

The **Case** for Promoting Multiple Vitamin/Mineral Supplements for Women of Reproductive Age in Developing Countries

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List of Acronyms

AI	adequate intake
CHD	coronary heart disease
CRN	Council on Responsible Nutrition
CI	confidence interval
DRI	Dietary Reference Intake
ESADI	Estimated Safe and Adequate Dietary Intake
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
GMP	good manufacturing practices
IDA	International Dispensary Association
IEC	information education and communication
IMR	infant mortality rate
IOM	Institute of Medicine
IU	international unit
IUGR	intrauterine growth retardation
LBW	low birth weight
LOAEL	Lowest Observed Adverse Effect Level
MOH	Ministry of Health
NAS	National Academy of Sciences
NOAEL	No Observed Adverse Effect Level
PROM	premature rupture of membranes
RDA	Recommended Dietary Allowances
RDA	Recommended Dietary Amount (UK)
RNI	Reference Nutrient Intakes
RR	Relative Risk
UL	Tolerable Upper Limit
WHO	World Health Organization

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Executive Summary

Women in developing countries often consume inadequate levels of micronutrients because of limited intake of animal products, fruits, vegetables, and fortified foods. Less than recommended intakes of micronutrients increase a woman's risk of being deficient, not having sufficient nutrients to meet physiologic requirements, to ensure health.

The adverse effects of deficiencies in vitamin A, iron, and folic acid, including night blindness in pregnant and lactating women and iron deficiency anemia, are well known. Low intakes of these and other nutrients, including zinc, calcium, riboflavin (B₆) and B₁₂, also have consequences for women's health, pregnancy outcome, and breastfed children's health and nutritional status.

Multiple deficiencies coexist, so the benefit of multiple micronutrient supplements is becoming increasingly apparent. It is difficult to meet nutrient needs with diet alone, especially for pregnant women and those whose consumption of animal products, fortified foods, and diverse diets is limited. Supplementation of women with multiple vitamins and minerals should be one component of a micronutrient strategy to improve micronutrient status among women in developing countries. However, there are several issues for program managers to consider prior to implementing programs, including:

- 1) Which reference standards will be used to determine nutrient levels to include in the supplements?
- 2) Which nutrients and what quantities will be included?
- 3) Which factors need to be considered in purchasing supplements?
 - a) availability of supplements
 - b) safety
 - c) costs of supplements
 - d) quality
 - e) acceptability and compliance

These issues are discussed, and guidance is provided on the selection of appropriate supplements for pregnant women and women of reproductive age in developing countries.

Introduction

Chronic energy deficiency and stunting among women in developing countries are the result of malnutrition during fetal growth in infancy and childhood with low energy intakes continuing into adulthood for many women. Micronutrient malnutrition can stem from deprivations in childhood but is primarily related to currently inadequate intakes. While stunting caused by early malnutrition cannot be reversed in adulthood, micronutrient malnutrition can be remedied with substantial benefits for women's and children's health.

Dietary patterns result in low intakes of several nutrients simultaneously. In addition to improving women's diets, multiple vitamin and mineral supplements should be part of a strategy to improve micronutrient status among women in developing countries. This paper provides program managers with information to facilitate incorporation of multiple micronutrient supplements into programs to improve the health and nutritional status of women.

Why is micronutrient malnutrition a concern among women in developing countries?

Poor dietary quality rather than quantity is the major determinant of inadequate micronu-

trient status among women in developing countries (Allen and Ahluwalia 1997). Low income populations consume most of their calories from low cost staple foods and less from more expensive foods such as animal products, fruits, and vegetables which are rich in micronutrients. Box 1 compares intakes of women in the U.S. to those in several developing countries.

Promoting improvements in dietary intake often are based on the inclusion of small amounts of animal foods and increasing fruits and vegetables through diets (Underwood 1994) such as the one shown in Table 1. This illustrates a relatively good Asian rice and wheat based diet for women consuming limited calories. Staple foods including rice, wheat, millet, potatoes, and corn provide needed energy and protein but few micronutrients except when fortified.

The diet in Table 1 has 41% of calories from staple foods and only 9% from animal products. However, even this diet might be difficult to promote throughout the year because of the seasonal availability of fruits (mangos) and the relatively high cost of some foods (fish, lentils) which would keep them out of reach of the very poor. While this diet exceeds vitamin A requirements (providing more than 11,000 IU of vitamin A), additional foods high in zinc, calcium, and folate would still

Box 1: What foods are typically limited in women's diets in developing countries?

- ♦ Compared with European and other developed countries, animal product intakes among women are generally lower in developing countries. For example, in the U.S., 60% of energy intake is from animal products (Allen et al 1992).
- Among pregnant women from a community study in Mexico, only 7% of total calories were from animal products. Tortillas provided 64% of calories illustrating the limited diversity of their diet (Allen et al 1992).
- ♦ In a corollary study in Egypt, pregnant women consumed only 17% of calories from animal products and 35% of calories from the traditional bread (Kirksey et al 1992).
- ♦ Fruits and vegetables are often only seasonally available or of limited variety. For example, a national survey in Honduras found that among households in the poorest region, the average number of servings of vegetables per day was only 1.2 (Rogers et al 1996).

Table 1. Vitamin A, zinc, calcium, and folate in a "relatively good" Asian diet meeting RDAs for vitamin A

Food	Amount	Vit AIU	Zinc mg	Calc mg	Folate g	Kcal
Rice (cooked)	3 cups (525 grams)	0	1 63	99	21	598
Lentils (cooked)	½ cup (150gm)	8	126	19	179	115
Potato	1 potato (122 grams)	0	36	6	11	113
Whole wheat bread/ chapatti	2 slices 1 chapatti (92 grams)	0	138	30	43	256
Oil	2 Tbs	0	01	0	0	200
Fish (bass)	1 piece (100 grams)	115	83	103	17	146
Mango	1 small (100 grams)	3 894	04	10	14	65
Banana	1 small	81	16	6	19	93
Kale (Greens)	100 grams	7 400	0 24	72	13	28
Sugar	2 Tbs	0	0	0	0	96
Total		11498	5 91	345	317	1710
Foods rich in folate						
Orange	1 lg (184 grams)	377	13	74	56	86
Garbanzo beans	½ cup (120 grams)	29	127	18	80	143
Spinach (cooked)	½ cup (90 gm)	7 371	68	122	131	21
Food rich in zinc						
Beef	100 grams	0	6 8	8	8	211
Chicken liver	1 liver = 6 grams	983	26	84	46	39
Food rich in calcium						
Cow s milk (whole)	1 cup	307	9	291	12	150
Chinese Cabbage	1 cup	4 365	29	158	69	20
RDA women 25-50		8,000*	12	1,000**	400**	
RDA pregnancy		8,000"	15	1,000**	600**	
RDA lactation		13,500"	15	1,000**	400**	

*Conversion from RE to IU based on 1 RE = 3.33 IU retinol 1 RE = 10 IU provitamin A carotenoid This level for RDA assumes food contains primarily betacarotene **The most recently published RDAs are given zinc and vitamin A are the 1988 RDAs calcium and folate are the 1998 RDAs The 1998 RDAs set average intake levels (AIs) rather than RDAs for calcium

be needed to meet the RDAs Animal flesh products such as red meat or liver are needed to provide sufficient zinc and iron Additional calcium rich sources (such as Chinese cabbage broccoli nuts or dairy products) are needed for this diet to meet calcium requirements Additional legumes and dark green leafy vegetables (such as spinach or mustard greens) are needed to provide sufficient folate

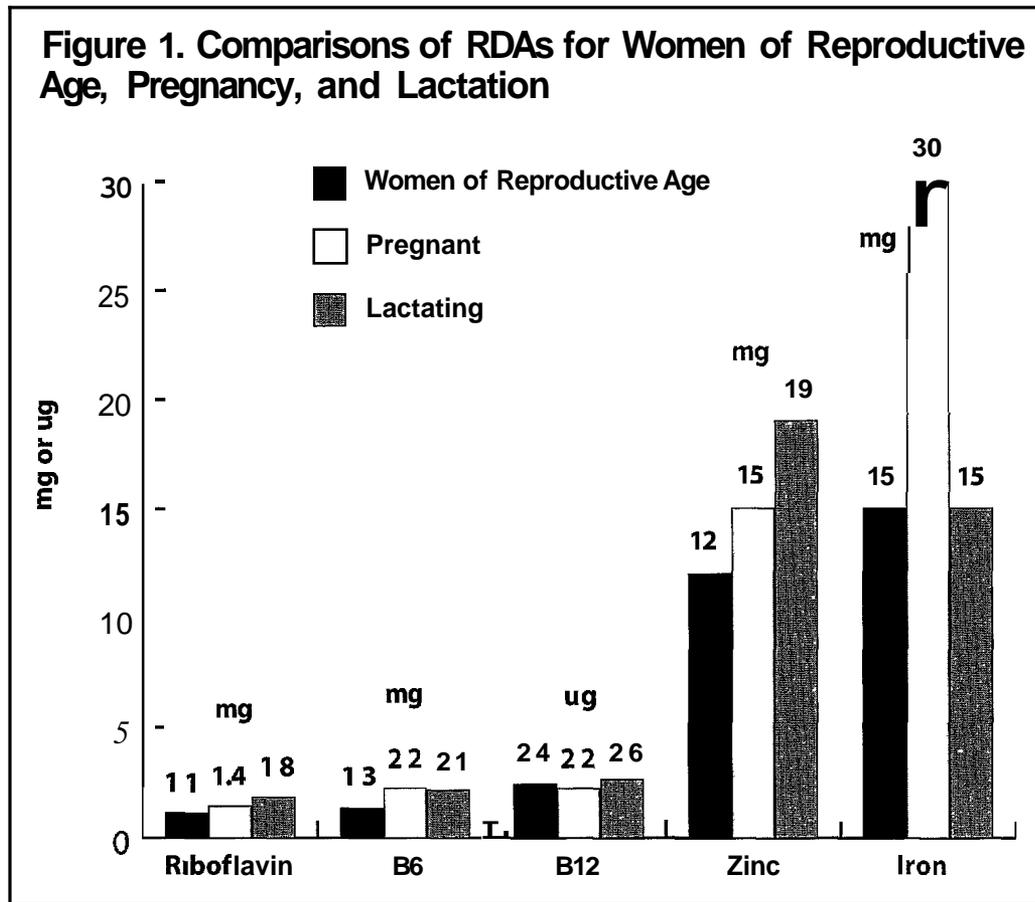
Improving micronutrient intake through dietary approaches by diversifying diets and increasing intakes of foods high in micronutrients is an important strategy to improve women's health However because of economic constraints seasonal harvests limited production poor infrastructure to distribute foods produced in

other areas and food consumption patterns other means of improving micronutrient intake are also needed Even in the U K a recent randomized controlled trial illustrates that fortification and supplement use have more beneficial effects on micronutrient status than do improvements in diet (Cuskelly McNulty and Scott 1996) ¹

Fortification of staple foods is increasingly being used to improve micronutrient intake but many nutrients missing in diets now are not included in fortificant pre mixes for technical and other reasons

As countries expand fortification efforts there are many logistical and quality control measures needed for fortificants to be added and sustained at appropriate levels It will also be necessary to assure that

Note 1 Women who received folic acid supplements had significantly greater intakes of folic acid than those who received fortified foods foods high in folate dietary advice on which foods to consume to improve folate status or controls Improvements in red cell folate were four to five times higher in those who received supplements or fortified foods than the dietary folate or dietary advice groups However these latter two groups still showed some improvement in red cell folate over controls



the target population consumes sufficient quantities of the fortified products. However, even in developed countries where fortification of foods has been a long standing practice, because of the low intakes of certain foods and limited number of foods that are fortified, significant proportions of women consume less than adequate intakes of micronutrients.

What is the evidence for poor micronutrient intake among women?

Adequacy of diets for women is determined by comparing their average nutrient intakes to recommended levels of intake such as the Recommended Dietary Allowance (RDA) (Appendices 1a-1c). The RDAs are calculated as the mean requirement for a nutrient + 2 standard deviations. Average micronutrient intakes are then reported as percentages of the RDAs. If the mean intake of a group exceeds 100% of the RDAs, the probability that an individual

in that group has inadequate intakes is quite small (less than 3%). As the mean intake of the population decreases below 100% of the RDAs, the risk of deficiencies in individuals increases.

Figure 1 compares the most recent U.S. RDAs for women of reproductive age (25-50), pregnant women, and lactating women. As illustrated, the RDAs increase substantially during pregnancy and lactation for several nutrients. Current developing country diets of many women are unable to meet even the lower RDAs for women of reproductive age. It becomes increasingly difficult to ensure adequate diets for pregnant and lactating women with their higher requirements.

National surveys of dietary intakes are routinely conducted in the U.S. and Europe but are less common in developing countries because of their high cost and technical difficulty. Localized studies have been conducted that indicate low intakes of mi

Box 2: What is the evidence for poor micronutrient intake among women in developing countries?

- ♦ In Mexico Peru and Argentina consumption at less than two thirds of the RDA for **vitamin A** was observed for adolescents or adult women (Allen 1993 CESNI 1992 reported by Mora and Mora(a) PAHO 1998)
- ♦ Studies in Brazil Guatemala Mexico India Nepal Nigeria Malawi Egypt and Kenya reported mean intakes of less than two thirds of the RDA for **zinc** (Gibson 1994 Allen 1993 Caulfield Zavaleta Shankar and Meriardi 1998 Mora and Mora(b) PAHO 1998)
- ♦ WHO (1996) reports that several national dietary surveys have shown that intakes are unlikely to meet requirements for **zinc and copper** for most age groups in Africa the Eastern Mediterranean South East Asia and the Western Pacific
- ♦ In South Africa Indian women and rural black women consumed less than two thirds of the RDA for **folate** (Robertson et al 1997)
- ♦ The average dietary intake of **B₆** was less than two thirds of the RDA for pregnant and lactating women in Egypt and Kenya (McCullough et al 1990 Neuman et al 1992)
- ♦ In Mexico and Kenya women consumed less than two thirds of the RDA for vitamin **B₁₂** (Neuman et al 1992)
- ♦ In Mexico Egypt and Kenya women consumed less than two thirds of the RDA for **riboflavin** (Allen 1993 Neuman et al 1992)
- ♦ **Calcium** intakes of less than two thirds of the RDA were reported in Colombia Thailand Jamaica (Repke and Villar 1991) and India (Banji and Lakshmi 1998)

micronutrients are common in many poor areas. Box 2 gives examples of several studies throughout the world showing low intakes among adolescent and adult women for several nutrients including iron vitamin A zinc folate B₆ B₁₂, riboflavin and calcium.

Figure 2 gives results for micronutrient intake from several country wide surveys conducted by the National Nutrition Monitoring Bureau of India. As shown pregnant and lactating women show low intakes in several nutrients especially iron vitamin A riboflavin and calcium (Banji and Lakshmi 1998).

What is the prevalence of micronutrient deficiencies in women?

When women become deficient in micronutrients they exhibit low serum, red blood cell or tissue levels of the nutrient. As the deficiency worsens clinical signs can be observed. Few assessments of micronutrient deficiencies through national

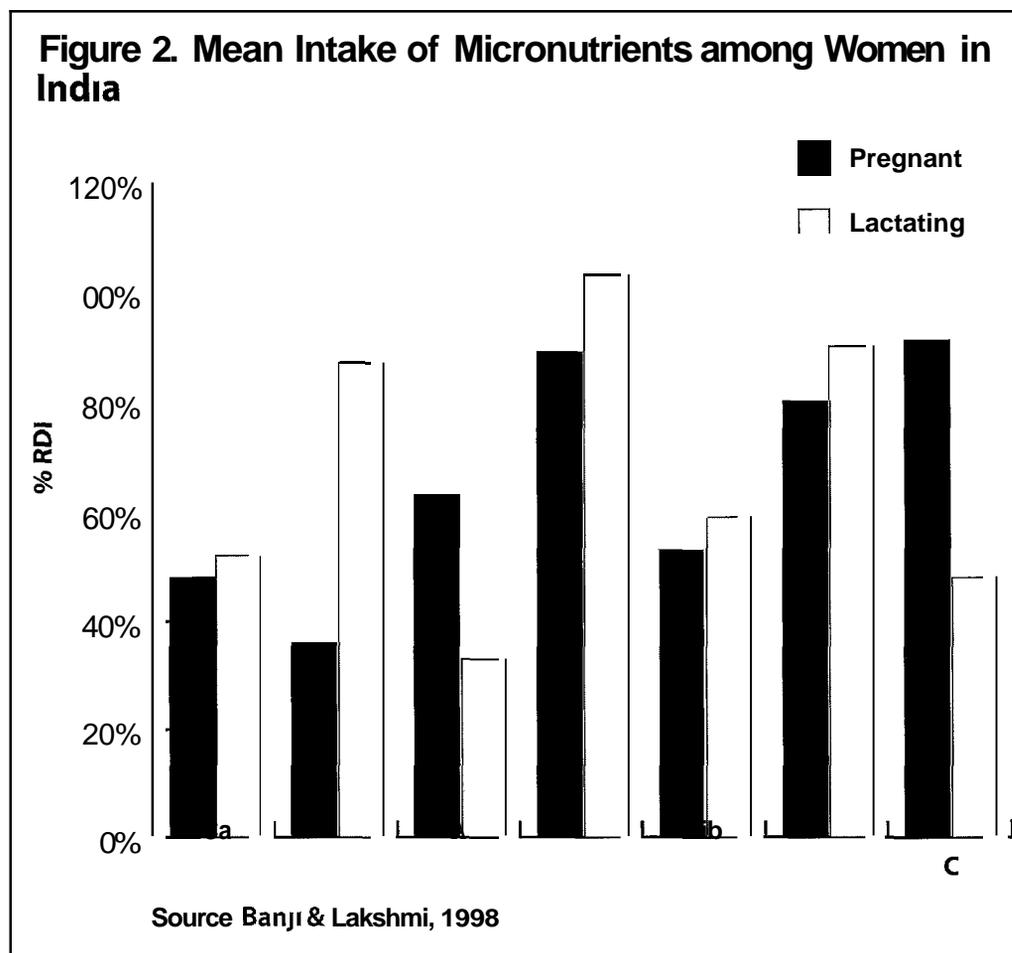
surveys have been conducted other than for iron iodine and vitamin A. However data from smaller scale studies indicate that micronutrient deficiencies of zinc folate B₆, B₁₂, and riboflavin among others are evident in many subpopulations. Box 3 reports on some of these studies.

What are the impacts of micronutrient deficiencies in women?

As discussed above poor diets among many women in developing countries result in insufficient intake of several nutrients. In conjunction with infections and infestations that increase demand for nutrients deficiencies occur that impair women's health, the outcome of their pregnancies and the growth development and health of their breastfed infants.

Impact on women's health

The impacts of iron and iodine deficiency on women's health are well known. Iron deficiency affects the function of sev-



eral organs in women it impairs work capacity (Yip et al 1998) and in adolescents it impairs learning (Watkins and Politt 1998) Iodine deficiency causes goiter in women and impairs intellectual functioning (Fernald 1998)

Recent placebo controlled trials illustrate the benefits of improvements in vitamin A status on women's health

- Enhanced vitamin A intake
- reduced the severity of morbidity in women in Nepal (West et al 1997 Christian et al 1997)
 - ♦ reduced anemia in pregnant and postpartum women in Nepal (Stoltzfus et al 1997) and among adolescents in Indonesia (Angeles Agdeppa et al 1997) and
 - ♦ reduced rates of malaria (*Plasmodium vivax*) in women in Nepal (Stoltzfus et al 1997)

Both increased folic acid and B₆ intake have been shown in large scale epidemiologic studies to be associated with reduced risk of fatal coronary heart disease (CHD) and non fatal myocardial infarctions and with reduced risk of arteriosclerosis among women (Rimm et al 1998 Robinson et al 1998) As morbidity and mortality among women from coronary disease increases in developing countries including many parts of Latin America (Peña 1995) these benefits will become increasingly vital

Osteoporosis is an increasing problem as the average age of populations of women in developing countries increases Calcium and vitamin D intake over a woman's life span are especially important

- ♦ A placebo controlled trial of calcium supplementation (1 000 mg of calcium carbonate) of postpartum women in

Box 3: What is the prevalence of micronutrient deficiencies in women?

- ♦ At least 50 million pregnant and 320 million non pregnant women in developing countries are anemic primarily due to **iron** deficiency (Stoltzfus 1995)
- ♦ **Iodine** deficiency and goiter among women are still found in many parts of India and Africa and isolated parts of Latin America and Eastern Europe
- ♦ In Nepal 20% of pregnant women and 27% of postpartum women (West et al 1997) were **vitamin A** deficient (based on serum retinol < 20 g/dl) In Indonesia 18% of postpartum women were deficient (< 70 mol/l) In a national survey in Costa Rica 25% of urban and 31% of rural women had low serum retinol levels (MOH as reported by Mora and Mora(a) PAHO 1998) Night blindness was observed in Nepal in 18% of pregnant and 8% of lactating women (Katz et al 1995) and in Bangladesh in 13–24% of women of reproductive age (Bloem DePee and Darnton Hill in press)
- ♦ In Indonesia a study of postpartum women observed that 24% were **zinc** deficient (Wieringa et al 1997) and a study of pregnant women in Peru found that 60% (Caulfield et al 1997a Caulfield et al 1997b) were zinc deficient (plasma zinc < 10.71 mol/l) In Egypt 33% were classified as zinc deficient (< 8.5 mol/l) (Kirksey et al 1994)
- ♦ **Folate** deficiency is a problem in some parts of India Western Africa and Burma (Sloan et al 1992) In a Kenyan study 6–8% of anemia in pregnancy was related to folate deficiency among the 48% of pregnant women found to be anemic (Calloway 1988)
- ♦ Suboptimal **vitamin B₆** status has been observed in Egypt among more than one third of breastfeeding women based on low breastmilk concentrations (Kirksey et al 1994)
- ♦ Low serum vitamin **B₁₂** has been observed among pregnant and lactating women in Mexico and low breastmilk **B₁₂** was reported in Kenya (Allen 1993) In India B₁₂ deficiency is widespread because of strict limitation of animal products
- ♦ **Riboflavin** deficiency is considered endemic in the Gambia and is common in other parts of Africa the former Soviet Union Indonesia and China (Powers 1998) Studies conducted by the National Institute of Nutrition in India found that more than two thirds of women were deficient (Banyal and Lakshmi 1998)

the US resulted in less bone loss or increased density of the lumbar spine in postpartum women though it did not affect total bone mass or forearm bone mineral density (Kalkwarf et al 1997)

Other benefits to improving micronutrient status for women's health are indirect. Reduced anemia leads to enhanced productivity which may result in increased incomes and overall improvements in diet health care and hygiene. Improved B₆ and iron levels among mothers can increase attentiveness to child rearing with possible

benefits for children's health and development. For example in Egypt mothers who were deficient in B₆ were less responsive to their infants' vocalizations showed less effective intervention to infant distress and were more likely to use older siblings as caregivers than were mothers with better vitamin B₆ status (McCullough et al 1990)

Impact on pregnancy outcome

Ramakrishnan et al (1998) summarized the relationship between micronutrient status and pregnancy outcome in a

recent review. They suggest that there is strong evidence from randomized controlled trials that zinc and magnesium supplementation improve birth weight and reduce prematurity and that supplementation with calcium improves birth weight and reduces prematurity and pre-eclampsia especially in high risk groups. Based on results of epidemiologic evidence they suggest that several other nutrients affect pregnancy outcome (including LBW, preterm births, premature rupture of membranes [PROM], fetal death, and pre-eclampsia). These nutrients include iron, iodine, vitamin A, folic acid, vitamin B₆, vitamin B₁₂, and vitamin D.

A review of nutritional interventions in randomized controlled trials and their effect on preventing intrauterine growth retardation (IUGR) was recently conducted by the World Health Organization (de Onis et al. 1998). There were only two trials of iron, four of zinc, two of magnesium, five of calcium, five of folate, and one of vitamin D that the authors considered adequately designed to assess impacts. Of these 19 trials, only six were conducted in developing countries where initial micronutrient status is likely to be worse than in developed countries. The authors observed that folate supplementation appears to reduce the incidence of term low birth weight and that zinc and magnesium supplementation may have beneficial effects and should be studied further.

Randomized controlled trials have examined the effect of daily doses of calcium among pregnant women on pregnancy outcome (Bucher et al. 1996). Recent analyses of the Cochrane data base of randomized controlled trials of pregnant women consuming low baseline calcium intakes (< 900 mg/day) found improvements in maternal health that were substantially greater than the impact of calcium supplementation observed among women with high calcium intakes (Villar and Belizan, in press). Among women with low baseline calcium intakes, the risk of high blood pressure was reduced by half (relative risk (RR) = 0.49, 95% confidence interval (CI) 0.38–0.62). The risk of pre-eclampsia was also reduced greatly

(RR = 0.32, 95% CI 0.21–0.49). Among women with high risk of hypertension there was also a major reduction in preterm delivery (RR = 0.42, 95% CI 0.23–0.78).

Research in Nepal illustrated that **maternal mortality** decreased by about half in women who received **vitamin A** for at least three months before and during pregnancy (West et al. 1997, UNICEF 1998). In the Nepal study the prevalence of **iron deficiency anemia** in pregnancy (hemoglobin < 11 g/dl) was reduced from 76% in controls to 69% among those receiving **vitamin A** (Stoltzfus et al. 1997).

Improving **folate** status prior to pregnancy is associated with reductions in neural tube defects (such as spina bifida). It is estimated that more than 200,000 such defects worldwide could be prevented by improving folate status prior to pregnancy (Molinari 1993). In North China it is estimated that 10% of the infant mortality rate (IMR) is due to neural tube defects. In South Africa, high rates (6/1,000 in 1986 in the Transkei and 3.6/1,000 in the Northern Province) have been reported (Robertson et al. 1997). Randomized controlled trials in the U.K., Hungary, Israel, Australia, Canada, Russia, and France reduced neural tube defects with a protective effect of 72% (MRC Vitamin Study Research Group 1991, Czeizel and Dudas 1992). A few other studies have shown benefits of multiple supplements in preventing cleft palate and other types of birth defects (Li et al. 1995, Shaw et al. 1995, Yang et al. 1997). Improving micronutrient status especially folate status prior to pregnancy would therefore help decrease infant mortality through the reduction in these defects.

Multiple supplements may also be beneficial for HIV positive women. When supplements were provided to HIV positive pregnant women in Tanzania in a randomized controlled trial, the risk of low birth weight decreased by 44%, preterm births (< 34 weeks of gestation) by 39%, and small size for gestational age by 43% (Fawzi et al. 1998). Supplements role in HIV transmission to the infant is now being assessed, however there were significant

improvements in maternal immune status associated with supplement use

Impact on health and nutritional status of breastfed infants

Micronutrient status in breastfeeding women affects breastmilk quality. Allen (1994) suggests the categorization of nutrients for lactating women based on their relationship with breastmilk quality.

Deficiencies of Priority I nutrients (thiamin, riboflavin, vitamin A, B₆, and B₁₂, iodine, and selenium) in lactating women result in lower concentrations in the breastmilk and have negative effects on infants. Increasing maternal intakes of Priority I nutrients results in improved concentrations in breastmilk and improved infant status since fetal storage of these nutrients is low and breastmilk is the major source for infants.

The concentrations of Priority II nutrients (folic acid, vitamin D, calcium, iron, copper, and zinc) in breastmilk are relatively protected during maternal deficiency and breastmilk concentrations are relatively unaffected by maternal supplementation. However, the mother is especially vulnerable to further depletion during lactation and postnatal supplementation is more likely to benefit the mother than her infant.

Improving maternal iron intake during pregnancy can improve the iron status of newborns. This was shown recently in Peru in a placebo-controlled trial in which the iron transfer to infants was significantly increased by the supplementation of pregnant women with 60 mg of iron (O'Brien et al., 1998).

In a randomized controlled trial of lactating women of low socioeconomic status in the U.S., multivitamin supplementation was shown to increase breastmilk concentrations of B₆, B₁₂, and Folate (Sneed, Zane, and Thomas, 1981). In a pre- and post-trial of supplements containing thiamin, riboflavin, niacin, and vitamin C among lactating women from the Gambia, breastmilk vitamin content was improved for these nutrients (Prentice et al., 1983).

Improving vitamin A status during pregnancy and/or lactation has been

shown to increase vitamin A in breastmilk in Bangladesh (Rice et al., 1997), Indonesia (Stoltzfus et al., 1993; Tanumihardjo et al., 1996), and Guatemala (Arroyave et al., 1974).

What is the role of multiple micronutrient supplements?

The above discussion has shown the prevalence of low intakes of many micronutrients in developing countries, associated deficiencies, and their consequences. Most supplement programs to date have provided iron/folic acid to pregnant women; some also have distributed vitamin A or iron/folic acid to postpartum women.

However, since women experience multiple deficiencies, use of multiple supplements should be considered (Trowbridge et al., 1993). The NAS (1998) suggests that a strategy to promote increased consumption of multiple micronutrients simultaneously would be more effective than the promotion of a select few. Combining multiple micronutrients in a single delivery mechanism has been suggested as a cost-effective way to achieve multiple benefits (Yip, 1997; Alnwick, 1998).

Do multiple micronutrient supplements improve nutrient levels?

Supplementing women with a single nutrient is an effective means to improve micronutrient status and is a long-standing approach used in clinical practice when deficiencies are found. However, some have questioned the effectiveness of nutrients combined within a supplement because of possible interactions of the nutrients or interference in their absorption (Allen, 1998; Argiratos and Samman, 1994). This section summarizes results of randomized controlled trials that illustrate that combined supplements are effective in improving micronutrient status (see Appendix 7).

* Daily supplements of vitamin A (retinol) with iron (elemental iron) increased hemoglobin and had a greater impact on reducing anemia in pregnant women in Indonesia than iron

- alone (Suharno et al 1993 Suharno et al 1992)
- ♦ A multiple supplement containing iron vitamin A and other nutrients reduced both **anemia** and **vitamin A** deficiency among adolescents in Indonesia' (Angeles-Agdeppa 1997)
- ♦ A multiple micronutrient-fortified beverage provided daily to school children in Tanzania improved **iron status** (measured by serum ferritin) significantly after six months (Ash Tatala Frongillo et al 1998)
- ♦ Multiple supplements containing **vitamin A** resulted in increased plasma vitamin A at delivery among HIV positive pregnant women in Tanzania (Fawzi et al 1998)
- ♦ While absorption of both zinc and iron are inhibited when combined (O'Brien et al 1998) improvements in both **iron** and **zinc** status were found among pregnant women receiving supplements in Peru (Caulfield et al 1997) and among children in Mexico (Rosado et al 1997)
- 4 In a Mexican study children were randomly assigned to receive a beverage (for five days a week) containing zinc (20 mg zinc methionine) iron (20 mg of iron sulfate) zinc and iron or a placebo (Munos et al 1997) After 12 months both zinc and iron (alone or together) supplementation led to increases in plasma **retinol**
- 4 Multiple supplements containing **foliacid** increased folate status in women of reproductive age in Hungary (Czeizel and Dudas 1993)
- ♦ Multiple supplements containing **B₆** resulted in increased levels of **B₆** among lactating women in the U S (Sneed et al 1981)
- ♦ Lactating women in the Gambia given ferrous sulphate plus **riboflavin** showed a significant increase in circulating plasma iron and iron stores (Powers Bates and Lamb 1985)

acid supplementation and iron fortification of staple products Questionnaires were sent to 163 countries where UNICEF has programs and 57 responded Policies for the universal distribution of iron or iron/folic acid during pregnancy were evident in 49 of 57 countries (86%) (Dalmiya 1998) Most countries distribute iron as ferrous sulfate but Thailand and Cuba provide ferrous fumarate (Dalmiya 1998) In parts of India iron folic acid and vitamin B₁₂ are distributed to pregnant women

However even though programs exist throughout the world the effectiveness of iron/folic acid supplementation programs for women during pregnancy has been questioned (Yip 1996) Evaluations of programs have shown thus far that this approach has limited benefits Aside from limited coverage and poor compliance the focus on pregnant women provides an insufficient time period to reduce iron deficiency In addition since developing country diets are limited in many other essential vitamins/minerals needed for the absorption transport metabolism and use of iron/folic acid the effectiveness of efforts including only these nutrients are limited even if they are successful in increasing supplement use among the target population

Use of iron/folate for postpartum women was reported by UNICEF for only four countries Bangladesh Pakistan Oman and Bhutan

Based on UNICEF field office reports (UNICEF/WHO 1995) of 78 countries with vitamin A deficiency 46 have policies to supplement postpartum mothers with high dose vitamin A However in only one fifth of all the countries with deficiency and only one third of those with policies did at least 10% of mothers receive high dose capsules following delivery A recent national survey in Honduras whose public health system reaches rural areas effectively reported that only 13% of women³ had received a high dose vitamin A capsule during their last postpartum period (Sec de Salud Publica 1997) Even where higher coverage of postpartum women has been achieved it is difficult to enhance

Note 2 Supplements containing iron folic acid and vitamins A and C led to reduced anemia and vitamin A deficiency when taken on a daily or weekly schedule The daily dose used in the study was 60 g iron and 750 g retinol and there were more side effects related to iron in the daily group

Note 3 Women living in households with children 12-71 months of age 9% were pregnant at the time of the survey

What are current policies and programs for supplements?

UNICEF collected information on government policies related to iron and folic

vitamin A stores with this one time approach (Rice et al 1997)

Only a few countries provide multiple micronutrient supplements through the health system (see Appendix 2) In Cuba a multiple supplement containing 35 mg of iron is provided to pregnant women At prenatal care visits pregnant women in Honduras receive a multiple vitamin/mineral prenatal supplement and an iron tablet containing 60 mg of iron (ferrous sulfate)(Caulfield 1997c) The contents of the prenatal supplement have changed over the last several years and appear to be selected based on bids received during the Ministry of Health's procurement process The only country to distribute multiple vitamins on a population basis is Cuba in response to the neuropathy epidemic related to thiamin and other micronutrient deficiencies National distribution of supplements to Cubans over one year of age began in 1993 (Macias Matos et al 1996)

The U S government recommends that all women of reproductive age consume daily supplements containing 400 µg of folic acid (Oakley et al 1998 Oakley et al 1992) The U S also recommends that pregnant women consume a supplement containing 30 mg/day of iron starting with the first prenatal visit in order to reduce iron deficiency during pregnancy (Yip et al 1998)

While there is no recognized policy in the U S concerning multiple supplement use 98% of obstetricians and gynecologists recommend supplements to their patients during pregnancy and 92% specifically recommend prenatal supplements (Levine 1993) The National Maternal and Infant Health Survey conducted in 1986 found that 81% of women reported consuming supplements during their last pregnancy (Yu et al 1996)

The National Health Interview Surveys collect information on adults in the U S regarding supplement use in the past year In the 1987 survey 51% of all adults reported that they had consumed any type of vitamin or mineral supplement within the last year 39% had taken a supplement for more than two days in the past

month and 23% reported that they had consumed a supplement on a daily basis over the last year (Subar and Block 1990) Among the age group 25-34 years 15% of white men and 23% of white women took a daily supplement The 1992 survey found that 27% of women used a daily supplement and 20% took daily multiple supplements (Sleskinski et al 1995)

A 1983 survey in Australia found that 37% of women were regular supplement users (taking a multiple vitamin or mineral supplement at least once a week) and another 13% were irregular users (Truswell 1985 as quoted in Schrijver et al 1993) In Finland 14% of women used supplements in 1985 and in the U K market research found that 31% of adults consumed supplements in 1984 (Schrijver et al 1993)

What issues should be considered in selecting micronutrient supplements?

The selection of an appropriate supplement for women of reproductive age requires decisions about the following

- 1) Which reference standards will be used to determine nutrient levels to include in the supplements?
- 2) Which nutrients and what quantities will be included?
- 3) Which factors need to be considered in purchasing supplements?
 - a) availability of supplements
 - b) safety
 - c) costs of supplements
 - d) quality
 - e) acceptability and compliance

Which reference standards will be used?

Reference standards commonly used to assess adequacy of micronutrient intakes have been set by the U S Institute of Medicine (National Academy of Sciences/National Research Council) the U K Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy (U K Department of Health) and the World Health Organization Several other European countries the European

Note 4 The RNI's are defined as the amount sufficient or more than sufficient to meet the nutritional needs of practically all healthy persons in a population and therefore exceed the requirements of both (Dept of Health 1991) As with the RDAs these are calculated as the mean requirement for a group of individuals + 2 standard deviations of mean requirements

Note 5 In contrast to RDAs and RNI's the newest WHO recommendations include two sets of requirements for each nutrient a basal requirement that is the intake needed to prevent pathologically relevant and clinically detectable signs of impaired function attributable to inadequacy of the nutrient and a normative requirement that is the intake that serves to maintain a level of tissue storage or other reserve judged to be desirable Also in contrast to the requirements above WHO figures for trace elements are given for the lower limits of the safe ranges of population mean intakes (which are higher than the average individual normative requirements for a trace element)

Note 6 Safe levels of intake for vitamin A iron folate and B₁₂ were set in 1988 Values for thiamin riboflavin and niacin were set in 1965 and for calcium in 1961

Note 7 The only nutrient value to change dramatically since 1968 is biotin which has an RDI of 300 µg while the current highest level in the 1988 RDAs is 30-100 µg There are separate RDIs for pregnancy and lactation for children under age two and for children ages two to four Infant formula has separate labeling requirements

Community Canada and some developing countries such as China and India also have established reference standards but these are not often used for international comparisons of population nutrient intakes

These reference standards are based on

- 1) Physiological requirements for healthy individuals (by age sex and reproductive status) based on
 - a) intakes associated with absence of deficiency diseases or to cure deficiency diseases
 - b) intakes needed to maintain nutrient balance and
 - c) intakes needed to maintain circulating levels or enzyme saturation or tissue concentration of the nutrient (enabling storage of the nutrient)
- 2) Bioavailability of nutrients (estimated as the proportion of nutrients consumed that are absorbed)
- 3) Nature of the diet
- 4) Toxicity levels for the nutrient

Because of emerging information on the health benefits of nutrients consumed at levels higher than physiologic requirements some revisions of the reference standards now also take into account such benefits (e.g. folic acid's role in preventing neural tube defects and coronary artery disease)

The U S Recommended Dietary Allowances (RDAs) are recommendations designed for *healthy* populations in the U S and thus may underestimate the requirements of populations in developing countries The U S RDAs are age and sex specific and separate values are given for pregnant and lactating women The most recent reference values published in 1998 are referred to as the Dietary Reference Intakes (DRIs) and include RDAs and adequate intakes (AIs) (IOM 1997 IOM 1998) Adequate intakes are based on average intakes that appear to sustain a defined nutritional state (IOM 1997) and are used when scientific evidence is too limited to develop RDAs

The U K Panel on Dietary Reference Values in 1991 revised its previous Recommended Daily Amounts (also known as

RDAs) The U K now uses the term Reference Nutrient Intake (RNI) to illustrate requirements for a particular nutrient (Dept of Health 1991)⁴ The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) (WHO 1996) have established lower and upper limits of safe ranges of population mean intakes to meet individual basal or normative requirements for trace minerals (such as zinc copper selenium iodine magnesium etc)⁵ WHO/FAO are now revising the standards for other micronutrients⁶

The U S Food and Drug Administration within the Department of Health and Human Services (HHS) sets labeling requirements for processed food or dietary supplements Unlike the RDAs which are age and sex specific a single set of reference values the Reference Daily Intake (RDI) is used for labeling purposes (USDA 1995)⁷ The intakes are based on the 1968 RDAs because when labeling requirements were first established these were the most recent ones available In general RDIs are set at the highest level for any subgroup within the 1968 RDAs Multiple vitamin and mineral supplements are labeled based on the percentage of the RDIs (referred to as Daily Reference Values or Daily Values)

Appendix 1a-1b compares RDIs RDAs RNI's and WHO values for women of reproductive age pregnant and lactating women

Which nutrients and quantities will be included?

Because there is no international consensus on the levels of nutrients that should be included in supplements we have suggested a supplement composition for women of reproductive age shown in Table 2 This formulation in part conforms with U S RDI levels since U S standards are often used by supplement manufacturers to determine their formulations Thus these levels are more likely to be available in already manufactured supplements sold in the U S and other parts of the Western Hemisphere

Some levels have been modified to take into account recent revisions in the

U S RDAs that are not accounted for in the U S RDIs. Because of the widespread problem of iron deficiency in developing countries, 27 mg of iron rather than the RDI of 18 mg is suggested. This level is lower than the recommended level of 60 mg for prophylactic iron supplementation of women of reproductive age in areas of high prevalence of iron deficiency (Stoltzfus and Dreyfuss, 1998). However, prophylactic iron is recommended daily for a period of one to three months, and the proposed supplement should be taken daily for longer periods of time. The 27 mg level reduces the risk of accidental iron poisoning among young children and complies with U S regulations. In addition, if women consume supplements at least twice a week, they will be consuming an amount similar to many of the iron supplements used in weekly supplementation trials, which have resulted in improvements in iron status among adolescents and women of reproductive age (Angeles Agdeppa et al., 1997).

Folic acid is included at the current RDA of 400 µg rather than the lower RDI level. Copper is included because both iron and zinc can inhibit copper absorption and copper is recommended for inclusion in supplements containing iron and zinc (NAS/NRC, 1989). Calcium levels have not been recommended because of the large amounts needed to meet the RDIs and the difficulty in producing a single, small tablet that contains sufficient calcium. Some calcium would be useful, however, depending on the ability of manufacturers to include bioavailable calcium. While iodine is often included in multiple supplements, we have excluded iodine from the proposed supplement for two reasons. Within populations consuming iodized salt, additional iodine is not necessary and could pose problems of toxicity among recently iodine-deficient women. Additionally, concern has been raised about the interaction of iodine with other elements in the tablet (Nilson, 1997).

In addition to this proposed formulation, ranges in appropriate nutrient levels are given in Table 2. The ranges can be used to choose appropriate formulations that may not meet this exact formulation

but that would also be appropriate for use by women in developing countries. These ranges are generally based on the lowest RDA, RNI, or WHO recommended level for women of reproductive age and the highest level of the RDI, RDA, RNI, or WHO levels for pregnant or lactating women when these are higher than the RDIs.

Providing supplements containing nutrients below the lower range would mean that diet would have to include a larger proportion of the daily requirements to ensure adequate intake by all women. Supplements containing levels of nutrients above the upper range would not necessarily be unsafe, but they could result in inappropriate mixes of nutrients that could impair their effectiveness. In addition, higher levels could also increase costs unnecessarily.

Because pregnant women need greater amounts of iron and other nutrients, a special formulation may be useful. We have proposed a formulation for a supplement for pregnant women in Table 3, based in part on the U S RDIs for pregnancy and lactation used in labeling prenatal supplements, with some changes to address recently revised recommendations.

In contrast to the decisions about selection of ranges in Table 1 using lowest and highest values for RDAs, RNIs, and WHO values, we have selected ranges between 1 and 2 RDAs. Since the U S RDAs in nearly all cases are higher than U K RNIs and WHO levels, these ranges also encompass the ranges for these levels. As shown in Tables 2 and 3, the selection of levels for supplements can be quite arbitrary but should balance scientific knowledge with practicality. However, a study conducted in the U S found that 50% of prenatal supplements sold there were formulated inappropriately (using the criterion of nutrient levels greater than twice the RDA [Bell and Fairchild, 1998]). Thus, it is essential to ensure that nutrient levels in the tablet are within suitable ranges.

A calcium/magnesium supplement could also be considered for pregnant women because of the beneficial effects of calcium in preventing pregnancy in

Table 2. Proposed ranges of nutrients in a multiple micronutrient supplement

Nutrients	US RDAs for women of reproductive age 1988*, 1998***	US RDIs	Proposed supplement for women of reproductive age	Proposed ranges for supplements for women of reproductive age
Vitamin A µg RE***	800*	875	875	500–1 300
Vitamin A IU***	2 664 retinol 8 000 beta carotene	2 914 retinol 8 750 beta	5 000	2 500–8 000
Vitamin D IU	200 (AI)**	400	400	100–400
Vitamin E IU	8**	30	30	8–30
Vitamin B ₁ (Thiamin) mg	1 1**	1 5	1 5	8–1 6
Vitamin B ₂ (Riboflavin) mg	1 1**	1 7	1 7	11–1 8
Niacin mg	14**	20	20	11 5–20
Folate µg	400**	400	400	400–1 000
Vitamin B ₆ mg	1 3**	2	2	1 6–2 1
Vitamin B ₁₂ µg	2 4**	6	6	2 0–2 6
Vitamin C mg	60*	60	60	60–100
Zinc mg	12*	15	15	7–25
Iron mg	15*	18	27	15–29
Calcium mg	1 000 (AI)**	1 000		100–1 200
Phosphorus mg	700**	1 000		0–1200
Magnesium mg	Age 19–30 310** Age 31–50 320**	400	100	100–400
Vitamin K µg	65*		65	0–65
Iodine µg	150*	150		0–200
Selenium µg	55*			30–75
Copper mg	1 5–3 0* (ESADI)	2 0	2 0	1 5–3 0
Manganese mg	2 0–5 0* (ESADI)			2 0–5 0
Fluoride mg	3 1 (AI)**			0
Chromium µg	50–200* (ESADI)			0–200
Molybdenum µg	30–100* (ESADI)			0–250
Biotin µg	30 (AI)**	300		30–200
Pantothenic acid mg	5 (AI)**	10		0–10
Choline	425 (AI)**			

***1µg RE = 3 33 IU retinol or 10 IU beta carotene

duced hypertension and pre eclampsia and the beneficial effects of magnesium on improving birth weight and reducing pre maturity. However, the logistics of supplying additional supplements along with prenatal multiple vitamin/mineral tablets has not yet been attempted on a large scale basis.

While it would be optimal to have at least two formulations for programs (one for women of reproductive age and one for pregnant women), many programs will not be able to manage this because of the associated costs (for supply, distribution, management, training, and education). The supplement for women of reproductive age could be used effectively during pregnancy as long as additional iron supplements containing 30–60 mg were provided in areas with a high prevalence of iron deficiency. The addition of the other nutrients to ensure that nearly all women consume 100% of the RDA for pregnancy may not warrant the additional costs of procuring two supplements.

Which factors need to be considered in purchasing supplements?

Programs generally will procure supplements from among those already available on the market. However, some of the available ones contain inappropriate amounts of nutrients for women of reproductive age, and others may be excessively expensive for a national program. To decide on what supplements should be procured, several issues need to be considered.

What supplements are currently available?

Multiple micronutrient supplements are not currently available from UNICEF, but the International Dispensary Association (IDA) and other nonprofit agencies procure them for sale to nonprofit organizations and developing country governments. However, as shown in Appendix 3a, the micronutrient supplements available for purchase through these agencies are inappropriate because they do not contain sufficient iron, zinc, copper, vitamin A, or folic acid.

Supplements can also be purchased wholesale from manufacturers or distribu-

tors or directly from pharmacies or other stores (depending on local regulations), but the cost and composition of the supplements vary greatly. Appendix 3b shows several common private label and generic brands of multiple vitamin/mineral supplements sold for women of reproductive age in the U.S., and Appendix 3c shows supplements sold for pregnant women in the U.S. and Europe. Many supplements for women of reproductive age contain 18 mg of iron, but those labeled with iron, such as Bayer One a Day with Iron, often include 27 mg of iron. Most prenatal supplements have 60 mg of iron (ferrous fumarate) (the RDA for pregnancy is 30 mg) and 15–25 mg of zinc (the RDA for pregnancy is 15).

Supplements available on the market in Bolivia and Zambia are shown in Appendix 4a–c. The amount of nutrients contained in these supplements varies widely and has no clear relationship with RDAs for women. The levels of nutrients in multiple supplements available in other developing countries need to be assessed to determine whether locally available products are suitable.

Appendix 5 shows the various forms of vitamins and minerals commonly used in supplements and the allowable tolerance levels proposed in the U.S. Pharmacopeia standards. Numerous forms of minerals are available (especially for iron and calcium), and they often vary in their absorbability, use, and color. Vitamin A can be included as either preformed vitamin A or beta carotene. Preservatives and stabilizers are often added to supplements to prevent interactions between nutrients. In some cases, minerals are encapsulated (in polysorbate or polymaltose) or iron is chelated (attached) to an amino acid, which keeps it from reacting to other elements and aids absorption.

What safety issues need to be addressed?

Some have questioned whether multiple micronutrient supplements are safe. Their use is widespread in the U.S. and other developed countries, and no negative consequences of using supplements with levels of nutrients normally provided

Table 3. Proposed ranges of nutrients in a multiple micronutrient supplement for pregnant women in developing countries

Nutrients	US RDAs ¹ for pregnancy 1988* 1998 ^{***}	US RDIs pregnant or lactating women	Proposed supplement for pregnant women	Ranges used in Table 2	1 to 2 times the US RDAs for pregnancy
Vitamin A µg RE ^{**}	800 ^{''}		800	500-1 300	800-1 600
Vitamin A IU ^{**}	2 664 retinol 8 000 beta-carotene	8000	2 664 retinol 8 000 beta carotene	2 500-8 000	2 664-5 328 retinol 8000-16000 beta carotene
Vitamin D IU	200 ^{''} (AI)	400	400	100-400	400-800
Vitamin E IU	10 ^{''}	30	30	8-30	10-20
Vitamin B ₁ (Thiamin)mg	14 ^{''}	1 7	1 7	8-1 6	14-2 8
Vitamin B ₂ (Riboflavin) mg	14 ^{''}	2 0	2 0	11- 18	1 4-2 8
Niacin mg	18 ^{**}	25	25	11 5-20	18-36
Folate µg	600 ^{**}	800	800	400-1 000	600-1 200
Vitamin B ₆ mg	1 9 ^{**}	2 5	2 5	1 6-2 1	1 9-3 8
Vitamin B ₁₂ µg	2 6 ^{**}	8	8	2 0-2 6	2 6-5 2
Vitamin C mg	70 ^{''}	60	60	60-100	70-140
Zinc mg	15 ^{''}	15	15	7-25	15-30
Iron mg	30 ^{''}	18	60	15-29	30-60
Calcium mg	1 000 ^{''} (AI)	1300		100-1 200	1 000-2 000
Phosphorus mg	700 ^{''} *	1300		0-1 200	700-1 400
Magnesium mg	350 ^{''} *	450	100	100-400	350-700
Vitamin K µg	65 ^{''}		65	0-65	65-130
Iodine µg	175 [*]	150		0-200	175-350
Selenium µg	65 [*]			30-75	65-130
Copper mg	1 5-3 0*(ESADI)	2 0	2 0	1 5-3 0	1 5-60
Manganese mg	2 0-5 0*(ESADI)			2 0-5 0	2 0-10 0
Fluoride mg	3 1 (AI) ^{''}			0	3 1-62
Chromium µg	50-200 ^{''} (ESADI)			0-200	50-400
Molybdenum pg	75-250 [*] (ESADI)			0-250	75-500
Biotin µg	30 (AI) ^{**}	300		30-200	30-60
Pantothenic acid mg	6 (AI) ^{**}	10		0-10	6-12
Choline	450 (AI) ^{**}				450-900

***1 g RE = 3 33 IU retinol or 10 IU beta carotene

in over the counter supplements have been reported (Bendich 1993 Hatchcock 1997a Hatchcock 1997b)

However safeguarding the safety of supplements depends on ensuring non toxic levels of nutrients and appropriate packaging Appendix 6 gives upper levels of safe intakes of nutrients published by the IOM (1997 1998) NAS/NRC (1989) WHO (1996) and the Council on Responsible Nutrition⁸ (Hatchcock 1997a) There are generally wide margins between the levels proposed in the formulations in Tables 2 and 3 and the upper levels of safe intake

Three different levels are used to assess excess intakes The No Observed Adverse Effect Level (NOAEL) identifies intake levels not associated with adverse effects The Lowest Observed Adverse Effect Level (LOAEL) is the intake level that has been associated with adverse effects Tolerable Upper Limits (UL) are values reported recently by IOM (1998) calculated from the LOAELs using an uncertainty factor that takes into account the reliability of the LOAEL figures

However several of the supplements sold in developing countries include levels of vitamin A fluoride thiamin and niacin higher than suggested as safe Labels should be examined for the amounts that are included and supplements outside the safe ranges should not be used on a daily basis

Excessive levels of vitamin A in the form of pre formed vitamin A (retinol) among pregnant women in the first trimester have been associated with birth defects Thus the limit for retinol has been suggested at 10 000 IU on a daily basis However if the vitamin A content includes both retinol and beta carotene as is common only the amount of retinol is of concern

In addition to preventing toxicity from nutrients within a single tablet it is also necessary to ensure that the combined consumption of nutrients in the diet and in supplements does not exceed toxic levels In populations where iodine deficiency was previously prevalent thyrotoxicosis can occur with increased iodine consumption because the thyroid uses iodine more ef

fectively In such populations toxic levels may be consumed especially if quality control of the fortification of salt with iodine process is inadequate

If supplements containing fluoride are consumed in addition to highly fluoridated water fluoride toxicity can result The Therapeutic Products Programme of Health Canada states that fluoride should not be given to children under age three (except on the advice of a doctor or dentist) and should not be consumed in areas with fluoridated water (FDC Reports February 16 1998)

Many anemia control programs promote the use of 60–120 mg of iron and 250–400 µg of folic acid (Stoltzfus and Dreyfuss 1998) for pregnant women The safety of intake of iron/folic acid in addition to a multiple supplement should be considered Iron levels exceeding 200 mg per day are not associated with health problems however side effects are likely (Stoltzfus et al 1995) Women who have previously delivered infants with neural tube defects are prescribed 4 000 µg of folic acid daily with no negative effects reported Thus the amount obtained from a daily iron/folic acid tablet in combination with a multiple supplement containing 60 mg of iron or 400 µg of folic acid does not pose a health risk

Overdosing of nutrients from supplements can occur among children because they require much lower levels of most nutrients and consumption at higher levels can be toxic In the U S a recent FDA ruling states that any pills containing 30 mg or more of elemental iron must be packaged in individual doses such as blister packs to reduce the number of deaths and hospitalizations among children from iron poisoning (*HHS News* 1997) Even if pills contain less than that amount they need to be sold in childproof (difficult to open) bottles because consumption of several tablets containing only 10 mg each (as found in children's vitamin/mineral supplements) can cause poisoning and 900 mg can be lethal

Note 8 Trade association of manufacturers or distributors of dietary Supplements in the US

What are the relative costs of the supplements?

The raw materials of most nutrients (such as thiamin, riboflavin, niacin, B₆, B₁₂, zinc, and folic acid) at RDI levels included in a multiple vitamin/mineral preparation cost less than 0.05 cents each. Nutrients such as ferrous fumarate and vitamin D have medium range costs of 0.05–0.1 cents each. Vitamin A (retinol) is more expensive (beta carotene is much more costly) at between 0.1 and 0.2 cents, and the most expensive are vitamins C and E (at costs of about 0.2 cents for 70 mg and 10 IU, respectively). The raw materials for a supplement containing all these nutrients cost less than about 1/10th of a U.S. cent (Nilson, 1997). The total retail cost of producing and packaging the supplement is generally about 10 times the cost of raw materials. When distribution, management, and information, education, and communication (IEC) are added, the cost of the individual nutrients in the supplement represents only a small portion of the total cost.

Some forms of iron (ferrous fumarate) are more expensive than others (ferrous sulfate) but ferrous fumarate reacts less with other nutrients in multiple supplements. The type of vitamin A used also differentially affects other nutrients within a tablet. Information on the forms of nutrients included in supplements should be requested from manufacturers.

In our survey of supplements sold in the Washington, D.C. area, the retail cost of a single multiple vitamin/mineral supplement containing most of the nutrients recommended by the RDAs ranged from \$0.05 to \$0.13 for women of reproductive age and \$0.10–0.13 for prenatal supplements. Retail costs include profit margins for distributors and retailers; wholesale costs are less. Our research suggests that it would be possible to purchase multiple supplements similar to the one recommended in Table 2 for about \$0.01 each if five to ten million tablets were procured.

A means of reducing costs considerably to women of reproductive age is through weekly rather than daily supplements. Weekly or biweekly doses of iron

iodine, vitamin A, vitamin D, and riboflavin (Alnwick, 1998; Bates et al., 1983) have been shown to be effective; however, few data exist on whether other nutrients would also work well on a weekly/bi-weekly basis. Theoretically, daily supplementation should not be necessary since requirements are based on *average* daily intakes.

What quality issues need to be considered?

The quality of the supplement depends on many factors, including the manufacturing practices used, nutrient interactions, storage, and packaging, dissolution time, and adulteration.

Good manufacturing practices

In many countries, including Canada, dietary supplements are regulated as drugs and thus have more stringent requirements (such as registry and approval of the tablets and their ingredients, sterile manufacturing environments, and expiration labels). In the U.S., dietary supplements are regulated as foods rather than as drugs. Manufacturers and distributors do not have to register their products or ingredients with the Food and Drug Administration (FDA) or get approval before they produce or sell dietary supplements. The FDA does not routinely test supplements; manufacturers are responsible for ensuring that the ingredients included in the supplement are safe and not contaminated, and that the amounts stated on the label match the amounts in the supplements.

Guidelines on good manufacturing practices (GMP) are described in *Good Manufacturing Practices for Pharmaceutical Products* (WHO, 1992) as well as by national regulatory authorities or independent agencies such as the U.S. Pharmacopeia (USP), British Pharmacopeia, International Pharmacopeia, the European Pharmacopeia, the Federal Chemical Codex, and the American Chemical Society standards. The Council on Responsible Nutrition has drafted a suggested list of good manufacturing practices (GMPs) for dietary supplements modeled on food GMPs (CRN, 1997).

Companies that follow the standards established by an independent quality control organization such as the USP can say that their product meets the standards of that organization. This tells consumers that the manufacturer claims to follow certain procedures to ensure the quality of the product. However, since the FDA does not routinely monitor products (due to lack of funds) there is no assurance that the practices have been followed. In many cases even with well known private label the manufacturer follows a specified quality control standard is not shown on the label.

An essential means of evaluating the quality of micronutrient supplements is to request information from manufacturers documenting their adherence to good manufacturing practices (GMP) guidelines. GMP helps ensure that products are produced consistently and meet quality standards. According to the WHO (1992) GMPs specify that

- ♦ All vendors and components are validated
- ♦ All manufacturing processes are clearly defined and systematically reviewed
- ♦ Critical steps of manufacturing processes and significant changes to the process are validated
- ♦ All necessary facilities are provided and appropriately maintained
- ♦ All production steps are adequately documented
- ♦ All workers are trained
- ♦ All batches are fully documented and samples retained
- ♦ Retained samples are systematically evaluated
- ♦ Complaints are recorded and investigated

When procuring supplements buyers should demand certificates of analysis preferably issued by an independent lab following USP or other testing protocols.

Nutrient interactions

Some concern has been raised about the negative effect of interactions between different nutrients in a multiple vitamin/mineral supplement. While it is true that

some nutrients compete to be absorbed if sufficient quantities are given the quantity of nutrients absorbed is generally not compromised substantially. There are often benefits to combining some nutrients because of the ability of one nutrient to enhance the transport, absorption, or use of another (e.g. vitamin A is needed for iron transport, vitamin C enhances iron absorption).

The largest concern about interactions is with minerals (iron, zinc, calcium, copper). Several studies have reported that when supplements include both iron and zinc there may be problems with zinc or iron absorption. However, results are conflicting and depend on the quantities included (Tamura and Goldenberg, 1996). When combined iron (60 mg)/folic acid (250 µg) and zinc (15 mg) were tested among pregnant women in Peru, that combination was as effective as iron/folic acid alone in improving hemoglobin levels (Zavaleta et al., 1997) and led to higher zinc levels during pregnancy and in the neonate even though absorption of iron was reduced with the addition of zinc (Caulfield et al., 1997b). Because iron can accelerate vitamin degradation (especially vitamins A and C) some forms of iron are better than others in a supplement. Forms of iron that are less reactive are preferable, however, this needs to be balanced with their bioavailability.⁹ Vitamin A is often encapsulated to prevent it from interacting with other vitamins or minerals.

Storage and packaging

The shelf life of the product is affected by packaging and types of nutrients used (e.g. whether encapsulated). Conditions that affect the potency of supplements include temperature, humidity, and light. Dark bottles are often required to prevent light from oxidizing the iron or vitamin A unless special forms of these nutrients have been used. Blister packaging offers the advantages of having each tablet sealed in an airtight space to prevent deterioration from exposure to air and humidity.

The expiration date should be included on the label so that supplements used are within the effective range.

Note⁹ While reduced iron is cheapest and reacts the least, its bioavailability is considered lower than many other forms of iron. The relative cost of the iron compounds thus needs to be estimated based on these factors.

Dissolution standards

If tablets do not dissolve within the expected time period their nutrients cannot be absorbed by the small intestine where most absorption takes place. Dissolution standards are given within the various Pharmacopeia and other standards.

Adulteration

Contamination of the supplement with undesirable microorganisms could be a concern if manufacturing practices are poor. No elements should be included in the product other than those listed on the label. Several recalls have been made by the Food and Drug Administration when supplements were found to be contaminated with lead or to contain dyes not approved by the FDA.

Poor manufacturing practices can also lead to toxic levels of nutrients being introduced by mistake. Ensuring quality control can be especially important for vitamins A and D, thiamin, niacin, B₆, selenium, fluoride, iodine, and copper. In the 1980s 13 people in the U.S. developed selenium intoxication after consuming manufactured supplements containing 27.3 mg of selenium per tablet (NAS/NRC 1989).

What factors influence compliance?

Iron supplement compliance has been studied but little is known about compliance with multiple supplements among populations in developing countries. With iron the side effects, color, stability of the supplement, information provided to the consumer, and recommended frequency of use all are known to affect compliance (MotherCare 1997). Tablet size is another factor likely to affect compliance.

While calcium is an important nutrient especially for pregnant women and adolescents the daily amount suggested in the RDAs requires a large tablet (more than a gram). Most multiple supplements are smaller, weighing half that amount, and most prenatal supplements contain only about 200 mg of calcium. More calcium can be packed into a tablet similar in size to a prenatal tablet but packing of calcium reduces its bioavailability.

The amount of iron in the tablet also influences compliance. Higher iron levels are associated with more symptoms including gastrointestinal problems and nausea (Schultink et al 1993; Schultink and Gross 1998).

Social marketing efforts can increase compliance of supplements and the messages used will need to be context specific. Special packaging and messages may be used to focus on selected target populations; this will affect compliance as well.

Conclusion

The use of multiple vitamin/mineral supplements by women in developing countries is an important strategy to improve micronutrient status and benefit women's health, pregnancy outcome, and child health.

For all women of reproductive age who are deficient, increasing micronutrient intake (iron, vitamin A, folic acid, and riboflavin) will reduce anemia with benefits to their health and work output. Increasing intake of these and other nutrients benefits women's overall health status, improves immunity, and reduces severity of such infections as malaria and such chronic diseases as coronary heart disease. Improving folic acid intake before pregnancy will reduce birth defects such as spina bifida, which in many countries contributes significantly to infant mortality. Improving iron status prior to pregnancy helps prevent the devastating effects of severe anemia in pregnancy.

During pregnancy both the mother and her fetus are at risk of micronutrient deficiencies, so this period deserves special attention. Iron deficiency, especially severe anemia, must be treated during pregnancy and it is clear that increasing the intake of other nutrients during pregnancy provides additional health benefits. Increasing vitamin A intake has been found to reduce maternal mortality, so it should be an essential component of the Safe Motherhood Initiative in vitamin A deficient areas.

Supplementation of postpartum women will benefit their own health and help ensure the presence of many nutrients in their breastmilk. But waiting until pregnancy and the postpartum period is often too late to benefit the child's micronutrient status. For example, although vitamin A status improved in both women and infants after supplementation in pregnancy and/or lactation, significant percentages of women and breastfed infants were still deficient after supplementation for several months postpartum (Bangladesh and Indonesia) or when supplemented prior to and throughout pregnancy and the postpartum period (Nepal).

Therefore, programs should consider the following options in order of priority to improve micronutrient status among women who are at high risk of being deficient in one or more micronutrients through the use of multiple vitamin mineral supplements:

- 1) Ensure that pregnant women receive daily micronutrient supplements for at least 180 days of pregnancy (during the second and third trimesters)
- 2) Ensure that breastfeeding women receive daily micronutrient supplements for the duration of breastfeeding
- 3) Ensure that adolescents and women of reproductive age who register to marry or begin sexual activity receive daily micronutrient supplements
- 4) Ensure that adolescents and women of reproductive age receive daily micronutrient supplements especially during seasons when micronutrient intake in diets is lowest.
Because health systems are often unable to reach pregnant women early in gestation or to reach women who are not pregnant, other distribution mechanisms will be needed. The effectiveness of the following approaches needs to be tested and assessed for their costs, especially in comparison to current programs promoting the use of iron/folic acid supplements during pregnancy and postpartum, high-dose vitamin A supplement provision to postpartum women.
 - ♦ Social marketing of multiple micronutrient supplements for sale through the private sector
 - ♦ Distribution of supplements at work sites and schools
 - ♦ Distribution of supplements at marriage registration or religious counseling sessions for engaged couples
 - ♦ Sales of supplements by community-based distribution workers to women of reproductive age and to pregnant and lactating women
 - ♦ Distribution of supplements to women attending family planning clinics, growth and development clinics for well children, integrated management of childhood illness programs, and HIV screening programs

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Appendix Ia: Comparison of Nutrient Reference Values for Women of Reproductive Age

Nutrients	US RDIs ¹	US RDAs for women of reproductive age 1988"/ 1998""	RNIs for women ages 19-50	WHO for women ages 20-59***
Vitamin A RE	875	800*	600	500
Vitamin A IU****		2 664 retinol 8 000 betacarotene		
Vitamin D IU	400	200 (AI)**	—	100
Vitamin E IU	30	8*	> 3	
Vitamin B ₁ (Thiamin)mg	1 5	1 1**	0 8	0 8
Vitamin B ₂ (Ribof) Mg	1 7	1 1**	1 1	1 4
Niacin mg	20	14""	13	11 5
Folate µg	400	400"*	200	170
Vitamin B ₆ mg	2	1 3**	1 23	
Vitamin B ₁₂ µg	6	2 4**	1 5	1
Vitamin C mg	60	60"	40	30
Zinc mg	15	12 *	7	
Low bioavailability				13 1
Med bioavailability				6 5
High bioavailability				4
Iron mg	18	15*	14 8	
Very low bioavailability				59
Low bioavailability				32
Med bioavailability				16
High bioavailability				11
Calcium mg	1000	1 000 (AI)** *	700	400-500
Phosphorus mg	1000	700 **	550	
Magnesium mg	400	Age 19-30 310** Age 31-50 320""	270	
Vitamin K µg		65*	1 g / kilo	
Iodine µg	150	150*	140	150
Selenium pg		55 *	60	30
Copper mg	2	1 5-3 0" (ESADI)	1 2	1 15
Manganese mg		2 0-5 0* (ESADI)	1 4	
Fluoride mg		3 1 (AI)**	—	
Chromium µg		50-200* (ESADI)	25 g	33
Molybdenum µg		75-250* (ESADI)	50-400	
Biotin µg	300	30 (AI)**	10-200	
Pantothenic acid mg	10	5 (AI)**	3-7	

* 1988 RDAs ** 1998 RDAs *** Requirements of vitamin A iron folate and vitamin B₁₂, from FAO/WHO Expert Consultation (FAO 1988) Requirements for thiamine riboflavin and niacin from Joint FAO/WHO Expert Group (FAO 1965) Requirements for calcium from FAO/WHO Expert Group (FAO 1961) Requirements for other trace elements from WHO 1996 WHO levels shown here are the lower limits of safe ranges of population mean intakes to meet normative requirements for ages 18-60+ **** 1 µg RE = 3 33 IU retinol or 10 IU beta-carotene

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Appendix 1b: Comparison of Nutrient Reference Values for Pregnant and Lactating Women

Nutrients	RDI Pregnant/ Lactating	U S RDAs ¹ Pregnant 1988*/1998**	RNIs Pregnant	WHO*** Pregnant	RDAs Lact 1st6 months 1988*/1998**	RNIs Lactating 0-4 mo	WHO*** Lactating
Vitamin A RE		800*	700	600	1 300*	950	850
Vitamin A IU****		2 664 retinol 8 000 beta carotene					
Vitamin D IU	400	200** (AI)	400	400	200** (AI)	400	400
Vitamin E IU	30	10*	—		12*	—	
Vitamin B ₁ (Thiamin) mg	1 5	1 4**	0 9	0 9	1 5**	1	1
Vitamin B ₂ (Ribof) mg	1 7	1 4**	1 4	1 5	1 6**	1 6	1 7
Niacin mg	20	18**	13	12 6	17**	15	14 2
Folate µg	400	600**	300	420	500**	260	270
Vitamin B ₆ mg	2	1 9**	1 2		2**	1 2	
Vitamin B ₁₂ µg	6	2 6**	1 5	1 4	2 8**	2	1 3
Vitamin C mg	60	70"	50	50	95*	70	50
Zinc mg	15	15'	7	(3rd trim)	19*	13	(0-3 months)
Low bioavailability				26 7			25 3
Med bioavailability				13 3			12 7
High bioavailability				8			7 6
Iron mg	18	30*	14 8		15*	14 8	
Very low bioavailability				179-299			33
Low bioavailability				92-152			17
Med bioavailability				46-76			9
High bioavailability				31-61			6
Calcium mg	1000	1 000** (AI)	700	1 000-1 200	1 000** (AI)		1 000-1 200
Phosphorus mg	1000	700 **	550		700**	990	
Magnesium mg	400	Age 19-30 350** Age 31-50 360**	270		19-30 310** 31-50 320 **	320	
Vitamin K µg		65*	—		65*	—	
Iodine µg	150	175*	140	200	200*	140	200
Selenium µg		65"	60	39	75*	75	42
Copper mg	2	1 5-3 0* (ESADI)	1 2	1 15	1 5-3 0*	1 5	1 2 5
Manganese mg		2 0-5 0" (ESADI)			2 0-5 0"		
Fluoride mg		3 1** (AI)			3 1** (AI)		
Chromium µg		50-200* (ESADI)			50-200'		
Molybdenum µg		75-250*			75-250'		
Biotin µg	300	30** (AI)			35** (AI)		
Pantothenic acid mg	10	6** (AI)			7** (AI)		

See Appendix 1a for explanation of symbols (* ** ** * ** ** ** **)

Appendix 2: Levels of Nutrients in Multiple Vitamin/Mineral Supplements Used in Selected Developing Countries

Nutrients	Cuba, Mass distribution (Macias- Matos, 1996)	Honduras Pregnancy (Caulfield, 1997c)	Cuba Pregnancy (Alnwick, 1997)	Institute of Public Health Mexico Pregnancy (Ramakrishnan, 1997)	US RDAs Pregnancy 1988*/1998**
Manufacturer	Quimfar Viterol Fluor				
Vitamin A IU*	750 g RE 2 500 IU	5000	2000	5000	800" 2,664 retinol 8,000 beta-carotene
Vitamin D IU		400		500	200" *(AI)
Vitamin E IU		10		15	10*
Vitamin B ₁ (Thiamin) mg	2	0 5		1 6	1 4**
Vitamin B ₂ (Ribof) mg	1 6	1 6		1 8	1 4**
Niacin mg	20	17		19	18"
Folic acid µg	270	400	250	800	600"
Vitamin B ₆ mg	2	2 2		2 6	19"
Vitamin B ₁₂ µg	6	2 2		4	2 6**
Vitamin C mg			150	100	70"
Zinc mg				7 5	15"
Iron mg		8 3 (as fumarate)	35 (as fumarate)	60 (as fumarate)	30"
Calcium mg		400		125	1,000" *(AI)
Phosphorus mg				125	700**
Magnesium mg				125	350**
Vitamin K µg					65"
Iodine µg					175"
Selenium µg					65*
Copper mg				1	1 5-3 0* (ESADI)
Manganese mg				1	2 0-5 0* (ESADI)
Fluoride mg		1			3 1** (AI)
Chromium µg					50-200* (ESADI)
Molybdenum µg					75-250* (ESADI)
Biotin µg		250		200	30** (AI)
Pantothenic acid mg		6		9 2	6** (AI)
Cost/Day (dollars)			< \$ 02 (\$1 50 per birth)		

Appendix 3a: Nutrients in Multiple Vitamin/Mineral Supplements Sold by Non-profit Agencies

Nutrients	US RDAs ¹ Women Repro Age 1988*/1998**	Tri-med	Orbi- Pharma	Echo	Action Medeor	Internat'l Dispens Assoc (IDA)	US RDAs ¹ Pregnancy 1988*/1998**
Vitamin A µg RE	800*						800"
Vitamin A IU	2,664 retinol, 8,000 beta- carotene	5 000 retinol	2 500 Vit A Acetate	2500 retinol	2500	2 500 retinol	2,664 retinol 8,000 beta carotene
Vitamin D IU	200(AI)**	500	300	300	300	300	200** (AI)
Vitamin E IU	8*	25					10"
Vitamin B ₁ (Thiamin)mg	11 " "	2	1 1	1	1	1	14 " "
Vitamin B ₂ (Riboflavin) mg	11 " "	2	0 5	0 5	0 5	0 5	14 " "
Niacin mg	14 ""	15	7 5	7 5		7 5	18 ""
Folic acid µg	400 ""	250					600 ""
Vitamin B ₆ mg	13 " "	2					1 9 **
Vitamin B ₁₂ µg	2 4 **	6					2 6 **
Vitamin C mg	60"	50	14 7	15	15	15	70"
Vitamin Zinc mg	12"						15"
Iron mg	15*	150 mg ferrous sulphate					30"
Calcium mg	1,000(AI)**						1,000** (AI)
Phosphorus mg	700 **						700**
Magnesium mg	Age 19-30 310** Age 31-50 320 ""						350**
Vitamin K µg	65*						65*
Iodine µg	150"						175"
Selenium µg	55 *						65"
Copper mg	1 5-3 0*(ESADI)						1 5-3 0*ESADI)
Manganese mg	2 0-5 0*ESADI)						2 0-5 0*ESADI)
Fluoride mg	3 1 (AI)**						3 1 ** (AI)
Chromium µg	50-200*ESADI)						50-200*ESADI)
Molybdenum µg	75-250*ESADI)						75-250*ESADI)
Biotin µg	30(AI)**						30 "" (AI)
Pantothenic acid mg	5 (AI)**	10					6 *(AI)
Cost/tablet (dollars)		NA	0 002	0003	0002	0 002	

NA = not available

Appendix 3b: Levels of Nutrients in Multiple Vitamin/Mineral Supplements in U.S. for Non-Pregnant Women

Nutrients	RDI	Centrum	Giant Choice	UNICAP - M	Women's One a Day Bayer	US RDAs ¹ Women Reproductive Age 1988*/1998**
Vitamin A µg RE						800"
Vitamin A IU	5000	5 000 (40% as beta carotene)	5 000 (25% as beta carotene)	5 000 (Vitamin A acetate)	5 000 (Vitamin A/ beta carotene)	2 664 retinol 8,000 beta-carotene
Vitamin D IU	400	400	400	400	400	200 (AI)**
Vitamin E IU	30	30	30	30	30	8*
Vitamin B ₁ (Thiamin) mg	1.5	1.5	1.5	1.5	1.5	11" "
Vitamin B ₂ (Riboflavin) Mg	1.7	1.7	1.7	1.7	1.7	11" "
Niacin mg	20	20	20	20	20	14" "
Folic acid µg	400	400	400	400	400	400**
Vitamin B ₆ mg	2	2	2	2	2	1.3**
Vitamin B ₁₂ µg	6	6	6	6	6	2.4**
Vitamin C mg	60	60	60	60	60	60"
Zinc mg	15	15	15	15	15	12"
Iron mg	18	18	18	18	27	15*
Calcium mg	1000	162	162	60	450	1 000 (AI)**
Phosphorus mg	1000	109	109	45		700**
Magnesium mg	400	100	100	400		Age 19-30 310** Age 31-50 320**
Vitamin K µg		25	25			65*
Iodine µg	150	150	150	150		150*
Selenium µg		20	20			55 *
Copper mg	2	2	2	2		1.5-3.0*(ESADI)
Manganese mg		3.5	1.5	1		2.0-5.0*(ESADI)
Fluoride mg						3.1 (AI)**
Chromium µg		65	25			50-200*(ESADI)
Molybdenum pg		160	25			75-250*(ESADI)
Biotin µg	300	30	30			30 (AI)**
Pantothenic acid mg	10	10	10	10	10	5 (AI)**
Cost/tablet (dollars)		0.13	0.05	0.08		

Appendix 3c: Levels of Nutrients in Multiple Vitamin/Mineral Supplements in U.S. and Europe for Pregnant Women

Nutrients	Over the Counter				Prescription		US RDAs Pregnancy 1988*/1998**
	Natalins Mead/ Johnson	Stuart Wyeth	CVS Generic	Elevit Pronatal (Europe)	Materna (Lederle) Enhanced	Copely Pharma	
Vitamin A µg R1							800*
Vitamin A IU	1 000	4 000	4 000	4 000	5 000	4 000	2 664 retinol 8 000 beta carotene
Vitamin D IU	400	400	400	500	400	400	200** (AI)
Vitamin E IU	5	11	11	15	30	22	10"
Vitamin B ₁ (Thiamin) mg	1.5	1.84	1.84	1.6	3	1.84	1.4**
Vitamin B ₂ (Riboflavin) mg	1.6	1.7	1.7	1.8	3.4	3	1.4**
Niacin mg	17	18	18	19	20	20	18**
Folic acid µg	500	800	800	250	1000	1000	600**
Vitamin B ₆ mg	2.6	2.6	2.6	2.6	10	10	1.9**
Vitamin B ₁₂ µg	2.5	4	4	4	12	12	2.6**
Vitamin C mg	70	100	100	100	100	120	70*
Zinc mg	15	25	25	7.5	25	25	15*
Iron mg	30 (ferrous fumarate)	60 (Ferrous fumarate)	60	60	60 (Ferrous fumarate)	65 (ferrous fumarate)	30*
Calcium mg	200	200	200	10	250	200	1 000*** (AI)
Phosphorus mg				125			700**
Magnesium mg	100			100	25		350**
Vitamin K µg				—			65*
Iodine µg				—	150		175*
Selenium µg				—			65*
Copper mg	1.5			1	2		1.5–3.0* (ESADI)
Manganese mg				1			2.0–5.0* (ESADI)
Biotin mg				0.2			30** (AI)
Total Cost (dollars)	0.25 (retail)	0.25 (retail)	0.10 (retail)	Sold in Europe		0.13 (retail)	

Iron/folate tablets From UNICEF contain 200 mg FeSO₄ equal to 60 mg elemental iron 250 µg folic acid with a cost of \$0.026 in 1998

Appendix 4a: Levels of Nutrients in Multiple Vitamin/Mineral Supplements Sold in Bolivia for Women of Reproductive Age

Nutrients	RDAs (women ages 25–50) 1988*/1998**	Generic -CEASS Belgium	Multivit Bolivia	Pan-vimin Bolivia	Polivitaminicos Chile	Supradyn Argentina
Manufacturer		Oterpo	IFA	INTI	Laboratorio Chile, S A	Roche
Vitamin A µg RE	800''					
Vitamin A IU*	2,664 retmol, 8,000 beta- carotene	800	5000	2500	3600	3333
Vitamin D IU	200 (AI)**	100	1000	1000	400	500
Vitamin E IU	8''		25	1		10
Vitamin B, (Thiamin) mg	1 1**	0 5	12 5	12	2	20
Vitamin B ₂ (Ribof) mg	1 1''	0 5	12 5	2 5	1 2	5
Niacin mg	14**	7 5	12 5	15	10	50
Folic acid µg	400''''		25	500	100	
Vitamin B ₆ mg	1 3**		12 5	2	2	10
Vitamin B ₁₂ µg	2 4**		250	2		5
Vitamin C mg	60''		50	50	75	150
Zinc mg	12*			0 3		0 5
Iron mg	15*		12 5	25		10
Calcium mg	1,000''* (AI)			200	500	50
Phosphorus mg	700 **					25 8
Magnesium mg	Age 19–30 310** Age 31–50 320**			5		36 2
Vitamin K µg	65''					
Iodine µg	150''					
Selenium µg	55''					
Copper mg	1 5–3 0*(ESADI)			1		1
Manganese mg	2 0–5 0*(ESADI)			1		0 5
Fluoride mg	3 1 (AI)**					
Chromium µg	50–200''(ESADI)					
Molybdenum µg	75–250*(ESADI)					100
Biotin µg	30 (AI)**		250			250
Pantothenic acid mg	5 (AI)**		12 5			11 6
Cost/Tablet (dollars)		0 01	0 08	0 14	0 03	0 34

Appendix 4b: Levels of Nutrients in Multiple Vitamin/Mineral Supplements Sold in Bolivia for Pregnant Women

Nutrients	RDAs Pregnancy 1988*/1998**	Iberol- Brazil	Iberol 500 Argentina	Supradyn- prenatal	Prenavit Colombia	Natabek F	testa vit multi vitamin prenatal	Sumavit Argentina
Manufacturer		Abbott	Abbott	Roche	Procaps	Parke Davis	Procaps	
Vitamin A µg RE	800*							
Vitamin A IU*	2,664 retinol 8 000 beta carotene	5000	5000	3333	3000	4000	12000	2500
Vitamin D IU	200* "(AI)			200	200	400	550	400
Vitamin E IU	10*			30	8		30	10
Vitamin B ₁ (Thiamin) mg	1.4 ""	1.5	10	100	0.6	3	5	10
Vitamin B ₂ (Riboflavin) mg	1.4 **	1.7	6	5	0.6	2	4	4
Niacin mg	18**	20	50	50	8	10	35	25
Folate µg	600**				100		0.4	
Vitamin B ₆ mg	1.9**	2	5	80				
Vitamin B ₁₂ µg	2.6**	6	2	0.5	1.5		12	
Vitamin C mg	70"	100	500	250	25	50	120	100
Zinc mg	15*			0.8				
Iron mg	30"	105	105	21.05	6		20	25
Calcium mg	1 000"" (AI)			100	100	600		50
Phosphorus mg	700""							25
Magnesium mg	350**		320	36.2				40
Vitamin K µg	65*		60					
Iodine µg	175"			153				
Selenium µg	65*							
ESADs Copper mg	1.5-3.0*			1.2				
Manganese mg	2.0-5.0*			0.65				1
Fluoride mg	3.1"" (AI)			0.226		2.2		0.045
Chromium µg	50-200"							
Molybdenum µg	75-250*							
Biotin µg	30"" (AI)			250				
Pantothenic acid mg	6** (AI)	10	10	11.615	4		18	10
Cost/Tablet (dollars)		0.24	0.21	0.39	0.19	0.05	0.33	0.43

Appendix 4c: Levels of Nutrients in Multiple Vitamin/Mineral Supplements Sold in Zambia

Nutrients	RDAs (Women 25–50) 1988*/1998**	Women of reproductive age			RDAs Pregnancy 1988*/1998**	Pregnant women Delhi, India
		Seven Seas	Artons	Medox, Zim		
Manufacturer		CAPS				lanbaxy
Vitamin A IU*	800" 2,664 retinol 8,000 beta carotene	300	5000	2500	300" 2,664 retinol 3,000 beta- carotene	
Vitamin D IU	200 (AI)**	100	1000	1000	200 (AI)**	100
Vitamin E IU	8*		25	1	10"	
Vitamin B ₁ (Thiamin) mg	11**	0.5	12.5	12	14**	8
Vitamin B ₂ (Riboflavin) mg	11****	0.5	12.5	2.5	14**	10
Niacin mg	14**	75	12.5	15	18**	
Folate µg	400**		25	500	600****	1000
Vitamin B ₆ mg	13****		12.5	2	19**	
Vitamin B ₁₂ µg	24**		250	2	26**	
Vitamin C mg	60"		50	50	70"	100
Zinc mg	12"			0.3	15"	
Iron mg	15"		12.5	25	30"	
Calcium mg	1,000 (AI)**			200	1,000** (AI)	
Phosphorus mg	700**				700**	
Magnesium mg	Age 19–30 310** Age 31–50 320**			5	350**	
Vitamin K µg	65*				65"	
Iodine µg	150"				175*	15
Selenium µg	55"				65"	
Copper mg	1.5–3.0"			1	1.5–3.0"	
Manganese mg	2.0–5.0"			1	2.0–5.0"	15
Fluoride mg	3.1 (AI)****				3.1** (AI)	
Chromium µg	50–200"				50–200"	
Molybdenum µg	75–250*				75–250*	
Biotin µg	30 (AI)**		250		30**** (AI)	
Pantothenic acid mg	5 (AI)**		12.5		6** (AI)	
Cost/Tablet (dollars)		3.01	0.08	0.14		0.34

Appendix 5: Forms of Vitamins and Minerals Used in Vitamins With Mineral Tablets and Tolerance Ranges in Reported Amounts (USP, 1995)

Vitamin/mineral	Forms used	USP ranges for amounts shown on labels
Vitamin A RE Retinyl palmitate* Retinyl acetate* Beta carotene*	Retinal*	≤ 90% and ≥ 165%
Vitamin D IU	Ergocalciferol (D2)* Cholecalciferol (D3)*	
Vitamin E IU	Alpha tocopherol* Alpha tocopheryl acetate* Alpha tocopheryl acid succinate*	
Vitamin B ₁ (Thiamin) mg	Thiamine hydrochloride** Thiamine mononitrate*	590% and ≥ 150%
Vitamin B ₂ (Riboflavin) mg	Riboflavin*	
Niacin mg	Niacin* Nicotinamide*	
Folate µg	Folic acid*	
Vitamin B ₆ mg	Pyridoxin hydrochloride*	
Vitamin B ₁₂ , µg	Cyanocobalamin*	
Vitamin C mg	Ascorbic acid* Calcium ascorbate* Sodium ascorbate*	
Zinc mg**	Zinc sulfate Zinc oxide	≤ 90% and ≥ 125%
Iron mg	Ionic iron Ferrous sulfate Ferrrous gluconate Ferrous fumarate	
Calcium mg	Calcium carbonate (unrefined refined) Calcium chelates (Citrate) Calcium gluconate Calcium lactate Calcium phosphate Dolomite Bone meal	
Phosphorus mg		
Magnesium mg	Magnesium aspartate malate succinate citrate Magnesium oxide gluconate sulfate chloride	
Vitamin K µg	Phytonadione*	
Iodine µg		590% and ≥ 200%
Selenium µg		≤ 90% and ≥ 200%
ESADIs Copper mg**	Copper oxide Copper sulfate	590% and ≥ 125%
Manganese mg**		≤ 90% and ≥ 125%
Fluoride mg		590% and 2200%
Chromium µg		
Molybdenum µg		
Biotin µg	Biotin	≤ 90% and ≥ 150%
Pantothenic acid mg	Calcium pantothenate Racemic calcium pantothenate	≤ 90% and ≥ 150%

* USP standard

**The sulfate forms of copper zinc and manganese are usually more bioavailable than the oxide forms (Johnson et al 1998)

Appendix 6 Upper Limits to Safe Ranges for Daily Consumption of Nutrients*

Nutrients	U S RDIs /ESADIs	NAS/NRC (1988*) or IOM(1997, 1998**)	WHO (1996)	CRN(1998)	
				NOAEL	LOAEL
Vitamin A µg RE	875	Adults 15 000RE = 50 000IU Pregnancy 6 000RE = 20 000 IU *		10 000 iu (3 000 µg RE)	21 600 iu (6 500 µg RE)
Vitamin D IU	400	LOAEL—3 800 IU NOAEL—2 400 IU UL Adults > 1—2 000 IU Pregnancy—2 000 IU Lactation—2 000 IU **		800 (20 µg)	2 000 (50 µg)
Vitamin E IU	30	No cases of toxicity reported"		1 200 (800 mg x TE)	None established
Vitamin B ₁ (Thiamin) mg	1.5	None reported UL cannot be determined **		50	None established
Vitamin B ₂ (Riboflavin) mg	1.7	None reported UL cannot be determined **		200	None established
Niacin mg	20	LOAEL—50 mg/day UL adults—35 mg/day rounded estimate	100 mg	500 250 for slow release *Dosage level rec for adults 500 mg	1000 500 for slow release
Folate µg	400	LOAEL—5 mg/day UL Adults—1 mg or 1 000 µg Pregnant—1 000 µg Lactating—1000 µg**		1000	None established
Vitamin B ₆ mg	2	NOAEL—200 mg/day LOAEL—500 mg/day UL Adults—100 mg/day Pregnant—100 mg Lactating—100 mg **		200	500
Vitamin B ₁₂ µg	6	No adverse effects have been associated with excess B ₁₂ , intake from food and supple ments in healthy individuals **		3000	None established
Vitamin C mg	60	None reported *		More than 1 000	None established
Zinc mg	15		35	30	60
Iron mg	18	3000 mg FeSo ₄ (about 900 mg elemental iron) is lethal for a 2 year old child"		65	100
Calcium mg	1000	LOAEL—5 000 UL for adults—2 500 mg pregnancy and lactation— 2 500 mg **		1 500	More than 2 500

Appendix 6 Upper Limits to Safe Ranges for Daily Consumption of Nutrients* (Con't)

Nutrients	U S RDIs /ESADIs	NAS/NRC (1988*) or IOM (1997,1998"")	WHO (1996)	CRN(1998)	
				NOAEL	LOAEL
Phosphorus mg	1000	NOAEL—10 200 UL Adults 19 to 70—4 000 UL Pregnancy—3 500 UL Lactation—4 000 **		1500	More than 2 500
Magnesium mg	400	LOAEL—360 mg UL Adolescents and Adults > 9 years—350mg non food magnesium Pregnancy—350 non food magnesium Lactation 350 non food magnesium **		700	None established
Vitamin K µg	80 (1988 highest RDA)	None reported *	(30mg)	30 000 established	None
Iodine µg	150	2 000 µg in adults and 1 000 µg in children caused no adverse reaction*	100–200 µg for those with previous deficiency	1000	None established
Selenium µg	75 (1988 highest RDA)	1 000 µg associated with toxic effects *	400 µg	200	910
ESADIs— Copper mg	2	Occasional intake of up to 10 mg is probably safe *	10	9	None established
Manganese mg	(2 0–5 0)	5 (occasional intake of up to 10 mg can be considered safe) *	none given	10	None established
Fluoride mg	(1 5–4 0)	LOAEL— 10 mg/kg/day UL Adults—10 mg/day Pregnancy—10 mg Lactation—10 mg **	2 mg		
Chromium µg	(50–200)	Toxicity is low *	250 µg	1000	None established
Molybdenum µg	(75–250)	Excessive intakes of 10 000–15 000 associated with gout like syndrome +	None given	350	None established
Biotin µg	300	No reports of adverse effects **		2500	None established
Pantothenic acid mg	10	No toxicity seen at 2–9g/day No reports of adverse effects of oral pantothenic acid **		1000	None established

Notes WHO levels shown here are the limits of safe ranges of population mean intakes

NOAEL No Observed Adverse Effect Level—a level of daily oral intake for a prolonged period at which no adverse reactions in humans have been observed

LOAEL Lowest Observed Adverse Effect Level—a longer term intake at which some adverse effects have been identified thus requiring adjustment downward by the application of a safety factor to calculate a safe intake referred to as the UL Upper Limit

Appendix 7: Multiple Micronutrient Supplements Used in Studies Discussed in this Paper

Country	Contents of Supplement	Reference
Indonesia	<ul style="list-style-type: none"> ♦ Vit A—2400 µg retinol ♦ Iron—60 mg elemental iron 4 Vit A + Iron 4 placebo 	Suharno et al 1993
Indonesia	<ul style="list-style-type: none"> ♦ 60 mg Fe 750 µg retinol 250 µg folic acid 60 mg vitamin C/day ♦ 60 mg Fe 6000 µg retinol 500 µg folic acid 60 mg vitamin C/week ♦ 120 mg Fe 6000 µg retinol 500 µg folic acid 60 mg vitamin C/week ♦ placebo 	Angeles Agdeppa 1997
Tanzania	<ul style="list-style-type: none"> ♦ multiple micronutrient fortified beverage— ♦ 30–120% Percent of RDAs provided A C E Folic acid B6 Riboflavin Niacin Iron (ferrous glutamate) Zinc Iodine—30% • placebo 	Ash et al 1998
Tanzania	<ul style="list-style-type: none"> ♦ Vitamin A (30 mg beta carotene plus 5000 IU preformed vitamin A) ♦ Multivitamins excluding vitamin A B1—20 mg B2—20 mg B6—25 mg Niacin—100 mg B12—50 µg C—500 mg E—30 mg Folic Acid—800 µg • Multivitamins including A ♦ placebo ♦ All groups were also given ferrous sulfate/folic acid tablets containing 120 mg of iron and 500 µg of folic acid 	Fawzi et al 1998
Peru	<ul style="list-style-type: none"> ♦ 60 mg iron as ferrous sulfate 250 µg folic acid 15 mg zinc as zinc sulfate ♦ iron and folate without zinc 	Caulfield et al 1997

Appendix 7: Multiple Micronutrient Supplements used in Studies Discussed in this Paper (Con't)

Country	Contents of Supplement	Reference
Mexico	<ul style="list-style-type: none"> ♦ 20 mg zinc as zinc methionine ♦ 20 mg Fe as ferrous sulfate ♦ 20 mg Zn + 20 mg Fe ♦ placebo 	Rosado et al 1997
Mexico	beverage with <ul style="list-style-type: none"> ♦ zinc (20 mg zinc methionine) ♦ iron (20 mg iron sulfate) ♦ zinc and iron ♦ placebo 	Munos et al 1998
Hungary	<ul style="list-style-type: none"> ♦ multivitamin (Elevit Pronatal Hoffmann LaRoche) 6 000 IU vitamin A until the end of 1989 and 4 000 thereafter 1.6 mg B1 1.8 mg B2 19 mg nicotinamide 2.6 mg B6 4 µg B12 100 mg C 500 IU D 15 mg E 10 mg calcium pantothenate 2 mg biotin 800 µg folic acid 125 mg calcium 125 mg phosphorus 100 mg magnesium 60 mg iron 1 mg copper 1 mg manganese 7.5 mg zinc Control ♦ trace elements 1 mg copper 1 mg manganese 7.5 mg zinc 7.5 mg C 	Czeizel and Dudas 1992
Gambia	<ul style="list-style-type: none"> ♦ 30 mg ferrous sulfate ♦ 5 mg riboflavin ♦ 30 mg Ferrous sulfate and 5 mg riboflavin ♦ placebo 	Powers Bates and Lamb 1985