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CONFIDENTIAL

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B-12308

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## Lead

Lead and lead compounds* have been reviewed according to the February 1988 EQC "Guidelines for Control of Carcinogenic, Reproductive, and Developmental Risks Posed by Chemicals Made or Used within Du Pont."

Lead has been considered a developmental and reproductive hazard by Du Pont for many years. The corporate policy concerning lead was clarified in a March 23, 1981 memo which states:

"The employment of women of childbearing potential in operations involving direct exposure to lead compounds should be avoided; however, contact with products containing trace quantities and exposure to airborne levels equivalent to normal ambient background levels are permitted."

In 1981, background levels of airborne and dietary lead translated into a blood-lead level of 30 ug/dL. Corporate policy as prescribed in the referenced memo indicated a program should be maintained to assure that workers who might become pregnant do not exceed blood-lead concentrations of 30 ug/dL. This hazard determination letter updates the corporate policy.

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* Lead and lead compounds include all forms of lead, metallic, inorganic, and organic, including organolead compounds such as tetramethyl- and tetraethyllead and lead naphthenate.

General Toxicity

The major route of exposure of workers to lead is by inhalation and ingestion of lead-bearing dusts and fumes. For the general public, the oral route (diet and drinking water) provides most of the lead intake with a small amount resulting from inhalation of airborne lead. However, reductions in the amount of lead in the environment have greatly reduced the amount of lead received from inhalation. Biological monitoring as a measure of occupational exposure to lead is most effectively determined by the measurement of blood-lead concentration (12).

Increased blood-lead levels above the normal range can occur without overt clinical symptoms or effects and biochemical changes can be detected within what is currently recognized as the normal range of blood-lead levels (< 35 ug/dL) (12).

Lead, like other chemicals, produces changes which range from those merely indicative of lead exposure, through those which are measurable but have no adverse impact on the organism, to those producing adverse effects. Lead has been extensively studied in both animal models and in man and support data for relating lead exposures to a wide variety of toxicity end-points can be found. However, many of these studies do not reliably allow precise definition of lead-induced toxicity with lead exposure (as measured by blood-lead levels). The discussion which follows recognizes this and points out areas in which the relationship between toxicity and blood-lead levels has been more clearly demonstrated.

In adult populations, a number of target organs or systems have been identified as being adversely affected by lead. Changes in the hematopoietic system (decrease in delta-amino-levulinic acid dehydrase activity in the red-blood cells, increase in erythrocyte protoporphyrins, changes in pyrimidine-5-nucleotidase levels) have been associated with lead exposure. Nerve conduction velocity decreases and suggestions of neurologic symptoms have been detected. Increased systolic blood pressure has been associated with blood-lead levels of about 30 ug/dL (42). Associations between blood-lead levels and blood pressure have been reported in middle-aged men 40 to 59 years old, with no apparent threshold through < 10 ug/dL; e.g., as blood lead increases, systolic blood pressure increases slightly (12,33,34).

Renal changes associated with blood-lead levels ranging from 40 to > 100 ug/dL have been reported in lead workers. However, the blood-lead levels measured at the time of renal function testing may not fully reflect the exposure history that contributed to the development of these renal effects (12).

It is not possible to establish lead exposures (as measured by maternal blood-lead levels) at which no effects are produced in the fetus. Several studies have revealed potential developmental effects in the form of reduced birth weight, pre-term birth, decreased growth rate, and lowered learning abilities. Lower birth weights were associated with maternal blood-lead levels of 12 to 13 ug/dL (4,8,9). IQ deficits of -5 points in children, indicating neurobehavioral impairment, are associated with mean blood-lead levels of 50 to 70 ug/dL in the children (7,39); and IQ deficits of -4 points are associated with blood-lead levels of 30 to 50 ug/dL (31). A significant association between cognitive ability and the children's blood-lead levels, with no apparent threshold down to the lowest blood-lead levels of about 6 ug/dL has been shown in two populations of children (15,18). Additional evidence of IQ deficits in children with blood-lead levels below 25 ug/dL has been reported (17).

Carcinogenic Potential

Certain lead compounds, e.g., lead acetate (11) and lead naphthenate (1), have been shown to be carcinogenic in animals, but epidemiological studies of lead workers have shown equivocal evidence of carcinogenicity (6,12,40). In the study in rats with lead acetate, administration of 500 ppm (as lead) of lead acetate for two years produced an increased incidence of kidney tumors. The mean blood-lead level of these rats was 77.8 ug/dL. Another group administered 100 ppm (blood lead of 35.2 ug/dL) had no kidney tumors (11). Lead naphthenate also produced kidney tumors in mice dermally administered a 20% benzene solution, twice a week, for up to 569 days (1).

Lead chromate has been associated with lung tumors in epidemiology studies. However, the lung cancers seen in one study might be related to chromium, especially zinc chromate, which was also produced in this plant (14).

Lead chromate and lead naphthenate are handled by Du Pont as potential carcinogens.

The studies in animals suggest that lead does produce kidney cancer generally following long-term, high-level exposures. The epidemiology studies do not readily yield the same kind of single-variable information and have been equivocal. It can be concluded that some lead compounds are weakly carcinogenic in rats and mice. No evidence for human carcinogenicity exists.

Genotoxic Potential

Tests for mutagenicity in microbial studies have yielded consistently negative results (10). Mammalian tests have given conflicting results, although the weight of evidence indicates lead may have clastogenic effects (2,38).

Developmental Toxicity

A number of animal studies have been conducted by the oral (5,16,19,21-23,25-27,29,30,36,37,41) and inhalation routes (35). Lead compounds do not appear to be teratogenic. Embryo- and fetotoxic effects suggest that the fetus is as sensitive, and maybe even more sensitive, to the effects of lead than the maternal animals.

In humans, prenatal exposure to lead produces toxic effects on the fetus including reductions in gestational age, birth weight, and mental development. However, no clear evidence of an association with congenital malformations was found (13,28,32).

Based on risk estimates, the risk of pre-term delivery increases four-fold as cord or maternal blood-lead levels increase from < 8 to > 14 ug/dL (28). A significant association between prenatal maternal blood-lead levels and birth weight has also been reported with the effect apparent at blood-lead levels as low as 12 to 13 ug/dL (4,8,9). IQ deficits of 4.8 points were detected in children 6 to 24 months old who had blood-lead levels at birth between 10 and 25 ug/dL (3).

Reproductive Toxicity

Sperm analysis indicates decreased fertility in occupationally exposed workers with blood-lead levels of about 50 ug/dL or more (24,43).

A group of 150 workers with long-term lead exposure was categorized by clinical and toxicological data into four groups: lead-poisoned (mean blood-lead level = 74.5 ug/dL), moderately-exposed (mean = 52.8 ug/dL), slightly-exposed (mean = 41 ug/dL), and physiologically-exposed (mean = 23 ug/dL). The lead-poisoned and moderately-exposed groups had significant decreases in fertility as measured by asthenospermia, hypospermia, and teratospermia (24). Effects on sperm were also observed in another group of lead-exposed workers with mean blood-lead levels of 44.6-46.1 ug/dL (however, these men had blood-lead levels of 50 ug/dL or more at least once prior to the study) (43).

Data from older literature indicate high-level exposure to lead may be related to abortion in women, but these studies had methodological problems and did not indicate a dose-response relationship (12). A higher incidence of miscarriage and stillbirth was reported among women living in a lead-smelter town than in women living outside of the town. However, maternal lead levels were lower in some cases of stillbirth than in cases of live birth (28).

Studies in rats indicate a NOEL for reproductive effects in females of 9 to 16 ug/dL and a lowest effect level of 18 to 29 ug/dL (16). In males, the NOEL is 19 ug/dL and the lowest effect level for testicular damage is 30 ug/dL (20).

Long-term, high-level exposure to lead can apparently interfere with the reproductive system of animals and humans. However, as mentioned above, these data do not permit any estimate of NOELs in women, and information on low-level exposures to lead and any potential effects on sperm or the testes is lacking. In animals, NOELs are below 30 ug/dL.

AEL Review

These and other data were reviewed by the Haskell Laboratory AEL Committee. Lead can be shown to have an adverse effect on most end points at blood-lead levels above 50 ug/dL. This was recognized years ago and is the basis for Du Pont's handling of lead and its compounds as developmental and reproductive hazards.

Blood-lead levels have already been reduced as indicated in determinations reported in EPA's Air Quality Criteria for Lead (12). The studies discussed above indicate that continued reduction in blood-lead levels would be prudent. When the current blood-lead threshold of 30 ug/dL to protect the fetus was adopted, airborne exposure to lead was estimated to be 5 $ug/m^3$. Reductions in the use of lead have substantially reduced the airborne lead levels. Accordingly, the current threshold of 30 ug/dL for women of childbearing capability should also be reduced to current background blood-lead levels in the range of 10-15 ug/dL.

Summary

We conclude that lead should continue to be handled as a reproductive and developmental hazard. A goal of reducing blood-lead levels of women of childbearing capability and other workers should be initiated. Some lead compounds are weakly carcinogenic in animals. The question of how to categorize lead compounds generically as to their carcinogenic potential will be dealt with separately.

For women of childbearing capability, exposures above background (as reflected by blood-lead levels of less than 15 ug/dL) should be avoided. For others, while no one piece of evidence suggests significant health effects following exposure to lead resulting in blood-lead levels of 50 ug/dL, the data taken together suggest a prudent practice would be to have a program to reduce blood-lead levels to 35 ug/dL or below.

According to the guidelines for carcinogenic, developmental and reproductive hazard designations, lead will continue to be categorized as D 1989 and r 1989.

Note: Those receiving copies of this letter, if they have an interest, should coordinate any actions they plan to take with K. D. Dastur of the C&P Department.

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