Lead and lead compounds

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Citation for most recent IARC review

IARC Monographs 87, 2006

Current evaluation

Conclusion from the previous Monograph:
Inorganic lead and lead compounds are probably carcinogenic to humans (Group 2 A).

Exposure and biomonitoring

The CDC has an ongoing exposure and biomonitoring program for a number of chemicals including lead (CDC, National Exposure Report, 2005) which follows changes in blood lead concentrations over time. More recently, the FLEHS Biomonitoring Study (Ketelslegers et al., 2008) has reported the results of multi-plex genotyping as a biomarker of susceptibility to carcinogenic exposures. These studies, which included lead, reported a positive relationship between lead exposure and the carcinoembryonic antigen BRCA2N^{372}H. Lead associated levels of this antigen were also found to be 1.9 times higher in persons carrying the double variant allele (heterozygous) and 1.6 times higher in persons carrying the wild type. An even greater increase was observed in smokers in response to lead exposure. The importance of these data rests with a better understanding of the relationship between genetic inheritance, lead exposure and risk of cancer.

Cancer in humans

(*limited***,** Vol 87, 2006).

The 2006 evaluation was based primarily on six larger historical cohorts exposed to inorganic lead. Data on the effects of exposure to organic lead was sparse and no conclusions could be drawn. Historical organic lead exposure was largely confined to tetra-ethyl lead used as an additive in gasoline (now discontinued); tetra-ethyl lead was broken down into inorganic lead when gasoline was burned.

Regarding the six cohorts exposed to inorganic lead, stomach cancer was consistently elevated (30-50%) in four of the five cohorts where stomach cancers were reported. Lung, kidney, and brain cancer showed elevation in some studies but were not consistent. Since 2006 there are five studies with new information, although none are large or would change the conclusions of the 2006 Working Group.

Wijngaarden et al. (2006) studied brain cancer in the National Longitudinal Mortality Study, a prospective census-based cohort study of the United States population in 1979-1989 (n=317,968). Using a job-exposure matrix and industry and occupation from the census, the authors found increased risk of brain cancer in jobs likely to have involved lead exposure (RR 1.5, 0.9-2.3)(18% exposed), with indications of an exposure-response trend based on

estimated intensity of exposure. This study is limited due to lack of direct data on exposure, but adds to the positive evidence for brain cancer.

Rousseau et al. (2007) conducted nested-case control studies for 11 types of cancers and estimated lead exposure, with exposure estimated based on work history and expert assessment (Montreal/Siemiatycki data base). 17% of subjects were exposed to inorganic lead, while 3% were exposed to organic lead. Stomach cancer was associated with organic lead (ORs 2.0 (1.1-3.8) and 3.0 (1.2-7.3) depending on control group), but there was no association with inorganic lead, nor were there any notable positive associations for other cancers. Again this study is limited due to lack of direct data on exposure, but the lack of association weakens the IARC 2006 conclusion.

Lam et al. (2006) linked 3192 lead-exposed workers in New Jersey, identified by a NIOSH-sponsored lead surveillance program, to the NJ Cancer Registry. All cohort members had measured blood leads >25 μg/Dl at some point in the past. They found 83 incidence cancer cases, with a deficit of cancer overall (0.51, 0.41-0.62). There were no notable excesses (stomach cancer SIR 1.1, 4 cases). This study is limited by small numbers, and possible under-ascertainment of cases due to out-of-state migration.

Siddiqui et al. (2006) conducted a case-control of breast cancer in India, with 50 malignant and 50 benign cases. Blood lead was significantly higher in the malignant case croups, as were zinc, iron, and calcium. This study is limited as blood lead was present at background environmental levels and reflected exposure in recent past (3 months).

Rajaraman et al. (2006) reported increased rates of brain tumors (gliomas and menigomas) in relation to genetic polymorphisms in the ALAD gene and lead exposure suggesting a need to take genetic inheritance of ALAD polymorphisms into account with respect to lead exposures and development of these types of cancer. The ALAD2 allele was found to increase the risk of menigioma from 1.1 to 5.6 and 12.8 based upon estimated based upon intermediate and longer term cumulative lead exposures respectively. ALAD may play an important role in the bioavailability of lead to sensitive molecular sites which is known to vary as a function of the ALAD2 allele (Scinicariello et al., 2007) and lead inhibition of this enzyme and others in the heme biosynthetic pathway may also contribute to the generation of oxidative stress via generation of reactive oxygen species.

Cancer in experimental animals

(*sufficient***,** Vol 87, 2006)

No new carcinogenicity assays have been reported since the last evaluation since 2002. In contrast, there have been a number of studies reporting the inhibitory effects of lead exposure on sperm development and motility in male experimental animals (Kaspercyk et al., 2008, Wang et al., 2008)

Mechanisms of carcinogenicity

The mechanisms of lead induced cancers in experimental systems are complex appear to involve oxidative stress (Jurczuk et al., 2006) and may involve lead interaction with zinc finger proteins (Jarzecki et al., 2007), induction of apoptosis (Xu et al., 2006, 2008), altered cell signaling pathways (Wang et al., 2008b, 2009) and regulation of lead interactions with cellular genetic machinery by high affinity lead - binding proteins (Fowler et al., 1994, Rajaraman, 2006).

Research needs and recommendations

Additional epidemiologic information can be provided by large cohorts with established exposure above background environmental levels. It appears likely that there will be a mortality study of approximately 50,000 workers with past measured blood lead levels above 25 µg/Dl in the United States (NIOSH ABLES surveillance program), which should prove informative. There are also an additional 50,000 subjects with lower blood leads. Subsequent possible case-control studies of cancers of interest (stomach, brain, kidney, lung) could also provide more information. This study could be strengthened by the addition of two components: 1) measurement of a sample of subjects for bone lead to determine the correlation of the blood lead measurements with cumulative exposure as measured by bone lead, and 2) assessment of whether *Helicobacter pylori* infection has been more common among those with higher blood leads. If so such infection could either be a mechanism by which lead caused higher rates of stomach cancer, or it could be a confounder.

In addition, given positive results from the FLEHS study (Keteleslegers et al., 2008) and the report by Rajaraman et al. (2006) it is clear that future epidemiological studies of relationships between lead exposures and cancer should include evaluation of genetic susceptibility factors if at all possible.

Further experimental research studies are needed to evaluate the complex mechanisms by which lead may cause cancer with particular emphasis on the roles of oxidative stress / apoptosis and the roles of cellular defense mechanisms, signaling pathways and intracellular lead binding patterns in mediating these processes.

Selected relevant publications

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