932 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Chromium

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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 (NR C) 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 0.10–16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day. Currently, the biological target for the e ssential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate. The function of chromodulin, an oligopeptide complex containing with 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.

Whether chromium(III) should be considered an essential element remains controversial. 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 sign s 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 le thality 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 res ulted 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 sh own 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 i mproved 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, LDLcholesterol, 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. 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) supplemen nts, 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, les s 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., $K_2Cr_2O_7$) 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 diet ary 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 or chromium. Chromium(VI) is reduced to chromium(III) via the intermediate forms of chromium(V), chromium(IV). Reduction of chromium(VI) to chromium(III) can give rise to reactive intermedia tes, 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 haemoglobin and other intracellular prote ins, 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.

Health Effects of Chromium. The health effects associate d 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 com plex. 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 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 t o 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 wit h 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), hem atological (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.

Respiratory Effects. The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds i n 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. Re spiratory 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, pneumonoconiosis, 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 effect s 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 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 exposes 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, gastrointestinal ulceration, hemorrhage and necrosis, and bloody diarrhea. Gastrointestinal effects have also been reported in associati on 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 worker s. 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 influence d 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 chron icduration 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 metapl asia 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, histopathogical changes were observed in the gastrointestinal tract of rats and mice. In male and female rats exposed t o 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 r ats 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 ulceratio ns in the stomach and intestinal mucosa; however, the potential of oral exposure via grooming behavior cannot be excluded.

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 sensiti zed, 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 chro mium-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 scre ws, 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 tann eries, 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 ma gnetic 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 produc ts 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 exposure, circulating IgE levels may decrease, resul ting 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 individu als 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 haemoglobin and other ligands. The c hromium-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, hyprochromic 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 i n 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 conte xt of multiple systemic effects observed leading up to death, including hemorrhage.

Results of acute-, intermediate-, and chronic-duration studies in animals identify the haematological system as one of the most sensitive effects of oral exposure to chromium(VI). Microcytic, hypochromic 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 dura tions 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, p resumably 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-adver se-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 seve rity 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 ra ts 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 morphologica lly abnormal sperm; significant decreases on sperm count and motility; and greater incidences of complications during 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 admin istration 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 obser ved (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, 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 dehydrate in drinking water did not produce morphologic al 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 fo r 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 were exposed to ≤37 mg chromium(VI)/kg/day as potassium dichromate in th e 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 potassium dichromate in drinking water for 20 or 9 0 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 implanta tions 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-viab le 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 dichr omate 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 i n 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. 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 nu mber of viable fetuses and increased number of resorptions, but did not alter the number of pregnancies. Exposure of female rats to ≥37mg 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 hemo rrhagic 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. 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 dich romate in the drinking water on gestation day 12 through lactation day 20.

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 t o 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 burn s. 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 an d 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, an d 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.

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 h igh concentrations of chromium trioxide fumes were present. High incidences of inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontis were also observed in chromate production workers. Oral doses of potassi um 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 dichro mate 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 as sociated 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, elevated lung cancer rates in comparison to reference populations (e.g., standard mortal ity 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.

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 incidenc e of lung tumors, compared to controls. In addition, numerous animal studies using the intratracheal, intrapleural, and intrabronhical 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 rats and mice to sodium dichromate dihydrate in drinking water for 2 years resulted in cancers of the gastroi ntestinal 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 inciden ce 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 (NTP) concluded that results demonstrate clear ev idence 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 c hromium(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 fore stomach adenomas alone, compared to control; however, study authors concluded that evidence of carcinogenicity was equivocal. NTP lists certain chromium compounds as substances that are *known to be human carcinogens* . This classification is based on suffici ent 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 in formation 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 ch romium(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-d uration 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.

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 segment ed 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), histop athological changes to respiratory tissues and increased lung weights were observed in rats exposed to ≥3 mg chromium(III)/m3chromic 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 chromiuminduced 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 se nsitized 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 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 fol lowing 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 unexpo sed 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 wat er, 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 wei ghts, 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 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 7 4 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 decrea sed 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 wer e observed. 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 incide nce 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, NTP 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.