Retained lead fragments such as gunshot pellets or bullet fragments may become a source of lead absorption. Risk factors include prolonged contact of the fragments with synovial, pleural or cerebrospinal fluid, position of the projectile near a bone or joint or an associated bone fracture, particularly a tarsal bone fracture *(86, 94, 95)*. Absorption is also greater if the projectile is fragmented or there are numerous pellets, as both increase the surface area for absorption *(86, 94, 95)*. The time between injury and raised blood lead concentrations is highly variable, ranging from 3 months to over 50 years in published reports *(86)*.

Distribution

Once absorbed, lead is initially bound to erythrocytes in the blood and is distributed to soft tissues and bone. Blood and soft tissues represent the active pool and bone the storage pool *(34, 93)*. The highest soft tissue concentrations in adults are in the liver and the kidney cortex *(34)*. Lead is also distributed to teeth and hair.

The blood lead concentration reflects recent exposure to lead from exogenous sources and, when there has been previous exposure to lead, also includes lead redistributed from skeletal stores. Most blood lead is in erythrocytes and the remainder, typically < 1%, in plasma *(34)*. It is the latter fraction that interacts with cells in tissues throughout the body. The binding sites on erythrocytes are saturable; consequently, as more lead is absorbed, a larger proportion is available in plasma to distribute to tissues *(93)*.

In individuals who are exposed chronically, bone contains > 90% of the body burden of lead in adults and > 70% in children *(96)*. Lead forms stable complexes with phosphate and can replace calcium in hydroxyapatite, which forms the main crystalline matrix of bone. Lead can therefore deposit in bone during growth and remodelling *(93)*. A labile pool of lead in bone readily exchanges with lead in plasma. As lead is excreted from blood by normal processes or after chelation therapy, it is replenished from the store in bone *(93)*. Lead can also be released from bone during metabolic processes that increase bone turnover, such as occur during pregnancy, lactation, the menopause, hyperthyroidism, bone cancer and immobilization due to bone fractures *(34, 97–99)*. Lead accumulates in bone over life up to the age of 50–60 years, followed by a decrease due to age-related changes in diet, hormonal concentrations and metabolism *(98)*.

During pregnancy, the blood lead concentration increases due to increased resorption of maternal bone to meet the calcium needs of the developing fetal skeleton. There is a decrease in the second trimester due to haemodilution, and the blood lead concentration rises again in the third trimester and continues for a period post-partum, particularly in lactating women *(93, 100)*. There is no placental barrier to lead, and maternal and fetal blood lead concentrations are similar *(34)*.

Lead is present in breast milk from exogenous sources or remobilized from skeletal stores. There is a non-linear relation between the concentrations of lead in blood and breast milk, with milk lead concentrations increasing disproportionately at blood lead concentrations > 40 µg/dL *(101)*. No cases of lead poisoning resulting from exposure to lead in breast milk alone have been identified.

Metabolism

Inorganic lead is not metabolized but is reversibly bound to amino acids, proteins and sulfhydryl compounds *(93)*. Organic lead compounds are metabolized to inorganic lead. Alkyl compounds such as tetraethyl lead and tetramethyl lead undergo oxidative dealkylation to form the highly neurotoxic compounds triethyl and trimethyl lead, respectively *(93)*.

Elimination

Absorbed lead is eliminated primarily in urine and faeces. Small amounts are excreted in sweat, saliva, hair, nails and breast milk *(93)*.

Lead is eliminated from blood and soft tissues fairly rapidly, 50–60% being eliminated from blood in 30–40 days *(34, 102)*. Lead is eliminated slowly from bone stores, the half-life depending on age and the intensity of exposure *(34)*. As children's bones are still growing, the bone compartment is more labile than that of adults, and lead moves faster from bone to blood, the half-life for cortical bone being estimated to range from 0.23 years at birth to 3.7 years at 15 years of age and 23 years in adults *(34)*. In individuals with an elevated bone lead burden, cessation of lead exposure typically results in an initial fairly fast decrease, with a half-life of several months, representing a reduction of lead in soft tissues, followed by a longer phase with a half-life of years, representing release of lead from skeletal tissues *(34)*.

4.4 Toxicity of lead

4.4.1 Mechanisms of toxicity

The pathophysiology of lead is complex. It has been reviewed extensively *(15, 18, 34, 93, 103)* and is only summarized here.

Lead has no apparent physiological function. It has an affinity for sulfhydryl groups and other organic ligands in proteins and can mimic other biologically essential metals, such as zinc, iron and, in particular, calcium *(18)*. As a result of these properties, lead has several modes of toxic action that depend on dose and target organ. The modes of action include changes in ion status and cell signalling, changes in protein binding, oxidative stress, inflammation, endocrine disruption, cell death and genotoxicity *(34)*.

4.4.2 Toxic effects

The toxic effects of lead affect almost all body systems *(15, 20, 34)*. The effects of the greatest public health significance, i.e. adverse neurodevelopmental effects in children and cardiovascular disease in adults, are nonspecific and largely subclinical. In addition, there is considerable inter-individual variation in dose–response relations for lead toxicity, and the presenting signs and symptoms are highly variable in both adults and children *(93)*. The toxic effects may include GI, haematological, neurological and renal effects, as well as effects on the reproductive, immunological, endocrine and cardiovascular systems. In severe poisoning, life-threatening encephalopathy may occur *(20, 104)*.