IARC Evaluation of Lead as a Human Carcinogen 2006 –Organic Lead (TEL/TML) & Skin / Dermal Exposure extracts

[Extracts collated by Elizabeth O'Brien, Editor of *LEAD Action News,* from: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Inorganic and organic lead compounds, by International Agency for Research on Cancer (IARC) Working Group of 20 experts from 11 countries (2006), at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono87.pdf

Note: all text in square brackets was added by the Editor of *LEAD Action News.*]

EXTRACTS

[page 209]

2.1.7 Exposure to organic lead

Organo-lead compounds such as tetraethyl and tetramethyl lead have been used historically as components in gasoline. Gasoline engine exhaust has been previously evaluated as possibly carcinogenic to humans (Group 2B) (IARC, 1989). Studies on gasoline are not further reviewed here as there are mixed exposures and the effects of lead cannot be characterized separately. A cohort study and a nested case–control study of workers employed in the manufacture of tetraethyl lead are described below. Sweeney et al. (1986) investigated the mortality of 2510 men employed at a chemical plant in east Texas, USA. Tetraethyl lead was produced during the study period from 1952 to 1977, together with ethylene dichloride and chloroethane. Vinyl chloride monomer was also manufactured from 1960 to 1975. Other chemicals (ethylene dibromide, ethylene, inorganic lead, dyes) were used in the manufacturing processes of tetraethyl lead. Male employees who had worked at least 1 day at the factory between 1952 and 1977 were eligible from company records and workers'union files. More than 50% of the total workforce had been employed at the plant for at least 5 years. Vital status was ascertained for 99.3% of the cohort members. Expected numbers were calculated from the national rates by ethnicity, age groups and 5-year calendar periods. Mortality from all causes of death was lower than expected (SMR [Standardized Mortality Ratios], 74; 156 observed; 95% CI [Confidence Interval], 64–84). The SMR for malignant neoplasms was 103 (38 deaths observed; 95% CI, 77–135). The SMR for lung cancer was 112 (14 observed; 95% CI, 68–175). There was a slight excess of laryngeal cancers (SMR, 364; two deaths observed; 95% CI, 65–1145) and of brain and central nervous system tumours (SMR, 213; four deaths observed; 95% CI, 73–487). Among white men [page 210] employed between 1952 and 1960, when the manufacture of tetraethyl lead was the principal process, the SMR for lung cancer was 122, based on 13 deaths (95% CI, 73–194) and the SMR for brain tumours was 186 (three deaths observed; 95% CI, 51–482).

When deaths among male workers employed before 1960 were restricted to those deaths occurring 15 or more years after first employment, the SMR for respiratory cancers was 154 (14 observed; 95% CI, 84–258); for length of employment < 10 years, the SMR was 199 (six observed; 95% CI, 73–432); and for

employment > 10 years, the SMR was 132 (eight observed; 95% CI, 57–260). [There were no further details on mortality by employment at departments using tetraethyl lead or with other chemical exposures.] Fayerweather et al. (1997) reported a case–control study among employees who worked at a tetraethyl lead manufacturing company in New Jersey, USA. The plant began producing tetraethyl lead in 1923 and production was closed in 1991; thereafter, the tetraethyl lead plant was involved in lead remediation. The study subjects, 735 male cases of cancer other than non-melanoma of the skin, and 1423 controls matched by year of birth, sex, and most recent payroll class, were drawn from the cancer and mortality registries of the company and from employment rosters. Neoplasms that occurred during 1956–87 were included. The cancer registry mainly covered active workers; workers who left the company were missing from the registry (but those who left the active workforce and were put on the company's disability rolls were included in the registry). The mortality registry covered all active and pensioned employees since 1957. Information on ever having worked in the tetraethyl lead area, years of employment in tetraethyl lead manufacture, rank (degree) of exposure to tetraethyl lead and cumulative exposure to tetraethyl lead were estimated using employment information from the personnel records, industrial hygiene data and records of biological measurements available at the factory. Tetraethyl lead exposure ranks were based on job titles. Employees manufacturing tetraethyl lead could have been exposed both to organic and inorganic lead compounds, but it was not possible to distinguish between these in the exposure assessment because of insufficient data. Exposure (ever/never) to other known or suspected carcinogens (such as aromatic amines, nitriles, benzene, asbestos, radioactive materials) was also assessed. Smoking histories were available from reports of periodical pulmonary function tests for 38% of the cases and 51% of the controls. Cases and controls for whom there was no available information on employment from personnel records were excluded.

Odds ratios for cancer of the digestive tract were elevated for the group who had ever worked in the tetraethyl lead manufacturing area compared with the group who had never worked in that area (odds ratio, 1.3; 45 cases observed; 90% CI, 0.9–1.9); the risk was increased for high (odds ratio, 1.3; 90% CI, 0.7–2.7) and very high (odds ratio, 2.2; 90% CI, 1.2–4.0) estimated cumulative exposure.

Further latency analyses, adjustments for smoking, and exposure to aromatic amines, radioactive materials and asbestos did not markedly change the results. Risk for rectal cancer was increased (odds ratio, 3.7; nine cases observed; 90% CI, 1.3–10.2), and was associated with high cumulative exposure to tetraethyl lead. The odds ratio for colon cancer was 1.3 (16 observed; 90% CI, 0.7–2.5) and was moderately elevated for the highest cumulative exposure category. Not all workers exposed to [page 211] organic lead were followed-up, e.g. workers who had terminated their employment without pension eligibility. Losses in tracing and follow-up were not described in this study. Quantitative information on the exposure categories was not available. Detailed results on other primary cancer sites were not reported.]

---

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

[page 254]

Dermal exposure

Little information is available regarding absorption of lead in humans after dermal exposure. Moore et al. (1980a) conducted a study in which commercially-available lead acetate solution (6 mmol/L lead acetate) or skin cream (9 mmol/kg lead), labelled with 203Pb acetate, was applied to the forehead skin of eight male volunteers for 12 h and then washed off. Blood and urine samples were collected. The percentage of absorption was estimated by measuring the 203Pb activity in blood samples, by counting over the subject's calf region using a whole-body monitor, and also by counting 24-h and 48-h urine samples. Absorption through intact skin was 0.18 ± 0.15% of the dose applied; that through scratched skin was 0.26 ± 0.46%. Lead exposure from the use of hair-colouring agents containing lead acetate was reported to be insignificant (Moore et al., 1980a; Cohen & Roe, 1991). However, this assumes that only adults will be in contact with the colouring agents and ignores human behaviour in the home environment (Mielke et al., 1997b). Measurements of lead on hands and surface wipes (including combs, hair dryer, faucet) from subjects using hair-colouring agents showed between 150 and 700 µg lead per hand and more than 100 µg/9.3 dm2 [~10 µg/dm2] on the surfaces. At such concentrations, there is a potential for hand-to-mouth and hand-to-surface transfer of lead not only to adults but also to children (Mielke et al., 1997b). The dermal absorption studies of Florence and colleagues (1988), although limited in subject numbers (nine workers), remain the most comprehensive to date. Following observations that workers in a lead battery factory exhibited high concentrations of lead in sweat, Florence et al. (1988) and Lilley et al. (1988) showed that finely-powdered lead metal and lead oxide (20 mg; particle size < 0.45 µm) or 60 µL of 0.5 M lead nitrate solution (6 mg lead) placed on the skin of one arm was rapidly absorbed. The absorbed lead [page 255] appeared in sweat (induced by pilocarpine iontophoresis) on the other arm and in saliva, but was not detectable in blood or urine. The authors found that the rate of lead absorption through the skin increased with increased sweating and, as observed by Moore et al. (1980a), suggested that the mechanism was one of rapid diffusion through filled sweat ducts followed by a slower diffusion through the stratum corneum (Lilley et al., 1988). The authors (as also observed by Moore et al., 1980a) noted that the absorbed lead must be transported in the plasma and concentrated quickly into the extracellular pool (sweat and saliva), that its mean residence time in the plasma is very short and that little lead enters the erythrocytes (Lilley et al., 1988). {No quantification of the amount of lead absorbed was undertaken and there were inconsistencies between the concentrations of lead in sweat from the two arms on certain days.} In later experiments using compounds made with 204Pb tracer and employing the sensitive thermal ionization–mass spectrometry (TIMS) and ICP–MS methods, lead acetate or lead nitrate was applied to the skin of four volunteers and perspiration induced by either pilocarpine iontophoresis or thermally in a sauna (Stauber et al., 1994). The lead compounds were rapidly absorbed through the skin and detected in sweat, blood and urine within 6 h of application. In one subject, 4.4 mg lead (as lead nitrate) was applied to the skin under a patch and perspiration induced by iontophoresis. Of the applied dose, 1.3 mg lead was not recovered from skin washings, indicating that 29% of the applied dose was absorbed into or through the skin. The authors suggested that some of the absorbed lead was still present in the epidermis and had not entered the circulatory system as the other experiments indicated that an equivalent of only 0.2% of the 204Pb applied to the skin was detected in blood. However, no measurable

increase of total lead in blood or urine was found in this study. {The Working Group agreed with the authors in their concern about this lack of increase in total lead in blood or urine, since blood lead is the accepted biomarker of exposure.} (ii) Distribution Lead enters and leaves most soft tissues reasonably freely. The clearance from the blood into both soft tissues and bone dominates lead kinetics during the first few weeks after an exposure, with an apparent half-life of several weeks (Table 83). Once an approximate equilibrium is reached between soft tissues and blood, the concentration of lead in blood is determined almost entirely by the balance among absorption, elimination, and transfer to and from bone. In the absence of continuing exposure, the whole-body half-life represents the loss of lead from bone. Lead enters and leaves bone by physiologically-distinguishable mechanisms (reviewed and summarized in O'Flaherty, 1991a, 1992, 1993), which include rapid exchange between blood plasma and bone at all bone surfaces, incorporation of lead into forming bone and its loss during bone resorption, and very slow diffusion of lead throughout undisturbed bone. Slow diffusion accounts for the gradual build-up of large quantities of bone-seeking elements such as lead in quiescent, largely cortical bone (Marshall & Onkelinx, 1968).

[page 258]

Blood

…Whole-body half-lives of lead in blood estimated for workers occupationally exposed to lead are commonly much greater than those shown in Table 83 for non-occupationally exposed individuals, and reflect a much greater loading of the skeleton with lead (O'Flaherty et al., 1982; Hryhorczuk et al., 1985; Schütz et al., 1987; Nilsson et al., 1991; Fleming et al., 1997, 1999). They are comparable to half-lives of lead measured in cortical bone (Christoffersson et al., 1986; Erkkilä et al., 1992).

[page 281]

4.1.2 *Organic lead compounds*

The toxicity of organic lead compounds is generally high, but varies widely between animal species and according to the chemical structure of the compound. Most of the information available concerns tetraethyl lead, but the toxicity of tetramethyl lead and some of its metabolites is also well described. Organic lead compounds are toxicokinetically distinct from inorganic lead compounds in terms of absorption and distribution and, owing to their greater lipophilicity, they are rapidly partitioned into soft tissues.

[page 282]

(*a*) *Humans*

(i) *Absorption*

Inhalation exposure

Inhaled tetraethyl and tetramethyl lead vapours behave as gases in the respiratory tract and, as a result, their pattern and extent of deposition and absorption differ from that of inhaled inorganic lead particles (US EPA, 1994; ATSDR, 1999). These differences result in a higher fractional absorption: approximately 60–80% of the deposited tetraethyl and tetramethyl lead was absorbed by the lungs (Heard *et al*., 1979).

Dermal exposure

Tetraethyl lead is a lipophilic substance that can penetrate intact skin in lethal quantities. The amount absorbed is proportional to the surface area exposed and the concentration. Accidents involving transdermal absorption of tetraethyl lead and tetramethyl lead in humans have been described (Hayakawa, 1972; Gething, 1975). Due to its higher lipophilicity, tetraethyl lead is more readily absorbed than tetramethyl lead.

(ii) *Distribution*

Inhalation of tetraethyl lead results in much higher concentrations of lead in the brain than does inhalation exposure to inorganic lead. Distribution of organic lead in humans has been observed to be highly variable and measurements are complicated by metabolism of the alkyl lead to inorganic lead. For example, in a man who ingested a chemical mixture containing 59% tetraethyl lead (38% lead w/w), the highest concentrations of triethyl lead and inorganic lead were found in the liver and kidneys followed by the brain, pancreas and heart (Bolanowska *et al*., 1967). In another report in which a man and a woman accidentally inhaled a solvent containing 31% tetraethyl lead (17.6% lead w/w), concentrations of triethyl lead and inorganic lead were highest in the liver and lower in the kidney, brain, pancreas, muscle and heart (Bolanowska *et al*., 1967), although the liver/kidney ratio for triethyl lead was 5:1 in the woman compared with that of 1.3:1 in the man. Trialkyl lead metabolites have also been detected in brain tissue of subjects not occupationally exposed to air pollution (Nielsen *et al.*, 1978).

Organic lead compounds are ultimately metabolized to inorganic lead and the latter is stored in the bones (Schwartz *et al*., 1999, 2000a).

(iii) *Metabolism*

Alkyl lead compounds are actively metabolized in the liver through oxidative dealkylation catalyzed by cytochrome P-450. Relatively few human studies that address the metabolism of alkyl lead compounds were found in the available literature (Bolanowska *et al.*, 1967; Nielsen *et al.*, 1978; ATSDR, 1999).

(iv) *Excretion*

Tetraethyl lead is excreted in the urine as diethyllead and inorganic lead (Turlakiewicz & Chmielnicka, 1985; Vural & Duydu, 1995). Following inhalation exposure, exhalation of tetraalkyl lead compounds is a major pathway of elimination in humans. Heard *et al.* (1979) showed that 48 h after inhalation exposure, 40% and 20% of inhaled tetramethyl and tetraethyl lead doses, respectively, that were initially deposited in the lung, were exhaled, and there was little urinary excretion. [Presumably, the lead that was not exhaled or excreted via the urine or sweat, was stored in the bones, teeth and soft tissues.]