Composition of a Multi-Micronutrient Supplement to be used in Pilot Programmes among Pregnant Women in Developing Countries


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Executive summary

In addition to a high prevalence of iron deficiency, studies in different developing countries have shown that deficiencies such as vitamin A, zinc, vitamin B12, iodine and folate are also widespread among pregnant women, and are known to have a negative impact on pregnancy outcome. Therefore, in addition to providing iron/folate supplements to pregnant women, there is also a need to supplement with other micronutrients, and combining different micronutrients into one supplement would be efficient from a programme point of view.

Such a multi-supplement specifically designed for women from developing countries does not exist. It was the aim of this workshop to decide upon the composition of such a multi-micronutrient supplement for pregnant women from developing countries to be used in effectiveness trials in pilot countries. The one-day workshop began with two oral presentations to provide background and basic information, and was followed by a group discussion by the 19 participants.

The discussion focused on four main issues:

- Which nutrients should be included
- At what levels each should be included
- Additional target groups besides pregnant women
- Adherence to intake

The selection of nutrients was based on available evidence of deficiencies, possible consequences of deficiencies for mother and child, weighing of risks versus advantages, and on interaction between nutrients. For some nutrients, limited information was available, and decisions were based more on weighing risks versus advantages for inclusion or exclusion. It was decided to use the USA/Canadian RDA reference as a basis for the amounts included for each nutrient because they were the most recent and best documented. Furthermore, information about toxicity levels, cost of nutrients, the size of the resulting supplement, and possible side effects related to supplement intake were considered. It was decided to include 15 micronutrients (vit A, D, E, B1, B2, B6, B12, C, Niacin, Folic Acid, Fe, Zn, Cu, I, Se) at the RDA level, except for folic acid, which was included at a level of 400 μg.

It was proposed that pregnant women should take the tablet on a daily basis for as much of the pregnancy as possible, and should continue until 3 months post-partum. Other possible target groups to be considered could be:

- Adolescent girls, in order to improve their micronutrient status in advance of pregnancy. For the sake of realistic programming it was recommended that the effectiveness of delivering supplements once or twice a week be further explored;

- Women in areas of civil strife or natural disaster, who can take the supplement according to their biological state (pregnant or not), and in case of severe deficiency could take two tablets a day.

It was recognized that many issues related to multi-micronutrient supplements remain to be explored. Several research topics were identified, including the assessment of risks versus benefits of regular supplement intake in an environment with many disease agents; factors influencing crucial adherence to tablet intake; and efficacy studies in different populations.

It is planned to use the multi-micronutrient supplement in pilot trials in at least 11 countries in order to assess its effectiveness. Many indicators to be monitored in these trials were proposed, including birth weight and length, weight gain during pregnancy, improvement in biochemical micronutrients status indicators, adherence to tablet intake, and reported side effects.
Background, aim, and workshop programme

1.1 Background
The high prevalence of anaemia in pregnant women in developing countries has been widely recognised as an important public health problem because of its negative consequences for pregnancy outcome and its impact on maternal mortality. The World Health Organization (WHO) recommends universal distribution of iron supplements to mothers when the prevalence of anaemia in pregnant women is higher than 40%. Now, dietary intake and micronutrient status studies in different countries show that, in addition to anaemia, deficiencies such as vitamin A, zinc, vitamin B12, iodine and folate are also widespread, and have a negative impact on pregnancy outcome.

While recognising that these micronutrients should ideally be obtained from food, it was noted that improvements in the natural diet are difficult to achieve over a short time span for populations in most developing countries. Some countries have established programmes to increase micronutrient intake through food fortification, but many more have yet to achieve appropriate food fortification goals. Moreover, the high needs of pregnancy are almost impossible to cover through dietary intake—in most industrialized countries, it is common for women to take multiple micronutrient supplements during pregnancy and lactation.

Increasing micronutrient intake in developing countries through the provision of pharmaceutical supplements—as is commonly practiced among many age groups in much of the industrialized world—therefore needs to be considered. Combining all micronutrients in a multi-supplement aimed at women should therefore be considered. Delivery of a multiple micronutrient supplement to women in targeted groups is more programmatically feasible than providing selected micronutrients through different parallel supplementation programmes or strategies.

1.2 Aim of the workshop
The aim of this technical workshop was therefore to propose the composition of a multi-micronutrient supplement (MuMS) for pregnant women from developing countries to be used in effectiveness trials in pilot countries. A secondary issue for consideration at the workshop was the suitability of such a supplement for other groups at risk.

1.3 Workshop programme
Workshop participants were welcomed by Marjorie Newman-Williams, Deputy Director, Programme Division, UNICEF, who confirmed UNICEF’s commitment to micronutrient programmes, stressing their tremendous impact on the survival, growth and development of children. Werner Schultink, Senior Adviser, Micronutrients, outlined the background and objectives of the workshop and the proposed pilot programmes. Participants then heard two presentations, the first by Rainer Gross, Senior Programme Officer, GTZ, who summarized the main outcomes of a workshop held in
Singapore in November 1998 about Micronutrient Supplementation and Safe Motherhood, and the second by Sandra Huffman, of the Linkages Project, Academy for Educational Development, who reviewed the rationale for, composition of, and experience with multiple micronutrient supplements for women.

Following the presentations, the workshop participants discussed and decided upon the composition of the multi-micronutrient supplement, its use for target groups besides pregnant women, remaining research issues, and the data to be collected in the effectiveness trials.

1.4  **Presentation: Summary of the Singapore Workshop on ‘Multiple Micronutrient Supplementation and Safe Motherhood’**

*by Rainer Gross, Senior Programme Officer, Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ)*

A two-day workshop organized by GTZ, together with the Southeast Asian Ministers of Education Organization (SEAMEO), UNICEF, and the Ottawa-based Micronutrient Initiative (MI) was held in Singapore in November 1998 in order to review available evidence on the possible benefits of multi-supplementation, and to discuss the justification for, and composition of such a supplement. Workshop participants included representatives of UNICEF, WHO, Ministries of Health from Indonesia and Singapore, Cessiam-Guatemala, GTZ, Helen Keller International, Linkages, Medical Research Council South Africa, SEAMEO, Wageningen University, Bonn University, University of California and the Bayer Corporation.

The workshop made the following recommendations:

- Diets of women in developing countries are lacking in a wide variety of micronutrients, possibly endangering pregnancy process and outcome. Improving nutrient intake during pregnancy was urgently recommended.

- Because of difficulties in achieving the behavioural and economic change necessary for dietary improvement, multi-micronutrient supplementation was the option for most rapid progress towards this goal.

- Many multi-micronutrient supplements already exist, but their suitability for use by pregnant women in developing countries has not frequently been tested.

- It would be optimal to focus on pre-and post pregnancy in addition to pregnancy itself.

- For programme delivery purposes, it would be expedient to produce one type of tablet rather than different types for pre-pregnant and pregnant women.

- The tablet should contain vitamin A, D, folate, zinc, vitamins B1, B2, B6, B12 at full recommended dietary allowances. The level of iron in the tablet should be 30-60mg. When supplemented at RDA levels there is no concern about toxicity. Vitamin A has a more narrow range of safety when taken during pregnancy. However, when supplemented at RDA level, even when taken in addition to a diet already providing adequate amounts of vitamin A, the combined intake from diet and supplement is still well below the suggested upper limit of intake of 10,000 IU per day.

- During pregnancy the tablet should be taken once a day, whereas pre-pregnancy one or two tablets should be taken once weekly.
• Support was expressed for weekly supplementation during pregnancy because of the lower cost and possible management advantages. However, more effectiveness studies should urgently be carried out in order to investigate the effects of weekly supplementation of other micronutrients besides iron and vitamin A.

• A common protocol to investigate the effect of weekly multi-supplementation must be developed.

• More research is needed on the key issue of adherence to recommended tablet intake. Experience should be gathered from other disciplines of science and interventions, and systematically discussed during a special workshop. Current iron supplementation programmes mostly attempt to educate pregnant women about the consequences of anaemia and how to prevent them. However, adherence to recommended tablet intake may be largely influenced by subjective factors which need further investigation.

• Because supplementation activities are usually carried out as part of public health programmes, the decision to switch from iron-folate to multi-micronutrient supplementation—which will involve additional costs—will need to be met with strong advocacy arguments, such as highlighting expected reductions in morbidity and mortality that can reduce health costs. More information is needed about multi-supplement composition and effectiveness of supplementation programmes, as well as policy agreement on issues such as price, supply and monitoring, before advocacy campaigns can be designed and implemented.

A question was raised as to why the anti-oxidants selenium and vitamin E were omitted from the supplement composition recommended by the Singapore workshop. Rainer Gross agreed that the omission had not been intentional, and that adding these two nutrients to a supplement should be considered.

1.5 Presentation: Multiple micronutrient supplements for women in developing countries

by Sandra Huffman, Linkages Project, Academy for Educational Development

The presentation reviewed target groups for multiple-micronutrient supplementation, composition of the supplement, including dosage levels, and the forms of nutrients to be applied. The presentation also looked at available supplements and nutrient pre mixes.

(i) Target groups

Three potential categories of women, or a combination of these groups, were presented as possible targets to receive supplementation.

Giving such a supplement to women before pregnancy takes place can prevent birth defects caused by folic acid deficiency and improve maternal stores of nutrients such as iron and vitamin A. However, this is a large sector of the population, and is not easy to reach. In addition, motivation to take the supplements may be low.

Providing the supplement during pregnancy means there are fewer women to treat, and many of them can be reached by health systems during visits to antenatal clinics. Adherence to taking the supplement might be higher, and the intervention can be added to current iron and folate supplementation programmes. However, contact may be too late to effectively treat iron and folate deficiencies.
Providing the supplement to **breastfeeding mothers** improves the quality of breastmilk and thereby infant nutrition. In addition, supplementation at this stage will improve the mother’s nutritional status.

The presenter proposed that because of the serious consequences of deficiency during pregnancy, pregnant women should be a target population to receive the multi-micronutrient. Supplementing women before conception in order to improve micronutrient status and build stores before requirements increase would also be ideal. But this category encompassed all women of reproductive age, a massive group, and often one that it is difficult to access since they are not in regular contact with health services.

The presenter highlighted the RDAs for the three categories of women. For many micronutrients (B-vitamins, vitamins A & C) the requirements are highest for lactating women, which stresses the importance of also considering this category.

(ii) **Which nutrients should be included in a new multi-micronutrient supplement?**

<table>
<thead>
<tr>
<th>Ten ‘basic’ nutrients were suggested for inclusion because of documented deficiencies among pregnant women in developing countries, and their effect on birth outcome and pregnancy. These basic nutrients are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
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<tr>
<td>Vitamin D</td>
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<tr>
<td>Folic Acid</td>
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<tr>
<td>Vitamin B6</td>
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</tbody>
</table>

Six other nutrients—vitamins C, E and K, along with copper, selenium and iodine—could also be considered for inclusion in the supplement. However, less information is available regarding deficiencies in some of these nutrients and their effects on pregnancy or, as is the case with iodised salt, these nutrients are already provided at least to some extent by other means.

Although deficiencies in calcium and magnesium are likely to exist, the RDA (especially of calcium) is so high that the presenter mentioned that including them in a supplement would increase the size of the tablet enormously. Therefore it was suggested that calcium and magnesium be left out of the supplement, or included only in small amounts.

(iii) **References that could be used as the standard for the new multi-micronutrient supplement**

Three references that could be used as the standard for a new supplement were presented:

1. US/Canada RDAs for women aged 25-50; during pregnancy; during lactation
2. UK-RNI for women aged 19-50; during pregnancy; lactation

The US/Canadian Recommended Dietary Allowances are recommendations designed for healthy populations in the US. WHO and the FAO 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) and are revising standards for other micronutrients. The WHO/FAO values are the least recent.

Although the US/Canadian RDAs are given for healthy populations and thus may underestimate the requirements for populations in developing countries, they tend to be higher than the UK RNIs and the WHO/FAO values. For example the vitamin A RDA for women of reproductive age is 800 RE, whereas the UK RNI is 600 RE and the WHO/FAO value 500 RE. Similar differences exist for example for zinc, vitamin C. The group noted that the US RDAs were more recently reviewed (1998) than the other reference values (See Annex 1 for comparison) and considered them most up-to-date with current knowledge.

(iv) Forms of nutrients and existing market availability

A number of multi-micronutrient supplements are already available. Companies such as Bayer, Roche, and Mead Johnson produce supplements which all contain more nutrients than the basic 10 outlined above, in many different compositions (See Annex 2). However, few are specifically designed for women in developing countries, and often the logic for amounts of nutrients in these supplements seems difficult to follow—one typical pre-pregnancy supplement, for example, contained 125% of the pregnancy RDA for Vitamin A.

Cost was clearly mentioned as being an important factor in deciding which nutrients to include. Many companies already have pre-mixes of nutrients available for purchase. Adding or removing nutrients to the pre-mix affects the price of the supplement. Raw materials for a supplement containing most nutrients are about 0.1 US cents. The most expensive nutrients are the vitamins A, E, and C. Other cost-influencing factors include place of production, tablet coating and taste, and packaging—for example, blister packs are expensive. For a supplement used in a relatively small study in Bolivia the cost was as high as 3.36 US cents per tablet because of specificity of composition, form, colour, and packaging.

Social marketing was highlighted as an important tool to improve adherence to tablet intake. In a project in Bolivia, a social marketing firm conducted research before launching their multi-micronutrient supplement programme in order to achieve maximum adherence with tablet intake. The firm discovered that women believed they would gain weight on the supplement. Such findings demonstrate the importance of market research to ensure that social marketing campaigns target audiences with well-designed messages.
Workshop report and outcomes

1.1 Target groups for supplementation

Workshop participants agreed that the target groups to be considered for supplementation are pregnant and lactating women, young children, and non-pregnant women, especially adolescent girls. Targeting these groups would ensure an integrated, life-cycle approach on the improvement of micronutrient status. Participants also stressed the need for micronutrient supplementation in emergencies such as natural disasters, civil strife or in refugee populations.

It was agreed, however, that this workshop would mainly focus on a supplement for pregnant and lactating women. The reason for extending the target group to lactating women was to assure that the high requirements during early lactation would be covered and that recovery after delivery would be supported. The reasons for focussing on pregnant women are listed below:

- High prevalence of micronutrient deficiencies
- Need for nutrients is highest
- Large potential impact on pregnancy and birth outcome
- Fewer women to treat
- Women can be reached through health systems
- Iron/folate distribution mechanism can be used
- Compliance might be higher
- At RDA level supplementation is safe

2.2 Discussion on nutrients to be included in the supplement

The selection of nutrients to be included in the supplement was discussed based on the following considerations:

- Likelihood of deficiency: Which nutrients are most necessary in health and nutrition terms, and are most likely to be inadequately provided by the diet.

- General use: the supplement should be designed in such a way that it can be safely recommended to pregnant women worldwide once its efficacy and effectiveness are demonstrated.

- Tablet size: The size of the tablet affects adherence to prescribed regimen. The size is particularly important with regard to calcium and magnesium because of their relatively high intake.

- Availability of pre-mixes: Manufacturers already have supplement pre-mixes. These premixes are mostly not optimal in terms of composition and quantity, and change in their composition will increase production cost. It might therefore be advisable to minimize changes, and to leave some cheap nutrients in rather than take them out.
Issues which were not discussed in detail but were recognized as important and would need to be looked into were:

- The chemical forms of micronutrients. For example the use of gluconate or fumarate salts for iron. The chemical form affects the biological efficacy and the different chemical forms also vary in price and stability.
- The issue of cost per tablet.

<table>
<thead>
<tr>
<th>Agreed upon nutrients to be included</th>
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<tbody>
<tr>
<td>Vitamin A</td>
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<td>Vitamin D</td>
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<tr>
<td>Vitamin E</td>
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<tr>
<td>Vitamin C</td>
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<tr>
<td>Pyridoxin (B6)</td>
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The arguments for including the above nutrients are outlined below:

**Iron**

Iron must be included in any supplement for pregnant women. The far-reaching and often hidden effects of iron deficiency anaemia or both the mother and newborn were recognized as a massive public health problem in most developing countries. Increased morbidity and mortality, low birth weight, premature delivery, impaired physical and cognitive development in infants and young children, and weakness and fatigue in adults were reviewed as major implications of this deficiency.

It was noted that in certain areas an additional cause of anaemia may be malaria or parasitic disease. Since iron supplementation alone will not correct anaemia due to malaria, malaria treatment in addition to supplementation is required in areas where the problem exists in order to eliminate the usual coexisting iron deficiency. Hookworm, Schistosomiasis, and Trichuris infestation are contributory causes of iron deficiency and should be treated as part of an anaemia control programme that includes iron supplementation. It was noted that higher amounts of iron are sometimes reported to lead to side effects.

**Vitamin A**

Recent research among pregnant women in Nepal indicated that vitamin A deficiency appeared to increase maternal mortality. Prevalence of vitamin A deficiency may be quite high among pregnant women in many developing countries. A proxy indicator is the high percentage of women suffering from night blindness during pregnancy. Low vitamin A stores also influence levels in breastmilk. Another reason for including vitamin A is because of its positive effect on iron metabolism and haemoglobin production and it's anti-infective properties.

**Iodine**

Arguments for and against including iodine in the supplement emerged. It was pointed out that because of the extraordinary success of Universal Salt Iodisation (USI) programmes in many
countries, most populations are already receiving iodine or will be very soon. It was argued that including iodine in a supplement could be perceived by governments as a disincentive to continue their USI efforts. A concern was also expressed that adding iodine to the supplement in areas covered by salt iodisation might also increase the risk of iodine-induced hyperthyroidism, especially in susceptible individuals.

But despite these concerns, the group felt that including iodine in the supplement was essential, in view of the critical importance of pregnant women being iodine replete for proper brain development of the infant. It was also pointed out that, although many countries claim that the majority of their households have access to iodized salt, there are still vulnerable and difficult to reach groups within many of those populations. Furthermore, salt intake may in reality not be as high as 10 g per day and would therefore not cover the required daily intake with an assumed level of iodine of 15 ppm.

**Folic Acid**

Folic acid, in conjunction with iron supplementation, is necessary to prevent anaemia in pregnancy. It is also needed to prevent neural tube defects, although for this purpose folate must be given very early in pregnancy during the first stage of neural tube development. In addition folic acid decreases homocysteine concentration in blood, which is important for prevention of cardiovascular disease. It is therefore currently included in the iron-folate tablet and there are no reasons for taking it out.

**Vitamin B6 (Pyridoxine)**

Adequate availability of vitamin B6 is especially necessary during fetal development because deficiency can negatively influence nervous system development. Marginal deficiencies, which may be associated with deficiencies in riboflavin, may occur in many developing countries. Several studies in developing countries have found vitamin B6 concentrations in breastmilk to be low.

**Vitamin B12 (Cobalamin)**

Diets in developing countries are very often poor in vitamin B12 since the main sources of vitamin B12 are animal foods. Publications describe existing deficiencies in countries such as India and Mexico. Deficiency leads to slowed DNA synthesis, elevated serum homocysteine and anaemia.

**Vitamin B2 (Riboflavin)**

Riboflavin catalyzes numerous oxidation-reduction reactions, is central to energy production, and has a powerful antioxidant activity. Riboflavin is also involved in the metabolism of folic acid, pyridoxine and niacin. Signs of advanced deficiency include angular stomatitis, cheilosis, anaemia, and brain dysfunction. Riboflavin influences the integrity of the gut, and may therefore cause lower absorption of micronutrients in case of deficiency. Good dietary sources include meat and dairy products and some green vegetables. Intake of these foods is often low in developing countries. Because of the consequences of this deficiency, it was decided to include riboflavin in the supplement.

**Zinc**

Zinc is essential for growth and has been shown to reduce the prevalence of infectious diseases such as diarrhoea and respiratory infections in children. Some studies have shown a positive
impact of zinc on birth weight. More data are becoming available to show that zinc deficiency is common in developing countries. Diets low in bioavailable iron are also likely to be low in bioavailable zinc; therefore it was decided to include zinc in the supplement.

**Copper**

There is little information on the influence of copper on pregnancy. However, there can be a risk of copper deficiency when iron and/or zinc supplements are being taken for a prolonged period of time. Healthy babies are born with copper stores that are used for new tissue in the first 6 months of life. Copper deficiency may also lead to anaemia.

**Vitamin C**

Vitamin C deficiency leads to scurvy, with fatigue as one of its first symptoms. Furthermore, it increases the absorption of non-heme iron, and it is an antioxidant. In some countries, intake of vitamin C is low, and clinical signs of scurvy have recently been observed. The amount of vitamin C in breast milk is correlated to the amount of vitamin C in the diet, and lactating women would therefore benefit. From a logistic and production standpoint, Vitamin C’s stability seems to be adequate in tablet form, but without a coating, humidity could destroy this nutrient—an important consideration in pricing calculations.

**Vitamin E**

Extensive literature exists on the effects of Vitamin E and selenium deficiencies on birth obstructions in livestock, but for humans, more data on intake levels are needed and many food composition tables are unhelpful.

There is still not a great deal of sound scientific evidence of the positive benefits of vitamin E related to pregnancy and birth outcome, although it may boost immunity, reduce stillbirth and prematurity, and have a positive effect on sub-clinical mastitis. One issue supporting its inclusion is that with increasing environmental toxins and pollution, vitamin E’s antioxidant properties might be protective. Studies from Peru, Indonesia and Nepal found low tocopherol levels compared to those in European countries.

**Selenium**

Selenium influences iodine metabolism and goitre formation. Soils deficient in iodine are often also likely to be deficient in selenium. Selenium further functions as an anti-oxidant. Risk of toxicity occurs only at high levels of intake (> 10 times RDA).

**Vitamin D**

Vitamin D is responsible for the maintenance of calcium homeostasis and is therefore important in preventing rickets in children and osteoporosis in women. Vitamin D deficiency for populations with reasonable sunshine exposure on the skin (the predominant route of vitamin D synthesis by the body) should not be a substantial problem. However, in countries where the culture dictates women must wear clothes that completely cover them, vitamin D deficiency may be a concern. Maternal vitamin D deficiency is still evident in many communities, contributing to the development of rickets in infancy if babies are not properly exposed to ultraviolet light. For this reason the participants opted for its inclusion.
Niacin

Niacin deficiency causes pellagra, which still occurs in India and Africa, and reports exist on pellagra cases among refugee populations. It was noted that although there might not be strong arguments for inclusion of niacin in the supplement, it would be substantially more expensive to take it out of a pre-made supplement mix than to leave it in.

Vitamin B1 (Thiamin)

Severe thiamin deficiency causes beri-beri, which is associated with extensive neurological and cardiovascular damage. Although severe deficiency is no longer a problem at population basis, sub-clinical thiamin deficiency is fairly common in developing countries. A recent study indicated that rice eating populations in Asia were deficient, especially the elderly.

Nutrients not to be included:

Calcium and Magnesium

Two arguments were made for calcium’s inclusion in the supplement. Firstly, data from dietary intake studies suggest that intake of calcium in developing countries is generally low. Secondly, it has been suggested that calcium may have a preventive effect on pre-eclampsia, but there is no conclusive evidence.

However, calcium absorption increases during pregnancy and, while new RDAs for calcium have just been set, the main argument against including calcium in a supplement is the quantity that would be required. For any beneficial effect to be seen an estimated 1-2 grams per day would be required, and the consequent increase in the tablet size would inevitably affect adherence to tablet intake. Furthermore, calcium and magnesium have interactions with other nutrients—calcium at relatively low levels such 300-400 mg per tablet would reduce the bioavailability of iron, and probably of zinc.

It was decided not to include calcium in the supplement because of the lack of confirming evidence on the benefits of calcium, as well as the increase in tablet size if calcium were to be added. There were no strong arguments put forward in favour of including magnesium, which was therefore also left out in the final composition.

Vitamin K

Vitamin K is passed on in breastmilk at low amounts from the mother to the child and therefore some participants believed it should be considered. However, it was pointed out that a woman would have to be severely malnourished before breastmilk levels of this nutrient are affected. Vitamin K is only poorly passed on through the placenta from mother to child. There is not much information on vitamin K deficiency in developing countries. It was decided not to include vitamin K in the supplement based on the lack of convincing evidence of benefit that might be derived from doing so.
2.3 References for quantities of included nutrients

Two points were raised about the usage of a daily intake reference value.

- RDAs are based on requirements from all intake sources and are calculated to maintain an adequate level of stores/status in a healthy population. While this may be the case in industrialised countries, the intake of many pregnant women in developing countries is much too low, and they lack adequate stores of the fat-soluble micronutrients and of iron. It was argued that adding a full RDA to the daily diet will not be harmful and will benefit the target group.

- RDAs for certain nutrients in food are different compared to those present in a pharmaceutical supplement. For Folate, for example, the bioavailability from supplements (folic acid) is twice as high as it is from the diet.

Based on the two points mentioned above the following options were considered:

- To use the RDAs as they stand for most nutrients.

- To increase the RDAs for certain nutrients based on the assumption that the population is deficient, thereby allowing an opportunity to replenish stores.

A reservation was expressed about both of these options. While there are undoubtedly populations with low intakes, there are also populations where intakes are reasonably adequate, and so this issue needed to be carefully considered. For example, if the population assumed to be deficient is in fact is consuming 50% of the RDAs and the supplement provides 100% or more of the RDAs, the total intake is 150% or more. Evidence is needed to prove that no harm is done in this scenario. One participant noted that even in a severely nutrient-depleted population with heavy loads of infection, high levels of sickness and malnourishment, it is not known whether supplementation with RDA level quantities of nutrients causes no harm. The participant went on to suggest starting with more modest levels of nutrients in the original supplement, and waiting for the results of the studies before higher levels are recommended.

One argument raised against this approach was the fact that many women in industrialized countries take these supplements without any known harm. It is well known that dietary intake levels among women in developing countries are unacceptably low and that scientific evidence exists on the beneficial influence of supplementation with nutrients such as iron, folic acid, zinc, and vitamin A. In fact, for some micronutrients, using RDA levels may even be on the low side for repairing deficiencies, and issues of toxicity are very unlikely to play a role. The large majority of the participants considered it would be more harmful from a public health point of view to withhold the supplement from malnourished women, while waiting for the outcome of more clinical research, than to start with large-scale effectiveness trials while recognizing that some scientific questions remain to be addressed and answered.

After discussing and reviewing all arguments it was finally decided to use the RDA level for the supplement.

2.4 Supplement composition

The proposed supplement should meet the US/Canadian RDAs for pregnancy for the following 15 nutrients. A single exception made was for folic acid content of 400ug, in order to be consistent with the recently amended WHO recommendations.
In contrast to the WHO/INACG recommendations, the supplement will contain 30 mg of iron (rather than 60 mg) for the following reasons:

- The absorption and/or utilisation of iron in the supplement will be enhanced over the currently used iron-folate tablet because of the inclusion of vitamin C, vitamin A, and riboflavin in the multi-micronutrient supplement. Lesser amounts of iron should therefore be sufficient to improve iron status and to increase hemoglobin concentration.

- Adherence is likely to be worse with higher iron content because of the increased possibility for occurrence of negative side-effects.

- Including 60 mg of iron would mean including at least 30 mg of zinc in order to avoid possible negative influence of iron on zinc absorption. This would bring the total amount of metals to 90 mg, which is likely to increase negative side-effects.

- The majority of pregnant women suffer from a mild anaemia (90-110 g haemoglobin/L). In individual cases of more severe anaemia (assuming it is caused by iron) the multi-micronutrient supplement could be used in conjunction with additional iron/folic acid tablets to achieve a quick increase in haemoglobin concentration.

### Composition

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<thead>
<tr>
<th>Vitamin</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Vitamin A</td>
<td>800 μg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>200 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10 mg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>70 mg</td>
</tr>
<tr>
<td>Vitamin B1</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Niacin</td>
<td>18 mg</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>1.9 mg</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2.6 μg</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>400 μg</td>
</tr>
<tr>
<td>Iron</td>
<td>30 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 m</td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
</tr>
<tr>
<td>Selenium</td>
<td>65 μg</td>
</tr>
<tr>
<td>Iodine</td>
<td>150 μg</td>
</tr>
</tbody>
</table>

#### 2.5 Frequency and duration of intake of the supplement

It was decided that the new supplement for use in the pilot trials should be taken on a daily basis as soon as the woman knows she is pregnant and in addition through a minimum of 3 months post partum. This recommendation is more or less in line with the current WHO recommendations: iron-folate supplementation for 6 months during pregnancy and, where the prevalence is greater or equal than 40%, an additional 3 months post partum. The workshop recommended continued use during lactation because the supplement also contains other micronutrients besides iron such as zinc and vitamin A which are also of crucial importance during lactation.

The supplement would preferably be continued throughout the duration of exclusive breastfeeding (about 6 months), and if possible throughout the complete period of breastfeeding (recommended 24 months). However, due to cost concerns to health systems, promotion of the supplement on a daily basis is recommended only during pregnancy and the first 3 months post partum.

#### 2.6 Issues for research on the composition and quantity of nutrients and the impact of the supplement

A number of issues were highlighted as needing further investigation. Some can be investigated in small scale clinical trials; for other issues a larger scale efficacy study is necessary. A list of these issues as they were raised during the workshop is presented in Annex 3.
Other Issues

3.1 Daily versus weekly supplementation schedules and use by other target groups

It was suggested that the supplement could also be promoted for use on a once or twice a week basis to non-pregnant non-lactating women and adolescents to prevent anaemia and other micronutrient deficiencies and to improve stores before the onset of pregnancy. The weekly use is suggested not only because of its lower cost but also because several studies have demonstrated improvement of iron and vitamin A status using weekly supplementation. Although efficacy of weekly supplementation among adolescents and school children has been demonstrated, there is as yet no firm evidence of its effectiveness in large-scale programmes. Further research is needed to examine the effectiveness of intermittent supplementation under various circumstances, but the following summary presents the most prudent but practical approach, based on existing information.

Summary of proposed schedules for giving the supplement

<table>
<thead>
<tr>
<th>Category</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>daily</td>
</tr>
<tr>
<td>Lactating women</td>
<td>daily until 3 months post partum</td>
</tr>
<tr>
<td>NP/NNL women</td>
<td>once or twice a week</td>
</tr>
<tr>
<td>Adolescents (prevention)</td>
<td>once or twice a week</td>
</tr>
<tr>
<td>Emergency/refugee</td>
<td>according to their state, pregnant, NP, NPNL etc. (if necessary in severe deficiency) 2 tablets a day during a brief period)</td>
</tr>
</tbody>
</table>

3.2 Adherence to prescribed intake

Workshop participants recognized that adherence to a prescribed tablet intake is a major stumbling block for the effectiveness of supplementation programmes, especially when supplements are given for longer periods without some kind of supervision. Programmes will need to pay special attention to the issue of ensuring and maximizing adherence. Experience on securing compliance should be gathered from other professional disciplines such as the pharmaceutical industry and social marketing/communication specialists. This experience and exchange could for example be organized through a workshop dedicated to the issue of adherence.
3.3 Infant supplementation

Another target group for iron supplementation besides pregnant women, are young children. They are at risk of multiple micronutrient deficiencies, because of frequent infectious diseases, inadequate dietary intake and rapid growth. Therefore multi-micronutrient supplementation for young children should also be considered. The participants felt that rapidly addressing this need and proposing a composition of an infant multi-micronutrient supplement for use in programmes should be made a priority.

The devastating effects of HIV on families, parenting and care for children in many parts of the world mean that infants are now being fed diets that bear small resemblance to either international recommendations or traditional practices. Some are being exclusively breastfed only to be abruptly switched onto a cereal-based diet; others are being brought up on cow’s milk from birth. One of the outcomes is that infants are increasingly exhibiting signs of anaemia at very young ages, despite being tested HIV-negative. This situation further emphasizes the urgent need for infant supplements.

3.4 Issues to be investigated or monitored when the supplement is used in pilot effectiveness trials

As stated in the introduction, the supplement is intended for use in pilot programmes in a number of countries. It is recognized that several issues still need to be investigated and the impact of the supplement under programme conditions needs to be carefully monitored. A comprehensive list of issues and topics is contained in Annex 4. It is not intended that all these indicators should be monitored in every country, but it would be worthwhile to agree upon a core list of indicators. There was no time left at the workshop to complete such a list.
Annexes

### Annex 1: Comparison of selected dietary reference values for micronutrients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A RE</td>
<td>800</td>
<td>600</td>
<td>1,300</td>
<td>850</td>
</tr>
<tr>
<td>Vitamin A IU</td>
<td>2,664 retinol</td>
<td>200</td>
<td>200 (AI)</td>
<td></td>
</tr>
<tr>
<td>8,000 beta-carotene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D IU</td>
<td>200 (AI)</td>
<td>400</td>
<td>200 (AI)</td>
<td></td>
</tr>
<tr>
<td>Vitamin E IU</td>
<td>10</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁ (Thiamin) mg</td>
<td>1.4</td>
<td>0.9</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin B₂ (Ribof.) mg</td>
<td>1.4</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Niacin mg</td>
<td>18</td>
<td>12.6</td>
<td>17</td>
<td>14.2</td>
</tr>
<tr>
<td>Folate µg</td>
<td>600</td>
<td>420</td>
<td>500</td>
<td>270</td>
</tr>
<tr>
<td>Vitamin B₉ mg</td>
<td>1.9</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ µg</td>
<td>2.6</td>
<td>1.4</td>
<td>2.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Vitamin C mg</td>
<td>70</td>
<td>50</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>Zinc mg</td>
<td>15</td>
<td>(3rd trim.)</td>
<td>19</td>
<td>(0–3 months)</td>
</tr>
<tr>
<td>Iron mg</td>
<td>30</td>
<td></td>
<td>26.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Low bioavailability</td>
<td></td>
<td></td>
<td>179–299</td>
<td>33</td>
</tr>
<tr>
<td>Med. bioavailability</td>
<td></td>
<td></td>
<td>92–152</td>
<td>17</td>
</tr>
<tr>
<td>High bioavailability</td>
<td></td>
<td></td>
<td>46–76</td>
<td>9</td>
</tr>
<tr>
<td>Calcium mg</td>
<td>1,000 (AI)</td>
<td>1,000–2,000</td>
<td>1,000 (AI)</td>
<td>1,000–1,200</td>
</tr>
<tr>
<td>Phosphorus mg</td>
<td>700</td>
<td></td>
<td>700</td>
<td></td>
</tr>
<tr>
<td>Magnesium mg</td>
<td>Age 19–30: 350</td>
<td></td>
<td>19–30: 310</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age 31–50: 360</td>
<td></td>
<td>31–50: 320</td>
<td></td>
</tr>
<tr>
<td>Vitamin K µg</td>
<td>65</td>
<td></td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Iodine µg</td>
<td>175</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Selenium µg</td>
<td>65</td>
<td>39</td>
<td>75</td>
<td>42</td>
</tr>
<tr>
<td>Copper mg</td>
<td>1.5–3.0 (ESADI)</td>
<td>1.15</td>
<td>1.5–3.0</td>
<td>1.25</td>
</tr>
<tr>
<td>Manganese mg</td>
<td>2.0–5.0 (ESADI)</td>
<td></td>
<td>2.0–5.0</td>
<td></td>
</tr>
<tr>
<td>Fluoride mg</td>
<td>3.1 (AI)</td>
<td></td>
<td>3.1 (AI)</td>
<td></td>
</tr>
<tr>
<td>Chromium µg</td>
<td>50–200 (ESADI)</td>
<td></td>
<td>50–200</td>
<td></td>
</tr>
<tr>
<td>Molybdenum µg</td>
<td>75–250</td>
<td></td>
<td>75–250</td>
<td></td>
</tr>
<tr>
<td>Biotin µg</td>
<td>30 (AI)</td>
<td></td>
<td>35 (AI)</td>
<td></td>
</tr>
<tr>
<td>Pantothentic acid mg</td>
<td>6 (AI)</td>
<td></td>
<td>7 (AI)</td>
<td></td>
</tr>
</tbody>
</table>

¹ RDAs = Recommended Daily Allowances
## Annex 2: Comparison of composition of some available micronutrient supplements for women

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin A IU</strong></td>
<td>5,000</td>
<td>5,000</td>
<td>5,000 (20% as beta-carotene)</td>
<td>5,000 (Vitamin A/ beta-carotene)</td>
</tr>
<tr>
<td></td>
<td>750 g RE</td>
<td>500</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>2,500 IU</td>
<td></td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td><strong>Vitamin D IU</strong></td>
<td>400</td>
<td>500</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Vitamin E IU</strong></td>
<td>10</td>
<td>15</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Vitamin B₁ (Thiamin) mg</strong></td>
<td>1.6</td>
<td>1.8</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Vitamin B₂ (Ribof.) mg</strong></td>
<td>20</td>
<td>19</td>
<td>800</td>
<td>20</td>
</tr>
<tr>
<td><strong>Folic acid µg</strong></td>
<td>270</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.6</td>
<td>2.6</td>
<td>20</td>
</tr>
<tr>
<td><strong>Vitamin B₆ mg</strong></td>
<td></td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Vitamin B₁₂ µg</strong></td>
<td>6</td>
<td>100</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td><strong>Vitamin C mg</strong></td>
<td></td>
<td>7.5</td>
<td>7.5</td>
<td>60</td>
</tr>
<tr>
<td><strong>Zinc mg</strong></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td><strong>Iron mg</strong></td>
<td></td>
<td></td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td></td>
<td>60 (as fumarate)</td>
<td>27</td>
</tr>
<tr>
<td><strong>Calcium mg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td>450</td>
</tr>
<tr>
<td><strong>Phosphorus mg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Magnesium mg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin K µg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Iodine µg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Selenium µg</strong></td>
<td></td>
<td>125</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Copper mg</strong></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Manganese mg</strong></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Fluoride mg</strong></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Chromium µg</strong></td>
<td>250</td>
<td>200</td>
<td>200</td>
<td>120</td>
</tr>
<tr>
<td><strong>Molybdenum µg</strong></td>
<td>6</td>
<td></td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td><strong>Biotin µg</strong></td>
<td></td>
<td></td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td><strong>Pantothenic acid mg</strong></td>
<td></td>
<td></td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td><strong>Cost/tablet (dollars)</strong></td>
<td>16</td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Annex 3: Research priorities

- Research on adherence to prescribed tablet intake and the influence of different communication/social marketing approaches.
- Interactions between zinc, iron and other micronutrients in the supplement.
- Risks in comparison to benefits of multi-micronutrient supplementation of pregnant women in developing countries (risk-benefit analysis).
- The chemical form of the nutrient included in the supplement, (eg, zinc oxides, Fe Chelates).
- Weekly vs. daily supplementation, specifically on nutrients other than iron (e.g. B-vitamins), both in its effectiveness and efficacy. There may also be different patterns of compliance with daily regimens (often stop and start again) and weekly (stop and give up for good).
- The level of iron available in a multi-supplement, and whether 30mg is the correct level to use.
- The effect of giving supplements with food or without, issues of binding properties.
- The interactions between certain micronutrients and HIV transmission need much more careful study (for example, vitamin A and zinc), in the light of escalating numbers of women HIV+ in Africa (now at 25% in the continent).
- The interaction between HIV and malaria in relation to micronutrient also needs more research
- The cost effectiveness of multi-micronutrients versus iron supplements.

Annex 4: Outcome indicators to be observed in the effectiveness trials

Indicators related to mothers/pregnancy

- Weight gain during pregnancy
- Biochemical markers of nutritional status of mother
- Breast milk composition
- Breastfeeding performance
- Maternal well being
- Pregnancy and delivery complications (eg, haemorrhage, infection, eclampsia, cerebral malaria, premature rupture of membranes, birth defects, prolonged labour)
- Morbidity & mortality
- In populations where HIV is a problem, relate to HIV status

Programme management issues

- Adherence to prescribed intake
- Coverage of supplementation
- Cost
- Distribution
- Whether multi-supplements reduce the need for other interventions
- Methods of supplement distribution
- Community involvement (care for pregnant women)
Indicators related to birth outcome

- Prevalence of LBW
- Anthropometry of infants in general, birthweight specifically
- Morbidity and mortality
- Child growth in first 12 months
- Biochemical measures in infants
- Mental/motor functions

Annex 5: List of participants

Henrietta Allen (WHO)
Lindsay Allen (University of California)
Bruno de Benoist (WHO)
Martin Bloem (HKI)
Ian Darnton-Hill (HKI)
Frances Davidson (USAID)
Leslie Elder (JSI)
Rainer Gross (GTZ)
Rick Guidotti (WHO)
Sandra Huffman (Linkages)
Allen Jackson (University of Southampton)
Marjorie Newman-Williams (UNICEF)
Barbara Macdonald (CIDA)
Andrew Tomkins (University of London)
Nevin Scrimshaw (UNU)
Werner Schultink (UNICEF)
Koen Vanormelingen (UNICEF)
Keith West (JHU)
Tim Quick (USAID)