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Introduction – The Current Status of Chromium(III)

When a member of the general public thinks about chromium and health, unfortunately the first thing to come to mind is probably one or more of the following claims:

- reduces body fat;
- causes weight loss;
- causes weight loss without exercise;
- causes long-term or permanent weight loss;
- increases lean body mass or builds muscle;
- increases human metabolism;
- controls appetite or craving for sugar; or
- 90% of US adults do not consume diets with sufficient chromium to support normal insulin function, resulting in increased risk of obesity, heart disease, elevated blood fat, high blood pressure, diabetes, or some other adverse effect on health.

In other words, most people think of chromium in terms of weight loss and lean muscle mass development as a result of nutraceutical product marketing. Yet the Federal Trade Commission (FTC) of the United States ordered entities associated with the nutritional supplement chromium picolinate to stop making each of the above representations in 1997 because of the lack of 'competent and reliable scientific evidence' [1]. This ruling is now well over a decade old; however, the situation has

changed little. In fact in 2000, products containing chromium picolinate had sales of nearly a half a billion dollars [2]. The FTC currently has pending law suits against entities associated with chromium picolinate-containing products, while the scientific support for most of these claims has completely eroded [3]. For example, recently the National Institutes of Health sponsored a study where male and female rats and mice were given diets containing up to 5% chromium picolinate by mass for up to two years; no effects were observed on body mass or food intake [4]. Studies of the effects of chromium picolinate will be presented in Chapter 4.

The basis for the use of chromium as a nutritional supplement stems from chromium being on the list of essential vitamins and minerals under examination by the National Research Council of the National Academies of Science, USA since 1980 [5], after initially being proposed as an essential element in 1959; (the history of the status of chromium as a trace element is reviewed in Chapter 3) [6]. In 2001, the National Academies of Science established an Adequate Intake (AI) of chromium of 35 $\mu\text{g}/\text{day}$ for men and 25 $\mu\text{g}/\text{day}$ for women [7]. AI is defined as 'the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate.' The AI 'is expected to cover the needs of more than 97–98% of individuals' [7]. Thus, almost all Americans are believed to be chromium sufficient, and little if any need exists for chromium supplementation. The bases for this determination are rather limited. Anderson *et al.* have established that self-selected American diets contain on average 33 $\mu\text{g Cr}/\text{day}$ for men and 25 $\mu\text{g Cr}/\text{day}$ for women [8], while nutritionist-designed diets [9] contain on average 34.5 $\mu\text{g Cr}$ for men and 23.5 $\mu\text{g Cr}/\text{day}$ for women. Offenbacher *et al.* have found that men (two subjects) could maintain their chromium balance when receiving 37 $\mu\text{g Cr}/\text{day}$ [10]. Bunker *et al.* have shown for 22 elderly subjects consuming, on average, 24.5 $\mu\text{g Cr}/\text{day}$ that 16 were in chromium balance, 3 were in positive balance and 3 were in negative balance [11]. The situation is likely to be similar in other developed nations; for example, pre-menopausal Canadian women eating self-selected diets have been found to have an average daily intake of 47 μg of chromium [12]. Currently, as discussed in Chapter 2, whether chromium is an essential element is at best an open question, and it probably should not currently be considered to be an essential element. If chromium is an essential element, it must interact specifically with some biomolecules in the body

and serve a specific function; attempts to identify such a molecule and a role in the body will be discussed in Chapter 6.

In addition to the purported use to reduce body mass and build muscle, chromium supplements have also been touted to alleviate the symptoms of type 2 diabetes and related cardiovascular disorders, in addition to other conditions. While administration of chromium(III) complexes has positive effects in rodent models of type 2 diabetes and other conditions, the situation in humans is currently ambiguous (see Chapter 5 for a thorough discussion). According to the American Diabetes Association in its 2010 Clinical Practices Recommendations, ‘Benefit from chromium supplementation in people with diabetes or obesity has not been conclusively demonstrated and therefore cannot be recommended’ [13]. The American Diabetes Association dropped any mention of chromium in its 2011 and 2012 recommendations.

In December 2003, Nutrition 21, the major supplier of chromium picolinate, petitioned the US Food and Drug Administration (FDA) for eight qualified health claims:

1. Chromium picolinate may reduce the risk of insulin resistance.
2. Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.
3. Chromium picolinate may reduce abnormally elevated blood sugar levels.
4. Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.
5. Chromium picolinate may reduce the risk of type 2 diabetes.
6. Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.
7. Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.
8. Chromium picolinate may reduce the risk of kidney disease when caused by abnormally high blood sugar levels [14].

After extensive review, the FDA issued a letter of enforcement discretion allowing only one (No. 5) qualified health claim for the labelling of dietary supplements [14, 15]: ‘One small study suggests that chromium picolinate may reduce the risk of type 2 diabetes. FDA concludes that the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes is highly uncertain.’ The small study was performed by Cefalu *et al.* [16]. This study was a

placebo-controlled, double-blind trial examining 1000 $\mu\text{g}/\text{day}$ of Cr as chromium picolinate on 29 obese subjects with a family history of type 2 diabetes; while no effects of the supplement were found on body mass or body fat composition or distribution, a significant increase in insulin sensitivity was observed after four and eight months of supplementation [16]. Mechanisms by which chromium has been proposed to potentially have an effect on type 2 diabetes and associated conditions will be discussed in Chapter 6.

A safety assessment was also part of the FDA evaluation of chromium picolinate [14]. As reviewed in Chapter 9, the safety of chromium picolinate has been questioned after cell culture and developmental toxicity studies in fruit flies have shown that the compound could be mutagenic and carcinogenic. However, the FDA determined that the 'use of chromium picolinate in dietary supplements . . . is safe' [14]. The European Food Safety Authority (EFSA) recently also determined that chromium supplements in doses not exceeding 250 μg Cr per day are safe [17, 18]. The safety of chromium picolinate as a nutritional supplement has been confirmed by a study commissioned by the National Toxicology Program of the National Institutes of Health. The study examined the effects of chromium picolinate comprising up to 5% of the diet (by mass) of rats and mice for up to two years and found no harmful effects on female rats or mice and, at most, ambiguous data for one type of carcinogenicity in male rats (along with no changes in body mass in either sex of rats or mice) [4]. The reasons behind the discrepancies between the toxicology studies will be examined in Chapter 9.

Chromium(III) complexes are often used as animal feed supplements, in addition to being a popular human supplement. The use of chromium as an animal feed supplement was evaluated in the mid-1990s by the Committee on Animal Research, Board of Agriculture of the National Research Council [19]. In general the available data were insufficient for conclusions to be drawn; for example, no conclusions could be reached about the need for supplemental chromium in the diets of fish, rats, rabbits, sheep and horses. Specific recommendations could not be made about the diets of poultry, swine and cattle, although chromium was determined possibly to have a beneficial effect for cattle under stress and improve swine carcass leanness and reproductive efficiency [19]. Chromium was, however, found to be safe as a food additive. As is reviewed in Chapter 8, the situation with regard to chromium dietary supplementation in animals has changed little in the last decade.

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