GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This eighty-seventh volume of *IARC Monographs* contains evaluations of inorganic and organic lead compounds. Lead salts and organic lead compounds were considered by the first *IARC Monographs* Working Groups (Volumes 1 and 2; IARC, 1972, 1973) and they have been reviewed in Volume 23 (IARC, 1980) and updated in Supplement 7 (IARC, 1987). Since 1987, new epidemiological and experimental studies have become available. An *IARC Monographs* Advisory Group recommended lead compounds as a high and urgent priority for re-evaluation (IARC, 2003).

Lead is found at low concentrations in the earth's crust, predominantly as lead sulfide, but the widespread occurrence of lead in the environment is largely the result of anthropogenic activity. As a result, human exposure to lead is universal, and all humans carry a body burden of lead. Lead has long been of concern for its adverse health effects other than cancer, in particular its neuro-developmental effects on the fetus, infants, and children. These health effects are discussed in this Volume in some detail. Nonetheless, the main focus of this Monograph is on the epidemiological studies and experimental investigations attempting to determine whether exposure to lead is associated with the development of some forms of cancer. In this database, however, there are several limitations that complicate the analysis and evaluation of the carcinogenic potential of lead compounds. Some of these limitations are discussed below.

In occupational studies on lead-exposed workers, exposure assessment is complicated by the historical fact that workers with high exposure often were removed from the job, either temporarily or permanently. This may introduce exposure misclassification, making it difficult to discern dose–response relationships using conventional measures such as cumulative exposure or duration of exposure to lead. It should be noted also that the presence of disease can influence the toxicokinetics of lead and, consequently, the reported concentration of lead in blood. Such effects may well affect the findings of clinical studies based on lead measurements made after diagnosis of disease.

Although inhalation is an important route of human exposure to lead, the Working Group noted that there was only one long-term inhalation study in experimental animals available for evaluation, and data on inhalation toxicokinetics in humans are very limited. To make inferences about human exposure to lead by inhalation, the Working Group considered information on the toxicokinetics of lead by the inhalation and ingestion routes in experimental animals. Likewise, because of the limited data in humans on mechanistic

aspects of lead carcinogenicity, the Working Group considered mechanistic data in experimental systems, in order to make inferences regarding mechanisms of lead carcinogenicity in humans. However, definitive conclusions regarding the mechanism of carcinogenesis of lead in humans could not be drawn.

In view of the magnitude of human exposure to organic lead, in particular tetraethyl lead, the Working Group found it remarkable that only a single, inadequately conducted study in experimental animals was available for evaluation, and that there are no studies for other organic lead compounds. In addition, in the epidemiological studies of tetraethyl lead it is not possible to separate with certainty the populations exposed to organic, but not inorganic, lead. On the other hand, various studies indicate that organic lead compounds are metabolized *in vivo*, at least in part, to ionic lead. To the extent to which ionic lead, generated from organic lead compounds, is present in the body, it will be expected to exert the toxicities associated with inorganic lead.

Despite these limitations and the resulting complexities in the analysis, several aspects of the database stand out, as discussed below.

- Among the many neurological effects of lead, there appears to be an unusual propensity for lead to induce brain gliomas in rats. There are also some suggestions from the epidemiological studies that this type of brain tumour may be associated with lead exposure in humans.
- Both water-soluble and water-insoluble lead compounds are capable of causing tumours in animals at sites distant from their administration. This indicates that biologically effective amounts of lead can be mobilized even from insoluble lead compounds. In humans, the observation that lead poisoning can occur from indwelling metallic lead shot indicates that toxicologically relevant amounts of lead can be mobilized *in vivo* from metallic lead.
- Unlike several other metals (for example, beryllium, cadmium, chromium, and nickel), lead compounds have repeatedly been shown to be carcinogenic in experimental animals by the oral route.
- The evidence indicating that various lead compounds cause renal tumours in male and female mice and rats cannot be accounted for by a male-rat-specific mechanism of renal carcinogenesis.
- The extensive data on lead in experimental systems support the concept that one expression of lead toxicity is genetic toxicity. Important mechanisms of lead genetic toxicity include increases in reactive oxygen species and interaction with proteins, including those involved in DNA repair.

Studies in experimental animals support the concept that the lead component of lead compounds is critical to the carcinogenic process. For compounds such as lead arsenate and lead chromate, whose non-lead moieties have been determined to be *carcinogenic to humans* (IARC 1990, 2004), a full characterization of the cancer risk must reflect the carcinogenic activity of both the lead and the non-lead moieties.

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