

ORGANIC LEAD TOXICOLOGY

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Summary: Lead is one of the oldest known and most widely studied occupational and environmental poison. Despite intensive study, there is still debate about the toxic effects of lead, both from low-level exposure in the general population owing to environmental pollution and historic use of lead in paint and plumbing and from exposure in the occupational setting. Significant position have organic lead compounds used more than 60 years as antiknock additives in gasoline. Chemical and toxicological characteristics of main tetraalkyl leads used as gasoline additives are discussed in this article. The majority of industries historically associated with high lead exposure have made dramatic advances in their control of occupational exposure. However, cases of unacceptably high exposure and even of frank lead poisoning are still seen, predominantly in the demolition and tank cleaning industries. Nevertheless, in most industries blood lead levels have declined below levels at which signs or symptoms are seen and the current focus of attention is on the subclinical effects of exposure. The significance of some of these effects for the overt health of the workers is often the subject of debate. Inevitably there is pressure to reduce lead exposure in the general population and in working environments, because current studies show that no level of lead exposure appears to be a 'safe' and even the current 'low' levels of exposure, especially in children, are associated with neurodevelopmental deficits.

Key words: *Organic lead compounds; Tetraalkyl lead; Trialkyl lead; Toxicity*

Introduction

Lead is found at low concentrations in the earth's crust predominantly as lead sulfide (*galena*), but the widespread occurrence of lead in the environment is largely the result of anthropogenic activity. Humans have been mining and using lead for thousands of years, poisoning themselves in the process due to accumulation and exposure. These dangers have long been known, though the modern understanding of their full extent is relatively recent. Lead poisoning, also known as saturnism or plumbism, is a medical condition caused by increased levels of the metal lead in the blood. Lead may cause irreversible neurological damage as well as renal disease, cardiovascular effects, and reproductive toxicity (19).

Recent trends show a continuous decline in the number of lead toxicity cases among workers and nonoccupational cases in adults and children, nevertheless lead remains important toxic heavy metal in environment and danger to human health. Lead presents hazard namely for pregnant women and children (34). Research has shown that blood lead levels in pregnant women of 100 micrograms per liter can cause miscarriage, premature birth, low birth weight, and subsequent developmental delays in their children. The lead concentration may be associated with the risk of anem-

bryonic pregnancy (AP). AP is a common presentation of first-trimester abortion in China and affected women usually miscarry at 8-13 weeks (61). Current studies show that no level of lead exposure appears to be 'safe' and even the current 'low' levels of exposure in children are associated with neurodevelopmental deficits (3).

Inorganic lead compounds and organic lead compounds are known but primarily was not quite clear if also toxicological differences exist and whether or not are significant for risk assessment to human health. At present is evident that organic lead compounds are well absorbed through the skin and by essentially all routes including inhalation whereas inorganic lead absorption through the skin is poor and its oral adsorption is quite low. From these reasons the toxicity of inorganic lead is very different to that of organic lead. The toxicology of inorganic divalent lead compounds was reviewed by Patočka and Cerný (2003). Organic compounds of divalent lead form a variety of transition metal complexes (8) and from the view of their occurrence and toxicity are not so important as a tetravalent lead compounds. Therefore only the toxicology of organic tetravalent lead compounds is the aim of this article. This review is focused on the chemical and toxicological properties of most widely known tetravalent lead compounds containing direct metal-to-carbon bonds. These al-

kylllead compounds are main representatives of organic lead substances.

Alkyllead Compounds in Environment

Alkyllead compounds such as tetramethyl and tetraethyl lead have been used for nearly 60 years as antiknock additives in gasoline. The toxicity of these compounds varies with the nature and the number of organic groups covalently bonded to lead. Tetraalkyl leads converted in environment to trialkyl lead halogenides or hydroxylates, which are more toxic than their initial compounds. For example LD_{50} of tetramethyl lead to rats at p.o. administration is 109.3 mg.kg^{-1} , whereas LD_{50} of trimethyl lead chloride at the same conditions is 25.5 mg.kg^{-1} (11). This conversion is slow and trialkyl lead compounds are stable (24) and cumulate in environment and were found also in rain (14) in potentially toxic concentrations (13).

Organically bound lead is a minor but important contribution to total lead intake by humans and animals. Although organolead may make only a small contribution to the total lead intake in an organism, it has been demonstrated that trialkyl lead salts arising in tissues from the degradation of tetraalkyl leads are important in lead toxicity (1). Lower dose levels produced typical slight to severe maternal organolead toxicity, dependent upon dose. Embryo or fetal toxicity was observed to accompany the administration of the organolead compounds and was characterized by growth retardation and delayed ossification of bone. Marked fetal effects were observed only in maternal animals that exhibited severe organolead toxicity and were, therefore, severely debilitated (35).

General Toxicity of Alkyllead Compounds

Lead's primary toxicity is due to its affinity for sulfhydryl groups allowing alteration of protein and enzymatic function (18). Lead is similar to calcium in its physiochemical properties, accounting for its osseous deposition and its effect within mitochondria where it competitively antagonises the action of calcium. Lead also appears to affect nucleic acids, through mechanisms which are not clear, giving rise to concerns about chromosomal abnormalities (5). Lead causes anaemia, both by inhibiting haeme synthesis and accelerating erythrocyte destruction.

Renal toxicity may be reversible with lower exposure, as early pathological changes affect only the proximal tubules. Higher exposure leads to interstitial fibrosis and progressive nephropathy (21). It is thought that lead affects the renin-angiotensin system, causing hypertension (50). There is no active elimination of lead. Elimination occurs through skin desquamation, nail growth, biliary secretion and glomerular filtration.

Tetraalkyl leads are oxidatively dealkylated in the body. It has been shown that these compounds induce swelling in mitochondria. The swelling is due to the opening of a trans-

membrane pore in the mitochondria. These pores can be responsible for the inhibition of the ATP synthesis, and, consequently for cell death. The opening of the pore could be one of the reasons for the toxicity of the organic tetra-valent lead compounds (6). In humans and rats exposed to tetraalkyl lead, concentrations of lead are highest in the liver and kidneys followed by the brain and heart. The rates of metabolite production are not known in detail for either humans or experimental animals.

In humans, tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead. In rats and rabbits, dialkyl lead is the major metabolite found in urine. In humans, exhalation of unmetabolized tetraethyl lead and tetramethyl lead from the lung is a major route of excretion (59).

Mutagenicity, Teratogenicity, and Reproductive Toxicity

Lead's reproductive toxicity is well recognised in both males and females. It is associated with sperm abnormalities and miscarriage. Carcinogenesis has been demonstrated in laboratory animals (44). The International Agency for Research on Cancer has classified inorganic lead in group 2A, concluding that on current evidence inorganic lead is probably carcinogenic to humans (25).

The Center for Disease Control has established $0.48 \text{ } \mu\text{mol.L}^{-1}$ as the blood level of concern in children. Because lead crosses the placental barrier readily, fetal blood levels are directly proportional to maternal levels. Thus, the maternal blood level should be no greater than $0.63 \text{ } \mu\text{mol.L}^{-1}$. Pregnancy and breastfeeding are both indications for workplace exclusion, although lead excretion in breast milk is a less important means of transmission. It is known that lead can exert toxic effects at levels well below $2.41 \text{ } \mu\text{mol.L}^{-1}$, which is the level at which a male worker must be excluded. For example, sperm morphology abnormalities and abnormal sperm counts have been demonstrated to occur at levels of $1.93 \text{ } \mu\text{mol.L}^{-1}$. The reproductive effects of paternal levels below $1.9 \text{ } \mu\text{mol.L}^{-1}$ are unknown (55). This remains a significant issue and further epidemiological research is needed.

Neurotoxicity

The tetra-alkyl forms of lead are metabolised to the more toxic tri-alkyl forms (10, 11). Tetra- and tri-alkyl lead compounds are relatively lipid-soluble and may accumulate in lipid tissues, including the CNS. Toxic manifestations of lead is being considered caused primarily due to the imbalance between pro-oxidant and antioxidant homeostasis and also due to a high affinity of this metal for thiol groups on functional proteins. It also interfere with a number of other body functions and is known to affect CNS. The brain in development is extremely sensitive to lead (33).

Relatively little work has been done on the structural effects of organic lead in the CNS, although this form of lead

may be a significant fraction of total brain lead. Ferris and Cragg (1984) tested some histological parameters of neuronal development in rats for sensitivity to normal growth between 18 and 28 days of life and the effect of weekly injections of tetramethyl lead, administered from 1 week after conception until post-natal day 6. Several of the histological parameters were found to be sensitive to normal growth, but none showed any effect of organic lead treatment. This was despite a small but significant decrease in brain weight, and a significant increase in body/brain weight ratio, with tetramethyl lead treatment. The body/brain weight ratio was the parameter most sensitive to tetramethyl lead treatment.

In recent years, epidemiologic studies have focused primarily on the neurotoxic effects of lead on children, particularly in terms of impaired intellectual ability and behavioral problems (2, 53). However, there is still insufficient information on the mechanisms of action that account for such toxicity (29).

Clinical Presentation

A difficulty with the presentation of lead toxicity is the nonspecific nature of symptoms.

These symptoms range from fatigue, concentration difficulties, sleep disturbances, headache, weight loss, nausea and myalgia with mild to moderate toxicity to the classic features of severe toxicity of abdominal cramps, renal disease, encephalopathy, convulsions and peripheral neuropathy (52). Motor neuropathy leads to the classic lead palsy, affecting the long extensor muscles of the limbs. Lead induced Fanconi syndrome is more likely to occur in children. Unique features include a blue line on the dental margins of the gums and 'saturnine' gout (23).

Lead's adverse effect on neurological development in children is long established. There is recent evidence that, in addition to its other neurological effects, lead causes cognitive abnormalities in adults which are demonstrable on neuropsychological testing (37). It is worth noting that the onset of symptoms or signs following lead exposure may be highly variable depending on the intensity of the exposure as well as host factors. For example, a high intensity dose may increase blood level concentration rapidly with the early onset of accompanying symptoms. Levels of 4-5 $\mu\text{mol.L}^{-1}$ may occur over the course of 1-3 days. With subacute and chronic exposure symptoms may take time to develop. There is also a significant degree of individual variability in susceptibility to overt lead intoxication. The reasons for this are uncertain, but are thought to be associated with specific lead binding proteins made in response to lead exposure (23). It should be noted that the toxicity of inorganic lead is very different to that of organic lead, which causes an organic psychosis (36, 38).

Important Tetravalent Lead Compounds

The most important organic tetravalent lead compounds are different tetraalkyl leads. There are used as antiknock

agents in gasoline and in dilute grade are used for blending of gasolines used in laboratory engine testing (28). Their use decline rapidly in all advanced countries. In 1977, world production was ca 700,000 tons, in 1980 500,000 tons, and at present less than 100,000 tons. Nowadays only lead-free gasoline may be used as an automobile fuel in the US and EU (47). Lead was removed from automotive gasoline, but aircraft fuel still contains this toxic substance. Currently, aviation gasoline for piston-engine aircraft contains four times more lead than was used in leaded automotive gasoline. Lead so come in on the atmosphere and also contaminates the engine oil. Waste oil contaminated with lead cannot be burned in a waste oil furnace, due to the high lead content.

Tetramethyl Lead (CASRN: 75-74-1)

Tetramethyl lead (molecular weight 267.3) is colorless, liquid of fruity odor, in commerce it is usually dyed red, orange, or blue, b.p. 110 °C, m.p. -30.2 °C. Its density 1.995 g.cm^{-3} at 20 °C (32), heat of combustion -2940 cal.g^{-1} , heat of vaporization 30.8 cal.g^{-1} (54), and partition coefficient $K_{\text{ow}} = 2.97$ (22). Compound is slightly soluble in benzene, petroleum ether, alcohol (31), ethyl ether, miscible in fats and oils (26) and slightly in water, 15 mg.L^{-1} (57). Index of refraction 1.512 at 20 °C (58), vapor density 6.5 (Air = 1) (56), vapor pressure 26 mm Hg at 20 °C (57).

Tetramethyl lead represents a very dangerous fire hazard when exposed to heat, flame, sparks or oxidizers. Vapors may form explosive mixtures with air and may travel to source of ignition and flash back (30). Its flash point is 38 °C (17). Because vapors are heavier than air, will collect in low areas.

Tetramethyl lead may be fatal if inhaled, ingested or absorbed through skin. Inhalation or contact with this chemicals will irritate or burn skin and eyes (46). Vapors may cause dizziness or suffocation. Immediately dangerous to life is in concentration 40 mg.m^3 (42), permissible exposure limit is 0.075 mg.m^3 , threshold limit values 0.15 mg.m^3 (7).

Tetraethyl Lead (CASRN 78-00-2)

Tetraethyl lead (molecular weight 323.44) is colorless, oily liquid of musty odor, in commerce it is usually dyed red, orange, or blue, b.p. 227.7 °C, m.p. -133 °C (12), density 1.653 g.cm^{-3} at 20 °C (32), partition coefficient $K_{\text{ow}} = 4.15$ (57). Compound is soluble in all organic solvents, for example in benzene, petroleum ether, gasoline, slightly soluble in alcohol (43), and minutely in water, 0.29 mg.L^{-1} (15). Index of refraction 1.5198 at 20 °C (32), vapor density 8.6 (Air = 1) (56), vapor pressure 0.26 mm Hg at 20 °C (57).

Tetraethyl lead is flammable when exposed to heat, flame, or oxidizers (30). Its flash point is 93 °C (17). Auto-ignition temperature is more than or equal to 110 °C (49).

Tetraethyl lead is skin, eye and respiratory irritant (48) and may be fatal if inhaled, ingested or absorbed through skin. In humans, a tetraethyl lead concentration of 100 mg.m^3 , for 1 hour may produce decisive intoxication. The

signs and symptoms included those of nervous irritability, insomnia, nightmares, anorexia, nausea and vomiting, diarrhea, headache, muscular weakness, and emotional instability. Subjective CNS symptoms such as irritability, restlessness, and anxiety are next evident. At this time there is usually hypothermia, bradycardia, and hypotension. With continued exposure, or in the case of intense short-term exposure, CNS manifestations progress to delusions, ataxia, exaggerated muscular movements, and finally, a maniacal state. In the case of severe exposure, death may occur within a few hours or may be delayed for several weeks (9). Minimum fatal dose of tetraethyl lead is 15 ml, i.e. 350 mg/kg body weight (60).

Toxicological studies suggest that the encephalopathy and death after gasoline sniffing is caused by the tetraethyllead additive in the petrol (27). Chronic, heavy abuse of leaded gasoline results in an encephalopathy, cerebellar and corticospinal symptoms and signs, dementia, mental status alterations, and persistent organic psychosis. Much of this is due to the hydrocarbons of gasoline while the tetraethyl lead answer for the altered mental status and is responsible for the persistent psychosis (51).

Diethyldimethyl Lead (CSNR 1762-27-2)

Diethyldimethyl lead (molecular weight 295.4) is colorless liquid, b.p. 51 °C at 13 mm Hg, (32), density 1.79 g.cm⁻³ at 20 °C (32), partition coefficient $K_{ow} = 4.04$ (57). Compound used as antiknock agent in aviation gasoline, is soluble in all organic solvents and slightly in water, 4.6 mg.L⁻¹. Vapor pressure 2.2 mm Hg at 25 °C (57). Diethyldimethyl lead is flammable when exposed to heat, flame, or oxidizers (30).

Diethyldimethyl lead is skin, eye and respiratory irritant and may be fatal if inhaled, ingested or absorbed through skin. Illness resulting from acute episodes may persist for days or weeks. Cause of death is direct damage to the brain (encephalopathy) involving capillary dysfunction, cerebral oedema, and interference with cerebral metabolism. Muscle damage is confirmed by elevated serum creatine phosphokinase (CPK), transient elevation of transaminases and proteinuria. Several cases due to accidental diethyldimethyl lead poisoning are described, mostly associated with aviatric gasoline sniffing or with cleaning a tank which had held leaded aviation gasoline. Exposure was followed shortly by illness in which mental symptoms were prominent. Blood lead levels were raised to 645 to 925 µg.L⁻¹. Lead was found predominantly in the lipid blood fraction. Erythrocyte protoporphyrin was slightly raised in largely cases, on the contrary blood delta aminolevulinic acid dehydratase activity was markedly reduced.

Some victims died 5-19 days after poisoning. Histological examination revealed degenerative alterations of the heart muscle, swelling and lipofuscin deposits in the muscle fiber, and myocardial fragmentation. Various pathological changes were also observed in the lung, spleen, kidney, adrenal gland, and nervous tissues (4).

Methyltriethyl Lead (CASRN 1762-28-3)

Methyltriethyl lead (molecular weight 309.4) is colorless liquid, b.p. 70 °C at 15 mm Hg (32), density 1.71 g.cm⁻³ at 20 °C (32), partition coefficient $K_{ow} = 4.39$ (57). Compound is used as gasoline additive. Compound is soluble in all organic solvents and slightly in water, 1.9 mg.L⁻¹. Vapor pressure 1.3 mm Hg at 25 °C.

Methyltriethyl lead is skin, eye and respiratory irritant and may be fatal if inhaled, ingested or absorbed through skin, analogous to diethyldimethyl lead. Also clinical presentation of illness resulting from acute episodes is very similar to diethyldimethyl lead poisoning.

Ethyltrimethyl Lead (1762-26-1)

Ethyltrimethyl lead (molecular weight 281.4) is colorless liquid, b.p. 27 °C at 10.5 mm Hg (32), density 1.88 g.cm⁻³ at 20 °C (32), partition coefficient $K_{ow} = 3.88$ (57). Compound is used as gasoline additive. Compound is soluble in all organic solvents and slightly in water, 7.65 mg.L⁻¹. Vapor pressure 7.3 mm Hg at 25 °C (57). Toxicological properties of ethyltrimethyl lead are similar to methyltriethyl lead. May be inhaled, ingested or absorbed through skin.

Conclusions

Organic compounds of lead have toxic properties which require precautions against both their percutaneous and respiratory absorption. Poisoning due to organic compounds is a consequence of industrial exposure. Indirect exposure arises from environmental contamination. Humans can be exposed to lead from breathing air, drinking water, and eating foods that contain lead. Poisoning by organic lead compounds presents mainly acute effects on the central nervous system. The central nervous system is particularly sensitive to organic compounds of lead. Lead exposure is a serious concern for children's health. Lead impairs children's brain development, and many scientists believe no dose is safe (39). Significant amount of lead of organic origin was found in human brain city inhabitants. The highest concentrations were present in individuals residing in the lower floors of buildings in the city (41). Though using of lead antiknock additives in gasoline is prohibited several years, trace amounts of these compounds are always present in environment (40). Of course, the use of lead as an antiknock compound is not yet prohibited world wide. In some parts of South America, Asia, Eastern Europe and the Middle East, leaded gasoline is still in use. A number of prospective studies have examined lead levels in umbilical cord blood at birth as predictors of infant mental development (20). More in-depth studies are also needed on the effects of lead exposure on bone, the central nervous system, the cardiovascular system, the kidneys, the liver, the male and female reproductive systems, and the endocrine system. The potential teratogenicity and carcinogenicity of lead, as well as its effect on pregnancy outcomes and neonatal growth and development, also require further study.

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