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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHROMIUM IN THE UNITED STATES

Chromium is a naturally occurring element present in the earth's crust. Chromium is released to the environment from natural and anthropogenic sources, with the largest release occurring from industrial releases. The industries with the largest contribution to chromium release include metal processing, tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production. The estimated atmospheric concentrations of chromium in U.S. urban and nonurban areas typically contains mean total chromium concentrations ranging from 5 to 525 ng/m³. The levels of chromium in U.S. fresh waters typically range from <1 to 30 µg/L, with a median value of 10 µg/L. Typical U.S. drinking water supplies contain total chromium levels within a range of 0.2–35 µg/L however, most supplies in the United States contain <5 µg/L of chromium. Recent monitoring data of drinking water supplies in California indicated that 86% of the sources tested had levels of chromium (reported for chromium(VI)) below 10 µg/L. U.S. soil levels of total chromium range from 1 to 2,000 mg/kg, with a mean level of 37 mg/kg. In ocean water, the mean chromium concentration is 0.3 µg/L.

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products or soils that contain chromium. The primary route of nonoccupational workers, however, is food ingestion. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels ranging from <10 to 1,300 µg/kg. Present-day workers in chromium-related industries can be exposed to chromium concentrations 2 orders of magnitude higher than the general population.

2.2 SUMMARY OF HEALTH EFFECTS

Chromium as an Essential Nutrient. Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM) of the National Research Council (NRC) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults. IOM reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–0.16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day. Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also

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referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate. The function of chromodulin, an oligopeptide complex containing four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven.

Although the Institute of Medicine considers chromium(III) an essential element, some critics question its essentiality. Reports of chromium(III) deficiency are rare and there is no recognized disease that is attributed to chromium deficiency as there is with most other essential minerals (e.g., Wilson's disease for people with copper deficiency). Evidence of overt signs of apparent chromium deficiency in humans is limited to a few case reports. In one such case report, a woman receiving total parenteral nutrition for 3 years exhibited peripheral neuropathy, weight loss, and impaired glucose metabolism. Administration of insulin did not improve glucose tolerance. Administration of 250 µg/day chromium without exogenous insulin resulted in normal glucose tolerance of an oral load of glucose and the absence of peripheral neuropathy. Thus, direct evidence of chromium(III) deficiency in humans is lacking. In animals, severe chromium deficiency is also difficult to induce, but when it was induced hyperglycemia, decreased weight gain, elevated serum cholesterol levels, aortic plaques, corneal opacities, impaired fertility, and lethality were observed. Administration of inorganic trivalent chromium compounds or extracts of brewers' yeast resulted in decreased blood glucose levels and cholesterol levels and regression of atherosclerotic plaques. Improved insulin sensitivity also resulted in an increased incorporation of amino acids into proteins and cell transport of amino acid in rats receiving supplemental chromium. Thus, whether chromium is a true essential element or a pharmacological agent is still under debate.

Studies have shown that chromium supplementation (Brewer's yeast, extracts of brewer's yeast, synthetic chromium compounds with biological activity, chromium(III) picolinate, and inorganic trivalent chromium) in deficient and marginally deficient subjects can result in improved glucose, protein, and lipid metabolism. In general, these studies have demonstrated improved glucose tolerance to an oral glucose load in Type II diabetics (adult onset) and nondiabetic elderly subjects receiving a 4–200 µg/day chromium supplement and improved plasma lipid profiles (e.g., decreased total cholesterol, LDL-cholesterol, and serum lipids and increased in HDL-cholesterol); improvements in serum lipids and cholesterol levels may be secondary to the decreased serum glucose levels.

Chromium picolinate has been used as a dietary supplement to aid in weight loss and increase lean body mass; however, the role of chromium in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature.

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Numerous studies have evaluated the relationship between weight loss or increases in lean body mass in active and sedentary adults and chromium picolinate supplementation, with mixed results reported. Information on adverse health effects of chromium(III) compounds, including dietary supplements, in humans and animals is reviewed below. However, based on a limited number case studies reporting adverse effects in humans ingesting high-dose chromium(III) supplements, individuals using chromium supplements are cautioned to avoid taking more than recommended doses.

Chromium Toxicokinetics. The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. For inhaled chromium compounds of any valence state, the amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g., CrCO_3), and is higher for soluble chromium(VI) compounds (e.g., $\text{K}_2\text{Cr}_2\text{O}_7$) than soluble chromium(III) (e.g., CrCl_3). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by nutritional status. The absorption fraction is higher when dietary intakes are lower. Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged.

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics of chromium. Chromium(VI) is reduced to chromium(III) via the intermediate forms of chromium(V) and chromium(IV). Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and deoxyribonucleic acid (DNA), and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms stable complexes with hemoglobin and other intracellular proteins, which are retained for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Chromium has been shown to be secreted in bile of animals following parenteral (e.g., intravenous) injection of chromium(VI) or chromium(III) compounds. Chromium can also be eliminated by transfer to hair and nails.

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Health Effects of Chromium. The health effects associated with exposures to chromium(VI), chromium(III) and chromium (IV) are reviewed in detail in Chapter 3. In general, chromium(VI) compounds are more toxic than chromium(III) compounds. The higher toxic potency of chromium(VI) compared to chromium(III) is complex. Chromium(VI) enters cells by facilitated uptake, whereas chromium(III) crosses cell membranes by simple diffusion; thus, cellular uptake of chromium(VI) is more effective than the uptake of chromium(III). Furthermore, in biological systems, reduction of chromium(VI) to chromium(III) results in the generation of free radicals, which can form complexes with intracellular targets. Health effects of chromium compounds can vary with route of exposure, with certain effects specific for the portal of entry. For example, respiratory effects are associated with inhalation of chromium compounds, but not with oral and dermal exposures, and gastrointestinal effects are primarily associated with oral exposure. However, as described below, effects of chromium are not limited to the portal of entry, with hematological, immunological, and reproductive systems also identified as targets for chromium. In addition to noncancer health effects, results of occupational exposure studies and chronic-duration animal studies indicate that inhalation and oral exposures to chromium(VI) compounds are associated with respiratory and gastrointestinal system cancers, respectively (see discussion under chromium(VI) below for additional information).

Chromium(VI)

The primary effects associated with exposure to chromium(VI) compounds are respiratory, gastrointestinal, immunological, hematological, reproductive, and developmental. In addition, dermal and ocular irritation may occur from direct contact. Based on available dose-response data in humans and animals, the most sensitive noncancer effects of chromium(VI) compounds are respiratory (nasal and lung irritation, altered pulmonary function), gastrointestinal (irritation, ulceration and nonneoplastic lesions of the stomach and small intestine), hematological (microcytic, hypochromic anemia), and reproductive (effects on male reproductive organs, including decreased sperm count and histopathological change to the epididymis). As reviewed below, respiratory and gastrointestinal effects appear to be portal-of-entry effects for inhalation and oral exposure, respectively. Similarly, chromium sensitization, the major immunological effect of chromium(VI), typically presents as allergic contact dermatitis resulting from dermal exposures in sensitized individuals, although respiratory effects of sensitization (asthma) may also occur. Accidental or intentional ingestion of extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment.

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Respiratory Effects. The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects have been observed in workers in the following chromium-related industries: chrome plating, chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. Intermediate- and chronic-duration exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia. In some chromium-sensitive patients, inhalation of airborne chromium(VI) compounds in the workplace has resulted in asthma. Nasal irritation and mucosal atrophy and decreases in pulmonary function have occurred at occupational exposure levels ≥ 0.002 mg chromium(VI)/m³ as chromium trioxide mist. Autopsies of humans who died from cardiopulmonary arrest after ingesting chromium(VI) compounds have revealed pleural effusion, pulmonary edema, bronchitis, and acute bronchopneumonia. Respiratory effects due to ingestion of nonlethal doses are not likely to occur. It is not certain whether skin contact with chromium compounds could result in respiratory effects.

Adverse effects on the respiratory system following inhalation exposure to chromium(VI) have also been observed in animals. Acute- and intermediate-duration exposure to moderate levels of chromium(VI) compounds generally caused mild lung irritation, accumulation of macrophages, hyperplasia, inflammation, and impaired lung function. A lowest-observed-adverse-effect level (LOAEL) of 0.025 mg chromium(VI)/m³ as potassium dichromate particles for increased percentage of lymphocytes in bronchoalveolar lavage (BAL) fluid in rats exposed for 28 or 90 days was identified. Obstructive respiratory dyspnea at ≥ 0.2 mg chromium(VI)/m³, fibrosis at ≥ 0.1 mg chromium(VI)/m³, and hyperplasia at ≥ 0.05 mg chromium(VI)/m³ were found in the lungs of rats exposed to sodium dichromate for 30 or 90 days. The fibrosis and hyperplasia were reversible. Increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and β -glucuronidase were observed in the bronchoalveolar lavage fluid. Nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, and emphysema developed in mice exposed to chromium trioxide mists for 1 year. Mice exposed chronically to 4.3 mg chromium(VI)/m³ as calcium chromate also had epithelial necrosis and hyperplasia of the bronchiolar walls.

Gastrointestinal Effects. Acute oral exposure of humans to lethal or near-lethal doses of chromium(VI) has produced adverse gastrointestinal effects, including abdominal pain, vomiting,

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gastrointestinal ulceration, hemorrhage and necrosis, and bloody diarrhea. Gastrointestinal effects have also been reported in association with chronic oral exposure of humans to chromium(VI). In a cross-sectional study conducted in 1965 of 155 people whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. Epigastric pain, irritation, and ulceration have been reported in occupational studies of chrome plating and chromate production workers. Exposures in these studies included inhalation and ingestion of chromium (e.g., mucocilliary clearance of inhaled chromium particles to the gastrointestinal tract and/or ingestion secondary to hand-to-mouth activity) and outcomes may have been influenced by other factors, such as stress and diet. Gastrointestinal effects from dermal exposures or absorption of inhaled chromium(VI) are not anticipated.

Studies in animals show that the gastrointestinal system is a primary target of intermediate- and chronic-duration oral exposure to chromium(VI). Adverse effects were observed in the gastrointestinal tract of F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with LOAEL values of 3.5 mg chromium(VI)/kg/day for duodenal histiocytic infiltration of the duodenum in male and female rats and of 3.1 mg chromium(VI)/kg/day for epithelial hyperplasia in mice. At a higher dose (20.9 mg chromium(VI)/kg/day), more severe effects (ulcer and epithelial hyperplasia and metaplasia of the glandular stomach) were observed in rats. Histopathological changes of the duodenum (epithelial hyperplasia and histiocytic cellular infiltrate) were also reported in a 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, a LOAEL values of 2.8 mg chromium(VI)/kg/day. After exposure for 2 years, histopathological changes were observed in the gastrointestinal tract of rats and mice. In male and female rats exposed to 0.77 and 2.4 chromium(VI)/kg/day, respectively, histiocytic infiltration of the duodenum was observed. In mice, duodenal epithelial hyperplasia was observed in males and females at 0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration of the duodenum was observed in males at 2.4 mg chromium(VI)/kg/day and in females at 3.1 mg chromium(VI)/kg/day.

Results of intermediate-duration inhalation studies in animals yield mixed results regarding the potential for gastrointestinal effects. Although rats exposed by inhalation to ≤ 0.2 mg chromium(VI)/m³ as sodium dichromate for ≤ 90 days did not have histopathological changes in the gastrointestinal tract, mice exposed chronically to 4.3 mg chromium(VI)/m³ were reported to have occasional small ulcerations in the stomach and intestinal mucosa; however, the potential of oral exposure via grooming behavior cannot be excluded.

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Immunological Effects. Exposure to chromium(VI) compounds may lead to allergic sensitization in some individuals. Sensitization to chromium is produced through two types of hypersensitivity reactions: type I, an immediate onset, IgE-mediated immune mechanism, and type IV, a delayed, cell-mediated immune mechanism. Following an induction phase during which the individual becomes sensitized, subsequent exposures result in an allergic response, with symptoms typically presenting as dermatitis or asthma. Sensitization may occur from inhalation, oral, and/or dermal exposure. Estimates of the prevalence of chromium sensitivity in the general U.S. population range from 0.08 to 7%, depending upon the population evaluated. For dermal responses, the allergic response following direct skin contact with chromium compounds is characterized by eczema or dermatitis; typically, chromium-induced allergic contact dermatitis is isolated to areas at the site of contact, rarely occurring in areas remote from the point of contact. However, oral exposure to chromium(VI) has been shown to exacerbate dermatitis of sensitive individuals. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin. Exposure to chromium compounds in chromium-related occupations appears to be the major cause of chromium contact dermatitis. Patch testing has identified chromium-sensitized workers in the printing and lithography industry, in automobile factories where assemblers handled nuts, bolts, and screws, in wet sandpapering of primer paint where workers were exposed to zinc chromate, in the cement industry, in railroad systems and diesel locomotive repair shops where antirust diesel-engine coolants and radiator fluids contained sodium chromate, in tanneries, and in the welding, plating, wood, and paper industries. Other sources of chromium that have resulted in chromium sensitivity include dichromate-containing detergents and bleach, glues, machine oils, foundry sand, match heads, boiler linings, and magnetic tapes. Exposure to low levels of chromium as found in consumer products could result in sensitization or a reaction in sensitized individuals; therefore, in hypersensitive individuals may develop rashes and erythema from contact with consumer products containing chromium. Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals.

Several studies have estimated the exposure level required to elicit a dermal response in chromium-sensitized individuals; exposure levels of 4–25 ppm produced sensitization and elicitation of chromium-induced allergic dermatitis. However, confounding factors, such as variability in testing methods (including different chromium compounds used in challenge testing) and individual sensitivity, complicate interpretation of results. Furthermore, the response of an individual to dermal challenge may vary over time due to changes in exposure to the sensitizing agents; if an individual is removed from

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exposure, circulating IgE levels may decrease, resulting in decreased sensitivity to dermal challenge. Therefore, it is anticipated that the exposure level required to elicit a dermal response in sensitized individuals will be highly variable.

Asthmatic attacks have occurred in chromium-sensitive individuals exposed by inhalation in occupational settings to chromium trioxide vapors and chromium fumes from stainless steel welding. When challenged with sodium chromate or potassium dichromate via nebulizer, chromium-sensitive patients displayed anaphylactoid reactions, characterized by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory volume. While chromium-induced asthma might occur in some sensitized individuals exposed to elevated concentrations of chromium in air, the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

Studies in animals also indicate that the immune system is a target for inhaled and ingested chromium(VI) compounds. Effects reported include stimulation of the humoral immune system and increased phagocytic activity of macrophages, increased proliferative responses of splenocytes to T- and B-cell mitogens and to the antigen mitomycin C and histopathological alteration (histiocytic cellular infiltration) of pancreatic lymph nodes; contact dermatitis has been elicited in guinea pigs and mice.

Hematological Effects. As discussed above (*Chromium Toxicokinetics*), chromium(VI) is distributed to and accumulated by the erythrocyte; once inside the cell, it is rapidly reduced to chromium(III) via the reactive intermediates chromium(V) and chromium(IV), and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is relatively stable and remains sequestered within the cell over the life-span of the erythrocyte, with approximately 1% of chromium eluting from the erythrocyte daily. Occupational studies and other studies in humans have not consistently reported hematological effects, although microcytic, hypochromic anemia has been reported in several recent animals studies on chromium(VI) compounds (detailed discussion follows). However, it is possible that small, exposure-related changes in hematological parameters may not have been detected in occupational exposure studies, if values were within normal clinical ranges. Hematological findings in humans exposed to lethal doses of chromium(VI) compounds are difficult to interpret in the context of multiple systemic effects observed leading up to death, including hemorrhage.

Results of acute-, intermediate-, and chronic-duration studies in animals identify the hematological system as one of the most sensitive effects of oral exposure to chromium(VI). Microcytic, hypochromic

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anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in rats and mice orally exposed to chromium(VI) compounds for exposure durations ranging from 4 days to 1 year. The severity of anemia exhibited dose- and duration-dependence, with maximum effects observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks–1 year), anemia is less severe, presumably due to compensatory hematopoietic responses. In general, effects observed in rats were more severe than those in mice.

Acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, produced a slight, but statistically significant decrease (2.1%) in MCH in rats exposed to 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (≥ 7.4 mg chromium(VI)/kg/day), additional decreases in MCH and decreased MCV were observed. Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively; a no-observed-adverse-effect level (NOAEL) was not established. Although the magnitude of changes to hematological parameters after acute exposure was minimal, since severe effects on hematological parameters were observed following intermediate exposure durations, with severity peaking at exposure durations of 22 days to 3 months, the minimal hematological alterations observed following acute exposure are considered to be indicative of adverse hematological effects.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days. Decreased Hct, Hgb, MCV, and MCH occurred at ≥ 0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day. After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days. Hematological effects, including decreased hematocrit, hemoglobin, and erythrocyte count, have also been reported in rats exposed to chromium trivalent oxide mist for 90 days, with a LOAEL value of 0.23 mg chromium(VI)/m³.

Reproductive Effects. Results of studies in humans and animals suggest that chromium(VI) causes adverse reproductive effects, although evidence from studies in animals is much stronger than from studies in humans. Although information regarding reproductive effects in humans is limited, the following effects have been reported: a significant increase in the number of morphologically abnormal sperm; significant decreases on sperm count and motility; and greater incidences of complications during

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pregnancy and childbirth (toxicosis and postnatal hemorrhage). There no evidence of reproductive effects in humans environmentally exposed to chromium(VI).

Studies in laboratory animals show that acute- and intermediate-duration exposure to chromium(VI) produces adverse reproductive effects, with the male reproductive system exhibiting the highest sensitivity. Following a 6-day gavage administration of ≥ 5.2 mg chromium(VI)/kg/day as chromic acid to Wister rats, decreased sperm count, increased percentage of abnormal sperm, and morphological changes to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed (observations were made 6 weeks after completion of treatment); a NOAEL was not defined in this study. The male reproductive system was identified as a target for oral chromium(VI) exposure in intermediate-duration studies in monkeys, rats, and rabbits. Decreased sperm count and motility and histopathological changes to the epididymis (ductal obstruction, development of microcanals, depletion of germ cells, hyperplasia of Leydig cells, and Sertoli cell fibrosis) have been reported in monkeys exposed to 2.1 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Effects on male reproductive organs and sexual behavior in rats and mice have been reported at doses of ≥ 2.6 mg chromium(VI)/kg/day.

In NTP studies designed to confirm or refute these findings of one study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated. Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects at daily doses up to 32.2 mg chromium(VI)/kg/day. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months.

Other reproductive effects reported in rats and mice include altered weights of female reproductive organs, decreased number of follicles and ova, increased pre- and/or postimplantation losses, and increased resorptions at doses of ≥ 5 mg chromium(VI)/kg/day. Mixed results have been found in studies designed to assess the effects of chromium(VI) exposure on fertility. No effects on fertility were observed in mice exposed to ≤ 37 mg chromium(VI)/kg/day as potassium dichromate in the diet. Decreased mating and fertility, increased preimplantation losses, and increased resorptions have been observed in rats and mice exposed to ≥ 37 mg chromium(VI)/kg/day or 52 mg chromium(VI)/kg/day as

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potassium dichromate in drinking water for 20 or 90 days prior to mating. Pre- and postimplantation loss and decreased litter size was also observed in mice exposed to ≥ 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water throughout gestation. Significant decreases in the number of implantations and viable fetuses were observed when male mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks were mated with unexposed female mice; however, sperm count was not measured and the classification of non-viable fetuses was not presented in this report. However, a similarly designed study did not find any alterations in the number of implantations or viable fetuses in unexposed female rats mated with males exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks. It is not known if the species difference contributed to these conflicting results. Decreases in the number of implantations and viable fetuses and an increase in the number of animals with resorptions were also seen in females exposed for 12 weeks to 6 mg chromium(VI)/kg/day as potassium dichromate mated with unexposed males.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to chromium compounds. A number of oral exposure animal studies have shown that chromium(VI) is a developmental toxicant following premating and/or *in utero* exposure, or lactational exposure. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed at relatively high doses (e.g., ≥ 35 mg chromium(VI)/kg/day). In mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3, a decreased number of pregnancies were observed; exposure on gestational days 4–6 resulted in decreased number of viable fetuses and increased number of resorptions, but did not alter the number of pregnancies. Exposure of female rats to ≥ 37 mg chromium(VI)/kg/day and mice to ≥ 52 mg chromium(VI)/kg/day to potassium dichromate(VI) in drinking water for 20 or 90 days followed by mating to unexposed males resulted in fetal mortality (postimplantation losses, resorptions, and decreased number of live fetuses), decreased growth (decreased fetal body weights and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails. Similar effects (increased resorptions, increased postimplantation losses, subdermal hemorrhages, decreased cranial ossification, tail kinking, and decreased fetal body weight and decreased crown-rump length) were observed in the offspring of mice exposed to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation. In mice exposed to 53 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestational days 6–14, fetal mortality, subdermal hemorrhagic patches, and reduced ossification were observed in the offspring.

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Impaired development of the reproductive system (delayed vaginal opening) was observed in the offspring of mice exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on gestation day 12 through lactation day 20. Delayed vaginal opening was also reported in offspring of rats exposed to ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on postnatal days 1–21. Perinatal exposure to doses ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate in the drinking water caused oxidative stress in the uterus, liver, kidney, and bone from the offspring. Microscopic examination of the kidney, liver, and bone showed morphological alterations in the three tissues. A single study reported that gavage administration of 4.4 mg chromium(VI)/kg/day as potassium dichromate to neonatal rats reduced mandibular growth and delayed tooth eruption.

Dermal Effects. Chromium(VI) compounds can produce effects on the skin and mucous membranes. These include irritation, burns, ulcers, and an allergic type of dermatitis. Irritation of respiratory mucosal tissues, nasal septum ulcers, and perforation are reviewed above under Respiratory Effects and allergic dermatitis is reviewed above under Respiratory Effects and Immunological Effects. Most dermal effects reported were either due to occupational intermediate-chronic exposure or acute exposure to high levels of chromium compounds. Environmental exposure to chromium compounds is not likely to result in dermal effects. Acute dermal exposure to chromium(VI) compounds can cause skin burns. Application of a salve containing potassium chromate to the skin of some individuals to treat scabies resulted in necrosis and sloughing of the skin, and some individuals even died as a result of infections of these areas. A worker whose skin came into direct contact with the chromic acid as a result of an industrial accident developed extensive skin burns.

Although skin contact with chromate salts may cause rashes, untreated ulcers or sores (also called chrome holes) on the skin can be a major problem because they can deeply penetrate the skin with prolonged exposure. For example, in an early case of a tannery worker, the penetration extended into the joint, necessitating amputation of the finger. However, chrome sores heal if exposure is discontinued, leaving a scar. Chrome sores are more often associated with occupational exposure to chromium(VI) compounds. Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to the development. Industries that have been associated with the development of chrome sores in workers include chromate and dichromate production, chrome plating, leather tanning, planographic printing, and chromite ore processing. Among the chromium(VI) compounds that workers in these industries are exposed to are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate.

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In addition, tonsillitis, pharyngitis, atrophy of the larynx, and irritation and ulceration of mouth structures and buccal mucosa can occur from exposure to high levels of chromium(VI) compounds. These effects were seen in workers in chrome plating plants, where excessively high concentrations of chromium trioxide fumes were present. High incidences of inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontitis were also observed in chromate production workers. Oral doses of potassium dichromate exacerbated the dermatitis of chromium sensitized individuals.

Dermal effects observed in animals after direct application of potassium dichromate to their skin include inflammation, necrosis, corrosion, eschar formation, and edema in rabbits and skin ulcers in guinea pigs.

Ocular Effects. Ocular effects can occur as a result of direct contact of eyes with chromium(VI) compounds. Effects reported include corneal vesication in a man with ocular exposure to a drop or crystal of potassium dichromate and congestion of the conjunctiva, discharge, corneal scar, and burns in chromate production workers as a result of accidental splashes.

Genotoxicity. Numerous studies have evaluated the genotoxicity of chromium(VI) compounds. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Although most of the older occupational exposure studies gave negative or equivocal results, more recent studies have identified chromosomal effects in exposed workers. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in human cell lines, mammalian cells, yeast and bacteria, and studies in cell-free systems.

Cancer. Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, and ferrochromium alloy production. Numerous studies of cancer mortality among chromate production workers have been reported. Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed. In chromate pigment and chrome plating workers,

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elevated lung cancer rates in comparison to reference populations (e.g., standard mortality ratios [SMRs]) and increased lung cancer rates in association with increased potential for chromium exposure (e.g., job type, employment duration) have been reported. Workers in the stainless steel welding and ferrochromium alloy industries are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in these populations have been mixed. Environmental exposure of humans to chromium(VI) in drinking water resulted in statistically significant increases in stomach cancer. However, a re-analysis of these data using a more relevant control group did not find a significant increase in stomach cancer. Another study reported an increased incidence of liver, lung, and kidney and urogenital organ cancers in residents living in an area of Greece with elevated chromium(VI) levels in the drinking water. Two other ecological studies have not found elevated cancer risks in populations with contaminated drinking water.

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m³ as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls. In addition, numerous animal studies using the intratracheal, intrapleural, and intrabronchial routes of exposure show that chromium(VI) produces respiratory tract tumors. However, no carcinogenic effects were observed in rats, rabbits, or guinea pigs exposed to 1.6 mg chromium(VI)/m³ as potassium dichromate or chromium dust 4 hours/day, 5 days/week.

Exposure of rats and mice to sodium dichromate dihydrate in drinking water for 2 years resulted in cancers of the gastrointestinal tract. In male and female rats, the incidences of neoplasms of the squamous epithelium of the oral mucosa and tongue were significantly increased in males (7.0 mg chromium(VI)/kg/day) and females (5.9 mg chromium(VI)/kg/day); in mice, the incidence of neoplastic lesions of the small intestine (duodenum, jejunum, and ileum) was increased in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. The National Toxicology Program concluded that results demonstrate clear evidence of carcinogenic activity in male and female F344/N rats (increased incidences of squamous cell neoplasms of the oral cavity) and in male and female B6C3F1 mice (increased incidences of neoplasms of the duodenum, jejunum, or ileum). Mice exposed to chromium(VI) as potassium chromate (9 mg chromium(VI)/kg/day) in drinking water for three generations (880 days) showed statistically significant increases in the incidence of forestomach adenoma or carcinomas of the forestomach and in the incidence of forestomach adenomas alone, compared to control; however, study authors concluded that evidence of carcinogenicity was equivocal.

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NTP lists certain chromium compounds as substances that are *known to be human carcinogens*. This classification is based on sufficient evidence for a number of chromium(VI) compounds (calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate). The International Agency for Research on Cancer (IARC) classified chromium(VI) as *carcinogenic to humans (Group 1)* and metallic chromium and chromium(III) compounds as *not classifiable as to their carcinogenicity to humans (Group 3)*. EPA has classified chromium(VI) as *a known human carcinogen* by the inhalation route of exposure.

Chromium(III)

Although much less information is available on the health effects of chromium(III) compounds compared to that for chromium(VI) compounds, chromium(III) compounds appear to be less toxic than chromium(VI) compounds. Health effects associated with exposure to chromium(III) compounds have been reported in studies of occupationally exposed populations and individuals; however, interpretation of study results is complicated by concomitant exposures to chromium(VI) or other compounds that can induce adverse health effects. Similarly, interpretation of findings in case reports of exposures to dietary supplements containing high-dose chromium(III) are also complicated, since most supplements contain numerous chemicals; thus, the most reliable information on adverse health effects of chromium(III) is obtained from studies in animals. Chromium(III) picolinate, a dietary supplement, has been shown to be mutagenic in bacterial and mammalian cells *in vitro*.

The primary effects of chromium(III) compounds are on the respiratory and immunological systems. As described below, respiratory effects appear to be portal-of-entry effects for inhalation exposure. Similarly, chromium allergic dermatitis, the major immunological effect of chromium(III), is typically elicited by dermal contact in sensitized individuals; however, initial sensitization may result from inhalation, oral, or dermal exposure or from a combination of these exposure routes. Conflicting results of studies in animals have been reported in developmental and reproductive studies of chromium(III) compounds; however, results provide evidence of adverse effects on the developing and adult reproductive system. Evidence of developmental or reproductive effects of chromium(III) in humans has not been identified. Based on results of chronic-duration oral studies in animals, chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) do not appear to produce gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, or musculoskeletal effects. This is in contrast to chromium(VI) compounds which produce effects in the gastrointestinal, hematological, hepatic and renal systems.

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Respiratory Effects. Occupational exposure studies and case reports indicate that respiratory effects occur from exposure of humans to chromium(III) compounds; however, results of these studies are difficult to interpret since most study populations were also exposed to chromium(VI) compounds or other compounds associated with respiratory effects, and/or the studies were not adequately controlled for other confounding factors (e.g., respiratory diseases). Acute- and chronic-duration studies in animals indicate that the respiratory tract is the primary target of inhaled chromium(III). Analysis of BAL fluid from rats exposed for 5 days to 3–30 mg chromium(III)/m³ as basic chromium sulfate (soluble) showed alterations, including increased amounts of cell debris and lysed cells and significant decreases in nucleated cells and in the percentage of segmented neutrophils and mononuclear cells; cytoplasmic accumulation of a yellow crystalline material in mononuclear cells was observed in BAL fluid of rats exposed to 3–30 mg chromium(III)/m³ as chromic oxide (insoluble). With longer exposure (13 weeks), histopathological changes to respiratory tissues and increased lung weights were observed in rats exposed to ≥ 3 mg chromium(III)/m³ chromic oxide or basic chromium sulfate. However, differences were observed in severity and location of respiratory effects produced by insoluble chromic oxide and soluble basic chromium sulfate; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). Differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Studies examining respiratory effects from chronic-duration inhalation exposure were not identified. Respiratory effects from oral or dermal exposure to chromium(III) compounds have not been reported.

Immunological Effects. As discussed above for chromium(VI) compounds, exposure to chromium compounds may induce allergic sensitization in some individuals. In patients with known chromium-induced allergic dermatitis, positive results have been reported using patch tests with chromium(III) compounds as the challenge agent, suggesting that allergic sensitization to chromium(III) can occur. In sensitized patients, dermal responses were elicited using a concentration of 1 mg chromium(III)/L as chromium trichloride. However, since positive responses were also observed on challenge with chromium(VI) compounds, it is unclear if individuals were sensitized to both chromium(VI) and chromium(III) or if cross-sensitivity occurs between chromium(VI) and chromium(III). Studies in animals show that chromium(III) can induce sensitization and that cross-reactivity occurs between chromium(VI) and chromium(III). Sensitization to chromium(III) was observed in guinea pigs treated with a series of intradermal injections of 0.004 mg chromium(III)/kg as chromium trichloride. In guinea

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pigs sensitized with chromium(III), cross-sensitivity with chromium(VI) was observed on patch test challenge.

Reproductive Effects. Adverse reproductive effects have been observed in rats and mice exposed orally to chromium(III) compounds, although conflicting results have been reported. Adverse reproductive effects have been reported following acute- and intermediate-duration exposure of animals to chromium(III) by gavage or in drinking water; effects include decreased number of pregnancies in female rats administered 33.6 mg chromium(III)/kg/day, alterations in sexual behavior, aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day), decreased number of pregnant female Swiss mice following the mating of unexposed females to exposed males (13 mg chromium(III)/kg/day), impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males, and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day). Decreased spermatogenesis was observed in BALB/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks.

In contrast to the reproductive effects of chromium(III) chloride in drinking water, dietary exposure to chromium picolinate or chromium nicotinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages, and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice. No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or 0.22 and 0.25 mg chromium(III)/kg/day, respectively, for 1 year.

In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed), or to differences in toxicity of the specific chromium(III) compounds evaluated.

Developmental Effects. Little information is available on the potential developmental effects of chromium(III) compounds, although results of available studies are conflicting. Chromium(III) did not

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produce developmental effects in offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period. Significant decreases were observed in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males and ovaries and uterus in females) of offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20; however, fertility was not affected when these exposed offspring were mated with unexposed animals. The number of pregnancies was decreased in rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by gavage as chromium chloride on gestational days 1–3, although when exposed on gestational days 4–6, no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed. In a different type of study, neurological testing of offspring of mice exposed during gestation and lactation to 25 mg chromium(III)/kg/day as chromium picolinate in the diet did not reveal significant differences, as compared to controls. Thus, the available evidence does not indicate that exposure to chromium(III) consistently produces adverse developmental effects.

Cancer. No studies evaluating the carcinogenic activity of chromium(III) compounds in humans were identified. In male rats exposed to dietary chromium picolinate for 2 years, the incidence of preputial gland adenoma was significantly increased in males at 61 mg chromium(III)/kg/day, with the incidence also exceeding the historical control ranges; however, the incidence was not increased at a higher dose (313 mg chromium(III)/kg/day) and similar lesions were not observed in corresponding tissues in female rats or in male and female mice. Therefore, one study considered the evidence of carcinogenic activity to be equivocal. The relationship of preputial gland adenoma to male reproductive function in this study was not defined.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for chromium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs—Chromium(VI)

Acute. The inhalation database for acute-duration exposure of humans to inhaled chromium(VI) compounds is limited to a few studies reporting signs of respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headaches in individuals or small numbers of workers ($n \leq 5$) exposed to high concentrations of chromium(VI) (Lieberman 1941; Meyers 1950; Novey et al. 1983). In addition, acute inhalation exposure of individuals previously sensitized to chromium compounds has produced symptoms of asthma and signs of respiratory distress consistent with a type I allergic response (decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, blocked nasal passages, cough, and wheeze) (Leroyer et al. 1998; Olaguibel and Basomba 1989); however, the available data are not adequate to characterize the exposure-response relationship for effects of acute inhalation challenge in sensitized individuals. No other effects of acute inhalation exposure of humans to chromium(VI) have been reported.

The acute toxicity of inhaled chromium(VI) in animals has not been well investigated, and most studies are 4-hour lethality studies (American Chrome and Chemicals 1989; Gad et al. 1986). Nasal hemorrhage was observed in two of five rats after inhalation for 10 days to $1.15 \text{ mg chromium(VI)/m}^3$ during a 13-week exposure study (Kim et al. 2004), with no nasal effects observed at $0.49 \text{ mg chromium(VI)/m}^3$. However, only a small number of animals were evaluated and histopathological evaluations of the respiratory tract (or other tissues) were not conducted following the acute-duration period; thus, data are not suitable for defining NOAEL or LOAEL values for respiratory effects. Although longer duration inhalation studies show that the respiratory tract is a sensitive target of inhaled chromium(VI), the data are insufficient to determine acute-duration exposure levels that would produce respiratory tract, or other effects. In the absence of studies that could be used to identify the targets of low level exposure, an acute-duration inhalation MRL for hexavalent chromium was not derived.

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Intermediate

- An inhalation MRL of 5×10^{-6} mg chromium(VI)/m³ has been derived for intermediate (15–364 days) exposure for dissolved hexavalent chromium aerosols and mists.

The available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects. Although the respiratory system is the most sensitive target for inhalation exposure to both types of chromium(VI) compounds, the primary respiratory effects of inhaled chromic acid mists are observed in the nose (see the following discussion), while the effects of inhaled particulate chromium(VI) compounds occur throughout the respiratory tract. Since toxic potencies of these compounds appear to be different and the likelihood for environmental exposure to chromium trioxide (e.g., chromic acid mist) and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

The intermediate-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists (Gibb et al. 2000a, 2000b; Gomes 1972; Kleinfeld and Rosso 1965; Lindberg and Hedenstierna 1983); these studies identify the upper respiratory tract as the primary target of exposure. Upper respiratory effects include nasal irritation, ulceration, and mucosal atrophy and rhinorrhea, with LOAEL values ranging from 0.002 to 0.1 mg chromium(VI)/m³. Other effects (e.g., non-respiratory) specific for dissolved chromium(VI) aerosols and mists in humans have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation.

Available animal studies on the effects of intermediate-duration exposure to dissolved chromium(VI) aerosols and mists identify the respiratory tract as the primary target, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m³ (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). Respiratory effects reported in animals exposed to chromium(VI) trioxide include alveolar inflammation in rats (Kim et al. 2004) and nasal septal perforation and symptoms of emphysema in mice (Adachi 1987; Adachi et al.

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1986). The only other effect (e.g., non-respiratory) observed in animal studies on dissolved chromium(VI) aerosols and mists were hematological effects and decreased body weight in rats exposed to chromium trioxide mist for 13 weeks. Hematological effects include decreased in hematocrit at ≥ 0.23 and 1.15 mg chromium(VI)/m³ (but not 0.49 mg chromium(VI)/m³) decreased hemoglobin at ≥ 0.49 mg chromium(VI)/m³ and decreased erythrocyte count at 1.15 mg chromium(VI)/m³ (Kim et al. 2004). In this study, body weight gain was also decreased by ~9%, with NOAEL and LOAEL values of 0.49 and 1.15 mg chromium(VI)/m³, respectively.

Based on a comparison of LOAEL values for respiratory effects, hematological effects, and decreased body weight gain, the respiratory tract was identified as the most sensitive effect of intermediate-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m³ was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters observed in workers exposed to chromic acid mist (Lindberg and Hedenstierna 1983); therefore, this value was selected as the basis for derivation of the intermediate-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated by Lindberg and Hedenstierna (1983) included 85 male and 19 female chrome plating workers exposed to chromic acid and a reference group of 119 auto mechanics not exposed to chromium. Workers were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, with a mean of 2.5 years, spanning both intermediate and chronic durations. Since the study population included workers exposed for an intermediate duration, data are considered appropriate for derivation of the intermediate-duration inhalation MRL. Nasal irritation ($p < 0.05$), mucosal atrophy ($p < 0.05$), and ulceration ($p < 0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to ≥ 0.002 mg chromium(VI)/m³ as chromic acid. Approximately 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Additional details on study methods and results are provided in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m³ was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL (LOAEL_{ADJ}) of 0.0005 mg chromium(VI)/m³. The intermediate-duration MRL of 5×10^{-6} was obtained by dividing the LOAEL_{ADJ} (0.0005 mg chromium(VI)/m³) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

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- An inhalation MRL of 0.0003 mg chromium(VI)/m³ was derived for intermediate exposures to particulate chromium(VI) compounds.

As discussed above, available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects (the primary target organ). Furthermore, since the likelihood for environmental exposure to chromium trioxide and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

Although few animal studies have reported adverse effects of intermediate-duration inhalation exposure to particulate chromium(VI) compounds (Cohen et al. 1998; Glaser et al. 1985, 1990), results of available studies conducted in rats indicate that the respiratory tract is the primary target organ. In rats exposed to inhaled sodium dichromate for 30–90 days, adverse respiratory effects included obstructive respiratory dyspnea, increased lung weights, hyperplasia of the lung, focal inflammation of the upper airway, and alterations to BAL fluid concentrations of lactate dehydrogenase, protein, and albumin, with a LOAEL value of 0.2 mg chromium(VI)/m³ (Glaser et al. 1990). Other effects reported in the Glaser et al. (1985, 1990) studies were an increased percentage of lymphocytes in BAL fluid (LOAEL of 0.025 mg chromium(VI)/m³), increased serum phospholipids and triglycerides (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m³, respectively), increased white blood cell count (LOAEL value of 0.05 mg chromium(VI)/m³), decreased body weight gain (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m³), and an enhanced immune response to sheep erythrocytes (LOAEL 0.025 mg chromium(VI)/m³); however, the toxicological significance of these findings is uncertain. Effects that may be indicative of altered immune function (altered white blood cell counts and cytokine levels in BAL fluid) were observed in rats exposed to 0.36 mg chromium(VI)/m³ as potassium chromate or barium chromate for 2–4 weeks (Cohen et al. 1998); however, results of this study are difficult to interpret, since effects were not clearly adverse, only one exposure level was evaluated, and histopathological assessment of respiratory tissues (or other tissues) was not conducted.

Based on the available data, respiratory effects were identified as the most sensitive target of intermediate-duration exposure to particulate chromium(VI) compounds, with the study by Glaser et al. (1990) selected as the critical study. In this study, 8-week-old male Wistar rats (30 animals/group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m³ as sodium

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dichromate aerosol particulates. Detailed discussion of study methods is presented in Appendix A. No deaths or abnormal clinical signs occurred at any of the exposures. Obstructive respiratory dyspnea occurred at ≥ 0.2 mg chromium(VI)/m³ after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at 0.05 mg chromium(VI)/m³ for 30 days, and at 0.1 mg chromium(VI)/m³ for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at 0.05 mg chromium(VI)/m³ at 30 days. Lung fibrosis occurred at 0.1 mg chromium(VI)/m³ for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase and β -glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m³ for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. Additional details on study results are presented in Appendix A.

Results of the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) were identified as the basis for derivation of an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs (defined as the 95% lower limit on the concentration corresponding to a 10% relative change in the end point compared to the control) for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day). Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs. The lowest BMCL, 0.016 mg chromium(VI)/m³ for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m³ was converted to a human equivalent concentration (BMCL_{HEC}) of 0.010 mg chromium(VI)/m³ using the regional deposited dose ratio (RDDR) program (EPA 1994c) (see Appendix A for details).

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The intermediate-duration inhalation MRL of 0.0003 mg chromium(VI)/m³ for hexavalent chromium particulate compounds was derived by dividing the BMCL_{HEC} of 0.010 mg chromium(VI)/m³ by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Chronic

- An inhalation MRL of 5×10^{-6} mg chromium(VI)/m³ has been derived for chronic (≥ 365 days) exposure for dissolved hexavalent chromium aerosols and mists.

The chronic-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists, reporting effects to the respiratory, renal, and gastrointestinal systems (Franchini and Mutti 1988; Gibb et al. 2000a, 2000b; Hanslian et al. 1967; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975). Respiratory effects included bleeding nasal septum, nasal mucosal atrophy, nasal septal ulceration and perforation, epistaxis, rhinorrhea, and decreased lung function, with LOAEL values ranging from 0.002 to 0.414 mg chromium(VI)/m³. Effects indicative of renal toxicity include increased retinol binding protein and tubular antigen and increased urinary β -2-microglobulin (Franchini and Mutti 1988; Lindberg and Hedenstierna 1983); LOAEL values for these effects range from 0.004 to 0.05 mg chromium(VI)/m³. Gastrointestinal effects reported in workers include stomach pains, cramps, and ulcers, with a LOAEL value of 0.004 mg chromium(VI)/m³ (Lucas and Kramkowski 1975). Other effects specific for dissolved chromium(VI) aerosols and mists in humans exposed for chronic exposure durations have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation. Studies in animals evaluating the effects of chronic-duration exposure to dissolved chromium(VI) aerosols and mists were not identified.

Based on a comparison of LOAEL values for respiratory, renal and gastrointestinal effects in workers, the respiratory tract was identified as the most sensitive effect of chronic-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m³ was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters in workers occupationally exposed to chromic acid mist (Lindberg and Hedenstierna 1983); therefore, this

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value was selected as the basis for derivation of the chronic-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated in this study had a mean exposure duration of 2.5 years, with a range of 0.1–23.6 years, spanning both intermediate and chronic durations. A description of study methods and results is provided above under the discussion of Intermediate-Duration Inhalation MRL for Chromium(VI) aerosols/mists and in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m³ was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL (LOAEL_{ADJ}) of 0.0005 mg chromium(VI)/m³. The chronic-duration MRL of 5x10⁻⁶ was obtained by dividing the LOAEL_{ADJ} (0.0005 mg chromium(VI)/m³) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

Few studies have evaluated the effects of chronic inhalation exposure to particulate hexavalent chromium compounds. In workers chronically exposed to inhaled chromium(VI) compounds at 0.0042 mg chromium(VI)/m³, the prevalence of high urinary N-acetyl-β-glucosamidase was increased, indicating possible renal damage (Liu et al. 1998); however, since the chemical form of chromium(VI) was not reported, data from this study are not suitable as the basis for the chronic-duration inhalation MRL specific for particulate hexavalent chromium compounds. The chronic-duration database in animals consists of studies that either did not identify adverse effects of chronic inhalation exposure to particulate hexavalent chromium compounds (Glaser et al. 1986, 1988; Lee et al. 1989) or older studies that did not report sufficient experimental details (Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Thus, due to inadequate data, a chronic-duration inhalation MRL for particulate hexavalent chromium compounds was not derived.

Oral MRLs—Chromium(VI)

Acute. Studies on the acute toxicity of orally-administered chromium(VI) in humans are mostly limited to case reports on ingestion of fatal doses (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Loubieres et al. 1999; Saryan and Reedy 1988). At lower doses (≥ 0.036 mg chromium (IV)/kg as potassium dichromate), oral exposure to chromium(VI) has been shown to enhance dermatitis in individuals with known chromium sensitivity (Goitre et al. 1982; Kaaber and Veien 1977).

In animals, acute-duration studies on oral exposure to chromium(VI) compounds have shown effects on hematology and clinical chemistry (NTP 2007, 2008a), male reproductive organs (Li et al. 2001) and development (Elsaieed and Nada 2002; Junaid et al. 1996b); however, the available studies did not

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evaluate comprehensive toxicological end points. Decreased MCV, MCH, and reticulocyte count were observed in rats exposed to ≥ 0.70 mg chromium(VI)/kg/day after 4–5 days of exposure (NTP 2007, 2008a); however, the magnitude of changes was small and may not yet represent an adverse effect of chromium(VI). Significant alterations in the serum activities of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and creatine kinase were observed at ≥ 4.0 – 4.1 mg chromium(VI)/kg/day in rats exposed for 4–5 days (NTP 2007, 2008a). Effects on male reproductive organs, including decreased sperm count, increased percentage of abnormal sperm, and morphological change to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed in Wistar rats following a 6-day gavage administration of ≥ 5.2 mg chromium(VI)/kg/day as chromic acid; observations were made 6 weeks after the dosing period (Li et al. 2001). A NOAEL was not defined in this study.

Developmental effects, including increased pre- and postimplantation loss, resorptions, dead fetuses/litter, and skeletal (incomplete ossification of skull bone) and visceral (renal pelvis dilatation) malformations were observed in Wistar rats exposed to 8 mg chromium(VI)/kg/day (the only dose tested) as potassium chromate in drinking water (Elsaieed and Nada 2002). Other studies reported total litter loss, decreased viable fetuses and increased resorptions in rats (Bataineh et al. 2007) and increased resorptions in mice (Junaid et al. 1996b) exposed at higher doses.

Results of acute-duration studies in animals show that exposure to oral chromium(VI) compounds may cause hematological (NTP 2007, 2008a), reproductive (Li et al. 2001), and developmental effects (Elsaieed and Nada 2002; Junaid et al. 1996b). However, since the available studies did not evaluate comprehensive toxicological end points, data are inadequate for derivation of an acute-duration oral MRL for chromium(VI). Therefore, an acute-duration oral MRL for hexavalent chromium was not derived.

Intermediate

- An oral MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate (15–364 days) exposure to hexavalent chromium compounds.

Hematological effects (microcytic, hypochromic anemia) in male rats and female mice observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI) for the purpose of derivation of an intermediate-duration oral MRL for chromium(VI) compounds of 0.005 mg chromium(VI)/kg/day. The basis for this determination is as follows.

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No human intermediate-duration studies on chromium(VI) were identified. Numerous animal studies examining systemic, neurological, reproductive, and developmental toxicity have reported effects following oral exposure to chromium(VI) compounds, with hematological effects (microcytic, hypochromic anemia) identified as the most sensitive. Microcytic, hypochromic anemia, characterized by decreased MCV, MCH, Hct, and Hgb, was observed in rats and mice exposed to chromium(VI) compounds in drinking water or feed for intermediate-duration exposures ranging from 22 days to 6 months (NTP 1996a, 1996b, 1997, 2007, 2008a). The lowest reported LOAEL values for hematological effects were 0.77 mg chromium(VI)/kg/day (with a NOAEL value of 0.21 mg chromium(VI)/kg/day) for decreased Hct, Hgb, MCV, and MCH in male rats; and 0.38 mg chromium(VI)/kg/day (a NOAEL was not established) for decreased MCV and MCH in female mice exposed to sodium dichromate dihydrate in drinking water for 22 days (NTP 2008a). Slightly higher LOAEL values were observed for hematological effects in rats and mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a, 1996b, 1997).

The duration-dependence of hematological effects was evaluated in rats and mice exposed to sodium dichromate dihydrate in drinking water from 23 days up to 6 months (NTP 2007, 2008a). Results of both studies show that the severity of microcytic, hypochromic anemia was dose-dependent, with maximum effects observed after 22–23 days of exposure. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. In female mice, microcytic, hypochromic anemia was also observed, with LOAEL values of 0.38, 1.4, and 3.1 mg chromium(VI)/kg/day at the 22-day, 3-month, and 6-month assessments, respectively, with effects less severe than those observed in rats.

Studies examining systemic toxicity in animals have reported numerous effects, including hepatotoxicity (Achaya et al. 2001; Kumar and Rana 1982, Kumar et al. 1985; NTP 1996a, 2007), gastrointestinal effects (NTP 2007), renal toxicity (Acharya et al. 2001; Diaz-Mayans et al. 1986; Kumar and Rana 1982, 1984), lymphatic and immunological effects (NTP 2007; Snyder and Valle 1991), and decreased body weight (Bataineh et al. 1997; Chowdhury and Mitra 1995; Elbetieha and Al-Hamood 1997; Kanojia et al. 1996, 1998; NTP 2007; Quinteros et al. 2007; Trivedi et al. 1989). However, LOAEL values for these effects were higher than those producing hematopoietic effects. Studies on reproductive toxicity in animals identify the male reproductive system as a target for intermediate-duration exposure to oral chromium(VI) (Aruldas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Subramanian et al. 2006; Yousef et al. 2006; Zahid et al. 1990), although these effects are less sensitive

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than hematological effects. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed high doses (e.g., ≥ 35 mg chromium(VI)/kg/day) (Al-Hamood et al. 1998; Bataineh et al. 2007; Junaid et al. 1996a; Kanojia et al. 1998; Trivedi et al. 1989).

Hematological effects (microcytic, hypochromic anemia) in male rats observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI). In this study, male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study, with hematological assessments conducted at 22 days, 3 months, 6 months, and 1 year (see Appendix A for a detailed description of study methods and results). To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a) (detailed results of the benchmark dose analysis are provided in Appendix A). Because several hematological parameters are used to define the clinical picture of anemia, the $BMDL_{2sd}$ values for hemoglobin, MCV, and MCH (none of the models provided an adequate fit for hematocrit) were averaged resulting in a $BMDL_{2sd}$ of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average $BMDL_{2sd}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Chronic

- An oral MRL of 0.0009 mg chromium(VI)/kg/day has been derived for chronic (≥ 1 year) exposure to hexavalent chromium compounds.

Nonneoplastic lesions of the duodenum in mice reported in a chronic drinking water study (NTP 2008a) was selected as the critical effect for derivation of a chronic-duration MRL for chromium(VI) compounds of 0.0009 mg chromium(VI)/kg/day. There are limited data on the chronic oral toxicity of chromium in humans. Gastrointestinal effects, including oral ulcer, diarrhea, abdominal pain, and vomiting, were observed in residents living in an area of the People's Republic of China with high chromium(VI) levels in the drinking water. However, the exposure levels associated with these effects is not well characterized. Other ecological studies have examined cancer mortality (Beaumont et al. 2008; Bednar and Kies 1991; Fryzek et al. 2001; Kerger et al. 2009; Linos et al. 2011), but did not report noncarcinogenic effects.

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The chronic-duration oral toxicity database in drinking water in humans consists of ecological studies of an area near a ferrochromium production plant in the Liaoning Province, China comparing cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). Evaluations of cancer mortality rates (cancers deaths per person-year in an 8-year observation period) show that the adjusted stomach cancer mortality rate was higher for the exposed population compared to the control population (Beaumont et al. 2008). However, it was not possible to estimate exposure levels based on the description of the pollution process. Thus, available human data are not adequate as the basis for the chronic-duration oral MRL.

Chronic-duration oral toxicity studies have been conducted in rats and mice (Mackenzie et al. 1958; NTP 2008a). No hematological, hepatic, or renal effects or changes in body weight were observed in study in Sprague-Dawley rats exposed to 3.6 chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (Mackenzie et al. 1958). NTP (2008a) exposed groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study (see Appendix A for a detailed description of all study methods and results). Results of this study identify several chromium(VI)-induced effects, including microcytic, hypochromic anemia, and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas, and salivary gland. Based on comparison of LOAEL values, the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice), and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups (see Appendix A for incidence data for all nonneoplastic lesions). Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL.

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (details of benchmark dose analysis are presented in Appendix A). Based on the lowest BMDL₁₀ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration MRL of 0.0009 mg chromium(VI)/

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kg/day was derived by dividing the $BMDL_{10}$ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas and salivary gland).

Inhalation MRLs—Chromium(III)

Acute. Studies evaluating the effects of acute exposure of humans to chromium(III) compounds were not identified. Acute-duration exposure studies in rats and hamsters indicate that the respiratory tract is a target of inhaled chromium(III) compounds (Derelanko et al. 1999; Henderson et al. 1979). Derelanko et al. (1999) evaluated effects of acute exposure to chromium(III) as chromic oxide (insoluble) or basic chromium sulfate (soluble) in rats (5 rats/sex/group) on composition of bronchoalveolar lavage (BAL) fluid. After exposure of rats for 5 days (6 hours/day) to 3, 10, or 30 mg chromium(III)/m³ as chromic oxide (insoluble), analysis of BAL fluid revealed cytoplasmic accumulation of a yellow crystalline material in mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein, and BAL fluid activities of β -glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated for 5 days (6 hours/day) with 3, 10, or 30 mg chromium(III)/m³ as basic chromium sulfate (soluble), BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m³ in males. Increased amounts of cellular debris and lysed cells were present in BAL fluid of rats treated with ≥ 3 mg chromium(III)/m³ as basic chromium sulfate (incidence data were not reported). In Syrian hamsters, changes in BAL fluid and lung tissue enzyme activities were observed following exposure to inhaled chromium trichloride for 30 minutes (Henderson et al. 1979); effects included “sporadic changes” in activities of acid phosphatase and alkaline phosphatase in the BAL fluid at 25 mg chromium(III)/m³ and increased acid phosphatase activity in lung tissue at 0.9 mg chromium(III)/m³. In addition, histological examination of the lung revealed focal accumulations of macrophages and polymorphonuclear cells. However, it is not clear that the effects observed in this study are toxicologically significant. Thus, results of acute-duration studies in rats and hamsters show that inhaled chromium(III) compounds produce alterations in BAL fluid composition and lung tissue enzyme activities; however, data are not adequate to characterize the exposure-response relationship for respiratory effects. Therefore, an acute-duration inhalation MRL for trivalent chromium was not derived.

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Intermediate. Studies evaluating the effects of intermediate-duration exposure of humans to chromium(III) compounds were not identified. In animals exposed to inhaled chromium(III) compounds for intermediate durations, the respiratory tract has been identified as the primary target organ, based on results of a 13-week study in rats exposed to chromic oxide (insoluble) or basic chromium sulfate (soluble) (Derelanko et al. 1999). In this study, which examined comprehensive toxicological end points, male and female CDF rats (15/sex/group) were exposed by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m³ as chromic oxide or as basic chromium sulfate for 6 hours/day, 5 days/week for 13 weeks. Of the 15 rats/sex/group, 10 rats/sex/group were sacrificed after 13 weeks of exposure and 5 rats/sex/group were sacrificed after an additional 13-week recovery period (e.g., no exposure). Assessments made in this study included mortality; clinical signs of toxicity; body weight; hematology; clinical chemistry; urinalysis; sperm morphology, count and motility; gross necropsy; microscopic examination of comprehensive tissues for all animals in the control and 30 mg chromium(III)/m³ groups; and microscopic examination of respiratory tissues (nasal tissues, trachea, lungs, larynx, and mediastinal and mandibular lymph nodes) in all animals. Both chromic oxide and basic chromium sulfate produced adverse respiratory effects (histopathological changes to respiratory tissues and increased lung weights) in male and female rats, with no adverse effects in other tissues. However, differences between the two compounds were observed with respect to severity and location of respiratory effects; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). The study authors suggested that differences in the respiratory toxicity of these compounds may be related to differences in chemical-physical properties (e.g., solubility, acidity). The only other intermediate-duration inhalation study in animals was conducted in rabbits exposed to 0.6 mg chromium(III)/m³ as chromium nitrate for 4–6 weeks (6 hours/day, 5 days/week) (Johansson et al. 1986b). Results of this study showed effects on pulmonary macrophages (altered functional and metabolic activities); however, the toxicological significance of this finding is uncertain and animals were not examined for other effects. Thus, the 13-week inhalation study by Derelanko et al. (1999) was selected as the critical study for derivation of intermediate-duration inhalation MRLs for chromium(III) compounds. Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, distinct intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds. Additional details of respiratory effects produced by chromic oxide and basic chromium sulfate are described below under derivation of intermediate-duration inhalation MRLs for insoluble trivalent chromium compounds and for soluble trivalent chromium compounds, respectively.

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- An inhalation MRL of 0.005 mg chromium(III)/m³ has been derived for intermediate (15–364 days) exposure to insoluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled insoluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to chromic oxide for 13 weeks, with histopathological changes to the respiratory lymphatic tissue occurring at ≥ 3 mg chromium(III)/m³ and to the lung at ≥ 10 mg chromium(III)/m³. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m³, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx.

For evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following a 13-week posttreatment recovery period, trace-to-mild septal cell hyperplasia and trace-to-mild chronic interstitial inflammation of the lung were observed at ≥ 3 mg chromium(III)/m³ in males and at ≥ 10 mg chromium(III)/m³ in females. In addition, pigmented macrophages and black pigment in peribronchial lymphatic tissues and the mediastinal lymph node in animals from all treatment groups were also observed; this finding, although not considered adverse, indicates that the test material had not been completely cleared from the lung during the treatment-free recovery period. Thus, for evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (based on severity) of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

The LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were considered as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A benchmark concentration for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. To determine the point of departure, the LOAEL value of 3 mg chromium(III)/m³

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was first adjusted for intermittent and converted to human equivalent concentrations (LOAEL_{HEC}) (see Appendix A for details).

Based on the lowest LOAEL_{HEC} of 0.43 mg chromium(III)/m³, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats were selected as the critical effect. The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m³ was derived by dividing the minimal LOAEL_{HEC} of 0.43 mg chromium(III)/m³ by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

- An inhalation MRL of 0.0001 mg chromium(III)/m³ has been derived for intermediate (15–364 days) exposure to soluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled soluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥ 3 mg chromium(III)/m³. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris; foci of “intense” inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation, and suppurative and mucoid exudates of nasal tissues and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Thus, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were evaluated to determine the specific end point for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used, with adjustment of the LOAEL for intermittent exposure and human equivalent concentrations (see Appendix A for details). Data for relative lung weights in males and females (presented in Appendix A) were modeled using all available continuous-variable models in the EPA Benchmark Dose program

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(version 1.4.1). The BMC and the 95% lower confidence limit (BMCL) calculated were estimated for doses associated with a change of 1 standard deviation from the control mean (BMDL_{1sd}). The BMCL_{1sd} values for the best fitting models in male and female rats were adjusted for intermittent exposure and human equivalent concentrations, yielding BMCL_{1sd,HEC} values of 0.17 and 0.34 mg chromium(III)/m³ in males and females, respectively (see Appendix A for detail of benchmark dose analysis).

Based on comparison of LOAEL_{HEC} values for respiratory tract lesions and BMCL_{1sd,HEC} values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m³ (the LOAEL_{HEC} for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m³ was derived by dividing the LOAEL_{HEC} of 0.04 mg chromium(III)/m³ by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability). It should not be concluded from comparison of the intermediate-duration MRLs for soluble particulate chromium(VI) and soluble particulate chromium(III) compounds that chromium(III) is more toxic than chromium(VI).

The respiratory tract is the major target of inhalation exposure to chromium compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. For chronic exposure of humans, the available occupational studies for exposure to chromium(III) compounds include or likely include concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors in estimating exposure levels for these effects for the purpose of deriving MRLs.

Chronic. No studies evaluating the effects of chronic-duration inhalation exposure of animals to chromium(III) compounds alone were identified. Exposure to mixtures of chromium(VI) and chromium(III) compounds (3:2 mixture of chromium(VI) trioxide and chromium(III) oxide) have resulted in adverse respiratory effects in Wistar rats, including increased lung weight and histopathological changes to lung tissues (interstitial fibrosis and thickening of the septa of the alveolar lumens; Glaser et al. 1986, 1988). However, these data not appropriate as the basis for a chronic-duration inhalation MRL for chromium(III) compounds due to concomitant exposure to chromium(VI).

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Oral MRLs—Chromium(III)

No acute-, intermediate-, or chronic-duration oral MRLs were derived for chromium(III) because studies evaluating the effects of chromium(III) in humans and animals following acute, intermediate, and chronic oral exposure were inadequate for establishing the exposure concentrations associated with adverse health effects (as discussed below). The IOM has recommended an adequate intake level of 20–45 µg chromium(III) for adolescents and adults, equivalent to 0.28–0.64 µg chromium(III)/kg/day (0.0003–0.0006 mg chromium(III)/kg/day), assuming a 70-kg body weight (IOM 2001).

Little information is available on the effects of acute-duration oral exposure to chromium(III) compounds. Information on the effects of intermediate-duration oral exposure of humans is limited to case reports of renal failure (Wani et al. 2006; Wasser et al. 1997) and rhabdomyolysis (Martin and Fuller 1998) following ingestion of dietary supplements containing chromium(III). In animals, acute exposure of rats to dietary chromium(III) picolinate did not produce alterations in hematology or clinical chemistry. Following acute exposure of mated rats, an increase in total litter loss was observed in female rats (at 33.6 mg chromium(III)/kg/day) (Bataineh et al. 2007). In a study evaluating effects of chromium(III) on maturation of the reproductive system in mice (74 mg chromium(III)/kg/day), significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) and a significant delay in timing of vaginal opening in the female offspring were observed (Al-Hamood et al. 1998). However, gestational exposure studies on chromium(III) compounds were conducted at high daily doses and do not provide sufficient information to characterize the dose-response relationship for adverse developmental effects. Thus, the data are inadequate for derivation of an acute-duration oral MRL.

Information on adverse effects of intermediate-duration oral exposure of humans to chromium(III) compounds was not identified. Results of most animal studies show no adverse effects associated with intermediate-duration oral exposure to chromium(III) compounds (chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate, and chromium potassium sulfate) (Anderson et al. 1997b; De Flora et al. 2006; Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007), even at very high daily doses. In the study conducted by NTP (2008b; Rhodes et al. 2005), daily doses of up to 506 and 1,415 mg chromium(III)/mg/day as chromium picolinate were evaluated in rats and mice, respectively, and in the Ivankovic and Preussmann (1975) study, daily doses up to 1,806 mg chromium(III)/kg/day as chromium oxide were evaluated in rats.

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Adverse reproductive effects have been reported following intermediate-duration exposure of animals to chromium(III) as chromium chloride administered by gavage or in drinking water. A series of studies by the same research group evaluated reproductive effects of exposure to chromium(III) as chromium chloride in drinking water for 12 weeks (Al-Hamood et al. 1998; Bataineh et al. 1997, 2007; Elbetieha and Al-Hamood 1997). Reproductive effects observed included alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day; only dose tested) (Bataineh et al. (1997); decreased number of pregnant female Swiss mice following the mating of unexposed females to exposed males (13 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997); impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males (Elbetieha and Al-Hamood 1997); and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997). Results of the study by Elbetieha and Al-Hamood (1997) should be interpreted with caution due to concerns regarding experimental methods, including decreased water consumption in the higher concentration group (resulting in a potential overestimate of exposure and uncertainty regarding daily dose calculations); the study was not conducted using a standard mating protocol; sperm counts were not conducted; and the definition and classification of non-viable fetuses was not described. Decreased spermatogenesis was observed in BABL/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks (Zahid et al. 1990); however, sensitivity of methods used to evaluate spermatogonia in this study have been questioned by NTP (1996a). NOAEL values for reproductive effects were not identified in these studies. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. The average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for male mice and were 0.35, 1.05, 2.1, and 8.4 mg/kg/day for rats (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

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In contrast to the reproductive effects of chromium chloride in drinking water, dietary exposure to chromium(III) picolinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice (NTP 2008b). No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or at 0.22 and 0.25 mg chromium(III)/kg/day, respectively for 1 year (Shara et al. 2005, 2007). In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed) or to differences in toxic potency of the specific chromium(III) compounds evaluated. Thus, available data are not sufficient to define the dose-response relationship for adverse reproductive effects of chromium(III) compounds.

Little information is available on the potential developmental effects of chromium(III) compounds. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975).

Results of studies in animals exposed to oral chromium(III) compounds indicate that adverse reproductive effects may occur. However, the available data do not identify NOAEL values for effects and, therefore, are not sufficient to characterize the dose-response relationship. Thus, data are inadequate for derivation of an intermediate-duration oral MRL.

Chronic-duration studies on oral exposure of humans to chromium(III) compounds were not identified. Several animal studies show no adverse effects associated with chronic-duration oral exposure to chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) (Ivankovic and Preussmann 1975; Mackenzie et al. 1958; Schroeder et al. 1965; Shara et al. 2007), even at very high daily doses. Thus, in the absence of data showing adverse effects of chronic oral exposure, a chronic-duration oral MRL for chromium(III) compounds was not derived.

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A summary of the inhalation and oral MRLs for chromium(VI) and chromium(III) is presented in Table 2-1.

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Table 2-1. Summary of MRL Values for Chromium(VI) and Chromium(III)

	Point of departure	UF	MRL
Inhalation MRLs			
Chromium(VI)			
Acute	Insufficient data to derive MRL		
Intermediate			
Aerosols and mists	LOAEL of 0.002 mg Cr/m ³ for nasal irritation, mucosal atrophy, impaired lung function in workers (Lindberg and Hedenstierna 1983)	100	5x10 ⁻⁶ mg Cr/m ³
Particulates	BMCL ₁₀ of 0.016 mg Cr/m ³ (converted to a BMCL _{HEC} of 0.010 mg Cr/m ³) based on alterations in lactate dehydrogenase levels in BAL in rats (Glaser et al. 1990)	30	3x10 ⁻⁴ mg Cr/m ³
Chronic			
Aerosols and mists	LOAEL of 0.002 mg Cr/m ³ for nasal irritation, mucosal atrophy, impaired lung function in workers (Lindberg and Hedenstierna 1983)	100	5x10 ⁻⁶ mg Cr/m ³
Particulates	Insufficient data to derive MRL		
Chromium(III)			
Acute	Insufficient data to derive MRL		
Intermediate			
Insoluble particulates	LOAEL of 3 mg Cr/m ³ (adjusted to 0.54 mg Cr/m ³ for 90 intermittent exposure and converted to a LOAEL _{HEC} of 0.43 mg Cr/m ³) for septal cell hyperplasia and chronic interstitial inflammation of the lungs in rats (Derelanko et al. 1999)	90	5x10 ⁻³ mg Cr/m ³
Soluble particulates	LOAEL of 3 mg Cr/m ³ (adjusted to 0.54 mg Cr/m ³ for 300 intermittent exposure and converted to a LOAEL _{HEC} of 0.04 mg Cr/m ³) for nasal and larynx lesions in rats (Derelanko et al. 1999)	300	1x10 ⁻⁴ mg Cr/m ³
Chronic	Insufficient data to derive MRL		
Oral MRLs			
Chromium(VI)			
Acute	Insufficient data to derive MRL		
Intermediate	BMDL _{2SD} of 0.52 mg Cr/kg/day for microcytic, hypochromic anemia in rats (NTP 2008a)	100	0.005 mg/kg/day
Chronic	BMDL ₁₀ of 0.09 mg Cr/kg/day for diffuse epithelial hyperplasia of the duodenum in mice (NTP 2008a)	100	9x10 ⁻⁴ mg Cr/kg/day
Chromium(III)			
Acute	Insufficient data to derive MRL		
Intermediate	Insufficient data to derive MRL		
Chronic	Insufficient data to derive MRL		

BAL = bronchoalveolar lavage; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; UF = uncertainty factor