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Chromium – An essential mineral

Merlin D Lindemann [1], Jin H Cho[1], and M Q Wang[2]

[1]Department of Animal and Food Sciences, University of Kentucky, Lexington, KY 40546, USA; Tel: +1 859 257 7524.
merlin.lindemann@uky.edu
[2]Department of Animal Science, Zhejiang University, Hangzhou, China

Summary

The status of chromium (Cr) is not a new question. Cr is clearly an essential nutrient; this is a position that has been held for over three decades by individual scientists, groups of scientists, and governmental committees. The most uniform response across species with regard to Cr deficiency symptoms that are responsive to Cr supplementation are alterations in glucose metabolism with special reference to peripheral tissue sensitivity to insulin. Because the body's ability to control blood glucose is critical to many life functions, and loss of ability to adequately control blood glucose can lead to many health debilitations, a consequence of Cr supplementation can be improved health and reproductive outcomes as well as improved survival rate or life span.

Key words*: chromium, mineral, mortality.*

Status of chromium as a nutrient

Because chromium (Cr) supplementation has not been a routine practice over the last century as has supplementation of such minerals as iron, zinc, copper, and manganese, there are at times question about whether Cr is an essential mineral. This, then, raises questions about what constitutes essentiality of a nutrient. Published reports of research into the biochemical role of Cr and its essentiality in the diet began to appear in the 1950's. Much of the work was done at the United States Department of Agriculture – Agricultural Research Service (USDA-ARS) facility in Beltsville, Maryland. Further pioneering work was reported in the 1960's with great attention paid to reports demonstrating that Cr deficiency in patients receiving total parenteral nutrition could be reversed with Cr inclusion in the administered solutions. The 1970's and 1980's saw a burgeoning of Cr research in many species in relation to many physiological parameters in a variety of nutritional and/or disease contexts.

The interpretation of any reported results by nutritionists with regard to classifying the essential nutrient status of an element is guided by sets of criteria that may vary from one nutritionist to another. These sets of criteria are the framework within which individual nutritionists interpret the response of various species to constituents of their food or feed supply. Though these criteria are not rigidly defined, an excellent presentation of guidelines for determining nutritional essentiality is provided by Underwood and Mertz (31) in the introduction to a text on trace elements. The authors state that essentiality of an element "is established when a further reduction below the

range of tolerable levels, better termed "range of safe and adequate intakes," results in a consistent and reproducible impairment of a physiological function."

They further cite an author who maintains "that a trace element can be considered essential if it meets the following criteria: 1) it is present in all healthy tissue of all living things; 2) its concentration from one animal to the next is fairly constant; 3) its withdrawal from the body induces reproducibly the same physiological and structural abnormalities, regardless of the species studied; 4) its addition either reverses or prevents these abnormalities; 5) the abnormalities induced by deficiencies are always accompanied by specific biochemical changes; and 6) these biological changes can be prevented or cured when the deficiency is prevented or cured."

The closing of the introduction to this text involves a discussion of the term deficiency. A short definition is given as "a state in which the concentration of an essential nutrient at its sites of action is inadequate to maintain the nutrient-dependent function at its optimal level." This is then further expanded with an excellent description of the physiological stages of the development of a deficiency state. It is interesting that the authors use the mineral Cr to illustrate this elaboration of the phases of a nutrient deficiency.

With specific regard to the element Cr, as a result of these early reports in the 1950's and 1960's, and with the continued research reports of the 1970's and 1980's of strictly controlled research in an experimental setting with non-human species, as a result of epidemiological surveys, and as a result of clinical research with different subpopulation groups and the subsequent interpretation of these reports by nutritionists with guidelines somewhat akin to those described by Underwood and Mertz (31), the status of Cr as an essential nutrient was firmly established. A sampling of positions taken in a variety of publications regarding the status of Cr is presented here chronologically:

> "Chromium (III), or Cr in the trivalent form, is now recognized as an essential nutrient that is required for utilization of glucose in peripheral tissues, acting in conjunction with insulin. Chromium (III) is an essential element that must be administered as a highly specific organic complex (es) to be effective" (11).
>
> Cr is listed as an essential trace element. "It is now established that trivalent Cr acts as a cofactor with insulin at the cellular level, through the formation of a complex with membrane sites, insulin, and Cr" (19).
>
> "Chromium III is required for utilization of glucose in peripheral tissues, acting in conjunction with insulin. Chromium III is essential in animal nutrition" (26).
>
> "The essentiality of Cr in animal and human nutrition is now well accepted" (33).
>
> "There is no disagreement concerning the essential nature of Cr" (21).
>
> "The Food and Nutrition Board of the U.S. National Research Council suggested a range of safe and adequate intakes for Cr of 1-4 μmol/d. Studies of a World Health Organization Expert Committee and of the International Programme on Chemical Safety described trivalent Cr as an essential nutrient with typical intakes of from 1-4 μmol/d" (cited in 23).
>
> "The results of the human studies reviewed here as well as data from in vitro and animal experiments lead to three conclusions: 1) Cr deficiency results in insulin resistance. 2) Insulin resistance caused by Cr deficiency can be ameliorated by Cr supplementation. 3) Cr deficiency does occur in populations in the United States and elsewhere; it may be an important cause of insulin resistance in those populations" (23).

An appraisal of the positions of eminent, published scientists, of texts used in undergraduate and graduate nutrition training, as well as national committees formed under the auspices of the National Academy of Sciences in the United States demonstrates that the status of Cr is unequivocally held to be that of a nutrient which is essential for optimal health and well being and, thus, for length of life. The identification in the late 1990's of a low molecular weight binding protein as an apo-oligopeptide form which binds 4 chromic ions and activates the insulin receptor (6, 32) has solidified the understanding of the manner in which Cr interacts with insulin to facilitate glucose movement across cellular membranes.

Determination of a particular species need

While Cr has been established as a nutrient, the practical need of nutritional supplementation of many species for Cr has not been established. Many of the various nutritional requirement specie guidelines do not establish a requirement estimate for Cr, even though they may recognize it as having a nutritional function and/or acknowledge that it may possibly be required in certain situations (24, 25, 27, 28). With regard to both the rat and poultry, an established requirement estimate is given (24, 27, respectively).

The recent research with organic forms of Cr has generated excitement but questions remain about the frequency and magnitude of the responses observed. This is not unique to Cr; whenever a new area of discovery is encountered, it takes a period of time to determine those situations or conditions most responsive to supplementation. It is reasonable to assume that minerals not historically supplemented are either needed in less quantity, that normal feedstuffs have an adequate supply, or that body stores take longer to deplete. In these situations a young, growing animal model may not be the best research model. Better models would be those animals having specific metabolic problems most related to the aspect of metabolism affected by that nutrient or animals that were aged or older where the nutrient stores may have declined to a degree. Additionally, research with nutrients is more difficult in this regard than some other compounds such as drugs. Drugs generally have a fairly uniform effect on a population of animals; whereas nutrients have a much more varied response depending on the individual status of the animal. Consequently, the population variation associated with nutrient need requires more effort to come to firm understandings of the role and value of the respective nutrients.

Clearly, the aspect of metabolism most closely linked to Cr would be glucose metabolism. So, do swine have glucose control problems? Swine are not known to have a situation like Type I diabetes in humans, where the body does not produce insulin. If that condition ever existed, it would have eventually been removed from the swine population because those pigs would have died early in life in the absence of insulin and the associated blood glucose problems. However, swine do develop Type II diabetic-like conditions where blood glucose levels rise and where health problems related to blood glucose occur.

Research in the 1950's (4) demonstrated both that swine do vary quite markedly in their glucose kinetic capabilities and that the ability to control blood glucose levels decreases as the animal grows. Because of this inherent variation in their capacity to control blood glucose and the declining ability to control that blood glucose as the animal grows (and ages), varying percentages of a swine herd will exhibit glucose-control problems. The exact percentage of a herd that is affected will depend also on the amount of other stressors in their life that would push them toward diabetic-like conditions.

One critical stressor common to both man and pigs is pregnancy. Often women develop gestational diabetes (also referred to as pregnancy-induced diabetes). There are glucose control problems during the period of pregnancy that return to normal after the child is born. Research with women who were pregnant (20) demonstrated that hair Cr content (an indicator of body Cr status) of first-pregnancy women was about three fold that of women having other-than-the-first child; pregnancy greatly diminishes the body Cr stores. Hair Cr did increase with time between pregnancies, but at least four years had to pass to make appreciable differences. Thus, frequent pregnancies predispose a woman to Cr-related glucose kinetic problems in pregnancy.

Likewise, in pigs there are glucose control problems associated with pregnancy. Research with sows in the 1970's (9) resulted in the authors' published conclusions that "pregnancy in the sow is a diabetogenic event". They further illustrated that the problem becomes worse in the latter stages of pregnancy. A study in the 1990's (13) from the Netherlands evaluated blood glucose levels after a meal in sows that were in late gestation (about two weeks before birth of the piglets) and they observed that sows that had the lowest ability to control blood glucose (that is, the blood glucose levels rose higher after eating and the blood levels took longer to return to normal) had the highest incidence of mortality in the newborn piglets. This is very consistent with what is observed in humans. In fact, Bouillon-Hausman *et al* (3) concluded that, with regard to gestational diabetes in humans, "the pig appears to be an appropriate animal model for studying etiology of gestational diabetes and for

further characterizing effects of diabetic pregnancies on pre and postnatal growth and development."

Thus sows are the individuals within the swine species most subject to glucose-control problems because of two factors. First, swine in general have glucose control problems as they age and secondly, pregnant swine (which would be older swine compared to those grown simply for meat production) are subject to gestational diabetes. Within any particular herd, then, the swine most subject to glucose-control problems would be the reproducing swine. And, then, by extension, the swine most likely to respond in a positive manner to Cr supplementation would be these same animals.

In the first reported reproductive study involving Cr supplementation (17), gilts were retained from a growing/finishing study and were continued on a 200 ppb level of Cr supplementation from CrPic through 2 parities. Blood samples taken in mid-gestation demonstrated very clear differences in tissue responsiveness to insulin with those gilts receiving Cr having greater tissue sensitivity to insulin. Amoikon *et al* (1) addressed the issue of Cr supplementation and its effects on glucose metabolism with the classic methodologies of intravenous Glucose Tolerance Tests (IVGTT) and Insulin Challenge Tests (IVICT). In the variety of metabolic measurements made during the IVGTT and IVICT tests, glucose disappearance rate was increased and glucose half-life was decreased in pigs fed Cr from Cr tripicolinate (CrPic) at 200 ppb ($p < 0.04$), thus demonstrating an improvement in tissue insulin sensitivity consistent with the improved insulin efficiency noted by Lindemann *et al* (17) in the first reproductive study.

Source or Form of Chromium

As with all minerals, various sources (or forms of Cr) would be expected to have different bioavailability. The relative bioavailability of the different sources will affect the ultimate tissue supply of the mineral and, consequently, both potential biological response(s) and the economics of mineral supply. The study that most clearly addresses the comparison of Cr forms (18) fed supra-supplementation levels of 5000 ppb Cr (the allowed level of supplementation in the US is 200 ppb Cr) to examine potential differences among several Cr sources including those currently commercially available in the United States. The results demonstrated that there are differences in deposition of Cr in several tissues among the various sources. This is not unexpected and is consistent with source differences that are known to exist for other minerals. It is consistent, specifically, with Cr deposition studies with rats (2) that demonstrate clear differences in Cr sources. The four forms of Cr evaluated by Lindemann *et al* (18) all showed some degree of bioavailability and they were CrPic, Cr methionine, Cr propionate, and Cr yeast. The source that seemed to have the greatest bioavailability was the CrPic. Recent research utilizing nanotechnology is indicating a nanoparticle Cr that has similar bioavailability to CrPic (34, 35).

Effects of Cr on mortality or life span

Some of the original studies from the 1960's (29, 30) were life-term studies with mice and rats given 5 ppm Cr from Cr acetate (an organic form of trivalent Cr) in drinking water showed increased growth over unsupplemented controls for both males and females and decreased mortality of males. In a study of controlled stress (a controlled acute hemorrhage), the percentage of rats surviving was greater for the Cr-supplemented group (22). Evans and Meyer (7) fed three groups of rats 1 ppm Cr from either Cr chloride, Cr nicotinate, or CrPic. The authors followed plasma glucose and glycated hemoglobin throughout the study. After 41 months of supplementation, all rats fed the supplemental Cr from Cr chloride or Cr nicotinate had died while 80% of the rats fed CrPic remained alive; median life span for the first two groups of rats was 33 months (a fairly normal life span for laboratory rats) while median life span for the rats supplemented with CrPic was 45 months (8).

A series of studies with broilers provides clear evidence of an effect of Cr on mortality. The first two studies (12) (Figure 1) were conducted in Brazil using a high Cr-yeast and the latter three studies (14, 15, 16) (Figure 2) in Korea using CrPic. Several points can be made from the studies. First, when mortality is low (and presumably the cumulative stress from crowding, disease challenge, heat, etc. is low) there is less of a response

to supplemental Cr but when mortality (and presumably stress load) is high then the response to Cr can be quite large. A second point to be made is that the response is clearly dose dependent.

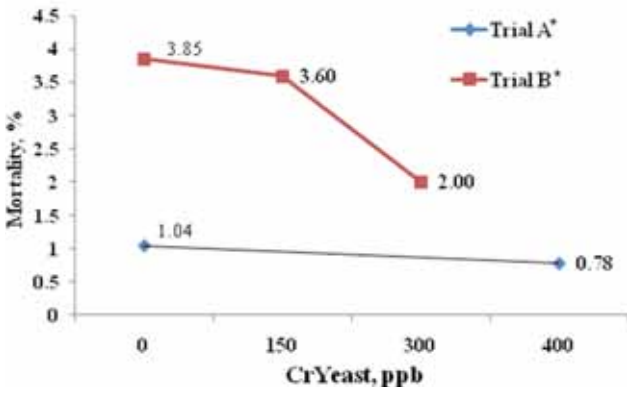

Figure 1. Effect of Cr yeast on broiler mortality (*Cr yeast effect, p≤0.05).

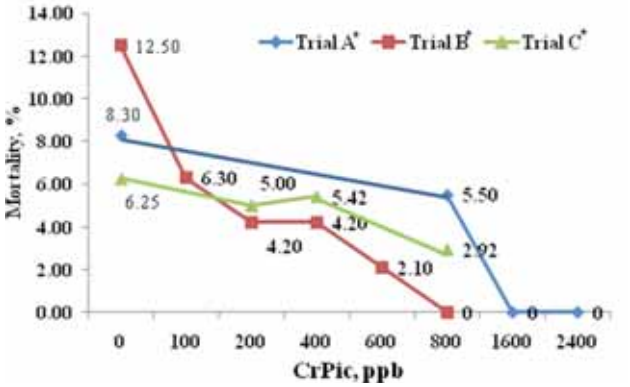

Figure 2. Effect of CrPic on chicken mortality (*CrPic effect, p<0.05).

A question that naturally arises is whether there are potential Cr effects on mortality in reproducing sows. It would seem from our understanding of nutrient responses that the potential for a response would be greatest in those situations where there was the greatest departure from normal performance, i.e. when performance was most compromised. The same concept would exist with regard to potential mortality benefits in sows. One of the earliest studies reported does illustrate very clearly the potential benefit of Cr supplementation on some of these parameters. A large study (5) from Australia involving over 800 sows (Table 1) wherein supplementation of 200 ppb Cr from CrPic resulted in a highly significant improvement in farrowing rate (from 79.0 to 92.4%; $p < .001$). Numerical reductions of more than 60% in abortions, natural sow deaths, and sows that returned to estrus and were rebred were also observed with the supplementation. Every aspect of reproductive health that was recorded was benefited by supplementation. Of particular note should be the reduction in mortality – a response consistent with the broiler observations.

Table 1. Effect of chromium picolinate on sow performance.

Chromium level, ppb:	0	200
Farrowing rate, %	79.0	92.4**
Abortion	3.0	0.8
Died	5.0	1.3
Return to estrus	11.0	2.8

Adapted from Campbell, 1996; a total of 847 first and second parity sows were utilized

** Significantly different, p<0.001.

Numerical improvements in mortality (Figure 3) were also observed in the study of Hagen *et al* (10). The reduction in mortality was greater in first litter sows and sows older than three parities (both of which had mortality substantially greater than that of the second and third parity sows). In this study, there were also improvements in litter size (Figure 4) and wean to first service interval (Figure 5). The improvements in litter size were seen for sows of all parities and the improvements in wean to first service interval were most pronounced in first parity females (when the interval was greater than that of older sows). These effects have much statistical strength given the size of the study; this study utilized 48,000 sows that farrowed almost 100,000 litters for almost 1,000,000 pigs.

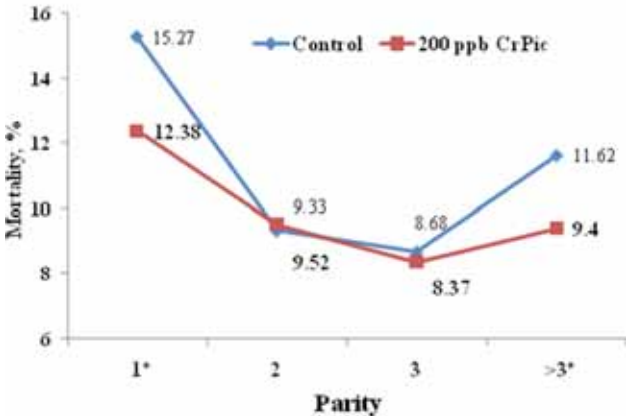

Figure 3. Effect of CrPic on sow mortality by parity (*CrPic effect, p=0.11); study involved 48,000 sows.

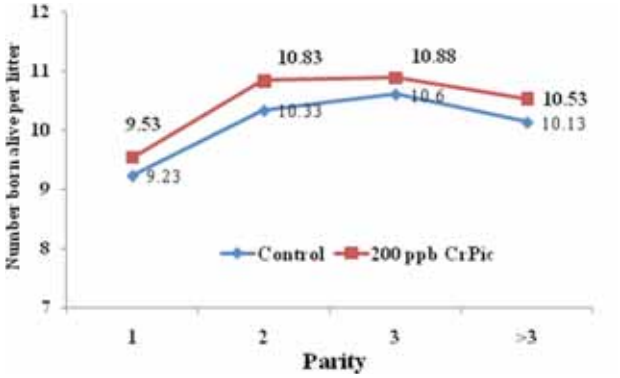

Figure 4. Effect of CrPic on number born alive by parity (CrPic effect, p=0.02); study involved about 100.000 litters.

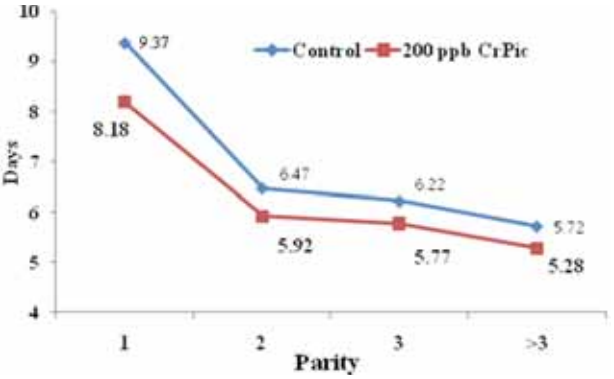

Figure 5. Effect of CrPic on the days to estrus by parity (CrPic effect, p=0.20); study involved 48.000 sows.

Closing comments

The status of Cr is not a new question. Cr is clearly a nutrient that is essential; this is a position that has been held for over three decades by individual scientists, groups of scientists, and governmental committees. However, because Cr is a nutrient and not a drug, a response to supplementation is not seen in all production situations, it is only seen in those situations in which some aspect of performance or health is compromised as a result of inadequate tissue stores resulting from depletion over time and/or inadequateCr supply. The most uniform metabolic response across species with regard to Cr deficiency symptoms that are responsive to Cr supplementation are alterations in glucose metabolism with special reference to peripheral tissue sensitivity to insulin. Because the body's ability to control blood glucose is critical to many life functions, a consequence of Cr supplementation can be improved health and reproductive outcomes as well as improved survival rate or life span.

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