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Chromium

SUMMARY

Chromium potentiates the action of insulin in vivo and in vitro. There was not sufficient evidence to set an Estimated Average Requirement (EAR) for chromium. Therefore, an Adequate Intake (AI) was set based on estimated mean intakes. The AI is 35 µg/day and 25 µg/day for young men and women, respectively. Few serious adverse effects have been associated with excess intake of chromium from food. Therefore, a Tolerable Upper Intake Level (UL) was not established.

BACKGROUND INFORMATION

Chromium occurs most commonly in valance states of +3 (III) and +6 (VI). Chromium III is the most stable oxidation state (Greenwood and Earnshaw, 1997) and presumably is the form in the food supply due to the presence of reducing substances in foods. Even a bolus dose of 5 mg chromium VI was reduced to chromium III in 0.5 L of orange juice (Kuykendall et al., 1996), and endogenous reducing agents within the upper gastrointestinal tract and the blood also serve to prevent systemic uptake of chromium VI (Kerger et al., 1997). However, chromium VI, which is a by-product of manufacturing stainless steel, pigments, chromate chemicals, and numerous other products, is strongly oxidizing, produces local irritation or corrosion, and is recognized as a carcinogen when inhaled (Greenwood and Earnshaw, 1997; O'Flaherty, 1994).

Function

Chromium potentiates the action of insulin in vivo and in vitro (Mertz, 1969, 1993; Mertz et al., 1961). Schwarz and Mertz (1959) identified chromium as the element that restored glucose tolerance in rats. Impaired glucose tolerance of malnourished infants responded to an oral dose of chromium chloride (Hopkins and Majaj, 1967; Hopkins et al., 1968); subsequently, benefits of chromium chloride were reported in a patient receiving total parenteral nutrition (TPN) (Jeejeebhoy et al., 1977).

A number of studies have demonstrated beneficial effects of chromium on circulating glucose, insulin, and lipids in a variety of human subjects and animal species; however, not all reports of supplementation are positive (Anderson, 1997; Anderson et al., 1991) (for reviews see Anderson, 1997; Mertz, 1993; Offenbacher et al., 1997; Stoecker, 1996). Progress in the field has been limited by lack of a simple, widely accepted method for identification of subjects who are chromium depleted, and thus who would be expected to respond to chromium supplementation, and by the difficulty in producing chromium deficiency in animals.

Recent work by Davis and Vincent (1997a, 1997b) and Vincent (1999) suggests that a low molecular weight chromium-binding substance (LMWCr) may amplify insulin receptor tyrosine kinase activity in response to insulin. It is proposed that the inactive form of the insulin receptor (IR) is converted to the active form by binding insulin, which stimulates the movement of chromium from the blood into the insulin-dependent cells and results in the binding of apoLMWCr to chromium (Figure 6-1). The holoLMWCr then binds to the insulin receptor activating the tyrosine kinase. The ability of LMWCr to activate insulin receptor tyrosine kinase depends on its chromium content. When insulin concentration drops, the holoLMWCr is possibly released from the cell to terminate its effects.

Physiology of Absorption, Metabolism, and Excretion

Absorption estimates for chromium III, based on metabolic balance studies or on urinary excretion from physiological intakes, range from 0.4 to 2.5 percent (Anderson and Kozlovsky, 1985; Anderson et al., 1983, 1991, 1993a; Bunker et al., 1984; Doisy et al., 1971; Offenbacher et al., 1986).

Most chromium compounds are soluble at the pH of the stomach, but less soluble hydroxides may form as pH is increased (Mertz,

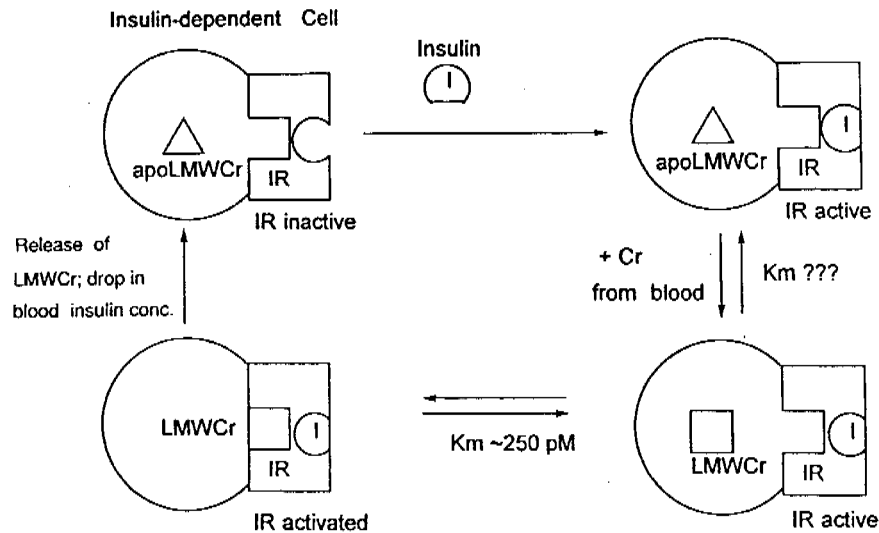


FIGURE 6-1 Proposed mechanism for the activation of insulin receptor by LMWCr in response to insulin. LMWCr = low molecular weight chromium-binding substance, I = insulin, IR = insulin receptor. Adapted from Vincent (1999).

1969). The environment of the gastrointestinal tract and ligands provided by foods and supplements are important for mineral absorption (Clydesdale, 1988). Several dietary factors that affect chromium absorption will be discussed in the bioavailability section of this chapter.

In humans consuming approximately 10 $\mu\text{g}/\text{day}$ of chromium, about 2 percent was excreted in urine, but only 0.5 percent was excreted when intakes approached 40 $\mu\text{g}/\text{day}$ (Anderson and Kozlovsky, 1985). These data suggest regulation of chromium absorption in these intake ranges.

A number of studies have reported increased urinary excretion of chromium with aerobic exercise (Anderson et al., 1982, 1984, 1988b). A recent study using ^{53}Cr demonstrated that acute and chronic resistive exercise may increase chromium absorption as determined by the increased urinary excretion of the ^{53}Cr isotope (Rubin et al., 1998). Further studies will be needed to clarify how much of the observed beneficial effects of exercise on glucose and insulin metabolism may be due to improved chromium absorption.

Chromium competes for one of the binding sites on transferrin (Harris, 1977). In rats fed physiological levels of $^{51}\text{CrCl}_3$, more than

80 percent of the ^{51}Cr in blood precipitated with the transferrin. Several studies have investigated possible interactions between iron and chromium. Human apo-transferrin in Earle's medium bound chromium in the presence of citric acid, and iron uptake by apo-transferrin was reduced by either aluminum or chromium (Moshtaghi et al., 1992). The excessive iron in hemochromatosis has been hypothesized to interfere with the transport of chromium, thereby contributing to the diabetes associated with this condition (Lim et al., 1983; Sargent et al., 1979). Supplementation of 925 $\mu\text{g}/\text{day}$ of chromium for 12 weeks did not significantly affect indexes of iron status in older adult men (Campbell et al., 1997), but one study in young men that provided a daily 200 μg supplement for 8 weeks found a tendency for a decrease in transferrin saturation (Lukaski et al., 1996). No long-term studies have addressed this question.

In humans, chromium concentrates in liver, spleen, soft tissue, and bone (Lim et al., 1983). Similar patterns are seen in rats with accumulation in kidney, spleen, and bone as well as liver and testes (Hopkins, 1965; Kamath et al., 1997; Onkelinx, 1977). A three-compartment model with half-lives of 0.5, 5.9, and 83 days was originally proposed based on the distribution of ^{51}Cr from $^{51}\text{CrCl}_3$ in rats (Mertz et al., 1965). Onkelinx (1977) also proposed a three-compartment model in rats, but suggested different characteristics for the third compartment. Additional modeling work with patients having adult onset diabetes and normal control subjects utilized a compartment within the blood and slow and fast tissue compartments (Do Canto et al., 1995). A half-life for urinary excretion of chromium of 0.97 days for the diabetic group and 1.51 days for control subjects was calculated. The compartment that represented long-term tissue deposition had an extremely slow return rate of 231 days for patients with diabetes and 346 days for control subjects.

Most ingested chromium is excreted unabsorbed in the feces (Mertz, 1969; Offenbacher et al., 1986). Excretion via bile is not a major contributor to fecal chromium (Davis-Whitenack et al., 1996; Hopkins, 1965). Most absorbed chromium is excreted rapidly in the urine (Anderson et al., 1983). A recent report from England indicated significant age-related decreases in the chromium concentrations in hair, sweat, and urine (Davies et al., 1997).

Clinical Effects of Inadequate Intake

Chromium deficiency has been reported in three patients who did not receive supplemental chromium in their TPN solutions

(Brown et al., 1986; Freund et al., 1979; Jeejeebhoy et al., 1977). The first, a female who had received TPN for more than 3 years, developed unexplained weight loss and peripheral neuropathy. Her plasma glucose removal was impaired, plasma free fatty acids were elevated, and her low respiratory quotient indicated poor utilization of carbohydrates. The addition of 250 μg of chromium to the daily TPN solution for 2 weeks restored the glucose removal rate, increased her respiratory quotient, and allowed an insulin infusion to be discontinued. The other two patients responded similarly to chromium supplementation (Brown et al., 1986; Freund et al., 1979)

Because chromium potentiates the action of insulin and chromium deficiency in TPN patients, impairs glucose utilization, and raises insulin requirements, it has been hypothesized that poor chromium status is a factor contributing to the incidence of impaired glucose tolerance and Type II diabetes. Prevalence of impaired glucose tolerance was 15.8 percent in adults from 40 to 74 years of age in the Third National Health and Nutrition Examination Survey (1988–1994) (Harris et al., 1998). Addressing this question is difficult because of the current lack of information about variability in dietary chromium intakes and because there is not an easily usable clinical indicator to identify potential study subjects with poor chromium status.

There is considerable interest in chromium supplementation in Type II diabetes, but no large-scale controlled trials have been reported in the United States. In China, 180 subjects with Type II diabetes took either a placebo, 200 μg , or 1,000 μg of chromium as chromium picolinate daily for 4 months. Mean body weight of the subjects was 69 kg. Data collected at baseline and after 2 and 4 months of supplementation included standard health histories, fasting glucose and insulin, glycosylated hemoglobin, and glucose and insulin concentrations 2 hours after a 75-g glucose load. After 2 months, fasting and 2-hour insulin concentrations were decreased significantly at both supplement levels. Glycosylated hemoglobin and fasting and 2-hour glucose concentration decreased significantly in the higher (1,000 $\mu\text{g}/\text{day}$) dose group. The reductions in glucose and insulin concentrations were maintained for 4 months; additionally, glycosylated hemoglobin became significantly lower in both dose groups at 4 months (Anderson et al., 1997b). There are no data available on the basal dietary intake of chromium in these diabetic subjects. Also, no doses between 200 and 1,000 μg were tested in this study, nor were other forms of chromium supplemented.

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR CHROMIUM

Balance Studies

Two men were monitored for 12 days in a metabolic ward and were in apparent balance when fed 37 $\mu\text{g}/\text{day}$ of chromium (Offenbacher et al., 1986). Bunker and coworkers (1984) conducted metabolic balance studies with 22 apparently healthy elderly people between 69 and 86 years of age. These subjects had mean chromium intakes of 24.5 $\mu\text{g}/\text{day}$ (12.8 $\mu\text{g}/1,000$ kcal) with a range of 13.6 to 47.7 $\mu\text{g}/\text{day}$ for men and 14.5 to 30.3 $\mu\text{g}/\text{day}$ for women. Of the 22 subjects, 16 were in equilibrium, three were in positive balance, and three were in negative balance.

Urinary Chromium Excretion

For healthy, free-living adults, the average urinary chromium excretion is typically 0.22 $\mu\text{g}/\text{L}$ (Paschal et al., 1998) or 0.2 $\mu\text{g}/\text{day}$ (Anderson et al., 1982, 1983) for both men and women. In another study, urinary chromium excretion was found to be approximately 0.5 percent of the amount in the diet when diets contained 40 μg of chromium. For persons whose diets contained only 10 μg of chromium, urinary excretion was approximately 2 percent. There was a negative linear relationship between dietary chromium in this range and percent urinary chromium excretion (Anderson and Kozlovsky, 1985). However, urinary chromium excretion appears to be related to recent chromium intake but has not been useful as a predictor of chromium status (Anderson et al., 1983). Further investigation of urinary chromium in response to very low levels of intake is warranted (Anderson et al., 1991).

Plasma Chromium Concentration

Reported plasma chromium concentrations have declined from greater than 3,000 nmol/L in the 1950s to 2 to 3 nmol/L in well-controlled studies conducted since 1978 (Anderson, 1987). This change can be attributed to improved analytic methods and better control of contamination. Because plasma chromium is very close to the detection limits for graphite furnace atomic absorption and easily contaminated, it is unlikely to be a viable clinical indicator (Veillon, 1989).

Blood Glucose and Insulin Concentration

There is only one study in which subjects were given controlled low chromium diets (Anderson et al., 1991). Seventeen adults were provided diets that contained 5 µg of chromium per 1,000 kcal for 14 weeks. Glucose and insulin concentrations in response to a glucose load were monitored at baseline, 4, 9, and 14 weeks. After adapting to the diet for 4 weeks, subjects were assigned to placebo or chromium supplementation groups for 5 weeks followed by a crossover without washout for another 5 weeks (Anderson et al., 1991).

As one approach to the analysis of these data (Anderson et al., 1991), the subjects who received the placebo for the first 9 weeks were analyzed separately. After 4 weeks on the diet containing 5 µg/1,000 kcal, there were no significant changes in variables measured. However, after subjects consumed 5 µg of chromium per 1,000 kcal for 9 weeks, a significant increase from baseline was observed in sums of glucose and in glucose at 90 minutes after the glucose load (Table 6-1). Supplementation with 200 µg of chromium as CrCl₃ for 5 weeks tended ($p < 0.10$) to reduce sums of glucose and insulin concentrations in these subjects. Although this study suggests a role of chromium in regulating blood glucose concentrations, further studies using graded levels of intake between less than

TABLE 6-1 Glucose and Insulin Concentrations of Eight Subjects Fed Low Chromium (5 µg/1,000 kcal) Diets for 14 Weeks and Supplemented with Placebo for 9 Weeks Followed by 200 µg CrCl₃ for 5 Weeks

	Week			
	0	4	9	14
Glucose (mmol/L)				
Fasting	4.9 ± 0.2	4.8 ± 0.1	4.9 ± 0.1	5.1 ± 0.1
90 minute	4.2 ± 0.4	4.5 ± 0.4	5.0 ± 0.6 ^a	4.4 ± 0.4
Sums (0-240 min)	33.6 ± 1.6	35.1 ± 1.4	37.0 ± 2.2	34.6 ± 1.6 ^b
Insulin (pmol/L)				
Fasting	38 ± 5	33 ± 5	48 ± 6	49 ± 7
Sums (0-240 min)	1,146 ± 130	1,214 ± 167	1,577 ± 354	1,319 ± 281 ^b

^a Different from baseline by paired t-test, $p < 0.05$.

^b Week 9 (end of placebo) vs. supplement by paired t-test, $p < 0.10$.

SOURCE: Reanalysis of Anderson et al. (1991), by personal communication.

5 µg/1,000 kcal and the usual dietary chromium levels (13 to 20 µg/1,000 kcal) and with different age groups are needed to estimate the average requirement for chromium.

FACTORS AFFECTING THE CHROMIUM REQUIREMENT

A number of dietary factors affect chromium absorption. Offenbacher (1994) noted plasma chromium concentrations in three women were consistently higher when they were given 1 mg chromium as CrCl₃ with 100 mg ascorbic acid than when given 1 mg chromium without ascorbic acid. In rats, concurrent dosing with ⁵¹CrCl₃ and ascorbic acid, as compared to dosing in water, produced significantly higher ⁵¹Cr in urine without decreasing ⁵¹Cr in tissues, a finding that suggests ascorbic acid enhanced ⁵¹Cr absorption (Davis et al., 1995; Seaborn and Stoecker, 1990).

Consumption of diets high in simple sugars (35 percent of total kcal) increased urinary chromium excretion in adults (Kozlovsky et al., 1986). Urinary chromium excretion was found to be related to the insulinogenic properties of carbohydrates (Anderson et al., 1990). Carbohydrate source also had a significant effect on tissue chromium concentration in mice, with values generally being higher in those fed a starch diet (Seaborn and Stoecker, 1989). When amino acids were added to a test meal perfused through the intestinal lumen of rats, the absorption of chromium was increased two-fold (Dowling et al., 1990).

In rats, phytate at high levels had adverse effects on ⁵¹Cr absorption (Chen et al., 1973), but lower levels of phytate did not have detrimental effects on chromium status (Keim et al., 1987). Oxalate (present in some vegetables and grains) enhanced ⁵¹Cr uptake (Chen et al., 1973). Bunker and coworkers (1984) commented that one subject in severe negative chromium balance ate a diet very high in fiber, but effects of high fiber diets on chromium absorption have not been investigated systematically.

Habitual consumption of certain medications that alter stomach acidity or gastrointestinal prostaglandins may affect chromium absorption and retention in rats. When rats were dosed with physiological doses (less than 100 ng) of ⁵¹CrCl₃ and prostaglandin inhibitors such as aspirin, ⁵¹Cr in blood, tissues, and urine was markedly increased (Davis et al., 1995). Medications, such as antacids or dimethylprostaglandin E₂, reduced ⁵¹Cr absorption and retention in rats (Kamath et al., 1997).

FINDINGS BY LIFE STAGE AND GENDER GROUP

*Infants Ages 0 through 12 Months**Method Used to Set the Adequate Intake*

No functional criteria of chromium status have been demonstrated that indicate response to dietary intake in infants. Thus, the recommended intakes of chromium are based on an Adequate Intake (AI) that reflects the observed mean chromium intake of infants principally fed human milk.

Ages 0 through 6 Months. According to the method described in Chapter 2, the AI for chromium is based on the milk content from healthy, well-nourished mothers who are not taking supplements. The average concentration of chromium in human milk was estimated to be 0.25 µg/L (Anderson et al., 1993a; Casey and Hambidge, 1984; Casey et al., 1985; Engelhardt et al., 1990; Mohamedshah et al., 1998) (Table 6-2). Based on the consumption of 0.78 L/day of human milk (Chapter 2), the AI for chromium for infants ages 0 through 6 months is 0.2 µg/day after rounding.

Ages 7 through 12 Months. Schroeder and coworkers (1962) reported a rapid decline in tissue chromium concentrations after birth. These tissue concentrations were generated before chromium measurement techniques were reliable (Anderson, 1987); nonetheless, the possibility that infants deplete their stores during the early months of life suggests that the AI possibly should not be based solely on human milk consumption.

There are no specific data on the chromium concentration of weaning foods; this indicates an area of needed research. An average daily caloric intake for this age group is 845 kcal and human milk provides 750 kcal/L (Fomon, 1974). During the second 6 months of lactation, the average volume of human milk consumed by the infant is 0.6 L/day (Chapter 2). Therefore, calories provided by human milk would be 450 kcal (0.6 L of human milk × 750 kcal/L) and the caloric content of the usual intake of complementary weaning foods would be 395 kcal (845 – 450).

Based on an average concentration of 0.25 µg/L, the chromium intake from human milk would be 0.15 µg/day (0.6 × 0.25). With an additional 400 kcal from complementary foods and the chromium content of well balanced meals containing approximately 13.4 µg/ 1,000 kcal (Anderson et al., 1992), the amount of chromium

TABLE 6-2 Chromium Concentration in Human Milk

Reference ^a	Study Group	Stage of Lactation	Milk Concentration (µg/L)	Estimated Chromium Intake of Infants (µg/d) ^b
Casey and Hambidge, 1984	45 women	0–14 d	0.29	0.22
		15–28 d	0.27	0.21
		1–3 mo	0.28	0.22
		4–6 mo	0.26	0.16
		7+ mo	0.46	0.27
Casey et al., 1985	11 women, 26–39 y	8 d	0.27	0.21
		14 d	0.22	0.17
		21 d	0.28	0.22
		28 d	0.26	0.20
Engelhardt et al., 1990			0.28	0.22
Anderson et al., 1993a	17 women	2 mo	0.18	0.14
Aquilio et al., 1996	14 women	21 d	1.2	0.93
Mohamedshah et al., 1998	6 women, 25–38 y	1–2 mo	0.09–0.46	0.07–0.36

^a Maternal intakes were not reported in these studies.

^b Chromium intake based on reported data or concentration (µg/L) × 0.78 L/day for 0–6 months postpartum and concentration (µg/L) × 0.6 L/day for 7–12 months postpartum.

consumed from weaning foods is estimated to be 5.36 µg/day. Therefore the amount of chromium consumed from human milk and complementary foods would be 5.5 µg/day (0.15 + 5.36). Downward extrapolation from an adult, according to the method in Chapter 2, would yield an average intake of 10 µg/day.

An AI of 5.5 µg/day is set for infants ages 7 through 12 months based on consumption of chromium from human milk and complementary foods.

*Chromium AI Summary, Ages 0 through 12 Months***AI for Infants**

0–6 months	0.2 µg/day of chromium	29 ng/kg/day
7–12 months	5.5 µg/day of chromium	611 ng/kg/day

Special Considerations

The mean concentration of chromium in cow milk and infant formula was reported to be 0.83 and 4.84 µg/L, respectively (Cocho et al., 1992). There is no information on the bioavailability of chromium in infant formula.

*Children and Adolescents Ages 1 through 18 Years**Method Used to Set the Adequate Intake*

No data were found on which to base an Estimated Average Requirement for children and adolescents; therefore AIs have been set. In the absence of information on the chromium content of children's diets, AIs for these age groups have been extrapolated from adults, ages 19 through 30 years, with use of the method described in Chapter 2 and rounding to the nearest 1 µg. Because urinary excretion of chromium is increased with exercise (Anderson et al., 1982, 1984, 1988b), metabolic weight ($\text{kg}^{0.75}$) was used to extrapolate from the adult AI.

*Chromium AI Summary, Ages 1 through 18 Years***AI for Children**

1–3 years	11 µg/day of chromium
4–8 years	15 µg/day of chromium

AI for Boys

9–13 years	25 µg/day of chromium
14–18 years	35 µg/day of chromium

AI for Girls

9–13 years	21 µg/day of chromium
14–18 years	24 µg/day of chromium

*Adults Ages 19 through 50 Years**Method Used to Set the Adequate Intake*

Data, as described earlier, are lacking for estimating an average requirement for adults. Furthermore, no national survey data are available on chromium intakes.

The mean chromium content of 22 well-balanced adult diets, designed by nutritionists, was 13.4 ± 1.1 $\mu\text{g}/1,000$ kcal (standard error of the mean [SEM]) (range 8.4 to 23.7 $\mu\text{g}/1,000$ kcal) (Anderson et al., 1992). The mean chromium intake of 13.4 $\mu\text{g}/1,000$ kcal and an energy intake estimate of 1,850 kcal/day for women and 2,800 kcal for men aged 19 through 30 years (Briefel et al., 1995) has been used as a basis for deriving AI estimates for chromium. For women and men aged 31 through 50 years, median energy intakes of 1,750 and 2,550 kcal/day, respectively, have been used (Briefel et al., 1995). Although there is no method available to adjust for the underreporting of intake, it is recognized that as much as 20 percent of energy intake may be underreported (Mertz et al., 1991). For this reason, the highest intake value for adults 19 through 30 years and 31 through 50 years was used to set the AI for each gender. Therefore, the AI for men is 35 $\mu\text{g}/\text{day}$ ($2,800 \times 13.4$) and 25 $\mu\text{g}/\text{day}$ ($1,850 \times 13.4$), after rounding.

*Chromium AI Summary, Ages 19 through 50 Years***AI for Men**

19–30 years	35 $\mu\text{g}/\text{day}$ of chromium
31–50 years	35 $\mu\text{g}/\text{day}$ of chromium

AI for Women

19–30 years	25 $\mu\text{g}/\text{day}$ of chromium
31–50 years	25 $\mu\text{g}/\text{day}$ of chromium

*Adults Ages 51 Years and Older**Method Used to Set the Adequate Intake*

As discussed for adults 19 through 50 years, the mean chromium content of 22 well-balanced daily diets, designed by nutritionists, was 13.4 ± 1.1 $\mu\text{g}/1,000$ kcal (SEM) (range 8.4 to 23.7 $\mu\text{g}/1,000$ kcal) (Anderson et al., 1992). The median energy intakes for men and women, 50 through 70 years of age, were 2,100 and 1,500 kcal/

day, respectively (Briefel et al., 1995). The energy needs for men and women older than 70 years of age are 1,700 and 1,300 kcal/day, respectively (Briefel et al., 1995). Although there is no method available to adjust for the underreporting of intake, it is recognized that as much as 20 percent of energy intake is underreported (Mertz et al., 1991). For this reason, the highest intake value for adults 51 through 70 years and greater than 70 years was used to set the AI for each gender. Therefore, the AI for men is 30 µg/day ($2,100 \times 13.4$) and 20 µg/day ($1,500 \times 13.4$) after rounding.

Research is imperative on chromium needs for this age group because of the paucity of data. Increased nutrient density is generally recommended for the elderly, and several factors suggest that the elderly might be more vulnerable to chromium depletion than younger adults. These factors include the severely negative chromium balance produced by a high fiber diet (Bunker et al., 1984), the possible impacts of medications on chromium absorption (Kamath et al., 1997; Martinez et al., 1985), the decrease with age of chromium concentrations in hair and sweat (Davies et al., 1997), and the increased prevalence of impaired glucose tolerance with aging (Harris et al., 1998).

Chromium AI Summary, Ages 51 Years and Older

AI for Men

51–70 years	30 µg/day of chromium
> 70 years	30 µg/day of chromium

AI for Women

51–70 years	20 µg/day of chromium
> 70 years	20 µg/day of chromium

Pregnancy

Method Used to Set the Adequate Intake

There are several reports that chromium is depleted throughout pregnancy and with multiple pregnancies (Hambidge, 1971; Mahalko and Bennion, 1976; Saner, 1981). Tissue analyses conducted before current instruments were available indicated that chromium is higher in tissues at birth (Schroeder et al., 1962) and declines rapidly with age. This suggests the need for deposition in the fetus from the mother. The low concentration of chromium in human milk also indicates that the infant may use stored chromium during the early

months of life. These earlier estimates of the chromium concentrations, however, cannot be used to accurately predict the additional needs of chromium during pregnancy.

Because of the lack of data to estimate the additional chromium requirement during pregnancy, the AI is determined by extrapolating up from adolescent girls and adult women, as described in Chapter 2. Carmichael and coworkers (1997) reported that the median weight gain of 7,002 women who had good pregnancy outcomes was 16 kg. In six studies of U.S. women, no consistent relationship between maternal age and weight gain was observed (IOM, 1990). Therefore, 16 kg is added to the reference weight for adolescent girls and adult women for extrapolation.

Chromium AI Summary, Pregnancy

AI for Pregnancy

14–18 years	29 µg/day of chromium
19–30 years	30 µg/day of chromium
31–50 years	30 µg/day of chromium

Lactation

Method Used to Set the Adequate Intake

The AI for lactation is estimated on the basis of the chromium intake necessary to replace chromium secreted in human milk plus the AI for women. The amount that must be absorbed to replace the chromium secreted in milk is $0.252 \mu\text{g/L} \times 0.78 \text{ L/day}$, or 200 ng/day. If absorption is estimated at 1 percent, 20 µg/day of chromium must be consumed beyond the usual intake to compensate for the milk losses. If absorption is only 0.5 percent, an additional 40 µg/day would be required. In the one study available on dietary intakes of lactating women, chromium intake was 41 µg/day (Anderson et al., 1993a).

Women do not appear to reduce urinary chromium excretion during lactation to compensate for increased needs (Mohamedshah et al., 1998). To calculate an AI for chromium during lactation, it is assumed that 1 percent of chromium is absorbed and 0.2 µg/day is secreted in human milk. Therefore 20 µg is added to the AI for adolescent girls and adult women, and the AI is rounded.

*Chromium AI Summary, Lactation***AI for Lactation**

14–18 years	44 µg/day of chromium
19–30 years	45 µg/day of chromium
31–50 years	45 µg/day of chromium

INTAKE OF CHROMIUM

Food Sources

Chromium is widely distributed throughout the food supply, but many foods contribute less than 1 to 2 µg per serving (Anderson et al., 1992). Determining the chromium content in foods requires rigorous contamination control because standard methods of sample preparation contribute substantial amounts of chromium to the foods being analyzed. In addition, chromium is quite variable among different lots of foods (Anderson et al., 1992) and may be influenced by geochemical factors (Welch and Cary, 1975). Consequently dietary chromium intakes cannot be determined from any currently existing databases.

The chromium content in foods may increase or decrease with processing. Early reports indicated chromium losses when grains and sugars were refined (Anderson, 1987). However, acidic foods accumulate chromium during preparation and processing, particularly when heated in stainless steel containers (Offenbacher and Pi-Sunyer, 1983). Cereals contribute variable, but potentially important, amounts of chromium to the total diet. The chromium content of a 50 g serving (dry weight) of 43 brands of cereal varied from 0.15 to 35 µg. High-bran cereals are generally, but not always, high in chromium. The bioavailability of chromium in these cereals was not evaluated (Anderson et al., 1988a). Most dairy products are low in chromium and provide less than 0.6 µg/serving. Meats, poultry, and fish generally contribute 1 to 2 µg per serving, but processed meats are higher in chromium and may acquire it from exogenous sources. Chromium concentrations of fruits and vegetables are highly variable (Anderson et al., 1992). Some brands of beer contain significant amounts of chromium, some of which presumably is exogenous (Anderson and Bryden, 1983). Cabrera-Vique and coworkers (1997) estimated that wine provides 4.1 µg chromium daily per resident in France, with red wines having the highest concentrations. Wines have not been analyzed for chromium in the United States.

Dietary Intake

Because chromium in foods cannot be analyzed from existing databases, paired food or duplicate meal analyses are required, and data are available from only a few laboratories and locations. In one study, self-selected diets were composited for 7 days and analyzed for chromium content. The mean chromium intake of 10 adult men was 33 $\mu\text{g}/\text{day}$ (range 22 to 48 $\mu\text{g}/\text{day}$), and the chromium intake for 22 women was 25 $\mu\text{g}/\text{day}$ (range 13 to 36 $\mu\text{g}/\text{day}$) (Anderson and Kozlovsky, 1985). Mean chromium intake was approximately 15.6 $\mu\text{g}/1,000$ kcal. The chromium content of 22 daily diets, designed by nutritionists to be well balanced, ranged from 8.4 to 23.7 $\mu\text{g}/1,000$ kcal with a mean of 13.4 $\mu\text{g}/1,000$ kcal (Anderson et al., 1992). In another study, a group of adults self-selected a mean chromium intake of 14.4 $\mu\text{g}/1,000$ kcal (Anderson et al., 1991), and lactating mothers consumed foods containing 18.8 $\mu\text{g}/1,000$ kcal (Anderson et al., 1993a). Chromium intake studies in Canadian women suggest median chromium intakes two or more times higher than the values reported from the eastern United States (Gibson and Scythes, 1984; Gibson et al., 1985). Further research is needed to define the contributions of differences in dietary patterns, regional variation in food chromium concentrations, and possible sample contamination in these disparate values.

Derivation of dietary intake based on duplicate meal analyses assumes that subjects do not change their intakes because of the collection; however, this assumption may underestimate actual food intake (Kim et al., 1984). In a controlled study in which actual energy requirements of subjects were estimated, Anderson and co-workers (1993b) found that the ratio of energy requirement to energy intake measured from the duplicate meal analysis was 1.29 for women and 1.46 for men. Applying these correction factors to chromium intakes would increase the estimated chromium intake of women in this study from 23.1 to 28.7 $\mu\text{g}/\text{day}$ and of men from 38.8 to 54.1 $\mu\text{g}/\text{day}$. This correction raises the question of whether some of the current estimates of dietary chromium intake are too low.

Intake from Supplements

In 1986, 8 percent of adults consumed supplements that contained chromium (Moss et al., 1989; see Table 2-2). Based on the Third National Health and Nutrition Examination Survey data, the median supplemental intake of chromium was 23 $\mu\text{g}/\text{day}$ for those

who took supplements, which is similar to the average dietary chromium intake (Appendix Table C-14).

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving chromium under medical supervision.

Hazard Identification

The toxicity of chromium differs widely depending on the valence state. This review is limited to evaluating trivalent chromium (III) because this is the principal form of chromium found in food and supplements. Hexavalent chromium (VI), which has a much higher level of toxicity than trivalent chromium, is not found in food. Ingested chromium III has a low level of toxicity which is due, partially, to its very poor absorption (Stoecker, 1999). Chromium supplement use (particularly chromium picolinate) has increased in popularity as a result of reports that chromium potentiates the action of insulin and reduces hyperglycemia and hyperlipidemia (Flodin, 1990). Several studies have demonstrated the safety of large doses of chromium III (Anderson et al., 1997a; Hathcock, 1997). The data on the potential adverse effects of excess intake of chromium III compounds are reviewed below.

Chronic Renal Failure

Chronic interstitial nephritis in humans has been attributed to ingestion of chromium picolinate in two case reports (Cerulli et al., 1998; Wasser et al., 1997). However, there is no evidence of kidney damage in experimental animals exposed for up to 2 years to oral chromium as chromium chloride, chromium trichloride, chromium picolinate, or chromium acetate (Anderson et al., 1997a; Schroeder et al., 1962).

Genotoxicity

Chromium VI is a well established human carcinogen, mutagen, and clastogen, but chromium III compounds are not. In vivo genotoxicity assays for chromium III have been negative (Cupo and Wetterhahn, 1985; Hamamy et al., 1987; Itoh and Shimada, 1996). Most studies of genotoxicity in cellular systems have yielded negative results as well (ATSDR, 1998), which in some cases may be due to poor uptake by cells. In eukaryotic cells, negative results were obtained for DNA fragmentation, unscheduled DNA synthesis, and forward mutation (Raffetto et al., 1977; Whiting et al., 1979). Mostly negative results were obtained in sister chromatid exchange assays (Levis and Majone, 1979; Stella et al., 1982; Venier et al., 1982), but both positive and negative results have been found for chromosomal aberrations (Fornace et al., 1981; Levis and Majone, 1979; Nakamuro et al., 1978; Newbold et al., 1979; Raffetto et al., 1977; Stella et al., 1982; Tsuda and Kato, 1977; Umeda and Nishimura, 1979). In prokaryotic cells, the genotoxicity results were mostly negative. Positive results of chromium III were found in intact cells; however, these results could be due to contamination of the test compounds with traces of chromium VI, which is readily taken up by cells (ATSDR, 1998). Several studies suggest that chromium III picolinate and tri-picolinate may cause DNA damage through the generation of hydroxyl radicals (Bagchi et al., 1997; Speetjens et al., 1999; Stearns et al., 1995).

Carcinogenicity

There is little evidence of carcinogenicity in humans or animals after oral intake of chromium III. Kusiak and coworkers (1993) reported increased mortality due to stomach cancer in gold miners in Canada. Although the authors suggest that chromium dust may be the causative agent, the study did not adjust for possible important confounding factors (e.g., role of dietary habits) and failed to show a clear pattern of disease incidence with increasing exposure. A 2-year feeding study in rats by Ivankovic and Preussmann (1975) showed no carcinogenicity after intake (5 days/week for 2 years) of 1, 2, or 5 percent chromium oxide (Cr_2O_3) baked in bread.

Hepatic Dysfunction

There are reports of hepatic adverse effects in humans (Fristedt et al., 1965; Kaufman et al., 1970; Loubieres et al., 1999). Several rat

studies show no morphological changes in livers following long-term ingestion of chromium compounds (Ivankovic and Preussmann, 1975; Mackenzie et al., 1958; Schroeder et al., 1965).

Reproductive Effects

There are no studies in humans to suggest that chromium III is a reproductive or developmental toxicant. However, various chromium III compounds have been studied in mice and rats with respect to their reproductive system toxicity. Chromium chloride (in drinking water) administered over 12 weeks reduced fertility in male mice, reduced the number of implantation sites and the number of viable fetuses, and delayed sexual maturity (Al-Hamood et al., 1998; Elbeticha and Al-Hamood, 1997). Intraperitoneal injections of chromium chloride (1, 2, or 4 mg/kg) for 5 days to male rats had no effect on testicular histology or sperm counts (Ernst, 1990). The ingestion of 1,000 µg/mL of chromium as chromium chloride in drinking water for 12 weeks led to significant reductions in the weight of the rat's testes and seminal vesicles (Bataineh et al., 1997).

Other Adverse Effects

Other adverse effects observed after high chromium intakes include rhabdomyolysis (Martin and Fuller, 1998). Rhabdomyolysis is characterized by skeletal muscle injury and release of muscle cell contents into the plasma. Reports of chromium-induced rhabdomyolysis failed to account for other potential etiologic factors including strenuous exercise, weight lifting, trauma, seizure, sepsis, and alcohol and drug abuse.

Identification of Distinct and Highly Sensitive Subpopulations

Data suggest that individuals with preexisting renal and liver disease may be particularly susceptible to adverse effects from excess chromium intake (ATSDR, 1998). These individuals should be particularly careful to limit chromium intake.

Dose-Response Assessment

The limited studies on renal, hepatic, reproductive, and DNA damaging effects of chromium III do not provide dose-response information or clear indications of a lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL). Thus,

there are insufficient data to establish a UL for soluble chromium III salts. Because of the current widespread use of chromium supplements, more research is needed to assess the safety of high-dose chromium intake from supplements. Data from randomized, double-blind, controlled clinical trials and surveillance studies would be most useful for assessing the safety of chromium intake in humans.

Intake Assessment

National survey data are not available on the intake of chromium at various percentiles. According to data from the Third National Health and Nutrition Examination Survey, the average supplemental intake of chromium at the ninety-fifth percentile was 100 µg/day for men and 127 µg/day for women (Appendix Table C-14).

Risk Characterization

No adverse effects have been convincingly associated with excess intake of chromium from food or supplements, but this does not mean that there is no potential for adverse effects resulting from high intakes. Since data on the adverse effects of chromium intake are limited, caution may be warranted.

RESEARCH RECOMMENDATIONS FOR CHROMIUM

- Controlled studies with low dietary intakes (less than 5 to 15 µg/1,000 kcal) to determine an Estimated Average Requirement.
- Chromium absorption, metabolism, and requirements during pregnancy and lactation.
- Information on variability in chromium concentration in the food and water supply.
- Development and validation of a useful clinical indicator to identify persons with marginal chromium status and investigation of effects of physiological levels of chromium supplementation in these patients.
- Investigation of possible relationships between chromium status and insulin resistance, impaired glucose tolerance, and Type II diabetes.
- Monitoring of any adverse effects of self-supplementation and of the design of controlled studies to assess potential beneficial, as well as adverse, effects of large-dose supplementation of chromium.

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