Planned National Toxicology Program Studies on Hexavalent Chromium

Updated 2004

A study of the carcinogenic potential of hexavalent chromium administered in drinking water (CAS number 18540-29-9) was nominated to the National Toxicology Program (NTP) by a number of California legislators, the California Environmental Protection Agency, and the California Department of Health and Human Services. The nomination is based on a document prepared by the California Environmental Protection Agency's (EPA) Office of Environmental Health Hazard Assessment titled "Public Health Goal for Chromium in Drinking Water."

Hexavalent chromium is an established human lung carcinogen in certain occupational settings, presumably as a result of inhalation exposure. Nonetheless there is uncertainty regarding long-term consequences of exposure to hexavalent chromium compounds in the water supply, and toxicological data on the chronic toxicity and carcinogenicity of hexavalent chromium after oral exposure are largely inadequate to establish or characterize a hazard.

Background

Chromium is a naturally occurring element, present in several valence states. Chromium III is an essential nutrient. Chromium compounds are stable in the trivalent state, and occur in nature most commonly at this oxidation level. Hexavalent chromium compounds are the next most stable form; however, these rarely occur in nature and are typically associated with industrial sources.

In general, hexavalent chromium is more toxic than the trivalent form. Hexavalent chromium is absorbed more readily than trivalent chromium and is taken up by cells through facilitated diffusion through nonspecific anion channels. Hexavalent chromium is an oxidant and reduces to trivalent chromium, passing through the reactive V and IV valence states. Toxicity is thought to result from either direct binding of these intermediates to cellular constituents or through generation of free radicals.

Prolonged inhalation of hexavalent chromium by chromate production workers and people engaged in the manufacture of chromate pigments has been established as a cause of occupational lung cancer. This finding is supported by inhalation studies in rats and mice that have also shown lung tumors following exposure to calcium chromate or sodium dichromate. Orally administered chromium compounds are relatively poorly absorbed, with most estimates in the range of 0.5 to 2%. Trivalent chromium is absorbed about one quarter as well as the hexavalent form, but hexavalent chromium is reduced to trivalent chromium in the stomach, potentially limiting the systemic availability of hexavalent chromium ingested orally. This “protective” mechanism is not complete; however, as sufficient hexavalent chromium has been given to rats and mice to result in liver and kidney toxicity in oral studies involving doses far below those shown to cause no adverse effects with trivalent chromium. Other concerns with hexavalent chromium given orally involve gastrointestinal effects. Acute gastritis is a common finding in

humans who accidentally or intentionally ingest various hexavalent chromium compounds. Also, a small increase in primarily benign forestomach papillomas was seen in mice exposed to potassium chromate in the drinking water at 9 mg/kg chromium VI for three generations over 880 days in a study reported in1968. Based on the above, the NTP is conducting definitive rodent studies to examine the carcinogenic potential of hexavalent chromium given by the oral route. The 13- week toxicity study of sodium dichromate dihydrate in F344 rats and B6C3F_1 mice is completed. Based on these results 2-year toxicity and carcinogincity studies of this chemical with a toxicokinetic component were designed. Dosing of rats and mice began in 10/2002. Results of the in-life portion of these studies will be available in 12/2004. There are two other studies with this chemical that are now in progress. These are: 1) Comparative 13-week toxicity study in BALB/C and AM3-C57Bl/6 transgenic mice and evaluation of *in vivo* mutagenicity study in the latter strain of mice 2) Immunological evaluation study in B6C3F_1. Protocols for the studies mentioned above, results of the 13-week toxicity study, and the in-life portion of the comparative toxicity study are posted at this site.

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