

Nutrient-Toxicant Interactions: Susceptible Populations

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Nutritional status can substantially modify the toxicity of environmental pollutants. Investigations with experimental animals and epidemiological observations on humans have established the role of nutrition in altering susceptibility to a variety of pollutants including pesticides and heavy metals. The degree of nutritional deficiency that alters susceptibility need not be severe. Frequently only biochemical indications of nutritional deficiency can be associated with changes in the dose-response of an animal or person to a toxic compound.

Introduction

The importance of nutrition on susceptibility to the development of various diseases or on their progress is becoming better understood for both infectious and chemically-induced diseases. Although nutrition is not the primary causative factor, poor nutritional status can greatly increase the chances that an individual will contract the disease and can affect the severity of the outcome. Tuberculosis and measles are two well known examples of the role of nutrition in influencing the course of infectious disease in humans. The role of nutritional status on the effects of disease produced by chemical contamination of the environment has been the subject of a number of research studies in laboratory animals and a very few clinical or epidemiological investigations in human populations. For example, specific dietary deficiencies are known to increase the toxicity of a number of pesticides including carbamate carbaryl, parathion and phthalidimide captan (1), a number of heavy metals including lead (2) and cadmium (3) and atmospheric contaminants including ozone (4). In this short overview we will discuss some of the general mechanisms through which nutrient/toxicant interactions occur and some of the practical nutritional problems seen in the United States.

Basis for Nutrient/Toxicant Interactions

The physiological basis for nutritional effects on chemical toxicity varies with the type of contaminant and occurs at different stages in the development of intoxication. At the very earliest stage of intoxication, absorption of the toxicant from the gastrointestinal tract may be greatly influenced by dietary intake of nutritionally significant compounds. For example, lead (Pb) absorption is known to be altered by dietary calcium (4), phosphorus (5), iron (6), fat (7), and vitamin D (8). Dietary factors can also be important in determining the absorption of inhaled compounds that are carried on particulate matter which may be cleared from the lungs by ciliary action and swallowed with subsequent absorption from the gastrointestinal tract. Besides absorption of the toxicant, nutrients also can influence cellular toxicity by sequestering the toxic compound into body depots such as adipose tissue or bone mineral where it is relatively unavailable for adverse effects on metabolism that would occur if the compound were deposited in organs such as liver or kidney. Examples of this type of sequestering include deposition of chlorinated hydrocarbons in body adipose tissue or lead in bone mineral. Under conditions such as low calcium diets where bone formation is lower or bone is resorbed to provide calcium, Pb content of kidney and blood increase dramatically (9). Although bone Pb content is increased several fold over that observed with a nutritionally adequate diet, the Pb concentration in

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Table 1. Effect of dietary calcium deficiency on blood, kidney and femur Pb concentration in rats.^a

	Blood Pb, μg/dl	Kidney Pb, μg/g ^b	Femur Pb μg/g ^b
Normal Ca ^c	<10 ^d	2.6 ± 1.2	2.2 ± 1.0
Low Ca ^c	<10	4.4 ± 0.6	9.7 ± 2.2
Normal Ca + Pb ^f	50 ± 10	29.6 ± 7.0	202.0 ± 22.2
Low Ca + Pb	180 ± 15	691.0 ± 203.0	225.0 ± 15.2

^a Data of Mahaffey-Six and Goyer (9).

^b Wet weight.

^c 0.7% of diet.

^d Mean ± 2 S.D.

^e 0.1% of diet.

^f Pb in drinking water; 200 ppm Pb added as lead acetate.

kidney increases to a far greater extent (Table 1). Chlorinated hydrocarbons are stored primarily in adipose tissue of mammals. Heath and Vandekar (10) reported marked increases in excretion of ³⁶Cl-dieldrin in rats after short periods of starvation and inferred that this was due to increasing blood levels of this compound following mobilization of fat from depots. Keane et al. (11) observed that the size of body stores of adipose tissue in dogs directly determined the duration of exposure to dieldrin needed to produce overt poisoning. Further, force-feedings of dogs delayed or prevented dieldrin poisoning, presumably by sequestering the dieldrin in adipose tissue.

Nutrients are involved at the cellular level in metabolizing some toxic compounds to an inactive form. Changes in diet can produce alterations in the concentrations of key compounds involved in detoxification reactions. For example, cytochrome P-450 concentration in liver microsomes can be lowered by protein-deficient diets (12) as well as by specific changes in type but not amount of dietary protein (13). Concentrations of various cytochromes, including cytochrome P-450, are decreased in liver, kidney, and adrenals of guinea pigs following ascorbic acid deprivation (14). Cytochrome C and myoglobin concentrations (15, 16) but not cytochrome P-450 (17) are reduced in rats made anemic by iron-deficient diets.

Alternatively, compounds that increase in toxicity following conversion to a more toxic metabolite may show decreased toxicity in malnourished animals. For example, heptachlor, a chlorinated hydrocarbon insecticide, is converted to its more toxic metabolite heptachlor epoxide by liver microsomes. In the rat this conversion is diminished in those animals fed low protein diets. Weatherholtz et al. (18) report that the LD₅₀ for heptachlor was increased three fold in rats fed protein-deficient diets although the LD₅₀ for heptachlor epoxide remained approximately equivalent in animals pair-fed defi-

Table 2. LD₅₀ values (± SE) for heptachlor and heptachlor epoxide for rats pair-fed diets containing various amounts of protein.^a

Dietary casein, %	No. of rats	Heptachlor LD ₅₀ , mg/kg	No. of rats	Heptachlor epoxide LD ₅₀ , mg/kg
5	50	97.4 ± 1.8	48	12.7 ± 2.8
20	50	30.6 ± 1.7	50	13.0 ± 1.6
40	50	28.6 ± 1.9	48	12.8 ± 1.4

^a Data of Weatherholtz et al. (18).

cient, adequate or high levels of protein (Table 2). The varying influence of dietary protein intake on pesticide toxicity is noted by Shakman (1); the toxicity of carbamate carbaryl, parathion and phthalidimide captan markedly increased; heptachlor toxicity decreased and dimethoate toxicity was unchanged.

Nutrients and toxicants may affect the same cellular enzymes or the same organ system. For example, the enzyme δ-aminolevulinic acid dehydratase (ALAD), which is inhibited by Pb, requires zinc for activity. As shown *in vivo* using rats, Zn has an antagonistic effect on ALAD inhibition produced by Pb (4). *In vitro* Pb inhibits ALAD activity over a range of Pb concentrations. Addition of Zn to incubation media containing Pb activated the enzyme; the degree of activation was proportional to Zn concentration above a threshold Zn concentration (19). Cellular synthesis of protein is inhibited by Pb and a portion of this inhibition can be overcome by adding higher concentrations of Fe to the incubation media (20).

Nutrients and toxicants frequently affect the same organ systems or parameters of toxicity although affecting different enzymes or different steps in biochemical syntheses. In the hematopoietic system, for example, an anemia occurs with deficiencies of cobalt, copper, iron, and fluorine as well as with toxicities of cadmium, lead, manganese, molybdenum, selenium, and zinc (21). Development of anemia due to poisoning can be shown to be dependent upon the level of the nutrients. In cattle, development of molybdenum toxicity is delayed until tissue stores of copper are depleted and molybdenum intoxication can be prevented by copper therapy (21). The anemia of manganese toxicity is associated with low iron levels in serum, liver, kidney and spleen and may be overcome by increasing dietary iron. Anemia due to cadmium toxicity is accompanied by low concentrations of iron in plasma and liver; improvement in hematopoiesis with increasing content of ascorbic acid in the diet was associated with increased liver iron concentration (3). Based on these data it appears that a primary effect of cadmium under conditions of the study was production of iron-deficiency anemia (3).

More complicated parameters of toxicity such as behavior also can be affected by both nutritional deficiency and exposure to toxic substances. In experimental animals, behavioral changes attributed to specific toxicity of a compound may be due to relatively nonspecific effects such as growth inhibition or voluntary reduction of food intake by the animals. Under some circumstances, behavioral deficits attributed to the toxic substances become much less reproducible when the dietary concentration of the toxic compound is lowered to a level that permits normal food consumption and/or growth. Examples of the importance of reduced food intake and impaired growth as factors in Pb-related hyperactivity in rodents are described by Maker et al. (22) and Hastings et al. (23). Clinically behavioral deficits, specifically hyperkinesis, have been associated with both iron deficiency (24) and lead intoxication (25) in children. Because Fe deficiency is common in the population of children having unusually high exposure to Pb, behavioral changes thought to be due to Pb may be due partly to Fe deficiency; this is the subject of current clinical investigation.

Severity of Nutritional Deficiency

Nutritional status and dietary changes can be important factors either in susceptibility to toxicants or in treatment of intoxication. Although diet may be a useful adjunct to therapy, methods of treatment for severe intoxication most frequently involve use of various pharmaceuticals. Accordingly, we will emphasize the preventive role of nutrition.

The degree and duration of low nutrient intake required to increase susceptibility to toxicity range from simply short-term fasting to prolonged deprivation permitting development of overt clinical stigmata of nutritional deficiency diseases. For example, Rabinowitz et al. (26) have shown that in humans absorption of Pb from the gastrointestinal tract increased from 6 to 14% when Pb was ingested with meals to 70% when Pb was ingested between meals. Similar effects of fasting resulting in increased Pb absorption are observed in experimental animals (27, 28). Practically, there are several situations in which humans may greatly modify their patterns of food intake. An individual worker who frequently rotates shifts may not have regular meal hours and may tend not to eat very much during his work period. Because of various circumstances, workers may not bring home-packed food or have access to industrial food service or vending machines that provide nutritionally balanced food. More severe food restriction can be observed among people wishing to reduce their body weight.

Many dieters believe it is easier not to consume food when they are away from their homes and practice their greatest food restrictions during work hours. An additional effect of food restriction is that homeostatic mechanisms of the body will mobilize adipose tissue to provide calories and mobilize bone mineral to maintain serum and soft tissue Ca concentrations. Because these are storage sites for some pesticides and heavy metals, pesticides and heavy metals will be released with the energy-providing compounds and Ca.

Long-term food restriction or an imbalanced diet can result in multiple or specific nutritional deficiencies. Certainly cases of the classic protein and vitamin deficiency diseases such as pellagra or scurvy are observed occasionally in the United States, although their prevalence is very low. Nutrients most frequently consumed in inadequate quantities are discussed in more detail below. However, studies with experimental animals and limited observations on humans show that these severe degrees of nutritional deprivation are not needed to increase susceptibility to toxic substances. The influence of Fe deficiency on susceptibility to Pb intoxication provides an example. In severe Fe deficiency, a marked hypochromic, microcytic anemia is produced, and if hemoglobin concentration is reduced to approximately 6 g/100 ml of whole blood or less, the cardiovascular system is severely taxed to provide adequate quantities of oxygen to tissues. However, alterations in heme synthesis can be observed prior to the development of anemia by measurement of compounds such as free erythrocyte protoporphyrin. Reductions in tissue stores of Fe as shown by serum ferritin concentration occur before increases in erythrocyte protoporphyrin are observed. Thus, severe anemia is a very late stage of Fe deficiency. Experiments with rats indicate that among groups of animals ingesting equivalent quantities of Pb, animals which are fed a low Fe diet but are not anemic will have greater tissue burdens of Pb than animals fed a diet adequate in Fe (29). An additional example of effects on a toxicant produced by dietary changes at nondeficient levels occurs with Pb and Ca. Balance studies on Pb absorption by human infants indicate that as dietary Ca decreased, Pb absorption increased, although all diets studied were nutritionally adequate in Ca by current standards for dietary requirements of human infants and children (30).

Nutritional Status in the United States Population

Although the prevalence of classic diseases of protein and vitamin deficiencies is low in the United

States, ingestion of diets containing less than adequate amounts of nutrients is not infrequent among young children, pregnant or lactating women and elderly individuals. Circumstances associated with inadequate dietary intake usually are combinations resulting either from high nutrient requirements relative to total caloric requirement, as for pregnant or lactating women and elderly persons, or from particular patterns of food consumption as with young children who reject meat or with various racial groups which limit consumption of milk and other dairy products. In all these groups, low income greatly increases the likelihood of inadequate nutritional intake. One result of limited purchasing ability is often a reduction in the types and variety of foods purchased, so that achievement of a nutritionally balanced diet is more difficult.

The nutrients most commonly found to be ingested in less than recommended quantities in the United States are iron, calcium, zinc, ascorbic acid, folic acid and vitamin A. Specific nutrients in shortest supply vary with age, sex, socioeconomic status and geographic location of the population surveyed. A number of excellent reviews have been published on the methodology for carrying out evaluation of nutritional status and of dietary intake of nutrients.

Nutritional Status of Infants and Children

Within the past decade three major surveys of the nutritional status of infants and children have been conducted in the United States; populations evaluated and characteristics are shown in Table 3. A number of regional and local studies of nutritional status in children have also been reported and are summarized in a general review of this topic by Owen and Lippman (31) from which Table 4 is derived. This review provides detailed information on nutritional status of children. Discussion is limited to dietary and biochemical data because severe de-

ficiencies, i.e., those producing physical stigmata, are seldom required for significant nutrient/toxicant interactions.

The nutrient most commonly limiting in the diets of infants and young children is iron. Iron deficiency and iron-deficiency anemia are the most common nutritional problems of infants and young children, especially those from low income groups. The highest prevalence of iron deficiency occurs in children under 5 years of age, particularly among children under 2. Quality and quantity of protein intakes for children are usually adequate. Overall, children tend to have adequate serum vitamin A levels, although in all three national surveys black children had consistently lower mean or median plasma vitamin A levels than did white children (31). Spanish-American children in south-central and southwestern states had a greater prevalence of unacceptably low plasma vitamin A concentrations than either whites or blacks. The percentage of children with unacceptably low plasma retinol (vitamin A) concentrations was 1.5, 10 and 30 to 50% for white, black and Spanish-American children, respectively (31). In all three national surveys, approximately one-third of lower income children reported dietary intakes of ascorbic acid less than one-half of Recommended Dietary Allowances for this vitamin. Although median calcium intakes were adequate, between 20 and 30% of black children and 10 to 15% of white children consumed diets containing less than 400 mg of calcium per day, which is about half the Recommended Dietary Allowances for these age groups. Local surveys indicate that less than adequate zinc intakes and biochemical changes indicative of zinc deficiency occur in children from low income groups (32).

Nutritional Status of Adults

Both the Ten-State Nutrition Survey (1968-1970) and the First Health and Nutrition Examination

Table 3. National surveys of nutritional status in infants and children.

Survey	Dates	Population
Preschool Nutrition Survey	1968-1970	Cross-sectional; 3400 children between 1 and 6 years of age; 36 states and District of Columbia
10 State Nutrition Survey	1968-1970	10 states; heavy sampling of poor and near poor income groups; 3700 children less than 6 years of age.
Health Assessment and Nutrition Evaluation Survey I	1971-1974	Sample population selected as representative of United States as a whole; 3500 children between 0 and 18 years in 1971-1972 half sample

Table 4. Selected regional and local studies of nutritional status of children."

Sample	Location	Findings and comments
170 Mexican-American, 0-66 months of age	San Ysidro, California	Some children with low intakes of energy, vitamin C, niacin and iron; vitamin A intakes good and plasma vitamin A concentrations normal; Iron deficiency prevalent Some with low plasma vitamin C
41 Black inner city preschoolers	Philadelphia	Comparable intakes of iron by day-care (0.7 mg/kg/day) and by non-day care (0.5 mg/kg/day) Anemia more prevalent among non-day care than among day-care children
50 Blacks of low income	Nashville	Approximately 10% of children were anemic and 15% had low plasma vitamin A
281 Mixed racial 2-3 years of age	Honolulu	Intakes of calcium, vitamin A, ascorbic acid and riboflavin low for some groups (inversely related to income) Anemia noted in 5-10%
168 Mexican-American, 6-9 years of age	Coachella Valley, California	52% had hemoglobin <10 g/dl
178 Black preschoolers	South Carolina	25% anemia (hemoglobin < 10 g/dl) 50% iron deficient (serum iron < 40 µg/dl)
115 Whites 2-6 years of age	Minnesota	Dietary survey only Some low intakes of iron and vitamin C
109 Black and whites, 4 months-5 years of age	Michigan	10% with severe iron-deficiency anemia; 13% mild iron-deficiency anemia; 23% with nonanemic iron deficiency
250 Mexican-American and whites, 0-17 years of age	Denver	Evidence of low zinc stores among 45% of children under 4 years of age (based on hair zinc determinations)
843 Eskimos, 2-6 years of age	Alaska	Low levels of intake of calories, calcium, and vitamin C among some children Protein intakes generally high
70 Whites, 0-18 months of age	Seattle	More than half of the nonanemic (hemoglobin > 11 g/dl) infants studied had iron deficiency (transferrin saturation < 15%)
36 Blacks 4-10 months of age	South Carolina	Approximately 10% of infants had low levels of albumin and plasma vitamin C
60 Families	Iowa and North Carolina	Dietary survey only Adequate intake of protein, calcium, vitamins C, B ₁ , and B ₂ as well as iron
113 Indian families	Fort Belknap, Montana	Some children with low intakes of vitamins A and C as well as of calcium Approximately one-third of children had low levels of hemoglobin, plasma vitamin A and erythrocyte riboflavin
40 Whites	Nebraska	Urinary thiamin and riboflavin excretion varied with income Approximately 10% of children had low levels of hemoglobin

Table 4 (Continued).

Sample	Location	Findings and comments
160 Mexican-American, 0-9 years of age	Lower Rio Grande Valley, Texas	Clinical signs of vitamin A and vitamin D deficiencies One-third of children with low level of vitamin A in plasma 10% anemic
100 Low income, 0-14 years of age	New York City	No clinical signs of riboflavin deficiency, although 10% had biochemical evidence of deficiency
386 Whites, 3-10 years of age	Tennessee	Many had low intakes of iron (6-18%), vitamin C (20%), energy (30%), and vitamin A (50%).

" Data of Owens and Lippman (31).

Survey, 1971-1972 (HANES I) indicate small but consistent clinical evidence of nutrient deficiencies (33). The most prevalent finding in the Ten-State Nutrition Survey was that of anemia. It is generally agreed among nutritionists that most anemia observed in adults is caused by iron deficiency although a few hematologists refute this assumption. Nevertheless, as many as one-fifth of the women of child-bearing age have hemoglobin levels considered to be low. The highest incidence was found among black women, followed by Spanish-American women and then white women. Other groups of women and most adult men had only a low level of anemia.

Deficiency symptoms for vitamin C were found in all adult populations especially over 60 years of age. Black populations had a higher prevalence than either Spanish-Americans or whites for ages below 60 years, but differences were not significant above age 60, where all groups were around 9% of the population. According to the HANES I survey, a low rate of vitamin A deficiency (less than 2%) exists for the entire population of adults except for blacks over 60 years of age. In this group, the deficiency rate was nearly 9%. The HANES I study also shows that niacin deficiency is still evident, primarily among black populations; however, the symptoms were those of only marginal deficiencies. Similarly, thiamine deficiencies were frequently found among black populations but again the symptoms were those indicating only a marginal deficiency.

Many older populations showed signs of deficiencies which occurred during infancy and childhood but are likely no longer a problem. Vitamin D was the most prominent example where bowlegs and knock-knees were frequently encountered. Evidence of calcium-phosphorus imbalance was prevalent for all adult populations; however, the incidence for black women were considerably higher than other adult groups. Finally, some evidence of protein deficiency were also found for blacks among

adult populations studied in HANES I. The largest percentage—approximately 80%—was found in the 45-59 age group.

Clinical studies for deficiencies of many nutrients have simply not been done. Some inferences can be drawn from dietary information; however, this does not prove the existence of deficiencies. In general, where data exist both from clinical examinations and nutrient intake there was excellent agreement. On the basis of such dietary intake data it would be logical to assume that marginal deficiencies for copper, magnesium, zinc, and manganese exist.

Summary

The interrelations between nutrients and toxicants are complex; however, current knowledge permits several generalizations. First, simply feeding higher levels of nutritionally significant compounds does not provide protection against toxic compounds. In addition to the danger of producing toxicity from the nutrient itself, the protective effects against toxicity produced by increasing dietary intake of a nutrient from deficient to adequate levels may be reversed or no further protection derived when still higher levels of the nutrient are fed. For some toxicants, feeding a higher level of the nutrient may merely facilitate conversion of the toxicant to a metabolically more active form. Second, understanding the physiological basis of nutrient/toxicant interactions is a key to identifying practical uses of nutrition in assessing population groups at risk and devising dietary strategies useful for minimizing the adverse effects of exposure to environmental toxicants. Third, it must be recognized that, although diets and environments of experimental animals can be manipulated to create deficiencies of a number of nutrients, the likelihood of some deficiencies occurring spontaneously in a human population may be quite small, perhaps even remote.

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