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Integrated Science Assessment for Lead

Appendix 10: Cancer

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DOCUMENT GUIDE

This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 12 appendices, which can all be found at https://assessments.epa.gov/isa/document/&deid=359536.

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ACRONYMS AND ABBREVIATIONS

ALAD	δ-aminolevulinic acid dehydratase
AQCD	Air Quality Criteria Document
APE-1	human AP endonuclease
BLL	blood lead level
BMI	body mass index
BW	body weight
Cd	cadmium
CGI	CpG island
CI	confidence interval
CLL	chronic lymphatic lymphoma
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CPS	Cancer Prevention Study
CRP	C-reactive protein
d	day(s)
DLBCL	diffuse large B-cell lymphoma
EPIC	European Prospective Investigation into Cancer and Nutrition
FL	follicular lymphoma
GFAAS	graphite furnace atomic absorption spectrometry
GFR	glomerular filtration rate
HR	hazard ratio
ICD	International Classification of Diseases
ICP-MS	inductively coupled plasma mass spectrometry
IC50	half maximal inhibitory concentration
IARC	International Agency for Research on Cancer
IL	interleukin type
ISA	Integrated Science Assessment
KNHANES	Korea National Health and Nutrition Examination Survey
LINE	long interspersed nuclear elements
ln	natural log
MM	multiple myeloma
MMP	matrix metalloproteinase-
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NSDHS	Northern Sweden Health and Disease Study
NTP	National Toxicology Program
OR	odds ratio
Pb	lead
PCR	polymerase chain reaction
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PIR	poverty-income ratio
PND	postnatal day
ppm	parts per million
PRMT	protein arginine methyltransferase
Q	quartile
RR	relative risk
ROS	reactive oxygen species
SCE	sister chromatid exchange
SD	standard deviation
Se	selenium
TK	thymidine kinase type
UC	urothelial carcinoma
WHO	World Health Organization
Zn	zinc

APPENDIX 10 CANCER

Summary of Causality Determinations for Pb Exposure and Cancer

This appendix characterizes the scientific evidence that supports the causality determination for lead (Pb) exposure and cancer. The types of studies evaluated within this appendix are consistent with the overall scope of the ISA as detailed in the Process Appendix (see Section 12.4). In assessing the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in Table 12-5 of the Process Appendix (Section 12.6.1). More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this appendix supports the following causality conclusion:

Outcome	Causality Determination
Cancer	Likely to be Causal

The Executive Summary, Integrated Synthesis, and all other appendices of this Pb ISA can be found at https://assessments.epa.gov/isa/document/&deid=359536.

10.1 Introduction and Summary of the 2013 Pb ISA

This appendix evaluates the toxicological and epidemiologic literature related to the potential contributions of Pb exposure to cancer effects, including cancer incidence and mortality. The 2013 Integrated Science Assessment for Lead (hereinafter referred to as the 2013 Pb ISA) continued to support the conclusions of the 2006 Pb Air Quality Criteria Document (AQCD) that Pb is a well-established animal carcinogen (U.S. EPA, 2013, 2006). In the 2013 Pb ISA (U.S. EPA, 2013), the toxicological literature provided consistent evidence of the carcinogenic potential of Pb and possible contributing modes of action, including genotoxic, mutagenic, and epigenetic effects. The development of cancer is a multistep process that involves the progressive accumulation of mutations, leading to upregulation of oncogenes and loss of function of tumor suppressor genes resulting in uncontrolled cell growth and invasion of cancer cells within organ tissue. Based on the toxicological literature reviewed in the 2013 Pb ISA, Pb appears to have some ability to induce DNA damage. Additionally, Pb has the ability to alter gene expression through epigenetic mechanisms and interact with proteins, which may be another potential means by which Pb induces carcinogenicity (U.S. EPA, 2013). Pb may act at a post-translational stage to alter protein structure of zinc (Zn)-finger proteins, which can in turn alter gene expression, DNA repair, and other cellular functions. In summary, cancer develops from one or a combination of multiple mechanisms including modification of DNA via epigenetics or enzyme dysfunction and genetic instability

or mutation. These modifications then provide cancer cells with a selective growth advantage and thus, Pb may contribute to epigenetic changes and chromosomal aberrations.

Multiple longitudinal epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) examined the associations between cancer incidence and mortality and Pb exposures, estimated with biological measures and exposure databases. The 2013 Pb ISA (U.S. EPA, 2013) reported mixed results for cancer mortality studies. While a high-quality National Health and Nutrition Examination Survey (NHANES) study demonstrated an association between blood Pb and increased risk of cancer mortality, other studies reported weak or null associations. Overall, the epidemiologic studies reviewed in the 2013 Pb ISA were well-conducted with control for important potential confounders such as age, smoking, and education. The epidemiologic studies of cancer incidence in the 2013 Pb ISA reported no associations between various measures of Pb and overall cancer incidence. These studies were limited by their ecological or cross-sectional study designs and a few studies did not collect biological measurements, nor did they control for potential confounders. Additionally, consistent evidence from animal toxicological studies demonstrated that Pb exposures can lead to cancer, genotoxicity, or epigenetic modification. Carcinogenicity in animal toxicology studies of Pb exposure were reported in the kidneys, testes, brain, adrenals, prostate, pituitary, and mammary glands, albeit at high doses of Pb. Furthermore, based on the previous existing bodies of evidence, International Agency for Research on Cancer (IARC) has classified inorganic Pb compounds as "probably carcinogenic to humans"[1] and the National Toxicology Program (NTP) has listed Pb and Pb compounds as "reasonably anticipated to be human carcinogen."[2] Overall, the consistent and strong body of evidence from toxicological studies on tumor incidence and potential modes of action, when considered together with the inconsistent epidemiologic evidence, was judged sufficient to conclude that there is likely to be a causal relationship between Pb exposure and cancer.

[1]The International Agency for Research on Cancer (IARC) classifies carcinogens into four groups. The categorization of "probably carcinogenic to humans" (Group 2A) applies when IARC has made at least two of the following evaluations, including at least one that involves either exposed to humans or human cells or tissues: limited evidence of carcinogenicity in humans; sufficient evidence of carcinogenicity in experimental animals; and strong evidence that the agent exhibits key characteristics of carcinogens. If there is inadequate evidence of carcinogenicity in humans, there should be strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens. More information on IARC cancer classifications can be found in the IARC Monographs on the Identification of Carcinogenic Hazards to Humans Preamble (IARC, 2019).

[2]The National Toxicology Program (NTP) prepares the Report on Carcinogens (RoC) on behalf of the Secretary of Health and Human Services and follows an established, multi-step process for the review and evaluation of selected substances. The classification of "Reasonably Anticipated to be Human Carcinogen" is defined as limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded; or there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset; or there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans (NTP, 2023).

10.2 Scope

The scope of this appendix is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements define the objectives of the review and establish study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[3] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies that were included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. With the exception of supporting evidence used to demonstrate the biological plausibility of Pb-associated cancer incidence and mortality, recent studies were only included if they satisfied all components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[4] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[5]; or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Cancer incidence and cancer mortality.

[3]The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

[4]Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area that was of particular relevance to the National Ambient Air Quality Standards (NAAQS) review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[5]Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with blood Pb levels (BLL) are lacking.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, Guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a (blood lead level) BLL of 30 μg/dL or below.[6,7]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcome: Cancer and cancer-related outcomes, such as genotoxicity, epigenetic, and mutagenic effects.

Study design: Controlled exposure studies of animals in vivo. In vitro mechanistic studies are supplemental evidence.

10.3 Mechanistic Pathways and Markers of Carcinogenesis

10.3.1 Introduction

The 2013 Pb ISA (U.S. EPA, 2013) reported consistent positive evidence from multiple animal chronic Pb exposure studies ranging in duration between 18 months to 2 years as well as from animal studies involving windows of Pb exposure such as gestation and lactation leading to cancers in adult offspring. Additionally, consistent mechanistic and genotoxicity evidence for cellular and DNA damage from multiple lines of evidence (human and animal in vitro models) provided further support for mechanistic pathways of Pb inducing carcinogenicity. The mechanistic toxicological literature evaluated in the 2013 Pb ISA (U.S. EPA, 2013) found that most evidence clearly supports Pb-induced carcinogenicity in animal models, but the exact chain of events supporting a mode of action has not been completely characterized. Furthermore, the IARC (IARC, 2006) classified inorganic Pb compounds as "probably carcinogenic to humans" (Group 2A), while NTP listed Pb and Pb compounds as "reasonably anticipated to be human carcinogens" (NTP, 2012). The reports from IARC and NTP based their

[6]Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[7]This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLLs. The 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey (NHANES) distribution of BLL in children (1–5 years; n = 2,321) is 2.66 μg/dL (Egan et al., 2021) and the proportion of individuals with BLLs that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

conclusion on evidence primarily from animal cancer bioassays of continuous exposure to Pb. While no PECOS-relevant animal studies of Pb exposure and cancer have been published since the 2013 Pb ISA, a number of recent in vitro studies have examined the potential mechanistic pathways by which Pb exposure could result in cancer initiation and/or promotion. These mechanistic studies are evaluated in more detail in the sections below: 10.3.2 Animal Models of Carcinogenicity; 10.3.3 Genotoxicity; 10.3.4 Oxidative Stress; 10.3.5 Cell Viability, Cytotoxicity, Apoptosis; 10.3.6 DNA Damage Repair Enzymes and Gene Expression; 10.3.7 Epigenetic Regulation of Gene Expression; 10.3.8 Gene Expression and Extracellular Matrix; and 10.3.9 Inflammation.

10.3.2 Animal Models of Carcinogenicity

The toxicological literature reviewed in previous AQCDs established that Pb has been shown to act as a carcinogen in animal toxicology models, albeit at relatively high concentrations. Chronic oral Pb acetate exposure for male and female rodents has consistently been shown to be a kidney carcinogen in multiple separate studies, inducing adenocarcinomas and adenomas after chronic exposure. The kidneys are the most common target of Pb-induced carcinogenicity (Kasprzak et al., 1985; Koller et al., 1985; Azar et al., 1973; Van Esch and Kroes, 1969). Other common targets of Pb-induced carcinogenicity include the testes, brain, adrenals, prostate, pituitary, and mammary gland (IARC, 2006). The typical cancer bioassays used by IARC or NTP as evidence of Pb-induced carcinogenicity were designed using rodents, typically males but occasionally both sexes, that were continuously exposed to Pb acetate in chow (i.e., 1,000 or 10,000 ppm Pb acetate) or drinking water (i.e., 26 or 2,600 ppm Pb acetate) for 18 months to two years in duration, the typical lifespan of a rodent (Kasprzak et al., 1985; Koller et al., 1985; Azar et al., 1973; Van Esch and Kroes, 1969).

The 2013 Pb ISA (U.S. EPA, 2013) focused on the importance of exposure windows for Pb-induced cancer bioassays in animal toxicology models. Gestational and lactational exposure of rats to inorganic Pb-induced (500, 750 or 1,000 ppm Pb acetate in drinking water) carcinogenicity in adult offspring (Waalkes et al., 1995). In another study, Tokar et al. (2010) considered Pb-induced carcinogenesis in mice with early life Pb exposure (gestation, lactation and continued until 8 weeks of age) and examined tumorigenesis in homozygous metallothionein I/II knockout mice and their corresponding wild-type controls (groups of ten mice each). The dams/mothers were exposed by drinking water to 2,000 or 4,000 ppm Pb acetate in utero, through birth and lactation, and then, postnatally, to drinking water until 8 weeks old and compared with untreated controls. The Pb-exposed metallothionein I/II knockout mice had increased testicular teratomas and renal and urinary bladder preneoplasia. The tumor burdens of Pb-exposed wild-type mice were not statistically significantly different than controls. The data suggest that metallothionein can protect against Pb-induced tumorigenesis. The study did not address whether metallothionein in humans would have any impact on Pb-induced carcinogenesis. The animal toxicology studies show that Pb is a well-established animal carcinogen in studies employing high-dose Pb exposure over a continuous, extended duration of exposure (i.e., 2 years), which is typical of

cancer bioassays. Studies show early-life maternal Pb exposure can contribute to carcinogenicity in offspring and suggest that metallothionein is protective against cancer in this pathway.

Since the 2013 Pb ISA, there are no new PECOS-relevant animal studies that have examined cancer endpoints. Several recent in vitro mechanistic studies have examined markers of potential carcinogenicity pathways as characterized by the IARC 10 key characteristics of carcinogenic mechanistic pathways (Smith et al., 2016). These in vitro mechanistic studies, which are categorized as supplemental under the PECOS criteria and do not abide by the blood Pb cutoff of 30 µg/dL, are short-term in nature, and principally inform mechanistic pathways that inform association to Pb exposure (see Section 10.2). These in vitro mechanistic studies are detailed below in Sections 10.3.3–10.3.9.

10.3.3 Genotoxicity

Multiple toxicological and epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) examined the relationship between Pb exposure and DNA and cellular damage. These studies reported consistent evidence of genotoxicity, oxidative stress, and related gene expressions. Genotoxic effects are effects from Pb exposure as measured by multiple lines of evidence such as DNA damage repair. In the case of DNA strand break detection, in vivo and in vitro studies using the comet assay (measured by multiple indices such as tail length, single cell electrophoresis, and others) yielded multiple positive results in various species (Yedjou et al., 2010; Nava-Hernández et al., 2009; Tapisso et al., 2009; Alghazal et al., 2008; Kermani et al., 2008; Xu et al., 2008; Gastaldo et al., 2007; Xu et al., 2006). The toxicological evidence was supported by several epidemiologic studies that reported associations between blood Pb and DNA and cellular damage (Khan et al., 2010; Olewińska et al., 2010; Shaik and Jamil, 2009; Wiwanitkit et al., 2008; Duydu et al., 2005).

Since the 2013 Pb ISA (U.S. EPA, 2013), there have been additional supplemental studies using comet assays that continue to indicate DNA strand breakage occurs after Pb exposure across multiple species (Jiang et al., 2020; Yadav et al., 2019; Ali, 2018; Nariya et al., 2018; Siddarth et al., 2018; Shah et al., 2016; Ahmad et al., 2015; Mckelvey et al., 2015; Zhang et al., 2014; Roy et al., 2013; Shakoori and Ahmad, 2013). In addition to DNA and cellular damage, there was a recent study of gamma-H2AX foci formation from the phosphorylation of the Ser-139 residue of the histone variant H2AX, which is an early cellular response to the induction of DNA double-strand breaks, with Pb exposure increased these foci formation (Liu et al., 2018).

The 2013 Pb ISA (U.S. EPA, 2013) noted Pb-induced micronucleus formation in both the toxicological and epidemiologic studies reviewed (Shaik and Jamil, 2009; Tapisso et al., 2009; Alghazal et al., 2008). The recently published literature contains multiple studies identifying Pb-induced micronucleus formation in the human lymphoblastoid cell line (Alimba et al., 2016) and in human lymphocytes from healthy volunteers (Nariya et al., 2018; Shah et al., 2016; Roy et al., 2013).

Sister chromatid exchange (SCE), exchanges of homologous DNA material between chromatids on a chromosome and are a test for mutagenicity or DNA damage as well as other chromosomal aberrations in toxicological studies, was outlined extensively in the 2013 Pb ISA (U.S. EPA, 2013). In a study of mice, the SCE in bone marrow was elevated after treatment with Pb acetate and increased in time, with co-exposure to cadmium (Cd) or Zn further increasing SCE levels (Tapisso et al., 2009). Similarly, recent in vitro studies found Pb-induced damage both in cell lines (Alimba et al., 2016; Banfalvi, 2014) and in human peripheral blood lymphocytes (Yadav et al., 2019; Nariya et al., 2018; Shah et al., 2016).

10.3.4 Oxidative Stress

At cellular level, Pb is known to induce oxidative stress either by generation of free radicals or through depletion of antioxidants (Ercal et al., 2001). Pb-induced free radicals initiate DNA oxidation and subsequent DNA damage (Hsu and Guo, 2002) as well as mitochondrial damage and intracellular depletion of glutathione (Sabath and Robles-Osorio, 2012).

Since the 2013 Pb ISA, multiple studies have investigated Pb-induced oxidative stress and diverse biomarkers in the context of genotoxicity and carcinogenic mechanisms. All these studies used in vitro cell culture (human and mammalian animal) systems exposed to either Pb acetate or Pb nitrate of varied concentrations/doses and durations. Some of these studies also examined the effect of antioxidant treatment on the reversal of oxidative stress endpoints and of genotoxic endpoints resulting from Pb-induced oxidative stress. Nariya et al. (2018) observed dose (Pb acetate; 0.379 µg/ml and 37.9 µg/ml) and duration (24 or 69 hours) dependent increases in oxidative stress and genotoxicity (chromosomal aberrations, micronuclei) and reversal of these effects when treated with antioxidant and anti-inflammatory curcumin (1.43 µg/ml). Similarly, Yadav et al. (2019) observed reversal of Pb nitrate (50–350 µg/ml for 24 hours) induced genotoxicity (as assessed by comet assay and sister chromatid exchange) by pretreatment of human peripheral blood lymphocytes with antioxidant, anti-inflammatory bioflavonoid, ‘morin’, at concentrations of 15–60 µg/ml.

Three recent studies evaluated Pb-induced oxidative stress and its effects on DNA damage. Liu et al. (2018) used thymidine kinase (TK) 6 cells exposed to Pb acetate (0–480 mM) for 6–24 hours and observed the formation of 8-OH guanosine adducts and gamma-H2AX foci, markers of DNA double-strand breaks. Pottier et al. (2013) also observed a dose dependent (Pb-nitrate; 0–1000 mM) loss of telomeres in clone B3 of the human EJ30 bladder carcinoma cell line. In these cells, formation of foci (indicative of cell transformation) was found only above 100 mM Pb. Jiang et al. (2020) observed Pb-induced DNA damage mediated by oxidative stress and inflammation mechanism in human lung cells at no-observed-adverse-effect level of 4 µg/ml Pb. Ali (2018) also observed Pb-induced DNA damage mediated by oxidative stress in human lung cells at half maximal inhibitory concentration (IC50) dose of

Pb. Furthermore, the IC50 dose of Pb-induced DNA damage was found to be reversed when treated with antioxidants (i.e., vitamin E or garlic extract) (Ali, 2018).

10.3.5 Cell Viability, Cytotoxicity, Apoptosis

Toxicant-induced oxidative stress, if left uncontrolled or depleted of cellular antioxidant resources, eventually leads to DNA or chromatin damage and cell death or apoptosis. Since the 2013 Pb ISA, a limited number of in vitro cell culture studies that observed Pb-induced oxidative stress further investigated cytotoxicity mechanisms. Ali (2018) found a dose dependent increase in cell viability and cytotoxicity in association with Pb exposure. In addition, garlic, vitamin E, and the combination mitigated these effects to different levels. The cytotoxicity was found to be associated with alterations in the expression of pro-apoptotic genes (bcl2, Bax, P53) and significant increase in Bax/Bcl2 ratio suggesting their role in an apoptotic mechanism of cytotoxicity. Jiang et al. (2020) also observed a dose-dependent decrease in cell viability associated with changes in the expression of specific proapoptotic genes (caspase 3, 8, and 9). Similarly, Siddarth et al. (2018) observed increased expression of caspase 3 and an increased number of annexin V positive cells by flow cytometric analyses, suggesting an apoptotic mechanism for cell death. These studies also found reversal of these effects when treated with diverse antioxidants (see Section 10.3.4 on oxidative stress). Ghosh et al. (2018) observed significant Pb chloride (5 mM and 10 mM) induced decreases in cell viability of A549 human lung and MCF-7 human breast cancer cell lines as assessed by trypan blue exclusion, MTT assay, and neutral red dye uptake methods.

10.3.6 DNA Damage Repair Enzymes and Gene Expression

Cells are equipped with robust, diverse DNA damage response mechanisms consisting of specific DNA repair pathways to remove damage and effect repair at different stages of the cell cycle. Since the 2013 Pb ISA, two in vitro studies have investigated the role of DNA damage repair enzymes by studying their expression after Pb exposure. Mckelvey et al. (2015), using the RT^2 Profiler polymerase chain reaction (PCR) array system, found that exposure to Pb nitrate (40 µg/ml and 80 µg/ml) impacted diverse DNA damage and signaling pathways in the HepG2 (human hepatocellular carcinoma) cell line. These investigations were carried out in the context of protection conferred by diverse chemical forms of selenium (Se) to Pb-induced DNA damage. The potential role for the changes in genotoxicity was complemented by the comet assay and other methods (discussed in Section 10.3.1). Both doses of Pb nitrate led to increased expression of several genes and the study reported differential fold increases between the 40 µg/ml and 80 µg/ml doses. The two most significant increases were found in the expression of GADD45G (growth arrest and DNA-damage inducible, gamma) and PPP1R15A (protein phosphatase 1, regulatory subunit 15 A) by 26- and 12-fold, respectively, in cells exposed at 40 mg/ml. Smaller increases were reported in cells exposed at 80 mg/ml (4- and 6-fold, respectively). The ATM gene that functions as a main sensor of DNA damage and is involved in DNA double-strand break (DSB)

repair was found to be suppressed by Pb nitrate. In this study the protection conferred by diverse Se-based compounds sodium selenite (Sel-Ni), selenium yeast (SeY), seleno-methionine (Sel-M), and sodium selenate (Sel-Na) were also investigated in the gene expression of Pb-induced DNA repair enzymes. It was observed that SeY and Sel-M influenced the Pb-induced expression of LIG1 (ligase I, DNA) and XRCC3, two important genes involved in the base excision repair pathway, indicating that Pb-induced oxidative stress might influence the expression and regulation of these enzymes and that these Se compounds confer protection against it.

10.3.7 Epigenetic Regulation of Gene Expression

The 2013 Pb ISA reported that the ability of Pb to alter gene expression through epigenetic mechanisms and to interact with proteins may be a means by which Pb induces carcinogenicity (Patel, 2013; Li et al., 2011; Wright et al., 2010; Pilsner et al., 2009). Cancer develops from one or a combination of multiple mechanisms including modification of DNA via epigenetics or enzyme dysfunction and genetic instability or mutation. These modifications can then provide the cancer cells with a selective growth advantage, in which Pb may contribute to epigenetic changes and chromosomal aberrations. Additionally, epigenetic modifications may lead to cancer by altering cellular functions without altering the DNA sequence. The most studied epigenetic change is methylation alterations. A small number of studies included in the 2013 Pb ISA show that Pb can induce epigenetic changes, but do not clearly tie these effects to Pb-induced carcinogenesis and genotoxicity (Patel, 2013; Li et al., 2011; Wright et al., 2010; Pilsner et al., 2009). Since the 2013 Pb ISA, additional studies have examined Pb-induced epigenetic modifications and the degree to which these modifications may underlie Pb-induced carcinogenicity. These studies are discussed below.

The role of epigenetic mechanisms such as DNA methylation (and demethylation), histone modifications, and non-coding RNAs in the regulation of gene expression is well established. Promoter methylation of DNA repair genes is a common event in tumorigenesis. Two recent in vitro cell culture studies investigated the potential effects of Pb on epigenetic regulation of gene expression. Liu et al. (2018), using methylation-specific PCR (M-PCR) that specifically enhances promoter methylation, investigated TK-6 cells exposed to Pb acetate at different time points. Expression of several DNA repair genes (XRCC1, hOGG-1, BRCA1, and XPD) was inhibited in this assay, suggesting a role for alterations in methylation profiles of these genes.

Histone and non-histone proteins are methylated by a family of protein arginine methyltransferase (PRMT) enzymes. One of the isoforms of this enzyme, PRMT5, is an oncogene and plays a critical role in cancer progression by promoting cell proliferation and inhibiting apoptosis; moreover, it is overexpressed in many forms of human cancers (Dai et al., 2022; Stopa et al., 2015; Bao et al., 2013; Nicholas et al., 2013). Using in vitro culture systems (A549 and MCF-7 cell lines) exposed to Pb chloride (5 and 10 μM) for 24 and 48 hours, Ghosh et al. (2018) investigated Pb-induced, global DNA hypomethylation and

methylation status specific to PRMT5 promoter CpG islands (CGIs). Pb-chloride exposure was found to reduce global methylation levels and either completely or partially demethylate only the upstream PRMT5 promoter CGI. Additional confirmational studies using bisulfite sequencing indicated an approximately five-fold reduction in the methylation by Pb chloride. These two recent studies (Ghosh et al., 2018; Liu et al., 2018) suggest the potential for Pb exposure to alter epigenetic control of gene expression.

10.3.8 Gene Expression and Extracellular Matrix

A single recent study examined gene expression related to cancer progression as assessed by epithelial-to-mesenchymal transition and invasiveness in Renca cells, a murine renal cortical adenocarcinoma cell line (Akin et al., 2019). In these cells, Pb-induced a concentration-dependent (0, 0.625, 1.25 μM) decrease in E- cadherin expression with no alteration in catenin expression, a substantial increase in matrix metalloproteinase-9 (MMP9; involved in cell migration) expression, significantly reduced cell aggregates, and increased cell migration and invasion. Pb exposure also enhanced wound healing in a functional "scratch" assay.

10.3.9 Inflammation

Inflammation is positively associated with the development and progression of cancer (Zhao et al., 2021). Two in vitro cell culture studies investigated markers of inflammation after Pb exposure using a cancer cell line (Jiang et al., 2020; Lin et al., 2015). Lin et al. (2015) investigated Pb nitrate-induced (0.1 μM) inflammation using human stomach adenocarcinoma cells. Pb nitrate was found to induce expression of the proinflammatory gene, interleukin type 8 (IL-8), in a time-dependent manner. Detailed molecular characterization studies on upstream events indicated transcription factor activator protein 1 to be a major transcription factor responsible for this activation while another transcription factor, NF-kB, played only a minor role. Lin et al. (2015) conducted additional experiments using promoter reporter assay. These experiments indicated that induction of IL-8 is mediated by activation of extracellular regulator kinase 1/2 and epidermal growth factor receptor upstream of extracellular regulated kinase 1/2 pathway, an important mediator of cytokine secretion. The observation of Pb-induced expression of the proinflammatory cytokines IL-8 and tumor necrosis factor-α in BEAS-2b human lung cells by Jiang et al. (2020) also confirms the role of inflammation in Pb exposure. Additional experiments suggest that Pb-induced oxidative stress may be the initial event triggering this response (Yadav et al., 2019; Nariya et al., 2018).

10.3.10 Summary of Mechanistic Pathways and Markers of Carcinogenesis

The toxicological literature provides consistent evidence for the carcinogenic potential of Pb, and the findings of Pb-induced genotoxic, mutagenic, and epigenetic effects are consistent with the conclusions drawn in the 2013 Pb ISA. Among the toxicological literature reviewed in the 2013 Pb ISA, laboratory studies in animals consistently report cancer following chronic Pb exposure for 18 months or two years to high concentrations, such as 10,000 ppm Pb acetate in diet or 2,600 ppm Pb acetate in drinking water. Chronic Pb exposure to male and female rodents has consistently induced kidney and brain carcinogenesis in multiple separate studies, inducing various tumors (i.e., adenocarcinomas, adenomas, and gliomas). Pb has also been shown to cause mammary gland, prostate, adrenal, and testicular tumors in animals. Developmental Pb acetate exposure also induced tumors in offspring whose dams received Pb acetate in drinking water during pregnancy and lactation.

In the absence of any new cancer bioassay studies using animal models, much of the toxicological evidence evaluated here comes from in vitro studies using several mammalian cell culture systems (micromolar to millimolar concentrations). These studies provide evidence supporting the Pb-induced activation of diverse mechanistic pathways that are normally associated with carcinogenesis. The new studies continue to support that exposure to multiple forms of Pb (i.e., Pb ions such as Pb acetate, Pb nitrate, or Pb chloride) induces cellular oxidative stress that triggers a set of biological pathways leading to DNA damage, cytotoxicity, and apoptosis. In several cases, the observed effects were exposure related and were both dose dependent and duration dependent. The molecular alterations are diverse in nature, including modified expression of various genes, epigenetic regulatory changes, and activation of upstream mediators for specific oncogenic pathways. Some of the studies also demonstrated that antioxidant administration prior to (or simultaneous with) treatment with Pb protected against Pb-induced effects. Studies of DNA damage and repair after Pb exposure, where oxidative stress seems to be involved, provide additional evidence in support of these observations. In addition, Pb-induced oxidative stress is implicated in multiple organ (liver and kidney) toxicity in animals and supports a strong role for this molecular pathway in Pb-induced toxicity and cancer. Most of the biological pathways implicated in Pb carcinogenesis reviewed here are part of the IARC-identified 10 key characteristics, further supporting conclusions derived in 2013 Pb ISA (U.S. EPA, 2013).

10.4 Cancer Incidence and Mortality

Recent studies have included epidemiologic evaluations of the associations between Pb exposure and both specific cancers (such as breast cancer and lymphoid malignancies), and overall cancer (cancer of any type). Table 10-1 provides an overview of the study characteristics and results for the epidemiologic studies that reported effect estimates.

10.4.1 Epidemiologic Studies of Overall Cancer Incidence

The epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) found no positive associations between various biological markers of Pb exposure and overall cancer incidence. The few epidemiologic studies evaluated were limited by the ecologic or cross-sectional study designs. Additionally, these studies were limited by the lack of biological measurements of Pb and the lack of adjustment for potential confounders. There were no recent PECOS-relevant epidemiologic studies of overall cancer incidence and Pb exposure.

10.4.2 Epidemiologic Studies of Overall Cancer Mortality

The 2013 Pb ISA (U.S. EPA, 2013) reviewed several epidemiologic studies that examined the associations between blood Pb concentrations and cancer mortality. The findings of these studies were inconsistent. More specifically, the findings were inconsistent among participants from NHANES III. In one NHANES III analysis, the cohort of 13,946 (n for cancer mortality = 411) was followed for 12 years and individuals with BLLs greater than 10 μg/dL were excluded from the study (mean baseline BLL was 2.58 μg/dL) (Menke et al., 2006). There were null associations between blood Pb and cancer mortality (hazard ratio [HR] of highest tertile [≥3.63 μg/dL] compared with lowest tertile [<1.93 μg/dL]: 1.10 [95% CI: 0.82, 1.47]). Another NHANES III study, which was restricted to individuals 40 years and older at the time of blood Pb collection and included 9,757 (N for cancer mortality = 543) individuals with all BLLs (including those greater than 10 μg/dL), reported positive associations between blood Pb and cancer mortality (Schober et al., 2006). The RRs were 1.69 (95% CI: 1.14, 2.52) for individuals with BLLs of at least 10 μg/dL and 1.44 (95% CI: 1.12, 1.86) for BLLs of 5–9 μg/dL, compared with individuals with BLLs less than 5 μg/dL. Overall, while the epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) were well-conducted longitudinal studies with control for wide range potential confounders, the studies were limited by the small number of cancer mortality cases, which reduces precision of the measures of associations.

There are a limited number of recent epidemiologic studies which examined the associations between exposure to Pb and overall cancer mortality (Table 10-2). Total mortality is discussed in Section 9.8 in Other Health Effects. Multiple population-based studies found inconsistent associations between blood Pb concentrations and overall cancer mortality (Byun et al., 2020; Duan et al., 2020; van Bemmel et al., 2011). A subset of NHANES III data (1984–1994) that included adults over the age of 40 (n = 3,223), in study participants with elevated BLLs (≥5 μg/dL), there were null associations with overall cancer mortality (HR: 1.083 [95% CI: 0.983, 1.194]), compared with those with lower BLLs (<5 μg/dL) (van Bemmel et al., 2011). Furthermore, the hazard ratio was nearly unchanged when the data were stratified by an δ-aminolevulinic acid dehydratase (ALAD) genetic polymorphism ($ALAD^{GG}$) that may influence a person's susceptibility to lead poisoning. In another NHANES study (1999–2014), which included adults over the age of 20 (n = 26,056), blood Pb was positively associated with cancer mortality

(1.47 [95% CI: 1.22, 1.78]) in the fully adjusted models (Duan et al., 2020). In the 2007–2015 Korea National Health and Nutrition Examination Survey (KNHANES), Byun et al. (2020) reported positive associations between blood Pb and cancer mortality, among the 7,308 study participants, who were at least 30 years of age at baseline. Compared with the lowest tertile (blood Pb <1.91 μg/dL), the HRs for cancer mortality in the second (blood Pb between 1.91 and 2.71 μg/dL) and third (blood Pb >2.71 μg/dL) tertile of blood Pb were 3.42 (95% CI: 1.65, 7.08) and 2.27 (95% CI: 1.09, 4.70), respectively. The nature of the concentration response relationship appears to be non-linear, but the imprecision in the estimates ultimately limits the ability to make any inferences about the relationship.

In summary, there are a limited number of recent epidemiologic studies that examined the association between blood Pb concentrations and overall cancer mortality (Table 10-2). These recent studies used exposure data from population-based national surveys linked to mortality records. The NHANES studies reported null associations between BLLs and overall cancer mortality. The median and geometric mean of BLLs among the NHANES studies were all below 10 μg/dL (median range: 1.49 μg/dL to 7.5 μg/dL; geometric mean: 2.26 μg/dL). In the population-based study in South Korea, there were positive associations with cancer mortality among participants with BLLs less than 10 μg/dL. Because the participants in the population-based South Korean study would likely have had higher past Pb exposures due to when the leaded gasoline was banned in South Korea, uncertainty exists as to the Pb exposure level, duration, frequency, and timing associated cancer mortality. Additionally, while these epidemiologic studies were conducted in well-established cohorts, there is uncertainty in their interpretation because the overall follow-up period was short (<11 years). These studies also had a small number of cancer mortality cases, which resulted in reduced precision across the studies. There was a lack of control for some potential influential confounders such as co-morbidities and body mass index (BMI).l

10.4.3 Epidemiologic Studies of Lung Cancer

The epidemiologic studies reviewed in the 2013 Pb ISA of Pb (U.S. EPA, 2013) exposure and lung cancer reported no evidence of an association. The studies available for review were conducted in occupational cohorts and only included male study participants, which limits the generalizability of the results. A few of the studies did not obtain Pb biomarker exposure levels or only used air sampling measurements. Furthermore, these studies may be confounded by other workplace exposures and covariates, such as smoking, that were not considered. There were no recent PECOS-relevant epidemiologic studies of Pb exposure and lung cancer.

10.4.4 Epidemiologic Studies of Brain Cancer

The 2013 Pb ISA (U.S. EPA, 2013) reviewed a few studies of brain cancer and occupational Pb exposure. The associations between occupational Pb exposure and brain cancer incidence and mortality

varied depending on the tumor type or genetic variant. The implications of the results from these studies were limited because they did not have individual-level biological Pb measurements, relied on self-reported occupational exposure history, and did not control for potential confounding by other workplace exposures. There were no recent PECOS-relevant epidemiologic studies of Pb exposure and brain cancer.

10.4.5 Epidemiologic Studies of Breast Cancer

The epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) of Pb exposure and breast cancer suggested that women with breast cancer may have higher BLLs than those without breast cancer. These studies were limited by their study designs, small sample sizes, and with one study, the method of Pb exposure measurement. There were also some inconsistent results among studies that compared breast tissue Pb concentrations between breast tumor and control samples.

Since the 2013 Pb ISA, a few epidemiologic studies of Pb exposure in blood and breast cancer have been published (Table 10-2). Gaudet et al. (2019) examined associations of circulating levels of Pb with breast cancer risk in three case-control studies nested withing three prospective longitudinal cohorts in the United States, Italy, and Sweden. Among the three cohorts, there were consistent null associations between circulating BLLs and breast cancer, both when Pb exposure was evaluated continuously (RR = 1.00) and when categorized into quintiles (RR range: 0.65–1.10). In a cross-sectional study of NHANES data, Wei and Zhu (2020) reported increased odds of breast cancer across quartiles of BLLs. The odds of breast cancer were 2.52 (95% CI: 1.35, 4.73) in the second quartile (0.8 – 1.2 μg/dL), 2.01 (95% CI: 1.05, 3.84) in the third quartile (1.2–1.8 μg/dL), and 2.63 (95% CI: 1.36, 5.09) in the highest quartile (≥1.8 μg/dL), compared with the lowest quartile (<0.8 μg/dL).

Overall, the current epidemiologic studies evaluating the associations between breast cancer and blood Pb reported inconsistent findings, with a cross-sectional NHANES study finding increasing odds of breast cancer across blood Pb quartiles, while another study using three longitudinal cohorts did not find associations between breast cancer and blood Pb. The inconsistency in findings may be related to differences in study design, biomarkers of exposure as Wei and Zhu (2020) measured Pb in whole blood, while Gaudet et al. (2019) measured Pb levels in stored erythrocytes, timing of exposure (blood draws were obtained from 1990–2006 in Gaudet et al. (2019), while Wei and Zhu (2020) used data from 2003–2012), and range of Pb levels.

10.4.6 Epidemiologic Studies of Other Cancer

The epidemiologic literature reviewed in the 2013 Pb ISA (U.S. EPA, 2013) for associations between Pb exposures and other specific cancers reported varying associations among occupational cohorts. Positive associations were observed between occupational exposure to Pb and adenocarcinoma of the esophagus and stomach cancer, but there were inconsistent associations with occupational Pb

exposure and rectal cancer and occupational leaded gasoline exposure and stomach cancer. These occupational cohort studies were limited to the study populations consisting of only men, no personal, biological, or exposure measurements for Pb, and no control for potential confounding by other occupational exposures. The current epidemiologic literature examining the associations of Pb exposure and specific cancer outcomes remains limited. Table 10-2 provides an overview of the current epidemiologic study details.

A single study evaluated the association between BLLs and urothelial carcinoma in a hospital-based case-control study in China (Chung et al., 2017). Study participants were recruited between 2011 and August 2014, resulting in 209 cases matched to 417 controls based on age (range: 26–96 years) and gender. Cases has slightly higher Pb blood levels (mean: 2.81 μg/dL) than controls (mean: 2.56 μg/dL). There were increased odds of urothelial carcinoma (OR: 1.66 [95% CI: 1.05, 2.61]) in the highest quartile (≥2.99 μg/dL) of blood Pb compared with the lowest (<1.76 μg/dL). There was also increased risk of urothelial carcinoma in the highest tertile of blood Pb (≥2.73 μg/dL) for both current smokers (OR:1.76 [95% CI: 0.69, 4.46]) and non-smokers (OR:1.48 [95% CI: 0.91, 2.39]).

In a hospital-based case-control study in China, Lin et al. (2018) examined the BLLs and associations with gastrointestinal cancers. There were 167 gastrointestinal cancer cases (70 esophageal, 51 gastric, and 46 colorectal), which were newly diagnosed and previously untreated, and 112 controls included in the study. The BLLs were slightly higher among cases (median: 6.003 μg/dL) than controls (median: 5.384 μg/dL). The 75th percentile of the BLL (9.09 μg/dL) of cases was used as a cutoff to assign study participants as either low (<75th percentile) or high (>75th percentile) blood Pb. There was an increased odds of 2.32 (95% CI: 1.01, 4.94) of gastrointestinal cancers for those with high BLLs, compared with those with low BLLs. When stratifying by clinical characteristics among cases with high BLLs (>9.09 μg/dL, 75th percentile), there were positive, but imprecise associations due to the small number of cases (i.e., <20 cases) (see Table 10-2).

Kelly et al. (2013) and Deubler et al. (2020) examined the associations between Pb exposure in blood erythrocytes and lymphoid malignancies, specifically B-cell non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), in large prospective cohorts in the United States, Italy, and Sweden. Kelly et al. (2013) conducted a case-control study nested within two prospective cohorts in Italy (n = 84 cases and n = 84 controls) and Sweden (n = 186 cases and n = 186 controls). Lymphoma cases were identified between 2–16 years of follow-up and controls were matched on gender, age, center (Italy or Sweden), and date of blood collection. With increasing quartiles of pre-diagnostic exposure levels of Pb, Kelly et al. (2013) reported null associations with B-cell NHL (OR: 0.93 [95% CI: 0.43, 2.02]) for the total study population (both cohorts), and the null associations remained when stratified by sex [OR for males: 0.74 (95% CI: 0.27, 2.04); OR for females: 0.42 (95% CI: 0.12, 1.47)]. When comparing the highest quartile of pre-diagnostic exposure levels of Pb to the lowest, there was increased odds of 1.63 (95% CI: 0.45, 5.94) for MM among the total study population, but this association was imprecise due to the small sample size. There were insufficient numbers to stratify by males, but for females there was no association between

MM and the highest quartile of pre-diagnostic exposure levels of Pb (OR:0.74 [95% CI: 0.14, 3.83]). When further stratified by NHL subtype, there were null associations: diffuse large B-cell lymphoma (OR: 0.60 [95% CI: 0.26, 1.40]), B-cell chronic lymphatic lymphoma (OR:0.71 [95% CI: 0.32, 1.57]), MM (OR:1.04 [95% CI: 0.57, 1.90]), and follicular lymphoma (OR:1.17 [95% CI: 0.52, 2.63]) per one unit increase in log-transformed pre-diagnostic exposure levels of Pb. There were null associations for females for MM (OR:1.28 [95% CI: 0.53, 1.96]), follicular lymphoma (OR:1.91 [95% CI: 0.54, 6.78]), diffuse large B-cell lymphoma (OR:0.29 [95% CI: 0.07, 1.18]), or B-cell chronic lymphatic lymphoma (OR:0.79 [95% CI: 0.17, 3.60]) per one unit increase in log-transformed pre-diagnostic exposure levels of Pb. There were null associations between males and MM (OR:0.83, 95% CI: 0.35, 1.96), diffuse large B-cell lymphoma (OR:0.97 [95% CI: 0.35, 2.64]), B-cell chronic lymphatic lymphoma (OR:0.63 [95% CI: 0.23, 1.74]), or follicular lymphoma (OR:0.80 [95% CI: 0.25, 2.55]) per one unit increase in log-transformed pre-diagnostic exposure levels of Pb.

Deubler et al. (2020) also conducted a case-control study, but among participants of the Cancer Prevention Study-II Nutritional Cohort (CPS-II NC) to assess the risk of lymphoid malignancies, B-cell NHL and MM, with pre-diagnostic erythrocyte Pb levels. There were 375 cases and 750 controls. There were positive associations with overall lymphoid malignancy (RR: 1.088 [95% CI: 1.009, 1.173] per 1-SD (1.76 µg/dL) increase of erythrocyte lead concentrations), all B-cell NHL (RR: 1.093 [95% CI: 1.005, 1.19] per 1-SD increase of erythrocyte lead concentrations), and follicular lymphoma (RR: 1.114 [95% CI: 1.085, 1.798] per 1-SD increase of erythrocyte lead concentrations), but null associations with diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), other B-cell lymphoma, and MM. When stratified by sex, for males, there were positive associations between overall lymphoid malignancy (RR: 1.131 [95% CI: 1.027, 1.246] per 1-SD (1.81 µg/dL) increase in erythrocyte Pb), all B-cell NHL (RR: 1.151 [95% CI: 1.03, 1.286] per 1-SD increase in erythrocyte Pb), CLL/SLL (RR: 1.274 [95% CI: 1.016, 1.598] per 1-SD increase in erythrocyte Pb), but null associations with diffuse large B-cell lymphoma, follicular lymphoma, other B-cell lymphoma, and MM. Among females, there was a positive association with follicular lymphoma (RR: 2.158 [95% CI: 1.07, 4.353] per 1-SD (1.56 µg/dL) increase in erythrocyte Pb), but null associations with all B-cell NHL, diffuse large B-cell lymphoma, CLL/SLL, other B-cell lymphoma, and MM.

10.4.7 Summary of Cancer Incidence and Mortality

The epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013) reported inconsistent findings across cancer endpoints. Among the studies that evaluated Pb exposure and overall cancer incidence, there were no positive associations with various biological markers of Pb exposure. The epidemiologic studies of overall cancer incidence were limited by the lack of biological measurements of Pb and the lack of adjustment for potential confounders. The epidemiologic studies that examined the associations between Pb concentrations and cancer mortality found inconsistent associations. Although the studies were well-conducted longitudinal studies with control for a wide range of potential

confounders, the studies were limited by the small number of cancer mortality cases, which reduces statistical power to determine the presence of an association. The epidemiologic studies of Pb exposure and lung cancer reported no evidence of an association. The studies available for review were conducted in occupational cohorts and only included male study participants, which limits the generalizability of the results. A few of the studies did not obtain Pb biomarker exposure levels or only used air sampling measurements. Furthermore, these studies may be confounded by other workplace exposures and covariates, such as smoking, that were not considered. There were a limited number of studies of brain cancer and occupational Pb exposure. The associations between occupational Pb exposure and brain cancer incidence and mortality varied depending on the tumor type or genetic variant. The implications of the results from these studies were limited because they did not have individual-level biological Pb measurements, relied on self-reported occupational exposure history, and did not control for potential confounding by other workplace exposures. The epidemiologic studies reviewed relating to Pb exposure and breast cancer suggested that women with breast cancer may have higher BLLs than those without breast cancer. These studies were limited by their study designs, small sample sizes, and, with one study, the method of Pb exposure measurement. There were also some inconsistent results among studies that compared breast tissue Pb concentrations between breast tumor and control samples. The epidemiologic literature reviewed for specific cancers and associations with Pb exposure reported varying associations among occupational cohorts. Positive associations were observed between occupational exposure to Pb and adenocarcinoma of the esophagus and stomach cancer, but there were inconsistent associations with occupational Pb exposure and rectal cancer and occupational exposure to Pb in gasoline and stomach cancer. These studies were limited to the study populations consisting of only men, no personal biological or exposure measurements for Pb, and no control for potential confounding by other occupation exposures.

While there were no recent PECOS-relevant epidemiologic studies of Pb exposure and overall cancer incidence, lung cancer, and brain cancer, there were a limited number of recent epidemiologic studies that examined the association between Pb concentrations and overall cancer mortality, breast cancer mortality, and mortality from other cancers.

The recent PECOS-relevant epidemiologic studies reviewed were inconsistent across cancer endpoints and support the conclusions from the 2013 Pb ISA (U.S. EPA, 2013). There were inconsistent findings in large population-based studies examining the relationship between Pb exposure and overall cancer mortality. While these recent epidemiologic studies were conducted in well-established cohorts, the overall follow-up period was short (<11 years), there were a small number of cancer mortality cases resulting in reduced precision across the studies, and there was a lack of control for some confounders such as co-morbidities. Of note, the cohorts in the recent epidemiologic literature would generally be expected to have had appreciable past exposures to Pb; however, the extent to which adult BLLs in these cohorts reflect the higher exposure histories is unknown as to the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit cancer incidence and/or mortality.

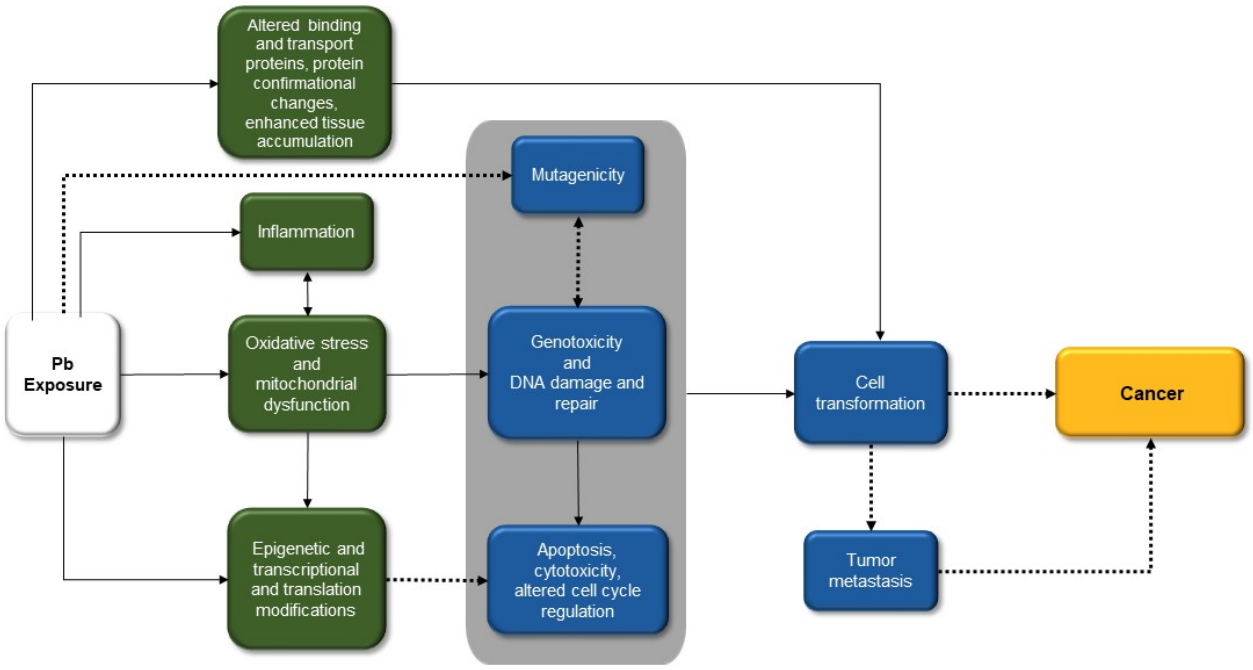
Recent epidemiologic studies evaluating the associations between breast cancer and blood Pb reported inconsistent findings, with an NHANES study finding increasing odds of breast cancer in higher quartiles of blood Pb, while another study using three longitudinal cohorts in Italy, Sweden, and United States did not find associations between breast cancer and blood Pb. The inconsistency in findings may be related to difference in study design, biomarker of exposure, timing of exposure, range of Pb levels, and difference in controlling for potential confounders (age at menarche, pregnancy history, oral contraceptive use, female hormone use, and menopause status).

The recent epidemiologic literature for site-specific cancers and Pb exposure is limited, reporting varied associations. The small body of evidence across various site-specific cancer endpoints limits the ability to judge coherence and consistency across these studies, although the positive associations reported demonstrate that Pb exposure could result in physiological responses that contribute to some site-specific cancers. While these studies did control for a wide range of potential confounders, the studies were limited by small number of cases, relatively short time between exposure and outcome, potential differences in Pb exposure based on study location, and different biomarkers of exposure.

Overall, there were inconsistent findings in the limited number of epidemiologic studies assessing associations between Pb exposure and cancer endpoints. While many of these studies utilized large population-based cohorts, they were limited by the small number of cases, short follow-up time, range of Pb levels, biomarkers of exposure, information of past Pb exposure, and lack of control of some potential confounders.

10.5 Biological Plausibility

This section describes the biological pathways that potentially underlie cancer effects resulting from exposure to Pb. Figure 10-1 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cancer events associated with exposures to Pb at concentrations observed in some epidemiologic studies (e.g., cancer incidence and mortality). Most studies cited in this subsection are discussed in greater detail earlier in this Appendix. Note that the structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the current Pb ISA are discussed in Section 10.6.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway or a genetic knockout model used in an experimental study involving Pb exposure. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color-coded (gray, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the ISA are discussed in Section 10.6.

Figure 10-1 Potential biological pathways for cancer from exposure to Pb.

The development of cancer is a multistep process that involves the progressive accumulation of mutations leading to upregulation of oncogenes and loss of function of tumor suppressor genes resulting in uncontrolled cell growth and invasion of cancer cells within organ tissue. Pb is well-known to cause cancers in animal models, however, the carcinogenic potential of Pb in humans is not well defined. As discussed in the 2006 Pb AQCD, the ability of Pb to cause neoplastic transformation in human cells is limited and is confounded by the fact that some studies utilize Pb chromate. Thus, observed effects may be related to the effects of chromate as opposed to effects of Pb. Despite this, Pb possesses several characteristics that were identified by the IARC that are common of human carcinogens (Smith et al., 2016). In addition, Pb is known to act on several pathways that could plausibly lead to cancer development. The multifaceted pathway outlined in Figure 10-1 connects Pb exposure to cancer incidence via Pb-protein binding, direct mutagenicity, genotoxicity, inflammation, oxidative stress, and epigenetic changes. Together, the experimental evidence can provide plausibility for the carcinogenic potential of Pb.

The most direct pathway to Pb-induced carcinogenesis would involve mutagenesis in response to Pb treatment that over time would result in cell transformation. As discussed in the 2006 Pb AQCD, there is little evidence of the mutagenic potential of Pb (U.S. EPA, 2006). A recent study suggests that Pb can directly interact with the DNA causing conformational change (Zhang et al., 2014). In this study Pb caused increased markers of DNA damage although it is not clear if the binding of Pb was responsible for the observed DNA damage. The potential for Pb to directly induce DNA mutations remains limited and, as mentioned in the 2006 Pb AQCD, may only occur at very high concentrations.

The strongest data for potential carcinogenesis comes from experiments related to oxidative stress-induced genotoxicity. The role of oxidative stress in the pathway of cancer is well documented (Hayes et al., 2020). Oxidative stress can result in the damage of proteins, lipids, and DNA. Pb exposure is well known to cause oxidative stress in several organ systems. Oxidative stress is controlled by a balance between the formation of reactive oxygen species (ROS) and the actions of antioxidant defenses. As discussed in the 2013 Pb ISA, multiple in vitro experiments using diverse mammalian cell cultures exposed to Pb compounds (Pb acetate, Pb chloride, Pb nitrate and divalent Pb ions) for different durations result in increased production of ROS (U.S. EPA, 2013). This is supported by more recent studies that consistently report increased ROS levels, decreased antioxidant defenses, and increased markers of oxidative damage in Pb-exposed cells (see Section 10.3.2). The source of increased generation of ROS in the context of cancer is not clear but could result as a byproduct of Pb-induced inflammation or Pb displacement of biologically relevant ions in enzymes, especially those involved with metabolism and energy production in the mitochondria.

Oxidative stress that damages DNA or impairs DNA repair can lead to mutation and subsequent cellular transformation. As discussed in the 2013 ISA and in more recent studies, several markers of DNA damage have been shown to be increased in Pb-exposed cells including 8-OH-deoxy guanine adducts (Liu et al., 2018), alterations in comet DNA content, comet tail movement (Siddarth et al., 2018; El Makawy et al., 2015; Shakoori and Ahmad, 2013), and DNA double strand breaks (as assessed by H2Ax foci) (Liu et al., 2018; Shah et al., 2016; Pottier et al., 2013) as well as diverse genotoxicity measures like micronuclei formation (Martini et al., 2020; Alimba et al., 2016; Shah et al., 2016; El Makawy et al., 2015) and SCE (Turkez et al., 2012). Similar increases in bone marrow micronuclei and increased comet tail movement are seen in animal studies following Pb exposure (Olatunji-Ojo et al., 2020; Okesola et al., 2019; Nascimento and Martinez, 2016; El Makawy et al., 2015). In addition, the DNA repair rate has been shown to be reduced in Pb treated cells (Martínez-Alfaro et al., 2012). For example, the base excision repair capacity of the DNA repair enzyme APE-1 is decreased by Pb treatment (Hernández-Franco et al., 2018). Another study showed reduced DNA repair was associated with decreased glutathione suggesting that oxidative stress might drive the reduction of DNA repair (Martínez-Alfaro et al., 2012). This data is further bolstered by an experiment in humans exposed occupationally to Pb that show increased markers of DNA damage and reduced DNA repair capacity (Jannuzzi and Alpertunga, 2016). In many experimental cases, treatment with antioxidant compounds can protect against DNA damage (Okesola et al., 2019; Siddarth et al., 2018; El Makawy et al., 2015) suggesting that oxidative stress is necessary for

Pb-induced genotoxicity. This data supports a solid line in Figure 10-1 from oxidative stress to genotoxicity.

Pb can also plausibly promote cancer development through induction of inflammation. Inflammation is a hallmark of a pro-cancer environment. Induction of inflammation could be direct effect by increased secretion of pro inflammatory markers. In addition, inflammation can result from cell damage caused by oxidative stress. The 2013 Pb ISA and 2006 Pb AQCD discuss evidence that Pb treatment can trigger the production of inflammatory mediators in vitro as well as in many organ systems (U.S. EPA, 2013, 2006). More recent in vitro evidence supports these findings in the context of cancer cell lines (Jiang et al., 2020; Lin et al., 2015). Many natural compounds that demonstrate anticancer activity in vitro possess both anti-inflammatory and antioxidant capacity suggesting that inflammation could be playing a role in the development of cancer.

Excessive DNA damage, as a result of inflammation and oxidative stress, can activate cell death pathways. Cancer can arise when mutated cells suppress cell death pathways. Alternatively, cell death often triggers compensatory expansion of surrounding cells. With chronic injury, a constant repair process activation can trigger hyperplastic growth and degradation of extracellular matrix that can promote cellular transformation and tumor invasiveness. While there is evidence that Pb treatment in vitro can lead to cell death (see Section 10.3.5), there is no evidence to suggest that Pb can cause resistance to cell death. However, there are some indications that Pb can stimulate cellular regrowth that over time could potentially promote cellular transformation. Wang et al. (2013) showed that Pb treatment of CL3 cells resulted in increased cell cycle progression. Another recent study showed that Pb treatment can lead to increased MMP expression resulting in greater cell migration in a wound healing assay (Akin et al., 2019). Together, there is strong evidence that Pb can cause cell death but the role of Pb in the development of apoptosis resistance or uncontrolled cell growth remains speculative.

Over time, accumulation of mutations that promote tumor growth and blunt anti-tumor defenses can lead to cell transformation and increased cancer incidence. In vitro assays can measure transformation as an increase in morphologically distinct cells (i.e., a foci). As discussed in the 2013 ISA, data from cellular transformation assays have shown that Pb acts as a promoter of cellular transformation in animal cells in vitro. In support of this, a recent study showed that Pb pretreatment of Balb/c-3T3 cells prior to transformation with n-methyl-n-nitrosoguanidine and 12-O-tetradecanoylphorbol-13-acetate resulted in increased foci formation suggesting that Pb can help to promote transformation (Hernández-Franco et al., 2018).

Changes in regulation of gene expression through epigenetic mechanisms represent another plausible pathway by which Pb can promote tumor formation. The 2013 ISA provided limited evidence from human studies that tibia Pb levels could be inversely related to global methylation markers (U.S. EPA, 2013). A new study of infant blood spots showed a general decrease in methylation at 33 CpG sites with increasing BLLs (Laurino et al., 2020). Interestingly, pathway enrichment analysis suggested that differentially methylated sites corresponded to cell morphogenesis and cell adhesion. This suggests that

changes in epigenetics regulation could play a role in changes in cell adhesion which could be important in the context of tumor invasiveness and metastasis. Increased methylation was also seen in the promoter regions of several DNA repair genes following Pb exposure which correlated with decreased repair protein levels (Liu et al., 2018). Alterations of methyltransferases levels following Pb exposure in vitro has also been reported and correlate with increased expression of an oncogene (Ghosh et al., 2018). Insight into the mechanism of epigenetic regulation by Pb was provided by Rabbani-Chadegani et al. (2011) who showed that Pb nitrate bound to rat liver chromatin. When analyzed separately, Pb bound histones with higher affinity than to DNA (Rabbani-Chadegani et al., 2011). The affinity of Pb nitrate was greater than Ni nitrate in these studies. Though the biological effects of histone binding were not investigated, it is possible that binding of Pb to histone chromatin or histones could result in epigenetics changes through alterations in accessibility of DNA or histones to modifying enzymes. Overall, there is evidence that Pb can affect epigenetic markers of genes that could affect cancer development.

Pb has been shown to replace biologically relevant ions within cellular proteins which can cause confirmational changes that can impair target protein function. Thus, direct binding of Pb to cellular proteins could form another plausible pathway to promote tumor formation. For example, Pb can compete with Zn in Zn finger domains which are present in several transcription factors (Ghering et al., 2005; Huang et al., 2004; Hanas et al., 1999). Pb-induced conformation changes in cellular proteins could have widespread effects on cellular functions and could theoretically promote cellular transformation. The potential of Pb to directly bind and alter cellular protein function represents another pathway by which Pb exposure could result in cell transformation and tumorigenesis.

Together, mechanistic toxicological data provides several possible pathways through which Pb exposure can result in the tumorigenesis that is seen in animal studies and that is reported in some epidemiologic studies. The evidence is strongest for a pathway that involves Pb-induced inflammation and oxidative stress which causes subsequent DNA damage that, in conjunction with suppression of proper DNA repair mechanisms, can lead to mutations that could result in neoplastic transformation. There is also increasing evidence for the plausibility of epigenetic changes caused by Pb to promote tumorigenesis. Given the widespread impacts of Pb on cellular proteins there are other plausible pathways for tumor formation including direct mutagenesis and chronic tissue damage with subsequent cell cycle disruption, although the evidence for these pathways is more limited.

10.6 Summary and Causality Determination

The 2013 Pb ISA concluded that there was a "likely to be a causal relationship" between Pb exposure and cancer (U.S. EPA, 2013). This causality determination was made on the basis that the toxicological literature provides consistent evidence of the carcinogenic potential of Pb and possible contributing modes of action, including genotoxic, mutagenic, and epigenetic effects. The toxicological literature provided strong evidence for cancer following long-term exposure (i.e., 18 months or 2 years) to

high concentrations of Pb (>2,6000 ppm) in drinking water. The consistent evidence indicating Pb-induced carcinogenicity in animal models was substantiated by findings from multiple high-quality toxicological studies in animal and in vitro models from different laboratories. Carcinogenicity in animal toxicology studies with relevant routes of Pb exposure has been reported in the kidneys, testes, brain, adrenals, prostate, pituitary, and mammary gland, albeit at high doses of Pb. Epidemiologic studies of cancer incidence and mortality reported inconsistent results; one strong epidemiologic study demonstrated an association between blood Pb and increased cancer mortality (Schober et al., 2006), but the other studies reported weak or no associations (Khalil et al., 2009; Weisskopf et al., 2009; Menke et al., 2006).

Although there are no recent PECOS-relevant animal toxicological studies evaluating the relationship between Pb exposure and cancer endpoints, the animal studies available in previous reviews continue to provide strong support for the carcinogenic potential of high Pb exposures (chronic 10,000 ppm Pb acetate diet or 2,600 ppm drinking water Pb acetate) (Tokar et al., 2010; Waalkes et al., 1995; Kasprzak et al., 1985; Koller et al., 1985; Azar et al., 1973; Van Esch and Kroes, 1969). Recent in vitro studies report Pb activation of pathways that are relevant and frequently reported to be involved in cancer development and/or progression, particularly pathways mediated by oxidative stress, genotoxicity, and inflammation. Other mechanistic pathways that may be involved in Pb-induced carcinogenesis include cell cycle regulatory genes, epigenetics, apoptosis, and necrosis with predictive regenerative proliferation. Additionally, new areas of research involving MMPs and metallothionines have emerged and provide evidence of other potential mechanistic pathways through which Pb exposure could contribute to cancer. This recent evidence has added to our understanding of how Pb exposures may activate the mechanistic pathways that can result in cancer.

Recent epidemiologic studies that examined the associations between Pb exposure and overall cancer mortality reported inconsistent results, similar to the epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013). The recent studies of overall cancer mortality used exposure data from population-based national surveys linked to mortality records. While there were positive associations between blood Pb and overall cancer mortality in large population survey studies in the United States and Korea (Byun et al., 2020; Duan et al., 2020), there were null associations in another NHANES study (van Bemmel et al., 2011). These epidemiologic studies were conducted in large, well-established population-based cohorts, but there are still limitations. These include short overall follow-up periods (<11 years), a small number of cancer mortality cases resulting in reduced precision across the studies, and a lack of control of some confounders such as co-morbidities. There were a limited number of recent epidemiologic studies evaluating the associations between Pb exposure and site-specific cancers. The studies reviewed reported inconsistent findings. While several of the studies were well-conducted in large cohorts, there remain uncertainties in the biomarkers of exposure (blood versus erythrocytes), timing of exposure, years of follow-up, range of Pb levels, exposure circumstances (magnitude, duration, timing, and frequency) and differences in controlling for potential confounders (co-morbidities, BMI, age at menarche, pregnancy history, oral contraceptive use, female hormone use, and menopause status).

In summary, the collective body of evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and cancer. The key evidence for this causal determination is in Table 10-1. There continues to be strong evidence from in vivo toxicological studies and from studies of mechanistic pathways indicating the carcinogenic potential of Pb exposure, including inflammation; oxidative stress; and genotoxic, mutagenic, and epigenetic effects. Recent mechanistic research further identifies biologically plausible molecular pathways through which Pb could contribute to the initiation and/or progression of cancer, and these pathways are consistent with the IARC 10 key characteristics of carcinogenic mechanistic pathways (Smith et al., 2016). Several of these pathways are consistent with the reported mechanistic pathways associated with Pb carcinogenicity reported in the 2013 Pb ISA. Recent epidemiologic studies provide inconsistent evidence of associations between Pb exposure and cancer incidence and/or mortality, for either overall or site-specific cancer. More specifically, the small body of epidemiologic evidence across various site-specific cancer endpoints limits the ability to judge coherence and consistency across these studies, although the positive associations observed in a small number of studies at relevant BLLs demonstrate that Pb exposure could result in physiological responses that contribute to urothelial carcinoma, gastrointestinal cancer, non-Hodgkin's lymphoma, and multiple myeloma. Despite uncertainty due to inconsistent findings across epidemiologic studies, animal toxicology studies and in vitro mechanistic studies provide strong evidence for the carcinogenic potential of Pb exposures.

Table 10-1 Summary of evidence for a likely to be causal relationship between Pb exposure and cancer

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent evidence from multiple animal studies with chronic Pb exposure	Consistent findings across multiple toxicology studies using 18-mo or 2-yr cancer bioassays in rats wherein rodents are fed chow or received drinking water enriched with Pb acetate and show tumor development.	Azar et al. (1973) Kasprzak et al. (1985) Koller et al. (1985) Van Esch and Kroes (1969) See Section 10.3.2	Chronic 10,000 ppm Pb acetate diet or 2,600 ppm drinking water Pb acetate, no blood Pb measurement available.
	Gestational and lactational Pb exposure induced carcinogenicity in adult offspring.	Waalkes et al. (1995) Tokar et al. (2010) See Section 10.3.2	500, 750, and 1,000 ppm Pb in drinking water, no blood Pb measurement available.
Most evidence clearly supports biological plausibility	Consistent toxicological evidence for mutagenicity, carcinogenicity, and genotoxicity of Pb reported by multiple laboratories in humans, animals and in vitro models using multiple assays (micronuclei, SCE, comet).	See subsections in Section 10.3 Toxicology evidence of DNA and cellular damage: Tapisso et al. (2009) Alghazal et al. (2008) Gastaldo et al. (2007) Xu et al. (2008) Nava-Hernández et al. (2009) Yedjou et al. (2010) Xu et al. (2006) Kermani et al. (2008) Epidemiology evidence of DNA and cellular damage: Wiwanitkit et al. (2008) Duydu et al. (2005) Khan et al. (2010) Olewińska et al. (2010)	

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
		Shaik and Jamil (2009)	
	Some evidence for epigenetic changes. Bone Pb levels were inversely associated with LINE-1 methylation in a study of adult men.	Wright et al. (2010) Patel (2013)	
	Study showed inverse association between maternal postpartum bone Pb levels and Alu and LINE-1 methylation in cord blood.	Pilsner et al. (2009)	
	Occupational battery workers had ALAD hypermethylation compared with controls; cell culture study of high dose Pb exposure caused ALAD hypermethylation.	Li et al. (2011)	
Toxicological evidence of clastogenic (SCE, micronucleus formation, chromosomal aberrations), mutagenic, and genotoxic effects with Pb chromate	Some toxicological studies employ Pb chromate when investigating the clastogenic, mutagenic, and genotoxic effects of Pb. The effect of the chromate ion in contributing to these effects cannot be ruled out.	Holmes et al. (2006a) Wise et al. (2006a) Holmes et al. (2006b) Wise et al. (2006b) Xie et al. (2007) Wise et al. (2010) Grlickova-Duzevik et al. (2006) Savery et al. (2007) Camyre et al. (2007) Stackpole et al. (2007) Li Chen et al. (2009) Wise et al. (2009) Wise et al. (2011)	

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Epidemiologic evidence is limited and inconsistent	Epidemiologic studies of overall cancer mortality have inconsistent findings. These are high-quality, longitudinal studies and control for potential confounders, such as age, smoking, and education. The follow-up period was short (<11 yr). There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure. There was the lack of control of potential important confounders such as co-morbidities.	Overall Cancer Mortality: See Section 10.4.2	In the mortality studies, the majority of the study participants' BLLs were <10 µg/dL (NHANES medians ranged from 1.49 to 7.5 µg/dL and KNHANES geometric mean was 2.26 µg/dL).
	Epidemiologic studies of specific cancer sites were limited. Many of the epidemiologic studies examining specific cancer sites were case-control studies and not all included potentially important confounders, such as smoking and co-morbidities. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure and impact of difference biomarkers (blood vs. stored erythrocytes).	Specific Cancer: Breast Cancer: See Section 10.4.5	In studies of breast cancer, the majority of the study participants' BLLs were <10 µg/dL (medians ranged from 1.15–8.78 µg/dL).
		Other Cancer: See Section 10.4.6	In studies of other cancer, the majority of the study participants' BLLs were <10 µg/dL (medians ranged from 3.05–9.191 µg/dL and means ranged from 2.56–2.81 µg/dL).

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.
ALAD = δ-aminolevulinic acid dehydratase; BLL = blood lead level; KNHANES = Korea National Health and Nutrition Examination Survey; LINE = long interspersed nuclear elements; mo = month; NHANES = National Health and Nutrition Examination Survey; Pb = lead; SCE = sister chromatid exchange; yr = year.

10.7 Evidence Inventories – Data Tables to Summarize Study Details

Table 10-2 Epidemiologic studies of exposure to Pb and cancer effects

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Overall Cancer Mortality					
Menke et al. (2006)† U.S. NHANES III (1988–1994), mortality follow-up in 2001 (12 yr follow-up) Cohort	NHANES III n = 13,946, ≥20 yr	Blood Blood was measured by GFAAS with Zeeman correction Mean: 2.58 µg/dL Blood Pb Tertiles: T1: <1.93 µg/dL T2: 1.94–3.62 µg/dL T3: ≥3.63 µg/dL Age of Measurement Mean 44.4 yr	Overall cancer mortality Cause of death was determined by the underlying cause of death listed on death certificates. ICD-9 codes (codes 140 to 239) were used for deaths between 1988 and 1998 and ICD-10 codes (C00-C97 and D00-D048) were used for deaths during 1999 and 2000. Age at Outcome: Age at death	Cox proportional hazard regression analysis adjusted age, race/ethnicity, sex, urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus, hypertension, GFR category	HR: T1: Reference T2: 0.72 (0.46, 1.12) T3: 1.10 (0.82, 1.47)
Schober et al. (2006)† U.S. NHANES III (1988–1994), mortality follow-up in 2006 ~8.55 yr of follow-up	NHANES III n = 9,686, ≥40 yr of age	Blood Blood was measured by GFAAS with Zeeman correction Age of Measurement: ≥40 yr Blood Pb Tertiles:	Overall cancer mortality Deaths due to malignant neoplasm (ICD-10 codes C00-C97) Age at Outcome: Age at death	Cox proportional hazard regression analysis adjusted for sex, age, race/ethnicity, smoking, education level	Relative Risk (RR): T1: Reference T2: 1.44 (1.12, 1.86) T3: 1.69 (1.14, 2.52)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort		T1 < 5 (median 2.6 µg/dL) T2 5–9 (median 6.3 µg/dL) T3 ≥ 10 (median 11.8 µg/dL)			
van Bemmel et al. (2011) U.S. NHANES III (1984–1994), mortality follow-up in 2007 (~7.8 yr of follow-up for low blood Pb and ~7.5 yr of follow-up for high blood Pb) Cohort	NHANES n: 3,349 (BLL <5 µg/dL n: 2,532; BLL ≥5 µg/dL n: 817) NHANES III (1984–1994) general population restricted to the participants who were successfully genotyped, excluding those under the age of 40; those with no baseline blood Pb measurements; missing data on ALAD genotype, education, and date of study entry	Blood Blood was measured by GFAAS Age at Measurement: 40+ Median for BLL <5 µg/dL: 2.6 µg/dL Median for BLL ≥5 µg/dL: 7.5 µg/dL Max: 52.9 µg/dL	Overall cancer mortality Mortality from malignant neoplasm (ICD-10 codes C00–C97) Age at Outcome: Age at death was defined as the time to event	Cox proportional hazard regression models were adjusted for age, education, sex, smoking status, race/ethnicity, ALAD genotype	HR: 1.08 (0.98, 1.19) for BLL ≥5 µg/dL, compared to <5 µg/dL HR for ALAD^{GG}: 1.08 (0.99, 1.19) for BLL ≥5 µg/dL, compared to <5 µg/dL
Duan et al. (2020) U.S. 1999–2014, mortality follow-up in 2015 (~7.1 yr of follow-up) Cohort	NHANES n: 26,056 NHANES participants aged 20 yr or older, not pregnant, or missing covariate data	Blood Blood was measured by multielement atomic absorption spectrometer with a Zeeman background correction (NHANES 1999–2002) or ICP-MS (after 2003) Age at Measurement: average age: 45.9 yr Median[b]: 1.49 µg/dL 75th[b]: 2.31 µg/dL	Overall cancer mortality Death certificates were used to determine the source and cause of death, specifically cancer-specific mortality (codes C00–C97) Age at Outcome: Age at death	Poisson regression models estimated the RR and adjusted for sex, age, age squared, and ethnicity (Model 1); plus education, PIR, cotinine category, BMI, and physical activity (Model 2); plus hypertension and diabetes (Model 3)	RR per one unit increase in blood Pb Model 1: 1.65 (1.38, 1.97) Model 2: 1.47 (1.22, 1.77) Model 3: 1.47 (1.22, 1.78)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Byun et al. (2020) Korea 2007–2015, mortality follow-up in 2018 (between 3 and 11 yr of follow-up) Cohort	KNHANES n: 7,308 Individuals with a BLL less than 10 µg/dL, who were aged 30 yr and over at the baseline examination, and who were not diagnosed with cancer or ischemic heart disease	Blood Blood was measured by GFAAS with Zeeman background correction Age at Measurement: 30+ yr Geometric mean: 2.26 (±1.52) µg/dL Blood Pb tertiles: T1: <1.91 µg/dL T2: 1.91–2.71 µg/dL T3: >2.71 µg/dL	Overall cancer mortality Deaths identified from all non-accidental causes (the International Classification of Disease tenth revision: ICD-10, A00-R99) and cancer (ICD-10, C00–97). Age at Outcome: Age at death	Cox proportional hazard models: Initial models (Model 1) were adjusted only for age and sex. Subsequent models (Model 2) were additionally adjusted for household income, education, occupation, smoking status, drinking frequency, BMI, and physical activity. Final models (Model 3) were further adjusted for intake of high-lead-containing food intake (grains, vegetables, and seafood).	HR Model 1: T1: Reference T2: 3.19 (1.47, 6.91) T3: 2.41 (1.17, 4.96) Model 2: T1: Reference T2: 3.46 (1.65, 7.26) T3: 2.26 (1.09, 4.69) Model 3: T1: Reference T2: 3.42 (1.65, 7.08) T3: 2.27 (1.09, 4.70)
Breast Cancer					
Gaudet et al. (2019) United States, Italy, Sweden U.S. CPS-II: 1998–2001; EPIC-Italy: 1993–1998; NSHDS: 1990–2006 Cohort	CPS-II n: 21,956; EPIC-Italy n: 32,578; NSHDS n: 40,256	Blood (erythrocytes) Blood was measured by ICP-MS Age at measurement: Median age (range): CPS-II: 68 (47–85); EPIC-Italy: 52 (35–70); NSHDS: 50 (30–61) Median[c]: CPS-II: 2.53 µg/dL; EPIC-Italy: 8.78 µg/dL; NSHDS: 3.897 µg/dL	Breast cancer CPS-II: Cancer incident to blood draw diagnosed through June 30, 2011 were self-reported on follow-up questionnaires and subsequently verified by obtaining medical records or through linkage with state registries when complete medical records could not be obtained. Deaths were obtained through linkage of the cohort with the National Death Index.	Logistic regression models estimated the relative risk (RR); adjusted for race, blood draw date and age for CPS-II; and age, year of blood collection, menopausal status and Italian study center for EPIC-Italy and NSHDS	CPS-II: RR per each unit increase in blood Pb (continuous): 1.00 (0.99, 1.00) Quintile RR: Q1: Reference Q2: 1.10 (0.81, 1.49) Q3: 1.07 (0.79, 1.45) Q4: 0.94 (0.69, 1.28) Q5: 0.94 (0.69, 1.28) EPIC-Italy:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	Breast cancer cases included 816 cases from CPS-II, 294 from EPIC-Italy and 325 from NSHDS. Each case was paired with one control. Eligible controls were selected among those who were alive and cancer-free at the time of the case's diagnosis and matched on race (CPS-II), birthdate (within 6 mo in CPS-II and within 2.5 yr in EPIC-Italy and NSHDS), menopausal status (NSHDS, EPIC-Italy), study center (EPIC-Italy) and blood draw date (within 6 mo in CPS-II and within the same year in EPIC-Italy and NSHDS).	75th[c]: CPS-II: 3.442 µg/dL; EPIC-Italy: 11.21 µg/dL; NSHDS: 5.288 µg/dL Blood Pb Quintiles[c]: CPS-II: Q1: 0–1.68 µg/dL Q2: 1.69–2.28 µg/dL Q3: 2.29–2.88 µg/dL Q4: 2.89–3.76 µg/dL Q5: 3.77–14.84 µg/dL EPIC-Italy: Q1: 2.40–6.35 µg/dL Q2: 6.36–7.99 µg/dL Q3: 8.00–9.99 µg/dL Q4: 10.00–12.50 µg/dL Q5: 12.51–39.18 µg/dL NSHDS: Q1: 0.80–2.64 µg/dL Q2: 2.65–3.57 µg/dL Q3: 3.58–4.54 µg/dL Q4: 4.55–5.53 µg/dL Q5: 5.54–22.37 µg/dL	EPIC-Italy: Newly identified cancer cases were identified through automated linkages to cancer and mortality registries, municipal population offices and hospital discharge systems. In Naples, follow-up information was collected through periodic personal contact. NSHDS: Newly identified cancer cases were identified through linkage with the Swedish Cancer Registry and the local Northern Sweden Cancer Registry. Age at Outcome: Age at diagnosis		RR per each unit increase in blood Pb (continuous): 1.00 (0.99, 1.00) Quintile RR: Q1: Reference Q2: 0.94 (0.57, 1.56) Q3: 0.96 (0.57, 1.61) Q4: 0.74 (0.43, 1.25) Q5: 0.77 (0.45, 1.33) NSDHS: RR per each unit increase in blood Pb: 1.00 (0.99, 1.01) Quintile RR: Q1: Reference Q2: 1.09 (0.68, 1.76) Q3: 0.99 (0.61, 1.60) Q4: 0.65 (0.39, 1.08) Q5: 1.06 (0.66, 1.71)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wei and Zhu (2020) U.S. 2003–2012 Cross-sectional	NHANES n: 9,260 Female participants 20 yr of age or older	Blood Blood was measured by ICP-MS Age at measurement: 20+ yr Geometric mean:1.09 µg/dL Median: 1.15 µg/dL Max: 25 µg/dL Blood Pb Quartiles: Q1: <0.8 µg/dL Q2: 0.8 to <1.2 µg/dL Q3: 1.2 to <1.8 µg/dL Q4: ≥1.8 µg/dL	Breast cancer Self-reported cancer diagnosis was obtained from the medical conditions questionnaires. Participants were being asked a question "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?'. Participants who answered "yes" were subsequently asked "What kind of cancer was it? Only women who reported "no cancer" diagnosis or a "breast cancer" diagnosis were included in our study population. The study population was categorized into with breast cancer and without breast cancer in the analytical models. Age at Outcome: age at diagnosis	Logistic regression models were adjusted for age, race/ethnicity, poverty status, education, BMI, physical activity, age at menarche, pregnancy history, oral contraceptive use, female hormone use, cigarette smoking, and alcohol consumption	OR: Q1: Reference Q2: 2.52 (1.35, 4.73) Q3: 2.01 (1.05, 3.84) Q4: 2.63 (1.36, 5.09)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Other Cancers					
Chung et al. (2017) Taichung Taiwan June 2011–August 2014 Case-control	n: 209 patients with UC and 417 control patients UC patients aged 26–96 yr, whose diagnoses were evaluated by a pathologist. Matched control participants with cases according to gender and age (±3 yr) from patients undergoing adult health examinations.	Blood Blood was measured by ICP-MS Age at Measurement: Mean age for cases: 67.18 ± 10.79; mean age for controls: 66.20 ± 10.06 Mean for cases: 2.81 µg/dL Mean for controls: 2.56 µg/dL Blood Pb Quartiles: Q1: <1.76 µg/dL Q2: 1.76–2.31 µg/dL Q3: 2.31–2.99 µg/dL Q4: ≥2.99 µg/dL Blood Pb Tertiles for Smoking Status: T1: <1.98 µg/dL T2: 1.98–2.73 µg/dL T3: ≥2.73 µg/dL	Other cancers: Urothelial carcinoma Patients with UC comprised outpatients or inpatients among men and women aged 30–90 yr old; UC cases were limited to patients with urinary tract urothelial carcinoma, whose diagnoses were evaluated by a pathologist. Age at Outcome: Mean age for cases: 67.18 ± 10.79; mean age for controls: 66.20 ± 10.06	Logistic regression models were adjusted for age, gender, smoking	OR: Q1: Reference Q2: 0.68 (0.40, 1.15) Q3: 1.05 (0.64, 1.70) Q4: 1.66 (1.05, 2.61) OR for smokers: T1: Reference T2: 1.71 (0.63, 4.60) T3: 1.76 (0.69, 4.46) OR for non-smokers: T1: Reference T2: 0.72 (0.43, 1.22) T3: 1.40 (0.91, 2.39)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lin et al. (2018) Chaoshan, China June–December 2014 Case-control	n: 180 cases and 120 controls Participants recruited were native inhabitants living in the Chaoshan area (including the cities of Shantou, Chaozhou, and Jieyang, and other neighboring areas). Cases and controls had no distinction between geographic or cultural groups since they were the native aborigines in Chaoshan.	Blood Blood was measured by GFAAS Age at Measurement: Cases mean age: 59.065; Controls mean age: 47.09 Median[c] for cases: 6.003 µg/dL Median[c] for controls: 5.384 µg/dL 75th[c] for Cases: 9.086 µg/dL 75th[c] for Controls: 7.627 µg/dL Blood Pb Quartiles: Q1: <25th percentile Q2: 25th–50th percentile Q3: 50th–75th percentile Q4: >75th percentile	Other cancers: Gastrointestinal cancers All cases were newly diagnosed and previously untreated. Clinical characteristics, including basic medical data, were obtained from medical records. Controls (n = 112) were recruited and found no disease in the subsequent B-ultrasound, imaging examination, and hematological examination. Age at Outcome: Cases mean age: 59.065; Controls mean age: 47.09	Logistic regression models were adjusted for gender, age, tobacco smoking, and alcohol drinking	OR: Q1: Reference Q2: 0.683 (0.328, 1.423) Q3: 0.865 (0.410, 1.822) Q4: 2.32 (1.01, 4.94) OR for Clinical Stages: I: Reference II: 2.099 (0.451, 9.759) III: 1.458 (0.419, 5.074) IV: 0.613 (0.210, 1.789) OR for T Classification: T1+T2: Reference T3+T4: 4.752 (1.299, 17.389) OR for N Classification: N0: Reference N1+N2+N3: 3.000 (0.822, 10.945) OR for M Classification: M0: Reference M1: 4.546 (0.757, 27.317)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Kelly et al. (2013) Italy and Sweden Italy: 1993–1998; Sweden: 1990–2006 Case-control	EnviroGenoMarkers Study n: Italy: n = 47,749; Sweden: n = 95,000 The EnviroGenoMarkers study is based on participants from two existing prospective cohort studies: EPIC-Italy and the NSHDS. EPIC-Italy: 47,749 volunteers aged 35–70 yr were enrolled in five participating centers across Italy. The NSHDS includes participants from the Västerbotten. A total of 95,000 healthy individuals aged 40–60 were invited for inclusion in the project between 1990 and 2006.	Blood (erythrocytes) Blood was measured by ICP-MS Age at Measurement: Mean age for cases: 53.08 yr Mean age for controls: 53.09 yr Median[c]: 9.191 µg/dL in Italy Median[c]: 4.499 µg/dL in Sweden Erythrocyte Pb Quartiles[c] for B-cell NHL: Q1: 1.5423–3.9286 µg/dL Q2: 3.9504–5.8763 µg/dL Q3: 5.8832–8.7218 µg/dL Q4: 8.7531–40.0843 µg/dL Erythrocyte Pb Quartiles[c] for B-cell NHL for Males: Q1: 1.5423–4.4989 µg/dL Q2: 4.5444–6.1498 µg/dL Q3: 6.1904–10.0201 µg/dL Q4: 10.0528–37.8943 µg/dL Erythrocyte Pb Quartiles[c] for B-cell NHL for Females: Q1: 1.7019–3.6079 µg/dL Q2: 3.6719–5.4739 µg/dL	Other cancers: B-cell non-Hodgkin's lymphoma and multiple myeloma Lymphoma cases that occurred within the two cohorts between 2 and 16 yr of follow up were identified. Lymphoma cases were classified into subtypes according to the SEER ICD-0-3 morphology codes. All eligible B-cell NHL cases, including multiple myeloma were included. Age at Outcome: mean age for cases: 53.08 yr mean age for controls: 53.09 yr	Conditional logistic regression models were adjusted for sex, age, center, batch and sample date	OR: B-cell NHL: Total study population Q1: Reference Q2: 0.93 (0.51, 1.67) Q3: 0.91 (0.47, 1.79) Q4: 0.93 (0.43, 2.02) p for trend: 0.849 Males: Q1: Reference Q2: 0.57 (0.23, 1.37) Q3: 0.83 (0.35, 1.99) Q4: 0.74 (0.27, 2.04) p for trend: 0.742 Females: Q1: Reference Q2: 0.62 (0.23, 1.65) Q3: 0.54 (0.20, 1.46) Q4: 0.42 (0.12, 1.47) p for trend: 0.17 MM: Total study population: Q1: Reference Q2: 1.30 (0.44, 3.86) Q3: 1.17 (0.38, 3.59) Q4: 1.63 (0.45, 5.94) p for trend: 0.533 Males: Insufficient data for models Females: Q1: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Q3: 5.5401–7.7823 µg/dL Q4: 7.8313–40.0843 µg/dL Erythrocyte Pb Quartiles[c] for MM: Q1: 1.1199–3.5133 µg/dL Q2: 3.5184–5.1973 µg/dL Q3: 5.2459–7.9079 µg/dL Q4: 8.1448–67.2484 µg/dL Erythrocyte Pb Quartiles[c] for MM for Males: Q1: 1.9898–3.6049 µg/dL Q2: 3.8613–5.2578 µg/dL Q3: 5.2808–9.3128 µg/dL Q4: 9.7683–67.2482 µg/dL Erythrocyte Pb Quartiles[c] for MM for Females: Q1: 1.1199–3.0604 µg/dL Q2: 3.2928–4.8623 µg/dL Q3: 4.9859–7.5424 µg/dL Q4: 7.6344–22.0943 µg/dL			Q2: 0.71 (0.20, 2.57) Q3: 0.71 (0.19, 2.61) Q4: 0.74 (0.14, 3.83) p for trend: 0.692 OR by NHL subtype associated with a one unit increase in log transformed exposure levels[d]: MM: Total study population: 1.04 (0.57, 1.90) Males: 0.83 (0.35, 1.96) Females: 1.28 (0.53, 3.08) DLBCL: Total study population: 0.60 (0.26, 1.40) Males: 0.97 (0.35, 2.64) Females: 0.29 (0.07, 1.18) B-cell CLL: Total study population: 0.71 (0.32, 1.57) Males: 0.63 (0.23, 1.74) Females: 0.79 (0.17, 3.60) FL: Total study population: 1.17 (0.52, 2.63) Males: 0.80 (0.25, 2.55) Females: 1.91 (0.54, 6.78)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					OR for BLL >10 µg/dL: B-cell NHL: Total study population: 1.10 (0.60, 2.02) Males: 0.93 (0.44, 1.98) Females: 1.50 (0.53, 4.21) MM: Total study population: 1.29 (0.48, 3.45) Males: 0.80 (0.21, 2.98) Females: 2.50 (0.49, 12.89)
Deubler et al. (2020) U.S. 1992-1993 (1998–2001) Case-control	Cancer Prevention Study-II Nutrition Cohort (CPS-II NC) n: 375 B-cell NHL or MM cases (95 DBLCL, 90 CLL/SLL, 62 FL, 76 MM and 52 other B-cell lymphoma) and 750 matched controls The CPS-II NC was initiated in 1992 to 1993 and enrolled 184,185 men and women aged 40 to 90 (median = 62.0) yr residing in 21 states. Participants self-reported exposure information and cancer diagnoses by completing an initial baseline questionnaire in 1992 to 1993 and biennial follow-up	Blood (erythrocytes) Blood was measured by ICP-MS Age at Measurement: Average age of cases at the time of blood draw: 69.8 yr Average age of controls at time of blood draw: 69.9 yr Median[c]: 3.05 µg/dL Max[c]: 13.88 µg/dL Erythrocyte Pb Quartiles[c]: Entire cohort: Q1: 0 to <2.1008 µg/dL Q2: 2.1008 to <3.0268 µg/dL Q3: 3.0268 to <4.094 µg/dL Q4: >4.094 µg/dL	Other cancers: B-cell NHL and multiple myeloma Self-reported cancer diagnoses were verified through medical records or state cancer registry linkage. Verified incident B-cell NHL (B-NHL) and MM were identified from CPS-II NC participants who were cancer-free at time of blood collection (1998 and 2001). B-NHL cases were further categorized into the following subtypes using the 2008 WHO classification scheme: CLL/SLL, DLBCL, FL, MM, and other B-cell lymphoma. Age at Outcome: Average age at diagnosis: 75 yr	Conditional logistic regression models estimated relative risks (RR) adjusted for smoking status (current, former, never), average alcohol consumption (none, <1, 1, ≥2, missing drinks per day) and multivitamin use in the week prior to blood draw (yes, no, missing), based on a 10% change in the parameter estimates criterion	RR: Overall lymphoid malignancy Entire cohort: 1.088 (1.009, 1.173) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.131 (1.027, 1.246) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 1.013 (0.886, 1.158) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration RR for Overall lymphoid malignancy and erythrocyte Pb quartiles: Entire cohort: Q1: Reference Q2: 1.35 (0.94, 1.95) Q3: 1.06 (0.71, 1.56) Q4: 1.52 (1.02, 2.25)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	questionnaires beginning in 1997.	Males: Q1: 0 to <2.4736 µg/dL Q2: 2.4736 to <3.2876 µg/dL Q3: 3.2876 to <4.4026 µg/dL Q4: >4.4026 µg/dL Females: Q1: 0 to <1.8132 µg/dL Q2: 1.8132 to <2.5087 µg/dL Q3: 2.5087 to <3.6404 µg/dL Q4: >3.6404 µg/dL			Males: Q1: Reference Q2: 1.53 (0.93, 2.52) Q3: 1.41 (0.84, 2.38) Q4: 1.85 (1.10, 3.12) Females: Q1: Reference Q2: 0.98 (0.57, 1.67) Q3: 1.04 (0.61, 1.78) Q4: 0.92 (0.51, 1.65) RR: All B-cell NHL: Entire cohort: 1.093 (1.005, 1.19) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.151 (1.03, 1.286) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 1.013 (0.869, 1.18) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration DLBCL Entire cohort: 1.088 (0.943, 1.256) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.07 (0.897, 1.276) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 1.183 (0.895, 1.565) per 1-SD (1.56 µg/dL)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					increase of erythrocyte Pb concentration CLL/SLL: Entire cohort: 1.083 (0.916, 1.28) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.274 (1.016, 1.598) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 0.736 (0.524, 1.034) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration FL: Entire cohort: 1.397 (1.085, 1.798) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.301 (0.951, 1.78) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 2.158 (1.07, 4.353) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration Other B-cell lymphoma: Entire cohort:0.93 (0.717, 1.206) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.022 (0.674, 1.549) per 1-SD (1.81 µg/dL)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					increase of erythrocyte Pb concentration Females: 0.803 (0.502, 1.284) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration MM: Entire cohort: 1.114 (0.932, 1.332) per 1-SD (1.76 µg/dL) increase of erythrocyte Pb concentration Males: 1.111 (0.887, 1.392) per 1-SD (1.81 µg/dL) increase of erythrocyte Pb concentration Females: 1.148 (0.81, 1.627) per 1-SD (1.56 µg/dL) increase of erythrocyte Pb concentration

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th-90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.
[b]Units assumed to be µg/dL (written as µg/L in the paper).
[c]Blood Pb measurements were converted from µg/L to µg/dL.
[d]Effect estimates unable to be standardized.
†From 2013 Pb ISA.
ALAD = δ-aminolevulinic acid dehydratase; BLL = blood lead level; BMI = body mass index; CLL = Chronic Lymphatic Lymphoma; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; CPS-II = Cancer Prevention Study-II (CPS-II) LifeLink Cohort; CRP = C-reactive protein; DLBCL = diffuse large B-cell lymphoma; EPIC- = European Prospective Investigation into Cancer and Nutrition; FL = follicular lymphoma; GFAAS = graphite furnace atomic absorption spectrometry; GFR = glomerular filtration rate; HR = hazard ratio; ICD = International Classification of Diseases; ICP-MS = inductively coupled plasma mass spectrometry; KNHANES = Korea National Health and Nutrition Examination Survey; MM = multiple myeloma; NHANES = National Health and Nutrition Examination Survey; NHL = non-Hodgkin's lymphoma; NSDHS = Northern Sweden Health and Disease Study; OR = odds ratio; Pb = lead; PIR = poverty-income ratio; RR = relative risk; SD = standard deviation; UC = urothelial carcinoma; WHO = World Health Organization.

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