Review Summary
NTP Executive Committee Working Group for the Report on Carcinogens (RG2)

Nomination: Lead and Lead compounds

Date: July 22, 2003

Major issues discussed

Application of criteria

Exposure: Environmental lead is ubiquitous with virtually every person exposed to some extent. The highest exposures occur in occupations where lead is mined, used in manufacturing or in jobs where products containing lead are handled. It is estimated that over a half million workers in the US are exposed to lead. 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.

Human studies: Lead exposure has been associated with increased risk of lung, pharynx, stomach, and kidney cancer in diverse populations. The strongest evidence is for lung cancer, with 15 studies of 18 different cohort populations reporting an association between lead exposure and lung cancer, eight of which were significant. Most studies had shortcomings including poor exposure assessment, failure to control for confounders (both co-exposure to other occupational exposure and lifestyle exposures) and an absence of dose-response relationships. The two available meta-analyses have reported an excess risk for lead exposure and lung cancer but the authors of the latest meta-analysis stated that the lung cancer findings were potentially confounded. Some RG2 members stated that the studies that had good exposure assessment (using biomarkers) and/or controlled for confounders reported an association between lead exposure and lung cancer thus establishing a causal relationship between lung cancer and lead exposure. Other members of RG2 felt the epidemiological evidence was limited and that there was no supporting mechanism data to support the human studies.

Experimental animal studies: Many lead compounds have been tested for carcinogenicity by various routes and for different durations but no inhalation studies in experimental animals have been reported. Both lead acetate and lead phosphate produce renal carcinomas in rats, which is the most common tumor observed; however, histopathological assessment of other organs was not performed in many studies. Other tumors induced by lead compounds include adenomas in brain and the lung. Some studies in experimental animals have been negative. Lead phosphate and lead acetate are listed in the RoC as *reasonably anticipated to be a human carcinogen* and IARC categories lead compounds as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in animals. RG2 felt the animal carcinogenicity data were positive.

Genotoxicity and mechanism: Lead was not mutagenic in bacteria and results in mammalian cells and human *in vivo* studies were conflicting. In cell free systems some lead compounds inhibited RNA and DNA synthesis and polymerase activity and induced strand breaks in the presence of H_2O_2. In plants, lead compounds induced chromosomal aberrations and micronuclei. In mammalian cells and human *in vivo* studies, lead induced chromosomal aberrations but conflicting results were observed for sister

chromatid exchange and micronuclei induction. It appears unlikely that lead compounds are directly genotoxic but may affect chromosomal processes through indirect mechanisms. RG2 concluded that the i*n vitro* genotoxicity and mutagenicity data were equivocal and the *in vivo* biomarker studies were positive.

The mechanisms of toxicity of lead are probably related to lead's ability to inhibit or mimic the action of calcium and to interfere with protein function. Lead may interfere with DNA synthesis and repair and cause oxidative damage, or interfere with tumor suppressor proteins. RG2 concluded that the mechanism of carcinogenicity was unknown but that plausibility exists.

Other concerns: Lead acetate and lead phosphate are currently listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. RG2 felt that considering lead and lead compounds for listing was warranted based of the human evidence of exposures to this class of compounds.

Recommendation

Motion: recommend that lead and lead compounds be listed as *reasonably anticipated to be human carcinogens,* based on limited evidence of the carcinogenicity in humans and sufficient evidence from laboratory animals studies.

Vote on the motion: 4 yes votes to 3 no votes. The no votes were cast because the members felt that human data for lead and lead compounds was sufficient to list them as *known to be human carcinogens*.