

controversy and conjecture in recent years. It is known that Cr(VI) is detoxified by reduction to Cr(III) in the acidic and reducing environment of the stomach. USEPA cited the gastric reductive capacity in support of their decision to raise the chromium maximum contaminant level (MCL) from 50 ppb to 100 ppb. USEPA and other agencies have also determined that there is insufficient evidence at this juncture to indicate that Cr(VI) poses an oral cancer risk. However, some uncertainties remain with respect to the quality of the available data, and as a result, the National Toxicology Program recently initiated a subchronic and chronic drinking water toxicity research project. The purpose of this study is to supplement the available animal pharmacokinetic and toxicity information. The potential hazards posed by Cr(VI) in drinking water, and the practical implications for assessing risk and setting health-based standards, depends on the weight of evidence from many scientific disciplines, including mechanistic and whole-animal toxicology, epidemiology, and kinetics. Significant new research in these fields has been conducted and will be discussed in this symposium. The use of new data for assessing the health risk from drinking water exposures, and the basis for setting health-based standards, will be presented with a case study of a recent risk assessment for Cr(VI) drinking water exposure in San Fernando Valley, California.

278 MECHANISM OF HEXAVALENT CHROMIUM [(CR(VI)) TOXICITY AND CARCINOGENICITY.

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Long term occupational inhalation exposure to chromium(VI)-containing dusts has been associated with an increased risk of respiratory cancers whereas other routes of exposure (dermal, ingestion) have not been associated with significant adverse health effects. Conversely, chromium(III) is an essential trace element in humans and animals and is essentially non-toxic. The basis for the differences in the biological effects of these two chromium valence states, and for the selective toxic effects of chromium(VI) which are restricted by chemical and physical form, route of exposure, and target tissue toxicity, are explained by the unique biology and chemistry of chromium and have been summarized in the cellular uptake-reduction model of Wetterhahn and the *in vivo* reduction model of De Flora. Chromium(III) is taken up very poorly by the gut and also does not easily cross cell membranes. An organic complex containing chromium(III) interacts with cell surface receptors to elicit effects on cell signaling that underlie its essential trace element role in glucose homeostasis. Chromium(VI) has the potential to cross cellular membranes through the anionic transport system but does not normally reach internal cellular targets due to the high reductive capacity of the body, especially the GI system and the skin, except under very high dose conditions which can overwhelm this capacity. However, under historical occupational conditions in which workers were exposed to very high concentrations of chromium(VI) dusts daily over several decades, the reductive capacity of the respiratory system was likely overwhelmed leading to increased risk of cancer, perforating ulcers and fibrosis. The available data, in conjunction with these models, is consistent with the prediction that there is no significant health risk associated with most environmental exposures to chromium(VI) including exposure *via* drinking water.

279 CHROME EXPOSURE AND LUNG CANCER, STOMACH CANCER AND OTHER CAUSES OF DEATH: AN EPIDEMIOLOGIC META-ANALYSIS.

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We reviewed the entire epidemiologic literature on chromium exposure and cancer published since 1950. This included more than 100 papers, 72 of which contained useful information on cancer risks. Eight epidemiologic design features of each study were evaluated and scored independently by the authors. The studies were then divided into two groups of higher and lower scoring studies. Findings were then compiled for All Causes of Death Combined, All Cancer Combined, Cancer of the Lung, Cancer of the Stomach and for each of six additional forms of cancer. This was done separately for the higher and lower-scoring studies. Nearly all of the studies related to occupational, not to drinking-water, exposures. However, 20% to 40% of inspired chromium particulates eventually reach the stomach. Among persons exposed to Cr(VI), there was a slight but significant deficit of All Causes of Death. There was a minimal, but significant, excess of deaths from All Cancer; this was due almost entirely to an excess of lung cancer. For lung cancer, the overall meta-standardized mortality ratio (mSMR) was 148 (95% CI=140-155) but among studies that controlled for cigarette smoking the mSMR was 120(113-128). There was a slight (mSMR=106) and non-significant excess of stomach cancer. However, among studies that controlled for the economic status of their subjects,

the mSMR was actually depressed to 79 (67-93). Discrepancies between the higher and lower-scoring studies will be discussed. This comprehensive evaluation indicates that there probably is a causal relationship between exposure to Cr(VI) and lung cancer. However, this relationship previously has been over-estimated because early studies did not adjust for the heavy smoking of their subjects. The findings also suggest that there is no association, much less a causal relationship, between exposure to Cr(VI) and stomach cancer. The implications of the findings for other forms of cancer will be discussed.

280 REFINING THE PBPK MODEL FOR CHROMIUM(VI) IN HUMANS.

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A physiologically based pharmacokinetic (PBPK) model for trivalent and hexavalent chromium [Cr(VI)] in humans was recently published (O'Flaherty et al., 2000). A critical parameter within the model is the rate at which Cr(VI) is reduced to Cr(III) in the gastrointestinal tract (GI). Two limitations of the current model are: 1) that it relies on limited data regarding the gastric reduction capacity of humans, and 2) the GI tract is described as a single combined stomach and small intestine (SI) compartment. This latter limitation requires that absorption and reduction processes be described as simultaneous competing reactions, whereas physiologically, reduction of Cr(VI) occurs primarily in the stomach followed by absorption in the SI. This work describes refinements to the current PBPK model. Specifically, we used new *in vitro* reduction rate data, simulating a variety of conditions (e.g., fasted, fed, antacids, diluted stomach fluid), to better quantify the rate of Cr(VI) reduction in the stomach, focusing on the rate within the first few minutes before transfer of stomach contents to the SI occurs while fasting. Based on these new data, first-order reduction rate constants and gastric half-lives were calculated to range from 10 to 0.7 minutes, with an average of 2.7 minutes. These rates are up to 14 times faster than that used in the current PBPK model. We also modified the current model, separating the stomach compartment (where reduction occurs) from the SI compartment (where reduction continues, but at a slower rate, and absorption occurs). The revised model provides vastly different estimates of the amount of Cr(VI) that might be absorbed systemically by humans following ingestion of Cr(VI), as compared to the first model. These results are valuable for understanding the potential risks associated with Cr(VI) in drinking water and the potential threshold for absorbing Cr(VI) following ingestion.

281 NATIONAL TOXICOLOGY PROGRAM STUDIES OF HEXAVALENT CHROMIUM.

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Hexavalent chromium (CrVI) is a known human carcinogen through occupational exposures, but there is inadequate information to characterize its carcinogenic hazard when consumed in drinking water. Consequently, private individuals, the State of California and members of the California Congressional delegation nominated CrVI to the NTP. In preliminary studies, CrVI (as sodium dichromate dihydrate in all studies) was administered in drinking water (1 to 300 mg Cr/L) for 3 weeks to rats, mice and guinea pigs. Significant differences were not apparent in the shapes of the dose response curves for total Cr accumulation (measured once following a two-day wash out) in blood and kidney in the three species, although absolute levels differed. In subsequent studies, rats and mice received 62.5 to 1000 mg sodium dichromate dihydrate/L (24 to 384 mg CrVI/L) in drinking water for 13 weeks. Significant toxic effects were limited to metaplastic (mice) and inflammatory and/or erosive lesions (rats) of the glandular stomach at 1000 mg/L, a microcytic, hypochromic, responsive anemia in all dosed groups of rats, and effects secondary to decreased water consumption primarily in the 1000 and 500 mg/L dose groups. Based on these results, a 2-year drinking water study in F344 rats and B6C3F1 mice is under design. Additional 13-week studies are examining the comparative toxicity of CrVI in BALB/c and C57BL/6 mice, and *in vivo* mutagenicity in the am3-C57BL/6 mouse. Immunotoxicity studies will be performed in female B6C3F1 mice. Protocols can be accessed at <http://ntp-server.niehs.nih.gov/html-docs/Studies/HexChromium/hexchromiumpg.html>

282 RISK ASSESSMENT FOR HEXAVALENT CHROMIUM IN DRINKING WATER.

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Hexavalent chromium has been detected in the drinking water of a number of communities in California. An evaluation of risk associated with chemicals in the drinking water supply should consider all relevant routes of exposure, such as inges-