization of working conditions for steel smelters in open-hearth process (Russ.). *Gig. Tr.*, *24*, 9-11

Belmont Metals (1989) *Typical Analysis: Electrolytic Chromium Metal*, Brooklyn, NY

Bennicelli, C., Camoirano, A., Petruzzelli, S., Zanacchi, P. & De Flora, S. (1983) High sensitivity of *Salmonella* TA102 in detecting hexavalent chromium mutagenicity and its reversal by liver and lung preparations. *Mutat. Res.*, *122*, 1-5

Bertazzi, P.A., Zocchetti, C., Terzaghi, G.F., Riboldi, L., Guercilena, S. & Beretta, F. (1981) Mortality experience of paint production workers (Ital.). *Med. Lav.*, *6*, 465-472

Beszedits, S. (1988) Chromium removal from industrial wastewaters. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, Wiley-Interscience, pp. 231-265

Beyersmann, D. & Köster, A. (1987) On the role of trivalent chromium in chromium genotoxicity. *Toxicol. environ. Chem.*, *14*, 11-22

Beyersmann, D., Köster, A., Buttner, B. & Flessel, P. (1984) Model reactions of chromium compounds with mammalian and bacterial cells. *Toxicol. environ. Chem.*, *8*, 279-286

Bhargava, O.P., Bumsted, H.E., Grunder, F.I., Hunt, B.L., Manning, G.E., Riemann, R.A., Samuels, J.K., Tatone, V., Waldschmidt, S.J. & Hernandez, P. (1983) Study of an analytical method for hexavalent chromium. *Am. ind. Hyg. Assoc. J.*, *44*, 433-436

Bianchi, V. & Levis, A.G. (1984) Mechanisms of chromium genotoxicity. *Toxicol. environ. Chem.*, *9*, 1-25

Bianchi, V. & Levis, A.G. (1985) Metals as genotoxic agents: the model of chromium. In: Irgolic, K.J. & Martell, A.E., eds, *Environmental Organic Chemistry*, Deersfield Beach, FL, VCH Publishers, pp. 447-462

Bianchi, V. & Levis, A.G. (1987) Recent advances in chromium genotoxicity. *Toxicol. environ. Chem.*, *15*, 1-24

Bianchi, V. & Levis, A.G. (1988) Genetic effects and mechanisms of action of chromium compounds. *Sci. total Environ.*, *71*, 351-355

Bianchi, V., Levis, A.G. & Saggioro, D. (1979) Differential cytotoxic activity of potassium dichromate on nucleoside uptake in BHK fibroblasts. *Chem.-biol. Interact.*, *24*, 137-151

Bianchi, V., Dal Toso, R., Debetto, P., Levis, A.G., Luciani, S., Majone, F. & Tamino, G. (1980) Mechanisms of chromium toxicity in mammalian cell cultures. *Toxicology*, *17*, 219-224

Bianchi, V., Debetto, P., Zantedeschi, A. & Levis, A.G. (1982a) Effects of hexavalent chromium on the adenylate pool of hamster fibroblasts. *Toxicology*, *25*, 19-30

Bianchi, V., Nuzzo, F., Abbondandolo, A., Bonatti, S., Capelli, E., Fiorio, R., Giulotto, E., Mazzaccaro, A., Stefanini, M., Zaccaro, L., Zantedeschi, A. & Levis, A.G. (1982b) Scintillometric determination of DNA repair in human cell lines: a critical appraisal. *Mutat. Res.*, *93*, 447-463

Bianchi, V., Celotti, L., Lanfranchi, G., Majone, F., Marin, G., Montaldi, A., Sponza, G., Tamino, G., Venier, P., Zantedeschi, A. & Levis, A.G. (1983) Genetic effects of chromium compounds. *Mutat. Res.*, *117*, 279-300

Bianchi, V., Zantedeschi, A., Montaldi, A. & Majone, F. (1984) Trivalent chromium is neither cytotoxic nor mutagenic in permeabilized hamster fibroblasts. *Toxicol. Lett.*, *23*, 51-59

Bidstrup, P.L. (1951) Carcinoma of the lung in chromate workers. *Br. J. ind. Med.*, *8*, 302-305

Bidstrup, P.L. & Case, R.A.M. (1956) Carcinoma of the lung in workmen in the bichromates-producing industry in Great Britain. *Br. J. ind. Med.*, *13*, 260-264

Bigaliev, A.B. (1981) Chromosomal aberrations in a lymphocyte culture from persons in contact with chromium (Russ.). *Tsitol. Genet.*, *15*, 63-68

Bigaliev, A.B., Elemesova, M.S. & Turebaev, M.N. (1977a) Evaluation of the mutagenic activity of chromium compounds (Russ.). *Gig. Tr. prof. Zabol.*, *6*, 37-40

Bigaliev, A.B., Turebaev, M.N. & Elemesova, M.S. (1977b) Cytogenetic study of the in vivo mutagenic properties of chromium compounds (Russ.). In: Dubinin, N.P., ed., *Genet. Posledstviya Zagryaznenia Okruzhayushehei Sredy* (Proceedings of a Symposium), Moscow, Nauka, pp. 173-176

Bigaliev, A.B., Turebaev, M.N., Bigalieva, R.K. & Elemesova, M.S. (1977c) Cytogenetic examination of workers engaged in chrome production (Russ.). *Genetika, 13*, 545-547

Bigaliev, A.B., Shpak, N.K. & Smagulov, A.S. (1979) Mechanisms of the cytogenetic action of chromium as an environmental pollutant. *Dokl. Biol. Sci.* (Engl. transl.), *245*, 809-810

Biggart, N.W. & Murphy, E.C., Jr (1988) Analysis of metal-induced mutations altering the expression or structure of a retroviral gene in a mammalian cell line. *Mutat. Res., 198*, 115-129

Bloomfield, J.J. & Blum, W. (1928) Health hazards in chromium plating. *Public Health Rep., 43*, 2330-2347

Bohgard, M., Jandiga, B.L. & Akselsson, K.R. (1979) An analytical procedure for determining chromium in samples of airborne dust. *Ann. occup. Hyg., 22*, 241-251

Bonatti, S., Meini, M. & Abbondandolo, A. (1976) Genetic effects of potassium dichromate in *Schizosaccharomyces pombe*. *Mutat. Res., 38*, 147-150

Bourne, H.G., Jr & Yee, H.T. (1950) Occupational cancer in a chromate plant. An environmental appraisal. *Ind. Med. Surg., 19*, 563-567

Bovet, P., Lob, M. & Grandjean, M. (1977) Spirometric alterations in workers in the chromium electroplating industry. *Int. Arch. occup. environ. Health, 40*, 25-32

Bragt, P.C. & van Dura, E.A. (1983) Toxicokinetics of hexavalent chromium in the rat after intratracheal administration of chromates of different solubilities. *Ann. occup. Hyg., 27*, 315-322

Brakhnova, I.T. (1975) *Environmental Hazards of Metals* (translation), New York, Consultants Bureau, pp. 41-42

Brambilla, G., Sciabà, L., Carlo, P., Finollo, R., Farina, A. & Parodi, S. (1980) DNA crosslinking in mammalian cells treated with potassium dichromate (Abstract No. 394). *Proc. Am. Assoc. Cancer Res., 21*, 98

Brams, A., Buchet, J.P., Crutzen-Fayt, M.C., De Meester, C., Lauwerys, R. & Léonard, A. (1987) A comparative study, with 40 chemicals, of the efficiency of the *Salmonella* assay and the SOS chromotest (kit procedure). *Toxicol. Lett., 38*, 123-133

Braver, E.R., Infante, P. & Chu, K. (1985) An analysis of lung cancer risk from exposure to hexavalent chromium. *Teratog. Carcinog. Mutagenesis, 5*, 365-378

Brinton, H.P., Frasier, E.S. & Koven, A.L. (1952) Morbidity and mortality experience among chromate workers. *Public Health Rep., 67*, 835-847

Brinton, L.A., Blot, W.J., Becker, J.A., Winn, D.M., Browder, J.P., Farmer, J.C., Jr & Fraumeni, J.F., Jr (1984) A case-control study of cancers of the nasal cavity and paranasal sinuses. *Am. J. Epidemiol., 119*, 896-906

British Chrome & Chemical Ltd (1988) *MSDS: Basic Chromic Sulphate (Chrometan)*, Eaglescliffe, Stockton-on-Tees

Brochard, P., Ameille, J., Brun, B., Gagnant, B. & Philbert, M. (1983) Bronchial cancer and chromium electroplating. About a new case (Fr.). *Arch. Mal. prof., 44*, 35-37

Bronzetti, G., Galli, A., Boccardo, P., Vellosi, R., Del Carratore, R., Sabbioni, E. & Edel, J. (1986) Genotoxicity of chromium *in vitro* on yeast: interaction with DNA. *Toxicol. environ. Chem., 13*, 103-111

Brune, D., Nordberg, G. & Wester, P.O. (1980) Distribution of 23 elements in the kidney, liver and lungs of workers from a smeltery and refinery in north Sweden exposed to a number of elements and of a control group. *Sci. total Environ.*, *16*, 13-35

Bryson, W.G. & Goodall, C.M. (1983) Differential toxicity and clearance kinetics of chromium (III) or (VI) in mice. *Carcinogenesis*, *4*, 1535-1539

Buckell, M. & Harvey, D.G. (1951) An environmental study of the chromate industry. *Br. J. ind. Med.*, *8*, 298-301

Bunker, V.W., Lawson, M.S., Delves, H.T. & Clayton, B.E. (1984) The uptake and excretion of chromium by the elderly. *Am. J. clin. Nutr.*, *39*, 797-802

Burges, D.C.L. (1980) Mortality study of nickel platers. In: Brown, S.S. & Sunderman, F.W., eds, *Nickel Toxicology*, London, Academic Press, pp. 15-18

Burrows, D. (1983) Adverse chromate reactions on the skin. In: Burrows, D., ed., *Chromium: Metabolism and Toxicity*, Boca Raton, FL, CRC Press, pp. 137-163

Byrne, C.J. & DeLeon, I.R. (1986) Trace metal residues in biota and sediments from Lake Pontchartrain, Louisiana. *Bull. environ. Contam. Toxicol.*, *37*, 151-158

Calder, L.M. (1988) Chromium contamination of groundwater. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, Wiley Interscience, pp. 215-229

Camusso, M. & Montesissa, C. (1988) Chromium (Part 1) (Ital.). *Chim. ind. (Milan)*, *70*, 30-32

Cantoni, O. & Costa, M. (1984) Analysis of the induction of alkali sensitive sites in the DNA by chromate and other agents that induce single strand breaks. *Carcinogenesis*, *5*, 1207-1209

Carelli, G., La Bua, R., Rimatori, V., Porcelli, D. & Iannaccone, A. (1981) Interferences in the spectrophotometric *s*-diphenylcarbazide determination of environmental hexavalent chromium in a chromium and zinc plating plant. *Scand. J. Work Environ. Health*, *7*, 56-61

Cary, E.E. (1982) Chromium in air, soil, and natural waters. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 49-64

Casto, B.C., Meyers, J. & DiPaolo, J.A. (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res.*, *39*, 193-198

Cavalleri, A. & Minoia, C. (1985) Monitoring exposure to Cr(VI) and Cr(III) in workers by determination of chromium in urine, serum and red blood cells (Ital.). *G. ital. med. Lav.*, *7*, 35-38

Celotti, L., Furlan, D., Seccati, L. & Levis, A.G. (1987) Interactions of nitrilotriacetic acid (NTA) with Cr(VI) compounds in the induction of gene mutations in cultured mammalian cells. *Mutat. Res.*, *190*, 35-39

Chalupski, V.H. (1956) The manufacture and properties of chromium pigments. In: Udy, M.J., ed., *Chromium*, Vol. 1, New York, Reinhold, pp. 364-376

Chemical Information Services Ltd (1988) *Directory of World Chemical Producers 1989/90 Edition*, Oceanside, NY

Choi, Y.-J., Kim, Y.-W. & Cha, C.-W. (1987) A study on sister chromatid exchanges in lymphocytes in some metal plating workers (Korean). *Korea Univ. med. J., 24*, 249-257

Christie, N.T., Cantoni, O., Evans, R.M., Meyn, R.E. & Costa, M. (1984) Use of mammalian DNA repair-deficient mutants to assess the effects of toxic metal compounds on DNA. *Biochem. Pharmacol., 33*, 1661-1670

Chromium Association (1989) *World Production of Ferrochromium*, Paris

Cikrt, M. & Bencko, V. (1979) Biliary excretion and distribution of ^{51}Cr(III) and ^{51}Cr(VI) in rats. *J. Hyg. Epidemiol. Microbiol. Immunol., 23*, 241-246

Clarkson, T.W., Nordberg, G.F. & Sager, P.R. (1985) Reproductive and developmental toxicity of metals. *Scand. J. Work Environ. Health, 11*, 145-154

Claude, J., Kunze, E., Frentzel-Beyme, R., Paczkowski, K., Schneider, J. & Schubert, H. (1986) Life-style and occupational risk factors in cancer of the lower urinary tract. *Am. J. Epidemiol., 124*, 578-589

Claude, J.C., Frentzel-Beyme, R.R. & Kunze, E. (1988) Occupation and risk of cancer of the lower urinary tract among men. A case-control study. *Int. J. Cancer, 41*, 371-379

Cobalt Development Institute (1985) *Cobalt in Superalloys*, London, Strobel & Sons

Collaborative Study Group for the Micronucleus Test (1986) Sex difference in the micronucleus test. *Mutat. Res., 172*, 151-163

Collaborative Study Group for the Micronucleus Test (1988) Strain difference in the micronucleus test. *Mutat. Res., 204*, 307-316

Commission of the European Communities (1975) Council Directive of 16 June 1975 concerning the quality required of surface water intended for the abstraction of drinking water in the Member States. *Off. J. eur. Communities, L194*, 26-30

Connett, P.H. & Wetterhahn, K.E. (1983) Metabolism of the carcinogen chromate by cellular constitutents. *Struct. Bonding, 54*, 93-124

Connett, P.H. & Wetterhahn, K.E. (1985) In vitro reaction of the carcinogen chromate with cellular thiols and carboxylic acids. *J. Am. chem. Soc., 107*, 4282-4288

Cook, W.A. (1987) *Occupational Exposure Limits — Worldwide*, Washington DC, American Industrial Hygiene Association, pp. 119, 133

Copson, R.L. (1956) Production of chromium chemicals. In: Udy, M.J., ed., *Chromium*, Vol. 1, New York, Reinhold, pp. 262-282

Corbett, T.H., Heidelberger, C. & Dove, W.F. (1970) Determination of the mutagenic activity to bacteriophage T4 of carcinogenic and noncarcinogenic compounds. *Mol. Pharmacol., 6*, 667-679

Cornelis, R. (1988) Analytical procedures and clinical reference materials in monitoring human exposures to trace metals with special reference to chromium, lead, and thallium. *Sci. total Environ., 71*, 269-283

Cornell, R.G. & Landis, J.R. (1984) Mortality patterns among nickel/chromium alloy foundry workers. In: Sunderman, F.W., Jr, ed., *Nickel in the Human Environment* (IARC Scientific Publications No. 53; IPCS Joint Symposia No. 4; CEC-EUR 916 EN), Lyon, IARC, pp. 87-93

Costa, R., Strolego, G. & Levis, A.G. (1988) Mutagenicity of lead chromate in *Drosophila melanogaster* in the presence of nitrilotriacetic acid (NTA). *Mutat. Res., 204*, 257-261

Cupo, D.Y. & Wetterhahn, K.E. (1984) Repair of chromate-induced DNA damage in chick embryo hepatocytes. *Carcinogenesis, 5*, 1705-1708

Cupo, D.Y. & Wetterhahn, K.E. (1985a) Binding of chromium to chromatin and DNA from liver and kidney of rats treated with sodium dichromate and chromium III chloride *in vivo*. *Cancer Res., 45*, 1146-1151

Cupo, D.Y. & Wetterhahn, K.E. (1985b) Modification of chromium(VI)-induced DNA damage by glutathione and cytochrome P-450 in chicken embryo hepatocytes. *Proc. natl Acad. Sci. USA, 82*, 6755-6759

Custer, T.W., Franson, J.C., Moore, J.F. & Myers, J.E. (1986) Reproductive success and heavy metal contamination in Rhode Island common terns. *Environ. Pollut. (Ser. A), 41*, 33-52

Cyprus Specialty Metals (1988) *Specification Sheets: Chromite (Chrome Ore) and Chromite, Supergray*, Malvern, PA

Dalager, N.A., Mason, T.J., Fraumeni, J.F., Jr, Hoover, R. & Payne, W.W. (1980) Cancer mortality among workers exposed to zinc chromate paints. *J. occup. Med., 22*, 25-29

Dams, R., Robbins, J.A., Rahn, K.A. & Winchester, J.W. (1970) Nondestructive neutron activation analysis of air pollution particulates. *Anal. Chem., 42*, 861-867

Danielsson, B.R.G., Hassoun, E. & Dencker, L. (1982) Embryotoxicity of chromium: distribution in pregnant mice and effects on embryonic cells *in vitro*. *Arch. Toxicol., 51*, 233-245

Danielsson, B.R.G., Dencker, L., Lindgren, A. & Tjälve, H. (1984) Accumulation of toxic metals in male reproduction organs. *Arch. Toxicol., Suppl. 7*, 177-180

Davies, J.M. (1978) Lung-cancer mortality of workers making chrome pigments (letter to the Editor). *Lancet, i*, 384

Davies, J.M. (1979) Lung cancer mortality of workers in chromate pigment manufacture: an epidemiological survey. *J. Oil col. chem. Assoc., 62*, 157-163

Davies, J.M. (1984a) Lung cancer mortality among workers making lead chromate and zinc chromate pigments in three English factories. *Br. J. ind. Med., 41*, 158-169

Davies, J.M. (1984b) Long term mortality study of chromate pigment workers who suffered lead poisoning. *Br. J. ind. Med., 41*, 170-178

Davis, G.K. (1956) Chromium in soils, plants, and animals. In: Udy, M.J., ed., *Chromium*, Vol. 1, New York, Reinhold, pp. 105-109

Davis, J.M.G. (1972) The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. *Br. J. exp. Pathol., 53*, 190-201

De Flora, S. (1978) Metabolic deactivation of mutagens in the *Salmonella*/microsome test. *Nature, 271*, 455-456

De Flora, S. (1981a) Study of 106 organic and inorganic compounds in the *Salmonella*/microsome test. *Carcinogenesis, 2*, 283-298

De Flora, S. (1981b) A 'spiral test' applied to bacterial mutagenesis assays. *Mutat. Res., 82*, 213-227

De Flora, S. (1982) Biotransformation and interaction of chemicals as modulators of mutagenicity and carcinogenicity. In: Sugimura, T., Kondo, S. & Takebe, H., eds, *Environmental Mutagens and Carcinogens*, Tokyo, University of Tokyo Press/New York, Alan R. Liss, pp. 527-541

De Flora, S. & Boido, V. (1980) Effect of human gastric juice on the mutagenicity of chemicals. *Mutat. Res.*, *77*, 307-315

De Flora, S. & Wetterhahn, K.E. (1990) Mechanisms of chromium metabolism and genotoxicity. *Life Chem. Rep.* (in press)

De Flora, S., Coppola, R., Camoirano, A., Battaglia, M.A. & Bennicelli, C. (1980) Mutagenicity and toxicity of chromyl chloride and its vapours. *Carcinogenesis*, *1*, 583-587

De Flora, S., Zanacchi, P., Bennicelli, C. & Arillo, A. (1982) Influence of liver S-9 preparations from rats and rainbow trout on the activity of four mutagens. *Toxicol. Lett.*, *10*, 345-349

De Flora, S., Zanacchi, P., Camoirano, A., Bennicelli, C. & Badolati, G. (1984a) Genotoxic activity and potency of 135 compounds in the Ames reversion test and in bacterial DNA-repair test. *Mutat. Res.*, *133*, 161-198

De Flora, S., Camoirano, A., Zanacchi, P. & Bennicelli, C. (1984b) Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other *Salmonella* strains. *Mutat. Res.*, *134*, 159-165

De Flora, S., Bennicelli, C., Zanacchi, P., Camoirano, A., Morelli, A. & De Flora, A. (1984c) In vitro effects of N-acetylcysteine on the mutagenicity of direct-acting compounds and procarcinogens. *Carcinogenesis*, *5*, 505-510

De Flora, S., De Renzi, G.P., Camoirano, A., Astengo, M., Basso, C., Zanacchi, P. & Bennicelli, C. (1985a) Genotoxicity assay of oil dispersants in bacteria (mutation, differential lethality, SOS DNA-repair) and yeast (mitotic crossing-over). *Mutat. Res.*, *158*, 19-30

De Flora, S., Morelli, A., Basso, C., Romano, M., Serra, D. & De Flora, A. (1985b) Prominent role of DT-diaphorase as a cellular mechanism reducing chromium(VI) and reverting its mutagenicity. *Cancer Res.*, *45*, 3188-3196

De Flora, S., Bennicelli, C., Camoirano, A., Serra, D., Romano, M., Rossi, G.A., Morelli, A. & De Flora, A. (1985c) In vivo effects of N-acetylcysteine on glutathione metabolism and on the biotransformation of carcinogenic and/or mutagenic compounds. *Carcinogenesis*, *6*, 1735-1745

De Flora, S., Russo, P., Pala, M., Fassina, G., Zunino, A., Bennicelli, C., Zanacchi, P., Camoirano, A. & Parodi, S. (1985d) Assay of phenacetin genotoxicity using in vitro and in vivo test systems. *J. Toxicol. environ. Health*, *16*, 355-377

De Flora, S., Badolati, G.S., Serra, D., Picciotto, A., Magnolia, M.R. & Savarino, V. (1987a) Circadian reduction of chromium in the gastric environment. *Mutat. Res.*, *192*, 169-174

De Flora, S., Camoirano, A., Serra, D., Basso, C., Zanacchi, P. & Bennicelli, C. (1987b) DT diaphorase and the action of chemical mutagens and carcinogens. *Chem. scripta*, *27A*, 151-155

De Flora, S., Camoirano, A., Romano, M., Astengo, M., Cesarone, C.F. & Millman, I. (1987c) Metabolism of mutagens and carcinogens in woodchuck liver and its relationship with hepatitis virus infection. *Cancer Res.*, *47*, 4052–4058

De Flora, S., Petruzzelli, S., Camoirano, A., Bennicelli, C., Romano, M., Rindi, M., Ghelarducci, L. & Giuntini, C. (1987d) Pulmonary metabolism of mutagens and its relationship with lung cancer and smoking habits. *Cancer Res.*, *47*, 4740-4745

De Flora, S., Bennicelli, C., Camoirano, A., Serra, D. & Hochstein, P. (1988) Influence of DT diaphorase on the mutagenicity of organic and inorganic compounds. *Carcinogenesis*, *9*, 611-617

De Flora, S., Serra, D., Camoirano, A. & Zanacchi, P. (1989a) Metabolic reduction of chromium, as related to its carcinogenic properties. *Biol. Trace Element Res.*, *21*, 179-187

De Flora, S., Camoirano, A., Serra, D. & Bennicelli, C. (1989b) Genotoxicity and metabolism of chromium compounds. *Toxicol. environ. Chem.*, *19*, 153-160

De Flora, S., Hietanen, E., Bartsch, H., Camoirano, A., Izzotti, A., Bagnasco, M. & Millman, I. (1989c) Enhanced metabolic activation of chemical hepatocarcinogens in woodchucks infected with hepatitis B virus. *Carcinogenesis*, *10*, 1099–1106

De Flora, S., Serra, D., Basso, C. & Zanacchi, P. (1989d) Mechanistic aspects of chromium carcinogenicity. *Arch. Toxicol., Suppl. 13*, 28-39

De Flora, S., Bagnasco, M., Serra, D. & Zanacchi, P. (1990) Genotoxicity of chromium compounds. A review. *Mutat. Res.* (in press)

Deknudt, G. (1982) In vivo study of the mutagenicity of heavy metals in mammals (Abstract no. 33). *Mutat. Res.*, *97*, 180

Delachaux (1989) *Vacuum Grade (Super Alloys); Chromium Powders; Double Degassed Briquettes*, Gennevilliers

De Marco, R., Bernardinelli, L. & Mangione, M.P. (1988) Death risk due to cancer of the respiratory apparatus in chromate production workers (Ital.). *Med. Lav.*, *79*, 368-376

Deng, C.Z., Ou, B.X., Huang, J.C., Zhuo, Z.L., Xian, H.L., Yao, M.C., Chen, M.Y., Li, Z.X., Sheng, S.Y. & Yei, Z.F. (1983) Cytogenetic effects of electroplating workers (Chin.). *Acta sci. circumst.*, *3*, 267-271

Deng, C.Z., Lee, H.H., Xian, H.L., Yao, M.C., Huang, J.C. & Ou, B.X. (1988) Chromosomal aberrations and sister chromatid exchanges of peripheral blood lymphocytes in Chinese electroplating workers: effect of nickel and chromium. *J. trace Elem. exp. Med.*, *1*, 57–62

Deutches Institut für Normung (German Standards Institute) (1987) *Photometric Determination of Chromium (VI) using 1,5-Diphenylcarbonohydrazide (D 24) (DIN 38405)*, Part 24, Berlin (West)

DiPaolo, J.A. & Casto, B.C. (1979) Quantitative studies of in vitro morphological transformation of Syrian hamster ceils by inorganic metal salts. *Cancer Res.*, *39*, 1008-1013

Dixit, M.N., Bhale, G.L. & Thomas, A. (1976) Emission spectrographic determination of trace elements in plant materials. *Indian J. pure appl. Phys.*, *14*, 485-487

Donaldson, R.M. & Barreras, R.F. (1966) Intestinal absorption of trace quantities of chromium. *J. Lab. clin. Med.*, *68*, 484-493

Donaldson, D.L., Smith, C.C. & Yunice, A.A. (1986) Renal excretion of chromium-51 chloride in the dog. *Am. J. Physiol.*, *246*, F870-F878

Douglas, G.R., Bell, R.D.L., Grant, C.E., Wytsma, J.M. & Bora, K.C. (1980) Effect of lead chromate on chromosomal aberration, sister-chromatid exchange and DNA damage in mammalian cells *in vitro*. *Mutat. Res.*, *77*, 157-163

Dry Color Manufacturers' Association (1982) *Classification and Chemical Description of the Mixed Metal Oxide Inorganic Colored Pigments*, 2nd ed., Arlington, VA

Dunkel, V.C., Pienta, R.J., Sivak, A. & Traul, K.A. (1981) Comparative neoplastic transformation responses of Balb/3T3 cells, Syrian hamster embryo cells, and Rauscher murine leukemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. *J. natl Cancer Inst.*, *67*, 1303-1315

Dunkel, V.C., Zeiger, E., Brusick, D., McCoy, E., McGregor, D., Mortelmans, K., Rosenkranz, H.S. & Simmon, V.F. (1984) Reproducibility of microbial mutagenicity assays: I. Tests with *Salmonella typhimurium* and *Escherichia coli* using a standardized protocol. *Environ. Mutagenesis*, *6*(Suppl. 2), 1-254

Dunstan, L.P. & Garner, E.L. (1977) Chemical preparation of biological materials for accurate chromium determination by isotope dilution mass spectrometry. *Trace Subst. environ. Health*, *11*, 334-337

Dvizhkov, P.P. & Fedorova, V.I. (1967) On blastomogenic properties of chromic oxide (Russ.). *Vop. Onkol.*, *13*, 57-62

Egilsson, V., Evans, I.H. & Wilkie, D. (1979) Toxic and mutagenic effects of carcinogens on the mitochondria of *Saccharomyces cerevisiae*. *Mol. gen. Genet.*, *174*, 39-46

Eisenberg, M. & Topping, J.J. (1986) Trace metal residues in finfish from Maryland waters, 1978-1979. *J. environ. Sci. Health*, *B21*, 87-102

Ekholm, U., Ulfvarsson, U. & Lindberg, E. (1983) *Exposure Conditions in Swedish Chromium Plating Industry* (Swed.) (Arbete och Hälsa 1983:24), Solna, Arbetarskyddsstyrelsen

Elias, Z., Schneider, O., Aubry, F., Danière, M.C. & Poirot, O. (1983) Sister chromatid exchanges in Chinese hamster V79 cells treated with the trivalent chromium compounds chromic chloride and chromic oxide. *Carcinogenesis*, *4*, 605-611

Elias, Z., Poirot, O., Schneider, O., Danière, M.C., Terzetti, F., Guedenet, J.C. & Cavelier, C. (1986) Cellular uptake, cytotoxic and mutagenic effects of insoluble chromic oxide in V79 Chinese hamster cells. *Mutat. Res.*, *169*, 159-170

Elinder, C.G., Gerhardsson, L. & Oberdoerster, G. (1988) Biological monitoring of toxic metals — overview. In: Clarkson, T.W., Friberg, L., Nordberg, G.F. & Sager, P.R., eds, *Biological Monitoring of Toxic Metals*, New York, Plenum, pp. 1-71

Elkem Metals Co. (1986) *Product Data Sheet: ELCHROMER® Electrolytic Chromium*, Pittsburgh, PA

Eller, P.M., ed. (1984) *NIOSH Manual of Analytical Methods*, 3rd ed., Vols 1 and 2 (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 7024-1–7024-3, 7200-1–7200-5, 7300-1–7300-5, 7600-1–7600-4, 8310-1–8310-6

Eller, P.M., ed. (1985) *NIOSH Manual of Analytical Methods*, 3rd ed., 1st Suppl. (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 8005-1–8005-5

Elofsson, S.-A., Gamberale, F., Hindmarsh, T., Iregren, A., Isaksson, A., Johnsson, I., Knave, B., Lydahl, E., Mindus, P., Persson, H.E., Philipson, B., Steby, M., Struwe, G., Söderman, E., Wennberg, A. & Widén, L. (1980) Exposure to organic solvents. A cross-sectional epidemiological investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. *Scand. J. Work Environ. Health*, *6*, 239-273

Enterline, P.E. (1974) Respiratory cancer among chromate workers. *J. occup. Med.*, *16*, 523-526

ERAMET-SLN (Entreprise de Recherches et d'Activités — Métaux — Société le Nickel) (1989) *Western World Stainless Steel Production*, Paris

Eurométaux (1986) *Usage of Nickel in Industry*, Brussels

Fabry, L. (1980) Relation between the induction of micronuclei in bone-marrow cells by chromium salts and their carcinogenic potency (Fr.). *C.R. Soc. Biol.*, *174*, 889-892

Fairhurst, S. & Minty, C.A. (1990) *The Toxicity of Chromium and Inorganic Chromium Compounds* (Health and Safety Executive Toxicity Review), London, Her Majesty's Stationery Office (in press)

Fan, A.M. & Harding-Barlow, I. (1987) Chromium. In: Fishbein, L., Furst, A. & Mehlman, M.A., eds, *Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure* (Advances in Modern Environmental Toxicology, Vol. XI), Princeton, NJ, Princeton Scientific Publishing, pp. 87-125

Farrell, R.P., Judd, R.J., Lay, P.A., Dixon, N.E., Baker, R.S.U. & Bonin, A.M. (1989) Chromium(V)-induced cleavage of DNA: are chromium(V) complexes the active carcinogens in chromium(VI)-induced cancer? *Chem. Res. Toxicol.*, *2*, 227-229

Filiberti, R., Ceppi, M. & Vercelli, M. (1983) Distribution in the environment and toxic and carcinogenic effects of chromium (Ital.). *Riv. med. Lav. Ig. ind.*, *7*, 245-259

Fishbein, L. (1976) Environmental metallic carcinogens: an overview of exposure levels. *J. Toxicol. environ. Health*, *2*, 77-109

Fishbein, L. (1984) Overview of analysis of carcinogenic and/or mutagenic metals in biological and environmental samples. I. Arsenic, beryllium, cadmium, chromium and selenium. *Int. J. environ. anal. Chem.*, *17*, 113-170

Fitzgerald, P.R., Peterson, J. & Lue-Hing, C. (1985) Heavy metals in tissues of cattle exposed to sludge-treated pastures for eight years. *Am. J. vet. Res.*, *46*, 703-707

Foa, V., Riboldi, L., Patroni, M., Zocchetti, C., Sbrana, C. & Mutti, A. (1988) Effects derived from long-term low-level chromium exposure in ferro-alloy metallurgy. Study of absorption and renal function in workers. *Sci. total Environ.*, *71*, 389-400

Fornace, A.J., Jr (1982) Detection of DNA single-strand breaks produced during the repair of damage by DNA-protein cross-linking agents. *Cancer Res.*, *42*, 145-149

Fornace, A.J., Jr, Seres, D.S., Lechner, J.F. & Harris, C.C. (1981) DNA-protein cross-linking by chromium salts. *Chem.-biol. Interact.*, *36*, 345-354

Fradkin, A., Janoff, A., Lane, B.P. & Kuschner, M. (1975) In vitro transformation of BHK21 cells grown in the presence of calcium chromate. *Cancer Res.*, *35*, 1058-1063

Franchini, I., Mutti, A., Cavatorta, A., Corradi, A., Cosi, A., Olivetti, G. & Borghetti, A. (1978) Nephrotoxicity of chromium. Remarks on an experimental and epidemiological investigation. *Contrib. Nephrol., 10*, 98-110

Franchini, I., Magnani, F. & Mutti, A. (1983) Mortality experience among chromeplating workers. Initial findings. *Scand. J. Work Environ. Health, 9*, 247-252

Franzen, E., Pohle, R. & Knoblich, K. (1970) Industrial hygiene studies in electroplating. III. Chromium in urine (Ger.). *Z. ges. Hyg., 16*, 657-661

Fregert, S. & Gruvberger, B. (1972) Chemical properties of cement. *Berufsdermatosen, 20*, 238-245

Frentzel-Beyme, R. (1983) Lung cancer mortality of workers employed in chromate pigment factories. A multicentric European epidemiological study. *J. Cancer Res. clin. Oncol., 105*, 183-188

Friedman, J., Shabtai, F., Levy, L.S. & Djaldetti, M. (1987) Chromium chloride induces chromosomal aberrations in human lymphocytes *via* indirect action. *Mutat. Res., 191*, 207-210

Fukunaga, M., Kurachi, Y. & Mizuguchi, Y. (1982) Action of some metal ions on yeast chromosomes. *Chem. pharm. Bull., 30*, 3017-3019

Furst, A. (1971) Trace elements related to specific chronic diseases: cancer. In: Cannon, H.L. & Hopps, H.C., eds, *Environmental Geochemistry in Health and Disease*, Boulder, CO, Geological Society of America, pp. 109-130

Furst, A., Schlauder, M. & Sasmore, D.P. (1976) Tumorigenic activity of lead chromate. *Cancer Res., 36*, 1779-1783

Gafafer, W.M., ed. (1953) *Health of Workers in Chromate Producing Industry: A Study (US Public Health Service, Division of Occupational Health Publications No. 192)*, Washington DC, US Public Health Service

Gale, T.F. (1978) Embryotoxic effects of chromium trioxide in hamsters. *Environ. Res., 16*, 101-109

Gale, T.F. (1982) The embryotoxic response to maternal chromium trioxide exposure in different strains of hamsters. *Environ. Res., 29*, 196-203

Gale, T.F. & Bunch, J.D., III (1979) The effect of time of administration of chromium trioxide on the embryotoxic response in hamsters. *Teratology, 19*, 81-86

Galli, A., Boccardo, P., Del Carratore, R., Cundari, E. & Bronzetti, G. (1985) Conditions that influence the genetic activity of potassium dichromate and chromium chloride in *Saccharomyces cerevisiae*. *Mutat. Res., 144*, 165-169

Gauglhofer, J. (1984) Chromium (Ger.). In: Merian, E., ed., *Metallen im Umwelt* (Metals in the Environment), Weinheim, Verlag Chemie, pp. 409-424

Gava, C., Perazzolo, L., Zentilin, L., Levis, A.G., Corain, B., Bombi, G.G., Palumbo, M. & Zatta, P. (1989a) Genotoxic potentiality and DNA binding properties of acetylacetone, maltol, and their aluminium(III) and chromium(III) neutral complexes. *Toxicol. environ. Chem., 22*, 149-157

Gava, C., Costa, R., Zordan, M., Venier, P., Bianchi, V. & Levis, A.G. (1989b) Induction of gene mutations in Salmonella and Drosophila by soluble Cr(VI) compounds: synergistic effects of nitrilotriacetic acid (NTA). *Toxicol. environ. Chem.* (in press)

Gentile, J.M., Hyde, K. & Schubert, J. (1981) Chromium genotoxicity as influenced by complexation and rate effects. *Toxicol. Lett.*, *7*, 439-448

Gilani, S.H. & Marano, M. (1979) Chromium poisoning and chick embryogenesis. *Environ. Res.*, *19*, 427-431

Glaser, U., Hochrainer, D., Klöppel, H. & Kuhnen, H. (1985) Low level chromium (VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. *Arch. Toxicol.*, *57*, 250-256

Glaser, U., Hochrainer, D., Klöppel, H. & Oldiges, H. (1986) Carcinogenicity of sodium dichromate and chromium [VI/III] oxide aerosols inhaled by male Wistar rats. *Toxicology*, *42*, 219-232

Gläss, E. (1955) Studies on the effect of heavy metal salts on mitosis in root tips of *Vicia faba* (Ger.). *Z. Botanik.*, *43*, 359-403

Gomes, E.R. (1972) Incidence of chromium-induced lesions among electroplating workers in Brazil. *Ind. Med.*, *41*, 21-25

Gómez-Arroyo, S., Altamirano, M. & Villalobos-Pietrini, R. (1981) Sister chromatid exchanges induced by some chromium compounds in human lymphocytes *in vitro*. *Mutat. Res.*, *90*, 425-431

Gray, S.J. & Sterling, K. (1950) The tagging of red cells and plasma proteins with radioactive chromium. *J. clin. Invest.*, *29*, 1604-1613

Green, M.H.L., Muriel, W.J. & Bridges, B.A. (1976) Use of a simplified fluctuation test to detect low levels of mutagens. *Mutat. Res.*, *38*, 33-42

Gresh, J.T. (1944) Chromic acid poisoning resulting from inhalation of mist developed from five per cent chromic acid solution. II. Engineering aspects of chromic acid poisoning from anodizing operations. *J. ind. Hyg. Toxicol.*, *26*, 127-130

Grogan, C.H. (1957) Experimental studies in metal carcinogenesis. VIII. On the etiological factor in chromate cancer. *Cancer*, *10*, 625-638

Gross, E. & Kölsch, F. (1943) On lung cancer in the chromium pigment industry (Ger.). *Arch. Gewerbepathol. Gewerbehyg.*, *12*, 164-170

Guillemin, M.P. & Berode, M. (1978) A study on the difference in chromium exposure in workers in two types of electroplating process. *Ann. occup. Hyg.*, *21*, 105-112

Haguenoer, J.M., Dubois, G., Frimat, P., Cantineau, A., Lefrançois, H. & Furon, D. (1981) Mortality from bronchopulmonary cancer in a zinc- and lead-chromate producing factory (Fr.). In: *Prevention of Occupational Cancer, International Symposium* (Occupational Safety and Health Series No. 46), Geneva, International Labour Office, pp. 168-176

Haguenoer, J.M., Leveque, G. & Frimat, P. (1982) Determinations of chromium, nickel and cobalt in cement of northern France and Belgium in relation to dermatoses (Fr.). *Arch. Mal. prof.*, *43*, 241-247

Haines, A.T. & Nieboer, E. (1988) Chromium hypersensitivity. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons, pp. 497-532

Hama, G., Fredrick, W., Millage, D. & Brown, H. (1954) Absolute control of chromic acid mist. Investigation of a new surface-active agent. *Am. ind. Hyg. Q.*, *15*, 211-216

Hamamy, H.A., Al-Hakkak, Z.S. & Hussain, A.F. (1987) Chromosome aberrations in workers at a tannery in Iraq. *Mutat. Res.*, *189*, 395-398

Hamilton, J.W. & Wetterhahn, K.E. (1986) Chromium(VI)-induced DNA damage in chick embryo liver and blood cells *in vivo*. *Carcinogenesis*, *7*, 2085-2088

Hamilton-Koch, W., Snyder, R.D. & LaVelle, J.M. (1986) Metal-induced DNA damage and repair in human diploid fibroblasts and Chinese hamster ovary cells. *Chem.-biol. Interactions*, *59*, 17-28

Handa, B.K. (1988) Occurrence and distribution of chromium in natural waters of India. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, Wiley Interscience, pp. 189-214

Hansen, K. & Stern, R.M. (1984) A survey of metal-induced mutagenicity *in vitro* and *in vivo*. *J. Am. Coll. Toxicol.*, *3*, 381-430

Hansen, K. & Stern, R.M. (1985) Welding fumes and chromium compounds in cell transformation assays. *J. appl. Toxicol.*, *5*, 306-314

Hanslian, L., Navrátil, J., Jurák, J. & Kotrle, M. (1967) The impairment of higher respiratory pathways by chromic acid aerosol (Czech.). *Prac. Lék.*, *19*, 294-298

Hartford, W.H. (1963) Chromium. In: Kolthoff, I.M. & Elving, P.J., eds, *Treatise on Analytical Chemistry*, Part II, Vol. 8, New York, John Wiley & Sons, pp. 273-377

Hartford, W.H. (1979) Chromium compounds. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 6, New York, John Wiley & Sons, pp. 82-120

Hartford, W.H. & Copson, R.L. (1964) Chromium compounds. In: Kirk, R.E., Othmer, D.F., Grayson, M. & Eckroth, D., eds, *Encyclopedia of Chemical Technology*, 2nd ed., Vol. 5, New York, John Wiley & Sons, pp. 485-486, 494, 499, 510

Hartwig, A. & Beyersmann, D. (1987) Enhancement of UV and chromate mutagenesis by nickel ions in the Chinese hamster HGPRT assay. *Toxicol. environ. Chem.*, *14*, 33-42

Harzdorf, A.C. (1987) Analytical chemistry of chromium species in the environment, and interpretation of results. *Int. J. environ. anal. Chem.*, *29*, 249-261

Hatch, G.G. & Anderson, T.M. (1986) Chemical enhancement of simian adenovirus SA7 transformation of hamster embryo cells: evaluation of diverse chemicals (Abstract No. OD5). In: Ramel, C., Lambert, B. & Magnusson, J., eds, *Fourth International Conference on Environmental Mutagens, Stockholm, June 24-28, 1985*, New York, Alan R. Liss, p. 34

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagenesis*, *5* (*Suppl. 1*), 3-142

Hayashi, M., Sofuni, T. & Ishidate, M., Jr (1982) High-sensitivity in micronucleus induction of a mouse strain (MS). *Mutat. Res.*, *105*, 253-256

Hayes, R.B. (1988) Review of occupational epidemiology of chromium chemicals and respiratory cancer. *Sci. total Environ.*, *71*, 331-339

Hayes, R.B., Lilienfeld, A.M. & Snell, L.M. (1979) Mortality in chromium chemical production workers: a prospective study. *Int. J. Epidemiol.*, *8*, 365-374

Hayes, S., Gordon, A., Sadowski, I. & Hayes, C. (1984) RK bacterial test for independently measuring chemical toxicity and mutagenicity: short-term forward selection assay. *Mutat. Res., 130*, 97-106

Hayes, R.B., Sheffet, A. & Spirtas, R. (1989) Cancer mortality among a cohort of chromium pigment workers. *Am. J. ind. Med., 16*, 127-133

Haynes, E. (1907) *Metal Alloy* (Kokomo, Ind.). Patent No. 873, 745 [Chem. Abstr., 1908, *2*]

Health and Safety Executive (1987) *Occupational Exposure Limits 1987* (Guidance Note EH 4d87), London, Her Majesty's Stationery Office, p. 11

Heck, J.D. & Costa, M. (1982a) In vitro assessment of the toxicity of metal compounds. I. Mammalian cell transformation. *Biol. Trace Element Res., 4*, 71-82

Heck, J.D. & Costa, M. (1982b) In vitro assessment of the toxicity of metal compounds. II. Mutagenesis. *Biol. Trace Element Res., 4*, 319-330

Heigl, A. (1978) Polarographic determination of copper, lead, tin, cadmium, nickel, zinc, iron, cobalt and chromium in waste water (Ger.). *Chimia, 32*, 339-344 [*Chem. Abstr., 90*, 76081f]

Heit, M. (1979) Variability of the concentrations of seventeen trace elements in the muscle and liver of a single striped bass, *Morone saxatilis*. *Bull. environ. Contam. Toxicol., 23*, 1-5

Hellquist, H., Irander, K., Edling, C. & Ödkvist, L.M. (1983) Nasal symptoms and histopathology in a group of spray painters. *Acta otolaryngol., 96*, 495-500

Hernberg, S., Collan, Y., Degerth, R., Englund, A., Engzell, U., Kuosma, E., Mutanen, P., Nordlinder, H., Hansen, H.S., Schultz-Larsen, K., Søgaard, H. & Westerholm, P. (1983a) Nasal cancer and occupational exposures. Preliminary report of a joint Nordic case-referent study. *Scand. J. Work Environ. Health, 9*, 208-213

Hernberg, S., Westerholm, P., Schultz-Larsen, K., Degerth, R., Kuosma, E., Englund, A., Engzell, U., Hansen, H.S. & Mutanen, P. (1983b) Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. *Scand. J. Work Environ. Health, 9*, 315-326

Hopkins, L.L., Jr (1965) Distribution in the rat of physiological amounts of injected ^{51}Cr(III) with time. *Am. J. Physiol., 209*, 731-735

Howarth, C.L. (1956) Chromium chemicals in the textile industry. In: Udy, M.J., ed., *Chromium*, Vol. 1, New York, Reinhold, pp. 283-290

Hueper, W.C. (1955) Experimental studies in metal cancerigenesis. VII. Tissue reactions to parenterally introduced powdered metallic chromium and chromite ore. *J. natl Cancer Inst., 16*, 447-462

Hueper, W.C. (1958) Experimental studies in metal cancerigenesis. X. Cancerigenic effects of chromite ore roast deposited in muscle tissue and pleural cavity of rats. *Arch. ind. Health, 18*, 284-291

Hueper, W.C. (1961) Environmental carcinogenesis and cancers. *Cancer Res., 21*, 842-857

Hueper, W.C. & Payne, W.W. (1959) Experimental cancers in rats produced by chromium compounds and their significance to industry and public health. *Am. ind. Hyg. Assoc. J., 20*, 274-280

Hueper, W.C. & Payne, W.W. (1962) Experimental studies in metal carcinogenesis. Chromium, nickel, iron, arsenic. *Arch. environ. Health, 5*, 445-462

Huff, J.W., Sastry, K.S., Gordon, M.P. & Wacker, W.E.C. (1964) The action of metal ions on tobacco mosaic virus ribonucleic acid. *Biochemistry, 3*, 501-506

Husgafvel-Pursiainen, K., Kalliomäki, P.-L. & Sorsa, M. (1982) A chromosome study among stainless steel welders. *J. occup. Med., 24*, 762-766

Hyodo, K., Suzuki, S., Furuya, N. & Meshizuka, K. (1980) An analysis of chromium, copper, and zinc in organs of a chromate workers. *Int. Arch. occup. environ. Health, 46*, 141-150

IARC (1973) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 2, *Some Inorganic and Organometallic Compounds*, Lyon, pp. 100-125

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 1, *Chemicals and Industrial Processes Associated with Cancer in Humans*, IARC Monographs *Volumes 1 to 20*, Lyon, pp. 29-30

IARC (1980a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 23, *Some Metals and Metallic Compounds*, Lyon, pp. 205-323

IARC (1980b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 23, *Some Metals and Metallic Compounds*, Lyon, pp. 325-415

IARC (1981) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 25, *Wood, Leather and Some Associated Industries*, Lyon, pp. 201-247

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans.* IARC Monographs *Volumes 1 to 29*, Lyon, pp. 91-93

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 165-168

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42*, Lyon, pp. 165-168

IARC (1988) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, No. 13, Lyon, pp. 34, 123, 259

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 307-326

Iijima, S., Matsumoto, N. & Lu, C.-C. (1983a) Transfer of chromic chloride to embryonic mice and changes in the embryonic mouse neuroepithelium. *Toxicology, 26*, 257-265

Iijima, S., Spindle, A. & Pedersen, R.A. (1983b) Developmental and cytogenetic effects of potassium dichromate on mouse embryos *in vitro*. *Teratology, 27*, 109-115

Il'inykh, S.V. (1977) Method for the determination of chromium in canned food packed into cans made of chrome-plated tin (Russ.). In: *Hygienic Aspect of Defence of Health of Workers*, Moscow, Erismana Institute of Hygiene, pp. 193-194 [*Chem. Abstr., 89*, 88934d]

Imreh, S. & Radulescu, D. (1982) Cytogenetic effects of chromium *in vivo* and *in vitro* (Abstract No. 56). *Mutat. Res., 97*, 192-193

Institut National de Recherche et de Sécurité (National Institute for Research and Safety) (1986) [*Limit Values for Dangerous Substances in Work Place Air*] (ND 1609-125-86) (in French), Paris, p. 562

Ivankovic, S. & Preussmann, R. (1975) Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. *Food Cosmet. Toxicol., 13*, 347-351

Iyengar, V. & Woittiez, J. (1988) Trace elements in human clinical specimens: evaluation of literature data to identify reference values. *Clin. Chem., 34*, 474-481

Jackson, J.F. & Linskens, H.F. (1982) Metal ion induced unscheduled DNA synthesis in *Petunia* pollen. *Mol. gen. Genet., 187*, 112-115

Jacquet, P. & Draye, J.P. (1982) Toxicity of chromium salts to cultured mouse embryos. *Toxicol. Lett., 12*, 53-57

Jayjock, M.A. & Levin, L. (1984) Health hazards in a small automotive body repair shop. *Ann. occup. Hyg., 28*, 19-29

Jin, X. & Hou, D. (1984) Chemical behaviour of chromium in the environment (Chin.). *Changchun Dizhi Xueyuan Xuebao, 3*, 91-99

Johansson, A., Wiernik, A., Jarstrand, C. & Camner, P. (1986) Rabbit alveolar macrophages after inhalation of hexa- and trivalent chromium. *Environ. Res., 39*, 372-385

de Jong, G.J. & Brinkman, U.A.T. (1978) Determination of chromium (III) and chromium (VI) in sea water by atomic absorption spectrometry. *Anal. chim. Acta, 98*, 243-250

Kada, T., Hirano, K. & Shirasu, T. (1980) Screening of environmental chemical mutagens in the rec-assay system with *Bacillus subtilis*. In: de Serres, F.J. & Hollaender, A., eds, *Chemical Mutagens: Principles and Methods for Their Detection*, Vol. 6, New York, Plenum, pp. 149-173

Kalinina, L.M. & Minseitova, S.R. (1983a) Induction of mutagenic repair in cells of *Escherichia coli* under the action of potassium bichromate (translation). *Dokl. Akad. Nauk SSR, 268*, 720-722

Kalinina, L.M. & Minseitova, S.R. (1983b) Mutagenic effects and DNA-damaging action in *Escherichia coli* cells treated with potassium bichromate (translation). *Genetika, 19*, 1941-1947

Kalinina, L.M. & Minseitova, S.R. (1983c) DNA repair pathways in *Escherichia coli* K-12 cells after mutation induction by potassium dichromate (translation). *Dokl. Akad. Nauk SSR, 272*, 208-210

Kaneko, T. (1976) Chromosome damage in cultured human leukocytes induced by chromium chloride and chromium trioxide (Jpn.). *Jpn. J. ind. Health, 18*, 136-137

Kanematsu, N., Hara, M. & Kada, T. (1980) Rec assay and mutagenicity studies on metal compounds. *Mutat. Res., 77*, 109-116

Kaths, D.S. (1981) *In Vivo Cytogenetic Effect of Some Salts of the Heavy Metals Cadmium, Chromium, Mercury, and Platinum in Assays of Micronuclei and Sister Chromatid Exchange*, Thesis, Freiburg, Freiburg University

Kawanishi, S., Inoue, S. & Sano, S. (1986) Mechanism of DNA cleavage induced by sodium chromate(VI) in the presence of hydrogen peroxide. *J. biol. Chem., 261*, 5952-5958

Kelly, W.F., Ackrill, P., Day, J.P., O'Hara, M., Tye, C.T., Burton, I., Orton, C. & Harris, M. (1982) Cutaneous absorption of trivalent chromium: tissue levels and treatment by exchange transfusion. *Br. J. ind. Med., 39*, 397-400

Kerr, L.A. & Edwards, W.C. (1981) Chromate poisoning in livestock from oil field wastes. *Vet. hum. Toxicol., 23*, 401-402

Kettrup, A., zur Mühlen, T. & Angerer, J. (1985) *Luftanalysen* (Air Analysis), Weinheim, Deutsche Forschungsgemeinschaft, pp. 1-9

Kharab, P. & Singh, I. (1985) Genotoxic effects of potassium dichromate, sodium arsenite, cobalt chloride and lead nitrate in diploid yeast. *Mutat. Res., 155*, 117-120

Kharab, P. & Singh, I. (1987) Induction of respiratory deficiency in yeast by salts of chromium, arsenic, cobalt and lead. *Ind. J. exp. Biol., 25*, 141-142

Kiilunen, M., Kivistö, H., Ala-Laurila, P., Tossavainen, A. & Aitio, A. (1983) Exceptional pharmacokinetics of trivalent chromium during occupational exposure to chromium lignosulfonate dust. *Scand. J. Work Environ. Health, 9*, 265-271

Kiilunen, M., Järvisalo, J., Mäkitie, O. & Aitio, A. (1987) Analysis, storage stability and reference values for urinary chromium and nickel. *Int. Arch. occup. environ. Health, 59*, 43-50

Kim, S., Iwai, Y., Fujino, M., Furumoto, M., Sumino, K. & Miyasaki, K. (1985) Chromium-induced pulmonary cancer. Report of a case and a review of the literature. *Acta pathol. jpn., 35*, 643-654

Kishi, R., Tarumi, T., Uchino, E. & Miyake, H. (1987) Chromium content of organs of chromate workers with lung cancer. *Am. J. ind. Med., 11*, 67-74

Kitagawa, S., Seki, H., Kametani, F. & Sakurai, H. (1988) EPR study on the interaction of hexavalent chromium with glutathione or cysteine: production of pentavalent chromium and its stability. *Inorg. chim. Acta, 152*, 251-255

Kjuus, H., Skjærven, R., Langård, S., Lien, J.T. & Aamodt, T. (1986) A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and occupation-based occupational information. *Scand. J. Work Environ. Health, 12*, 193-202

Klein, F. (1985) Nickel and chromium concentrations in ambient air of work places in the iron and steel industry (Fr.). In: Brown, S.S. & Sunderman, F.W., Jr, eds, *Progress in Nickel Toxicology*, Oxford, Blackwell Scientific, pp. 195-197

Kleinfeld, M. & Rosso, A. (1965) Ulcerations of the nasal septum due to inhalation of chromic acid mist. *Ind. Med. Surg., 34*, 242-243

Kleisbauer, J.-P., Poirier, R., Favre, R. & Laval, P. (1972) The problem of bronchial carcinomas of occupational origin (two cases) (Fr.). *Marseille méd., 109*, 699-704

Knudsen, I. (1980) The mammalian spot test and its use for the testing of potential carcinogenicity of welding fume particles and hexavalent chromium. *Acta pharmacol. toxicol., 47*, 66-70

Koli, A.K. & Whitmore, R. (1983) Trace elements in fish from the Savannah River near Savannah River nuclear plant. *Environ. int., 9*, 361-362

Kolihova, D., Sychra, V. & Dudova, N. (1978) Atomic absorption spectrometric analysis of ilmenite and inorganic pigments based on titanium dioxide. III. Determination of copper, manganese, chromium and iron by atomic absorption spectrometry with electrothermic atomization (Czech.). *Chem. Listy, 72*, 1081-1087 [*Chem. Abstr., 90*, 40259f]

Kominsky, J.R., Rinsky, R. & Stroman, R. (1978) *Goodyear Aerospace Corp.* (Health Hazard Evaluation Report No. 77-127-516), Cincinnati, OH, National Institute for Occupational Safety and Health

Koponen, M. (1985) *Applications of Some Instrumental Methods in Metal Aerosol Characterization* (Original Reports 2/1985), Kuopio, University of Kuopio

Koponen, M., Gustafsson, T., Kalliomäki, P.-L. & Pyy, L. (1981) Chromium and nickel aerosols in stainless steel manufacturing, grinding and welding. *Am. ind. Hyg. Assoc. J., 42*, 596-601

Korallus, U., Ehrlicher, H. & Wüstefeld, E. (1974a) Trivalent chromium compounds: results of a study in occupational medicine. Part 3: Clinical study (Ger.). *Arbeitsmed. Sozialmed. Präventivmed., 9*, 248-252

Korallus, U., Ehrlicher, H. & Wüstefeld, E. (1974b) Trivalent chromium compounds: results of a study in occupational medicine. Part 1: General; technology; preliminary study (Ger.). *Arbeitsmed. Sozialmed. Präventivmed., 9*, 51-54

Korallus, U., Ehrlicher, H. & Wüstefeld, E. (1974c) Trivalent chromium compounds: results of study in occupational medicine. Part 2: Analysis of disease status (Ger.). *Arbeitsmed. Sozialmed. Präventivmed., 9*, 76-79

Korallus, U., Lange, H.-J., Neiss, A., Wüstefeld, E. & Zwingers, T. (1982) Relationships between environmental hygiene control measures and mortality from bronchial cancer in the chromate producing industry (Ger.). *Arbeitsmed. Sozialmed. Präventivmed., 17*, 159-167

Kortenkamp, A., Ozolins, Z., Beyersmann, D. & O'Brien, P. (1989) Generation of PM2 DNA breaks in the course of reduction of chromium(VI) by glutathione. *Mutat. Res., 216*, 19-26

Koshi, K. (1979) Effects of fume particles from stainless steel welding on sister chromatid exchanges and chromosome aberrations in cultured Chinese hamster cells. *Ind. Health, 17*, 39-49

Koshi, K. & Iwasaki, K. (1983) Solubility of low-solubility chromates and their clastogenic activity in cultured cells. *Ind. Health, 21*, 57-65

Koshi, K., Yagami, T. & Nakanishi, Y. (1984) Cytogenetic analysis of peripheral blood lymphocytes from stainless steel welders. *Ind. Health, 22*, 305-318

Koshi, K., Sertia, F., Sawatari, K. & Suzuki, Y. (1987) Cytogenetic analysis of bone marrow cells and peripheral blood lymphocytes from rats exposed to chromium fumes by inhalation (Abstract No. 21). *Mutat. Res., 181*, 365

Kramer, H.L., Steiner, J.W. & Vallely, P.J. (1983) Trace element concentrations in the liver, kidney, and muscle of Queensland cattle. *Bull. environ. Contam. Toxicol., 30*, 588-594

Kretzschmar, J.G., Delespaul, I., De Rijck, T. & Verduyn, G. (1977) The Belgian network for the determination of heavy metals. *Atmos. Environ., 11*, 263-271

Krishnaja, A.P. & Rege, M.S. (1982) Induction of chromosomal aberrations in fish *Boleophthalmus dussumieri* after exposure *in vivo* to mitomycin C and heavy metals mercury, selenium and chromium. *Mutat. Res., 102*, 71-82

Kroner, R.C. (1973) The occurrence of trace metals in surface waters. In: Sabadell, J.E., ed., *Proceedings of a Symposium on Traces of Heavy Metals in Water Removal Processes and Monitoring*, Springfield, VA, National Technical Information Service, pp. 311-322

Kumpulainen, J.T., Lehto, J., Koivistoinen, P., Uusitupa, M. & Vuori, E. (1983) Determinations of chromium in human milk, serum and urine by electrothermal atomic absorption spectrometry without preliminary ashing. *Sci. total Environ., 31*, 71-80

Kurokawa, Y., Matsushima, M., Imazawa, T., Takamura, N., Takahashi, M. & Hayashi, Y. (1985) Promoting effect of metal compounds on rat renal tumorigenesis. *J. Am. Coll. Toxicol.*, 4, 321-330

Kuschner, M. & Laskin, S. (1971) Experimental models in environmental carcinogenesis. *Am. J. Pathol., 64*, 183-196

Lalor, E. (1973) Zinc and strontium chromates. In: Patton, T.C., ed., *Pigment Handbook*, Vol. 1, New York, John Wiley & Sons, pp. 847-859

Lane, B.P. & Mass, M.J. (1977) Carcinogenicity and cocarcinogenicity of chromium carbonyl in heterotopic tracheal grafts. *Cancer Res., 37*, 1476-1479

Lanfranchi, G., Paglialunga, S. & Levis, A.G. (1988) Mammalian cell transformation induced by chromium(VI) compounds in the presence of nitrilotriacetic acid. *J. toxicol. environ. Health, 24*, 251-260

Langård, S. (1980) Chromium. In: Waldron, H.A., ed., *Metals in the Environment*, London, Academic Press, pp. 111-132

Langård, S. (1982) Absorption, transport and excretion of chromium in man and animals. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 149-169

Langård, S. & Kommedal, T.M. (1975) Bronchial carcinoma in a young man exposed to chromates (Norw.). *Tidsskr. Nor. Lægeforen., 95*, 819-820

Langård, S. & Norseth, T. (1975) A cohort study of bronchial carcinomas in workers producing chromate pigments. *Br. J. ind. Med., 32*, 62-65

Langård, S. & Norseth, T. (1979) Cancer in the gastrointestinal tract in chromate pigment workers. *Arch. Hig. Rada Toksicol., 30 (Suppl.)*, 301-304

Langård, S. & Vigander, T. (1983) Occurrence of lung cancer in workers producing chromium pigments. *Br. J. ind. Med., 40*, 71-74

Langård, S., Gundersen, N., Tsalev, D.L. & Gylseth, B. (1978) Whole blood chromium level and chromium excretion in the rat after zinc chromate inhalation. *Acta pharmacol. toxicol., 42*, 142-149

Langård, S., Andersen, A. & Gylseth, B. (1980) Incidence of cancer among ferrochromium and ferrosilicon workers. *Br. J. ind. Med., 37*, 114-120

Langård, S., Andersen, A. & Ravnestad, J. (1990) Incidence of cancer among ferrochromium and ferrosilicon workers; an extended observation period. *Br. J. ind. Med., 47*, 14-19

Langerwerf, J.S.A., Bakkeren, H.A. & Jongen, W.M.T. (1985) A comparison of the mutagenicity of soluble trivalent chromium compounds with that of potassium chromate. *Ecotoxicol. environ. Saf.*, *9*, 92-100

Laskin, S., Kuschner, M. & Drew, R.T. (1970) Studies in pulmonary carcinogenesis. In: Hanna, M.G., Jr, Nettesheim, P. & Gilbert, J.R., eds, *Inhalation Carcinogenesis* (US Atomic Energy Commission Symposium Series No. 18), Oak Ridge, TN, US Atomic Energy Commission, Division of Technical Information Extension, pp. 321-351

Lautner, G.M., Carver, J.C. & Konzen, R.B. (1978) Measurement of chromium(VI) and chromium (III) in stainless steel welding fumes with electron spectroscopy for chemical analysis and neutron activation analysis. *Am. ind. Hyg. Assoc. J.*, *39*, 651-660

LaVelle, J.M. (1986a) Potassium chromate potentiates frameshift mutagenesis in *E. coli* and *S. typhimurium*. *Mutat. Res.*, *171*, 1-10

LaVelle, J.M. (1986b) Chromium(VI) comutagenesis: characterization of the interaction of K_2CrO_4 with azide. *Environ. Mutagenesis*, *8*, 717-725

LaVelle, J.M. & Witmer, C.M. (1984) Chromium(VI) potentiates mutagenesis by sodium azide but not ethylmethanesulfonate. *Environ. Mutagenesis*, *6*, 311-320

Lee, K.P., Ulrich, C.E., Geil, R.G. & Trochimowicz, H.J. (1988) Effects of inhaled chromium dioxide dust on rats exposed for two years. *Fundam. appl. Toxicol.*, *10*, 125-145

Léonard, A. & Deknudt, G. (1981) Mutagenicity test with chromium salts in mouse (Abstract). *Mutat. Res.*, *80*, 287

Léonard, A. & Lauwerys, R.R. (1980) Carcinogenicity and mutagenicity of chromium. *Mutat. Res.*, *76*, 227-239

Letterer, E., Neidhardt, K. & Klett, H. (1944) Chromate lung cancer and chromate pneumoconioses. A clinical, patho-anatomical, and occupational hygiene study (Ger.). *Arch. Gewerbepathol. Gewerbehyg.*, *12*, 323-361

Levis, A.G. & Bianchi, V. (1982) Mutagenic and cytogenetic efects of chromium compounds. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 171-208

Levis, A.G. & Majone, F. (1979) Cytotoxic and clastogenic effects of soluble chromium compounds on mammalian cell cultures. *Br. J. Cancer*, *40*, 523-533

Levis, A.G. & Majone, F. (1981) Cytotoxic and clastogenic effects of soluble and insoluble compounds containing hexavalent and trivalent chromium. *Br. J. Cancer*, *44*, 219-235

Levis, A.G., Buttignol, M. & Vettorato, L. (1977) DNA synthesis inhibition in BHK fibroblasts treated *in vitro* with potassium dichromate. *Experientia*, *33*, 82-84

Levis, A.G., Bianchi, V., Tamino, G. & Pegoraro, B. (1978a) Cytotoxic effects of hexavalent and trivalent chromium on mammalian cells *in vitro*. *Br. J. Cancer*, *37*, 386-396

Levis, A.G., Buttignol, M., Bianchi, V. & Sponza, G. (1978b) Effects of potassium dichromate on nucleic acid and protein syntheses and on precursor uptake in BHK fibroblasts. *Cancer Res.*, *38*, 110-116

Levy, L.S. & Venitt, S. (1986) Carcinogenicity and mutagenicity of chromium compounds: the associaton between bronchial metaplasia and neoplasia. *Carcinogenesis*, *7*, 831-836

Levy, L.S., Martin, P.A. & Bidstrup, P.L. (1986) Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. *Br. J. ind. Med.*, *43*, 243-256

Lewalter, J., Korallus, U., Harzdorf, C. & Weidemann, H. (1985) Chromium bond detection in isolated erythrocytes: a new principle of biological monitoring of exposure to hexavalent chromium. *Int. Arch. occup. environ. Health, 55*, 305-318

Li, M.-C., Sheng, K.-L., Ching, C.-F., Chen, C.-H., Chin, P.-K., Jung, T.-W. & Wang, H.-P. (1979) Determination of trace elements in environmental samples by proton-induced X-ray emission analysis (Chin.). *K'o Hsueh Tung Pao, 24*, 19-21 [*Chem. Abstr., 90*, 145297v]

Lindberg, E. & Hedenstierna, G. (1983) Chrome plating: symptoms, findings in the upper airways and effects on lung function. *Arch. environ. Health, 38*, 367-374

Lindberg, E. & Vesterberg, O. (1983) Monitoring exposure to chromic acid in chrome plating by measuring chromium in urine. *Scand. J. Work Environ. Health, 9*, 333-340

Littorin, M., Högstedt, B., Strömbäck, B., Karlsson, A., Welinder, H., Mitelman, F. & Skerfving, S. (1983) No cytogenetic effects in lymphocytes of stainless steel welders. *Scand. J. Work Environ. Health, 9*, 259-264

Llagostera, M., Garrido, S., Guerrero, R. & Barbé, J. (1986) Induction of SOS genes of *Escherichia coli* by chromium compounds. *Environ. Mutagenesis, 8*, 571-577

Löfroth, G. (1978) The mutagenicity of hexavalent chromium is decreased by microsomal metabolism. *Naturwissenschaften, 65*, 207-208

Loprieno, N., Boncristiani, G., Venier, P., Montaldi, A., Majone, F., Bianchi, V., Paglialunga, S. & Levis, A.G. (1985) Increased mutagenicity of chromium compounds by nitrilotriacetic acid. *Environ. Mutagenesis, 7*, 185-200

Love, A.H.G. (1983) Chromium — biological and analytical considerations. In: Burrows, D., ed., *Chromium: Metabolism and Toxicity*, Boca Raton, FL, CRC Press, pp. 1-12

Luciani, S., Dal Toso, R., Rebellato, A.M. & Levis, A.G. (1979) Effects of chromium compounds on plasma membrane Mg^{2+}-ATPase activity of BHK cells. *Chem.-biol. Interact., 27*, 59-67

Lumio, J. (1953) On the lesions in the upper airways among chromium platers (Swed.). *Nord. hyg. Tidskr., 5-6*, 86-91

Ma, T.H., Harris, M.M., Van Anderson, A., Ahmed, I., Mohammad, K., Bare, J.L. & Lin, G. (1984) Tradescantia-micronucleus (Trad-MCN) tests on 140 health-related agents. *Mutat. Res., 138*, 157-167

Machle, W. & Gregorius, F. (1948) Cancer of the respiratory system in the United States chromate-producing industry. *Public Health Rep., 63*, 1114-1127

Macrae, W.D., Whiting, R.F. & Stich, H.F. (1979) Sister-chromatid exchanges induced in cultured mammalian cells by chromate. *Chem.-biol. Interactions, 26*, 281-286

Majone, F. (1977) Effects of potassium dichromate on mitosis of cultured mammalian cells. *Caryologia, 30*, 469-481

Majone, F. & Levis, A.G. (1979) Chromosomal aberrations and sister chromatid exchanges in Chinese hamster cells treated *in vitro* with hexavalent chromium compounds. *Mutat. Res., 67*, 231-238

Majone, F. & Rensi, D. (1979) Mitotic alterations, chromosome aberrations and sister chromatid exchanges induced by hexavalent and trivalent chromium on mammalian cells *in vitro*. *Caryologia, 32*, 379-392

Majone, F., Marin, G. & Levis, A.G. (1982) Chromium-induced sister chromatid exchanges in CHO cells. *Caryologia, 35*, 225-235

Majone, F., Montaldi, A., Ronchese, F., De Rossi, A., Chieco-Bianchi, L. & Levis, A.G. (1983) Sister chromatid exchanges induced *in vivo* and *in vitro* by chemical carcinogens in mouse lymphocytes carrying endogenized Moloney leukemia virus. *Carcinogenesis, 4*, 33-37

Makarov-Zemlyanskii, Y.Y., Men'shikov, B.I. & Strakhov, I.P. (1978) Persulphate method for determining chromium (III) in solutions with a 'silver free' catalyst (Russ.). *Kozh.-Obuvn. Prom-st., 20*, 43-45 [*Chem. Abstr., 89*, 76343x]

Maltoni, C. (1974) Occupational carcinogenesis. *Excerpta med. int. Congr. Ser., 322*, 19-26

Maltoni, C. (1976) Predictive value of carcinogenesis bioassays. *Ann. N.Y. Acad. Sci., 271*, 431-443

Maltoni, C., Morisi, L. & Chieco, P. (1982) Experimental approach to the assessment of the carcinogenic risk of industrial inorganic pigments. *Adv. mod. environ. Toxicol., 2*, 77-92

Mancuso, T.F. (1975) Considerations of chromium as an industrial carcinogen. In: Hutchinson, T.C., ed., *Proceedings of the International Conference on Heavy Metals in the Environment, Toronto, 1975*, Toronto, Institute for Environmental Studies, pp. 343-356

Mancuso, T.F. & Hueper, W.C. (1951) Occupational cancer and other health hazards in a chromate plant: a medical appraisal — I. Lung cancer in chromate workers. *Ind. Med. Surg., 20*, 358-363

Marzin, D.R. & Phi, H.V. (1985) Study of the mutagenicity of metal derivatives with *Salmonella typhimurium* TA102. *Mutat. Res., 155*, 49-51

Matsui, S. (1980) Evaluation of a *Bacillus subtilis* rec-assay for the detection of mutagens which may occur in water environments. *Water Res., 14*, 1613-1619

Matsumoto, N., Ijima, S. & Katsunuma, H. (1976) Placental transfer of chromic chloride and its teratogenic potential in embryonic mice. *J. toxicol. Sci., 2*, 1-13

McGean-Rohco (1984) *Data Sheet: Speciality Chromium Chemicals*, Cleveland, OH

McGregor, D.B., Martin, R., Cattanach, P., Edwards, I., McBride, D. & Caspary, W.J. (1987) Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay to coded chemicals. I: Results for nine compounds. *Environ. Mutagenesis, 9*, 143-160

McLean, J.R., McWilliams, R.S., Kaplan, J.G. & Birnboim, H.C. (1982) Rapid detection of DNA strand breaks in human peripheral blood cells and animal organs following treatment with physical and chemical agents. *Progr. Mutat. Res., 3*, 137-141

Mellor, J.W. (1931) *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. 11, Chapt. 60, *Chromium*, London, Longmans, Green & Co.

Merian, E. (1984) Introduction on environmental chemistry and global cycles of arsenic, beryllium, cadmium, chromium, cobalt, nickel, selenium, and their derivatives. *Toxicol. environ. Chem., 8*, 9-38

Mertz, W. (1969) Chromium occurrence and function in biological systems. *Physiol. Rev., 49*, 163-239

Mertz, W., Roginski, E.E. & Reba, R.C. (1965) Biological activity and fate of intravenous chromium (III) in the rat. *Am. J. Physiol., 209*, 489-494

Meyers, J.B. (1950) Acute pulmonary complications following inhalation of chromic acid mist. *Arch. ind. Hyg. occup. Med.*, *2*, 742-747

Michel-Briand, C. & Simonin, M. (1977) Bronchopulmonary carcinomas in two workers employed in the same workshop of a chrome electroplating factory (Fr.). *Arch. Mal. prof.*, *38*, 1001-1013

Miller, C.A. & Costa, M. (1988) Characterization of DNA-protein complexes induced in intact cells by the carcinogen chromate. *Mol. Carcinogenesis*, *1*, 125-133

Miller, C.A. & Costa, M. (1989) Immunological detection of DNA-protein complexes induced by chromate. *Carcinogenesis*, *10*, 667-672

Min, B.C. (1976) A study on the concentration of heavy metals in the tributaries of Han river (Korean). *Kongjung Poken Chapchi*, *13*, 337-347 [*Chem. Abstr.*, *90*, 92066k]

Mineral Pigments Corp. (undated a) *Specification Sheet: Jet Milled Dark Chromium Oxide (J-5351)*, Beltsville, MD

Mineral Pigments Corp. (undated b) *Specification Sheet: Jet Milled Light Chrome Yellow (J-1222)*, Beltsville, MD

Mineral Pigments Corp. (undated c) *Specification Sheet: Jet Milled Medium Chrome Yellow (J-1238)*, Beltsville, MD

Mineral Pigments Corp. (undated d) *Specification Sheet: Jet Milled Strontium Chromate (J-1365)*, Beltsville, MD

Ministry of Health & Welfare (1978) *Drinking Water Standards*, Tokyo

Mitchell, A.J. (1969) An unsuspected hazard of chrome stripping. *Trans. Soc. occup. Med.*, *19*, 128-130

Mitchell, A.D., Rudd, C.J. & Caspary, V.J. (1988) Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: intralaboratory results for sixty-three coded chemicals tested at SRI International. *Environ. mol. Mutagenesis*, *12* (Suppl. 13), 37-101

Miyaki, M., Murata, I., Osabe, M. & Ono, T. (1977) Effect of metal cations on misincorporation by *E. coli* DNA polymerases. *Biochem. biophys. Res. Commun.*, *77*, 854-860

Mohn, G.R. & Ellenberger, J. (1977) The use of *Escherichia coli* K12/343/113 (λ) as a multipurpose indicator strain in various mutagenicity testing procedures. In: Kilbey, B.J., Legator, M., Nichols, W. & Ramel, C., eds, *Handbook of Mutagenicity Test Procedures*, Amsterdam, Elsevier, pp. 95-118

Molina, D. & Abell, M.T. (1987) An ion chromatographic method for insoluble chromates in paint aerosol. *Am. ind. Hyg. Assoc. J.*, *48*, 830-835

Molos, J.E. (1947) Use of plastic chips in the control of chromic acid mist. *Ind. Med.*, *16*, 404-405

Montaldi, A., Zentilin, L., Paglialunga, S. & Levis, A.G. (1987a) Solubilization by nitrilotriacetic acid (NTA) of genetically active Cr(VI) and Pb(II) from insoluble metal compounds. *J. Toxicol. environ. Health*, *21*, 387-394

Montaldi, A., Zantilin, L., Zordan, M., Bianchi, V., Levis, A.G., Clonfero, E. & Paglialunga, S. (1987b) Chromosomal effects of heavy metals (Cd, Cr, Hg, Ni and Pb) on cultured mammalian cells in the presence of nitrilotriacetic acid (NTA). *Toxicol. environ. Chem.*, *14*, 183-200

Moreton, J., Bettelley, J., Mathers, H., Nicholls, A., Perry, R.W., Ratcliffe, D.B. & Svensson, L. (1983) Investigation of techniques for the analysis of hexavalent chromium, total chromium and total nickel in welding fume: a co-operative study. *Ann. occup. Hyg., 37*, 137-156

Morimoto, K. & Koizumi, A. (1981) Inhibition repair of radiation-induced chromosome breaks: effects of chromium trioxide on cultured human lymphocytes. *Ind. Health, 19*, 259-262

Morning, J.L. (1975) *Chromium* (Bulletin 667, Bureau of Mines), Washington DC, US Department of the Interior

Morning, J.L. (1978) Chromium. In: *Minerals Yearbook 1976*, Vol. 1, *Metals, Minerals and Fuels*, Washington DC, Bureau of Mines, US Government Printing Office, pp. 297-308

Morris, B.W., Griffiths, H., Hardisty, C.A. & Kemp, G.J. (1989) Increased concentrations of chromium in plasma, urine and red blood cells in a group of stainless steel welders. *At. Spectr., 10*, 1-3

Mukubo, K. (1978) Studies on experimental lung tumor by the chemical carcinogens and inorganic substances. III. Histopathological studies on lung tumour in rats induced by pertracheal vinyl tube infusion of 20-methylcholanthrene combined with chromium and nickel powders (Jpn.). *J. Nara med. Assoc., 29*, 321-340

Mutti, A., Cavatora, A., Borghi, L., Canali, M., Giaroli, C. & Franchini, I. (1979) Distribution and urinary excretion of chromium. Studies on rats after administration of single and repeated doses of potassium dichromate. *Med. Lav., 70*, 171-179

Mutti, A., Pedroni, C., Arfini, G., Franchini, I., Minoia, C., Micoli, G. & Baldi, C. (1984) Biological monitoring of occupational exposure to different chromium compounds at various valency states. *Int. J. environ. anal. Chem., 17*, 35-41

Myhr, B.C. & Caspary, W.J. (1988) Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. *Environ. mol. Mutagenesis, 12* (*Suppl. 13*), 103-194

Nagaya, T. (1986) No increase in sister-chromatid exchange frequency in lymphocytes of chromium platers. *Mutat. Res., 170*, 129-132

Nagaya, T., Ishikawa, N. & Hata, H. (1989) Sister chromatid exchange analysis in lymphocytes of workers exposed to hexavalent chromium. *Br. J. ind. Med., 46*, 48-51

Nakamura, S.-I., Oda, Y., Shimada, T., Oki, I. & Sugimoto, K. (1987) SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: examination with 151 chemicals. *Mutat. Res., 192*, 239-246

Nakamuro, K., Yoshikawa, K., Sayato, Y. & Kurata, H. (1978) Comparative studies of chromosomal aberration and mutagenicity of trivalent and hexavalent chromium. *Mutat. Res., 58*, 175-181

National Chemical Co. (undated a) *Specification Sheet: No. 10 Chromium Phosphate*, Chicago, IL

National Chemical Co. (undated b) *Specification Sheet: No. 4 Calcium Chromate*, Chicago, IL

National Chemical Co. (undated c) *Specification Sheet: No. 6 Barium Chromate*, Chicago, IL

National Chemical Co. (undated d) *Chrome Yellow Specifications*, Chicago, IL

National Chemical Co. (undated e) *Specification Sheet: Molybdate Orange Nos. 1720, 1730 and 1740*, Chicago, IL

National Chemical Co. (undated f) *Specification Sheet: No. 3 Strontium Chromate*, Chicago, IL

National Institute for Occupational Safety and Health (1973) *Occupational Exposure to Chromic Acid*, Cincinnati, OH, pp. 15-16

National Institute for Occupational Safety and Health (1975) *Occupational Exposure to Chromium VI*, Cincinnati, OH, pp. 23-24

National Institute for Occupational Safety and Health (1977) *National Occupational Hazard Survey 1972-74*, Cincinnati, OH

National Institute for Occupational Safety and Health (1984a) Method 7024. Chromium compounds as Cr. In: *NIOSH Manual of Analytical Methods*, Vol. 1, Cincinnati, OH, pp. 1-3

National Institute for Occupational Safety and Health (1984b) Method 7600. Chromium hexavalent. In: *NIOSH Manual of Analytical Methods*, Vol. 1, Cincinnati, OH, pp. 1-4

National Institute for Occupational Safety and Health (1988) NIOSH recommendations for occupational safety and health standards 1988. *Morbid. Mortal. wkly Rep.*, *37*(Suppl. 7), 9

National Oceanic and Atmospheric Administration (1987) *National Status and Trends Program for Marine Environmental Quality. Progress Report. A Summary of Selected Data on Chemical Contaminants in Tissues Collected During 1984, 1985, and 1986 (NOAA Technical Memorandum NOS OMA 38)*, Rockville, MD, National Ocean Service, US Department of Commerce, pp. 1-23, D-10–D-11, E-3

National Research Council (1974) *Chromium*, Washington DC, National Academy of Sciences

Nestmann, E.R., Matula, T.I., Douglas, G.R., Bora, K.C. & Kowbel, D.J. (1979) Detection of the mutagenic activity of lead chromate using a battery of microbial tests. *Mutat. Res.*, *66*, 357-365

Nettesheim, P., Hanna, M.G., Jr, Doherty, D.G., Newell, R.F. & Hellman, A. (1971) Effect of calcium chromate dust, influenza virus, and 100 R whole-body X radiation on lung tumor incidence in mice. *J. natl Cancer Inst.*, *47*, 1129-1144

Newbold, R.F., Amos, J. & Connell, J.R. (1979) The cytotoxic, mutagenic and clastogenic effects of chromium-containing compounds on mammalian cells in culture. *Mutat. Res.*, *67*, 55-63

Newman, D. (1890) A case of adeno-carcinoma of the left inferior turbinated body, and perforation of the nasal septum, in the person of a worker in chrome pigments. *Glasgow med. J.*, *33*, 469-470

Newton, M.F. & Lilly, L.J. (1986) Tissue-specific clastogenic effects of chromium and selenium salts *in vivo*. *Mutat. Res.*, *169*, 61-69

Ngaha, E.O. (1981) Renal effects of potassium dichromate in the rat: comparison of urinary enzyme excretion with corresponding tissue patterns. *Gen. Pharmacol.*, *12*, 497-500

Nickel Development Institute (1987a) *Design Guidelines for the Selection and Use of Stainless Steel*, Toronto

Nickel Development Institute (1987b) *Nickel Base Alloys*, Toronto

Nieboer, E. & Jusys, A.A. (1988) Biological chemistry of chromium. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons, pp. 21-79

Nieboer, E. & Shaw, S.L. (1988) Mutagenic and other genotoxic effects of chromium compounds. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons, pp. 399-441

Nieboer, E., Yassi, A., Haines, A.T. & Jusys, A.A. (1984) *Effects of Chromium Compounds on Human Health*, Toronto, Ontario Ministry of Labour

Nijs, M. & Kirsch-Volders, M. (1986) Induction of spindle inhibition and abnormal mitotic figures by Cr(II), Cr(III) and Cr(VI) ions. *Mutagenesis, 1*, 247-252

Nise, G. & Vesterberg, O. (1979) Direct determination of chromium in urine by electrothermal atomic absorption spectrometry. *Scand. J. Work Environ. Health, 5*, 404-410

Nishimura, M. & Umeda, M. (1978) Mutagenic effect of some metal compounds on cultured mammalian cells (Abstract No. 19). *Mutat. Res., 54*, 246-247

Nishio, A. & Uyeki, E.M. (1985) Inhibition of DNA synthesis by chromium compounds. *J. Toxicol. environ. Health, 15*, 237-244

Nishioka, N. (1975) Mutagenic activities of metal compounds in bacteria. *Mutat. Res., 31*, 185-189

Nishiyama, H., Yano, H., Nishiwaki, Y., Kitaya, T., Matsuyama, T., Kodama, T., Suemasu, K., Tamai, S. & Takemoto, K. (1985) Lung cancer in chromate workers — analysis of 11 cases. *Jpn. J. clin. Oncol., 15*, 489-497

Nishiyama, H., Nishiwaki, Y., Kodama, T., Matsuyama, T., Araki, T. & Takemoto, K. (1988) Lung cancer in chromate workers found by mass survey (Abstract No. 1.15). *Lung Cancer (J. int. Assoc. Study Lung Cancer), 4 (Suppl.)*

Nissing, W. (1975) Trace-element pollution of the Lower Rhine and its significance in drinking-water supply (Ger). *Ber. Arbeitsgem. Rheinwasserwerke, 32*, 83-94 [*Chem. Abstr., 88*, 176854n]

Nomiyama, H., Yotoriyama, M. & Nomiyama, K. (1980) Normal chromium levels in urine and blood of Japanese subjects determined by direct flameless atomic absorption spectrophotometry, and valency of chromium in urine after exposure to hexavalent chromium. *Am. ind. Hyg. Assoc. J., 41*, 98-102

Norseth, T. (1980) Cancer hazards caused by nickel and chromium exposure. *J. Toxicol. environ. Health, 6*, 1219-1227

Norseth, T. (1981) The carcinogenicity of chromium. *Environ. Health Perspect., 40*, 121-130

Norseth, T. (1986) The carcinogenicity of chromium and its salts. *Br. J. ind. Med., 43*, 649-651

Norseth, T., Alexander, J., Aaseth, J. & Langård, S. (1982) Biliary excretion of chromium in the rat: a role of glutathione. *Acta pharmacol. toxicol., 51*, 450-455

Nriagu, J.O. & Nieboer, E., eds (1988) *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons

Oberly, T.J., Piper, C.E. & McDonald, D.S. (1982) Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. *J. Toxicol. environ. Health, 9*, 367-376

O'Brien, D.M. & Hurley, D.E. (1981) *An Evaluation of Engineering Control Technology for Spray Painting* (DHSS (NIOSH) Publ. No. 81-121), Cincinnati, OH, National Institute for Occupational Safety and Health

Occidental Chemical Corp. (1987a) *Technical Bulletin: Chromic Acid*, Niagara Falls, NY

Occidental Chemical Corp. (1987b) *Technical Bulletin: Potassium Bichromate*, Niagara Falls, NY

Occidental Chemical Corp. (1987c) *Technical Bulletin: Sodium Chromate Anhydrous*, Niagara Falls, NY

Ogawa, H., Misawa, S., Morita, M., Abe, T., Kawai, K. & Nishioka, H. (1978) Sister chromatid exchanges of human lymphocytes induced by metal compounds (Jpn.). *Progr. Med. (Tokyo), 107*, 584-585

Ohno, H., Hanaoka, F. & Yamada, M.-A. (1982) Inducibility of sister-chromatid exchanges by heavy-metal ions. *Mutat. Res., 104*, 141-145

Ohsaki, Y., Abe, S., Homma, Y., Yozawa, K., Kishi, F., Murao, M., Sato, H., Date, F., Kawauchi, F., Kobayashi, T. & Fujita, I. (1974) High incidence of lung cancer in chromate workers (Jpn.). *J. Jpn. Soc. intern. Med., 63*, 1198-1203

Ohsaki, Y., Abe, S., Kimura, K., Tsuneta, Y., Mikami, H. & Murao, M. (1978) Lung cancer in Japanese chromate workers. *Thorax, 33*, 372-374

Okada, S., Ohba, H. & Taniyama, M. (1981) Alterations in ribonucleic acid synthesis by chromium (III). *J. inorg. Biochem., 15*, 223-331

Okada, S., Suzuki, M. & Ohba, H. (1983) Enhancement of ribonucleic acid synthesis by chromium (III) in mouse liver. *J. inorg. Biochem., 19*, 95-103

Okada, S., Tsukada, H. & Ohba, H. (1984) Enhancement of nucleolar RNA synthesis by chromium (III) in regenerating rat liver. *J. inorg. Biochem., 21*, 113-124

Okubo, T. & Tsuchiya, K. (1977) An epidemiological study on lung cancer among chromium plating workers. *Keio J. Med., 26*, 171-177

Okubo, T. & Tsuchiya, K. (1979) Epidemiological study of chromium platers in Japan. *Biol. Trace Elem. Res., 1*, 35-44

Okubo, T. & Tsuchiya, K. (1987) Mortality determined in a cohort study of chromium-plating workers (Abstract). *Scand. J. Work Environ. Health, 13*, 179

Olivier, P. & Marzin, D. (1987) Study of the genotoxic potential of 48 inorganic derivatives with the SOS chromotest. *Mutat. Res., 189*, 263-269

Olsen, J. & Sabroe, S. (1984) Occupational causes of laryngeal cancer. *J. Epidemiol. Community Health, 38*, 117-121

O'Neill, I.K., Schuller, P. & Fishbein, L., eds (1986) *Environmental Carcinogens. Selected Methods of Analysis*, Vol. 8, *Some Metals: As, Be, Cd, Cr, Ni, Pb, Se, Zn* (IARC Scientific Publications No. 71), Lyon, IARC

Osaki, S., Osaki, T., Shibata, S. & Takashima, Y. (1976) Determination of hexavalent and total chromium in sea water by isotope dilution mass spectrometry (Jpn.). *Bunseki Kagaku, 25*, 358-362 [*Chem. Abstr., 86*, 126960g]

Pacyna, J.M. & Nriagu, J.O. (1988) Atmospheric emissions of chromium from natural and anthropogenic sources. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons, pp. 105-123

Pagano, G., Esposito, A., Bove, P., De Angelis, M., Rota, A. & Giordano, G.G. (1983) The effects of hexavalent and trivalent chromium on fertilization and development in sea urchins. *Environ. Res., 30*, 442-452

Papp, J.F. (1983) Chromium. In: *Mineral Commodity Profiles 1983*, Washington DC, Bureau of Mines, US Department of the Interior, pp. 1-21

Papp, J.F. (1985) Chromium. In: *Bulletin 675, Mineral Facts and Problems*, Washington DC, Bureau of Mines, US Department of the Interior, pp. 1-18

Papp, J.F. (1987) Chromium. In: *1986 Bureau of Mines Minerals Yearbook*, Washington DC, Bureau of Mines, US Department of the Interior, pp. 1-20

Papp, J.F. (1988) Chromium. In: *1987 Bureau of Mines Minerals Yearbook*, Washington DC, Bureau of Mines, US Department of the Interior, pp. 1-17

Paschin, Y.V. & Kozachenko, V.I. (1981) Mutagenic activity of chromium compounds (Russ.). *Gig. Sanit., 5*, 46-49

Paschin, Y.V. & Kozachenko, V.I. (1982) The modifying effect of hexavalent chromate on the mutagenic activity of thio-TEPA. *Mutat. Res., 103*, 367-370

Paschin, Y.V. & Toropsev, S.N. (1982) Chromosome damage induced *in vivo* by heavy metal ion detected by indirect testing. *Acta biol. acad. sci. hung., 33*, 419-422

Paschin, Y.V. & Toropsev, S.N. (1983) Induction of micronuclei in mouse red cells by chromium ion (Russ.). *Bull. exp. Biol. Med., 95*, 72-74

Paschin, Y.V., Kozachenko, V.I. & Zacepilova, T.A. (1981) Complex testing of the genetic activity of the hexavalent chromium ion *in vitro* and *in vivo* (Russ.). *Tsitol. Genet., 15*, 66-69

Paschin, Y.V., Zacepilova, T.A. & Kozachenko, V.I. (1982) Induction of dominant lethal mutations in male mice by potassium dichromate. *Mutat. Res., 103*, 345-347

Paschin, Y.V., Kozachenko, V.I. & Sal'nikova, L.E. (1983) Differential mutagenic response at the HGPRT locus in V79 and CHO Chinese hamster cells after treatment with chromate. *Mutat. Res., 122*, 361-365

Patel, B., Balani, M.C. & Patel, S. (1985) Sponge 'sentinel' of heavy metals. *Sci. total Environ., 41*, 143-152

Patierno, S.R., Banh, D. & Landolph, J.R. (1988) Transformation of C3H/10T1/2 mouse embryo cells to focus formation and anchorage independence by insoluble lead chromate but not soluble calcium chromate: relationship to mutagenesis and internalization of lead chromate particles. *Cancer Res., 48*, 5280-5288

Payne, W.W. (1960a) Production of cancers in mice and rats by chromium compounds. *Arch. ind. Health, 21*, 530-535

Payne, W.W. (1960b) The role of roasted chromite ore in the production of cancer. *Arch. environ. Health, 1*, 20-26

Pedersen, N.B. (1982) The effects of chromium on the skin. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 249-277

Pedersen, P., Thomsen, E. & Stern, R.M. (1983) Detection by replica plating of false revertant colonies induced in the *Salmonella*-mammalian microsome assay by hexavalent chromium. *Environ. Health Perspect., 51, 227-230*

Pedersen, B., Thomsen, E. & Stern, R.M. (1987) Some problems in sampling, analysis and evaluation of welding fumes containing Cr(VI). *Ann. occup. Hyg.*, 31, 325-338

Pelkonen, L. & Fräki, J. (1983) Prevalence of dichromate sensitivity. *Contact Derm.*, *9*, 190-194

Perone, V.B., Moffitt, A.E., Jr, Possick, P.A., Key, M.M., Danzinger, S.J. & Gellin, G.A. (1974) The chromium, cobalt, and nickel contents of American cement and their relationship to cement dermatitis. *Am. ind. Hyg. Assoc. J.*, *35*, 301-306

Petrilli, F.L. & De Flora, S. (1977) Toxicity and mutagenicity of hexavalent chromium on *Salmonella typhimurium*. *Appl. environ. Microbiol.*, *33*, 805-809

Petrilli, F.L. & De Flora, S. (1978a) Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. *Mutat. Res.*, *58*, 167-173

Petrilli, F.L. & De Flora, S. (1978b) Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat. Res.*, *54*, 139-147

Petrilli, F.L. & De Flora, S. (1980) Mutagenicity of chromium compounds. In: *Chromium Symposium 80. Focus of a Standard*, Pittsburg, PA, Industrial Health Foundation, pp. 76-99

Petrilli, F.L. & De Flora, S. (1982) Interpretations on chromium mutagenicity and carcinogenicity. In: Sorsa, M. & Vainio, H., eds, *Mutagens in Our Environment*, New York, Alan R. Liss, pp. 453-464

Petrilli, F.L., De Renzi, G.P. & De Flora, S. (1980) Interaction between polycyclic aromatic hydrocarbons, crude oil and oil dispersants in the *Salmonella* mutagenesis assay. *Carcinogenesis*, *1*, 51-56

Petrilli, F.L., Camoirano, A., Bennicelli, C., Zanacchi, P., Astengo, M. & De Flora, S. (1985) Specificity and inducibility of the metabolic reduction of chromium(VI) mutagenicity by subcellular fractions of rat tissues. *Cancer Res.*, *45*, 3179-3187

Petrilli, F.L., Zanacchi, P., Camoirano, A., Astengo, M., Basso, C. & De Flora, S. (1986a) Selective genotoxicity of chromium compounds. In: Serrone, D., ed., *Chromium Symposium 1986. An Update*, Pittsburg, PA, Industrial Health Foundation, pp. 100-111

Petrilli, F.L., Bennicelli, C., Serra, D., Romano, M., De Flora, A. & De Flora, S. (1986b) Metabolic reduction and detoxification of hexavalent chromium. In: Serrone, D., ed., *Chromium Symposium 1986. An Update*, Pittsburg, PA, Industrial Health Foundation, pp. 112-130

Petrilli, F.L., Rossi, G.A., Camoirano, A., Romano, M., Serra, D., Bennicelli, C., De Flora, A. & De Flora, S. (1986c) Metabolic reduction of chromium by alveolar macrophages and its relationships to cigarette smoke. *J. clin. Invest.*, *77*, 1917-1924

Petruzzelli, S., De Flora, S., Bagnasco, M., Hietanen, E., Camus, A.-M., Saracci, R., Izzotti, A., Bartsch, H. & Giuntini, C. (1989) Carcinogen metabolism studies in human bronchial and lung parenchymal tissues. *Am. Rev. respir. Dis.*, *140*, 417-422

Pfeil, E. (1935) Lung tumors as occupational disease in chromate plants (Ger.). *Dtsch. med. Wochenschr.*, *61*, 1197-1200

Pokrovskaya, L.V. & Shabynina, N.K. (1973) Carcinogenous hazards in the production of chromium ferroalloys (Russ.). *Gig. Tr. prof. Zabol.*, *10*, 23-26

Pokrovskaya, L., Tushnakova, N., Gorodnova, N. & Andreeva, T. (1976) Dust factor and occupational disease of workers at open-cast mining of chromium-ore (Russ.). In: Domin, S., Kaznelson, B. & Zislin, D., eds, *Occupational Diseases of Dust Etiology*, Vol. 3, Moscow, Medizina, pp. 38-43

Polak, L. (1983) Immunology of chromium. In: Burrows, D., ed., *Chromium: Metabolism and Toxicology*, Boca Raton, FL, CRC Press, pp. 51-123

Polak, L., Turk, J.L. & Frey, J.R. (1973) Studies on contact hypersensitivity to chromium compounds. *Progr. Allergy, 17*, 145-226

Poschenrieder, C., Barceló, J. & Gunsé, B. (1986) The impact of chromium in the environment. I. Natural and anthropogenic presence of chromium in the environment (Sp.). *Circ. Farm., 290*, 23-38

Price-Jones, M.J., Gubbings, G. & Chamberlain, M. (1980) The genetic effects of crocidolite asbestos: comparison of chromosome abnormalities and sister-chromatid exchanges. *Mutat. Res., 79*, 331-336

Princi, F., Miller, L.H., Davis, A. & Cholak, J. (1962) Pulmonary disease of ferrochromium workers. *J. occup. Med., 4*, 301-310

Raffetto, G., Parodi, S., Parodi, C., De Ferrari, M., Troiano, R. & Brambilla, G. (1977) Direct interaction with cellular targets as the mechanism for chromium carcinogenesis. *Tumori, 63*, 503-512

Rafnsson, V. & Jóhannesdóttir, S.G. (1986) Mortality among masons in Iceland. *Br. J. ind. Med., 43*, 522-525

Rainaldi, G., Colella, C.M., Piras, A. & Mariani, T. (1982) Thioguanine resistance, ouabain resistance and sister chromatid exchanges in V79/AP4 Chinese hamster cells treated with potassium dichromate. *Chem.-biol. Interact., 42*, 45-51

Raithel, H.J., Ebner, G., Schaller, K.H., Schellmann, B. & Valentin, H. (1987) Problems in establishing norm values for nickel and chromium concentrations in human pulmonary tissue. *Am. J. ind. Med., 12*, 55-70

Rasmuson, A. (1985) Mutagenic effects of some water-soluble metal compounds in a somatic eye-color test system in *Drosophila melanogaster*. *Mutat. Res., 157*, 157-162

Rasmussen, L. (1977) Epiphytic bryophytes as indicators of the changes in the background levels of airborne metals from 1951-75. *Environ. Pollut., 14*, 37-45

Retnev, V.M. (1960) On the effect produced by chromium compounds contained in cement dust on the development of bronchial asthma (Russ.). *Gig. Tr. prof. Zabol., 7*, 29-33

Reuzel, P.G.J., Beems, R.B., De Raat, W.K. & Lohman, P.H.M. (1986) Carcinogenicity and in vitro genotoxicity of the particulate fraction of two stainless steel welding fumes. *Excerpta med. int. Congr. Ser., 676*, 329-332

Riley, E.C. & Goldman, F.H. (1937) Control of chromic acid mists from plating tanks. *Public Health Rep., 52*, 172-174

Rivedal, E. & Sanner, T. (1981) Metal salts as promoters of in vitro morphological transformation of hamster embryo cells initiated by benzo[*a*]pyrene. *Cancer Res., 41*, 2950-2953

Rivolta, G., Tomasini, M. & Colombi, A. (1982) Case study of lung cancer due to chromates diagnosed through cytologic examination of the sputum without X-ray evidence (Ital.). *Med. Lav., 73*, 40-44

Robison, S.H., Cantoni, O. & Costa, M. (1982) Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. *Carcinogenesis, 3*, 657-662

Robison, S.H., Cantoni, O. & Costa, M. (1984) Analysis of metal-induced DNA lesions and DNA-repair replication in mammalian cells. *Mutat. Res., 131*, 173-181

Rodriguez-Arnaiz, R. & Molina Martinez, R.F. (1986) Genetic effects of potassium dichromate and chromium trioxide in *Drosophila melanogaster*. *Cytologia, 51*, 421-425

Roe, F.J.C. & Carter, R.L. (1969) Chromium carcinogenesis: calcium chromate as a potent carcinogen for the subcutaneous tissues of the rat. *Br. J. Cancer, 23*, 172-176

Rogers, S.J., Pagano, D.A. & Zeiger, E. (1987) Mutagenicity of CrIII and CrVI compounds in the presence of mannitol, dithiothreitol and anaerobiosis (Abstract No. 237). *Environ. Mutagenesis, 9* (Suppl. 8), 91

Rosensteel, R.E. (1974) *Harris Structural Steel Company (Health Hazard Evaluation Report No. 73-99-108)*, Cincinnati, OH, National Institute for Occupational Safety and Health

Roskill Information Services (1974) *Chromium: World Survey of Production, Consumption and Prices*, 2nd ed., London, pp. 8, 80-93

Rossi, S.C. & Wetterhahn, K.E. (1989) Chromium[V] is produced upon reduction of chromate by mitochondrial electron transport chain complexes. *Carcinogenesis, 10*, 913-920

Rossman, T.G. & Molina, M. (1986) The genetic toxicology of metal compounds: II. Enhancement of ultraviolet light-induced mutagenesis in *Escherichia coli* WP2. *Environ. Mutagenesis, 8*, 263-271

Rossman, T.G., Molina, M. & Meyer, L.W. (1984) The genetic toxicology of metal compounds: I. Induction of λ prophage in *E. coli* $WP2_s(\lambda)$. *Environ. Mutagenesis, 6*, 59-69

Rössner, P., Bencko, V. & Šrám, R.J. (1981) Combined action of chromium and nickel on mouse and hamster fibroblast cell lines. *J. Hyg. Epidemiol. Microbiol., 25*, 252-258

Royle, H. (1975a) Toxicity of chromic acid in the chromium plating industry (2). *Environ. Res., 10*, 141-163

Royle, H. (1975b) Toxicity of chromic acid in the chromium plating industry (1). *Environ. Res., 10*, 39-53

Rudnykh, A.A. & Saichenko, S.Pl (1985) Reparative DNA synthesis in the lymphocytes of rats exposed to potassium dichromate and manganese chloride *in vivo* (Russ.). *Tsitol. Genet., 19*, 391-392

Ruiz-Rubio, M., Alejandre-Durán, E. & Pueyo, C. (1985) Oxidative mutagens specific for A.T base pairs induced forward mutations to L-arabinose resistance in *Salmonella typhimurium*. *Mutat. Res., 147*, 153-163

Ryberg, D. & Alexander, J. (1984) Inhibitory action of hexavalent chromium (Cr(VI)) on the mitochondrial respiration and a possible coupling to the reduction of Cr(VI). *Biochem. Pharmacol., 33*, 2461-2466

Sadiq, M., Zaidi, T.H., Hoda, A.-U. & Mian, A.A. (1982) Heavy metal concentrations in shrimp, crab, and sediment obtained from AD-Damman sewage outfall area. *Bull. environ. Contam. Toxicol., 29*, 313-319

Salmon, L., Atkins, D.H.F., Fischer, E.M.R. & Law, D.V. (1977) Retrospective analysis of air samples in the UK 1957-1974. *J. radioanal. Chem., 37*, 867-880

Sanderson, C.J. (1976) The uptake and retention of chromium by cells. *Transplantation, 21*, 526-529

Saner, G., Yüzbasiyan, V. & Çigdem, S. (1984) Hair chromium concentration and chromium excretion in tannery workers. *Br. J. ind. Med., 41*, 263-266

Sano, T. (1978) Pathology of chromium lesions (Jpn.). *Rodo no Kagaku, 33*, 4-14

Sarto, F., Levis, A.G. & Paulon, C. (1980) Clastogenic activity of hexavalent and trivalent chromium in cultured human lymphocytes. *Caryologia, 33*, 239-250

Sarto, F., Cominato, I., Bianchi, V. & Levis, A.G. (1982) Increased incidence of chromosomal aberrations and sister chromatid exchanges in workers exposed to chromic acid (CrO_3) in electroplating factories. *Carcinogenesis, 3*, 1011-1016

Sasaki, I. (1985) Inorganic pigments. In: Japan Chemical Week, ed., *Japan Chemical Annual 1985*, Tokyo, The Chemical Daily Co. Ltd, p. 78

Sasaki, I. (1986) Inorganic pigments. In: Japan Chemical Week, ed., *Japan Chemical Annual 1986*, Tokyo, The Chemical Daily Co. Ltd, p. 78

Sasaki, I. (1987) Inorganic pigments. In: Japan Chemical Week, ed., *Japan Chemical Annual 1987/1988*, Tokyo, The Chemical Daily Co. Ltd, p. 88

Satoh, K., Fukuda, Y., Torii, K. & Katsuno, N. (1981) Epidemiological study of workers engaged in the manufacture of chromium compounds. *J. occup. Med., 23*, 835-838

Sax, I.R. & Lewis, R.J., Sr (1987) *Hawley's Condensed Chemical Dictionary*, 11th ed., New York, Van Nostrand-Reinhold, pp. 66, 118, 278-281, 953-954, 1057-1058, 1098

Sayato, Y. & Nakamuro, K. (1980) Chromium as an inorganic pollutant (Jpn.). *Kagaku no Ryoiki Zokan, 126*, 111-117

Schaaper, R.M., Koplitz, R.M., Tkeshelashvili, L.K. & Loeb, L.A. (1987) Metal-induced lethality and mutagenesis: possible role of apurinic intermediates. *Mutat. Res., 177*, 179-188

Schaller, K.-H., Essing, H.-G., Valentin, H. & Schäcke, G. (1972) Quantitative chromium determination in urine by flameless atomic absorption spectrometry (Ger.). *Z. klin. Chem. klin. Biochem., 10*, 434-437

Schiek, R.C. (1973) Lead chromate pigments. Chrome yellow and chrome orange. In: Patton, T.C., ed., *Pigment Handbook*, Vol. 1, New York, John Wiley & Sons, pp. 357-363

Schroeder, H.A., Balassa, J.J. & Vinton, W.H., Jr (1964) Chromium, lead, cadmium, nickel and titanium in mice: effect on mortality, tumors and tissue levels. *J. Nutr., 83*, 239-250

Schroeder, H.A., Balassa, J.J. & Vinton, W.H., Jr (1965) Chromium, cadmium and lead in rats: effects on lifespan, tumors and tissue levels. *J. Nutr., 86*, 51-66

Sen, P. & Costa, M. (1986) Incidence and localization of sister chromatid exchanges induced by nickel and chromium compounds. *Carcinogenesis, 7*, 1527-1533

Sen, P., Conway, K. & Costa, M. (1987) Comparison of the localization of chromosome damage induced by calcium chromate and nickel compounds. *Cancer Res., 47*, 2142-2147

Sequi, P. (1980) Behaviour of chromium and mercury in soil (Ital.). In: Frigerio, A., ed., *Rischi Tossic. Inquin. Met.: Cromo Mercurio [Conv. Naz.]*, Milan, DST Publishers, pp. 27-50

Sharma, B.K., Singhal, P.C. & Chugh, K.S. (1978) Intravascular haemolysis and acute renal failure following potassium dichromate poisoning. *Postgrad. med. J., 54*, 414-415

Sheehy, J.W., Mortimer, V.D, Jones, J.H. & Spottswood, S.E. (1984) *Control Technology Assessment: Metal Plating and Cleaning Operations* (NIOSH Technical Report), Cincinnati, OH, National Institute for Occupational Safety and Health

Sheffet, A., Thind, I., Miller, A.M. & Louria, D.B. (1982) Cancer mortality in a pigment plant utilizing lead and zinc chromates. *Arch. environ. Health, 37*, 44-52

Shimkin, M.B. & Leiter, J. (1940) Induced pulmonary tumors in mice. III. The role of chronic irritation in the production of pulmonary tumors in strain A mice. *J. natl Cancer Inst., 1*, 241-254

Shimkin, M.B., Stoner, G.D. & Theiss, J.C. (1977) Lung tumor response in mice to metals and metal salts. *Adv. exp. Med. Biol., 91*, 85-91

Sibley, S.F. (1976) Cobalt. In: *Mineral Facts and Problems*, Washington DC, Bureau of Mines, US Government Printing Office, pp. 269-280

Silverstein, M., Mirer, F., Kotelchuck, D., Silverstein, B. & Bennett, M. (1981) Mortality among workers in a die-casting and electroplating plant. *Scand. J. Work Environ. Health, 7 (Suppl. 4)*, 156-165

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. & Bradley, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res., 113*, 357-391

Singh, I. (1983) Induction of reverse mutation and mitotic gene conversion by some metal compounds in *Saccharomyces cerevisiae*. *Mutat. Res., 117*, 149-152

Sirover, M.A. & Loeb, L.A. (1976) Infidelity of DNA synthesis *in vitro*: screening for potential metal mutagens or carcinogens. *Science, 194*, 1434-1436

Slavin, W. (1981) Determination of chromium in the environment and in the work place. *Atmos. Spectrosc., 2*, 8-12

Smith, D.E., Slade, M.D., Spencer, O.K., Roberts, W.L. & Ruckman, J.H. (1976) Metal concentrations in air particulate in the Four Corners area. *Utah Acad. Proc., 53*, 75-83

Snow, E.T. & Xu, L.-S. (1989) Effects of chromium(III) on DNA replication *in vitro*. *Biol. Trace Element Res., 21*, 61-72

Snyder, R.D. (1988) Role of active oxygen species in metal-induced DNA strand breakage in human diploid fibroblasts. *Mutat. Res., 193*, 237-246

Sokolowska, D.M. & Jongen, W.M.F. (1984) Heavy metals and *Salmonella typhimurium*: mutagenicity and interaction with model compounds (Abstract No. I.1.7). *Mutat. Res., 130*, 168

Sontag, G., Kerschbaumer, M. & Kainz, G. (1977) Determination of toxic heavy metals in effluent Austrian medicinal and table water (Ger.). *Z. Wasser Abwasser Forsch., 10*, 166-169 [*Chem. Abstr., 88*, 110183m]

Sora, S., Agostoni Carbone, M.L., Pacciarini, M. & Magni, G.E. (1986) Disomic and diploid meiotic products induced in *Saccharomyces cerevisiae* by the salts of 27 elements. *Mutagenesis, 1*, 21-28

Sorahan, T., Burges, D.C.L. & Waterhouse, J.A.H. (1987) A mortality study of nickel/chromium platers. *Br. J. ind. Med., 44*, 250-258

Sponza, G. & Levis, A.G. (1980) Effects of potassium dichromate, mitomycin C and methyl-methane-sulphonate on the in vitro synthesis of poly dT catalyzed by DNA-polymerase α from calf thymus with poly dA.$(dT)_n$ (Abstract). In: *Atti Associazione Genetica Italiana*, Vol. 26, Sassari, Poddighe, pp. 303-305

Steffee, C.H. & Baetjer, A.M. (1965) Histopathologic effects of chromate chemicals. Report of studies in rabbits, guinea pigs, rats and mice. *Arch. environ. Health, 11*, 66-75

Steinhoff, D., Gad, S.C., Hatfield, K. & Mohr, U. (1986) Carcinogenicity study with sodium dichromate in rats. *Exp. Pathol., 30*, 129-141

Stella, M., Montaldi, A., Rossi, R., Rossi, G. & Levis, A.G. (1982) Clastogenic effects of chromium on human lymphocytes *in vitro* and *in vivo*. *Mutat. Res., 101*, 151-164

Stern, R.M. (1982) Chromium compounds: production and occupational exposure. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 5-47

Stern, R.M., Thomsen, E. & Furst, A. (1984) Cr(VI) and other metallic mutagens in fly ash and welding fumes. *Toxicol. environ. Chem., 8*, 95-108

Stern, F.B., Beaumont, J.J., Halperin, W.E., Murthy, L.I., Hills, B.W. & Fajen, J.M. (1987) Mortality of chrome leather tannery workers and chemical exposures in tanneries. *Scand. J. Work Environ. Health, 13*, 108-117

Stoner, G.D., Shimkin, M.B., Troxell, M.C., Thompson, T.L. & Terry, L.S. (1976) Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res., 36*, 1744-1747

Stowe, H.D., Braselton, W.E., Kaneene, J.B. & Slanker, M. (1985) Multielement assays of bovine tissue specimens by inductively coupled argon plasma emission spectroscopy. *Am. J. vet. Res., 46*, 561-565

Sugiyama, M., Patierno, S.R., Cantoni, O. & Costa, M. (1986a) Characterization of DNA lesions induced by $CaCrO_4$ in synchronous and asynchronous cultured mammalian cells. *Mol. Pharmacol., 29*, 606-613

Sugiyama, M., Wang, X.-W. & Costa, M. (1986b) Comparison of DNA lesions and cytotoxicity induced by calcium chromate in human, mouse and hamster cell lines. *Cancer Res., 46*, 4547-4551

Sugiyama, M., Ando, A., Foruno, A., Furlong, N.B., Hidaka, T. & Ogura, R. (1987) Effects of vitamin E, vitamin B_2 and selenite on DNA single strand breaks induced by sodium chromate(VI). *Cancer Lett., 38*, 1-7

Sugiyama, M., Costa, M., Nakagawa, T., Hidaka, T. & Ogura, R. (1988) Stimulation of polyadenosine diphosphoribose synthesis by DNA lesions induced by sodium chromate in Chinese hamster V-79 cells. *Cancer Res., 48*, 1100-1104

Sullivan, C.P., Donachie, M.J., Jr & Morral, F.R. (1970) *Cobalt-base Superalloys 1970*, Brussels, Centre d'information du Cobalt, pp. 1-4, 38-44

Sunderman, F.W., Jr (1976) A review of the carcinogenicities of nickel, chromium and arsenic compounds in man and animals. *Prev. Med., 5*, 279-294

Sunderman, F.W., Jr (1984) Recent advances in metal carcinogenesis. *Ann. clin. Lab. Sci., 14*, 93-122

Sunderman, F.W., Jr (1986) Carcinogenicity and mutagenicity of some metals and their compounds. In: O'Neill, I.K., Schuller, P. & Fishbein, L., eds, *Environmental Carcinogens: Selected Methods of Analysis*, Vol. 8, *Some Metals: As, Be, Cd, Cr, Ni, Pb, Se, Zn* (IARC Scientific Publications No. 71), Lyon, IARC, pp. 17-43

Sunderman, F.W., Jr, Lau, T.J. & Cralley, L.J. (1974) Inhibitory effect of manganese upon muscle tumorigenesis by nickel subsulfide. *Cancer Res.*, *34*, 92-95

Sunderman, F.W., Jr, McCully, K.S., Taubman, S.B., Allpass, P.R., Reid, M.C. & Rinehimer, L.A. (1980) Manganese inhibition of sarcoma induction by benzo[*a*]pyrene in rats. *Carcinogenesis*, *1*, 613-620

Suzuki, Y. (1988) Reduction of hexavalent chromium by ascorbic acid in rat lung lavage fluid. *Arch. Toxicol.*, *62*, 116-122

Suzuki, Y., Homma, K., Minami, M. & Yoshikawa, H. (1984) Distribution of chromium in rats exposed to hexavalent chromium and trivalent chromium aerosols. *Ind. Health*, *22*, 261-277

Takahashi, W., Pfenninger, K. & Wong, L. (1983) Urinary arsenic, chromium, and copper levels in workers exposed to arsenic-based wood preservatives. *Arch. environ. Health*, *38*, 209-214

Takemoto, K., Kawai, H. & Yoshimura, H. (1977) Studies on the relation of chromium and pulmonary disease. II. Chromium contamination of lung cancer (Jpn.). In: *Proceedings of the 50th Annual Meeting of the Japan Association of Industrial Health*, Tokyo, Japan Association of Industrial Health, pp. 368-369

Tamaro, M., Banfi, E., Venturini, S. & Monti-Bragadin, C. (1975) Hexavalent chromium compounds are mutagenic for bacteria (Ital.). In: *Proceedings of the 17th National Congress of the Italian Society of Microbiology*, Padua, Società Italiana di Microbiologia, pp. 411-415

Tamino, G. & Peretta, L. (1980) Variations of DNA physico-chemical parameters in its interactions with mutagenic and/or carcinogenic compounds. In: Borsellino, A., Omodeo, P., Strom, R., Vecli, A. & Wamke, E., eds, *Developments in Biophysical Research*, New York, Plenum, pp. 335-346

Tamino, G., Peretta, L. & Levis, A.G. (1981) Effects of trivalent and hexavalent chromium on physico-chemical properties of mammalian cell nucleic acids and synthetic polynucleotides. *Chem.-biol. Interactions*, *37*, 309-319

Tandon, S.K., Mathur, A.K. & Gaur, J.S. (1977) Urinary excretion of chromium and nickel among electroplaters and pigment industry workers. *Int. Arch. occup. environ. Health*, *40*, 71-76

Taylor, F.H. (1966) The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. *Am. J. public Health*, *56*, 218-229

Teleky, L. (1936) Cancer in chromium workers (Ger.). *Dtsch. med. Wochenschr.*, *62*, 1353

Teraoka, H. (1987) Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. *Arch. environ. Health*, *36*, 155-165

Thomsen, E. & Stern, R.M. (1979) A simple analytical technique for the determination of hexavalent chromium in welding fumes and other complex matrices. *Scand. J. Work Environ. Health*, *5*, 386-403

Tkeshelashvili, L.K., Shearman, C.W., Zakour, R.A., Koplitz, R.M. & Loeb, L.A. (1980) Effects of arsenic, selenium and chromium on the fidelity of DNA synthesis. *Cancer Res., 40*, 2455-2460

Torgrimsen, T. (1982) Analysis of chromium. In: Langård, S., ed., *Biological and Environmental Aspects of Chromium*, Amsterdam, Elsevier, pp. 65-99

Tossavainen, A. (1976) Metal fumes in foundries. *Scand. J. Work Environ. Health, 2* (Suppl. 1), 42-49

Traul, K.A., Takayama, K., Kachevsky, V., Hink, R.J. & Wolff, J.S. (1981) A rapid in vitro assay for carcinogenicity of chemical substances in mammalian cells utilizing an attachment-independence endpoint. *J. appl. Toxicol., 1*, 190-195

Triebig, G., Zschiesche, W., Schaller, K.H., Weltle, D. & Valentin, H. (1987) Studies on the nephrotoxicity of heavy metals in iron and steel industries. In: Foá, V., Emmett, E.A., Maroni, M. & Colombi, A., eds, *Occupational and Environmental Chemical Hazards. Cellular and Biochemical Indices for Monitoring Toxicity*, Chichester, Ellis Horwood, pp. 334-338

Tsapakos, M.J. & Wetterhahn, K.E. (1983) The interaction of chromium with nucleic acids. *Chem.-biol. Interactions, 46*, 265-277

Tsapakos, M.J., Hampton, T.H. & Jennette, K.W. (1981) The carcinogen chromate induces DNA cross-links in rat liver and kidney. *J. biol. Chem., 256*, 3623-3626

Tsapakos, M.J., Hampton, T.H. & Wetterhahn, K.E. (1983a) Chromium(VI)-induced DNA lesions and chromium distribution in rat kidney, liver and lung. *Cancer Res., 43*, 5662-5667

Tsapakos, M.J., Hampton, T.H., Sinclair, P.R., Sinclair, J.F., Bement, W.J. & Wetterhahn, K.E. (1983b) The carcinogen chromate causes DNA damage and inhibits drug-mediated induction of porphyrin accumulation and glucuronidation in chick embryo hepatocytes. *Carcinogenesis, 4*, 959-966

Tso, W.-W. & Fung, W.-P. (1981) Mutagenicity of metallic cations. *Toxicol. Lett., 8*, 195-200

Tsuchiya, K. (1965) The relation of occupation to cancer, especially cancer of the lung. *Cancer, 18*, 136-144

Tsuda, H. & Kato, K. (1977) Chromosomal aberrations and morphological transformation in hamster embryonic cells treated with potassium dichromate *in vitro*. *Mutat. Res., 46*, 87-94

Tsuneta, Y. (1982) Investigations of the pathogenesis of lung cancer observed among chromate factory workers (Jpn.). *Hokkaido J. med. Sci., 57*, 175-187

Työsuojeluhallitus (National Finnish Board of Occupational Safety and Health) (1987) *HTP-Arvot 1987* (TLV-Values 1987) (Safety Bull. 25), Helsinki, p. 19

Udy, M.C. (1956) The physical and chemical properties of compounds of chromium. In: Udy, M.J., ed., *Chromium*, Vol. 1, New York, Reinhold, pp. 164-165, 206

Ulitzur, S. & Barak, M. (1988) Detection of genotoxicity of metallic compounds by the bacterial bioluminescence test. *J. Biolumin. Chemilumin., 2*, 95-99

Umeda, M. & Nishimura, M. (1979) Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. *Mutat. Res., 67*, 221-229

US Department of Commerce (1978) *US Imports for Consumption and General Imports* (FT 246/Annual 1977), Washington DC, Bureau of the Census, US Government Printing Office, pp. 231-233, 247, 293

US Environmental Protection Agency (1977) *Environmental Monitoring Near Industrial Sites, Chromium* (US NTIS PB-271 881), Washington DC

US Environmental Protection Agency (1978) *Reviews of the Environmental Effects of Pollutants. III. Chromium* (US EPA 600/1-78-023), Washington DC

US Environmental Protection Agency (1979) Facilities engaged in leather tanning and finishing; effluent limitations guidelines, pretreatment standards, and new source performance standards. *Fed. Regist., 44*, 38746-38776

US Environmental Protection Agency (1983) *Methods for the Chemical Analysis of Water and Wastes* (US EPA-600/4-79-020), Cincinnati, OH, Environmental Monitoring and Support Laboratory

US Environmental Protection Agency (1984) *Health Assessment Document for Chromium, Final Report* (US EPA-600/8-83-014F), Research Triangle Park, NC, Environmental Criteria and Assessment Office

US Environmental Protection Agency (1986) *Test Methods for Evaluating Solid Waste*, Vol. 1A, *Laboratory Manual Physical/Chemical Methods* (SW-846), 3rd ed., Washington DC, Office of Solid Waste and Emergency Response

US Environmental Protection Agency (1988) Maximum contaminant levels for inorganic chemicals. *US Code fed. Regul., Title 40*, Part 141.11, p. 530

US Occupational Safety and Health Administration (1987) Air contaminants. *US Code fed. Regul., Title 29*, Part 1910.1000, pp. 676-682

Uyeki, E.M. & Nishio, A. (1983) Antiproliferative and genotoxic effects of chromium on cultured mammalian cells. *J. Toxicol. environ. Health, 11*, 227-235

Van Bemst, A., Beaufils, B., Hewett, P.J. & Stern, R.M. (1983) Interlaboratory calibration of a standardized analytical method for hexavalent and total chromium in welding fumes. *Weld. World, 21*, 10-15

Vandenbalck, J.L. & Patriarche, G.J. (1987) Electrochemical micro-determinations of thallium(I) and chromium (VI) ions using DPASV and DP polarography. *Sci. total Environ., 60*, 97-104

Vandervort, R. & Cromer, J. (1975) *Peabody Galion Corp.* (Health Hazard Evaluation/Toxicity Determination Report NIOSH-TR-73-47-172), Cincinnati, OH, National Institute for Occupational Safety and Health

Venier, P., Montaldi, A., Majone, F., Bianchi, V. & Levis, A.G. (1982) Cytotoxic, mutagenic and clastogenic effects of industrial chromium compounds. *Carcinogenesis, 3*, 1331-1338

Venier, P., Montaldi, A., Busi, L., Gava, C., Zentilin, L., Tecchio, G., Bianchi, V. & Levis, A.G. (1985a) Genetic effects of chromium tannins. *Carcinogenesis, 6*, 1327-1335

Venier, P., Montaldi, A., Gava, G., Zentilin, L., Tecchio, G., Bianchi, V., Paglialunga, S. & Levis, A.G. (1985b) Effects of nitrilotriacetic acid on the induction of gene mutations and sister-chromatid exchanges by insoluble chromium compounds. *Mutat. Res., 156*, 219-228

Venier, P., Gava, C., Zordan, M., Bianchi, V., Levis, A.G., De Flora, S., Bennicelli, C. & Camoirano, A. (1987) Interactions of chromium with nitrilotriacetic acid (NTA) in the induction of genetic effects in bacteria. *Toxicol. environ. Chem.*, *14*, 201-218

Venier, P., Montini, R., Zordan, M., Clonfero, E., Paleologo, M. & Levis, A.G. (1989) Induction of SOS response in *Escherichia coli* strain PQ37 by 16 chemical compounds and human urine extracts. *Mutagenesis*, *4*, 51-57

Venitt, S. (1986) Genetic toxicology in chromium and nickel compounds. In: Stern, R.M., Berlin, A., Fletcher, A.C. & Järvisalo, J., eds, *Health Hazards and Biological Effects of Welding Fumes and Gases*, Amsterdam, Excerpta Medica, pp. 249-266

Venitt, S. & Bosworth, D. (1983) The development of anaerobic methods for bacterial mutation assays: aerobic and anaerobic fluctuation test of human faecal extracts and reference mutagens. *Carcinogenesis*, *4*, 339-345

Venitt, S. & Levy, S.L. (1974) Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. *Nature*, *250*, 493-495

Verschoor, M.A., Bragt, P.C., Herber, R.F.M., Zielhuis, R.L. & Zwennis, W.C.M. (1988) Renal function of chrome-plating workers and welders. *Int. Arch. occup. environ. Health*, *60*, 67-70

Versieck, J., Hoste, J., Barbier, F., Steyaert, H., De Rudder, J. & Michels, H. (1978) Determination of chromium and cobalt in human serum by neutron activation analysis. *Clin. Chem.*, *24*, 303-308

Vieux, B., Garland, J., Warren, G. & Rogers, S. (1986) Mutagenic mechanisms of substitutionally inert metal complexes of PtII, PtIV, CrIII and potassium dichromate (Abstract No. PM 30). In: Ramel, C., Lambert, B. & Magnusson, J., eds, *Proceedings of the Fourth International Conference on Environmental Mutagens, Stockholm, June 24-28 1985*, New York, Alan R. Liss, p. 262

Vigliani, E.C. & Zurlo, N. (1955) Experiences of the 'Clinica del Lavoro' with some MAKs of industrial toxins (Ger.). *Arch. Gewerbepathol. Gewerbehyg.*, *13*, 528-534

Vos, G., Hovens, J.P.C. & Hagel, P. (1986) Chromium, nickel, copper, zinc, arsenic, selenium, cadmium, mercury and lead in Dutch fishery products 1977-1984. *Sci. total Environ.*, *52*, 25-40

Wacker, W.E.C. & Vallee, B.L. (1959) Nucleic acids and metals. I. Chromium, manganese, nickel, iron and other metals in ribonucleic acid from diverse biological sources. *J. biol. Chem.*, *234*, 3257-3262

Wahlberg, J.E. & Skog, E. (1963) The percutaneous absorption of sodium chromate (^{51}Cr) in the guinea-pig. *Acta dermatovenerol.*, *43*, 102-108

van der Wal, J.F. (1985) Exposure of welders to fumes, Cr, Ni, Cu and gases in Dutch industries. *Ann. occup. Hyg.*, *29*, 377-389

Wallach, S. & Verch, R.L. (1984) Placental transport of chromium. *J. Am. Coll. Nutr.*, *3*, 69-74

Wapner, K.L., Morris, D.M. & Black, J. (1986) Release of corrosion products by F-75 cobalt base alloy in the rat. II: Morbidity apparently associated with chromium release *in vivo*: a 120-day rat study. *J. biomed. Mat. Res.*, *20*, 219-233

Warner, J.S. (1984) Occupational exposure to airborne nickel in producing and using primary nickel products. In: Sunderman, F.W., Jr, ed., *Nickel in the Human Environment* (IARC Scientific Publications No. 53), Lyon, IARC, pp. 419-437

Warren, G., Schultz, P., Bancroft, D., Bennett, K., Abbott, E.H. & Rogers, S. (1981) Mutagenicity of a series of hexacoordinate chromium(III) compounds. *Mutat. Res., 90*, 111-118

Watanabe, S. & Fukuchi, Y. (1984) Cancer mortality of chromate-producing workers. In: Eustace, I.E., ed., *XXI International Congress on Occupational Health, 9-14 September, 1984, Dublin, Ireland*, London, Permanent Commission and International Association on Occupational Health, p. 442

Watanabe, M., Takayama, Y.-I., Koike, M. & Yamamoto, M. (1985) In vivo clastogenicity of lead chromate in mice. *Tohoku J. exp. Med., 146*, 373-374

Waterhouse, J.A.H. (1975) Cancer among chromium platers (Abstract). *Br. J. Cancer, 32*, 262

Watling, H.R. & Watling, R.J. (1982) Metal concentrations in oysters from the southern African coast. *Bull. environ. Contam. Toxicol., 28*, 460-466

Wayne Pigment Corp. (1985a) *MSDS: Molybdate Orange Light 64*, Milwaukee, WI

Wayne Pigment Corp. (1985b) *MSDS: Molybdate Orange Dark 664*, Milwaukee, WI

Weast, R.C., ed. (1985) *CRC Handbook of Chemistry and Physics*, 66th ed., Boca Raton, FL, CRC Press, pp. B-70, B-75, B-82, B-88—B-89, B-106, B-127, B-142, B-147, B-159

Wedrychowski, A., Schmidt, W.N. & Hnilica, L.S. (1986a) DNA-protein crosslinking by heavy metals in Novikoff hepatoma. *Arch. Biochem. Biophys., 251*, 397-402

Wedrychowski, A., Schmidt, W.N., Ward, W.S. & Hnilica, L.S. (1986b) Cross-linking of cytokeratins to DNA *in vivo* by chromium salt and *cis*-diamminedichloroplatinum(II). *Biochemistry, 25*, 1-9

Westbrook, J.H. (1979) Chromium and chromium alloys. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 6, New York, John Wiley & Sons, pp. 54-82

Wetterhahn-Jennette, K. (1981) The role of metals in carcinogenicity: biochemistry and metabolism. *Environ. Health Perspect., 40*, 233-252

Whiting, R.F., Stich, H.F. & Koropatnick, D.J. (1979) DNA damage and DNA repair in cultured human cells exposed to chromate. *Chem.-biol. Interactions, 26*, 267-280

Whitney, R.G. & Risby, T.H. (1975) *Selected Methods in the Determination of First Row Transition Metals in Natural Fresh Water*, University Park, PA, Pennsylvania University Press

Wiegand, H.J., Ottenwälder, H. & Bolt, H.M. (1984a) Disposition of intratracheally administered chromium(III) and chromium(VI) in rabbits. *Toxicol. Lett., 22*, 273-276

Wiegand, H.J., Ottenwälder, H. & Bolt, H.M. (1984b) The reduction of chromium (VI) to chromium (III) by glutathione: an intracellular redox pathway in the metabolism of the carcinogen chromate. *Toxicology, 33*, 341-348

Wild, D. (1978) Cytogenetic effects in the mouse of 17 chemical mutagens and carcinogens evaluated by the micronucleus test. *Mutat. Res., 56*, 319-327

Windholz, M., ed. (1983) *The Merck Index*, 10th ed., Rahway, NJ, Merck & Co., pp. 76-77, 140, 229, 315-319, 777, 1100, 1233-1234, 1267, 1456-1457

Wong, M.H., Choy, C.K., Lau, W.M. & Cheung, Y.H. (1981) Heavy-metal contamination of the Pacific oysters (*Crassostrea gigas*) cultured in Deep Bay, Hong Kong. *Environ. Res.*, *25*, 302-309

World Health Organization (1970) *European Standards for Drinking Water*, 2nd ed., Geneva, p. 33

World Health Organization (1988) *Chromium* (Environmental Health Criteria 61), Geneva, International Programme on Chemical Safety

Yagi, T. & Nishioka, H. (1977) DNA damage and its degradation by metal compounds. *Sci. Eng. Rev. Doshisha Univ.*, *18*, 1-8

Yamamoto, A., Wada, O. & Ono, T. (1981) A low-molecular-weight, chromium-binding substance in mammals. *Toxicol. appl. Pharmacol.*, *59*, 515-523

Yassi, A. & Nieboer, E. (1988) Carcinogenicity of chromium compounds. In: Nriagu, J.O. & Nieboer, E., eds, *Chromium in the Natural and Human Environments*, New York, John Wiley & Sons, pp. 443-495

Yasuda, Y. (1980) Abnormalities in mouse sperm and sterility after injection of potassium bichromate (Abstract). *Teratology*, *22*, 13A

Yunusova, K.K. & Pavlovskaya, G.S. (1975) The effect of the chromium plating regimen on the protective properties of chromine (Russ.). *Zashch. Met.*, *11*, 248-250 [*Chem. Abstr.*, *83*, 123027k]

Zakour, R.A. & Glickman, B.W. (1984) Metal-induced mutagenesis in the *lacI* gene of *Escherichia coli*. *Mutat. Res.*, *126*, 9-18

Zey, J.N. & Aw, T.-C. (1984) *American Transportation Corp.* (*Health Hazard Evaluation Report No. 82-025-1413*), Cincinnati, OH, National Institute for Occupational Safety and Health

Zhang, X., Jixun, D. & Tsungci, F. (1984) The mutagenic effect of hexavalent chromium and antimutagenic effect of cysteine detected by the Tradescantia-micronucleus technique (Chin.). *Zhandong Haiyang Xueyan Xuebao*, *14*, 81-83

Zimmering, S. (1983) The *mei-9*^{a} test for chromosome loss in *Drosophila*: a review of assays of 21 chemicals for chromosome breakage. *Environ. Mutagenesis*, *5*, 907-921

Zober, A. (1979) On the problems of evaluating bronchial carcinoma after exposure to chromium compounds (Ger.). *Int. Arch. occup. environ. Health*, *43*, 107-121