

# THE EFFECTS OF LEAD ON REPRODUCTION

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## INTRODUCTION

Increasing numbers of women are now seeking employment outside the home. Because of this changing employment pattern, Government, Industry and Labor, for the first time, have been forced to focus attention on the health hazards of occupational exposures to women and to the reproductive processes involving exposure to either sex. Because lead is a known abortifacient, women are being transferred out of high lead exposure areas in lieu of industrial engineering control. The alternative to transfer for some companies has been the requirement that women present medical evidence that they cannot bear children in order to maintain employment in areas of sustained high lead exposure. Such approaches ignore possible toxic effects on reproduction through male occupational exposures. Therefore, available evidence is assessed to evaluate the role of lead exposure on the total spectrum of risks associated with reproduction.

For more than a century, lead has been known to affect the reproductive process. Observations among human populations indicate that lead is associated with sterility, spontaneous abortions or miscarriages, stillbirths, birth defects, increased infant mortality, increased prematurity, increased chromosomal aberrations, and abnormal spermatogenesis. Additionally, animal test systems have indicated that lead is associated with (1) impotency (Hilderbrandt, et al., 1973), (2) sterility (Dalldorf and Williams, 1945), (3) teratogenesis (McClain and Becker, 1970), (4) mutagenesis (Varma, et al., 1974), (5) decreased learning ability in the offspring following lead exposure of either parent (Brady, Herrera and Zenick, 1975), and (6) carcinogenesis (Boyland, et al., 1962).

## TERATOGENESIS

### Laboratory Observations:

Numerous experimental studies have assessed the teratogenic effects of lead in a variety of animal species (Table 1). In 1928, Hammett and Wallace observed growth retardation in the head region of chicks by injecting lead nitrate into the yolk sac of the embryo. Other investigators injected lead into chick embryos and observed harmful effects on the development of head primordium (Catizone and Gray, 1941), the development of anterior meningoceles

and hydrocephalus, (Butt, Pearson and Simonsen, 1952; Karnofsky and Ridgway, 1952), other cerebral anomalies and limb reduction deformities (Gilani, 1973). The addition of 1% lead acetate to the diet of female chickens has induced limb deformities in the hatched chicks (Stowe, et al., 1972).

Formal studies for the passage of lead through the placenta began in the 1930's, with the development of better chemical analytical techniques. In 1938, Morris, et al. studied the transplacental passage of lead acetate in rats. They observed significant increases in kidney weight and liver size and a decrease in femur weight. Lead also has been shown to cross the placenta rapidly and in significant amounts, even at relatively low maternal blood levels (Carpenter, 1974). In the mouse and rat, lead nitrate has induced cleft palate and hydronephrosis, respectively (McClain and Becker, 1970). In these same species, pup mortality and runting also has been significantly associated with maternal intake of unspecified lead salts (Schroeder and Mitchener, 1971).

In the hamster, lead nitrate, lead chloride and lead acetate have induced tail anomalies (Ferm and Carpenter, 1967). Anomalies induced by lead acetate also have been potentiated into more severe caudal malformations by the addition of cadmium (Ferm, 1969).

A study of the effects of lead metal ingested for two generations by both male and female rats also has been reported. Growth and reproduction in the F<sub>1</sub> and F<sub>2</sub> generations was assessed (Dollendorf and Williams, 1945). They observed normal growth in the first generation. In the second generation, however, (1) a 50% increase in mortality was observed, (2) the surviving young were stunted in growth, and (3) some animals of both sexes became sterile.

#### Human Observations:

Just as animal data have demonstrated the ability of lead to cross the placenta, so too have observations among humans. As early as 1916, Oliver reported that lead had been found in the liver and other organs of a stillborn child and in the placenta of a mother who was a "white lead worker." More recently, studies have shown a high correlation between maternal and neonatal blood lead levels in humans,  $r=0.64$  (Gershanik, Brooks and Little, 1974).

Although the animal data incriminating lead as a teratogen first surfaced in the 1920's, data demonstrating similar effects among humans surfaced much earlier. In 1916, Oliver reviewed data from earlier publications showing adverse effects of lead on reproduction. Included in this review is a study published in 1860 by Constantin Paul, who reported the results of 123 pregnancies where both the father and mother had occupational exposures to lead at an unspecified industry. Of these pregnancies, 52% ended in miscarriage, 4.1% ended in stillbirth, and 3.3% ended in

prematurity. Of the 54 remaining live births, 37% (20/54) died within the first year of life. In a second series of 43 pregnancies, where only female lead exposures (unspecified) were involved, Paul reported that 74.4% ended in miscarriage and 7% ended in stillbirth. Thus, both human and experimental studies have demonstrated transplacental passage and teratogenic effects of maternal exposure to lead.

## MUTAGENESIS

### Laboratory Observations:

Evidence of the paternal effect of lead intoxication on perinatal mortality in experimental animals was first demonstrated by Cole and Bachhuber in 1914 (Table 2). They fed a diet containing lead acetate to two strains of male rabbits and mated them with non-exposed females. The results from lead-exposed males only demonstrated: (1) lower birth weights resulting from these pregnancies and (2) higher mortality within the first four days after birth (a two-fold excess) as compared to controls.

A year later, these findings were corroborated in guinea pigs (Weller, 1915). Commercial white lead was given orally to male pigs, which were then mated with lead-free females. The observed effects were: (1) sterility; (2) reduction in birth weight by 20%; (3) increased number of dead in the first week; and (4) offspring of lead-poisoned males remained permanently underweight.

A recent study of reproductive performance from male rats fed 1% lead acetate in their diets by Stowe and Goyer (1971), has demonstrated a significant reduction in pup birth weight, a 15% reduction in the number of pups per litter, and an 18% reduction in survival rate as compared to controls.

In 1973, Hilderbrand, et al. studied the effects of lead acetate ingestion on reproduction in the rat. A significant increase in prostatic weight (to as much as twice the control values) due to hyperplasia resulted from blood lead levels of 30 ug/100 ml. These blood lead levels are only one-half those (60 ug/100 gr whole blood) currently being proposed for biological monitoring of lead workers to provide an adequate margin of safety against adverse health effects (Dunlop, 1975). At the 30 ug/ml blood level, a 70% reduction in testicular weight, impotency and reduced sperm mobility also were observed. (Female rats exhibited ovarian cysts.)

Muro and Goyer (1969) demonstrated a significant increase in gap-break type of chromosomal aberrations by lymphocyte culture from mice fed a diet containing 1% lead acetate. Subsequently, Varma, Joshi and Adeyemi (1974) fed a diet containing 2% lead sub-acetate to mice and demonstrated a dominant lethal mutation effect, i.e. a significant excess of post-implantation fetal deaths resulting from exposures to the male animal only. These

investigators also observed a 50% reduction in male fertility.

Other assessments of potential mutagenic risks of lead also have been made. Gene frequency differences in the fruit fly (*Drosophila melanogaster*) have been significantly correlated with distance from lead smelter operations (Lower, 1975).

#### Human Observations:

Oliver, in 1916, also summarized data for pregnancy outcome among the wives of males employed as house painters, many of whom suffered from lead colic. Of 467 deliveries, 23% (107/467) were stillborn as compared to 8% for the entire town.

Oliver also reviewed data from Lewin for 32 pregnancies from "healthy" women, who were married to lead workers. The industry was not specified. Of these, 34.4% ended in miscarriage, 3.1% ended in stillbirth. Of live births, 40% died within the first year of life, and only two children lived to adulthood.

The effects of lead on human lymphocyte chromosomes have been studied. As a result of human lymphocytes cultured in vitro in the presence of lead acetate, Beek and Obe (1974) induced archromatic lesions, chromatid breaks and isochromatic breaks well in excess of the control group (Table 3).

From the study of occupational lead exposure, several investigators (Schwanitz, Lehnert and Gebhart, 1970; De Knudt, Leonard and Ivanov, 1973; Forni, Cambiaghi and Secchi, 1976) have concluded that lead is associated with a definite increase in the number of chromatid and chromosomal changes in circulating lymphocytes of workers. Others have reported negative cytogenetic findings (Schmid, et al., 1972; Bauchiner and Schmid, 1972; O'Riordan and Evans, 1974). Although O'Riordan and Evans reported no significant difference between the study group and "inplant" controls, chromosomal anomalies in the study group were significantly greater than general population control,  $P < 0.001$ . This observation led these investigators to conclude that individual variability in scoring chromosomal gaps might have accounted for these apparently conflicting results. However, "inplant" controls may have been exposed to other mutagens.

Of even greater significance are the findings in 1975 by Lancranjan, et al. who studied the reproductive ability in 150 male workers exposed to lead in a storage battery facility. In workers with moderately increased lead absorption (53 ug/ml of lead in whole blood), a significant decrease in fertile ability was observed. This observation was related to a direct toxic effect on the gonads, which resulted in significant alterations in spermatogenesis--asthenospermia (decreased motility), hypospermia (decreased numbers), and teratospermia (malformed sperm). Even in workers with slightly increased lead absorption (mean of 41 ug/ml

blood), significant differences in asthenospermia and hypospermia were observed. Thus, both human and experimental studies have demonstrated mutagenic effects and reproductive impairment following paternal exposure to lead.

### CARCINOGENESIS

Respiratory cancers have been observed in laboratory animals following inhalation exposure to lead oxide mixed with benzo(a)-pyrene, whereas groups given these agents singularly did not develop cancer (Kobayashi and Okamoto, 1974). Kidney cancers have been reported in animals following subcutaneous injection of lead phosphate (Zollinger, 1953; Matthews and Walpole, 1959; Tonz, 1957) and by oral ingestion of lead acetate (Boyland, et al., 1962; Van Esch and Kroes, 1969). The study of Cooper and Gaffey (1975) presents suggestive evidence for excessive human respiratory cancer among lead smelter and battery plant workers.

Cancer mortality experience in Shoshone County, Idaho, where primary lead and zinc smelters are located, is also of interest. During the period 1968-72, the respiratory cancer rate for Shoshone County was the highest recorded in the State (Bax, 1975). An additional report has indicated that end-stage renal disease shows a four-fold excess and kidney cancer shows a two-fold excess for Shoshone County as compared to the State average (Landrigan, 1975). These observations suggest that lead may be carcinogenic as well as mutagenic.

### SUMMARY

Evidence based on animal and human studies clearly demonstrates a teratogenic response following maternal exposure to lead. Of equal concern is evidence demonstrating that lead may be mutagenic, or adversely affect reproduction as a result of paternal lead exposure. In light of these findings, must we now transfer male employees from high lead exposure areas, or require proof of their inability to reproduce as has previously been the public health approach for females?

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TABLE 1  
 TERATOGENIC RESPONSE INDUCED BY LEAD

<u>SPECIES</u>	<u>INVESTIGATORS</u>
Chick	Hammet and Wallace (1928)
Chick	Catizone and Gray (1941)
Chick	Butt, Pearson and Simonsen (1952)
Chick	Karnofsky and Ridgway (1952)
Chick	Stowe, Goyer and Cates (1972)
Chick	Gilani (1973)
Hamster	Ferm and Carpenter (1967)
Hamster	Ferm (1969)
Mouse & Rat	McClain and Becker (1970)

TABLE 2

EVIDENCE FOR MUTAGENIC OR REPRODUCTIVE EFFECTS  
FROM MALE EXPOSURE TO LEAD

<u>SPECIES</u>	<u>FINDINGS</u>
A. Rabbit	1. Reduction in Birth Weight 2. Higher Postnatal Mortality
B. Guinea Pigs	1. Sterility 2. Reduction in Birth Weight 3. Higher Postnatal Mortality
C. Rat	1. Reduction in Birth Weight 2. Reduction in Litter Size 3. Higher Postnatal Mortality
D. Rat*	1. 2-fold Increase in Prostatic Weight 2. 70% Reduction in Testicular Weight 3. Reduction in Sperm Motility
E. Mice	Chromosome Anomalies
F. Mice	Excess of post-implantation Fetal Deaths
G. Drosophila	Increased Gene Frequency

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\*Occurred at blood lead levels which are  $\frac{1}{2}$  those currently being recommended for biological monitoring of lead workers

TABLE 3  
 HUMAN EVIDENCE FOR THE MUTAGENICITY  
 OR REPRODUCTIVE EFFECTS OF LEAD

<u>OBSERVATION IN HUMANS</u>	<u>RESULTS FROM OCCUPATIONAL EXPOSURES</u>
A. Effects on Lymphocytes	Chromosome Changes
B. Effects on Reproductive Ability	Decreased Fertility Due To: 1. Asthenospermia 2. Hypospermia 3. Teratospermia
C. Pregnancy Outcome From Male Lead Exposure	1. Increased Miscarriages 2. Increased Stillbirths 3. Increased Postnatal Mortality



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