CHAPTER 1
INTRODUCTION

Compromised nutrition in any age group has been identified as the world’s most serious health problem and the single largest contributor to foetal or child mortality. Under nutrition is a status which affects not only current generation, but it is often extended into future generations while they are in the gestational stages into the wombs of their mothers. Lack of the essential nutrients- vitamins and minerals continue to be pervasive and they overlap considerably with problem of malnutrition (Kotecha PV 2008). Growth faltering observed in foetal stage as well as in the malnourished children which hampers intelligence, psycho motor and cognitive development. These in turn lead to slowing down of socioeconomic growth which can increase poverty and reduces productivity. Therefore economic cost of malnutrition is very high (Mason JB 2003).

India is second after Bangladesh with respect to the prevalence of underweight children in the world. India has 49 % of underweight children which contributes to 39 % of the world’s underweight children. Approximately 21.8 % of the country’s population consist of school going children. School children aging between 6-14 yrs, carry almost 63-73% prevalence of under nutrition. The prevalence varies from state to state, socioeconomic status of the population and their residential location. The most affected group is rural population (World Bank 2006) and lower strata of urban communities. Maternal nutrition has also the most important determinant influence during the development of foetus. Poor nutritional status during pregnancy is associated with inadequate weight gain, anaemia, retarded foetal growth, low birth weight, still births, preterm delivery, IUGR (intrauterine growth retardation), morbidity and mortality rates (Kansel et al. 2003, Sachdeva 2009). Thus, it may threaten the health and life of the mother and the newborn.

A review of such studies examining the relationship between mental development and severe malnutrition concluded that school-age children who suffered from early childhood malnutrition generally have poorer IQ levels, cognitive function, school achievement and greater behavioural problems than matched controls, and to lesser extent
siblings. The detrimental effect was observed to affect their adolescence and later age (Grantham-McGregor 1995). Malnutrition in early stages has been found to have a long term effect on the growth and development of children, particularly on cognitive development.

Further it has been known to have short and long term effects on disease response, cognitive function, reproductive competence, work output and social behaviour of individuals (Osman et al 1993). It also encompasses micronutrient deficiencies. Among these deficiencies, Iron deficiency is the most detrimental for foetal life and childhood. However, iodine deficiency is been proven to be life threatening during foetal development and hazardous for the developing brains of the children. Thus, WHO has described reproductive age and childhood as the most vulnerable period for malnutrition. Iodine and iron deficiencies are highly prevalent in all the classes of the community in silent forms and thus have been tagged as ‘Hidden Hunger’.

Despite recent progress in the fight against hunger and malnutrition in many countries, global food and nutrition security is still a far away goal (Stein A et al 2008). An estimated 820 million people in developing countries are undernourished (FAO 2006). Many more suffer from specific deficiencies in certain micronutrients: 2 billion people are anemic, many due to iron deficiency (WHO 2007) and 2 billion are iodine deficient (ACC/SCN 2004).

**IODINE**

Iodine is a micronutrient of crucial importance for the health and well being of all individuals. It is a trace element, just 5 gms of which are sufficient to meet the life-time needs of an individual with a life-span of 70 years (Dhaar GM and Robbani I 2008). Iodine deficiency disorders (IDD) is a collective term, which reflects the clinical and subclinical manifestations of iodine deficiency. Thus, making it the most common endocrinopathy in the world and also the most preventable cause of mental retardation (Patrick L 2008). The two major factors responsible for IDD are inadequate iodine intake
(due to inadequate supply from foods) and inadequate iodine utilization (due to consumption of goitrogens).

Hence, sustained insufficiency of iodine for a longer period in the circulation of human body leads to dysfunction of thyroid gland. Thus, it becomes one of the leading reasons for thyroid disorders amongst the population. The global goitre prevalence is more than 2 billion with more than 40 millions in India. The true prevalence and incidence in India of thyroid disorders is difficult to estimate, even conservative estimates put the geographical prevalence between 42 million including cases of iodine deficiency disorders. India is now predominantly iodine sufficient we are nearing the peak prevalence of the autoimmune epidemic. It is estimated that about 7.1 crores Indians are suffering while 20 crores people are at the risk of iodine deficiency disorders (IDD) in our country. As reported by (Sinha 2011), the Union Health Ministry is targeting to reduce IDD prevalence nationally to less than 10% by 2012 and 5% by the end of 2017.

IODINE SUPPLY AND DEFICIENCY DURING PREGNANCY

Over the past several years it has been proven that thyroid dysfunction is more common in adolescent girls than boys and thus may be a factor during reproductive age (Glinoer 1997). Pregnancy is a euthyroid state that is normally maintained by complex changes in thyroid physiology. Adequate iodine supply throughout life span can result into a successful pregnancy outcome.

As per thyroidological terminology, pregnancy is a physiological condition, in which a number of modifications may occur to affect thyroid economy. These events may take place at any point of gestation, leading to transient phase or may persist until term. Sometimes these alterations are permanent (Glinoer D, De Nayer P 1993). The key is to recognize and treat thyroid insufficiency at reproductive age before conception, since it may influence the outcome of mothers and fetus during and after pregnancy. It is associated with fetal loss, placental abruptions, pre-eclampsia, preterm delivery and reduced intellectual function in the offspring.
The prevalence of hypothyroidism during pregnancy is estimated to be 0.3-0.5% for overt hypothyroidism (OH) and 2-3% for subclinical hypothyroidism (SCH). The most contributing cause of hypothyroidism is iodine deficiency, known to affect over 1.2 billion individuals in the world (Ablovich M. Glicin 2009).

Throughout the life cycle an individual’s ability to alter synthesis, secretion or turnover of thyroid hormones in response to the changes in nutrient intake and ambient temperature has a large impact on heat production and body composition. This interaction is most striking during pregnancy and perinatal development when large perturbations in thyroid status within the mother, fetus or neonate may occur. Thyroid hormones are necessary to ensure normal development of brain, lung muscle, nerves, adipose tissue, heart and cardiovascular function in both fetus and neonate, although their role varies with gestational age and maturity at birth. Alterations in thyroid-hormone regulation, therefore, can cause large changes in growth, development and maturation of a number of organs and tissues that ultimately determine if an individual will survive (Symonds 1995).

**IODINE DEFICIENCY DURING SCHOOL AGE**

There have been many cross-sectional studies comparing cognition and motor function in children from chronically iodine-deficient and iodine-sufficient areas among children from Asia. The results have revealed that, compromised iodine nutrition leads to mean reduction in IQ of 12-13.5 points (Hetzel BS 1983, Zimmerman MB 2009). However, a set of few more studies reviewed by the author also revealed that in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion (Zimmerman MB 2006).

Iodine status may also influence somatic growth through its effects on pituitary-thyroid axis. Thyroid hormone promotes growth hormone secretion and modulates the effects on the receptors. IGF-I and IGFBP-3 are also dependent of thyroid status. A metaanalysis by (Mason JB et al 2002) found positive correlation between anthropometric indices of the children and iodized salt access of the households.
THYROID PHYSIOLOGY AND IODINE METABOLISM IN HUMAN SYSTEM

The thyroid gland plays a vital role in the metabolism of iodine. It is the largest of the exclusively function organs as an endocrine gland, weighing about 20 g in an adult. The thyroid gland comprises a unique structure, with a multiple follicles lined by follicular cells resting on a basement membrane. The follicular cells produce colloids. Thyroid follicular cells are cuboidal to columnar, and their secretory polarity is directed toward the lumen of the follicles. Polarity of follicular cells is important for iodine uptake, but the follicle structure is required for the synthesis of thyroid hormones. The luminal surfaces of follicular cells protrude into the follicular lumen and have numerous microvillus projections that greatly increase the surface area in contact with colloid. An extensive network of interfollicular and intrafollicular capillaries provides the follicular cells with an abundant blood supply (Capen 2000).

Follicular cells have long profiles of rough endoplasmic reticulum and a large Golgi apparatus in their cytoplasm for synthesis and packaging of substantial amounts of protein that are then transported into the follicular lumen. Numerous electron dense lysosomal bodies are present in cytoplasm, which are important in the secretion of thyroid hormones.

The individual steps in thyroid hormone formation and secretion (Ahad F. and Ganie S. 2010) may be characterized as follows (Figure 1.1):

1. **Iodine trapping:** It is the first step in the metabolism of iodine. The process commences with the uptake of iodide from the capillary into the follicular cell of the gland by an active transport system. This occurs against chemical and electrical gradients by sodium/iodine symporter protein (NIS) found in the basolateral membrane of the follicular cell; the energy required by thus process is linked to the ATPase dependent Na$^+$-K$^+$ pump.
Transport of iodide ion across the thyroid cell membrane is linked to transport of Na⁺. The ion gradient generated by Na⁺-K⁺-ATPase appears to be the driving force for the active co-transport of iodide. I- is then passively translocated via a putative I- channel across the apical membrane into the colloid, located in the follicular lumen. Other tissues such as the salivary gland, gastric mucosa, choroid plexus, ciliary body or the eye, and lactating mammary gland also have the capacity to actively transport iodide although at a much lower level than the thyroid. Only the thyroid follicular cells accumulate iodide in a TSH-dependent manner.

2. Synthesis and Secretion of Thyroglobulin: It is the second step. It occurs by another independent process within the follicular cell; the synthesis starts on the rough endoplasmic reticulum as peptide units of molecular weight 330,000 (the primary translation product of its messenger RNA). Later these units combine into a dimer,
followed by addition of carbohydrate moieties, after which the molecule moves to the Golgi apparatus. The completed thyroglobulin molecule contains about 140 tyrosine residues, which serve as substrate for the synthesis of thyroid hormones. The thyroglobulin is contained within small vesicles which then move towards the apical surface of the plasma membrane before being released into the follicular lumen.

3. **Oxidation of iodide:** The iodide within the follicular cell moves towards the apical surface of the plasma membrane, to enter into the follicular lumen; this transport by a sodium independent iodide/chloride transporter called pendrin. The iodide (I\(^{-}\)) is then immediately oxidized to iodine by (I).  

4. **Organification of Thyroglobulin:** wherein iodination of the tyrosine residues present within the thyroglobulin molecules occurs. Iodination first occurs at position 3 to form monoiiodotyrosine (MIT) and then at 5 to form diiodotyrosine (DIT). Iodination of tyrosine is followed by coupling reaction, whereby, two molecules of DIT couple to form thyroxine (T\(_4\)) hormone; and one molecule of MIT couples with one molecule of DIT to form Triiodothyronine (T\(_3\)) hormone. The reaction is catalyzed by thyroid peroxidises (TPO). The thyroid hormones are stored inside the thyroid follicles as colloid for several months. The stored hormones can meet the body requirements for 3 months.  

The colloid containing iodinated thyroglobulin undergoes endocytosis, whereby it is salvaged from the follicular lumen by the epithelial cells; this is facilitated by TG receptor **megalin** which is present on the apical membrane. The colloid now enters the cytoplasm in the form of colloid droplets, which move towards the basal membrane possibly by way of microtubule and microfilament function. The colloid droplet next fuses with lysosome vesicles which contain proteolytic enzymes. The proteases help digest the thyroglobulin molecule releasing T\(_4\), T\(_3\), DIT and MIT into the cytoplasm. While T\(_4\) and T\(_3\) diffuse via the basal surface into the blood stream, the MIT and DIT get rapidly deiodinated by enzyme deiodinase. This mechanism helps to retrieve iodide for recycling along with tyrosine for recycling.
In the blood stream, T₄ and T₃ may circulate in the bound or free form; whereas 99% of T₄ and T₃ circulate in the bound form. The binding proteins include thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA) and thyroxine binding albumin (TBA). Binding of hormones apart from serving as a reservoir also helps to prevent urinary loss of hormones. The unbound hormones are biologically active. About 80% of circulating T₃, the most active thyroid hormone is derived from peripheral deiodination of T₄ hormone.

Thyroid secretion is regulated by pituitary gland through TSH which operates on a feedback mechanism tuned to T₄ level in blood. A fall in T₄ level stimulates the pituitary to increase its TSH secretion which in turn stimulates the thyroid gland to release T₄ in circulation to maintain normal level of the hormone in blood.

Thyroid gland secretes 80 micrograms of iodine in the form of T₃ and T₄ hormones per day; 40 micrograms of iodine secreted appear in extracellular fluid (ECF) per day. T₃ and T₄ are metabolized in liver which releases about 60 micrograms of iodine in ECF and 20 micrograms of iodine into the bile to be excreted in stools. On an average, 480 micrograms of iodine get extracted in urine and 20 micrograms in stools per day.

**Regulatory adjustments due to Iodine deficiency**

*Endemic goitre* is an adaptive disease that develops in response to an insufficient supply of dietary iodine. When iodine intake is abnormally low, adequate secretion of thyroid may still be achieved by marked modification of thyroid activity (Zimmerman MB 2009).

These adaptive processes include stimulation of the trapping mechanism as well as of the subsequent steps of the intra-thyroidal metabolism of iodine leading to preferential synthesis and secretion of T₃. They are triggered and maintained by increased secretion of TSH. The morphologic consequence of prolonged thyrotropic stimulation is the development of goitre, which therefore appears as a mechanism of adaptation to iodine deficiency.

*Increased iodide trapping*, a fundamental mechanism of thyroid gland adapts to iodine deficiency to increase the trapping of iodide. This results in accumulation within the
gland of a larger percentage of ingested iodide and a more efficient reuse of iodide directly released by the thyroid or generated by the degradation of thyroid hormones. The increased iodide trapping is the result of both TSH stimulation of the iodide pump and perhaps TSH-independent augmentation of membrane iodide trapping involving the thyroid sodium symporter. This in turn must lead to two physiological changes:

1. Decreased amount of iodine excretion in the urine to preserve pre-existing iodine stores.
2. Ensure the accumulation in the thyroid of definite amounts of iodide per day (about 100 μg). This parameter is extremely important because it quantitatively controls all further steps of intrathyroidal iodine metabolism, including the secretion rate of thyroid hormones.

**Stimulation of TSH and altered circulatory thyroid hormones**- Clinically euthyroid adults in areas with severe iodine insufficiency leads to lower serum T₄, elevated TSH and normal T₃. However, only under conditions of extreme thyroid failure like in myxedematous endemic cretinism that both serum T₄ and T₃ are particularly low and serum TSH is dramatically elevated. In less severe goitre endemics, serum T₄ and T₃ levels are only slightly modified or remain normal.

Due to iodine fluctuating levels state of euthyroidism or hypo/hyperthyroidism precipitates in the human systems, where the up and down regulation of thyroid hormones takes place and leads to various conditions. These conditions are depicted in table 1.1.

**Table 1.1: Changes in thyroid hormones in a variety of medical conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>TSH</th>
<th>TT₄</th>
<th>TT₃</th>
<th>FT₄</th>
<th>FT₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroidism</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Decrease</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Increase</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

(Reference: www.thyroidmanager.org)
DIETARY ALLOWANCES FOR IODINE

The dietary allowances of iodine recommended by the World Health Organization (WHO) are 150 μg/day for adolescents and adults, 250 μg/day for pregnant and lactating women, 120 μg/day for children 6 to 12 years of age and 90 μg/day for children below 6 years of age (WHO/UNICEF 2007).

Iodine requirements during pregnancy are increased due to: (1) an increase in maternal T4 production to maintain maternal euthyroidism and transfer thyroid hormone to the fetus early in the first trimester, before the fetal thyroid is functioning (12th week of gestation); (2) iodine transfer to the fetus particularly in the later gestation and (3) an increase in renal iodine clearance (RIC) (Glinoer 1997). Increased RIC leads to misleading results on iodine deficiency prevalence, since increase renal clearance would increase UIE levels (an indicator of iodine deficiency in epidemiological studies), leading to decreased plasma inorganic iodide (PII) and thus the thyroid gland would lead to conservation mechanism of trapping iodine.

If these requirements are not met for a notable period of time in a given population, then thyroid dysfunctions may occur in a number of ways affecting functional and developmental efficiencies, including thyroid function abnormalities, when severe iodine deficiency occurs then- endemic goitre and cretinism, decreased fertility, increased perinatal death and infant mortality. These complications are preventable by appropriate iodine supply. The socioeconomic, cultural and political limitations may also hinder the sustained programs for iodine supplementation.

THYROID PHYSIOLOGY DURING PREGNANCY

Pregnancy leads to profound changes in thyroid function and iodine requirements (Glinoer D 2007). Increased concentration of estrogen leads to marked increase in the concentration of serum thyroxine binding globulin, which begins during early gestation, reaches a plateau at mid-gestation and is maintained thereafter.
During early gestation, there is an increased renal blood flow and glomerular filtration, which leads to an increased iodide clearance from the plasma and thus to an obligatory loss of iodine. This transition near the end of the first trimester, directs the stimulation of the thyroid gland by an increase in the concentration of human chorionic gonadotrophin that may lead temporarily to a slightly increased concentration of free thyroxine (FT₄) and decreased thyrotropin levels (TSH) due to competency of hCG. Finally, significant changes occur in the peripheral metabolism of maternal thyroid hormones during the second half of gestation, mainly under the influence of placental type 3 iodothyronine deiodinase (Bianco 2002). This further leads to reciprocation in the levels of FT₄ and TSH levels compared to first trimester.

Together, these events represent profound metabolic changes associated with the first half of gestation that constitutes a transition from a preconception steady-state thyroid gland to a pregnancy steady-state thyroid gland (Glinoer D 2004). In order for such metabolic changes to happen, this needs an increase in hormone production by the maternal thyroid.
gland of about 50%. As Figure 1.2 shows, once the new equilibrium has been reached, the increased demand for hormones during pregnancy is sustained until full term.

FETAL THYROID DEVELOPMENT

Thyroid system development in human foetuses can be divided into three phases that roughly correlate with the three classic trimesters of pregnancy.

**Phase I:** development during first trimester includes embryogenesis of the hypothalamus, the pituitary gland, and the thyroid gland

**Phase II:** during second trimester, is a period of continuing foetal growth and relatively quiescent thyroid function.

**Phase III:** during the third trimester and the neonatal period, includes maturation of hypothalamic-pituitary-thyroid interaction and control. It also includes maturation of thyroid hormone metabolism and actions.

NEURONAL COMPROMISES DUE TO IODINE DEFICIENCY

Thyroid deficiency during the latter two thirds of gestation and the first months after delivery can result in mental retardation, since it would disrupt the migration of neuron in the fetal cortex and hippocampus (Lavado-Autric 2003). Thyroid hormones regulate the process of terminal brain differentiation such as dendritic and axonal growth, synaptogenesis, neuronal migration and myelination (Eayrs and Tylor 1951, Eyers and Horne 1955, Eyers 1955). There is retarded development of neutrophils in cerebral cortex and cerebellar Purkinje cells. Neuronal bodies are smaller and more densely packed, there is diminished dendritic branching and elongation, altered distribution of dendritic spines and delayed cell proliferation and migration (Nicholson and Altman 1972). Deficiencies of myelination are observed in the cerebral cortex, visual and auditory cortex, hippocampus and cerebellum. All these effects can be reversed by iodine supplementation but only if the supplementation is started at early stage (Chan S and Kilby MD 2000).
Thus, the lack of supply at maternal, fetal and young age would lead to thyroid anomalies; lower IQ and cognitive function are observed as the predominant ones with the effects on the developing brains.

**IRON**

Iron is one of the most essential micronutrient at every stage of human life, other than iodine and Vitamin A. It’s deficiency is termed as iron deficiency, which is a major contributor of anaemia amongst the population, computed as iron deficiency anaemia (IDA). One third of the world’s population suffer from anaemia. India has continued to be one of the countries with high prevalence of iron deficiency anaemia. According to NFHS III (2005-2006), the prevalence of anaemia is 70-80% in children. Anaemia affects the oxygen carrying capacity of the cells and thereby reduces the work capacity of the children. Iron deficiency along with iodine deficiency affects the developing brains, physical and mental growth of the children. However, there were >60% of the pregnant women in India suffered from IDA during NFHS-III (2005-2006). The percentages have remained unchanged till date, respite existing deficiency control programs. The prevalence is irrespective of economic grades of the women. However, severity is observed to be higher amongst lower income groups.

**IRON DEFICIENCY DURING PREGNANCY**

A high proportion of women in both industrialized and developing countries become anaemic during pregnancy. Estimates from the World Health Organization report (1992) that, from 35% to 75% (56% on average) of pregnant women in developing countries, and 18% of women from industrialized countries are anaemic. However, most of these women are already anaemic at the time of conception, with an estimated prevalence of anaemia at 43% in non-pregnant women in developing countries and 12% in women of wealthier regions. The prevalence of iron deficiency is far greater than the prevalence of anaemia and iron deficiency (low serum ferritin and sparse or absent stainable iron in bone marrow) often develops during the later stages of pregnancy even in women who enter pregnancy with relatively adequate iron stores (NFHS-III, 2005-2006). Hence, it
becomes essential to study the impact of iron supplementation during pregnancy on their own iron status as well as on the pregnancy outcome (Puolakka J. et al 1980).

DIETARY ALLOWANCES AND REQUIREMENTS FOR IRON

At the time of birth, neonates are born with ≈270 mg iron in their body. However, the total iron requirement for pregnancy is much higher than this. The mother’s red blood cell count increases, the size of other tissues increases and the placenta itself has a substantial iron requirement. The placenta contains ≈90 mg of iron at term. The maternal red blood cell expansion accounts for ≈450 mg iron and the total basal losses are ≈230 mg. In sum, the total cost of pregnancy in terms of iron is ≈1.2 g (Bothwell 2000). In terms of balance, the mother can recover ≈600 mg of iron from cessation of menses and the recovery of red blood cells synthesized during pregnancy. This leaves a net requirement for iron of ≈600 mg. However, according to Indian data (NFHS III, 2005-2006) with 60-70% prevalence of anemia during pregnancy and mean hemoglobin concentration to be 9.17-9.19 g/dl, the requirement of iron is been set as per the health status and weight gain in all three trimesters. NIN has provided (Table 1.2) average calculation towards iron requirements during each trimester of pregnancy.

Table 1.2: Iron requirements during pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Requirements of iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 kg GWG</td>
</tr>
<tr>
<td>1st trimester</td>
<td>130</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>320</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>310</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
</tr>
</tbody>
</table>

*GWG- Gestational weight gain

(Source: NIN 2009)

The recommended daily allowance for young children 6-9 years is 16 mg/day. The requirement increases with age. Hence, it goes about 21mg/d and 27mg/day for boys and girls of (10-12 years) respectively, it is 32 mg/d and 27mg/day for children 13-15 years (adolescents) of both the genders respectively.
MECHANISMS OF IRON UPTAKE AND TRANSFER TO THE FETUS

Gambling L. (2011) has demonstrated the possible mechanism in a very simple and understandable manner between feto-maternal complex. It reveals that, after it is absorbed across the maternal gut, iron is carried to the liver. In the serum, iron is bound to transferrin. Transferrin has 2 iron-binding sites with approximately equal affinities for iron. It is glycosylated, and, of interest, the glycosylation patterns change during pregnancy (Van Dijk JP, van der Zande FG, Kroos MJ et al 1993). The functional consequence(s) of these alterations is unknown (Jeschke U, Wang X, Briese B et al 2003).

In non pregnant conditions, 40% of the iron is taken up by the liver on the first pass through the portal circulation. Whether this is so in pregnancy is not known, but the liver still plays an important role in iron homeostasis. Iron stores in the liver is transferred to the fetus has not been studied directly. However, concentrations decrease significantly during pregnancy, so the process does occur, and presumably it is mediated by signals from the developing fetus. The nature of these signals is not yet known (Millard KN, Frazer DM, and Wilkins SJ et al 2004).

Although the release of iron from ferritin has been studied extensively, the underlying mechanism is still a matter of discussion. After it is released, the iron [as Fe(II)] is oxidized by ceruloplasmin to Fe (III) and incorporated into transferrin. The site of this interaction is also not clear, but presumably it occurs at the hepatocyte cell surface. Thereafter, transferrin is carried in serum to the placenta, where the steps outlined (Figure 1.3) take place. The transferrin binds to the transferrin receptor on the placental microvillar membrane surface.

After binding is completed, the complex is incorporated into clathrin-coated vesicles and internalized. The pH inside the vesicle is reduced, probably by an H+-ATPase. This has a very interesting effect: the iron is released from the transferrin. At pH 7.4, apo-transferrin (transferring with no iron on it) has a relatively low affinity for the receptor, therefore, apo-transferrin will not bind on the cell surface.
At pH 5.5 (the approximate pH inside the vesicle), the affinity of transferrin for Fe is greatly decreased; consequently, the iron is released from the protein and the protein becomes apo-transferrin. At this low pH, the receptor affinity reverses and apo-transferrin has a much higher affinity than diferric transferrin. Hence, in the clathrin-coated vesicle, as the pH drops and the iron is released, the transferrin protein stays bound to the receptor (Gambling L 2011).

This complex will eventually recycle back to the surface, where the apo-transferrin will be released, as the pH returns to 7.4. Inside the vesicle, iron [as Fe (II)] moves through a channel known as **divalent metal transporter 1 (DMT1)** (now formally classified as slc11a2) into the cytoplasm (Chong WS, Kwan PC, Chan LY et al 2005). Its transfer to the fetal side of the cell is not known. It is possible that carriers are used to ensure that the iron stays as Fe (II) and is not reoxidized, and also to prevent it from being involved in chemical reactions; however, to date, none have been identified.
Of interest, DMT1 may not be essential for the intracellular transport process. (Gunshin et al 2005) showed that the channel is not essential for iron transport across the placenta. This is a very intriguing observation that has some important implications. Either there is an alternative pathway of iron transport, or there is redundancy that allows iron to escape from the vesicle without a specific channel requirement.

The iron is released from the cell through a protein called ferroportin. Fetal transferrin (in fact, all transferrins) bind Fe as Fe (III), and hence it must be oxidized once it is released in order for it to bind to its carrier protein. This is carried out by a protein called zykloopen, a copper ferrooxidase from a family of ferrooxidases that are central to iron release (Chen H, Attieh ZK, Syed BA, et al. 2010). The mechanisms and steps involved are presented in Figure 1.3 (McArdle HJ, Danzeisen R, Fosset C, et al 2003 and McArdle HJ, Andersen HS, Jones H et al 2008).

**REGULATION OF UPTAKE AND TRANSFER BY FETUS**

Iron is a very reactive element, with the capacity to accept and donate electrons. This ability is central to its function, but it can also cause problems. Uncontrolled reactions can generate free radicals, with consequent peroxidation of lipids and membrane damage. A series of regulatory steps have evolved to minimize the risk of this happening. At the same time, because iron is essential, systems have evolved to make sure iron supplies are adequate for optimal function. This is especially true during pregnancy.

The amount of iron that is transferred from mother to fetus rises as gestation proceeds (McArdle HJ, Douglas AJ, Bowen BJ, et al 1985). The number of transferrin receptors on the placenta increases in parallel with iron accumulation, implying that it is the availability of transferrin-binding sites on the surface of the placenta that limits iron transfer (Gambling L, Danzeisen R, Gair S, et al. 2001).

The number of receptors rises as the amount of iron in the maternal diet decreases, meaning that a larger proportion of the iron absorbed is carried to the fetus. Most of the transferrin receptors are located on the microvillar membrane of the placenta (Bradley J,
Leibold EA, Harris ZL, et al 2004). When a cell accumulates excess iron, it stores it in ferritin. Ferritin and transferrin are regulated in an exceedingly elegant manner.

Each of the 2 mRNAs has an iron regulatory element (IRE) at either the 5’ (ferritin) or 3’ (transferrin receptor) end (Rouault TA et al 2006). This is a loop of RNA to which the iron regulatory protein (IRP) binds. When iron is present, it binds to the IRP and causes its release from the IRE. This release has different effects depending on where the IRP binds. Increased iron means increased iron stores, and releasing the IRP from transferrin receptor (TfR) mRNA destabilizes it so that it is degraded, whereas removing the IRP from ferritin mRNA releases it from being blocked from translation, so that ferritin protein is produced (Rouault TA et al 2006).

This very simple but neat system of interdependent regulation also applies to other iron-regulated proteins, such as DMT1, but it is important to note that there are other proteins that are not regulated like this. In the case of the placenta, ferroportin and zykloopen are 2 of the iron proteins that are not regulated by the IRE/IRP system. All of these systems are modulated by fetal liver iron concentrations. In fact, the fetal liver seems to regulate the whole process of iron absorption, from transfer across the maternal gut to storage in the maternal liver, concentrations in the plasma, and transfer across the placenta (Gambling L, Czopek A, Andersen HS, et al 2009).

**NEURONAL COMPROMISES DUE TO IRON DEFICIENCY**

During fetal development, iron is prioritized to red cells at the expense of other tissues, including the brain (WHO 1998, Lozoff B 2007). When iron supply does not meet iron demand, the brain is at risk even though the infant may not be anemic, since iron distributions are sensitive to stages of neurodevelopment, metabolic activity and neurigenerative pathologies of central nervous system (Beard J 2003). The most common etiology of reduced iron supply to the fetus is maternal iron deficiency (Lozoff B 2007).

Iron is required for proper myelination of the spinal cord and white matter of cerebellar folds (Kwik-Uribe CL et al 2000; Larkin EC and Rao GA 1990) and it is a cofactor for a
number of enzymes involved in neurotransmitter synthesis (Yehuda S and Youdim MBH 1989) as well as neurotransmitter catabolism. Iron is also a cofactor in a ratelimiting step in DNA synthesis.

The predominant brain cell type containing iron are Oligodendrocytes, plays a role in myelin formation. Lack of iron leads to decreased amount of these cells and composition of myelin (Aoki et al 1989; Morley R et al 1999; Siddapa et al 2002). Deficiency of iron is also been reported to affect energy metabolism of brain. Iron deficiency inutero is associated with significant decrease in GABA transaminase activities and thus affects hippocampus, striatum and globus pallidus (Beard II. 2003).

These damaging effects of iron deficiency lead to the birth of neonates with lower IQ, cognitive functions and motor skills, which progresses with the age. There has been a significant correlation established between iron deficiency and lower cognition. Thus, it also leads to hampered scholastic performance and active participation in the school children. This has also been proven by many research studies.

**IRON DEFICIENCY DURING SCHOOL AGE**

Iron is required by the body in very minute quantities, and yet plays a leading role in the production of enzymes, hormones and other substances, helping to regulate growth, activity, development and the functioning of the immune and reproductive systems. In IDA, physical work capacity (PWC) is reduced because the decrease in haemoglobin reduces the availability of oxygen to the tissues, which in turn affects the cardiac output (Beaton, Corey and Steel 1989). Further, in iron deficiency, changes in brain iron content and distribution, and in neurotransmitter function may affect cognition (Beard JL 2001). Anemia may produce scholastic under-achievement and behavioural disturbances in school children (Pollitt and Liebel 1976).

Research on preschool children has shown that iron deficient children performed lower on psychomotor tests than did non-anemics (Bhatia and Sheshadri 1992). However, little
is known as regards impact of anemia among children entering adolescence and those undergoing the pubertal growth spurt.

**INTERRELATION BETWEEN IRON AND IODINE DEFICIENCIES**

As reported by WHO 2001, Multiple micronutrient deficiencies coexists in developing countries at a higher rate due to monotonous diets (Zimmerman MB et al 2005) based on staple foods of low nutrient density. Along with iodine, other essential micronutrient deficiencies like iron, Vitamin A and Selenium may adversely affect the thyroid. Deficiencies of these micronutrients can act in concert with iodine deficiency to impair thyroid function and modify the response to prophylactic iodine (Arthur et al 1999; Zimmerman MB et al 2002; Zimmerman MB et al 2004). It is assumed that, IDA may induce alterations in central nervous system control of the thyroid axis (Beard JL et al 1998) and reduce T\textsubscript{3} binding to hepatic nuclear receptors (Smith SM, Johnson PE and Lukaski HIC 1993).

IDA may also impair thyroid metabolism by decreasing oxygen transport, similar to the thyroid impairment in hypoxia (Galton 1972, Surks MI 1969). Chronically hypoxic children have lower level of circulating T\textsubscript{4} and T\textsubscript{3} and increased concentration of rT\textsubscript{3}.

A study suggests the mechanism for impaired thyroid hormone metabolism in IDA is reduced activity of the iron-dependent enzyme, thyroid peroxidise (TPO). TPO is glycosylated heme enzyme active at the apical membrane of the thyrocyte (Yavuz et al. 2004). It catalyzes the two initial steps of thyroid hormone synthesis- iodination of thyroglobulin and coupling of the iodotyrosine residues (Figure 1.4) (Dunn JT and Dunn AD 2001). The justification suggests impaired thyroid function in IDA is due to reduced TPO activity, likely caused by decreased intracellular heme concentrations (Hess et al 2002).

Thus, pregnancy and school age are two crucial stages of life cycle, where the future generations are going to be affected.

**Figure 1.4: The role of iron dependent thyroid peroxidise in iodine pathway**
Figure 1.4 The role of thyroid peroxidase in the iodine pathway in the thyroid cell. Iodide (I⁻) is transported into the thyrocyte by the sodium iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. The I⁻ is oxidized by thyroid peroxidase (TPO) together with hydrogen peroxidase (H₂O₂) and attached to tyrosyl residues in thyroglobulin (Tg) to produce the hormone precursors iodotyrosine (MIT) and diiodotyrosine (DIT). In a second step catalyzed by TPO, the residues then couple to form thyroxine (T4) and triiodothyronine (T3) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T4 and T3 are released into the circulation, and nonhormonal iodine on MIT and DIT is recycled within the thyrocyte.

PUBLIC HEALTH DETERMINANTS OF IODINE AND IRON DEFICIENCIES

Iron and iodine deficiencies may adversely affect each and every age group of human life cycle. The targeted effect at each level has been described in Table 1.3 and 1.4, indicating the importance of these essential micronutrients for humans.
Table 1.3: Consequences of IDD amongst humans

<table>
<thead>
<tr>
<th>Pregnant women and their foetuses</th>
<th>Neonates</th>
<th>Infant/child/Adolescent</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortions</td>
<td>Goitre</td>
<td>Goitre</td>
<td>Goitre and its complications</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>Overt or subclinical hypothyroidism</td>
<td>Subclinical or overt hypothyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Cretinism</td>
<td>Mental retardation</td>
<td>Endemic mental retardation</td>
</tr>
<tr>
<td>Increased perinatal and infant mortality</td>
<td>Retarded physical development</td>
<td>Increased susceptibility of the thyroid gland to nuclear radiation</td>
<td>Spontaneous hyperthyroidism in the elderly</td>
</tr>
<tr>
<td>Neurological cretinism: Mental deficiency, deaf mutism, spastic diplegia and squints</td>
<td>Increased susceptibility of the thyroid gland to nuclear radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxedematous cretinism: Mental deficiency, hypothyroidism and dwarfism</td>
<td></td>
<td>Increased susceptibility of the thyroid to nuclear radiation</td>
<td></td>
</tr>
<tr>
<td>Psychomotor defects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Source: Marwah RK 2011)

Table 1.4: Consequences of IDA amongst humans

<table>
<thead>
<tr>
<th>Consequences of Iron Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased maximum aerobic capacity</td>
</tr>
<tr>
<td>Decreased athletic performance</td>
</tr>
<tr>
<td>Lowered endurance</td>
</tr>
<tr>
<td>Decreased work capacity</td>
</tr>
<tr>
<td>Impaired temperature regulation</td>
</tr>
<tr>
<td>Depressed immune function</td>
</tr>
<tr>
<td>Increased rates of infection</td>
</tr>
</tbody>
</table>


STRATEGIES TO COMBAT MICRONUTRIENT MALNUTRITION

The main strategies suggested for improving community nutrition include: food-based strategies like dietary diversification and food fortification, for ensuring adequate
nutrition at household level; addressing behaviour modification to bring about dietary change in the population. This can be achieved through community-based nutrition interventions, using a social marketing approach, behaviour change through communication and mobilizing families and communities; control of micronutrient deficiencies; regular nutrition assessment and counselling; care during pregnancy and postnatal period and intersectoral linkages at community.

Food-Based strategy includes:

1. **Dietary Diversification**
2. **Food fortification**
3. **Nutrition Education, Public health and Food safety measures**
4. **Supplementation**

**MICRONUTRIENT FORTIFICATION**

Food fortification as the practice of deliberately increasing the content of an essential micronutrient, i.e. Vitamins and Minerals (including trace elements) in a food, in order to improve the nutritional quality of the food supply and provide a public health benefit with minimal health risk. Food fortification, sometimes called ‘enrichment’, refers to the addition of one or more vitamins or minerals to a food product or ingredient (WHO 2004).

**IODIZED SALT- AS AN EFFECTIVE TOOL**

India being a land of dietary contrasts, due to various dietary culture in between and within regions, salt iodization has been the most simplest, traditional and widely practiced method. Salt has been proven to be the best vehicle for fortification. The reasons for the salt iodization as a strategy are,

- It is one of the few commodities that come closest to being universally consumed by almost all sections of a community irrespective of economic levels or geographic locations.
In India, there is a well established network of production, distribution and sale for common salt is existing.

It is consumed at an approximate same level every day, throughout in a given region. Average intake in India 10gms/day/person. Thus a micronutrient like iodine introduced through salt will be administered to each individual at a uniform dosage every day, throughout in ones lifetime.

In many remote areas of the world, that incidentally are also severely affected by IDD, salt is one of the few commodities that comes from outside the area thereby lending itself to processing on an economic scale under controlled conditions.

The mixing of iodine compound Potassium Iodate (KIO₃)/ Potassium Iodide (KI) or Sodium Iodate (NaIO₃)/ Sodium Iodide (NaI) with salt is a simple operation. It produces no chemical reaction.

The equipment required for salt iodization is simple, easy to operate and maintain.

The addition of iodine to salt doesn’t impart any colour, taste or odour to the salt. In fact iodized salt is indistinguishable from uniodized salt.

It is economically lesser costly than any other food commodity as the cost is approximately 5 US cents/person/year- less than the price of a cup of tea.

Even when considering economic cost which includes cost of land, building, labor, equipment and other operating cost, addition of KIO₃ is only 10% of total economic cost.

Therefore salt iodization is the preferred strategy for elimination of IDD and is being currently practiced in more than 130 countries. In India over the past few years considerable progress has been made in improving the availability and accessibility of quality of iodized salt to the population across the country (IDD Newsletter 2005).

“By consuming iodized salt, families can better protect themselves against IDD and can provide their children with an improved chance of physical and mental development. It will not only improve children’s health, but it will have a significant impact on the
development of the nation itself. A generation as a prerequisite to a prosperous and productive nation!!”- (UNICEF 2004)

Thus, to prevent the detrimental implications to the vulnerable population, salt fortification has been proven to be the best strategies, than the others, since it makes it reach the fortified food ingredient to each and every member of the community along with their daily diet. Thus, the legislation for procurement and consumption of iodized salt by every human and livestock’s has promised to improve iodine nutrition in the population. Salt iodization program has also undergone many political and community level ups and downs for universal acceptance, which had hampered its sustained functioning by making government to lift the ban for a while and again the scientific committees has provided sufficient evidences for the benefits of iodized salt consumption for the community (Figure 1.5).

**Figure 1.5: Overview of salt iodization program in India**

<table>
<thead>
<tr>
<th><strong>Kangra Valley study 1956</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>National Goitre Control Programme Launched in 1962</strong></td>
</tr>
<tr>
<td><strong>Private sector invitation to produce iodized salt 1983</strong></td>
</tr>
<tr>
<td><strong>Iodized salt brought under revised PFA act 1987</strong></td>
</tr>
<tr>
<td><strong>Sale and storage of uniodized salt banned 1997</strong></td>
</tr>
<tr>
<td><strong>Ban on sale of uniodized salt lifted in 2000</strong></td>
</tr>
<tr>
<td><strong>Proposed to ban sale of uniodized salt May 2005</strong></td>
</tr>
<tr>
<td><strong>Ban on sale of uniodized salt May 2006</strong></td>
</tr>
</tbody>
</table>

Salt iodization program in India, has passed through decades of acceptability and rejection by the community and political influences, though it is a 100 percent gain for the community. However, the struggle for the survival has brought favourable results with successful implementation of salt iodization program in current times and being headed towards increased iodized salt production and consumption since 2006. However,
small scale salt producers/ crushers are posing a main challenge. According to the field experiences and discussions it was gathered that, the cost of KIO₃ is assumed to compromise on their small margin of profit and thus their gain ends with almost nil. However, the lack of political commitment and unawareness of the democratic population on the incredible benefits of iodized salt consumption in the country are opined to be major reasons for the current status.

It is understood that, salt iodization process elicits 10 paisa/kg cost for the small scale salt industry and thus, the producers started escaping the iodization step. This resulted in closing of many of the salt plants due to very narrow profit margin. On the other hand malpractices of mislabelling for brand and iodine content started taking place. Thus, the small scale salt producers, who were unregistered with the salt department were became the target groups, to improve the salt iodization production and distribution in the community.

India has also been fortunate enough to have coastal regions and desserts, which are rich with suitable climatic conditions for quality salt crystal formations. Thus, in global map India has achieved and maintained its position in top five countries from last few decades.

**Figure 1.6: Global salt production for year 2007 (‘000 Metric tonnes)**

![Pie chart showing global salt production for 2007](image)

Global database on salt production for year 2007-2008 (*Figure 1.6*) has revealed salt production in India was 16 million tonnes, securing forth highest rank in the world.
Gujarat, the largest manufacturer of salt in the country, contributes 71% of the total salt production. Thus, Gujarat should be the major area of focus considering its current production and its potential to increase quality production according to the demand of iodized salt.

**Figure 1.7: Statewise production of salt in India (Production-’000 tonnes)**

![Diagram showing statewise production of salt in India]

(Source: Annual Report 2007-2008, Salt Dept., GOI, Jaipur)

India is poised to show unprecedented economic growth by 2050. However in the South East Asia region, India is the worst performer after Pakistan and Afghanistan in consuming adequately iodized salt as per ICCIDD, 2008. The introduction of USI in deficient population can increase the average IQ of the population as much as 13.5 points. As a consequence, cognitive development and school performance are enhanced, leading to greater economic productivity for the population as a whole. Iodine deficiency can be eliminated for pennies per day. The cost benefit is enormous using iodized salt.

India is one of the 18 priority countries of United Nations who are yet to achieve USI. Despite the presence of an adequate programme and legislation, India is lagging behind in the consumption of iodized salt with 51% (NFHS-III). Thus India’s effort to keep its prestigious role in shaping the global economy will face detrimental obstacles and will be unable to defeat the chronic deficiency of iodine by 2015 (Pandav CS 2008).
Unless iodine nutrition is maintained, the symptoms and signs of iodine deficiency will recur in a short period of time. Hence a steady progress up to 90% consumption of iodized salt, by all households is essential. Therefore sustenance of the programme is a major aspect to be focused on. It requires active commitment and advocacy on the part of the member states, based on national investments by salt producers, the public and the body politic (Hexton D. 2007).

To achieve this, an awareness campaign has to be generated and strong public private partnership to be forged with a firm commitment to resolve the issue soon (MI 2006).

Strengthening the salt iodization process in India is one of the most critical interventions needed. While the relatively easier task of getting the large and medium scale units to comply is on the way to being achieved, compliance by small and some medium scale salt producers continues to pose the main challenge.

Thus, the study of economics of salt trade becomes an important element of the strategy for USI. It would assist in identifying the trade related aspects which hamper salt iodization and at the same time help in promoting consumption of adequately iodized salt through better targeting. It is our hope that, the study would serve to initiate a meaningful dialogue with producers for quality production.

However, medium and large scale industries are doing well with quality iodized salt production and thus meeting the requirements of the all urban and few rural settings of the country. I can be expected that, the vigorous efforts towards upgraded of the iodized salt production at small scale industries would also earn the success in a nearing future.

Along with iodine deficiency disorder (IDD) prevalence of iron deficiency anaemia (IDA) is also one of the greatest challenges faced by vulnerable age groups especially the pregnant mothers and young children. The provision of iron supplements to pregnant women is one of the most widely practiced public health measures, yet the net results of attaining sufficient iron stores remain a challenge. Hence, the need for an intervention, which can target both the micronutrient deficiencies, was conceptualized using salt as a vehicle.
CONCEPTUALIZATION OF DOUBLE FORTIFIED SALT (DFS)

Typical Indian diets contain adequate amounts of iron, but the bioavailability of iron from rice and wheat, the staple cereals of Indians goes down, since it is affected by phytates and other inhibiting factors. In addition to that, the intake of meat products which are rich in heme iron is low due to low-socioeconomic status. Thus only 2-5% of the iron intake is absorbed, and it is one of the major causes of widespread iron deficiency.

As effectively advocated public health approaches towards the control and prevention of iron deficiency are the distribution of supplements of medical iron and fortification of foods with a suitable iron compound. Medical input of iron is recommended for a short-term measure for the correction of anemia, while fortified foods are used to improve the iron balance over a period of time and build up iron reserves. Since, India already has a program to supply iodized salt, double fortification of salt with iron and iodine makes eminent sense (Vinodkumar M. and Rajgopalan S. 2007). In India the efforts towards producing a stable formula containing iron first and later merging iodine and iron together, were pioneered by Dr. Narsinga Rao in early 70s.

As a sequel to the introduction of universal iodization of edible salt as a National Policy in the country, NIN evolved the concept of double-fortification of salt (DFS) with iodine and iron for controlling the deficiencies of both these micronutrients in a single measure as “one intervention controlling two problems.” NIN-DFS was developed with good-quality food grade salt and chemicals. SHMP is a permitted food additive (JECFA 1992) and is extensively used in the food industry. SHMP (Sodium hexametaphosphate) in NIN-DFS is intended to protect and prevent the interaction of iodine from undesirable reactions with iron and other constituents of the salt in DFS. Good-quality food grade common salt (magnesium < 0.10%, moisture < 1.5%, NaCl > 98%) and food grade chemicals are used in the production of NIN-DFS. Higher levels of magnesium or moisture in salt are detrimental to the stability of iodine in DFS (Ranganathan S. et al 1996).
COMPARISON BETWEEN VARIOUS DFS FORMULATIONS IN INDIA

Table 1.5: Comparative features of different formulations of DFS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NIN formulation</th>
<th>MI formulation</th>
<th>Nutrisalt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine (ppm) source</td>
<td>30-40 KIO₃</td>
<td>50 KI</td>
<td>30, KIO3</td>
</tr>
<tr>
<td>Iron (ppm) source</td>
<td>1000, Ferrous sulphate</td>
<td>1000, Ferrous Sulphate</td>
<td>1000, Iron salt</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>SHMP</td>
<td>Encapsulation of iodine by dextran</td>
<td>Stabilizer and promoter</td>
</tr>
<tr>
<td><strong>Laboratory studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability/ salt quality</td>
<td>Stable upto 9 months with the salt commercially used for iodization</td>
<td>Stable for 12 months. Salt used- refined quality.</td>
<td>Published data claims good stability. Iodine quality not indicated</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Full fledged acceptability/ organoleptic properties described. No colour or smell. Good acceptability.</td>
<td>Develops slight yellow or brown colour with the time. Found less acceptable with some foods in all population studied compared to local salt</td>
<td>Reports claim acceptability and stability during cooking.</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Demonstrated on human and rat models. Mean absorption with rice based diet in humans is 6.1%. Urinary iodine excretion increased significantly equal to iodized salt</td>
<td>Demonstrated on human and rat models. Iron mean 13.5% absorption and 4.0% inhibition. Urinary iodine excretion increased significantly equal to iodized salt</td>
<td>Not reported</td>
</tr>
<tr>
<td>Production</td>
<td>Large-scale production</td>
<td>Not reported</td>
<td>Not known.</td>
</tr>
</tbody>
</table>

(Source: Sivakumar B and Nair S 2002)

The current status of DFS revealed by The Ministry of Health & Family Welfare, Govt. of India, constituted a Technical Committee under the Chairmanship of Dr. M. K Bhui, Secretary, Dept. of Biotechnology, Govt. of India, and Prof. N. K. Ganguly, Director-General, Indian Council of Medical Research, as Co-Chairperson on “Formulations of guidelines for use of double-fortified salt as a measure to reduce prevalence of anemia” The main Committee and the Sub-Committees met as per requirements and analyzed the data available on different formulations of DFS and finally approved only NIN-DFS because of convincing evidence from NIN-DFS based on (1) scientific publications, (2)
formulation, (3) nutrient level, (4) process, (5) ultrastructure, (6) salt quality, (7) stability, (8) organoleptic studies, (9) acceptability, (10) factory production, (11) community acceptance, (12) safety evaluation, (13) bioavailability, (14) iron impact, (15) iodine impact, and (16) cost (Ranganathan S. and Sesikeran B 2008). Furthermore, the Dr. Bhan Committee recommended the introduction of NIN-DFS in nutrition programs (Bhan Committee 2006).

OPERATIONAL FEASIBILITY OF NIN-DFS

The operational feasibilities of NIN-DFS were successful, which are described as below:

Production- The technology of NIN-DFS is based on a simple method of dry mixing salt with iodine and iron compounds and does not involve elaborate or expensive measures (Ranganathan S. et al 1996). Large-scale production of DFS (9 to 60 metric tons) was successful in salt factories located at different cities throughout the country.

Transportation- Packing of NIN-DFS in 0.5-kg or 1-kg low-density polyethylene pouches and long-distance transportation by road to different parts of the country was found to be feasible and smooth (Brahmam GNV et al 1994, 2000; Rao N. 1994; Ranganathan S. et al 1996, 2005, 2007; Interim Report 2003).

Distribution- NIN-DFS was distributed to households periodically in 1-kg pouches in the community study in tribal areas of the East Godavari district of AP, while it was supplied in 50-kg sacs to the residential schools in Hyderabad for over 2 years in each study (Brahmam GNV et al 1994, 2000; Sivakumar B. et al 2001).

Biosafety SHMP (Sodium hexametaphosphate) is an internationally permitted food additive (JECFA 1992). Furthermore, the daily ingestion of phosphorus is 30 mg through the intake of 10 g NIN-DFS. Nevertheless, the biosafety of NIN-DFS was reevaluated as an item for daily consumption through foods. The SHMP being a polyphosphate, perhaps could alter calcium/phosphorus turnover and thus bone metabolism. Therefore, the safety of long-term (9 months) feeding of DFS in relation to Ca and P metabolism was tested in rats. In addition, the hemoglobin regenerating ability of diet with DFS was compared
with both iron-fortified salt (IFS) and unfortified salt using a depletion-repletion rat model. The results at the end of 4 week revealed that the amounts of hemoglobin regenerated in both the fortified-salt-fed groups (DFS: 13.0 ± 1.4 and IFS: 11.7 ± 1.4 g/dL) were significantly higher than that in the unfortified salt group (7.6 ± 4.0 g/dL); at the end of 9 months, the hemoglobin levels increased to 15g/dL in both DFS and IFS groups; no untoward effect was observed on the integrity of bone and the histopathology of various tissues in experimental rats (Nair M et al 1998a). It was concluded from the results that long-term feeding of NIN-DFS containing SHMP does not apparently impair Ca and P balances in rats and is relatively safe in day-to-day use in the diets. Similar results were obtained for Ca and P balances in children (Nair M et al 2000). Thus, the daily consumption of DFS was proved to be safe.

**Efficacy** - NIN-DFS has provided sufficient evidences on the efficacy to improve iron and iodine status of the consumers at its best. The community based interventional studies have provided the scientific proofs in the form of biochemical parameters.

**Cost** - All the ingredients to manufacture NIN-DFS are readily available in the country at low cost. From the current cost of the materials, the approximate cost of production works out to be Rs. 4.85 (0.121 US$) per kg and when profits and transport costs are included it would be Rs. 6.85 (0.171 US$) per kg. Thus, the expenditure would be about a paisa (0.00025 US $) per head per day (Technical Report 2005).

**BENEFIT: COST RATIO OF FORTIFIED FOODS**

The World Bank estimated that the combined economic costs of iron deficiency, iodine deficiency and Vitamin A deficiency in developing countries could waste as much as 5% of gross domestic product (GDP). On the same lines (Murray and Lopez 1996) calculated the ‘global burden of disease’ in which iron-deficiency anaemia, iodine deficiency and Vitamin A deficiency accounted for 2.4% of the overall disease burden of developing countries. However, four times higher percentage (9% to 10% of the disease burden in developing countries with high mortality) to iron-deficiency anemia, Vitamin A deficiency and Zinc deficiency were reported by WHO in 2002. GDP loss due to single
micronutrient deficiency- IDA was calculated to be 4.5% in India (Horton S and Ross 2003).

Thus, the concept of biofortification of the foods gains the importance to defeat the prevalent deficiencies affecting India’s economy and obstructing its way to become super economy by 2015. However, the circle again comes to the starting point, indicating a need for a universally consumed food item or ingredient for Indian population and the only answer is “Double Fortified Salt”.

Salt as a vehicle to supplement iodine also has been proven to be an effective fortificant to provide iron also. NIN has ventured with a stable formula of Double Fortified Salt providing Iodine- 40 ppm and Iron- 1000 ppm / gm of salt. Efficacy trials in rice based population have been carried out and have given motivating results by improving iodine and iron status of the subjects. It has also showed a good stability of both micronutrients in DFS. Hence it was necessary to run an efficacy trial amongst wheat consuming population in rural and urban scenario.

Thus, the present work was undertaken to assess the impact of double fortified salt supplementation at life cycle approach and putting a step ahead towards the possibilities of production at local level.

Thus, this study was conceptualized as an attempt and determination to improve micronutrient status of the target groups, using multiple approaches inculcating with the supply of an incredible food ingredient-DFS. The broad objective of the research work carried out was “To study the efficacy of Double Fortified Salt supplementation amongst pregnant women and school aged children on iodine and iron status and feasibility assessment for DFS production at local level”.
Specific objectives

The study was comprised of three phases:

Phase I: Impact assessment of Double Fortified Salt supplementation amongst pregnant women

• Screening of pregnant women of urban Vadodara for iodine and iron deficiencies.
• To assess nutritional status through anthropometry.
• To assess socioeconomic status (SES), knowledge-attitude-practices (KAP) and dietary consumption pattern.
• To assess iodine and iron content of Double Fortified Salt.
• To supplement DFS amongst pregnant women and assess the impact on iodine and iron status.
• To provide nutrition health education and behavior change communication for iodine and iron nutrition.
• To assess impact on neonatal anthropometry and cord blood thyroid hormone analytes.

Phase II: Impact of Double Fortified Salt supplementation amongst rural school children

• To assess nutritional status through anthropometry of the school children.
• To map the prevalence of iodine and iron deficiency.
• To assess parental SES, KAP and food consumption pattern of the families.
• To assess cognitive parameters of the school children.
• To assess iodine and iron content of Double Fortified Salt.
• To supplement DFS to experimental group.
• To provide NHE and BCC, to mothers and family members regarding the usage, storage and cooking practices using iodized salt or double fortified salt.
• To assess the impact of DFS supplementation or encouraged iodized salt consumption on anthropometry, iodine, iron and cognitive parameters of the children.
• To assess the impact of NHE and BCC on the KAP of the mothers of the children.

**Phase III: Feasibility for Double Fortified Salt Production at local level**

• To map the small scale salt units and assess the salt iodization levels in Anand, Nadiyad, Vadodara, Bharuch and Kheda districts of Gujarat.
• To build up the capacity of small scale salt producers of these districts for salt iodization.
• To provide technical support for optimal iodization.
• Selecting salt producers for initiation of double fortified salt at medium scale and large scale.
• To initiate the conversation on feasibility for DFS production at local level.
• Laisoning efforts for the producers.