EFFECTS AND METABOLISM OF TOXIC TRACE METALS IN THE NEONATAL PERIOD

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INTRODUCTION

Exposure of the neonate to toxic metals occurs because of their presence in foods and the human biosphere. Nursing infants may ingest these metals in mother’s milk. After weaning, their presence in formula, cow’s milk and weanling foods is of major importance. Additional environmental metal contaminant sources become important when the infants begin to creep on the floor and have access to objects which they can chew or mouth. Infants are at particular hazard when their environment is contaminated by vapors, by metal-containing dust and particulate fallout or entrainment on articles brought into the home, or by building materials, such as plaster or lead-containing paints.

After toxic metals are ingested their bioavailability for intestinal absorption is a major factor in affecting toxicity. Bioavailability is influenced by the composition of foods and by the maturity of homeostatic mechanisms that either exclude toxic metals from absorption or increase their excretion. Apparently exclusion mechanisms are less effective in infants than in adults. After absorption, toxic metals may have both acute and chronic effects. The clinical manifestations of injury depend on dose, chronicity of exposure and tissue retention. Long-term sequelae can significantly impair function and well being of persons later in life.

In this review we summarize experimental and clinical findings that support the above statements. Our conclusions and recommendations are based in part on discussions that occurred during this Symposium.

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Maternal lactation, diet composition and intestinal absorption are the major factors that influence both the nutrition of infants and their exposure to toxic metals. Relationships between nutritional factors and susceptibility to toxic metals have been revealed through studies on experimental animals. While translation of research findings from experiments with animals directly to humans is not appropriate because of differences in physiology and rates of maturation, data from such studies should alert caretakers of infants of potential hazards and provide a guide for research on humans and prevention of injury.

Studies in rats reviewed by Kostial (this volume) suggest that the neonate has greater susceptibility to dietary lead, cadmium, mercuric mercury and manganese than older animals. When radionuclides of these elements were given orally, uptake and retention were substantially greater during the first week of life than at three or more weeks. A finding that might be particularly important for humans was the observation that all four elements were retained in infant brain to a greater extent than in older animals. High bioavailability and greater intestinal absorption (compared to adults) of lead, cadmium and mercury from milk were responsible for the high uptake of these elements by the sucklings. Apparent absorption of lead (60-80 percent), manganese (40-70 percent) and mercuric mercury (50-70 percent) were greater than apparent absorption of cadmium (20-40 percent). The high absorption of lead and manganese was primarily related to a carcass retention of 80-90 percent of the absorbed metal. In contrast, only 20-40 percent of absorbed cadmium and mercury was in the carcass. The remainder was retained by the intestinal mucosal cells. Presumably the metal retained in the intestinal mucosal cells did not traverse the mucosal cells but was returned to the intestinal lumen as cells were lost into the lumen as a consequence of cell turnover.

In contrast to metallic mercury, methyl mercury readily traverses the mucosa (Zepp et al., 1974). According to work of Kostial (this volume) and Keller and Doherty (1980a,b), it appears that the absorption of toxic metals by the neonatal rodent occurs in part through endocytosis. This phenomenon stops as the gut mucosa matures. Research in humans suggests that endocytic absorption occurs in premature and newborn infants. Permeability to protein macromolecules from milk and soy appears to diminish in humans after three months of life (Walker, 1978). Whether this phenomenon facilitates absorption of toxic metals in human infants is unknown.

Studies on rodents suggest that a feature of milk that might contribute to a greater absorption of lead (Barltrop and Khoo, 1976) is its fat content. The low contents of the elements of iron, zinc, and copper may not be factors in suckling animals because addition of iron to milk did not suppress lead absorption in suckling rats, and all of these elements did not suppress the intestinal absorption
of cadmium, mercuric mercury and manganese from milk (Kostial, this volume). On the other hand, it seems possible that calcium and phosphorus in milk tend to suppress lead absorption (Barltrop and Kho, 1976; Mahaffey, 1981). Studies presented at the Symposium illustrated the complexities of these relationships in rhesus monkeys (Gilbert et al., 1982). The monkeys displayed a substantially greater absorption of lead when fed a diet based on milk, compared to a commercial monkey diet. This occurred even though the animals were not infants and had been maintained on a commercial monkey diet for a substantial interval of time prior to the feeding of the milk diet. In this experiment, the calcium and phosphorus contents of the milk diet were inadequate to suppress a facilitating effect fat may have had on lead absorption; this interpretation is consistent with findings in rodents (Kostial, et al., 1971).

Lead consumed by nursing mice appears in their milk. Thus, studies using a radioactive tracer of lead showed that suckling mice litters received a substantial portion (25 percent) of the blood lead of their intravenously dosed mothers (Keller and Doherty, 1980c), and that as much as 3 percent of total body lead acquired by rat mothers prior to lactation was passed on to the pups by suckling (Keller and Doherty, 1980b).

In contrast to lead, relatively little cadmium fed to nursing mice appears in milk. This is probably related to the retention of cadmium by the maternal intestinal mucosa, breast, and other tissues (Kostial, this volume; Chang et al., 1980). Similar phenomena occur in cattle; high dietary intakes of cadmium have little influence on milk cadmium (Miller et al., 1967).

Organ distribution of toxic metals in neonatal animals may have implications for human infants. For example, lead accumulation in brains of rats during early life has been associated with poor subsequent behavioral function (Jason and Kellogg, 1981; Zenick and Goldsmith, 1981), and lead accumulated in kidneys has been associated with increased blood pressure (Perry et al., 1979) and abnormal renin-angiotensin responsiveness to sodium deprivation in rats (Victery et al., 1982a,b).

Though not done in sucklings, cadmium accumulation in kidneys was presumably responsible for the increase in blood pressure that occurred in rats exposed to 0.01-0.5 ppm in drinking water subsequent to weaning (Perry et al., 1979; Kopp et al., 1982). (0.5 ppm cadmium was equivalent to a dose of about 10 μg/kg body weight or about 12 times the level present in infant diets noted subsequently in this review.) Chronic exposure to 1 ppm cadmium in drinking water impaired cardiac function of the rats; inorganic orthophosphate levels in heart muscle were increased and ATP was decreased (Kopp et al., 1982). These findings are consistent with in vitro effects of
cadmium on oxidative phosphorylation and ATPase (Jacobson and Turner, 1980). Possible relevance of these studies for infants is suggested by observations on rats exposed to 0.06 ppm cadmium, a level believed to simulate the environment (Sabbioni et al., 1978). When exposed for 745 days, growth and development were unimpaired even though the level of intake was similar to levels associated with increased blood pressure in the studies noted previously. Of interest was a rapid early increase in tissue cadmium with a later continued gradual accumulation in kidney, lung, testicle and brain. Levels in liver did not increase after 100 days of exposure. Another effect of cadmium observed in neonatal rats that might be of some significance to humans was the effect of feeding 0.1 to 1.0 μg of cadmium daily on glucose metabolism. After 45 days, hyperglycemia and suppressed in vitro release of insulin from islet cells occurred (Merati and Singhal, 1980). Research on animals suggests that diet composition has an influence on the toxicity of dietary lead, cadmium and mercury. Interactions of some diet constituents with the toxic metals can influence their absorption. For example, intestinal absorption and toxicity of lead is influenced by the level of dietary calcium, iron, zinc, copper, protein, vitamin D and fat (Mahaffey and Michaelson, 1980; Mahaffey, 1981). When dietary calcium, iron or zinc are low, absorption and toxicity of lead is enhanced. It seems possible that plant substances, such as hemicellulose and phytate, which form insoluble complexes with some essential trace elements, might also complex with dietary lead and inhibit its absorption. Substances that enhance lead absorption include fat (Barltop and Khoo, 1976) and vitamin D (Mahaffey and Michaelson, 1980).

The lead-vitamin D interaction is complex, lead exposure is associated with reduced serum 1,25-dihydroxy vitamin D concentrations in children (Mahaffey et al., 1982b). This vitamin D metabolite has been demonstrated to be active in stimulating lead absorption in rats (Mahaffey et al., 1979).

Cadmium toxicity is influenced by the levels of dietary zinc, iron, copper, selenium, calcium, ascorbic acid, vitamin D and protein (Fox, 1974). Low dietary zinc, iron, copper, calcium, vitamin D and protein enhance cadmium absorption and/or toxicity, while increased levels of dietary zinc, ferrous iron, copper, selenium, ascorbic acid and protein have the opposite effect. Because hemicellulose and phytate suppress zinc absorption (Sandstead, 1981), and because cadmium has chemical properties similar to zinc and competes with zinc for binding ligands (Fox, 1974), it seems likely that these plant substances will also suppress the absorption of cadmium.

The influence of dietary substances on mercury absorption is not as well characterized as for lead and cadmium. The bioavailability of methylmercury for absorption is extremely high (>90 percent) (Suzuki, 1977). Factors that inhibit the intestinal
absorption of organomercury compounds are incompletely understood. Landry et al. (1979) have observed large differences in whole body methylmercury elimination rates related to quality of diet. Mice fed a high protein liquid diet excreted mercury more rapidly than mice fed a standard pellet diet. Mice fed the standard pellet diet excreted mercury more rapidly than mice fed a diet of milk. As described in this Symposium (Rowland et al., this volume), studies in mice indicate that demethylation by intestinal flora is an important mechanism contributing to methylmercury excretion in adults, but is apparently not operative until after weaning when gut flora has changed. Marked qualitative and quantitative changes in intestinal flora occur at this time. These microbial changes are correlated with a large increase in the rate of demethylation of methylmercury in the gut contents and an increase in the fecal excretion of mercury. Body burden subsequent to the methylmercury exposure is thus decreased.

Another factor in the elimination of methylmercury from the body is its secretion in bile complexed with glutathione. The rat liver develops this capacity between 2 and 4 weeks after birth (Ballatori and Clarkson, 1982). After re-entering the gut, some of the methylmercury is reabsorbed. The majority is demethylated and excreted in the feces, presumably by the microflora as noted above.

The effects of toxic metals on human infants are less well defined than in animals. This is in part related to the fortunate circumstance that severe exposure of infants to toxic elements is unusual. Some potential adverse effects of exposures to relatively low levels of toxic metals are suggested by findings in animals noted previously.

**Lead**

Of the toxic elements to which infants are exposed, lead is the most intensively studied. Lead is widely distributed in the infant's environment. High levels in dirt and dust represent a hazard because infants may eat dirt, may mouth lead-containing dust from their hands and toys, and thus ingest substantial amounts of lead. Similarly, lead-containing paint, plastic, newsprint and other materials that infants ingest contribute substantially to their lead intake. Parents who work in lead related industries may entrain lead on their clothing into the home and thus expose their infants to significant hazard. As indicated by data reviewed by Lin-Fu (1973) and Mahaffey (1983), environmental sources of lead are usually a greater hazard for infants than food. The most important sources appear to be lead-contaminated dirt, household dust and paint. Mahaffey (this volume) reported that children living in an urban setting had about 2,400 ppm lead on their hands when outdoor dirt contained 1,200 ppm lead, and indoor dust contained 11,000 ppm. It was estimated that
young children exposed to urban street dust had an average daily intake from these sources of 50 μg of lead (range, 20-200 μg). In contrast, surveys of the U.S. Food and Drug Administration indicate that food lead intake of infants and toddlers in the U.S. has averaged 25.2 and 28.8 μg daily. On a body weight basis, the lead intake from food by U.S. infants is nearly three times greater than adult intakes. Thus, lead intake from environmental sources and food is substantially greater relative to body size in infants than in older children and adults.

In addition to the hazards engendered by their relatively higher exposures to lead, infants are also at greater risk because they absorb a greater percentage of lead via the gastrointestinal tract than do adults. According to Alexander (1974), infants may absorb more than 50 percent and retain more than 15 percent of dietary lead. These findings are supported by Ziegler et al. (1978) who found that infants with daily intakes of more than 5 μg per kilogram absorbed about 40 percent and retained about 30 percent of ingested lead. In contrast, adults are reported to absorb 5-10 percent of dietary lead (Kehoe, 1982). This difference in absorption might be related to the about one-third slower intestinal peristalsis of infants compared to adults (Barbero et al., 1958). Another speculative explanation for the greater absorption is immaturity of an unidentified heavy metal exclusion mechanism.

A third possible explanation for greater lead absorption by infants is the composition of infant diets. Observations on nonhuman primates reported at this Symposium revealed that substantially greater amounts of lead were absorbed when monkeys previously fed a commercial monkey food were given a milk formula (Gilbert et al., 1982). For most contemporary U.S. infants and toddlers, human milk, commercial formula prepared from heat treated cow milk, and cow milk are major dietary constituents during the first two years of life, providing about 46 percent and 33 percent of the food intake at six months and two years, respectively (Mahaffey, 1983). The findings in monkeys noted above may indicate that the high milk consumption of infants and toddlers is a contributory factor to their higher absorption of lead. An alternate explanation for these findings in monkeys is that binding substances, such as phytate and hemicellulose in the control food, inhibited lead absorption, and that their absence allowed high lead absorption to occur. The interpretation that milk facilitated lead absorption in the monkeys seems at variance with findings in human infants that showed an inverse retention of lead when dietary calcium was increased (Ziegler et al., 1978), and findings in rodents that show that increased dietary calcium suppresses intestinal absorption of lead (Mahaffey, 1981).

Other components of a diet in which the primary energy source is milk that might contribute to an increased susceptibility to lead is its relatively low content of zinc and iron. When weaned rats
were fed low intakes of these elements, susceptibility to lead intoxication was increased (Mahaffey and Michaelson, 1980). Because rapidly growing infants and toddlers have a relatively high requirement for these elements, whose levels in milk are low, it seems conceivable that such a condition would favor increased intestinal absorption of lead. It should be noted that dietary inadequacies of iron, zinc, and calcium are apparently more common among children from lower socio-economic strata (Lin-Fu, 1973; Sandstead, 1981) than from higher strata. On the other hand, as cited previously, Kostial (this volume) did not find that the addition of iron to milk decreased the intestinal absorption of lead by suckling rats. After the first several months of life human infants and toddlers usually consume a mixed diet consisting of foods in addition to milk or infant formula. Also human infants are much more mature than suckling rats. It seems possible, therefore, that their responses to low intakes of iron and zinc or to additions of these elements to a diet would be more like those of weaned rats than of suckling rats.

The well known consequences of severe lead poisoning have been reviewed by Goyer (1981). Less well understood are effects of lead exposure at levels that were, until recently, not considered hazardous. While central nervous system injury in infants from eating lead-containing paint has been known for at least 40 years (Byers and Lord, 1943) it is now recognized that lead exposures substantially below those associated with clinical lead poisoning can have adverse effects on the central nervous system of young children (Needleman et al., 1979; Landrigan et al., 1975; Perino and Ernhart, 1974; Thatcher et al., 1982). Studies in experimental animals have shown that uptake of lead by brains of neonates is substantially greater than in adult animals. Similar increased uptake in infants and toddlers may account for their greater susceptibility to neurobehavioral effects compared to adults. As reviewed elsewhere in this volume, the sensitivity of the brain to injury by toxic substances is much greater during early life when it is undergoing rapid growth and maturation.

Because lead is readily transferred across the placenta, blood lead concentrations of neonates are quite similar to those of their mothers. Usually blood levels of the newborn infant are within 1 to 2 μg/dl of the mother's blood lead concentration; specific studies demonstrating this association are reviewed in this volume (Mahaffey, this volume). If women are employed in lead trades or have substantial exposure to lead during pregnancy, the neonate's blood lead concentration will be comparably evaluated with that of the mother (Ryu et al., 1978,1983). The World Health Organization recommended in 1980 (WHO, 1980) that blood lead levels for female workers of child-bearing age remain under 30 μg pb/dl whole blood. At that time the 30 μg/dl level was considered to be not associated with impairment of central nervous system development and behavioral
effects in young children (CDC, 1978). Current research suggests that this level may be revised downward based on greater understanding of the range of health effects produced by lead. Data from the general population of the United States, ages 6 months through 74 years, indicated that blood lead concentrations among women of child-bearing age are generally the lowest of any age and sex group (Mahaffey et al., 1982a). Between the years 1976 and 1980, women between the ages of 18 and 45 years had average blood lead concentrations between 10 and 13 μg/dl.

Body burden of lead is only estimated by blood lead concentration. Studies with experimental animals have demonstrated that the very young have higher tissue lead concentrations than mature animals having the same blood lead concentration (Mahaffey, 1983; Kostial, 1983). Depending on the balance between body burden of lead at birth, environmental lead exposure and growth rate, tissue concentrations of lead (expressed per unit body weight) may decrease but total body burden of lead increases.

Erythrocyte protoporphyrin levels reflect interference with heme synthesis as does activity of aminolevulinic acid dehydratase. These effects of lead, and others, on heme containing enzymes and cytochromes have been reviewed (Goyer, 1981; Pomelli et al., 1982). Indeed, these indices are profoundly affected by increased body level burdens in infants and children, and, because of their sensitivity, they are useful markers of lead burden and provide a means of identifying infants and children who are at risk of lead-induced central nervous system injury.

Refinements of tests of nervous system function have indicated that concentrations of blood lead observed in the upper range of those present in the general population are associated with a significant risk of neurobehavioral deficits in young children (CDC, 1978; Needleman et al., 1979; Perino and Ernhart, 1974; Needleman, 1982).

Increased levels of lead in unconventional tissues, such as teeth, have been found associated with impaired neurobehavioral function (Needleman, 1982). Increased levels of lead in this tissue probably reflects increased lead in bone. Accumulation of bone lead stores begins during gestation (Barltrop, 1968). Animal experiments have shown that a greater percent of an ingested lead dose is retained in the femur of young animals than mature animals (Mahaffey, 1983). Human bone lead concentrations double between infancy and the late teen years (Barry, 1975). During this period skeletal mass increases about 40-fold indicating the total amount of skeletal lead increases by 80-fold. Skeletal stores of lead are a significant endogenous source of this toxic metal for critical organs under physiological conditions in vivo. Recycling rates of bone mineral are much higher in children because of the constant physiological
processes of bone remodeling during growth. The contribution of bone lead to blood and soft tissue lead is likely to be considerable as recycling rates for bone are 8 to 10 times higher in children than adults (Rosen, 1983). Levels in blood are in part a reflection of the movement of lead from bone to soft tissue. Thus, the finding of a blood level >30 μg/dl not only may reflect current intake, but may reflect redistribution of lead previously accumulated in bone.

A recently reported national survey has shown that many thousands of children in the United States from low socio-economic groups, and particularly those who live in cities, have levels of blood lead that exceed 30 μg/dl (Mahaffey et al., 1982a). The research of Needleman et al. (1979), Landrigan et al. (1975), and Perino and Ernhart (1974) suggest that some of these children probably have impairments in neuropsychological function. Thatcher et al.'s (1982) findings also suggest the problem is not limited to inner city populations or to a particular socio-economic group, but also can occur among children in rural settings who live "down wind" from cities and thus are exposed to fallout that contains lead.

**Cadmium**

In contrast to lead there is limited clinical evidence suggesting that cadmium poisoning is a problem among infants of the United States. Environmental sources of cadmium include dust, paint, newsprint, cigarette smoke and objects that infants may mouth. Under usual circumstances, diet appears to be the most important source of cadmium for infants. Even small concentrations in food are potentially important because of the large amounts of food consumed by infants relative to their body size. Food and Drug Administration surveys indicate that dietary cadmium of U.S. infants is about 4-6 μg/day. By two years of age the level is increased to about 9-10 μg/day (Mahaffey, 1983). According to Alexander et al. (1974), infants absorb up to 55 percent of ingested cadmium as compared to adults who absorb less than 10 percent. Of the cadmium absorbed most is accumulated in the kidneys and liver with as much as a 200 percent increase in concentration during the first three years of life (Henke et al., 1970). In contrast to other tissues, cadmium accumulation in the brain is small.

Amounts of cadmium in milk are very low (0.005 ppm average in dairy products) (Mahaffey et al., 1975). Introduction of other foods such as cereals (0.028 ppm cadmium) and fruits (0.042 ppm cadmium) as is common practice at 3-6 months of life substantially increases the infants dietary cadmium relative to amounts that would be consumed if the infant were fed only human milk or a milk based formula. Other potentially important food sources of cadmium are leafy vegetables (0.051 ppm), potatoes (0.046 ppm), oils and fat (0.27 ppm), root vegetables (0.021 ppm) and garden fruits (0.019 ppm).
Observations in experimental animals cited previously in studies of biochemical effects of cadmium on activity of certain enzymes, its binding to certain amino acids such as histidine, and to DNA, and its adverse effects on oxidative phosphorylation cytochrome P450 protein synthesis and cell replication suggest that even small amounts of cadmium accumulation are undesirable (Jacobson and Turner, 1980).

Mercury

Significant exposure of the human infant to mercury compounds other than methylmercury is often presumed to be rare, but there have been important exceptions.

Acrodynia (painful extremities), also known as pink disease (red hands and feet), is now a very rare disorder, although thousands of infants were afflicted during earlier decades of this century, apparently from exposure to mercuric chloride "teething powders", mercuric oxide ointments for impetigo or mercurials administered as vermifuges (Cheek, 1972). Though hundreds of thousands of infants were repeatedly exposed, only a small fraction developed the disease. Following the nearly complete cessation of use of these medications during the last two decades, acrodynia has become an increasingly rare clinical observation.

Recently in Argentina, several thousand infants were exposed to phenylmercury-contaminated diapers (EHSC, 1982). The diaper contamination was a consequence of use of a phenylmercury fungicide in a large urban diaper washing facility. A few cases of acrodynia were observed, but clinical effects seemed to be surprisingly mild given the mercury urine levels found in exposed infants. The question of long-term adverse effects is being studied. Further exposure has been prevented by banning the use of mercury fungicides.

Significant exposure of infants to mercury vapor is always a potential hazard if liquid mercury is released in households, especially if it is trapped in rugs or carpeting or is taken up and aerosolized and vaporized through vacuum cleaners. Poisoning of a family following exposure in the home to mercury vapor generated by heating liquid mercury has also been reported (EHSC, 1978). Such exposures, except possibly for some dental offices is presumably rare.

Exposure of neonates in closed (nursery) incubators to mercury vapor generated from broken liquid mercury thermometers and hemostats has been of recent concern (Waffarn and Hodgman, 1979).

Methylmercury is exceptional among mercury compounds in that it is a normal constituent of foods, especially fish and fish products
(WHO, 1976). Methylmercury body burden is the result of degree and duration of exposure, rate and extent of absorption, and rate of elimination. It has been well documented that ingested methylmercury is nearly completely absorbed at all ages.

Using a mouse model, Doherty et al. (1973) observed that compared to adults, suckling mice excrete minimal amounts of their body burdens of methylmercury until weaned. If these findings can be applied to human infants, risks from methylmercury accumulated in utero, or by suckling or other routes postnatally, may be greater than expected from the assumption that early postnatal excretion rates are comparable to those of adults.

As noted previously, experimental studies in animals indicate that elimination of methylmercury from the body is sharply accelerated after weaning. The mechanism may involve changes in biliary excretion and markedly increased demethylation by intestinal bacteria.

The rapidly developing infant is protected to some extent by "growth dilution" i.e. distribution of body content of methylmercury into a rapidly increasing total body mass due to growth. Nevertheless, since cumulative methylmercury body burden is directly related to elimination half-times at different life cycle stages, developmental changes in mercury excretion must be considered in estimating hazards to human health from dietary intake of methylmercury.

In 1971-72 in Iraq, a large outbreak of methylmercury poisoning occurred from ingestion of bread made from seed wheat contaminated with a methylmercury fungicide. Early in the outbreak it was found that amounts of mercury in mothers' milk correlated closely with amounts of mercury in blood (Bakir et al., 1973). It was later shown that infants not exposed prenatally could accumulate a significant amount of mercury in blood (some as high as 1000 ng/ml) when suckled by mothers who consumed methylmercury-contaminated bread after delivery (Amin-Zaki et al., 1974). These infant blood mercury levels were well above the minimum toxic blood levels for adults. As shown in Figure 1, the suckled infant's blood mercury concentration remained higher than the pair mother's blood level during a number of months of breast feeding, reflecting continued methylmercury intake by suckling and perhaps reduced mercury excretion in the infant compared to the mother. In Iraq, maternal milk averaged 8.6 percent of the simultaneous mothers' blood mercury levels, but the relationship was non-linear at blood mercury levels below 50 ng/ml (Amin-Zaki et al., 1976).

Certain subpopulations with very high dietary methylmercury intake may be at special risk. Wheatley (1979) reported elevated blood mercury levels in Eskimo populations in Northern Quebec who
Figure 1 Concentration of total mercury in 1-cm segments of sample of mother's hair, whole blood and milk, and baby's blood (postnatal exposure). Concentrations in milk and blood are plotted according to dates of collection.

have large dietary intakes of seal liver. In one village of 150 families, 50 individuals were found to have blood mercury concentrations greater than 100 ng/ml (normal range, 5-15 ng/ml). Eleven females of child-bearing age had blood mercury levels between 100 and 200 ng/ml. A recent Canadian report describes probable neurobehavioral effects in children born and suckled by Indian mothers with high fresh water fish intake (McGill Report, 1980). The fish were taken from lakes with no known industrial mercury contamination. Hair mercury levels of 10-30 ng/ml (equivalent to blood levels of 30-100 ng/ml) were reported to be associated with probable adverse effects in offspring.

The Iraqi experience documents that infants exposed only by suckling milk of mothers heavily exposed to methylmercury through dietary intake can ingest and absorb enough mercury to produce
significant adverse neurobehavioral effects (Amin-Zaki et al., 1980). This degree of maternal exposure is unusual and would not be expected to result from dietary intake of fish from non-industrially-contaminated lakes or oceans.

It has been established that the developing fetal and neonatal central nervous system is the critical human organ system for methylmercury toxicity. Prenatal exposure of the developing fetus to methylmercury from dietary fish intake remains the most significant potential hazard relevant to populations who consume very large quantities of fish. Safe levels of dietary methylmercury intake for pregnant women continue to be evaluated and definitive recommendations are not yet determined. It has become evident from human and animal studies that for a small segment of certain populations exposed to methylmercury through heavy dietary fish intake, there is a potential hazard for adverse neurobehavioral effects on the developing fetus and infant mainly through transplacental exposure but possible augmented by postnatal intake from nursing.

CONCLUSIONS - POSTNATAL METABOLISM AND EFFECTS OF TOXIC ELEMENTS

1. Most of the information on early postnatal metabolism and toxic effects of metals comes from studies of experimental animals. Information from such studies must be extrapolated to humans with caution because of differences in metabolism and rates of maturation between species.

2. The long-term functional effects of "low dose" exposures to toxic elements during infancy are not well understood in either experimental animals or humans. Emerging data on humans suggests that previously unsuspected, cryptic effects can occur that have undesirable implications for health and performance.

3. The intake of toxic elements on a per kilogram basis in infants is greater than in adults. The relatively greater requirements of infants for energy, water and oxygen contribute to their greater exposure to toxic elements.

4. The absorption, distribution and excretion of toxic elements are developmentally dependent processes. In infants intestinal absorption of toxic elements is generally greater than in adults; uptake of toxic elements into soft tissues is generally greater; and excretion of toxic elements is generally less.

5. Rapidly developing organ systems appear to be particularly vulnerable to toxic elements. Thus injury to the brain during its critical postnatal period of growth and maturation can result in poorly reversible functional sequelae.
6. From studies of rodents, a variety of dietary factors, and nutritional states appear to influence the absorption of metals and susceptibility of animals to metal toxicity. While these relationships are not so well defined in humans, observations on interactions that influence essential trace element nutriment in man suggest that the findings in animals on toxic element bioavailability are probably applicable to humans.

7. In rodents, maternal absorption of certain toxic elements is increased during lactation. These elements are subsequently transferred in milk to pups. The amount of transfer differs among the elements. It is presumed that similar phenomena occur in humans.

8. Exposure of human infants to toxic elements occurs not only from air, food and water, but from dirt, dust and fomites that are contaminated with these elements largely as a result of human activity.

RECOMMENDATIONS

1. Pharmacokinetic data are needed to accurately define the relation between dose and effect in infants.

2. Dose cannot be quantitatively extrapolated between species. Therefore data are needed on humans.

3. Research should focus on functional endpoints that reflect damage to organ systems.

4. Multigenerational studies at "low levels" of exposure are needed to ascertain if functional deficits occur.

5. Interactions of toxic elements with nutrients and non nutrients that influence absorption, excretion and the effects of toxic elements on homeostasis, need further definition.

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