A Systems Approach to Optimizing Plant Nutrition for Human Health

Ross M. Welch
Robert W. Holley Center for Agriculture & Health at Cornell University
Why Should Plant Nutritionists Improve the Nutritional Quality of Plant Foods?
Why Does Agriculture Exist?

- To produce food and fiber and provide livelihoods to farmers and profits to the agricultural and food industries alone?
- Why do we need “Food”? – because we need Nutrients!
- Agriculture is the primary source of energy, protein and all essential minerals and vitamins required for human life!
- Farmers are nutrient providers!
- “Nutrient security” not “food security” should be our goal!
- If food systems, based in agriculture, cannot provide all the essential nutrients in adequate quantities to sustain human life during all seasons, diseases ensue, societies suffer and development efforts stagnate.
The Known **43 (51)** Essential Nutrients for Sustaining Human Life  

<table>
<thead>
<tr>
<th>Air, Water &amp; Energy (3)</th>
<th>Protein (amino acids) (9)</th>
<th>Lipids-Fat (fatty acids) (2)</th>
<th>Macro-Minerals (7)</th>
<th>Trace Elements (9) (17)</th>
<th>Vitamins (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Histidine</td>
<td>Linoleic acid</td>
<td>Na</td>
<td>Fe</td>
<td>A</td>
</tr>
<tr>
<td>Water</td>
<td>Isoleucine</td>
<td>Linolenic acid</td>
<td>K</td>
<td>Zn</td>
<td>D</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Leucine</td>
<td></td>
<td>Ca</td>
<td>Cu</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Lysine</td>
<td></td>
<td>Mg</td>
<td>Mn</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>Methionine</td>
<td></td>
<td>S</td>
<td>I</td>
<td>C (Ascorbic acid)</td>
</tr>
<tr>
<td></td>
<td>Phenylalanine</td>
<td></td>
<td>P</td>
<td>F</td>
<td>B1 (Thiamin)</td>
</tr>
<tr>
<td></td>
<td>Threonine</td>
<td></td>
<td>Cl</td>
<td>Se</td>
<td>B2 (Riboflavin)</td>
</tr>
<tr>
<td></td>
<td>Tryptophan</td>
<td></td>
<td></td>
<td>Mo</td>
<td>B3 (Niacin)</td>
</tr>
<tr>
<td></td>
<td>Valine</td>
<td></td>
<td></td>
<td>Co (in B12)</td>
<td>B5 (Pantothenic acid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cr</td>
<td>B6 (Pyridoxine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Si</td>
<td>B7/H (Biotin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>B9 (Folic acid, folacin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ni</td>
<td>B12 (Cobalamin)</td>
</tr>
</tbody>
</table>

*Numerous other beneficial substances in foods are also known to contribute to good health.*
Malnutrition accounts of ≈ 30 million deaths per year (about 1 death per second)
Food Systems, Diet and Disease

• Global food systems are failing to provide adequate quantities of essential nutrients and other factors needed for good health, productivity and well being for vast numbers of people in many developing nations.

• *Green revolution* cropping systems have resulted in reduced food-crop diversity and decreased availability of many micronutrients.

• Nutrition transitions (double burden of malnutrition) are causing increased rates of chronic diseases (e.g., obesity, cancer, heart disease, stroke, diabetes, osteoporosis) in many nations.

• Holistic, sustainable improvements in the entire food system are required to solve the massive problem of malnutrition and increasing chronic disease rates in developed and developing countries.

• Agricultural systems are a major factor affecting human health
Global Food Systems’ Problems

• Agriculture’s primary focus has been on production alone, with little concern for nutritional or health-promoting qualities of products
• Nutritionists tend to emphasize unsustainable medical approaches to solve malnutrition problems
  — supplements
  — food fortificants
• These strategies do not address the underlying causes of malnutrition - dysfunctional food systems based in agricultural systems that do not have a goal of promoting human health
• Simplistic views are the norm – looking for “silver bullet” approaches for solutions
• Agriculture and human health have never been generally recognized as closely linked disciplines
Micronutrient Malnutrition
Causes....

- More severe illness
- More infant and maternal deaths
- Lower cognitive development
- Stunted growth
- Lower work productivity

And ultimately -

- Lower GDP (e.g. an estimated >5% annual loss in Pakistan)
- Higher population growth rates
Global Micronutrient Deficiencies

> 3 billion people afflicted

(Map from USAID)
Worldwide Prevalence of Anemia in Pregnant Women

Figure 3.1b Anaemia as a public health problem by country: Pregnant women

( WHO, 2008 )
Other Micronutrient Deficiency Problems

Zn deficiency
Se deficiency
Scurvy (vitamin C)
Beriberi (thiamine/B₁)
Rickets (both vitamin D & Ca deficiencies)
Pernicious Anemia (cobalamine/vitamin B₁₂)
Folate
Riboflavin
% Changes in Cereal & Pulse Production & in Populations Between 1965 & 1999

(FAO data, 1999)
Table to Farm: A New Agriculture Paradigm

Making a closer connection between agriculture and health will require that research address gaps at the intersection of agriculture and food, food and people, and people and health.

Agricultural policy and production have great effects on national diets (i.e., health). Governments can influence agricultural production through many policy measures. As emphasis on health increases and consumption patterns change, Member States need to take healthy nutrition into account in their **agricultural policies**.
International Obesity Task Force, Global Prevention Alliance (2006)

• Nutrition criteria should be included in agricultural policy
• Agricultural policy should undergo health impact assessment
• Support should be provided for agricultural programs aimed at meeting WHO dietary guidelines
New 2006 Mandate for the Food & Agriculture Organization, UN

- Extended to encompass entire food chain – from farm to plate – food chain approaches

- Assistant Director-General, Louise Fresco

  - “We are witnessing a ‘paradigm shift’ away from tonnes, calories and hectares towards issues of quality – quality of life, quality of environment, quality of nutrition”

  - Puts improved nutrition & health goals into production agriculture goals
Routs to Better Nutrition
(The World Bank)

<table>
<thead>
<tr>
<th>Short routes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Community-based nutrition and health services (community growth promotion programs, community Integrated Management of Childhood Illnesses [C-IMCI])</td>
</tr>
<tr>
<td>• Facility-based nutrition and health services (health and nutrition services, and antenatal care)</td>
</tr>
<tr>
<td>• Micronutrient supplements</td>
</tr>
<tr>
<td>• Micronutrient fortification</td>
</tr>
<tr>
<td>• Targeted food aid</td>
</tr>
<tr>
<td>• Conditional cash transfers</td>
</tr>
<tr>
<td>• Microcredit cum nutrition education</td>
</tr>
<tr>
<td>• Food supplementation</td>
</tr>
<tr>
<td>• Micronutrient supplements</td>
</tr>
<tr>
<td>• Food stamps</td>
</tr>
<tr>
<td>• Targeted food aid</td>
</tr>
</tbody>
</table>

“The HarvestPlus program is a promising initiative in which the international agricultural and research centers have begun to develop new breeds of staple foods that are rich in key vitamins and minerals using a new approach to fortification termed biofortification.”

The World Bank, Directions in Development. Repositioning Nutrition as Central to Development. A strategy for large scale action (2006)
Copenhagen Consensus 2008 Global Challenges

Ranked Top Five Challenges

<table>
<thead>
<tr>
<th>SOLUTION</th>
<th>CHALLENGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Micronutrient supplements for children (vitamin A and zinc)</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>2. The Doha development agenda</td>
<td>Trade</td>
</tr>
<tr>
<td>3. Micronutrient fortification (iron and salt iodization)</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>4. Expanded immunization coverage for children</td>
<td>Diseases</td>
</tr>
<tr>
<td>5. Biofortification</td>
<td>Malnutrition</td>
</tr>
</tbody>
</table>

Malnutrition and Hunger

The expert panel examined the following solutions to this challenge: micronutrient supplementation (Vitamin A and Zinc), micronutrient fortification (iron and salt iodization), biofortification (agricultural improvements through research and development), de-worming (which also improves education), and nutritional education campaigns. The panel ranked solutions to this challenge very highly, because of the exceptionally high ratio of benefits to costs. Micronutrient supplements were the top-ranked and fortification was the third-ranked solution, with tremendously high benefits compared to costs.
Linking Agriculture to Human Health: The Norway Example

- Necessary policy reorientation was made to increase available micronutrient-rich foods within local food systems
- Implemented agricultural and food production policies in a national nutrition plan of action
- Provided economic incentives for producer and consumer in support of healthful diets
- Resulted in sustained improvement in life expectancy and a reduction in deaths from cardiovascular disease and other chronic diseases

From: FAO/WHO. Vitamin and mineral requirements in human nutrition, 2nd ed. 2004
Some Ways Plant Nutrition Can Be Used to Improve Human Health

• Increase the availability to roots of essential micronutrient metals in the rhizosphere
• Use fertilizers in ways that increase micronutrients (essential trace elements and vitamins) in edible portions of food crops
• Design agronomic systems that maximize nutrient output of farming systems to improve human health
• Decrease the available levels of toxic heavy metals in the rhizosphere and translocation to edible plant parts
Soil-Plant Factors Effecting Nutrient Composition of Edible Parts

Diagram from Allaway, 1975
Soil-Plant Factors Effecting the Nutritional Quality of Plant Foods

- Factors effecting available essential element supplies in soils
  - Soil type (pH, organic matter, parent material, subsoil, etc.)
  - Root-soil interactions - rhizosphere effects
  - Agronomic practices (fertilizers, amendments, organic matter, cropping systems, variety selection, etc.)

- The available supplies of essential minerals (as influenced by genetic & environmental variables) also affect the accumulation of numerous other nutrients (i.e., vitamins) and other health promoting factors accumulated in edible portions of plant foods
Food Systems Approach to IDD

**Effects of Iodination of Irrigation Water**
Long Ru, China

<table>
<thead>
<tr>
<th>I Concentration (μg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before I, 3/92</td>
</tr>
<tr>
<td>After I, 3/92</td>
</tr>
<tr>
<td>After I, 6/93</td>
</tr>
</tbody>
</table>

- Wheat
- Other Cereals
- Oil Crops
- Vegetables
- Meat, eggs, and milk

**Effects of Iodate Irrigation on Urinary I**
Children 2-6 years old

- Long Ru Site (+ I)
- Control Site

Importantly — also ≈ 30% increase in livestock productivity!
Using iodized salt can not achieve this benefit.
The root cause of I deficiency is not enough I in the soil!

Data from Cao, et al., 1994
Se Map of 48 U.S. States

Map developed by Drs. Joe Kubota & William H. Allaway
Decade-long, placebo-controlled, double-blind clinical trial

1312 older Americans, 10 years

+200 µg Se/day (Se-yeast)

Slide from Gerald F. Combs, Jr.
Using the Selenium Fertilizer Tool to Improve Selenium Status of the Finish People

Adding Se to fertilizers greatly > Se in cereal grain

Adding Se to fertilizers greatly > Se eaten each day

Resulted in a doubling of the blood-Se levels in the whole Finish population

From: Combs, 2005
Effects of Increasing Se Fertilizer Rates on Wheat-Grain Se Levels

(From Lyons et al., 2004)
Link Between Zn-Deficient Soils & Zn Deficiency in Humans

Figure from A. Green, 2009
### Effects of Zinc Fertilization on Wheat Yield & Grain Level

<table>
<thead>
<tr>
<th>Zn application methods</th>
<th>Zn concentration</th>
<th>Increases in yield by Zn Fertilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole shoot</td>
<td>Grain</td>
</tr>
<tr>
<td></td>
<td>(mg kg(^{-1}))</td>
<td>(%)</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Soil</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Seed</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Foliar</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>Soil + foliar</td>
<td>69</td>
<td>35</td>
</tr>
<tr>
<td>Seed + foliar</td>
<td>73</td>
<td>29</td>
</tr>
</tbody>
</table>

Using both soil and foliar Zn fertilizers can maximize grain yields and grain-zinc.

Yilmaz et al., 1997
Effects of Increasing Zn Fertilizer Rates on Wheat Grain-Zn Levels

(From Genc et al., 1999)
N-Zn Relationships in Wheat Grain

Kutman et al., 2009, in press
Effects of Crop Rotations on Wheat Grain-Cu

![Bar Graph]

Effects of Maize Intercropping on Fe Deficiency in Peanuts

Mono-cropping  Intercropping

(Zuo et al., Plant and Soil, 2000)
Effect of Intercropping (Maize-Peanut) on Fe Levels in Peanuts

(Zuo et al., Plant and Soil, 2000)
HarvestPlus Biofortification Program Strategy

Breed for micronutrient-dense staple food crops (using the best traditional breeding practices and modern biotechnology) to achieve provitamin A, iron, and zinc concentrations that can result in **measurable** improvements in the nutritional status of target populations.
HarvestPlus Progress

• Shown the human efficacy of biofortified
  – Orange-flesh sweet potatoes (also effectiveness shown)
  – High-Fe rice

• Shown enough genetic diversity in bioavailable levels of Fe and/or Zn in
  – Wheat
  – Beans

to have measurable effects in humans
The Importance of Bioavailability

• Bioavailable amount of a trace element in a meal, not the total amount, is the critical factor for human health.

• Most staple plant foods (cereal grains and legume seeds) fed alone contain very low levels of bioavailable Fe (e.g., about 5%) because of the antinutrients they contain (phytate, polyphenols, etc.).

• Increasing the bioavailability of Fe from 5% to 30% would have the same effect as increasing total amounts of Fe in staples by 6 fold.
Some Ways to Improve Fe and Zn Bioavailability

• Increase promoter substances
  • Ascorbic acid (vitamin C)
  • Meat factor(s)
  • Sulfur-containing amino acids (e.g., cysteine)
  • Provitamin A carotinoids (vitamin A)
  • Prebiotics (e.g., inulin)
  • Certain fibers (e.g., sugar beet fiber)

• Decrease antinutrients
  • Phytic acid \((\text{myo-inositolhexaphosphoric acid})\)
  • Certain polyphenolitics, fibers, etc.

• Increase / introduce other micronutrient-rich compounds (phytoferritin, hemoglobin, etc.)
The Phytate Conundrum – to Decrease or Not to Decrease in Staple Plant Foods

- Phytate is a known antinutrient that has been shown to inhibit the bioavailability of Fe, Zn, Ca and other polyvalent cations (e.g., Cd, Pb) in humans fed staple plant foods.
- Phytate has also been shown to provide health benefits (e.g., colon cancer prevention).
- Phytate plays essential roles for all life including higher plants (essential for i-RNA editing enzyme; storage site for seed-P, -Fe, -Mg, etc.).
Flavonoid Fe(III)-binding Sites

Kaempferol: \( R_1 = H, R_2 = OH \)
Astragalin (kaempferol-3-O-glucoside): \( R_1 = H, R_2 = O\text{-glucoside} \)
Quercetin: \( R_1 = OH, R_2 = H \)
Quercitrin: \( R_1 = OH, R_2 = O\text{-rhamnoside} \)
Structure of Ferritin

Simplified Model of Iron-mineral Core
### Bioavailable Fe in Intrinsically $^{55}$Fe-labeled Soybeans (Tokyo cv.) Fed to Fe-depleted Women

<table>
<thead>
<tr>
<th>Feeding day</th>
<th>Soy soup (% absorbed)$^a$</th>
<th>Soy muffin (% absorbed)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 14</td>
<td>25.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Day 28</td>
<td>24.5</td>
<td>27.0</td>
</tr>
</tbody>
</table>

$^a$Mean of 18 subjects with depleted Fe stores

Tokyo soybeans contained 30-50% of their total Fe as phytoferritin and 2.1% phytic acid ($\approx 30:1$ phytate to Fe molar ratio).

Data from Murray-Kolb et al., 2002
The Role of Beneficial Hind Gut Microorganisms on Human Health

**Beneficial Bacteria**

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. acidophilus</td>
<td>B. adolescentis</td>
</tr>
<tr>
<td>L. amylovorus</td>
<td>B. animalis</td>
</tr>
<tr>
<td>(L. casei)</td>
<td>B. bifidum</td>
</tr>
<tr>
<td>L. crispatus</td>
<td>B. breve</td>
</tr>
<tr>
<td>L. gallinarum b</td>
<td>B. infantis</td>
</tr>
<tr>
<td>L. gasseri</td>
<td>B. lactis c</td>
</tr>
<tr>
<td>L. johnsonii</td>
<td>B. longum</td>
</tr>
<tr>
<td>L. paracasei</td>
<td></td>
</tr>
<tr>
<td>L. plantarum</td>
<td></td>
</tr>
<tr>
<td>L. reuteri</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td></td>
</tr>
</tbody>
</table>
The Human Body & Microbiota: the “Superorganism”

- Human body contains 10 trillion ($10^{13}$) cells
- Intestine contains 100 trillion ($10^{15}$) microbes (60% of fecal dry weight)
- Metabolic activity of these microbes is equal to that of the vital organs in the body
- Microbes perform a host of functions both mutualistic and symbiotic.
Intestinal Microflora Interactions
Some beneficial roles of “healthful” gut bacteria

• Non-digestible carbohydrates → SCFA → gene induction, > Mineral absorption
• Bound phytonutrients → available phytonutrients, > Health
• Lignans → Phytoestrogens → < Cancers
• Antioxidants → Available antioxidants → Epithelial protection, > Gut health
• Sphingolipids → Sphingosine → > Cell growth
Prebiotic Oligosaccharides

- Lactulose
- Fructo-oligosaccharides (inulin, levan, etc.)
- Galacto-oligosaccharides
- Soybean oligosaccharides
- Lactosucrose
- Isomalto-oligosaccharides
- Gluco-oligosaccharides
- Xylo-oligosaccharides
- Palatinose (isomaltulose)
- Resistant starch
$\beta(2-1)$-linked Inulin Type Fructans (Prebiotics)

1-ketose

Some Inulin Effects on Mineral Bioavailability

- Stimulates bifidobacteria and lactobacilli growth in the hind gut
  - increases colon acetate, propionate and butyrate levels through fermentation
  - lowers the pH within the lumen of the colon
  - stimulates proliferation of epithelial intestinal cells in the colon
  - induces increased mineral absorption in the colon
- Increases metal solubility and paracellular uptake from large intestine
- Induces Calbindin-D9k gene expression in plasma membrane of mucosa cells in the colon
- Induces mRNAs expression that code for Fe transport proteins by mucosal cells in both the colon and duodenum
- Increases deposition of Ca into bones in post-menopausal women
- Stimulates true Ca absorption in adolescents
- Increases Fe bioavailability from maize-soy diets in pigs
- Stimulates apparent absorption of Fe, Zn, and Cu in monogastric animals
- Stimulates phytate degradation in the gut
- Increases Cu absorption in post-menopausal women
Effects of Dietary Inulin on Iron Bioavailability in Pigs

Maize-soybean-based diet containing 0.8% phytate

Effects of 4% Dietary Inulin on Bacterial Populations in the Pig Cecum

Pig Duodenal Mucosal Cell mRNA Expression (+/- Inulin Diets)

Increasing Available Fe Supplies
What Needs to be Done?

• Increase crop productivity
  — Making more land available for diversifying food crops
• Increase Fe density in edible parts
  — Supply more available Fe to the plant (soil fertilizers/foliar sprays?)
  — Increase Fe uptake efficiency
  — Increase Fe translocation rates (xylem & phloem)
  — Increase Fe accumulation in edible parts (e.g., seed & grain)
  — Avoid Fe toxicity in the plant
• Increase bioavailable Fe level in edible plant parts
  — Accumulate Fe in bioavailable forms
  — Increase promoters (i.e., enhancer substances)
  — Decrease inhibitors (i.e., antinutrients); use caution
  — Increase Zn, provitamin A carotenoids, etc.

• Using:
  — conventional breeding (short term)
  — transgenic approaches (longer term)

• Use in combination with complementary foods containing promoter substances (livestock & fish meats, foods high in ascorbic acid, etc.)
• Re-diversify farming systems to assure sustainability
Agriculture’s Agenda For Better Health

**Item 1:** Declare a goal of agriculture to produce high quality food that promotes human health and well-being in sustainable ways.

**Item 2:** Design seeds, cropping & livestock systems that help achieve primary goal—design for maximum nutrient output of farming systems.

**Item 3:** Genetically modify food crops, increasing nutritional and health while promoting crop productivity.

**Item 4:** Use agronomic practices (e.g., cropping systems and fertilizers) to improve nutrient output of farming systems.

**Item 5:** Define sustainable agriculture, as agriculture that yields “healthy foods” for healthy and productive people!
Sir Albert Howard

“related subjects as agriculture, food, nutrition and health have become split up into innumerable rigid and self-contained little units, each in the hands of some group of specialists. The experts, as their studies become concentrated on smaller and smaller fragments, soon find themselves wasting their lives in learning more and more about less and less. The result is the confusion and chaos now such a feature of the work of experiment stations and teaching centers devoted to agriculture and gardening. Everywhere knowledge increases at the expense of understanding. The remedy is to look at the whole field covered by crop production, animal husbandry, food, nutrition, and health as one related subject, and then to realize the great principle that the birthright of every crop, every animal, and every human being is health.” — March, 1945


“Western civilisation is suffering from a subtle form of famine – a famine of quality.”— November, 1947