C-01516

FOR DU PONT USE ONLY

HASKELL LABORATORY

LEAD (ORGANIC AND INORGANIC)

Embryotoxicity

For more than fifty years it has been recognized that chronic exposure to lead can adversely affect the human reproductive system. However, most of these effects resulted from the heavy industrial exposures which were common in the early part of this time (7, 16. But see 15 for disagreement).

Effects of Organolead Compounds on Rat Embryonic and Fetal Development. McCLAIN, R. M., and BECKER, B. A. (1972). *Toxicol. Appl. Pharmacol.* 21, 265–274. Tetraethyl lead (TEL) and tetramethyl lead (TML) and trimethyl lead chloride (TriML), were found to be essentially nonteratogenic in Sprague-Dawley rats. Oral doses of TEL (7.5, 15, or 30 mg/kg), TML (40, 80, 112, or 160 mg/kg) and TriML (15, 30, or 38 mg/kg) were administered as 3 divided doses during early organogenesis (days 9, 10, and 11) or late organogenesis (days 12, 13, and 14), the day of positive sperm being day 1. In addition, TriML was administered iv at doses of 20, 28, 33, or 40 mg/kg on individual gestation days 8 through 15 inclusive. The highest dose of each compound in each experiment was lethal to the maternal animal. 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.

Infusion studies with TriML revealed that the rate of placental transfer was minimal when blood concentrations were below an apparent saturation of binding sites on maternal erythrocytes and was greatly increased at maternal blood concentrations above this saturation point. When the maternal animal was by-passed by direct intra-amniotic injections of TriML (10–100 μg/fetus) dose-related fetal lethality was observed.

Abstract—Groups of pregnant albino mice and rats were treated by gavage with doses up to 714 mg lead acetate/kg or 10 mg tetraethyllead (TEL)/kg. The compounds were administered daily during the period of rapid organogenesis (days 5–15 of pregnancy for mice and days 6–16 for rats). Maternal toxicity was observed and foetal resorption and general retardation of development were encountered at the higher dosage levels. Neither lead compound caused any congenital malformations. Foetuses derived from lead-exposed females were examined grossly and for internal structural and skeletal development but no teratogenic response was evident, even at dose levels at which frank signs of maternal toxicity were observed. It is concluded that lead, as the acetate or as tetraethyllead, is not teratogenic to the mouse or rat. FCT 13: 629 (1975)

A National Academy of Sciences review expresses the view that industrial lead exposure is also not a genetic hazard currently - because of improved hygienic controls*. However, there is disagreement on this point; Haley urges exclusion of pregnant women from lead-using industries, citing recent reports (Bourret and Mehl) of increased spontaneous abortion rates among lead-exposed typographers. Ragucci agrees, noting that absorption of as little as 1-2 mg. lead/day can cause abortion, premature birth, and intrauterine death.

Part of the uncertainty concerning industrial lead effects on child-bearing females arises from a lack of epidemiological data (1, 8, 15, 16). Women have been excluded from most lead industries since about 1920**. Only one study of the type needed has been reported since that time: a survey of lead arsenate-exposed orchardists and consumers of sprayed fruit (11). It concludes that "a clinical state approaching that of frank lead poisoning is necessary before the fertility of men or women is affected".

A second cause for confusion is the difficulty in diagnosing low-level lead poisoning. With the exception of motor palsy, the symptoms of plumbism are nonspecific (8), and it is possible that fetal abnormalities due to chronic poisoning in the parent have not been identified as such.

The most serious reproductive hazard from lead in this country is caused by pregnant women drinking lead-contaminated whiskey. Auto radiators soldered with lead are used as moonshine stills, resulting each year in cases of sterility, abortion, and fetal deformity. In 1966, 17,000 of these stills were seized in the Southeastern United States (13).

* "The effect of lead on human reproduction is primarily of historical importance". (1)

**Reports of high fetal morbidity among female lead workers led to this exclusion.

References Attached

Reference in C-1516

References

1. Airborne Lead in Perspective, Committee on Biological Effects of Atmospheric Pollutants, National Academy of Sciences. Washington, D. C. (1972), pages 117, 153 and 154 enclosed.

2. Anon. Food Cosmet. Toxicol. 7:255-60 (1969). "Lead astray?" Enclosed.

3. Baker, J. B. E. Pharmacol. Rev. 12:37-90 (1960). Summary* attached.

4. Butt, E. M. and D. G. Simonsen. Am. J. Clin. Path. 20:716-23 (1950). Summary enclosed.

5. Fahim, M. S. et al. Science News 101:264 (April 1972). Enclosed.

6. Greenfield, I. N. Y. State J. Med. 57:4032-4 (1957). Summary enclosed.

7. Haley, T. J. Clin. Toxicol. 4:11-29 (1971).

8. Hardy, H. L. Clin. Pharmacol. and Therapeut. 7:713-22 (1966). Summary enclosed.

9. Koppich, F. et al. Acad. Repub. Pop. Rom. Fil. Cluj, Studii Cerc. Stiint 3(1-2):339-54 (1954). Summary enclosed.

10. Lambin, P. Cahiers Med. Travail 4:191-216 (Apr.-July 1966). Summary enclosed.

11. Neal, P. A. et al. Public Health Bull. #267, Wash., D. C. U.S.G.P.O. (1941). No copy enclosed.

12. Nogaki, K. Igaku Kenkyu 27(6):1314-38 (1957). Summary enclosed.

13. Palmisano, P. A. Clean Air and Water News 2(43):3 (Oct. 1970). Enclosed.

14. Ragucci, N. Minerva Ginecolog. 21:1163-71 (Sept. 1969). Summary enclosed.

15. Scanlon, J. Clin. Ped. 11:135-41 (Mar. 1972). Summary enclosed.

*All summaries, unless otherwise noted, are taken from The Biological Aspects of Lead: An Annotated Bibliography, I. R. Campbell and E. G. Margard; Kettering Laboratory, Cincinnatti (1972), covering the 1950-64 literature, and The Kettering Abstracts on Lead, Lead Industries, Inc. covering 1965-74.

16. Symposium on Air Quality Criteria J. Occ. Med. 10:437-567 (1968). Summary enclosed.

17. Valyi-Nagy, T. et al. Acta Physiol. Acad. Scien. Hungar. 5:537-42 (1954). Summary enclosed.

18. Van Assen, F. J. J. Nederlands Tijdschrift Verloskunde Gyn. 58(3-4):258-63 (1958). Summary enclosed.

19. Vermande-Van Eck, G. J. and J. W. Meigs Fertil. and Steril. 11:223-34 (1960). Summary enclosed.

20. Waldron, H. A. and D. Stofen Sub-clinical Lead Poisoning. Academic Press, N. Y. (1974).

Also Enclosed:

Chemcon printout of recent (1972 to present) references.

Copies of Haskell "Lead File" references on reproductive effects.

Basis Of Embryotoxic Classfication

Historical - dates back to years ago in TEL areas of Chambers Works (See C-1516).

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C.01516

Lead

Carcinogenicity:

Although many human diseases have been correlated with lead exposure, cancer is not one of them (1). Some salts of lead are known to be carcinogenic in animals (2) with the kidney the main target organ, but the equivalent dose level which would be needed to induce such tumors in man is well above the maximum tolerated dose (3).

Mutagenicity:

There is no firm experimental evidence that lead can affect animal cell mutations at physiological concentrations (1).

Teratogenicity:

The fetal effects of chronic lead exposure were recently reviewed (4); a copy is attached.

REFERENCES

1. Airborne Lead in Perspective, National Academy of Sciences, Wash.,D.C. (1972) pp. 157 and 169.

2. Lead acetate to rats and mice; lead subacetate and lead phosphate to rats; possibly lead arsenate and lead carbonate (see Ref. 1).

3. IARC Monographs on the Evaluation of Carcinogenic Risk, Vol. I Internatl. Agency for Res. on Cancer,Lyon (1972), p. 48.

4. Letter, N. Hunt to B. W. Karrh 3/31/75.

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