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Food and Chemical Toxicology 43 (2005) 21–29
www.elsevier.com/locate/foodchemtox

Absence of toxic effects in F344/N rats and B6C3F$_1$ mice following subchronic administration of chromium picolinate monohydrate

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Received 20 April 2004; accepted 10 August 2004

Abstract

Chromium picolinate monohydrate (CPM) is a synthetic compound heavily marketed to consumers in the United States for use as a dietary supplement for muscle building and weight loss. The National Toxicology Program (NTP) tested the toxicity of this compound based on the potential for widespread consumer exposure and lack of information about its toxicity. Groups of 10 male and 10 female F344/N rats and B6C3F$_1$ mice were exposed to 0, 80, 240, 2000, 10,000, or 50,000 ppm CPM in feed for 13 weeks. CPM administration produced no effect on body weight gain or survival of rats or mice. Organ weights and organ/body weight ratios in exposed animals were generally unaffected by CPM. No compound-related changes in hematology and clinical chemistry parameters were observed. There were no histopathological lesions attributed to CPM in rats or mice.

Keywords: Chromium; Feed; Mice; NTP; Picolinate; Rats; Subchronic; Supplement; Toxicity

1. Introduction

Chromium picolinate monohydrate (CPM, also known as chromium trispicolinate) is a synthetic compound that has widespread use as a nutritional supplement. In the past decade, chromium-containing supplements have become very popular, generating an estimated $500 million in retail sales in 1999 (Mirastol, 2000). Advocates of the trace mineral claim that it promotes a variety of beneficial health effects including weight loss, serum cholesterol reduction, treatment of diabetes, and increased muscle mass. However, recent reviews examining the effectiveness of chromium picolinate indicate that the supplement has little or no demonstrated effects on body composition of healthy individuals, even when taken in combination with an exercise training program (Campbell et al., 2002; Pittler et al., 2003; Vincent, 2003).

Supplements can contain CPM either alone or in combination with other compounds that are believed to be pharmacologically active. The only regulation on the sale of this compound is by the Federal Trade Commission, which prohibits the making of health claim benefits without reliable scientific evidence supporting such claims (Federal Trade Commission, 1996). CPM is commonly supplied in 200–500 μg tablets (0.48–1.19 μmol), and a daily dose in this range is typically suggested by the supplier. Such doses are comparable to the estimated safe and adequate daily dietary intake of chromium, 25–45 μg/day (0.48–0.87 μmol) for adults

Abbreviations: CPM, chromium picolinate monohydrate; NTP, National Toxicology Program; 8-OHdG, 8-hydroxydeoxyguanosine

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doi:10.1016/j.fct.2004.08.006

(Trumbo et al., 2001). However, chromium complexed with picolinate is more efficiently absorbed (2–5%) than dietary chromium (0.5–2%) (Anderson et al., 1996; Olin et al., 1994). Increased absorption of CPM could render this supplement more or less toxic than dietary chromium; the potential positive and negative effects of chromium supplementation have been reviewed elsewhere (Vincent, 2003). Numerous acute adverse drug reactions have been reported by humans after ingesting supplements containing chromium picolinate, including chest pain, anemia, thrombocytopenia, rhabdomyolysis, dermatitis, dehydration, agitation, dizziness, headache, and cognitive, perceptual, and motor changes (Fowler, 2000; Huszonek, 1993; Martin and Fuller, 1998). 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).

There are a number of studies examining the genotoxicity of chromium supplements. Chromium picolinate was reported to be negative in the Ames *Salmonella* mutagenicity assay (McCarty, 1996). Soluble chromium picolinate induced chromosomal aberrations in Chinese hamster ovary cells in vitro (Stearns et al., 1995). Picolinic acid was also reported to be clastogenic with the same assay, but it was nonmutagenic when tested in several strains of *Salmonella*, and did not induce unscheduled DNA synthesis in UV-irradiated human lymphocytes (Bowden et al., 1976). Hepburn et al. (2003) recently demonstrated that chromium picolinate causes sterility and lethal mutations in *Drosophila melanogaster*. Intravenous injection of rats with 5 μg chromium picolinate daily for 60 days resulted in significant increases in urinary 8-hydroxydeoxyguanosine (8-OHdG), a product of oxidative DNA damage (Hepburn et al., 2003).

Chromium picolinate fed to weanling Sprague–Dawley rats at 5000 ng Cr/g of diet for three weeks resulted in significant increases in chromium incorporation into the kidney, liver, spleen, heart, and lung when compared to controls fed basal diet containing 30 ng Cr/g of diet; the greatest concentration of chromium was in the kidney (Anderson et al., 1997). No adverse effects were reported in Sprague–Dawley rats administered chromium picolinate in feed at concentrations of 0, 5, 25, 50, or 100 ppm for 20 weeks (Anderson et al., 1997).

Chromium in CPM is trivalent. Chromium (III) is an essential trace element, serving as a component of the glucose tolerance factor (GTF) (Evans and Pouchnik, 1993). It is a cofactor for insulin action and has a role in the peripheral activities of this hormone by forming a ternary complex with insulin receptors, facilitating the attachment of insulin to these sites (Goyer and Clarkson, 2001). Picolinate is a metabolite of tryptophan and is normally found in the liver and kidneys (Mehler and May, 1956). Prior to the onset of this study, the NTP conducted distribution and metabolism studies of CPM. These studies were limited by the solubility of CPM. Urinary excretion of radiolabel following oral doses of up to 20 mg/kg [^{14}C]CPM to rats and mice was nearly all in the form of a single metabolite that was identified as *n*-picolinoylglycine. Urinary excretion of chromium was much lower than urinary excretion of radiolabel, with less than 2% of the administered dose in rats and less than 5% of the administered dose in mice being excreted in urine for orally dosed animals. For rats, 98% of the chromium was excreted in feces. In NTP disposition studies from 3 animals 52 h following a 15.3 mg/kg oral dose of CPM, chromium levels in the lung, spleen, and kidney were 70–120 ng/g, while levels in the liver were below 60 ng/g, the level of quantification. CPM was incubated in vitro with the stomach or small intestine to determine the stability. After up to 2 h, 90–100% of the CPM was recovered by extraction with methanol. This coupled with the absorption of the organic portion of CPM, but not the chromium, led to the conclusion that most of the CPM is broken down in or near the intestinal wall.

Because little is known about the toxic potential of CPM, and because CPM is chronically ingested at relatively high amounts by a large number of people in the United States, the present studies were performed to characterize the toxicity of CPM in rodent models. Since the primary route of exposure to humans is by the ingestion of supplements, animals were administered CPM in the diet.

2. Materials and methods

2.1. Chemical

Chromium picolinate monohydrate (CAS# 27882-76-4, ~99% pure by HPLC analysis) was obtained from TCI America (Portland, OR).

2.2. Preparation and analysis of dose formulations

The dose formulations were prepared with irradiated NTP-2000 open formula diet (Zeigler Brothers, Inc., Gardners, PA) four times throughout the study. Dose formulations were analyzed three times during the studies; all samples were within 10% of the target concentrations. CPM in feed was stable for at least 42 days when stored at room temperature, protected from light, and under simulated animal room conditions at a concentration of 82 ppm for 8 days at room temperature.

2.3. Animals

All rodent studies were conducted at Southern Research Institute, Birmingham, Alabama. Animal use was in accordance with the United States Public Health