Review Summary of the National Institute of Environmental Health Sciences (NIEHS/NTP) RoC Review Committee (RG1)

Nomination: Lead and lead compounds
Review committee: RG1
Date: December 03, 2002

Major issues discussed

Application of criteria

Exposure: A significant number of persons residing in the United States are exposed to lead or lead compounds either occupationally or environmentally. Lead is absorbed into the body through inhalation, ingestion and, to a limited extent, through the skin. The largest amount of lead presently released into the environment is released to landfill sites. Lead-containing wastes result from ore production, household renovation and remediation of lead paint, use of lead in ammunition, solder, weights, and bearing metals, and production of iron and steel. The most common source of environmental lead exposure for young children is from direct ingestion of paint chips and leaded dusts and soils resulting from aging painted surfaces. Workers in many occupations including battery production, battery recycling, lead smelting and refining, radiator repair, firing range instruction, house renovation, lead mining, auto repair, plumbing and pipe fitting, and manufacture of pigments, pottery glazes, leaded glass, and stained glass, are exposed to lead or lead compounds.

Human Studies: More than 20 published cohort and case-control studies consistently find that exposure to lead or lead compounds is associated with increased cancer risk, particularly for lung and stomach cancer. The increase in risk was small, a meta-analysis over nine cohort studies reported relative risks of ~1.3 for both sites. Exposure misclassification may account for the small size of the risk estimates. The range of exposure was also limited by the acute toxicity of lead, which would prevent chronic high-dose exposure. Studies that adjusted for smoking and arsenic exposure were also positive, indicating that confounding does not explain the increase in cancer risk.

Experimental animal studies: Carcinogenicity has been observed for insoluble (lead phosphate), soluble (lead acetate and lead subacetate) and organic (tetraethyl lead) lead compounds. Lead has been shown to be carcinogenic in two species of rodents (rats and mice), is effective by multiple routes of exposure (oral, parenteral, transplacental), and has been associated with malignant tumor development in multiple sites (kidney, brain, hematopoietic system). Lead exposure can also increase the incidence or accelerate the appearance of tumors induced by organic chemical carcinogens in various systems. Although systemic exposure to lead can induce benign lung tumors in Strain A mice, the fact that inhalation studies are unavailable in animals may account for the lack of site concordance with human studies associating lead inhalation with the development of malignant pulmonary tumors.

Genotoxicity: Though the mechanism of carcinogenic action is unknown, a variety of lead compounds have been shown positive for a wide range of genotoxicity endpoints. These include mutations, sister chromatid exchange, micronuclei, chromosomal aberrations, malignant cellular transformation, DNA strand breakage and inhibition of DNA repair . Lead shows evidence of genotoxicity in both *in vitro* and *in vivo* experimental systems and in lead-exposed workers. Studies of exposed workers that controlled for potential confounders, including smoking, found dose-related increases in chromosome aberrations.

Other information: Lead absorption in humans and laboratory animals is affected by age, chemical form of the lead, and minerals in the diet (e.g., iron, calcium, and zinc). After absorption, lead is distributed to blood plasma, nervous system and soft tissues. It subsequently redistributes and accumulates in bone, with up to 90% of the lead body burden found in bones and teeth. The mechanisms leading to the carcinogenic effects of lead are not understood. Lead compounds do not appear to be directly genotoxic but may cause genetic damage through several indirect mechanisms including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor suppressor proteins.

Other concerns: Title - RG1 discussed whether the listing should be "lead and lead compounds" or something more specific (i.e. "occupational exposures to lead and lead compounds")and agreed that "lead and lead compounds" was appropriate and supported by the evidence.

Recommendation: RG1 recommended by a vote of 8 yes to 0 no to list lead and lead compounds in the Report on Carcinogens as *known to be a human carcinogen,* based on the consistency of the evidence from human studies that is supported by animal and mechanistic data.