Teratogenesis and Mutagenesis Associated with the Exposure of Human Males to Lead: A Review

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Major sectors of the lead-related industries have traditionally supported the view that the exposure of human males and females to lead is associated with significantly different reproductive-related risks. This review examines selected data pertaining to teratogenesis and mutagenesis associated with the exposure of human males to lead. The existing body of epidemiologic data examining reproductive-related effects associated with lead exposure of human males is relatively sparse and incomplete. Data findings are also conflicting. On the basis of selected available data, however, the exposure of human males to lead may be associated with significant reproductive-related harms. Too little attention has been directed by the scientific community toward possible reproductive-related effects of lead exposure on human males. There is a strong need for further good studies.

Major sectors of the lead-related industries have supported the view that maternal lead exposure may seriously jeopardize the health of the unborn child but that there is no comparable epidemiologic data indicating that paternal lead exposure creates any risk of injury to the fetus. The view that reproductive-related effects of lead exposure of human males and females are significantly different has affected the development of workplace policies pertaining to lead exposure and has further resulted in legal challenges [1–8]. The possibility exists that the exposure of human males to lead in the workplace, and elsewhere, may be associated with significant reproductive-related risks. This possibility is the subject of the following review.

A body of clinical and epidemiologic data dating back to 1860 indicates that paternal lead exposure may adversely affect pregnancy outcome, causing specifically an increased incidence of miscarriage, stillbirth, and postnatal mortality. Male exposure to lead may affect reproductive ability and cause decreased fertility, due to an increased incidence of asthenospermia, hypospermia, and teratospermia. The exposure of human males to lead may further affect lymphocytes and be associated with chromosomal changes [9].

Constantin Paul, in 1860, observed that in 32 pregnancies in seven women, whose husbands were lead workers and had shown signs of lead poisoning, there were 11 abortions and one stillbirth [10]. Among the 20 surviving children, eight died in the first year of life, four in the second, and five in the third.

In 1910, Rudeaux reported data showing that of 442 pregnancies among the wives of 75 lead workers, there were 66 abortions and 241 miscarriages [11].

Torelli, in 1930, published data showing that the abortion rate in Milan, Italy, for

1Letter, dated May 30, 1980, submitted on behalf of the LIA in response to a request by the Equal Employment Opportunity Commission for comments on proposed interpretive guidelines on employment discrimination and reproductive hazards. 45 Fed. Reg. 7514 et seq. (February 1, 1980)
the general population was 4 to 4.5 percent. The corresponding rate among the wives of males exposed to lead in the printing trade was 14 percent [12].

Spermatic alterations may be associated with an increased incidence of miscarriage, stillbirth, and increased postnatal mortality rates among the wives of lead-exposed males. Lancranjan et al., in 1975, reported data regarding the effects of long-term exposure to lead on the reproductive ability of 150 males employed at a storage battery plant [13]. This study has been the subject of extended critical evaluation by the scientific community and will be analyzed closely.

Four groups of “cases” were established by Dr. Lancranjan: lead-poisoned workers, workers with moderately increased lead absorption, workers with slightly increased lead absorption, and workers with physiologic lead absorption. Placement in one of the groups was based on complaints presented by the workers and on the results of clinical examination and toxicologic testing. The mean age of the sample population was 38.5 years. Materials collected by the investigators included information about occupational history and information about possible non-occupational toxic exposures, specifically including information about tobacco use and alcoholic consumption. A detailed sexual history of each man in the study was taken. Clinical and toxicologic data used to place men in the study in one of the four groups included measurement of lead in the blood and urine. Lead levels in the urine and blood were determined by means of a modification of the “dithizone” method. Mean values of lead in the blood and urine for the four groups of workers are shown in Table 1.

Evidence of decreased libido as well as difficulties with erection and ejaculation were found in the sample population. Data pertaining to decreased libido, orgasm reduction, and difficulties with erection and ejaculation in the four groups of workers are shown in Table 2.

On the basis of data presented by this study, toxic causes associated with libido decrease and difficulties with ejaculation are not certain. The distribution of libido

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**TABLE 1**
Mean Lead in Blood and Urine Values of a Sample Population of Males
Occupationally Exposed to Lead

| Group                        | Lead in Blood (micrograms/100 ml) | Lead in Urine (micrograms/liter) |
|------------------------------|-----------------------------------|----------------------------------|
| Lead-poisoned                | 74.50 ± 26                        | 385 ± 71                         |
| (n = 23)                     |                                   |                                  |
| Moderately increased         | 52.80 ± 21                        | 251 ± 106                        |
| absorption                   |                                   |                                  |
| (n = 42)                     |                                   |                                  |
| Slightly increased           | 41 ± 12                           | 100.6 ± 41                       |
| increased absorption         |                                   |                                  |
| (n = 35)                     |                                   |                                  |
| Physiologic absorption       | 23 ± 14                           | 92 ± 34                          |
| (n = 23)                     |                                   |                                  |

Source: Lancranjan I, Popescu H1, Gavanescu O, et al: Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 30:396–400, 1975
TABLE 2
Sexual Dynamics in a Sample Population of Males Occupationally Exposed to Lead

| Group                              | Libido Decrease (%) | Pathologic Erection (%) | Pathologic Ejaculation (%) | Orgasm Decrease (%) |
|------------------------------------|---------------------|-------------------------|---------------------------|---------------------|
| Lead-poisoned (n = 23)             | 21                  | 48                      | 30                        | 3                   |
| Moderately increased absorption    | 33                  | 33                      | 38                        | 4                   |
| (n = 42)                           |                     |                         |                           |                     |
| Slightly increased absorption      | 28                  | 22                      | 40                        | 5                   |
| (n = 35)                           |                     |                         |                           |                     |
| Physiologic absorption             | 16                  | 14                      | 16                        | 2                   |
| (n = 50)                           |                     |                         |                           |                     |

Source: Lancranjan I, Popescu HI, Gavanescu O, et al: Reproductive ability of workmen occupation-ally exposed to lead. Arch Environ Health 30:396–400, 1975

decrease and difficulties with ejaculation among lead-poisoned workers and among workers with either moderately increased or slightly increased lead absorption tended to be uniform, despite significant differences in lead in blood and urine values for these groups of workers. The lack of positive association between lead in blood values and lead in urine values, and the frequency of decreased libido and difficulties with ejaculation suggests that factors other than lead exposure may have been associated with the frequency of libido decrease and pathologic ejaculation among this sample population of workers. Lead in blood values and lead in urine values showed positive association with the frequency of pathologic erection among lead-poisoned workers and workers with moderately or slightly increased lead absorption.

Lancranjan reported that investigation of the reproductive ability of lead workers in the study was inconclusive with respect to the number of normal pregnancies per couple, the frequency of miscarriages and induced abortions, and the incidence of ectopic pregnancies and premature births. Data compiled for these parameters was doubtful, partly because of insufficient cooperation of subjects in the study with the investigators, and also because of the lack of exact knowledge of the number of abortions of the female partner. The association between lead exposure and the number of pregnancies per couple was also indeterminate because about 50 percent of the couples conceived before any occupational exposure to lead. In addition, after the start of occupational lead exposure, men in the study having one to three children had used various contraceptive methods.

Dr. Lancranjan sought to determine the fertility of sample members by means of semen analysis. Semen analysis was carried out in 89 cases, selected from 115 volunteers. Semen samples were collected after at least three days of sexual inactivity. Results were compared to 50 controls, of similar mean age (37.6 years), without exposure to occupational toxic materials. Controls were selected on the same grounds, and similarly examined, as exposed cases. Semen analysis was not performed on those presenting evidence of varicocele or hydrocele, or on those who had a prior medical
Incidence of Spermatic Alterations in a Sample Population of Males Occupationally Exposed to Lead

| Group                        | Spermatogenesis No. (%) | Asthenospermia No. (%) | Hypospermia No. (%) | Teratospermia No. (%) |
|------------------------------|-------------------------|------------------------|---------------------|-----------------------|
| Lead-poisoned (n = 16)       | 15(93)                  | 8(50)                  | 8(50)               | 14(86)                |
| Moderately increased absorption (n = 29) | 22(68)                  | 15(51)                 | 13(44)              | 17(58)                |
| Slightly increased absorption (n = 19) | 12(63)                  | 8(42)                  | 8(42)               | 6(31)                 |
| Physiologic lead absorption (n = 25) | 7(28)                   | 6(24)                  | 7(28)               | 4(16)                 |

Source: Lancranjan I, Popescu Hl, Gavanescu O, et al: Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 30:396–400, 1975

history of venereal disease or genital tuberculosis. Studies were also not performed on those with recent febrile diseases, on alcoholics, or on those afflicted with other unspecified diseases known to affect spermatogenesis.

Data pertaining to the incidence of spermatic alterations in the groups of men under epidemiologic investigation is presented in Table 3.

Among the group of lead-poisoned workers, 75 percent were hypofertile, and 50 percent were infertile. In the group of workers with slightly increased lead absorption, only hypospermia and asthenospermia were statistically more frequent, compared to controls.

Toxic causes of asthenospermia and hypospermia in this relatively small population of workers are not certain. Lead-poisoned workers, as well as workers with moderately and slightly increased lead absorption, showed a fairly uniform frequency of asthenospermia and hypospermia, despite sizable differences in mean values of lead in the blood and urine. The frequency of teratospermia showed positive association with lead in blood and urine values for all four groups of workers.

Dr. Lancranjan stated that long-term exposure to lead has a noxious effect on the germinal epithelium, inducing alterations in spermatogenesis. It was hypothesized that spermatic alterations were caused by a direct toxic effect on the gonads. The results of Leydig tissue investigation showed the absence of any significant influence of lead on androgen secretion. The investigators stated that the results of tests for total urinary gonadotropic elimination excluded the possible contribution of a hypothalomopituitary hyposecretion in the cause of the spermatic alterations.

Several variables potentially confound an analysis of the Lancranjan data. Alcohol consumption varied among the sample population. Five percent of the sample population drank more than two liters of wine or over 500 ml distilled liquor per week; 17 percent drank one to two liters of wine or 300 to 500 ml of distilled liquor per week;
and 77 percent drank less than one liter of wine or under 300 ml of distilled liquor per week. Smoking history also varied among the men in the study. Forty-four percent were smokers: 7 percent smoked more than 20 cigarettes per day; 22 percent smoked 10 to 20 cigarettes per day; and 15 percent smoked fewer than 10 cigarettes per day. Duration of exposure of the sample population to occupational lead hazards varied significantly, ranging from one to 27 years. One hundred workers had a mean occupational lead exposure of 8.5 years, with a range of one to 23 years; 50 technicians and office workers presented a mean occupational lead exposure of six years, with a range of one to 27 years.

Cullen et al. have recently described endocrine and reproductive dysfunction in seven patients referred to an occupational medicine clinic for lead intoxication [14]. Four of the patients presented with typical syndromes of acute intoxication with lead colic; three had clinical diagnoses of chronic poisoning with diffuse central nervous system dysfunction and renal involvement. Three sample members had reported sexual or reproductive problems, including impotence, infertility, or decreased libido.

Germinal function was initially abnormal in most of the men in this study sample. The study data showed that four cases had fewer than 20 million sperm per ml after abstinence. Based on evaluation of two separate specimens, two of these four were azoospermic. One patient had been vasectomized. Sperm motility was decreased in all but one case. Follicle-stimulating hormone was elevated in serum in the two azoospermic men, but normal in the rest. On the basis of testicular biopsies, the investigators further reported abnormalities, including depressed spermatogenesis and Leydig (interstitial) cell hyperplasia in the azoospermic patients. One of the azoospermic patients was challenged with gonadotropin-releasing hormone and showed a normal response.

Toxic causes possibly associated with endocrine and reproductive dysfunction in the seven men in the sample are not certain. Blood lead (μg/dl) levels in the sample population ranged from 39 to 98. The two men in the study with the relatively highest blood lead levels (90 and 98 μg/dl) did not report reproductive or sexual problems. The study data did not show a positive association between blood lead levels and decreased sperm count. Decreased sperm motility also was not positively associated with blood lead levels.

On the basis of the study data, duration of lead exposure compared with blood lead level may be relatively more closely associated with observed spermatic abnormalities. The three cases with the relatively longest duration of lead exposure (7, 11, and 15 years) included the two azoospermic cases and a third patient with an abnormally low sperm count (18 million/ml) and an abnormally low percentage (40 percent) of motile sperm. However, duration of lead exposure did not show a direct positive association with abnormalities in germinal function.

The relatively small size of the sample population (n = 7) affects the statistical significance of the Cullen et al. data. Since the patients came from different sites and job categories, exposure to toxins other than lead is a variable possibly confounding an analysis of the study data. The investigators stated that none of the cases had prior exposure other than lead to environmental agents suspected of causing endocrine disease. It was further reported that only one case had a medical condition (diabetes mellitus) known to be associated with endocrinopathies. None had had mumps orchitis, and none had infections or anatomic abnormalities of the lower genital tract. Two cases, however, were reported to be alcohol users to a "significant" degree.
The investigators suggest several interpretations of their data. It is suggested that the data results, showing decreased urinary 17-hydroxycorticosteroids and blunted responses to challenge with insulin hypoglycemia and vasopressin, are supportive of a defect in the gonadal-pituitary axis. The normal cortisol response to cortrosyn in one of the azoospermic cases, who had depressed responses to other challenges, suggests a mild central lesion. The investigators, however, further state that semen findings and testosterone levels compared with pituitary hormonal levels support a primary testicular effect on the gonadal-pituitary axis. It is concluded that observed high levels of serum gonadotropins in the azoospermic cases and the findings of Leydig cell hyperplasia on biopsies in these cases exclude a primary pituitary or hypothalamic basis for gonadal failure. Because of the central effects noted on thyroid and adrenal axes, and the failure of the investigators to perform challenge tests of pituitary and hypothalamic gonadotropic responsiveness on all but one case, Cullen et al. conclude that it is possible that both central and testicular lesions may occur in some patients.

Conflicting data findings have been reported in the literature pertaining to rates of chromosomal damage in males occupationally exposed to lead. O'Riordan and Evans, in 1974, published data obtained from a sample population of males occupationally exposed to oxides of lead in a shipbreaking yard [15]. Thirty-five men were employed as burners. Another 35 men were not actively engaged in burning and formed a control population. Data collected from the lead-exposed workers showed very small increases in the frequencies of chromatid breaks, and in the total number of cells with chromosomal aberrations. The study investigators reported that data analysis did not reveal any consistent and significant differences in the incidence of chromosome and chromatid aberrations between cases and controls.

The O'Riordan and Evans data findings may be confounded by the fact that all 70 workers had periodic mass chest X-rays, and many received further radiation exposure for investigation of bone fractures and ulcers. The length of occupational lead exposure of cases varied significantly, from three months to 43 years. The age range of cases similarly varied significantly, from 21 to 63 years. The size of the sample population of lead-exposed workers \( n = 35 \) is relatively small.

Some investigators have reported positive findings for chromosomal-related aberrations among lead-exposed males. Schwanitz et al., in 1970, reported positive findings for chromosomal-related aberrations in a sample population of eight workers from a lead oxide factory [16]. Chromosomal analysis of the lead-exposed workers showed an increased proportion of secondary chromosome aberrations. The difference from a control group of healthy blood donors not exposed to lead was statistically highly significant by the chi-square test. Gaps and breaks were much increased in cases as compared to controls. Eight hundred mitoses from the lead workers showed 118 isochromatid and 70 chromatid aberrations. Fifteen hundred mitoses from the control group showed 62 chromatid and 33 isochromatid abnormalities. The frequency of tetraploid mitoses was higher in the cultures of cases compared to controls; among cases, 18/800 mitoses were tetraploid, whereas the corresponding figure for the control group was 1/1,700. The lead workers showed a greater percentage of cells in division (46.5 percent), as compared to controls (25.9 percent).

The relatively small size of the sample population \( n = 8 \) affects the statistical significance of the data findings reported by the Schwanitz et al. study. A question of relevant controls is raised, inasmuch as cases were employed in a lead oxide factory but the control group consisted of blood donors at a University surgery department. The
blood lead levels of cases ranged from 62 to 89 micrograms/100 ml of blood. The age of cases ranged from 22 to 57.

Forni et al., in 1976, presented chromosomal and biochemical data collected from a sample population of male workers before and during first occupational exposure to lead fumes in a storage battery plant [17]. In this sample population, the percentage of abnormal metaphases in cultured lymphocytes approximately doubled (4.88 percent to 9.50 percent), after one month of occupational lead exposure. An increase in the percentage values of abnormal metaphases persisted up to seven months of exposure. After that time, the data collected either were not analyzed because of the small number of observations, or the data collected were not significantly different statistically. The absolute increase in the rates of abnormal metaphases was due primarily to chromatid changes (gaps and breaks). The relative increase was most evident for unstable chromosome aberrations, principally acentric fragments. Lead in urine values increased from 37.88 ± 16.86 to 105 ± 62.76 micrograms/liter after one month of occupational lead exposure. Blood lead levels increased progressively in the first few months of occupational lead exposure and then levelled off. Biochemical data results did not differ significantly in the analysis of variance.

The relatively small size of the sample population (n = 11) affects the epidemiologic significance of this study. The precise level of occupational exposure to lead of men in the sample is not reported. Plant workers in the study were employed in jobs described as involving “mild or moderate exposure to lead.” Air sampling performed during or at the end of the study period showed lead levels not higher than 0.8 mg/cu m of air in the work areas of the “worst” departments. The age of the 11 subjects varied from 21 to 42 years.

In 1978, Nordenson et al. reported the results of a study of chromosomal aberrations among 26 lead-exposed workers at a smelter in northern Sweden [18]. The frequencies of gaps, chromatid aberrations, and chromosome aberrations were all significantly higher among cases as compared to controls. For all three types of aberrations, the frequency increased with the lead level in the blood. This increase was statistically significant for chromosome aberrations only.

The scoring of chromosomal and chromatid aberrations may be relatively subjective and thus partly explain the apparently discordant findings reported by different laboratories regarding these aberrations. The lymphocytes in the O'Riordan and Evans study were cultured with bovine serum, whereas the cultures in the study by Forni et al. contained autologous plasma. This factor may further affect the findings reported by the respective laboratories.

Several recent studies have presented cytogenetic data findings from lead-exposed workers confounded by the fact that the workers were further exposed to other potential mutagens. Bauchinger et al., in 1976, reported cytogenetic data obtained from 24 males exposed to lead, zinc, and cadmium at a smelting plant [19]. The number of cells with structural chromosome aberrations was significantly increased in the 24 cases (mean blood lead level of 19.29 ± 6.62 micrograms/100 ml) compared to 15 controls. Observed chromosomal damage consisted mainly of single breaks and exchanges, with acentric fragments.

Deknudt et al., in 1973, reported chromosomal findings from the peripheral blood lymphocytes of 14 males normally exposed to dust and fumes containing lead, zinc, and cadmium [20]. Gaps, fragments, chromatid exchanges, rings, and dicentrics were observed. The difference in the number of cells with complex aberrations, including
chromatid exchange, disturbance of spiralization, ring, and dicentric, was statistically significantly different between the control population and all workers ($p$ less than 0.02). All 14 workers presented with clinical symptoms of saturnism. The investigators therefore concluded that the observed increase in abnormal cells resulted chiefly from lead intoxication.

In 1978, Deknudt and Deminatti reported data from the investigation of the action, on chromosomes, of zinc chloride, lead acetate, and cadmium chloride added separately to cultures of human lymphocytes [21]. The lymphocytes were cultured for 48 or 72 hours. The investigators observed more chromosomal fragments in all treated groups in comparison to controls, but differences were not significant. Severe aberrations, such as dicentric chromosomes, were recorded only in lymphocyte cultures treated with the lowest concentration of zinc chloride (three times $10^{-5}$ M), added at time zero, and regardless of whether the cultures were fixed after 48 or 72 hours.

The length of culture time may affect the frequency of observed chromosomal aberrations in human lymphocytes treated in vitro with lead acetate. Beek and Obe, in 1974, published data pertaining to the effects of lead acetate on human leukocyte chromosomes in vitro [22]. In human 72-hour leukocyte cultures, a 24-hour treatment with lead acetate induced a rate of open chromatid-type aberrations well over the baseline. However, the frequencies of chromatid-type aberrations were not elevated in 48-hour cultures, despite a relatively longer treatment time (48 hours + 3 hours before PHA addition).

Data pertaining to teratogenesis and mutagenesis associated with the exposure of human males to lead is relatively meager and incomplete. Conflicting data findings have been published. There is a strong need for further good studies. However, on the basis of currently available selected data, it is incorrect to assume that paternal lead exposure may not be associated with reproductive-related harm. Available epidemiologic data suggest that the exposure of human males to lead may be associated with significant reproductive-related harm. A unisexual workplace lead policy which excludes only females from exposure to occupational lead hazards leaves male workers, and their offspring, unprotected from reproductive-related and other harm possibly associated with paternal lead exposure.

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