CRITERIA FOR ADEQUACY AND SAFETY OF TRACE ELEMENTS IN ANIMAL NUTRITION

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Much of our present knowledge of trace element nutrition is derived from field observations in farm animals (Underwood, 1971). Nutritional imbalances of cobalt, copper, molybdenum, manganese, zinc, and selenium were well identified in these species, long before the recognition of such nutritional problems in man. This time interval may be related, among other factors, to the fact that the farm animal is exposed much more than man, to the influences of the geochemical environment. In fact, the farm animal serves as an effective buffer in the food chain, by reducing the impact of environmental factors on the consumer (Subcommittee on GERHD, 1974).

On the other hand, animals and man have in common the changing background of nutritional practices and preferences. The trend toward rations with a high degree of caloric density, containing relatively pure substances, is equally prevalent in animal and human nutrition, as is the increasing use of new, non-conventional feedstuffs and foods. Furthermore, modern production practices have resulted in a marked reduction of the animals' exposure to contamination from soil and dirt, a development paralleled by great advances in the hygiene of raising children. Obviously, the impact on trace element balance and on health of these new practices is not yet fully understood, but it can be stated with some confidence that in the United States the main concern of nutritionists is not with pronounced excesses and deficiencies, but with marginal imbalances. These do not generally result in clinical disorders, but in slight deviations of biological function and tissue concentrations; therefore, they present a difficult problem of diagnosis and analysis both in animal and human nutrition (Mertz, 1975b).

Criteria for Animals Vs Criteria for Man. Although in a strict sense, the criteria for adequacy and safety of trace element intake should be the same for farm animals and human populations, and recommendations of safe intakes should differ only quantitatively, practical considerations of animal production call for criteria that are basically different. This was emphasized by Mills (1974) who contrasted the relatively short life span of most farm animals with the long life span of man and who suggested that less vigorously defined criteria may be acceptable for animal nutrition than those applied to human nutrition. This suggestion is logical, but it must be modified to some extent when animal products are used as foods for man. In this case, restrictions are added to the relaxed criteria.

Whereas the criteria for adequacy and safety of trace element intakes of man have to permit the maintenance of optimal health throughout a lifetime and become extremely stringent in the light of the many existing chronic degenerative diseases of middle and old age, the criteria for animals are concerned with optimal productivity during a measured life span only. Thus, for animals, those intakes of trace elements can be considered adequate and safe which permit the fastest growth rate with the best feed efficiency between birth and the age of slaughter. Under most conditions these criteria are compatible with optimal health of the animal, but this is not always the case. For example, the demands of the European consumer for a pale color of veal have resulted in practices for iron nutrition of calves which result in a pronounced anemia, carefully managed to decrease the color of the meat but not to interfere


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markedly with growth rates (Kirchgessner et al., 1974). These criteria which call for the induction of a deficiency disease would be totally unacceptable in human nutrition, but they are appropriate and widely used under these special circumstances.

Although, from this point of view, the criteria for adequacy and safety of trace elements intakes of animals are less stringent than those for man, the fact that animal products serve as human foods necessitates certain restrictions. The use of arsenicals, beneficial to the performance of poultry has been suspect for some time because of the fear of imposing an undesirable arsenic burden on man. Supplementing selenium deficient rations with selenium is still prohibited for ruminant animals in the U.S.A. because of the fear of increasing selenium exposure in man. The inclusion of high levels of copper in swine rations, clearly beneficial to the performance of the animals, is not yet permitted in the United States because of the possibility of increasing the exposure of man to this element. While the merits and dangers of these practices have to be assessed individually, the existing controversies emphasize the restrictions that consideration for human safety impose on the criteria for adequacy and safety in animals.

The Optimal Range Concept of Trace Element Intake. The old concept of "beneficial" vs "harmful" elements is unscientific and is rapidly becoming replaced by the understanding that beneficial or detrimental effects are a function of concentration ranges but not of the element itself. Traditionally, concern about "toxic" and "beneficial" elements originated in geographic areas where gross excesses or deficiencies existed. It has become clear in the past 22 years, however, that elements previously known only for their toxicity have essential functions in animals and man. This is true for molybdenum, selenium, chromium, fluorine (Underwood, 1971) and, on the basis of recent experiments, perhaps even lead (Schwarz, 1974) and arsenic (Nielsen et al., 1975). The modern concept of the biological response to trace elements in the environment was formulated by Bertrand (1912) and more recently modified by Venchikov (1960). It recognizes that with a deficiency of an essential element a specific biological function is minimal, and that with increasing concentrations of the element the function will increase until a plateau is reached. Depending on the regulatory capacity of the system under study, the plateau may vary in width, but with excessive concentrations, capable of overcoming these regulatory defense mechanisms, toxicity will result and the biological function will decline again. To establish criteria for adequacy and safety of trace elements ultimately means to define a range of intakes which maintains specific functions at or near their optimum. The logical advantages of the optimal range concept, in the light of recent advances of trace element research, are obvious. It is compatible with the possibility that essential functions can be proved for additional trace elements in the future, and it alerts the researcher to the detrimental effects of overexposures, even for essential elements. It must be realized that a range of safe intakes is not absolute because it depends on interaction of trace elements with each other and with other dietary ingredients; these interactions are more important in the farm animal than they are in man (Subcommittee on GERHD, 1974). The influence of molybdenum in the environment on copper requirements is an example of eminent practical importance in animal nutrition (Proc. of Internat'l Symp. on Molybdenum in the Environment); the complicated interactions between selenium and cadmium and mercury are still of academic interest but may become practically important in the future (Parizek et al., 1974).

Criteria for Adequacy. Nutrition research in the past has resulted in a significant reduction of severe, easily recognizable deficiency diseases in most areas. Thus, the main remaining concern is the detection and prevention of marginal deficiency diseases. This task places great demands on the nutritionist and on the analytical chemist, because deviations from normal functions or tissue concentrations can be expected to be small (Mertz, 1975b). The detection of marginal deficiencies is possible only when the criteria for normal function and performance have been established and agreed upon. It is important to realize that an established "normal" value need not coincide with an average. The norm is an ideal value; the average is an expression of how much of the ideal performance actually has been attained. As discussed above, the criteria by which such norms can be established in animal nutrition are more varied and less stringent than those in human nutrition. In the latter area, longevity is as important as the initial growth rate, mental and emotional development, as important as the physical
development; and the absence of debilitating disease during old age as important as good health during the first part of a lifetime. On the other hand, the criteria for adequacy of trace element intake in animals are determined by the purpose for which the animal is raised. Growth rate, feed efficiency and egg or milk production are valid criteria to assess the performance of an animal.

In order to establish normal values of growth or productivity and correlate these with a sufficient intake of a given trace element the concept of saturation is helpful in both animal and human nutrition. Most, but not all trace element-dependent biological functions reach a plateau with increasing levels of supplementation. This plateau is an expression of the efficiency of the organism's regulatory mechanisms to maintain near optimal trace element concentrations in the tissue, by regulating absorption, excretion, or both. When excessive exposure to trace elements overcomes these defense mechanisms, tissue levels may then further increase, and biological function may decline to very low levels. The characterization of this plateau of biological function and its correlation with a plateau of corresponding tissue trace element concentrations offers a useful tool with which to establish adequate and safe trace element intakes. However, this correlation has been obtained only for a few trace elements, and the choice of a biological function as a measure of adequacy of trace element supplementation is difficult. This can be illustrated by discussing three examples. Hemoglobin concentration, although influenced by many additional nutrients, is an acceptable indicator of iron nutriture. It represents a function which can be saturated and which can therefore be used to establish norms for iron intake. A "normal" hemoglobin level is one that cannot be further increased by additional iron intake, and a "subnormal" level is one that increases with additional iron intake. From this a "normal" intake can be established for any one animal or human subject, i.e., one that in a well nourished subject is able to maintain optimal function. This level of intake can be identical with the average, but for iron intake of U.S. women it is vastly different (Recommended Dietary Allowances, 1974).

The second example represents a more complicated picture. For selenium levels in swine, the existence of a plateau has been shown to exist in several tissues; it is maintained over a range of dietary intakes that varies almost 10-fold (Groce, 1972). However, a biological function for which selenium is specific, glutathione peroxidase activity in red blood cells, is known to reach a plateau of activity only with dietary intakes and tissue concentrations which are detrimental to growth rates (Hoekstra, 1974). These findings would eliminate a meaningful correlation between a biological function and tissue selenium concentrations; they would also challenge the use of glutathione peroxidase as a meaningful indicator of selenium status. However, a good correlation of this enzyme activity with selenium concentrations and selenium nutriture may exist in certain tissues not yet investigated.

The third example, xanthine oxidase activity as an expression of molybdenum nutrition in man is a function for which no saturation has yet been shown. The activity of this enzyme increases over wide ranges of dietary intakes, therefore, this system cannot be used to assess adequacy or even safety of molybdenum intakes, and other criteria (e.g., gout or undesirable high uric acid concentrations) have to be used (Mertz, 1975a).

The combination of the assessment of a biological function with the analysis of tissue concentrations of a trace element, as discussed above, is the most desirable way to determine adequacy for trace element nutrition. It is realized that not many functions are known that correlate well with the overall performance of the animal and which can be useful indices of trace element status. Where such a combination of assessments is not possible, some helpful information can be obtained from trace element analyses in tissues alone. This is possible in all those cases where tissue concentrations can be titrated against increasing amounts of trace element intakes. For this approach, the choice of a "meaningful" tissue is essential, one that adequately reflects the performance criteria of the animal species under study. Equally important are specificity, precision, and sensitivity of the analytical methods applied. Where most of the well known trace elements can be analyzed with some confidence, very considerable difficulties exist in the analysis for the "newer" trace elements. These aspects have been discussed in detail (Mertz, 1975b).

Complications in the Determination of Adequate Trace Element Nutrition. It is difficult to arrive at recommendations for an adequate and safe intake of trace elements in man, even
though human populations are less directly influenced than farm animals by the geochemical environment and their dietary intakes show relatively little variation with season or location. The recent assessment of iron (Joint FAO/WHO Expert Group, 1970) and zinc requirements of man by WHO expert committees (1973) and of calcium (Recommended Dietary Allowances, 1974) requirement by the Food and Nutrition Board are good examples for the problems involved in determining one recommended intake. Three recommendations are given for zinc and iron, depending on the composition of the diet consumed. Similarly, the recommended allowance for calcium is made dependent on the protein intake. These examples demonstrate the great difficulties in arriving at estimates for trace element requirements of animals, taking into account the much greater variability in these species of the dietary background. The many interactions of trace elements that are known or suspected to occur would require establishment of a series of "adequate" levels of intake, depending on levels of exposure to other elements that interact with the element in question and on other influences from diet and environment which are poorly understood. It has been emphasized recently that it is impossible to establish universally valid recommended intakes for copper or for molybdenum; each recommended value must be adjusted to the presence of the other in diet and environment (Proc. of Internation'l Symp. on Molybdenum in the Environment). In this connection, it is interesting to note the trend in experimental nutrition toward the use of ratios between trace element concentrations in relation to health, rather than absolute tissue concentrations. Notable examples are cadmium to zinc ratios in kidney in relation to hypertension (Schroeder and Balassa, 1961), and the copper to zinc ratios in the diet in its postulated relation to hypercholesteremia and cardiovascular disease (Klevay, 1975). However, it must be realized that wide differences in the apparent trace element requirement exist that cannot yet be explained on the basis of known interactions. An example is the well demonstrated occurrence of zinc deficiency in cattle in Greece, in spite of a zinc concentration in forage of 40 µg/g (Spais and Papasteriadis, 1974). In Australia, on the other hand, where zinc concentrations are considerably lower, zinc deficiency is rare. A similar situation in human nutrition is the occurrence of pronounced zinc deficiency in population groups of Iran where zinc intakes are much in excess of the average U.S. consumption.

It has been suggested that certain feed ingredients, perhaps rapeseed meal and cabbage in the former example, and phytate or dietary fiber in the latter may decrease the availability of zinc, but much work remains to be done to elucidate the principles that govern the availability of zinc and many other elements as well.

Criteria for Safety. The criteria for a safe intake of trace elements of animals are determined by the concern for the performance of the animal and for the safety of the product for the consumer. Theoretically, these two concerns should result in identical criteria; in practice, they have been found to differ greatly. These differences, which have been of great consequence to agriculture, have been caused by misinterpretation of existing knowledge in some cases. In others, they represent valid concern for human health and a justifiable, cautious approach in the absence of sufficient data on which a "safe" intake of man could be established. An example of this dichotomy is selenium nutrition of animals and man. Prior to its identification as an essential trace element, selenium had been known as a toxic substance and this aspect prevailed for a long time among the agencies regulating food additives. Although it was quickly established that selenium is essential for health and life of many species and that areas of selenium deficiency exist within the United States and abroad, the use of selenium supplements to animal feeds was not allowed for a long time. The concern was not so much for the health of the animal, since safe levels could be readily established; it was for the health of the consumer. However, this concern was based on faulty scientific premises. The then predominant concern with toxic effects of selenium is being modified by the more recent knowledge of selenium deficiencies. The fear in the past of carcinogenic properties is being replaced by data suggesting a protective effect of physiologic amounts of selenium against various forms of cancer (Committee on Animal Nutrition, 1971) and the hitherto futile attempt to define adverse health effects of high environmental levels of selenium in man is complemented by an interest in the potential effects of human selenium deficiency. The discovery of protective effects of selenium against acute (Parizek et al., 1974) and chronic (Ganther et al., 1972) consequences of heavy
metal exposure also has contributed to a more balanced approach concerning the safety of selenium levels in animal feeds.

The second example, that of dietary supplementation with high levels of copper in swine is more complicated. It is true that supplementation with high levels (250 ppm) of copper in swine rations produces an improved performance of the animals, but the mechanism of this action is a matter of conjecture. The effective concentration is so much above the nutritional requirement that under these conditions copper must be considered a pharmacological agent, not an essential nutrient. In view of the many known and suspected interactions of copper with other dietary ingredients which occur even at lower concentrations, a cautious approach is clearly indicated. Even though the concentrations of copper in the muscle of the treated animals are not excessive and, by themselves, would not present a danger to human health, they cannot be considered safe until their effect on concentration and balance of all other essential trace elements have been thoroughly defined.

A highly complicated situation arises when gross imbalances of one trace element exist in the geochemical environment of an area. For example, excessive concentrations of molybdenum can induce a secondary copper deficiency in animals in spite of copper intakes adequate under normal situations. Molybdenum deficiency can be counteracted by feeding levels of copper that would be considered excessive under ordinary conditions. In this case there exists a reasonable understanding of the nutritional interaction between trace elements which can justify the supplementation of higher than ordinary amounts of copper (Proc. of Internat'l Symp. on Molybdenum in the Environment, 1977). It follows from these considerations that, just as it is difficult to determine adequate levels, it is also difficult if not impossible to define any level of a trace element as safe. The complicated and incompletely understood interactions among trace elements and the complex effects of other dietary ingredients on the biological availability of inorganic micronutrients create a wide variety of situations that affect the safety of intakes. Each of these situations must be assessed individually.

CONCLUSIONS

The criteria for adequacy and safety of trace element intakes of animals are determined by the requirement of the animal for optimal performance during its youthful life span and, equally important, by the consideration of adequacy and safety of the animal product for the ultimate consumer. Adequacy and safety of intakes for the animal itself can be determined by titrating intakes against a biologic function, specific for the element under study, if this function has some saturation characteristics. For some elements, tissue concentrations show a similar behavior; a plateau of concentrations is reached and maintained over a definite range of intake.

The concern for adequacy and safety of animal products to the human consumer has been centered in the past around the undesirable effects of potential overexposure. This concern is justifiable, but it should be counterbalanced by an equal concern for the adequacy of trace elements in animal products for the human consumer. It has been shown in the past decade that trace element deficiencies occur in the population of the United States and abroad and that the danger from suboptimal trace element nutrition may be as important as that from overexposure. Iron deficiency is widespread in women of child bearing age (U.S. Dept. Health, Education, and Welfare, 1972). Zinc deficiency has been described in children and in hospital patients (Hambidge, 1974), and chromium deficiency appears to exist, possibly related to old age (Mertz, 1974). Pronounced differences in exposure to selenium have been described, (Allaway et al., 1968) and a substantial number of “new” trace elements have been shown to have a biologically essential function in experimental animals. Although it is not yet possible to define an exact human requirement for these new trace elements, the possibility of marginal or inadequate intakes remains of concern. Because of the superior biological availability of many trace elements in animal products, their importance for human trace element nutrition cannot be overemphasized. It is for this reason that the concern for adequacy of trace element nutrition should be considered as important as that for safety.

LITERATURE CITED


