4 Iodine

Iodine is the only element whose deficiency is linked to a clear clinical manifestation, the goitre, which is a consequence of thyroid disorder in the production of thyroid hormones. The series of diseases carrying out in case of iodine deficiency or excess, classified as Iodine Deficiency Disorders (IDD), were scientifically correlated to iodine deficiency only in the 19th century with discoveries that salts of iodine could be used successfully in the treatment of human goitre and that the occurrence of endemic goitre was inversely correlated with concentrations of iodine in soils, food and waters in particular areas in Europe. Within 20 years of that discovery was isolated the first hormone of thyroid gland, the tetraiodothyronine or thyroxine (T4), subsequently was found the active form triiodothyronine, T3 (Underwood & Suttle, 1999). These hormones have fundamental roles in the regulation of basal metabolism and other physiological function which will be explained afterwards.

Currently, the World Health Organization and the non-profit International Council for the Control of Iodine Deficiency Disorders (ICCIDD) are sustaining a campaign towards the total eradication of iodine deficiency and for optimal iodine nutrition around the world.

4.1 Metabolism and function of iodine and thyroid hormones

The physiological active form of iodine is the iodide anion (I^-). It is a halogen with quite low reactivity but capable of forming many salts with other elements, for instance potassium iodide (KI) and potassium iodate (KIO_3). Its most common oxidation state is -1 and the natural isotope is ^{127}I.

Iodide is efficiently absorbed from the gastrointestinal tract and then transported in the bloodstream bound to plasma proteins. Iodine can be absorbed dermally when applying in the damaged skin or mucosal membranes preparations such as the povidone iodine (Fradkin & Wolff, 1983). Once iodine enters the circulation, up to 90% of the circulating iodide is actively up-taken in the thyroid gland by a Na:K - dependent ATPase pump; through the thyroid cells iodide passes to the colloid where it is oxidized to elemental iodine by the enzyme thyroid peroxidase. Elemental iodine is incorporated into the tyrosine residues of thyroglobulin. The incorporation of tyrosine can be done with one or two molecule of iodine, in the first case it is obtained the monoiodotyrosine (MIT), in the second the diiodotyrosine (DIT) external sites of thyroglobulin. The oxidative condensations between MIT/DIT and DIT/DIT generate the hormones T3 and T4. The active form of the hormone is T3, while T4 is an inactive transport. The activation of T4 in T3 is achieved by three deiodinase seleno-enzymes (types I, II and III). Only the type I deiodinase operates just in thyroid gland, while the other two types can synthesise the hormone T3 where needed; in animals with normal iodine status, 80% or more of the T3 can be formed extra-thyroidally, especially in liver and kidney. Approximately 80% of iodine in the mammalian body is found in the thyroid gland, but when excess of iodine is consumed, some iodine accumulates in soft tissues, such as muscle and liver (Underwood & Suttle, 1999).

Every step of iodine metabolism is hormonal mediated according to the body needs by thyroid stimulating hormone (TSH), secreted by the anterior pituitary gland. The

feedback control of T4 and T3 circulating levels is regulated by thyrotropin releasing hormone (TRH), secreted by the hypothalamus. Between the variuos Na:K ATPase pumps present in the organism, the iodide pump is the only active transport regulated by hormones feedbacks (Cavalieri, 1997).

Iodide is largely excreted in the urine; all circulating iodine is cleared, regardless of the circulating plasma levels. The majority of urinary iodine is in the form of iodide with only a small proportion being organically bound. Severe impairment of renal function causes high iodine level in plasma, contra, diuresis reduces the plasma level. Iodide is also secreted into the large bowel and excreted, but this accounts for only 1% of total body iodide clearance (Cavalieri, 1997).

In ruminants, abomasum is the major site for the recirculation and concentration of iodide into the digestion tract; this mechanism may promote the conservation of iodide by its transfer from vascular to extravascular compartments, so reducing the losses via urine (Miller *et al.,* 1974).

Iodine has the unique physiological role to be a constituent of thyroid hormones, particularly T3 which controls many important physiological pathways throughout the organism. Triiodothyronine controls the oxidation rate and protein synthesis; set the basal metabolism rate and play active role in digestion, thermoregulation, intermediary metabolism, growth, muscle function, immune defence, circulation and the seasonality of reproduction. Regarding fetus, T3 controls the development of its brain, heart, lungs and wool follicles (Underwood & Suttle, 1999).

4.2 Iodine deficiency disorders

The first consequence of iodine deficiency in the daily diet is the lower synthesis of thyroid hormones, resulting in the case of a long deficiency in hypothyroidism, goitre and a series of functional and developmental abnormalities listed in table 1, and named iodine deficiency disorders. Goitre is the most evident manifestation of iodine deficiency and occurs because, in response to low concentrations of T4, the hormone TSH stimulates the thyroid gland to increase and to raise the up-taking of iodine. Apart from the rare case of euthyroid goitre (the gland is sufficient large to produce the right amount of T4), when the production of T4 is under normal requirements the result is hypothyroidism. The clinical manifestations of hypothyroidism are clearly linked with a slower metabolism: lethargy, weakness, cold intolerance, increased weight, poor mental concentration, somnolence, parathesia, angina pectoris, dyspnoea, oedema, constipation, irregular menstruation and muscle ache. Perpetuate deficiency of iodine and continue stress of thyroid gland by TSH can become responsible of the formation of nodular goitres or most dangerous hyper-functioning autonomous nodules (Delange & Hetzel, 2000). The enlargement of gland is also a physical concern for obstruction of trachea, oesophagus and blood vessels of the neck.

Table 1. The spectrum of IDD across the life-span

	Type of Iodine Deficiency Disorder
Fetus	-Abortions -Stillbirths -Congenital anomalies -Increased perinatal mortality -Endemic cretinism -Deaf mutism
Neonate	-Neonatal goitre -Neonatal hypothyroidism -Endemic mental retardation -Increased susceptibility of the thyroid gland to nuclear radiation
Child and adolescent	-Goitre -(Subclinical) hypothyroidism -(Subclinical) hyperthyroidism -Impaired mental function -Retarded physical development -Increased susceptibility of the thyroid gland to nuclear radiation
Adult	-Goitre, with its complications -Hypothyroidism -Impaired mental function -Spontaneous hyperthyroidism in the elderly -Iodine induced hyperthyroidism -Increased susceptibility of the thyroid gland to nuclear radiation

Source: Hetzel, 1983

Goitre is a clear clinical manifestation that occurs in poor and mountainous areas of the world, above all in the developing countries but also in Europe (Vitti *et al.,* 2001). The magnitude of the IDD seriousness is correlated to the status of iodine intake. The recommended daily allowance (RDA) of iodine are shown in table 2. It is evident that for pregnant and lactating women the daily requirements of iodine is quite important and more difficult to meet. The most efficient and immediate method to evaluate the current iodine status of a population is the measurement of urinary iodine concentration (UIC), from which WHO, UNICEF and ICCIDD (2001) settled the different level of iodine deficiency (table 3). Thanks to the UIC method and the engagement of WHO, UNICEF and ICCIDD, the knowledge of the global magnitude of IDD, and of the real significance for the public health and socioeconomic development, has improved considerably during the last decades. Currently the iodine deficiency is a public health and economic concern in 118 countries, above all for pregnant women and children (Vitti *et al.,* 2001). It is estimated that 6% of American women, compared to 1% of men, suffer thyroid disorders and the difference with men is attributed to the iodine deficiency occurring in pregnancy. In the United Kingdom a report of general practitioners indicates that thyroid disorders are in prevalence 4-10 times higher amongst women than men (Wynn and Wynn, 2000). The effects of iodine deficiency in pregnant women have a serious impact on society development because that deficiency has a detrimental effect on the brain and nervous system growth of fetus. This kind of risk is not only related to areas with severe iodine

deficiency, but also in populations with moderate or mild iodine deficiency the likelihood of generating a great number of children with cretinism and candidates to suffer brain damages is quite high. Despite the incidence of cretinism is not too high, the iodine deficiency could be responsible for mental impairment leading to poor school performance, reduced intellectual ability and impaired work capacity. For instance, the Intellectual Quotient (IQ) falls down 13.5 points in the populations living in iodine deficient areas (Bleichrodt et al., 1994).

Table 2. Recommended daily allowance (RDA) of iodine

Class of population	Iodine, µg/day
Infants and children (0 – 6 yr)	90
Children (7 – 10 yr)	120
Adolescent and adults	150
Pregnant and lactating women	200

Source: Delange, 1993

Table 3. Recommended daily allowance (RDA) of iodine

Median UI, µg/L	Iodine intake	Iodine nutrition
< 20	Insufficient	Severe iodine deficiency
20 – 49	Insufficient	Moderate iodine deficiency
50 – 99	Insufficient	Mild iodine deficiency
100 – 199	Adequate	Optimal iodine nutrition
200 – 299	More than adequate	Risk of iodine-induced hyperthyroidism within 5-10 years following introduction of iodized salt in susceptible groups
≥ 300	Excessive	Risk of adverse health consequence (iodine-induced hyperthyroidism, auto-immune thyroid diseases)

Source: WHO, ICCIDD and UNICEF, 2001

If hypothyroidism is related to clinical symptoms characterized by a slow basal metabolism, hyperthyroidism is exactly the opposite. The clinical manifestations of hyperthyroidism are goitre, tachycardia, tremor, sweating, weight loss, nervousness, fatigue, increased appetite and lid lag. Except when too high amount of iodine are ingested by people having suffered a long period of iodine depletion (Jod-Basedow phenomenon), the reason of hyperthyroidism is not simply nutritional. The chronic toxicity can develop when intake is major than 1.1 mg/day, however, it is frequent that most people remain euthyroidal despite feeding toxic level of iodine. The excess uptake of iodine by the thyroid may also inhibit thyroid hormone synthesis (called Wolff-Chaikoff effect). The causes that generate hyperthyroidism are various (Grave's disease, inappropriate TSH secretion, multinodular goitre or thyroiditis, etc.) and generally have poor relation with nutrition. Thus, iodine toxicity can eventually cause iodide goiter, hypothyroidism, or myxedema. Very large amounts of iodide may cause a brassy taste in the mouth, increased salivation, GI irritation, and acneiform skin lesions (Merck, 2008).

4.2.1 The role of goitrogen substances

The iodine deficiency disorders are often caused by the presence in the diet of goitrogen substances (goitre stimulating) more than a real iodine deficiency. The negative effect of goitrogen was firstly discovered by Chesney *et al.* (1928), who observed enlargement of thyroid gland in rabbits fed cabbage even with a good amount of iodine in the diet; the thyroid status returned optimal when additional iodine was incorporated in the diet. The goitrogen substances can be divided into two principal groups, thiouracil type, which inhibits the iodide oxidation in thyroid colloid, and cyanogenetic type, which reduces uptake of iodine by the thyroid.

The cyanogenetic type goitrogens contains in their structure the chemical group thiocyanate (CNS^-) or iso-thiocyanate (NSC^-), which have the similar ionic size as I^- and therefore can competitively inhibit absorption of iodine by the thyroid. These chemical groups have been isolated in the family of *cruciferae* and particularly the genus *Brassica* after the hydrolisis of glycosides of type R−N=C=S or R−S−C=N. The thyocianate groups are also formed in the body when assuming foods containing cyanide (CN^-), which react with sulphide or thiosulphate in the gut. Hydrocyanic acid is synthesised in plants of genus *Brassica* after structural damage to plant cells. Being the effect of the cyanogenetic goitrogen simply competitive and linked to dimension of the ions, an increase of iodine in the diet is sufficient to avoid deficiency disorders (Davies, 1979).

The goitrogen molecules often have good fungicidal and insecticidal properties, for this reason in the early years of plant breeding, selection for disease and pest resistance also increased goitrogenicity. Currently the genetic trend is to reduce the goitrogen activity above all for the plants carrying thiouracil type molecules, such as rape: rapeseed meals are effectively important source of edible oil and nutrient for livestock, but can contribute both types of goitrogen. The thiouracil type goitrogen cannot be overcome by feeding more iodine because they interfere directly on the enzymatic iodide oxidation. The techniques to reduce the amount of glycosides are heat, the season of cultivar or the type of fertilization (Underwood & Suttel, 1999). For instance the concentration of goitrogen precursors is not reduced by minimizing the available sulphate concentration in the soil but may be reduced when nitrogen is applied at some sites (Alderman & Stranks, 1967).

4.3 Iodine status in Europe and Italy

Europe

According to Vitti *et al.* (2001) in Europe 97 millions of people are affected by goitre, while 141 millions are at risk of IDD and 0.9 millions have impaired mental development. If we compare the iodine status map for Europe on 2002 (figure 1) with the last data provided by Iodine Network (2008), only Germany has moved its iodine status from *mild deficient* to *adequate.* Despite a comprehensive European regulation on the distribution of iodized salt does not exist, many European countries foresee laws about the distribution of iodized salt, unfortunately only in few country, like Switzerland and peninsula Scandinavian, these regulation started many years ago (about 1920) with mandatory use of iodized salt in the food industry processing (Vitti *et al.,* 2001). A lack of

health public education completes the picture and nowadays despite a distribution supposedly higher than 90% for almost all Europe, this is insufficient to guarantee an adequate consumption of iodized salt, which is also difficult to understand because of the lacking data. In the Global Scorecard 2008 table of Iodine Network (2008) 80% of European countries have no data in the voice "percentage of households consuming iodized salt, 2000-2006". Despite some of these countries do have data on iodized salt consumption (as will be showed for Italy) this lack in the Iodine Network databases (originated from WHO and ICCIDD) may be explained either by the non total participation of countries to the campaigns for the eradication of IDD or by the difficulty of having the government to participate and understand the importance of this "simple", economic and important health policy.

It is, therefore, evident that iodine deficiency is a real health concern in Europe and that the weakness and youth of many iodized salt campaigns can be successfully helped out by a wide fortification of milk and dairy products through animal nutrition, as it will be showed in paragraph 4.4.2.

Figure 1. Europe picture on iodine nutrition updated to 2002 (source: iccidd.org)

Italy

The goitre is known in Italy since the Roman times as old pictures, sculpture and coins prove. For instance the Latin writers *Plinio il Vecchio*, *Giovenale* and *Vitruvio* correlated goitre with intake of water in particular areas. The first clear connection between endemic goitre and cretinism was documented in 1848 by an *ad hoc* committee appointed by the King of Sardinia (Vitti *et al.,* 2001). Once in the 1950s it was cleared the relationship between iodine and goitre and the wide distribution of goitre, many pathological studies on iodine deficiency, goitre and cretinism were developed independently in almost all Italian regions. Aghini-Lombardi *et al.* (1993) reviewed

epidemiological data from 1978 up to 1991 including 72.112 schoolchildren (6 -14 years), of whom 5046 living in urban areas and 66.066 in extra urban areas (hilly, mountainous or suspected to be endemic zones). The mean UIC of suspected areas ranged between 50 and 75 μg/g creatinine, compared to the control values of 85-175 μg/g creatinine. The prevalence of goitre in schoolchildren of endemic areas ranged from 14% to 73% and was it greater in Central and Southern Italy. In the control areas goitre prevalence was below 10%. Cases of cretinism and mental defects were found in some areas with moderate or severe iodine deficiency. Minor neuropsychological impairments were detected in schoolchildren living in moderate iodine deficiency areas such as Val Tiberina in Tuscany and Sicily.

Table 4. Italian household consumption of iodized salt

Regions of Italy	***% of iodized salt consumption***
Trentino Alto Adige	58,2
Valle d'Aosta	55,8
Basilicata	52,7
Umbria	42,1
Emilia-Romagna	40,1
Molise	37,7
Veneto	35,8
Friuli Venezia Giulia	35,4
Toscana	33,3
Puglia	32,3
Calabria	31,7
Lombardia	30,9
Campania	30,3
Marche	28,9
Lazio	24,9
Abruzzo	24,8
Piemonte	24,2
Liguria	23,7
Sicilia	18,2
Sardegna	15,0

The current average of household iodized salt consumption in Italy is 34.1% with different distribution throughout the regions or cities. Apart from the peak of excellence in the city of Bolzano where the average consumption is 72.7%, about half of the regions range between 15 and 33% (table 4). Only Basilicata, Valle d'Aosta and Trentino Alto Adige have values higher than 50%.

The Italian distribution of iodized salt is regulated by the law 21 March 2005, number 55 (G.U. Serie Generale n. 91, 2005). The weakness of this law is that the distribution of iodized salt is guaranteed in OGD, retailing shops, bar, restaurant and public caterings but is not mandatory for the industrial food processing.

4.4 IDD prevention

4.4.1 Universal salt iodization

Since the first comprehensive review on iodine worldwide situation published by WHO in 1960, only in 1983 it was finally recognized the role of iodine deficiency for impaired mental functions and brain damages. Two years after, 1985, thanks to the engagement of WHO, UNICEF and Australian authorities, the International Council for Control of Iodine Deficiency Disorders (ICCIDD) was funded (Iccidd.org). Currently the strategy for IDD control is based on correcting the deficiency by increasing iodine intake

through supplementation or food fortification. The first oral administration of iodine solution, named Lugol, had only medical purpose, and it was given in case of serious iodine deficiency. Nowadays, the IDD eradication policies have got much attention on the use and diffusion of iodized salt, which was firstly introduced in the 1920s in Switzerland and USA. According to the previous cited milestones about IDD eradication history, only in the 90s the WHO assembly adopted Universal Salt Iodization (USI) as the main strategy for IDD eradication. In order to meet the iodine requirements of a population household salt should be fortified with 20 to 40 mg I /Kg of salt (assuming an average salt intake of 10 g per capita/day). The two forms of allowed iodine as salt are potassium iodate (KIO_3) and potassium iodide (KI). Because iodate is more stable under extreme climatic conditions it is preferred to iodide, especially in hot and humid climates.

The pictures 2 and 3 show that the magnitude of iodine deficiency does not correspond with diffusion of iodized salt, for instance Europe has the same assumed distribution of iodized salt than USA, however, many countries suffer mild deficiency of iodine. Thus, the real consumption of iodized salt does not correspond to the real diffusion. The universal salt iodization needs four main components to be efficient: correction of iodine deficiency, surveillance including monitoring and evaluation, inter-sectorial collaboration and advocacy and communication to challenge public health authorities and to educate the public. The mandatory law used in Switzerland (Vitti *et al.,* 2001) is surely a good and efficacy policy for IDD eradication.

The Universal salt iodization is not the unique solution for IDD. The importance of nutrition and its related risk was observed by Remer et al. (1999) in a study conducted on a group of integral vegetarians (Vegan diet) and vegetarians. The vegans had a very low iodine intake (<20 µg/day), and expose themselves at high risk of IDD.

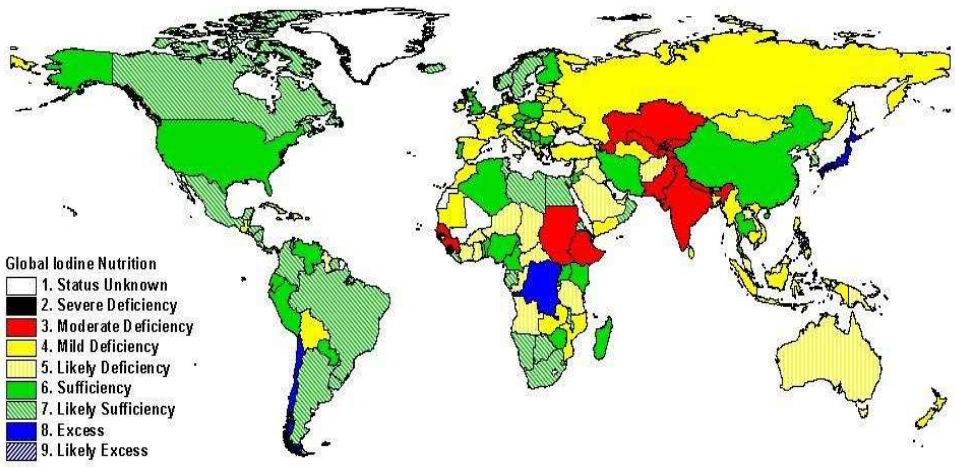

Figure 2. Global picture on iodine nutrition updated to 2002 (source: iccidd.org)

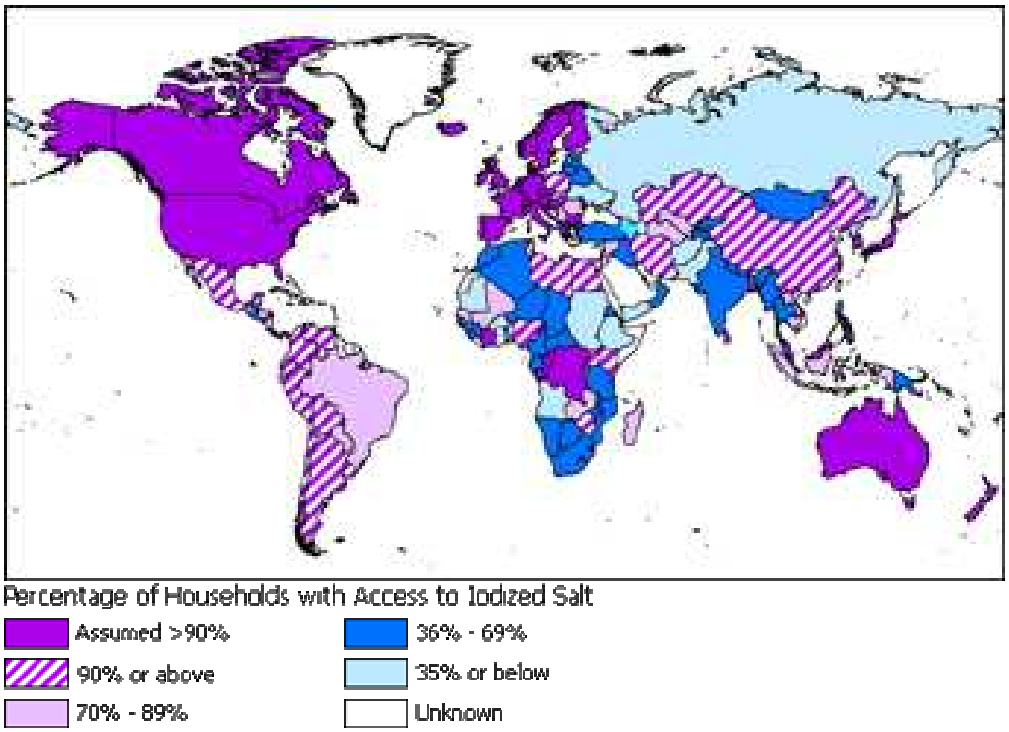

Figure 3. Global picture on diffusion of iodized salt updated to 2008 (source: iccidd.org)

4.4.2 Milk and dairy products

Dairy products are among the most important foods for prevention and eradication of IDD. Many researchers agree, with various social evidences, on the high iodine intake percentage granted by dairy products ingestion. In Finland, the iodization of dairy cattle feedstuffs increased the cows' milk iodine content from 30 µg/l of the 1950s to 189 µg/l of the 1970s (Varo *et al.*, 1982). In Britain, during winter, half of the daily dietary intake of iodine for the adult population is from milk and dairy products (Lee *et al.*, 1994). In Denmark, more than 25% of iodine intake derives from milk, whose content of iodine has seasonal variations: iodine concentration of milk is higher in March than in June, 250-370 vs 220-240 µg/kg respectively (Rasmussen *et al.,* 2000). Another study conducted in Denmark shows that, except for a low intake of milk and fish, it is not possible to identify any eating patterns or any behaviour with relation to diet which could cause an increased risk for iodine deficiency (Rasmussen *et al.,* 2002). Even in Switzerland milk is an important source of iodine, particularly in winter months for children. Milk consumption is more directly correlated to UIC in children than in adults due to the fact that Swiss children are fed at breakfast about 200-600 ml milk/head/day, whereas adult milk ingestion is limited to 0-150 ml/head/day. Therefore, according to the authors, the iodine status could depend mainly on iodized salt for adults and on milk for children (Als *et al.,* 2003). Also, Girelli *et al.* (2004) discovered a correlation between milk intake and UIC in children. The authors, observing a group of schoolchildren in the Veneto region, Italy, found a significant correlation between UIC and milk ($P = 0.0001$) and cheese ($P = 0.03$)

intakes, and a trend for UIC and yogurt consumption (P = 0.06). No significant correlations were found between UIC and meat, fish and iodized salt intake.

The previous data demonstrate the very important role of milk and dairy products as iodine source for human nutrition.

4.5 Iodine in dairy cows

4.5.1 Natural source of iodine

The incidence of goitre in livestock was principally linked to the presence of iodine in the soil and plants, highly variable and related to the seasonal condition, plant species and strain differences or to a smaller extent of soil fertilizations. Also, the marine salt deposition can vary the concentration of iodine in soil, and therefore the distance from the sea represents a primary step to evaluate the iodine potentiality of soils and plants. Season is also important, the winter rains dilute the summer deposition of iodine and, therefore, generally spring harvest have a lower iodine level (Groppel and Anke, 1986). Plants differ on the capacity to absorb iodine, Johnson and Butler (1957) reports that the concentration of available iodine in plants from a similar soil can range up to ten-fold and it is much probably linked with the season. Silage, generally, has a concentrations ranging from 0 to 1 mg/Kg. Water does not contribute significantly to iodine recruitment, which depends over 90% on dry matter intake. Forages, cereals and oil-seed are poor source of diet iodine and the use of other inorganic or organic source was fundamental to reduce the incidence of goitre in livestock (Underwood & Suttle, 1999).

4.5.2 Other source of iodine and European regulation

The health and economic damage caused by IDD and cyanogenetic goitrogens can be easily prevented by iodine supplementation. Depending on the source and nature of the fortification, methods are divided into two groups: continuous and discontinuous. Salt licks and mineral mixture concentrates are continuous methods. Only some inorganic sources of iodine are permitted in Europe (figure 4) and the most common used for the continuous method are potassium iodide and calcium iodate despite the latter has potential losses of iodine by volatilization and leaching in hot and humid climate, unless stabilised. This is why some American workers prefer to use cuprous iodide, which is more stable, easily absorbed but less soluble (Underwood & Suttle, 1999). The concentration of iodine in fresh forages and silage is surely a continuous method to improve animal iodine nutrition, but being the herbage iodine concentration low and the iodine soil fertilization inefficient, a feed supplement is generally the most suitable alternative (Whiteland, 1975). An organic source for continuous method is ethylenediamine dihydroiodine (EDDI) which appears having no different effect on iodine milk and blood concentration of dairy cows compared to potassium iodide (Swanson *et al.,* 1990).

The use of iodine as feed additive for zootechnical purposes is regulated by 1459/2005/EC (figure 4), which substitutes the 1970/524/EEC directive. The organic source, such as EDDI or iodinated fatty acid esters (IFAE) are not permitted in Europe, however EDDI is regulated in the USA by the Food and Drug Administration since 1996.

Discontinuous methods are used to re-establish the iodine status of animals and are done by drenching or other veterinary treatments. These methods are effective in resolving the incidence of goitre but can result expensive if not integrated in other veterinary treatments. Apart from drenching with potassium iodide or iodate, organic source like IFAE (Herzig *et al.,* 2003) or iodized poppy oil (Underwood & Suttel, 1999) can be injected by intra-muscular puncture or by drenching. An efficient but poorly used technique is the slow-release of iodine intraruminal from capsule (Mason & Laby, 1978).

Another source of iodine particularly important for milk iodine concentration is the iodophor solution used as teat dipping. The European Food and Safety Authority opinion on iodine (EFSA, 2005) states that the effect of iodophor is not still clear due to discrepant results (Amount, 1987; Galton *et al.*, 1986 and 2004; Flachowsky, 2007). Nowadays, the iodine content of teat dipping preparations may vary between 0.1 and 0.5 %, and iodine source are predominantly polyvinyl-pyrrolidone-iodine and nonoxinol(9)-iodine.

Additive	Chemical formula and description	Maximum content of the element in mg/kg of complete feedingstuff with a moisture content of 12 %
Calcium iodate, hexahydrate	$Ca(IO_3)_2 \cdot 6H_2O$	Equines: 4 (total)
Calcium iodate, anhydrous	$Ca(IO_3)_2$	Dairy cows and laying hens: 5 (total)
Sodium iodide	NaI	Fish: 20 (total)
Potassium iodide	KI	Other species or categories of animals: 10 (total)

Figure 4. Extract from the annex of the regulation 1459/2005/EC

4.5.3 Requirements, deficiency and toxicity of iodine in dairy cows

The daily thyroxin production of non-pregnant heifers, late gestation cattle and lactating cows needs respectively 1.3, 1.5 and 4.5 mg/day of iodine (Sorensen, 1962), and generally increases in winter because the rising of basal metabolism (Goodman & Middlesworth, 1980). The daily production of thyroxin is not exclusive done using fresh ingested iodine and about 15% of the amount comes from the recycling system of iodine from the degradation of secreted thyroxin. Therefore, the daily iodine requirement of a non-lactating and lactating cow is about 0.33 and 0.45 mg/kg DM, respectively (NRC, 2001). In case of cyanogenic goitrogens into the diet the daily requirement can be raise up to 0.6 mg/Kg DM.

The deficiency of iodine during pregnancy is dangerous for the health of future calves which will probably bear with goitre, hairless, weak or dead (Miller *et al.,* 1968). The most dangerous symptoms of iodine deficiency in adult cattle are the reduction of fertility and the increase of morbidity (NRC, 2001).

The intoxication with iodine, occurring at level of just 5 mg/Kg DM per day, is quite rare. The symptom are excessive nasal and ocular discharge, salivation, decreased milk production, coughing and dry, scaly coats (Olson *et al.,* 1984). The upper intake limit of iodine (as inorganic source) for dairy cows is set by Europe (1459/2005/EC) at 5 mg I / Kg

of complete feedingstuffs with a moisture content of 12%; whereas in the USA the upper limit for iodine as organic source (EDDI) is 10 mg I / Kg DM (NRC, 2001).

4.6 Carry over of iodine in milk and cheese

The excretion of iodine occurs mainly via urine but in case of lactating cows, a considerable amount of iodine is excreted in milk, and the iodine in milk reflects the dietary iodine intake, the iodine status of the animal (Berg *et al.*, 1988) and its plasma concentrations (Alderman and Stranks, 1967). Being strictly related to the element concentration in the diet, the iodine concentration in cow milk ranges widely and, over a wide range, it increases linearly with intake (Underwood and Suttle, 1999). According to Miller *et al.* (1974), the carry over of iodine in milk is 10% of the ingested iodine, but in case of feed fortification increases up to 30% and reaches a plateau condition at about 7-10 days after treatment (Hemken *et al.,* 1972). The first equations for predicting iodine concentration of milk were proposed by Binnerts (1958) and Alderman & Stranks (1967). The two equations are quite different: Binnerts suggested a 4^{th} degree polynomial, whereas Alderman & Stranks a linear equation. By solving the two equations using 10 mg/day as iodine intake and assuming a DM intake of 20 Kg/day, the iodine concentration in milk is 340 and 429 μg/L, respectively (EFSA, 2005). The previous values of carry over are possible when the animal is in good iodine status, in the case of iodine depletion even when feeding cows with iodine supplements the amount excreted through the mammary gland is effectively reduced to prevent the reduction of thyroxin (Swanson, 1972). Regarding the organic source of iodine, the oral treatment does not seem to be efficient in cow ($P<0.001$) compared to the intramuscular when using IFAE as iodine source (Herzig *et al.,* 2003). Feed supplement with EDDI produce milk with an iodine concentration as similar as animal fed with potassium iodide (Swanson *et al.,* 1990), despite an older study by the same author showing that cows fed 81 mg I / day as KI and EDDI produced a milk iodine content of 379 and 895 μg/L , respectively (Miller and Swanson, 1973).

Various studies on dairy products revealed seasonal and regional variations in iodine content of milk caused by different methods of breeding, use of mineral mixture with iodine, pre and post-dipping treatment and iodine soil concentration (Hamman & Heeschen, 1982; Pennington, 1990; Als *et al.*, 2003).

Iodine differs from most mineral nutrients in milk in the extent to which it is retained by the fat (Underwood & Suttle, 1999) but the chemical form iodide, which is predominant in cow milk (Fernandez-Sanchez & Szpunar, 1999), is highly soluble and it is, therefore, generally lost during cheese manufacturing and is in end up into the whey fraction (Sieber, 1998).

As previously described, since the wide range between optimal and upper limit of iodine ingestion in cow and the efficiency of milk as iodine source, feed fortification with iodine is a good feasible way to prevent and control the IDD. The potentiality of feed-to-milk way can however produce milk with an excess of iodine for human nutrition, therefore, it always necessary to consider the final user (children, women or men) within an iodine fortification program.