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6-mo	Age(-group) 6 months
12-mo	Age(-group) 12 months
AI	Adequate intake
AFSSA	Agencie Française de Sécurité Sanitaire des Aliments
BAG/FOPH	Bundesamt für Gesundheit/Federal Office of Public Health, Bern-Liebefeld, Switzerland
BFS	Bundesamt für Statistik/Swiss Federal Statistical Office
BF/ not BF	(Not) breast-feeding/-fed
BM	Breast milk
BMIC	Breast milk iodine concentration
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CF	Complementary food
CI	Confidence interval
cps	Counts per second
CSH	Conseil supérieur d'Hygiéne (Belgium)
CV	Coefficient of variation
D-A-CH	Deutschland (D) - Österreich (A) - Schweiz (CH)
DARLING Study	Davis Area Research on Lactation, Infant Nutrition and Growth (USA)
DIT	Diiodothyronine
DONALD Study	Dortmund Nutritional and Anthropometric Longitudinal Designed Study (Research Institute of Child Nutrition, Dortmund, Germany)
EAR	Estimated average requirement
EBISpro	Ernährungsanamnese, Beratungs- und Informationssystem (Software for evaluation of dietary questionnaires)
EDI	Eidgenössisches Departement des Inneren/ Federal Department of Home Affairs (Switzerland)
EK SGP	Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie/ Nutrition Commission of the Swiss Pediatric Society
EQUIP	Ensuring the Quality of Urinary Iodine Procedures
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition

ETH	Eidgenössische Technische Hochschule Zürich, Swiss Federal Institute of Technology Zurich
FAO	Food and Agriculture Organization
FF	Family food
FFQ	Food Frequency Questionnaire
FM	Formula (infant/follow-on formula = breast milk substitutes)
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
I	Iodine
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
ICP-DRC-MS	Inductively Coupled Plasma - Dynamic Reaction Cell - Mass Spectrometry
ICP-MS	Inductively Coupled Plasma Mass Spectrometry/Spectrometer
IDA	Isotope dilution analysis
ID	Iodine deficiency
IDD	Iodine deficiency disorders
IF	Infant formula
IQR	Interquartile range
IS	Iodine sufficiency
ISE	Ion-selective electrode
K-W	Kruskal-Wallis test
K-S	Kolmogorov-Smirnov test
LOD	Limit of detection
LOQ	Limit of quantification
MIT	Monoiodothyronine
MWU	Mann-Whitney U test
µg/l	Microgram per liter
n	Number (of), quantity
NHANES	National Health and Nutrition Examination Survey
NIS	Na+/iodide-symporter
NIST	National Institute of Standards & Technology
n.s.	Not significant
ppm	Parts per million

PPS	Probability Proportion to Size/Proportionate to Population Size
PRI	Population reference intake
r	Pearson's correlation coefficient
r_s	Spearman's correlation coefficient
RDA	Recommended dietary allowance
RNI	Reference nutrient intake
RT	Room temperature
SAC	School-age children
SCF	Scientific Committee for Food (European Commission)
SD	Standard deviation
SGE	Schweizerische Gesellschaft für Ernährung
SGGG	Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe
T_3	Triiodothyronine
T_4	Thyroxin
Tg	Thyroglobulin
TMAH	Tetramethylammonium Hydroxide
TPO	Thyroperoxidase
TSH	Thyrotropin = Thyroid - stimulating hormone
UI	Urinary iodine
UIC	Urinary iodine concentration
UNICEF	United Nations International Children's Emergency Fund
US	United States of America
USI	Universal salt iodization
US FDA	US Food and Drug Administration
US FITS	US Feeding Infants and Toddlers Study
US TDS	US Total Diet Study
WHO	World Health Organization
yr	Year(s)

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1. INTRODUCTION & STUDY AIMS

"The three most common forms of micronutrient malnutrition worldwide are iron, vitamin A and iodine deficiency. Together they affect at least one third of the world's population (Allen et al., 2006)". The World Health Organization (WHO) estimates that about two billion people in the world have inadequate iodine nutrition. The majority of them live in developing countries (de Benoist et al., 2008). In Europe however, iodine deficiency (ID) also forms an ongoing public health problem (Andersson et al., 2007).

Iodine is an essential component of the thyroid hormones (T_3/T_4) (Delange and Dunn, 2005). These hormones are required for normal growth, development and metabolism throughout life, beginning with the fetal stadium (Delange, 1994; Yen, 2001; Zimmermann, 2009). When dietary iodine intake is insufficient, thyroid hormone synthesis is impaired. This results in a series of functional and developmental abnormalities termed "iodine deficiency disorders" (Delange, 1994; Zimmermann et al., 2008). ID during pregnancy or infancy increases the risk of stunted growth as well as neuromotor and neurocognitive impairment of the child. In extremis, this results in cretinism (Glinoer, 2007; Zimmermann, 2007a). Worldwide, ID is the most common cause of preventable brain damage (World Health Organization et al., 2007; Zimmermann et al., 2008).

The reason for the high prevalence of ID is that soils in many regions in the world (especially inland and mountainous regions) are poor in iodine. Hence, crops that are grown on these soils are also poor in iodine and do not provide adequate amounts of iodine to the population (Haldimann et al., 2005; Zimmermann et al., 2008). In order to eliminate iodine deficiency disorders, universal salt iodization is the recommended and best long-term strategy that supplies iodine to a population (World Health Organization et al., 2007). In the first year of life, infants[1] rely on the iodine content of breast milk as well as iodine fortification of formula and complementary food. Salt should not be given to the infant during this time period (Swiss pediatric society, 2002).

Urinary iodine concentration (UIC) reflects recent iodine intake as most of

[1] Several definitions of "infant" exist. In this thesis, it describes children up to two years of age.

ingested iodine is finally excreted in urine (Vought and London, 1967; World Health Organization et al., 2007). Therefore, the most commonly used indicator to assess the iodine status of a population is the median UIC of spot urine specimens from a representative sample of the target group (Zimmermann, 2008b). Median UIC could also be a good indicator for monitoring iodine nutrition in infants. However, no well-established reference range for UIC exists in this age group because only few studies have been carried out. The main difficulty is the urine collection in infants (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). The WHO presently recommends an iodine intake of 90 µg/day for children less than two years of age and proposes that a median UIC ≥ 100 µg/l reflects an adequate iodine intake in this population group (World Health Organization et al., 2007). In 2007, however, a Technical Consultation of the WHO concluded that the median UIC value that indicates iodine-sufficiency in infants should be revised based on further studies. Additionally, the Consultation proposed studies on UIC in lactating women and on breast milk iodine concentration (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).

Switzerland has a well-monitored and long established national salt iodization program. The latest national monitoring on UIC in school age children and pregnant women showed adequate iodine intake in these population groups (Zimmermann et al., 2005). Measurement of thyroid-stimulating hormone (TSH) and of UIC in newborns in a recent national study also showed iodine sufficiency (Dorey and Zimmermann, 2008). Thus, Switzerland could be an ideal country for establishing a reference range of UIC in infants.

Therefore, the overall aim of the study was to assess the urinary iodine excretion of 6- and 12-month-old infants in Switzerland by measuring UIC in spot urine specimens from a nationally representative sample. This study could serve as a basis for establishment of a reference range of median UIC in infants, which is required for monitoring the iodine status in infants on a national and international level.

For a more precise evaluation of the iodine status, the dietary iodine intake of the infants was estimated by a dietary questionnaire. Moreover, the iodine

concentration in breast milk of their mothers was analyzed. The UIC of the mothers was also determined for comparison with the UIC of the infants to confirm their iodine-sufficiency.
Another aim of the study was to examine if the iodine status of infants varied with the feeding practice. Kersting made the assumption that infants who mainly consume home-made food have a lower iodine status compared with those who mainly eat commercial infant food (Kersting, 2001).

The tasks of this diploma thesis during the study were:

1) Set-up and execution of the study during the first months of sampling, which specifically included:
   - Contacting and selecting pediatric practices for the study
   - Preparing information material for practices and study participants
   - Creating a registration form for collection of required personal data on study participants including infant feeding practices
   - Arranging materials for urine and breast milk sample collection
   - Developing a dietary questionnaire to determine the iodine intake of infants and preparing the evaluation of the dietary questionnaires (i.e. development of an infant food database for EBISpro, definition of standard portion sizes)
   - Visiting pediatric practices to give them study instructions, staying in touch with them during sampling and being contact person for questions from study participants and practices
   - Managing incoming samples and their storage and input of data from subject registration forms
2) Examination and evaluation of iodine status in infants and their mothers in Switzerland (with focus on infants) based on an interim analysis of the incoming study data, which included:
   - Analysis of iodine concentration in collected urine samples of infants and their mothers (modified Sandell-Kolthoff method) and in breast milk samples (ICP-MS method)
   - Evaluation of the data looking at various aspects (gender, anthropometry, nationality, pediatric practices, regions, urban/rural area, season, feeding

mode, supplements, salt use, social demographics, correlations) and comparison with reference values/ recommendations and previous studies

- Analysis and evaluation of iodine content in selected commonly consumed Swiss infant/follow-on formulae and commercial infant foods

2. BACKGROUND

2.1. Physiology & deficiency disorders of iodine

2.1.1. The role of iodine in the body

Iodine is an integral component of the hormones T_3 (Triiodothyronin) and T_4 (Thyroxin), which are produced by the thyroid gland. T_3 and T_4 contain three (59% of hormone weight) and four (65% of hormone weight) iodine atoms, respectively (Oetting and Yen, 2007; Rousset and Dunn, 2004). These hormones are the only iodine-containing molecules in the human body with established physiologic relevance (Rousset and Dunn, 2004). Thyroid hormones and therefore iodine are essential for human life. They are important for the differentiation, growth, metabolism, and physiological function of many tissues in the body. Their major target organs and tissues are the brain, bones, muscles, heart, fat tissue, liver, kidney and pituitary. In these, thyroid hormones regulate various important biochemical reactions (Institute of Medicine et al., 2001; Yen, 2001). Thyroid hormones induce and stimulate RNA-/protein synthesis and enzymatic activity. Thereby, they mainly influence growth and maturation of the brain and bones and control metabolic processes in the body. For example, thyroid hormones elevate O_2-usage and basic metabolic rate with increased caloric production in the body. They are also known to increase lipolysis in fat tissue and liver and regulate gluconeogenesis and glycogenolysis in the liver (Elmadfa and Leitzmann, 2004; FAO and WHO, 2004; Thews et al., 2007; Yen, 2001). Furthermore, they have influence on other hormones of the body through direct stimulation of adenylatcyclase (Elmadfa and Leitzmann, 2004).

2.1.2. Bioavailability, metabolism and excretion of dietary iodine

Most of ingested iodine (e.g. iodate in salt) is reduced to iodide before absorption in the gut, predominantly in the small intestine (FAO and WHO, 2004; Institute of Medicine et al., 2001). Iodide is almost completely absorbed (Nath et al., 1992). Iodinated amino acids including T_3 and T_4 are absorbed intact (FAO and WHO, 2004; Institute of Medicine et al., 2001). Iodide enters the plasma and is transported in the circulation as free plasma iodide. It is

cleared form the circulation mainly by the thyroid gland and kidney, besides the salivary glands and stomach. During lactation, the breast clears some iodide from the circulation as well (Rousset and Dunn, 2004).
Plasma iodide has usually a concentration < 10 µg/l (DeGroot, 1966; Rousset and Dunn, 2004) and a half-life of about 10h under normal circumstances (Zimmermann et al., 2008).
Under normal conditions, the thyroid clears iodide from 10 - 25 ml of serum per minute (DeGroot, 1966; Rousset and Dunn, 2004), which can increase to over 100 ml/min during iodine deficiency (Rousset and Dunn, 2004). The renal clearance of iodide is about 30 – 50 ml plasma/min and is widely independent of the iodide load (DeGroot, 1966; Rousset and Dunn, 2004).
The amount of excreted iodine in urine is a good indicator of iodine intake (FAO and WHO, 2004). More than 90% of ingested iodine is finally excreted in urine (Nath et al., 1992; Vought and London, 1967; Zimmermann et al., 2008). The rest (~10%) is mainly excreted in feces (Glinoer, 2007).

A healthy adult has 15 to 20 mg of iodine in the body most of which is in the thyroid gland (70 – 80%). To maintain an adequate thyroid hormone synthesis and to balance iodine losses, the thyroid has to collect about 60 µg of iodide per day (Clugston and Hetzel, 1994; DeGroot, 1966). Iodide is actively transported through the thyroidal membrane via Na^+/Iodide-symporter (NIS) against a concentration gradient of 20:1 up to 50:1 (Eskandari et al., 1997; Rousset and Dunn, 2004). At the apical membrane, thyroidal iodide is oxidized by thyroperoxidase (TPO) in the presence of H_2O_2 and bound to the tyrosine residues of thyroglobulin (Tg) to build the hormone precursors MIT (monoiodothyrosine) and DIT (diiodothyrosine). T_3 is formed by one MIT and one DIT molecule and two DIT molecules form T_4. Both reactions are catalyzed by TPO (+ H_2O_2). The iodinated Tg (containing MIT, DIT, T_3 and T_4) is stored in the follicle lumen. When required, T_3 and T_4 are released into the circulation after proteolytic cleavage from Tg in the thyrocytes (Rousset and Dunn, 2004; Thews et al., 2007; Yen, 2001). Most of secreted thyroid hormones are in the form of T_4 (Yen, 2001). Bound to transport proteins, thyroid hormones arrive at target tissues where most T_4 is deiodinated to T_3, the major bioactive form. The

deiodinase contains selenium. Therefore, selenium deficiency can impair iodine metabolism (Institute of Medicine et al., 2001; Oetting and Yen, 2007). Thyroid hormones (mainly T_3) form a hormone-receptor-complex in the cell nucleus of the target cell and influence thereby the gene expression (Oetting and Yen, 2007; Thews et al., 2007; Yen, 2001).
The half-life of T_3 and T_4 is about 1.5 - 3 days and 5 days, respectively. After release into the plasma, iodine is either trapped by the thyroid again or is excreted by the kidney (Zimmermann et al., 2008).

TSH (thyrotropin) is able to influence almost every stage of thyroid hormone synthesis and release (Delange and Dunn, 2005; Dunn and Dunn, 2001). It also plays an important role in growth and development of the thyroid gland (Yen, 2001). If not enough iodine is available, thyroid hormone production is reduced and TSH is released from the pituitary stimulating the thyroid (Rousset and Dunn, 2004). In most individuals, the TSH level starts to increase when the iodine intake falls below 100 µg/day (Zimmermann, 2009). TSH stimulates the expression of NIS and some other thyroid genes by binding to the trans-membrane TSH-receptor and activating an intracellular signal transduction. Consequently, the uptake load of iodide from the thyroid increases to maintain an adequate thyroid hormone production and the thyroidal iodine content (Yen, 2001; Zimmermann, 2009). More T_3 is produced relative to T_4 (Dunn and Dunn, 2001). Renal iodine excretion is progressively reduced as a greater part of plasma iodide is cleared by the thyroid (Zimmermann, 2009). If the iodine intake falls below the critical threshold of about 50 µg/day, the iodine content of the thyroid decreases and many people develop goiter (Delange and Dunn, 2005). The formation of goiter is an attempt by the thyroid gland to compensate for the lower iodine availability and to keep the thyroid hormones, especially T_3, at the required level (Clugston and Hetzel, 1994; Delange and Dunn, 2005). TSH itself is regulated by a “feedback” mechanism (Clugston and Hetzel, 1994).

Substances called goitrogens can interfere with iodine metabolism and have clinical effects especially when iodine deficiency coexists (Vanderpas, 2006; Zimmermann et al., 2008). They are present in some foods such as cassava,

linseed and sorghum (cyanogenic glycosides and their metabolite thiocyanate), cruciferous vegetables (glucosinolates), soy and millet (flavonoids) (Zimmermann et al., 2008). Glucosinolates and thiocyanates compete with iodine for thyroidal uptake. Perchlorate and thiocyanate from smoking also negatively affect iodine metabolism (Vanderpas, 2006). Deficiencies of other essential nutrients aggravate iodine deficiency: Selenium, which is part of TPO and deiodinase (Vanderpas, 2006), iron (Zimmermann et al., 2007a) and vitamin A (Zimmermann et al., 2007c).

2.1.3. Iodine deficiency disorders

Insufficient iodine intake results in inadequate production of thyroid hormones. This has multiple adverse health effects grouped under the heading of “Iodine Deficiency Disorders” (IDD) (Delange and Dunn, 2005; Hetzel, 1983; Zimmermann, 2009). Table 1 shows an overview of the health consequences of IDD in different life stages (Hetzel, 1983; World Health Organization et al., 2007).

Table 1: The health consequences of iodine deficiency, by life stage (adapted from (Hetzel, 1983; World Health Organization et al., 2007))

Life stage	Health consequences of iodine deficiency
All ages	• Goitre • Hypothyroidism • Increased susceptibility to nuclear radiation
Fetus	• Spontaneous abortion • Stillbirth • Congenital anomalies • Perinatal mortality
Neonate	• Endemic cretinism including mental deficiency with a mixture of mutism, spastic diplegia, squint, hypothyroidism and short stature • Infant mortality
Child and adolescent	• Impaired mental function • Delayed physical development • Iodine-induced hyperthyroidism
Adults	• Impaired mental function • Iodine-induced hyperthyroidism

The best-known and most visible IDD is goiter, which can occur throughout life. The most critical periods of IDD are pregnancy and infancy as in these stages the most severe and irreversible consequences of IDD occur with its extreme manifestation, cretinism (World Health Organization et al., 2007).
Iodine deficiency (ID) is the greatest cause of preventable brain damage worldwide. In this context, more subtle degrees of mental impairment, which lead to reduced intellectual ability, are even more important than cretinism (de Benoist et al., 2008; World Health Organization et al., 2007).
Most IDD that occur in adults are reversible with adequate iodine treatment. On the contrary, during development, especially in fetus and infant, ID may lead to irreversible damage (Bernal, 2009).

In the past, the likely occurrence of IDD in a region was defined by its geographical situation (e.g. iodine deplete mountainous regions) confirmed by the prevalence of goiter in the population. Today, better assessment methods (e.g. urinary iodine excretion) are available. Hence, it was shown that IDD also occurred in areas where the above-mentioned factors were not present. Iodine deficiency (ID) was detected, for example, where goiter prevalence was low, in coastal areas, in large cities, in highly developed countries and where ID was thought to have been eliminated. Therefore, it is important that the iodine status in populations is monitored periodically (World Health Organization et al., 2007).
Most iodine monitoring is done in school age children (SAC). The WHO estimates that about one third of SAC worldwide have an insufficient iodine intake. The highest proportion of SAC with insufficient iodine intake (UIC < 100 µg/l) is found in Europe (52%) and the Eastern Mediterranean (49%), the lowest in Western Pacific (23%) and the Americas (11%). Extrapolating the data of SAC, it is estimated that about 2 billion people worldwide have an insufficient iodine intake (de Benoist et al., 2008). Also in Europe, ID is an ongoing public health concern (Andersson et al., 2007). Worldwide, the WHO classified iodine intake as insufficient in 47 countries, as adequate in 49 countries, as more than adequate in 27 and as excessive in 7 countries (no data from 63 countries). Since the last survey in 2003, an improvement of the global iodine status was observed. Switzerland was classified as a country with optimal iodine intake (de

Benoist et al., 2008).

2.1.4. Fetal period and infancy

Fetal thyroid hormonogenesis is detected in the 11^{th} - 12^{th} week of gestation together with the appearance of TSH in the fetal plasma (Brown et al., 2005; Kratzsch and Pulzer, 2008; Polk, 1995). Other authors suggest that fetal thyroid hormone secretion does not start until midgestation (de Escobar et al., 2008). However, during the first half of pregnancy, fetal thyroid hormone levels are low and the fetus is entirely dependent on maternal thyroid hormones (Bernal, 2009; Brown et al., 2005). After that period, fetal thyroid hormone secretion increases (Polk, 1995) and the placenta has under normal circumstances limited permeability for maternal thyroid hormones. Hence, the fetal hypothalamic-pituitary-thyroid system develops relatively independently from maternal influence. Nevertheless, the iodine for thyroid hormone synthesis has to be provided by the mother (Brown, 2009; Kratzsch and Pulzer, 2008). Maternal TSH and Tg do not cross the placenta (Brown, 2009).

Thyroid hormone receptors and T_3 are already present in the fetal brain around the 10^{th} week of gestation. Thenceforward, the receptor concentration increases constantly parallel to rapid brain growth (Bernal and Pekonen, 1984), which indicates the early influence of thyroid hormones on brain development (Obregon et al., 2007). In other organs, thyroid hormone receptors are detected a few weeks later (liver, heart and lung) (Bernal and Pekonen, 1984; Brown et al., 2005).

If the infant has an inborn error in thyroid hormone production, the placental permeability for thyroid hormones increases and the infant may have a normal clinical appearance at birth (e.g. in case of congenital hypothyroidism). If both mother and infant are hypothyroid due to iodine deficiency, the infant shows impairment in neurointellectual development (Brown et al., 2005; Obregon et al., 2007).

At birth, the thyroid gland weighs about 1 g and grows approximately 1 g per year until it reaches a size of 15 – 20 g at about 15 years of age (Brown, 2009; Brown et al., 2005; Kratzsch and Pulzer, 2008). Thyroid hormone stores and

iodine content of the thyroid are low at birth and increase progressively thenceforward (van den Hove et al., 1999). The thyroidal iodine content is about 0.3 mg at birth and increases to 16 mg in adolescents and adults in iodine-sufficient areas (Brown et al., 2005).

The iodide space in the body increases progressively in volume, but the relative size (liter/kg, expressed as percentage of body weight) decreases from about 50% of body weight at birth to about 35 % of body weight in adults (Brown et al., 2005; DeGroot, 1966).

Within the first day after birth, TSH increases rapidly and decreases again (see Figure 1) (Vanderpas, 2006), followed by an increase in T_4 and T_3 levels in the newborn (Abuid et al., 1973; Brown et al., 2005; Kratzsch and Pulzer, 2008).

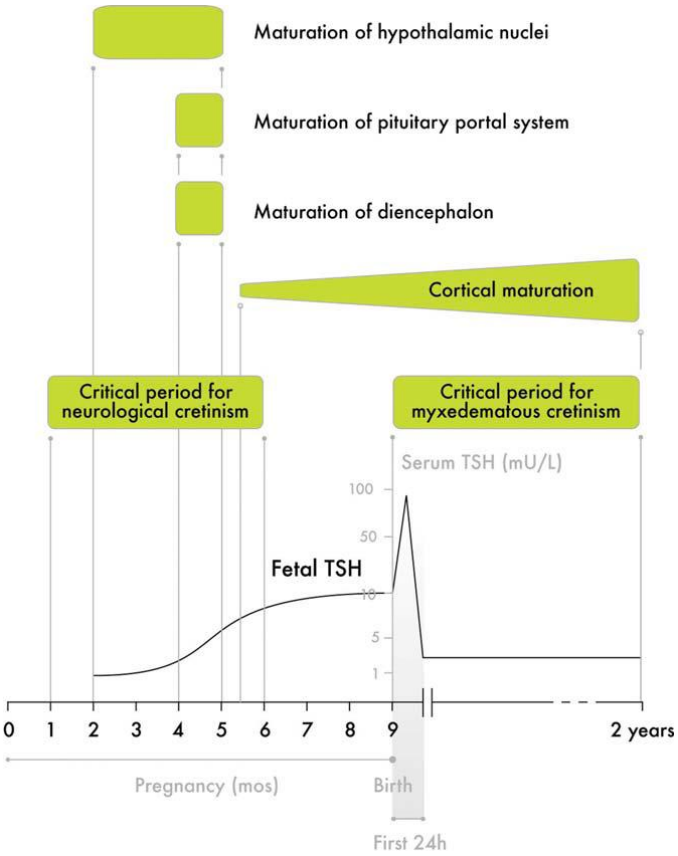


Figure 1: Development of the central nervous system from pregnancy until two years of age and critical periods of cretinism development. The TSH (thyrotropin) profile shown is from a population with normal iodine supply. Source: (Vanderpas, 2006).

Infants have a markedly higher T_4 turnover compared with adults. It is estimated that T_4 production rates range from 5 - 6 µg/kg/day in infancy and that they

decrease to 2 – 3 µg/kg/day at 3 to 9 years of age. In adults, the T_4 production rate is about 1.5 µg/kg/day (Brown, 2009). Serum T_3 concentration reaches the level of adults within a few weeks after birth which indicates that deiodinase maturation is completed by then (Brown et al., 2005). Serum Tg levels reach the concentration of adults by 6 months of age (Brown, 2009).

Thyroid hormones are essential for growth and development of the brain and central nervous system from the 15th week of gestation to three years of age (FAO and WHO, 2004). In this period, thyroid hormones provide the induction signal for differentiation and maturation programs of the central nervous system and mediate neuronal differentiation, neurite outgrowth, synaptogenesis, cerebellar neurogenesis, cell migration, gliogenesis and myelinization of neurons (Bernal, 2009; Porterfield and Hendrich, 1993). Thyroid hormones directly act on the brain through regulation of gene expression (e.g. expression of myelin gene, neuronal growth factor gene, genes for proteins in terminal cell differentiation and genes for cell signaling) (Bernal, 2005; Kohrle, 2000; Yen, 2001). Thyroid hormones also regulate normal growth and bone development through direct (e.g. endochondral ossification and chondrocyte differentiation in the growth plate) and indirect (e.g. growth hormone gene expression) mechanisms (Brown et al., 2005). Besides these, thyroid hormones are important for various other metabolic processes in infants (Yen, 2001). This shows the importance of reliable methods to assess the iodine status in order to enable optimal iodine nutrition and thus, optimal development in the specified age group.

Iodine and consequently thyroid hormone deficiency (hypothyroidism) during the critical period of fetal and infant development may result in stillbirth, abortion or in irreversible damages of physical and mental development (FAO and WHO, 2004; Hetzel, 1983; Porterfield and Hendrich, 1993). The severity of impairment depends on the grade and timing of iodine deficiency (Bernal, 2009; Delange, 2000). The most serious damage due to severe iodine deficiency[2] is (endemic)

[2] Severe iodine deficiency in a population is defined as a median urinary iodine concentration < 20 µg/l in adults/school age children of the respective population (see chapter 2.4.1.2) (World Health Organization et al., 2007).

cretinism (FAO and WHO, 2004; Hetzel, 1983). However, the more subtle forms of brain damage and cognitive capacity are of even greater importance for public health because they might reduce the potential of a whole population (World Health Organization et al., 2007).

Figure 1 shows the stages of brain development from pregnancy until two years of age and the critical periods of cretinism development (Vanderpas, 2006). There are two forms of endemic cretinism. Neurological cretinism, in which damage to the child due to ID of the mother already occurs in the first/second trimester of pregnancy, is characterized by severe mental retardation with squint, deaf mutism and motor spasticity. Myxedematous cretinism, in which damage occurs during the last trimester of pregnancy and postnatal period, is characterized by a less severe degree of mental retardation, but with all signs of severe hypothyroidism present since early life such as severe growth retardation, myxedema, craniofacial abnormalities, delayed sexual development (Bernal, 2009; Vanderpas, 2006; Zimmermann, 2009). Based on several intervention studies in regions with severe ID, Zimmermann concluded in a recent review that iodine supplementation during pregnancy could prevent neurological damages, especially when applied in early pregnancy (Zimmermann, 2009).

It remains unclear whether mild-to-moderate[3] ID in pregnancy/neonatal life causes more subtle impairment of cognitive and/or neurological capacity in the progeny as only a few studies have been conducted that measured neurocognitive performance of infants in areas with mild-to-moderate ID (Vitti et al., 1992; Zimmermann, 2009). A recent intervention study in a Spanish area with moderate ID compared the neurocognitive development of infants (3 – 18 months) whose mothers received 300 µg KI per day during their pregnancy (n = 133) with infants whose mothers did not receive any supplement (n = 61) (Velasco et al., 2009). The study showed that infants whose mothers were

[3] Mild or moderate iodine deficiency in a population is defined as a median urinary iodine concentration of 50-99 µg/l or 20-49 µg/l in adults/school age children of the respective population (see chapter 2.4.1.2) (World Health Organization et al., 2007).
For pregnant women mild-to-moderate ID can also be defined as a median urinary iodine concentration of 50-150 µg/l (Zimmermann, 2007a).

supplemented with iodine had a better psychomotor evaluation. The supplementation during pregnancy also resulted in significantly higher iodine levels in breast milk (BM), which was beneficial for the infants as well (Velasco et al., 2009). Another recent Spanish intervention study found that a delay of 6 – 10 weeks in iodine supplementation of women with mild ID increased the risk for permanent alterations in motor coordination and social development in their children (measured at 18 months of age) (Berbel et al., 2009).

ID may also increase infant mortality. Zimmermann recently reviewed that several studies suggested that iodine supplementation during pregnancy and infancy could reduce infant mortality rate by 50% (Zimmermann, 2009).

Postnatal effects of ID on cognitive function are less clear than the effects during the fetal period (Zimmermann, 2007a). The neonatal brain, however, is just one third of the adult's brain size. ID during brain development after birth could lead to irreversible brain damage (Sethi and Kapil, 2004). It was assumed from several studies that chronic ID reduces IQ in populations. However, the studies could not differentiate whether this effect already originated from fetal development or resulted from iodine status thereafter (Zimmermann, 2007a). A recent intervention study (24 weeks) on moderately iodine-deficient schoolchildren in Albania (n = 310, 10 – 12-year-old) showed that iodine supplementation (single dose of 400 mg iodine as iodized oil) improved cognitive performance (e.g. information processing and fine motor skills) (Zimmermann et al., 2006a).

Also less clear are the effects of ID on postnatal growth (Zimmermann, 2009). Survey data from Asian countries with mild ID indicated that the use of iodized salt was significantly correlated with higher weight-for-age and mid-upper-arm circumference, especially in the second year of life (Mason et al., 2002). An intervention study in schoolchildren showed that iodine supplementation increased the IGF-I and IGF-binding protein-3 levels in body and also showed higher z-scores for weight-for-age and height-for-age (Zimmermann et al., 2007b).

2.1.5. Lactation

During pregnancy, renal iodine clearance and thyroid hormone production are increased (Glinoer, 2007). During lactation, renal iodine clearance and thyroid hormone production return to normal even though the iodine requirement is increased during this time for secretion into breast milk (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). Glinoer et al. (Glinoer et al., 1992) and Eltom et al. (Eltom et al., 2000) observed normalization of the thyroid function six months respectively nine months post-partum. The studies neither measured iodine concentration in breast milk nor assessed if the women increased their iodine intake during lactation (Eltom et al., 2000; Glinoer et al., 1992).

During lactation, the mammary gland concentrates iodide actively to ensure an adequate iodine supply to the infant (Azizi and Smyth, 2009; Rousset and Dunn, 2004). The concentration of iodide in breast milk is 20 – 50 times higher in relation to the plasma concentration (Azizi and Smyth, 2009). Almost 80% of total iodine in breast milk is in the form of iodide (Semba and Delange, 2001). Iodide is transported to the mammary gland in the same way as to the thyroid gland, by a Na^+/Iodide-symporter (NIS). NIS expression increases during lactation (Tazebay et al., 2000). The secretion of iodide into breast milk is influenced by several hormones (prolactin, oestradiol, oxytocin) (Azizi and Smyth, 2009).
Thyroid hormones and metabolites are also found in breast milk in various concentrations as reviewed by Dorea (Dorea, 2002).

The iodine intake level of the mother influences the iodine content of breast milk. Mothers who use iodized salt or iodine-containing supplements usually have higher breast milk iodine concentrations compared with non-users (Azizi and Smyth, 2009; Zimmermann, 2007b). However, some studies found no influence of iodized salt or supplements (Azizi and Smyth, 2009).

It has been shown that maternal smoking interferes with the iodine transport to breast milk. This is probably mediated by thiocyanate from smoke that inhibits the NIS (Laurberg et al., 2004).

2.2. Dietary iodine requirements

2.2.1. Overview

Dietary iodine requirement is based on adequate synthesis of thyroid hormones in order to meet physiological needs and to avoid iodine deficiency disorders (D-A-CH, 2008; Zimmermann, 2008a).

Various factors need to be considered to determine recommendations of iodine intake such as iodine uptake rate, reutilization, storage, excretion in urine and stool, variations in iodine content of food, goitrogens and cooking losses (D-A-CH, 2008; Prentice et al., 2004). Iodine turnover studies and balance studies are methods to define iodine requirements and recommendations of iodine intake. Another approach is epidemiological studies that observe correlations between iodine supply, urinary iodine concentration and goiter frequency (D-A-CH, 2008; FAO and WHO, 2004; Zimmermann, 2007b).

For adults, WHO/ICCIDD (> 12 yr), D-A-CH (Switzerland, > 15 yr), US Institute of Medicine (≥ 14 yr, RDA) and the Nordic Nutrition Recommendations (> 10 yr) recommend an iodine intake of 150 µg/day (Becker et al., 2004; D-A-CH, 2008; Institute of Medicine et al., 2001; World Health Organization et al., 2007). The Scientific Committee for Food (SCF) of the European Commission recommends only 130 µg/day (SCF (Scientific Committee for Food), 1993).

The iodine requirements for infants, young children, pregnant and lactating women are different from adults' requirements due to varying physiological situations. Consequently, the recommendations for iodine intake differ (D-A-CH, 2008; Institute of Medicine et al., 2001; World Health Organization et al., 2007). The recommendations for infants and lactating women are described in the following sections.

2.2.2. Recommendations for infants

The recommendations of iodine intake for adults are rather consistent in different organizations and countries. In contrast, there is a large variation among recommendations for infants. Table 2 shows recommendations for infants.

Table 2: Recommendations for iodine intake: Infants

Infants	**Age group**	**Recommended iodine intake** [µg/day]	*Source*
UNICEF, ICCIDD, WHO	≤ 2 yr	90	(World Health Organization et al., 2007)
D-A-CH			
Germany, Austria	0 to < 4 mo [a]	40	(D-A-CH, 2008)
	4 to < 12 mo	80	
	1 to < 4 yr	100	
Switzerland	0 to < 4 mo [a]	50	
	4 to < 12 mo	50	
	1 to < 4 yr	90	
US Institute of Medicine			
AI	0 to 6 mo	110	(Institute of Medicine et al., 2001)
	7 to 12 mo	130	
EAR/RDA	1 to 3 yr	65/90	
SCF European Commission (PRI)	6 to 11 mo	50	(SCF (Scientific Committee for Food), 1993)
	1 to 3 yr	70	
COMA (United Kingdom) (RNI)	0 to 3 mo	50	Recommendations of the Department of Health, UK, 1991, data from (Thomson, 2002)
	4 to 12 mo	60	
	1 to 3 yr	70	
Nordic Nutrition Recommendations	< 6 mo	--	(Becker et al., 2004)
	6 to 11 mo	50	
	12 to 23 mo	70	
AFSSA (France)	0 to 6 mo	40	Recommendations of Agencie Française de Sécurité Sanitaire des Aliments (AFSSA), France, 2001, data from (EU Scientific Committee on Food, 2003)
	7 to 12 mo	50	
CSH (Belgium)	0 to 1 yr	90	Recommendations of Conseil supérieur d'Hygiéne (CSH), Belgium, 2000, data from (EU Scientific Committee on Food, 2003)
Spanish Dietetic and Food Science Association	0 to 1 yr	35	Data from (EU Scientific Committee on Food, 2003)

[a] Estimated value
Abbreviations: AI = Adequate intake, EAR = Estimated average requirement, RDA = Recommended dietary allowance, PRI = Population reference intake, RNI = Reference nutrient intake

Compared to adults, infants and children need nutrients not only for maintenance of body functions and stores, but also for growth and development. These aspects need to be considered in recommendations of dietary intakes for infants and children (Prentice et al., 2004).

Explanations on recommendations:

UNICEF, ICCIDD, WHO: The currently recommended iodine intake for infants was updated in 2001 (FAO and WHO, 2004) from the earlier recommendation of WHO/UNICEF/ICCIDD (50 µg/day in the first 12 months of age) (WHO et al., 1996) and the earlier recommended dietary allowances (RDAs) of the Food and Nutrition Board of the United States National Academy of Sciences (Subcommittee on the tenth edition of the RDAs et al., 1989).

Gushurst et al. and Delange et al. reported that the iodine recommendation of 40 - 50 µg/day for infants in the 1980's edition of the RDAs was derived from breast milk iodine concentration (equates to about 50 µg/l) because it was assumed that normally growing infants have an adequate nutrient intake. Nevertheless, Gushurst et al. and Delange et al. expressed their uncertainty about the adequacy of that earlier recommendation (Delange et al., 1988; Gushurst et al., 1984).

In 1984, Gushurst et al. measured a mean breast milk iodine concentration (BMIC) of 178 µg/l in US women (median 146 µg/l) (Gushurst et al., 1984). In a revision of the RDAs in year 1989, based on the study of Gushurst et al. (Gushurst et al., 1984) it was stated that the BMIC of North American women was much higher than the infants' needs for iodine due to elevated iodine intakes of the women. Therefore, BMIC was not a good basis for the recommendations. Thus, relative energy requirements of adults were used as a basis for the revised recommendations in 1989 (Subcommittee on the tenth edition of the RDAs et al., 1989). However, the recommended dietary allowances for iodine were basically the same as before: 40 µg/day for 0 – 6-month-old infants and 50 µg/day for 7 – 12-month-old infants (approximately 7.5 µg/kg/day) (Subcommittee on the tenth edition of the RDAs et al., 1989).

FAO and WHO explained the last update of their recommendation in 2001 as follows (FAO and WHO, 2004): Infants have an iodine intake of about 60 µg/day

in Europe and about 120 µg/day in the USA. These assumptions were based on several studies on BMIC and an average breast milk intake of 750 ml/day (FAO and WHO, 2004). FAO and WHO also considered a balance study of Delange et al. conducted with one month old infants (n = 20) in 1983 (Delange et al., 1988). Delange et al. concluded from this study that a positive iodine balance, which is required in infants for building up iodine stores, is only achieved with an iodine intake of 15 µg/kg/day (for full term infants) (Delange et al., 1993). The infants had a mean iodine retention of 7.3 µg/kg/day in this balance study (mean intake 20 µg/kg/day, excretion in feces 1.3 respectively in urine 11.4 µg/kg/day) (Delange et al., 1988). On the basis of Delange et al.'s study, FAO and WHO concluded that a 6-month-old infant of 6 kg body weight has an iodine requirement of approximately 90 µg/day (6 kg * 15 µg/kg/day) (FAO and WHO, 2004). Based on the estimated iodine intakes in Europe and the USA and Delange et al.'s study, the updated recommendation for iodine intake was set at 90 µg/day for children ≤ 2 yr (FAO and WHO, 2004; World Health Organization et al., 2007).

D-A-CH: No detailed explanation for the iodine recommendations for infants is given by D-A-CH (D-A-CH, 2008). In general, it is indicated, however, that the reference values for infants in the first four months of life apply to exclusively breast-fed infants. It is referred to Souci et al. for the nutrient contents of breast milk. Souci et al. specified an average BMIC of 5.1 µg/100g (Souci and Deutsche Forschungsanstalt für Lebensmittelchemie (Garching), 2008). Furthermore, an average BM quantity of 750 ml/day (CV about 12.5%) is indicated for infants after two months of age (D-A-CH, 2008). This would result in a daily iodine intake of 38.25 µg (51 µg/l * 0.75 l), which is very close to the recommended 40 µg/day for infants aged 0 to < 4 months in Germany and Austria. It is emphasized, however, that the recommendations, which were extrapolated from breast milk, are just estimated values due to variations in nutrient content of BM and lack of systematic investigations on requirements of infants for most of the essential nutrients (D-A-CH, 2008).

For infants aged 4 to < 12 months and 1 to < 4 years in Austria and Germany the iodine recommendations are higher compared with Switzerland. According

to the explanation for adults, this is because iodine supply in Germany is still not adequate in some regions and age groups and because several interfering factors were considered (variations in iodine content of food, iodine losses in food preparation, potentially low selenium supply and goitrogenic substances) (D-A-CH, 2008). Switzerland has a better iodine nutrition than Austria and Germany due to a salt iodization program which has existed for decades (D-A-CH, 2008). Therefore, the iodine recommendations for Switzerland were derived from the WHO/UNICEF/ICCIDD recommendations of 1996 (50 µg/day in the first 12 months of age; 90 µg/day for 2 – 6 years of age) (WHO et al., 1996).

US Institute of Medicine (IOM): The AI for infants (0 – 12 months) represents the observed mean iodine intake of exclusively breast-fed infants. The IOM used Gushurst's study (Gushurst et al., 1984) which measured a median BMIC of 146 µg/l in US women and calculated an iodine intake of 114 µg/day for infants fed with 0.78 l breast milk per day. Additionally, they considered Delange et al.'s iodine balance study (see above UNICEF, ICCIDD, WHO) (Delange et al., 1988) and calculated a total iodine excretion of 90 µg/day for a 6-month-old infant with a body weight of 7 kg (12.7 µg/kg/day iodine excretion in urine and feces * 7 kg). Based on these two calculations they set the AI of 110 µg/day for infants aged 0 - 6 months. The AI of 130 µg/day for infants aged 7 - 12 months was extrapolated from data of younger infants ($AI_{7\text{-}12mo} = AI_{0\text{-}6mo} * (weight_{7\text{-}12mo}/weight_{0\text{-}6mo})^{0.75}$; $weight_{0\text{-}6mo}$ = 7 kg, $weight_{7\text{-}12mo}$ = 9 kg) (Institute of Medicine et al., 2001).

The EAR (estimated average requirement) for children aged 1 - 3 years was based on a 4-day balance study that was performed with seven Senegalese infants (aged 1.5 to 2.5 yr). These had recovered from protein-calorie malnutrition one month before. Their mean iodine intake was 63.5 µg/day and they had a positive iodine balance (+ 19 µg/day) (Ingenbleek and Malvaux, 1974). As no better data were available, the EAR for children aged 1 - 3 years was derived from Ingenbleek and Malvaux's balance study and set at 65 µg/day (Ingenbleek and Malvaux, 1974; Institute of Medicine et al., 2001). If the EAR for children of this age group had been extrapolated from the adults EAR

(based on body weight), it would have been only 36 µg/day (Institute of Medicine et al., 2001).
The RDA is: EAR + 2 * CV(20%) (Institute of Medicine et al., 2001).

***SCF*:** The recommendations for infants were calculated from the recommendation for adults (130 µg/day) based on energy requirements (SCF (Scientific Committee for Food), 1993).

COMA (United Kingdom): The UK recommendations for infants up to 12 months of age were based on the observation that infants who received breast milk containing 30-40 µg iodine per liter did not show signs of deficiency (Gushurst et al., 1984). A margin of safety was added to the recommendations (data from: (Thomson, 2002)).
For older infants and children recommendations were extrapolated from adults' recommendations using estimated average requirements (EAR) for energy (data from: (Thomson, 2002)).

Nordic Nutrition Recommendations: No detailed information was found as only an excerpt of the recommendations (Becker et al., 2004) was available online.

AFSSA, CSH (Belgium), Spanish Dietetic and Food Science Association (data from (EU Scientific Committee on Food, 2003)) no detailed explanation for recommendations could be found.

The "Swiss regulation of infant food" specifies 80 µg of iodine as reference value for daily iodine intake on labels of infant food. No further explanations are given in the regulation (EDI, 2005b).

2.2.3. Recommendations for lactating women

Lactating women have higher recommendations for iodine intake compared to non-pregnant, non-lactating women because of iodine secretion into breast milk (D-A-CH, 2008; Institute of Medicine et al., 2001; WHO Secretariat on behalf of the participants to the Consultation et al., 2007). Table 3 shows recommendations of several organizations.

Table 3: Recommendations for iodine intake: Lactating women

Lactating women	**Recommended iodine intake [µg/day]**	***Source***
UNICEF, ICCIDD, WHO	250	(World Health Organization et al., 2007)
D-A-CH Germany, Austria Switzerland	 260 200	(D-A-CH, 2008)
US Institute of Medicine EAR RDA	 209 290	(Institute of Medicine et al., 2001)
SCF (PRI)	160	(SCF (Scientific Committee for Food), 1993)
Nordic Nutrition Recommendations	200	(Becker et al., 2004)

Abbreviations: EAR = Estimated average requirement, RDA = Recommended dietary allowance, PRI = Population reference intake

The US Institute of medicine assumed an average daily loss of 114 µg iodine through breast milk (Institute of Medicine et al., 2001). Delange estimated that the daily iodine excretion via breast milk is 75 – 200 µg (in iodine-sufficient women) depending on the amount of breast milk produced (0.5 – 1.1 l) (Delange, 2007).

The WHO recently increased the recommendation for iodine intake from 200 µg/day to 250 µg/day for lactating women (which is the same recommendation as for pregnant women) (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).

2.2.4. Upper limits of intake

According to WHO/FAO, the save upper limit of iodine intake is 150 µg/kg/day for infants aged 0 – 6 months, 140 µg/kg/day for infants aged 7 – 12 months, 50 µg/kg/day for 1 - 6 year old children and 40 µg/kg/day for lactating women (FAO and WHO, 2004).

2.3. Dietary iodine sources

2.3.1. Iodine in the food chain – salt iodization

The iodine content of plants depends on the iodine content of soils in which they are grown. Therefore, the iodine content of foods in the food chain can vary markedly. European inland soils are depleted in iodine presumably mainly due to glaciations (Haldimann et al., 2005). The most depleted areas in the world are the Himalayas, the Andes, the European Alps and the mountains of China (Clugston and Hetzel, 1994). Soils in coastal areas and seawater, on the contrary, contain higher amounts of iodine.

Marine fish, shellfish and seaweed have the highest natural iodine concentrations (up to 1100 µg/kg) (FAO and WHO, 2004; Haldimann et al., 2005). Iodine concentrations of plant foods, in contrast, are usually very low (see Table 4). Milk and eggs have a rather high iodine concentration which is due to the use of iodine-containing feed supplements (Haldimann et al., 2005). Als et al. reported that in Switzerland cow milk has a higher iodine concentration in winter compared with summer because in winter, cows are fed indoors with processed iodine-enriched food (Als et al., 2003). Dahl et al. made the same finding for Norwegian milk (Dahl et al., 2003). Muscle flesh only contains very small amounts of iodine even after feed supplementation (Franke et al., 2008; Haldimann et al., 2005). The iodine content of cheese and bread depends on the use of iodized salt during production and processing (Haldimann et al., 2005). Iodine content of tap water can vary much as shown in a Danish study, < 1.0 - 139 µg/l (Pedersen et al., 1999).

Table 4 shows mean iodine contents which were measured in Swiss foods (Haldimann et al., 2005). Iodine contents of Swiss foods can be found also in the Swiss food composition table (SwissFIR, 2008) (available online: www.swissfir.ethz.ch/datenbank).

Thomson et al. recently found in a New Zealand study that 65% of analyzed foods had an iodine content of less than 0.02 µg/g (n = 121, about 70% of the most commonly consumed foods in New Zealand) (Thomson et al., 2008).

Table 4: Iodine contents in Swiss food samples [µg/kg] (adapted from (Haldimann et al., 2005))

Food	**Iodine content in fresh weight samples** [µg/kg]
Marine fish	486 (89 – 1593) [a]
Freshwater fish	98 (3 – 408)
Meat	17 (2 – 155)
Poultry	18 (10 – 169)
Milk (winter)	124 (59 – 199)
Eggs	324 (247 – 428)
Wholemeal	33 (11 – 47)
Bread	310 (20 – 815)
Fruits	3 (0.3 – 13)
Vegetables	5 (1 – 22)

[a] Mean (range) (all such values)

Populations living in iodine-depleted areas suffer from iodine deficiency and its consequences. Strategies to eliminate iodine deficiency are fortification of foods and feed, use of iodine in fertilizers and irrigation water and dietary diversification with foods from iodine-sufficient areas (Zimmermann et al., 2008).

The recommended strategy to bring iodine into the food chain and to eradicate IDDs is universal salt iodization (iodization of all salt for food industry, households and animal food). Salt is a good vehicle for iodine because nearly everybody uses salt throughout the year. Iodized salt is technically easy to produce and cost effective (World Health Organization et al., 2007; Zimmermann et al., 2008). WHO recommends adding 20-40 mg iodine/kg salt (Allen et al., 2006). In Switzerland, salt currently has an iodization level of 20 mg/kg (since 1998) (Zimmermann, 2005). Salt producers and retailers must offer iodized and non-iodized salt (Zimmermann, 2008c). In Switzerland, there are only two salt producers, and they supply the whole of the country (Bürgi, 2005). It is estimated that about 95% of the salt used in Swiss households is iodized (Zimmermann, 2005). In the USA, household salt only contributes 15% to daily salt intake, whereas the major part of salt comes from processed foods (Pearce, 2007). A recent study in Switzerland (Geneva) calculated that discretionary salt delivers 35% and 41% of total salt intake to women and men,

respectively. Consequently, the remaining part comes from processed foods (Beer-Borst et al., 2009). The use of iodized salt by food industries in Switzerland is voluntary (Zimmermann et al., 2005). It is estimated that about 50 – 70% of salt in processed foods is iodized (Haldimann et al., 2005; Zimmermann, 2008c).

2.3.2. Major dietary iodine sources – general population

In Switzerland, Haldimann et al. estimated per capita exposure to iodine from Swiss foods based on food consumption statistics and measurements of iodine content in Swiss foods. Bread (with iodized salt) (41%) and milk (21%) were identified as the major iodine sources in Switzerland followed by cheese (9%) and eggs (7%). Other food groups contributed only to a minor extent to iodine exposure. This study excluded the use of iodized kitchen salt (Haldimann et al., 2005).

The following studies assessed the major iodine sources in some other countries.

Manz et al. identified bakery products and milk products as main iodine sources for adults in Germany (n = 2500, > 13 yr), followed by iodized table salt, cold water fish and meat products (specialized FFQ) (Manz et al., 2002). In another German study, which was performed in school children, milk, fish, egg, meat and sodium intake were significant predictors of iodine status (Remer et al., 2006).

A study in Norway (n > 2500) reported that the main iodine sources for Norwegian adults were milk and dairy products, fish and fish products (80% of iodine intake). The study used an FFQ (iodized salt not included) and measured iodine concentration in food with ICP-MS (Dahl et al., 2004).

Pearce et al. regarded milk and dairy products and bread and iodized salt as the most important iodine sources in the USA. Moreover, multivitamins were suggested as possible important source for the US population (Pearce, 2007; Pearce et al., 2004). New results of the US Total Diet Study showed that dairy and grain products were the most important iodine sources for US adults (Murray et al., 2008).

A recent study examined dietary iodine exposure with typical simulated diets in New Zealand. Dairy foods were the dominant iodine source in all population groups except in 6 - 12-month-old infants. For them, iodine in infant formulae and weaning foods contributed to 60% of the iodine exposure. Eggs, mussels, fresh fish and oysters were also important for most population groups. Use of household salt was not taken into account (Thomson et al., 2008).
In a Korean study, seaweed contributed to 66% of iodine intake in adults (Kim et al., 1998) and in fact the iodine intake solely by seaweed consumption was 1200 µg/day (Nagataki, 2008).

2.3.3. Infants

Infants have different food sources compared to adults and therefore different iodine sources.

2.3.3.1. Infant nutrition

The WHO recommends exclusive breast-feeding for the first six months of life. Thereafter, complementary foods (CF)[4] should be introduced while continuing breast-feeding (World Health Organization, 2001). In Switzerland, the "Nutrition Commission of the Swiss Pediatric Society" (EK SGP) recommends exclusive breast-feeding during the first four to six months of life (ideally six months). If breast-feeding is not possible, infant formula should be used during this time. Afterwards, starting from the 5th to 7th month of life, feeding with breast milk (BM) or formula (FM)[5] together with CF is recommended (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). CF should be introduced at the latest from the 7th month onwards as breast milk does not thereafter deliver enough nutrients (Agostoni et al., 2008; Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). A feeding plan is included in Appendix 2 (Swiss pediatric society, 2002).
The Swiss Nutrition Society (SGE) and EKSGP recommend replacing one daily

[4] Complementary food is defined as follows: Any food (solid or liquid) suitable as a complement to breast milk or infant/follow-on formula. Other terms used to describe CF are ''weaning foods'' and ''Beikost'' (WHO, 2003; Agostoni et al., 2008).
[5] Formula (FM) = Breast milk substitutes, usually cow milk based, sometimes soy protein based, including infant formulae and follow-on formulae (EDI, 2005b).

BM/FM meal by a CF meal (porridge/puree) month by month. Finally, the infant receives 3 – 4 CF meals per day and BM or FM at the remaining meal occasions. The typical dish to start with CF is vegetable puree. New foods should be introduced stepwise with at least 3 – 4 days in between before introducing the next one. Continuously, potatoes, oil and meat/egg are added to the vegetable meals. Alternatively, complementary feeding can be started by a milk-cereal-porridge; otherwise, it usually is the second introduced meal. Next, a fruit-cereal-porridge is introduced (Dähler et al., 2007; Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). The selection of CF is influenced by various individual, traditional and cultural factors (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008).

Between the end of the first and beginning of the second year, infants continuously start eating family foods. CF meals slowly start adapting to adult meals (e.g. fruit-cereal-porridge becomes a snack composed of bread and fruit) considering specific needs of the growing young child (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008; Forschungsinstitut für Kinderernährung, 2007; Tönz et al.).

The SGE gives examples of typical daily meal sequences for infants in their recommendations (Dähler et al., 2007):

- For a 6-month-old infant: first meal: BM/FM → second meal: vegetable-potato-meat-puree → third meal: BM/FM → fourth meal: milk-cereal-porridge.
- For a 10- to 12-month-old infant: first meal: BM/FM and bread → second meal (snack): bread and fruit juice (1:1 diluted with water) or muesli → third meal: vegetable-potato-meat meal → fourth meal: same as second → fifth meal: milk-cereal-porridge maybe with fruits.

Examples of meal compositions are given in the nutrition recommendations of Dähler et al. and Kersting (Dähler et al., 2007; Kersting, 2001).

In Switzerland, undiluted cow milk is recommended for infants at the earliest from the second year of life (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). Before this, diluted cow milk can be added to cereal-milk-porridges if desired even though FM is preferable to cow milk during the whole first year of life (Tönz et al.).

During the periods of breast-/formula-feeding and complementary feeding, salt is not the ideal vehicle for providing iodine as salt intake should be limited during these periods (Glinoer, 2007). EK SGP and SGE recommend not giving salt to infants below one year of age and, even until 36 months of age, only tiny quantities and only iodized and fluoridated salt should be given (Dähler et al., 2007; Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008; Swiss pediatric society, 2002).

A Swiss study on feeding practices of infants up to 9 months of age was conducted in 2003 (n = 2868). A self-administered 24h-dietary-recall questionnaire was used, but no frequencies or quantities were inquired (Dratva et al., 2006; Merten et al., 2005). Table 5 shows the percentage of infants by age [mo] who were exclusively/fully (= predominantly) breast-fed and the percentage of infants who had received BM, FM and CF at least once (Merten et al., 2005).

Table 5: Infant feeding in different months of age (modified after (Merten et al., 2005))

Month of life [mo]	**Exclusive BF [%]**	**Full/ predominant BF [%]**	**Within the last 24h at least [%]**		
			BF once	FM once	CF once
1st and 2nd	58	73	83	23	5
3rd and 4th	53	64	76	34	5
5th and 6th	21	27	60	51	57
7th, 8th, 9th	2	2	40	61	97
≥ 10th	0	0	29	60	99

Abbreviations: BF = breast-fed; FM = formula milk; CF = complementary food; mo = months

Figure 2 shows the prevalence of different milk types by month of life (Dratva et al., 2006). The study found that > 50% of infants were introduced to CF by the age of 6 months. The first introduced foods were vegetables and fruits, followed by cereals. Figure 3 shows the prevalence of different types of CF by month of life (Dratva et al., 2006). A high percentage of mothers cooked infant food themselves at least once in the last 24 hours. 81% of fruit, vegetable, meat or fish meals and 17% of cereal meals were home-made (Merten et al., 2005).

No other studies on infant feeding in Switzerland were found.

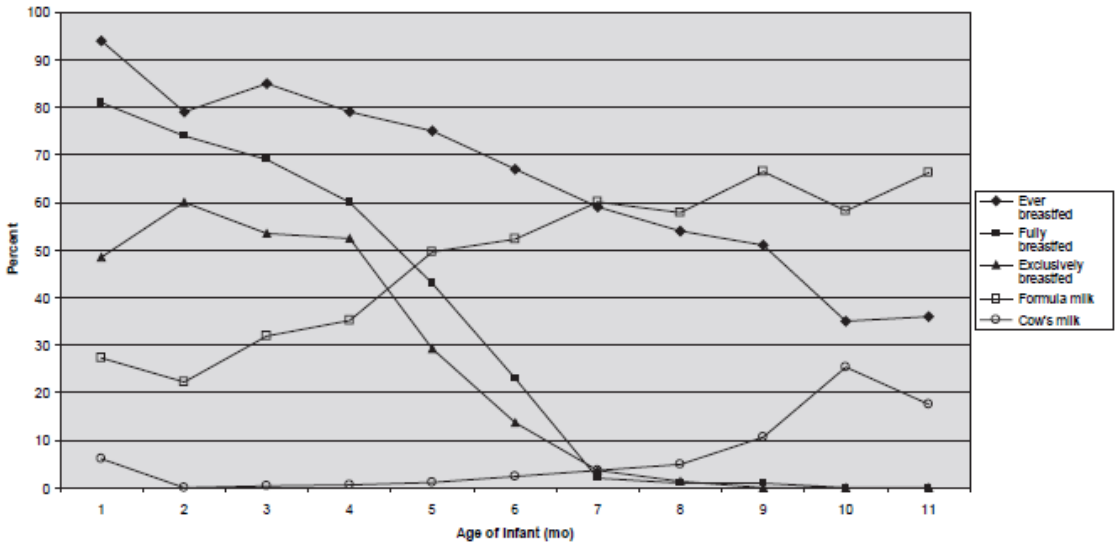


Figure 2: Milk feeding in different months of life. Source: (Dratva et al., 2006)

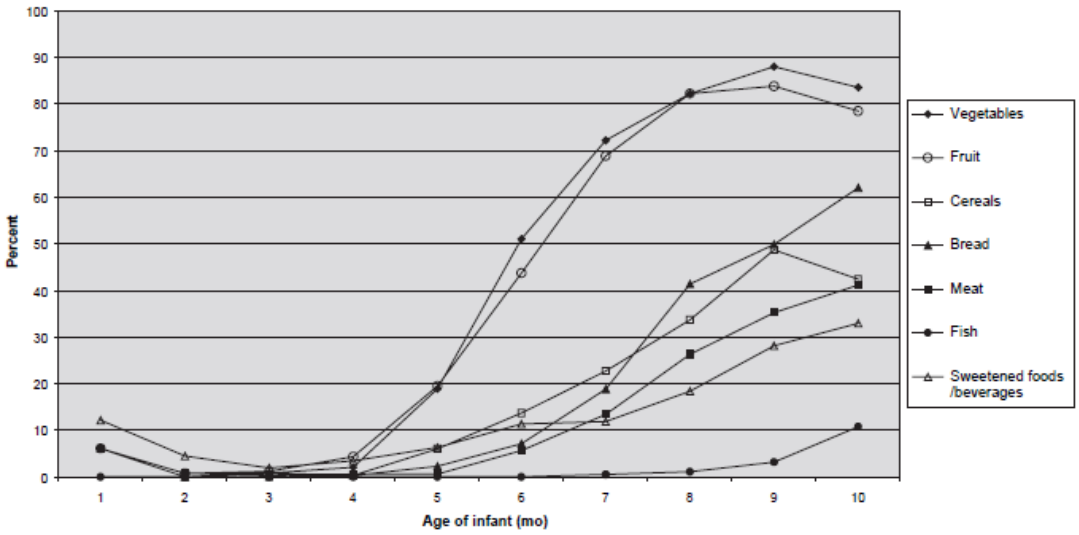


Figure 3: Complementary foods in different months of life. Source: (Dratva et al., 2006)

In the German DONALD study, the contribution of different foods to the total food intake (g/d) of 6- respectively 12-month-old infants was: 25% resp. 1% BM, 33% resp. 13% FM, 10% resp. 9% commercial infant cereals, 10% resp. 15% commercial baby foods and 13% resp. 62% other foods (homemade infant food, family food, cow milk) (Kersting et al., 1998).

In the US Feeding Infants and Toddlers Study, the most important energy sources for 6- to 11-month-old infants were infant formula (43%), BM (11%) and infant cereals (6.5%). For 12- to 24-month-old infants it was milk (cow/goat/soy,

24%), juice (6%), sweetened beverages (5%), cheese (4%) and bread (various kinds, 4%) (Fox et al., 2006).

2.3.3.2. Iodine sources for infants

Infants depend completely on the iodine concentration of BM or FM in their first months of life, then gradually also on iodine content in CF and by the end of the first year, progressively on iodine content in family foods.

To our knowledge no study on iodine intake of Swiss infants has been conducted before this study.

According to Kersting (2001), the major iodine source for infants is FM (about 55%), followed by milk-cereal-porridges (about 22%), vegetable-potato-meat-purees (about 15%) and fruit-cereal-porridges (about 8%) (estimation is based on home-made CF) (Kersting, 2001).

A national British study assessed food intake of 6- to 12-month-old infants (n = 488) by a 7-day dietary record in 1986 (Mills and Tyler, 1992). The median daily iodine intake was 164 µg/day for 6 – 9-month-old infants and 236 µg/day for 9 – 12-month-old infants. The highest percentage of iodine was observed from milk: 71% for 6 – 9-month-old infants (46% cow milk, 22% FM, 3% BM) and 68% for 9 – 12-month-old infants (62% cow milk, 5% FM, 1% BM). Family foods contributed to 19% respectively 28% of the iodine intake of 6 – 9- respectively 9 – 12-month-old infants. Commercial infant food (jars, instant foods, rusks) supplied 10% respectively 4% of iodine to 6 – 9- respectively 9 – 12-month-old infants. No further details were given about iodine intake. Salt use was not taken into account in the calculations. The contribution of foods to energy intake was: 6% resp. 1% BM, 23% resp. 7% FM, 18% resp. 28% cow milk, 30% resp. 53% family foods and 23% resp. 11% infant foods for 6 – 9-month resp. 9 – 12-month-old infants. Within family foods, bread and cereals delivered the highest percentage of energy (Mills and Tyler, 1992).

In a more recent study in south-west England, which assessed food intake in 8-month-old infants (n = 1130) by a 3-day unweighed dietary record, a median iodine intake of 75.3 µg/day was found (Noble and Emmett, 2001). Milk accounted for 52% of the energy intake (13% BM, 30% FM, 9% cow milk). The contribution of foods to iodine intake was not indicated (Noble and Emmett,

2001).

In the New Zealand Total Diet study (Thomson et al., 2008) typical diets were simulated. In non-breast-fed 6- to 12-month-old infants, exposure to iodine was dominated by iodine content of infant and follow-on formula. The contribution (in %) of food groups to dietary iodine exposure in 6 – 12-month-old infants was: 60% infant formulae and weaning foods (cereal based/custard and fruit dish/savoury), 25% dairy, 7 % chicken/eggs/fish/meat, 3% grains, 2% take-aways, 3% other foods. For a 1 – 3-year-old toddler it was: 67% dairy, 13% chicken/eggs/fish/meat, 7% grains, 4% take-aways, 3% infant formulae and weaning foods, 6% other foods. This study estimated an exposure to iodine of 49 µg/day for infants and 47 µg/day for toddlers (iodized salt was not taken into account) (Thomson et al., 2008).

In the US FDA Total Diet Studies (1982 – 1991) the major contributors to iodine intake in 6 – 11-month-old infants were milk and cheese (59%) and grain products (18%) (Pennington and Schoen, 1996a) with an estimated daily iodine intake of 131 µg (Pennington and Schoen, 1996b). Household salt was not taken into account (Pennington and Schoen, 1996a). New results of the US Total Diet Study showed that 90% of iodine intake in 6 – 11-month-old non-breast-fed infants is provided by baby foods (including all baby foods and FM, no adult foods consumed by the infant) and dairy products. Their estimated total daily iodine intake was 144-155 µg (around 85 µg from baby foods and 50 µg from dairy) (Murray et al., 2008).

2.3.3.3. Iodine in formula and commercial infant food

Swiss legislation regulates the iodine contents of infant formula and follow-on formula (definition see Appendix 1) and of cereal-based and other complementary food (“Beikost”, definition see Appendix 1) in the regulation on “special foods” of the Federal Department of Home Affairs (“Eidgenössisches Department des Inneren”) (EDI, 2005b). In March 2008, the required minimum iodine content of infant and follow-on formula was elevated from 5 µg/100 kcal (1.2 µg/100 kJ) to 10 µg/100 kcal (2.5 µg/100 kJ). The upper level of iodine was set at 50 µg/100 kcal (10 µg/100 kJ). The allowed energy value for formula was reduced from 75 respectively 80 kcal/100 ml for infant respectively follow-on

formula to 60 – 70 kcal/100ml (250 – 295 kJ/100 ml) for both in 2008 (all values refer to the ready-to-eat product) (EDI, 2005b). The regulation restricts the forms of iodine which are allowed for fortification (EDI, 2005b). The new regulations for iodine content of infant and follow-on formulae were made based on the recommendations of the European Commission in 2003 (EU Scientific Committee on Food, 2003) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2005 (Koletzko et al., 2005). The 31st March 2010 was set as date of implementation of the new regulations. Permission was given to launch, produce and label products according to the former regulations up to this date and the products can still be sold until depletion of stocks (EDI, 2005b).

For cereal-based and other complementary foods, there is no regulation in Switzerland and the EU requiring a minimum iodine content in the products. In case of fortification, the allowed upper level is 35 µg iodine/100 kcal product (ready-to-eat) (Commission of the European Communities, 2006; EDI, 2005b). Concerning fortification of CF through iodized salt, Swiss regulation only allows the addition of sodium salts to cereal-based CF if necessary for technical reasons and in this case, a sodium content of maximally 100 mg/100 kcal (25 mg/100 kJ) is allowed. For other CF (e.g. vegetable-meat-purees), a sodium content of maximally 200 mg/100 kcal (48 mg/100 kJ) or 200 mg/100g is allowed in the finished product. It is not allowed to add sodium salts to fruit dishes, desserts and puddings except for technological purposes (EDI, 2005b).

According to SGE (Dähler et al., 2007) and Kersting (Kersting, 2001), the recommended iodine intake for infants is often only fulfilled by feeding them fortified commercially available CF because home-made food has low amounts of iodine.

In a recent German market survey for infant foods, 64% of products (n = 305) were fortified with iodine, 51% of CF products and all formulae (min. 7 µg/100g). Most milk-cereal-porridges were fortified with iodine (83%). A minor part of menus (37%) and fruit-cereal-porridges (13%) was fortified with iodine (Alexy et al., 2009). In a scenario, the survey compared the iodine intake of an 8-month-old breast-fed infant, who received home-made CF, with a formula-fed infant,

who received commercial CF. The breast-fed infant had an estimated iodine intake of about 40 µg/day (BMIC 6.4 - 9.1 µg/100g) and the formula-fed infant had an intake ranging from 125 – 187 µg/day. Accordingly, the breast-fed infant reached only about half of the recommended iodine intake in Germany (80 µg/day) and the formula-fed infant had an intake of 50 – 130% above the recommendation (Alexy et al., 2009).

2.3.4. Supplements

The Nutrition Commission of the Swiss Pediatric Society states in its recommendations for infant feeding in 2008 that infants and children who have a well-balanced diet do not need iodine supplementation as struma prophylaxis (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). The Federal Office of Public Health in Switzerland does not recommend iodine supplementation of lactating mothers either (Camenzind-Frey and Hesse-Lamm, 2008).

The WHO does not recommend iodine supplementation for infants and lactating women living in countries where iodized salt is used in > 90% of households and universal salt iodization is achieved and where iodine intake is adequate (according to WHO criteria (World Health Organization et al., 2007)). The WHO recommends, however, ensuring that complementary foods are fortified with iodine. If iodine intake in a country is insufficient, WHO suggests supplementation with potassium iodide (daily) or iodized oil (annual dose) for women of reproductive age, pregnant and lactating women in order that their recommended daily iodine intake is met. In this case, breast-fed infants receive supplementation through BM or fortified weaning foods (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).

2.4. Assessment of a population's iodine status

SAC are an easily accessible population group and are particularly vulnerable to IDDs. Therefore, they are the "golden standard" for determination of a population's iodine status (World Health Organization et al., 2007). Most studies on iodine status in the WHO "Global Database on ID" (a database that lists the iodine status in countries based on available studies) were performed in SAC (WHO Nutrition, 2008b). The other recommended target groups are women of childbearing age and pregnant women (15 - 44 yr) because ID particularly in fetus and neonates is dangerous (World Health Organization et al., 2007).

The WHO recommends two survey methods for monitoring the iodine status in a population: 1) cross-sectional surveys, which are usually performed to obtain representative population data, 2) sentinel surveillance, which is useful to see trends in iodine nutrition (World Health Organization et al., 2007). In cross-sectional surveys there are often two stages of selection. In the first stage, clusters (e.g. schools) are selected by "probability proportion to size"/"proportionate to population size" (PPS) method, simple random sampling or systematic sampling. In the second stage, individuals are selected randomly or systematically. Usually, 30 clusters are used (Sullivan et al., 2000; World Health Organization et al., 2007).

2.4.1. Recommended methods to assess iodine status

2.4.1.1. Overview

Four recommended parameters exist to assess the iodine status in a population. These are urinary iodine concentration (UIC), goiter rate, serum thyroid stimulating hormone (TSH) and thyroglobulin (Tg) (Zimmermann, 2008b).

UIC (µg/l) is a short-term measure of the iodine status (days) and reflects the current dietary iodine intake. It is well established for SAC, adults and pregnant women (World Health Organization et al., 2007). UIC analysis is the most widespread method worldwide to assess the iodine status biochemically (Caldwell et al., 2005) and is also the recommended method by the WHO (World Health Organization et al., 2007). For a more detailed description of the

method, see below.

Goiter rate (%) is a long-term measure of iodine status (months to years) and is usually examined in SAC (Zimmermann, 2008b). It can be assessed either by palpation or by ultrasound. A goiter rate < 5% in a population indicates iodine sufficiency. This method is not applicable for infants (World Health Organization et al., 2007; Zimmermann et al., 2004).

In many countries, TSH is assessed in newborn screening by blood spots to detect congenital hypothyroidism (Zimmermann, 2008b). Measuring TSH to determine iodine status is only valuable in newborns, as TSH increases only in newborns to a distinguishable level between iodine sufficiency and deficiency. The measurement is expensive and only feasible if a sufficiently sensitive TSH assay is available. Therefore, the WHO does not recommend it universally as an assessment method for iodine status (World Health Organization et al., 2007). If less than 3% of newborns (3 – 4 days old) have a TSH value > 5 mU/l whole blood, this indicates iodine sufficiency in a population (Zimmermann et al., 2005).

Tg reflects the iodine intake over the last weeks to months (Zimmermann, 2008b). Tg measured in dried whole blood spots of SAC is a sensitive indicator of the iodine status in a population (reference range 4 - 40 µg/l) (World Health Organization et al., 2007; Zimmermann et al., 2006b).

2.4.1.2. Urinary iodine concentration (UIC)

Over 90% of ingested iodine finally appears in urine. Therefore, UIC is a good indicator of recent iodine intake (Zimmermann, 2008b).

For an individual, a single urine specimen does not reflect the iodine status, because there is a high variation of UIC within a day (Als et al., 2000a; Rasmussen et al., 1999). The only reliable specimen is a 24-hour urine sample and even this shows a marked variation from day to day (Dunn, 1993). For better results more than one 24-hour urine sample should be analyzed for an individual (Rasmussen et al., 1999).

However, spot urine samples have been shown to be an accurate measure in assessing the iodine status of a population(-group) when a sufficient number of samples are collected to compensate for varying degrees of subject hydration

and other biological differences between subjects and to attain a narrow confidence interval (Andersen et al., 2008; World Health Organization et al., 2007).

A spot urine sample is usually easy to obtain in field conditions. Iodine in urine is stable even without refrigeration and the measurement is generally simpler and cheaper compared with other biomarkers (Dunn, 1993; World Health Organization et al., 2007).

2.4.1.2.1. Measurement

Many analytical techniques for assessing UIC exist. Most of them are based on the Sandell-Kolthoff reaction (Sandell and Kolthoff, 1937), which is a quantitative colorimetric method. In this reaction, iodide acts as catalyst in the reduction of ceric ammonium sulfate (yellow) to the colorless cerous form in the presence of arsenious acid (Gnat et al., 2003). A modification of the Sandell-Kolthoff method (Pino et al., 1996) was successfully implemented at the laboratory of human nutrition at ETH Zurich some time ago (for a description of the method, see chapter 3.6.1). This modified method (with ammonium persulfate digestion) is also the recommended technique of the WHO (World Health Organization et al., 2007).

Another analytical method is ICP-MS (inductively coupled plasma mass spectrometry). This technique provides a high degree of accuracy and precision. It has become popular as a reliable method for the determination of trace elements in biological samples (Caldwell et al., 2005; Haldimann et al., 1998). However, the equipment costs for ICP-MS are very high and therefore it is only used as a reference method in specialized laboratories (Vanderpas, 2006).

The CDC (Centers for Disease Control and Prevention) compared the ICP-MS method (used in NHANES 2000) with the modified Sandell-Kolthoff method (used in NHANES III) and found a strong correlation between the two methods ($r^2 = 0.980$). There was no significant difference between the results of the ICP-MS and the Sandell-Kolthoff method (Caldwell et al., 2003).

EQUIP (Programme for Ensuring the Quality of Iodine Procedures) is an international external quality control program for UIC measurements (World

Health Organization et al., 2007).

2.4.1.2.2. Interpretation

Since analyzed UICs of study subjects are usually not normally distributed, the median UIC value is used for data interpretation. It is usually indicated as µg iodine per liter urine (µg/l) (World Health Organization et al., 2007).

Table 6: Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentration (World Health Organization et al., 2007)

Population group	**Median UIC** [µg/l]	**Iodine intake**	**Iodine nutrition**
School-age children (≥ 6yr) and adults	< 20	Insufficient	Severe ID
	20 – 49	Insufficient	Moderate ID
	50 – 99	Insufficient	Mild ID
	100 – 199	Adequate	Optimal
	200 – 299	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk in the overall population.
	≥ 300	Excessive	Risk of adverse health consequences
Pregnant women	< 150	Insufficient	
	150 – 249	Adequate	
	250 – 499	More than adequate	
	≥ 500	Excessive	
Lactating women	< 100	Insufficient	
	≥ 100	Adequate	
Infants < 2 yr	< 100	Insufficient	
	≥ 100	Adequate	

Abbreviations: UIC = urinary iodine concentration; ID = iodine deficiency; yr = years

A median UIC below 100 µg/l in a population has been associated with an increase in median thyroid size (FAO and WHO, 2004) and it has been shown in school-age children that the largest thyroid sizes are associated with the lowest UICs (Delange et al., 1997). Studies which associated low UICs with high goiter prevalence, high radioiodine uptake and low thyroidal organic iodine

content showed a steady-state as soon as UIC reached ≥ 100 µg/l (Delange et al., 1993; FAO and WHO, 2004).
The epidemiological criteria for assessing iodine nutrition in a population are shown in Table 6. In children and non-pregnant women, a median UIC between 100 and 299 µg/l defines a population without ID. Additionally, less than 20% of samples should have a UIC < 50 µg/l to categorize a population as iodine-sufficient (World Health Organization et al., 2007).

The daily iodine intake of a population can be estimated based on extrapolation from median UIC (for SAC or adults). For the extrapolation, mean 24-h urine volume (0.0009 l/h/kg for ages 7 – 15 years and about 1.5 l for adults) was estimated and an iodine bioavailability of approximately 92% was assumed, resulting in the following formula: UIC (µg/l) * 0.0235 * body weight (kg) = iodine intake per day (Institute of Medicine et al., 2001). With this formula, a median UIC of 100 µg/l corresponds to an average iodine intake of approximately 150 µg per day in adults (Zimmermann, 2009).

2.4.1.2.3. Infants

Following the reliability of UIC as a biomarker for iodine status in SAC, a WHO Consultation recently proposed that the median UIC could also be a good indicator for infants. However, they admitted that further studies are required to better support this theory (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).
Currently, WHO/UNICEF/ICCIDD define a median UIC of ≥ 100 µg/l as adequate for children below two years of age. No other categories of UIC could be defined due to lack of data (see Table 6) (World Health Organization et al., 2007). In 2007, a Technical Consultation of the WHO recommended that the median UIC value that indicates iodine-sufficiency in infants should be revised based on further studies (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).
Based on their current recommended iodine intake of 90 µg/day, FAO/WHO reported that UIC should be between 150 – 220 µg/l for an iodine-sufficient infant aged 0 - 3 yr (assumed urine volume: 4 - 6 dl/day) (FAO and WHO,

2004). This calculation was made using the formula for adults (see 2.4.1.2.2) and ignores the fact that iodine should be partially retained by infants to build up iodine stores (Delange, 2007). Moreover, the calculated UIC range is much higher than the current cut-off (≥ 100 µg/l) (Zimmermann, 2009).

Delange et al. supplemented 111 Belgian infants aged 6 - 36 months with 90 µg iodine per day and found that their UIC plateaued between 220-240 µg/l after 30 weeks of supplementation (Delange et al., 2001). Their median UIC was 101 µg/l at baseline, which Delange et al. classified as clearly iodine-deficient, especially since it took several weeks until the infants reached a plateau of iodine excretion. This observation was suspected to be due to refilling of iodine stores (Delange et al., 2001).

Dorey and Zimmermann recently performed a study to establish UIC reference values for newborns in Switzerland. They indicated that the current UIC cut-off was probably set too high and suggested a reference range of 70 – 100 µg/l to define iodine sufficiency in the first 4 – 5 days after birth (Dorey and Zimmermann, 2008). They also recognized increasing UIC in newborns from day 0 to day 5 after birth indicating that UIC might be lower in the first few days after birth due to lower breast milk intake (Dorey and Zimmermann, 2008). In our study, this UIC increase should be further examined and new information gathered about UIC in the course of the first year of life.

The main problem in assessing UIC in infants is that they are more difficult to reach than SAC or newborns. Moreover, the urine collection itself is difficult (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). Possible methods for urine collection in infants are clean catch method, urine bags and pads (Liaw et al., 2000). The “pad method” was recently applied in the Swiss newborn study (Dorey and Zimmermann, 2008).

2.4.1.2.4. Lactating women

In lactating women, iodine metabolism, which is altered during pregnancy (Glinoer, 2007), returns to that of non-pregnant women, except that iodine is excreted in breast milk. Therefore, despite having the same iodine intake recommendation as pregnant women, the cut-off for adequate iodine status in

lactating women is ≥ 100 µg/l (= median UIC) (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). Similar to infants, no other categories of UIC could be defined (see Table 6) (World Health Organization et al., 2007).

2.4.2. Alternative methods to assess iodine status in infants

2.4.2.1. Iodine concentration in breast milk (BMIC)

The WHO has not made a recommendation on the level of BMIC which indicates iodine sufficiency as there is no consensus (Zimmermann, 2009).
In a recent publication, Azizi and Smyth (Azizi and Smyth, 2009) reported that in conditions of iodine sufficiency BMIC is between 150 – 180 µg/l based on studies reviewed by Dorea and Semba and Delange (Dorea, 2002; Semba and Delange, 2001). Based on studies reviewed by themselves, Azizi and Smyth indicated that BMIC should be between 100 - 150 µg/l in iodine-sufficient areas (Azizi and Smyth, 2009). Zimmermann reviewed studies on BMIC in iodine-sufficient countries and found medians/means between 50 µg/l and 270 µg/l. He stated, however, that it was difficult to specify the adequate BMIC from this data, as the sample size of the studies was very small (Zimmermann, 2007b; Zimmermann, 2009). Semba and Delange suggested in 2001 that BMIC could be another indicator for the iodine status of a population. This could be the proportion of lactating women with BMIC ≥ 100 µg/l (Semba and Delange, 2001). Bazrafshan et al. used a cut-off of ≥ 50 µg/l for BMIC to define BM as iodine-sufficient in their study in Iran (Bazrafshan et al., 2005). Azizi and Smyth proposed that values > 75 µg/l might be considered as an index of sufficient iodine nutrition (Azizi and Smyth, 2009).

The daily breast milk intake of 6-month-old exclusively breast-fed infants is about 854 ± 118 ml (mean ± SD) (Butte et al., 2002) and 95% of the BM's iodine is assumed to be absorbed (Zimmermann, 2009). Based on these assumptions and the recommended iodine intake of 90 µg/day (World Health Organization et al., 2007), BMIC would need to be at a minimum of 111 µg/l to fulfill the infants' needs (calculation by N Wüst).

A recent study of Boston women found no intrafeed variation in BMIC (Pearce et al., 2007). Kirk et al. found considerable within day and day-to-day variation of iodide concentration in breast milk (Kirk et al., 2007).

2.4.2.1.1. Measurement

Contrary to UIC, the WHO does not recommend a method for the determination of BMIC. Many different methods and methodic variations used for the sample preparation and determination of BMIC exist, which also makes it more difficult to compare different studies.

Hedayati et al. gave a short overview of the various determination methods in use (Hedayati et al., 2007). Two main methodic ways of determination were specified: 1) instrumental methods such as X-ray fluorescence, ICP-MS, polarography, atomic absorption spectrometry and 2) colorimetric methods based on the Sandell-Kolthoff reaction. The instrumental methods require expensive high-tech equipment and are time consuming (Hedayati et al., 2007). In all the methods, the iodine must be released from organic compounds in a first step and interfering substances must be eliminated from the breast milk. Three sample preparation methods exist: alkaline ashing, alkaline digestion and acid digestion. The sample preparation is the critical step as iodine can be lost by volatilization (Haldimann et al., 1998; Hedayati et al., 2007).

In the laboratory of human nutrition at ETH Zurich, iodine was analyzed in cow milk by a modified Sandell-Kolthoff reaction which included an alkali ashing digestion step with potassium hydroxide. However, high iodine losses occurred with this method and this problem has not yet been solved (Richard, 2008). Therefore, this method could not be used for the analysis of breast milk samples in the present study.

The analysis of iodine in human and cow milk has been successfully performed by isotope dilution analysis with ICP-MS at the Swiss Federal Office of Public Health (FOPH, Liebefeld) (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000; Haldimann et al., 2000). ICP-MS has been proven to be a very precise method for iodine

determination in biological samples (Haldimann et al., 2000). A recently ameliorated version of the method, which was already used for analysis of cow milk at FOPH (Crnkic et al., 2006), has been used for analysis of breast milk samples in the present study (for method description see method section).
Several recent studies on BMIC used a method based on ICP-MS for their analysis (see Appendix 4) (Bader et al., 2005; Chan et al., 2003; Dasgupta et al., 2008; Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000; Fernandez-Sanchez et al., 2007).

There is no external control program for BMIC in place. The only possibility is to use cow milk reference material as a control (Gills, 1993). Studies, which used ICP-MS for milk analysis, showed good results measuring the reference material (Crnkic et al., 2006; Fernandez-Sanchez et al., 2007; Haldimann et al., 2005; Sturup and Buchert, 1996).

2.4.2.2. Dietary assessment of iodine status in infants

2.4.2.2.1. Methods

The WHO does not indicate the dietary assessment as a method to determine the iodine status. Only few studies were found which assessed the dietary iodine intake in infants.
A national British survey in 6 – 12-month-old infants (n = 488) used a 7-day unweighed structured food diary to assess total daily iodine intake and iodine intake in different food categories (Mills and Tyler, 1992). Another regional British study assessed daily iodine intake in 8-month-old infants (n = 1131) by a 3-day unweighed dietary record (Noble and Emmett, 2001).
A Dutch study group recently developed a simulation model to estimate dietary iodine intake in a population (1 to ≥ 18yr) based on a 2-day food record. The model included the iodine intake from natural sources, industrially added iodized salt, discretionary added iodized salt and iodine-containing supplements. Finally, the total iodine intake was calculated and statistical modeling for within/between-person variability was performed. The measured urinary iodine excretion values were compared with the calculated iodine intake values from the model and good associations were found (Verkaik-Kloosterman

et al., 2009).

A recent New Zealand study indirectly calculated the daily iodine exposure for non-breast-fed 6 – 12-month-old infants, 1 – 3-year-old toddlers and other age groups by simulating typical diets (14d) and measuring the iodine content in foods (Thomson et al., 2008).

The US Total Diet Study (TDS) has been monitoring food intake for 46 years and regularly calculates the dietary iodine intake of 6 – 11-month-old non-breast-fed infants with the help of specially developed TDS diets and by measuring iodine in foods (Murray et al., 2008).

For adults, some studies developed special iodine questionnaires that contained only questions regarding the intake of iodine rich foods (Leung et al., 2007; Manz et al., 2002).

The US Feeding Infants and Toddlers Study (FITS) assessed dietary intake (not iodine) in 3022 subjects. This study used an interviewed 24-hour dietary recall and a second 24-hour dietary recall in a subsample (n = 703) (Devaney et al., 2004). The 24-hour dietary recall method was chosen as it provided a standardized methodology, minimal respondent burden, detailed brand names as well as types and quantities of consumed foods and beverages. It was assumed that parents are usually familiar with their infant's food intake schedule and know the amount they feed to their infants (Ziegler et al., 2006).

A recent study compared a 24-hour dietary recall with a 3-day weighed food record in 7 – 11-month-old infants and 12 – 24-month-old toddlers. The study found an overestimation in energy intake in 13% of infants respectively in 29% of toddlers by the 24-hour dietary recall method (Fisher et al., 2008). Accordingly, higher macro- and micronutrient intakes were measured with the 24-hour dietary recall. The overestimation of portion sizes in the 24-hour dietary recall was seen as major error source, especially driven by overestimation of dairy and grain food intakes. However, eating patterns (frequency and location) did not differ in the two methods (Fisher et al., 2008).

For the present study, it was necessary to assess the dietary iodine intake of the day before the urine collection was carried out as UIC examines short-term iodine intake. However, it was not possible to inform the subjects about the

dietary assessment before urine collection. Therefore, the dietary questionnaire had to be filled out on the day of sampling. It was also not possible to carry out interviewed questionnaires due to lack of human resources. Thus, a retrospective method with a self-administered questionnaire had to be used. However, detailed data was required to calculate the iodine intake of the infants accurately. Among existing dietary assessment methods (Elmadfa and Leitzmann, 2004; Gibson, 2005), the diet history and the food frequency questionnaire method were considered to be not suitable for infants as their food intake changes constantly during the first year of life. Weighed or unweighed dietary food records are probably the most precise methods to assess dietary iodine intake in infants. However, these methods are prospective, rather time consuming, need clear personal instructions and could lead to changes in infant feeding practices either to make recording easier or to demonstrate good feeding practices (Elmadfa and Leitzmann, 2004; Gibson, 2005). The 24-hour dietary recall is retrospective and usually interviewer based. It is less time consuming than other methods, but it requires good memory of the interviewed subject and the ability to estimate portion sizes accurately. Also in the 24-hour dietary recall, it is possible that respondents report only “good feeding habits” (Elmadfa and Leitzmann, 2004; Gibson, 2005).
In accordance with our study purpose, it was therefore necessary to use a method based on a 24-hour dietary recall, but it had to be self-administered and, hence, well structured in order to help parents to remember as accurately as possible what they fed their infant. It also had to be assumed that parents usually know quite well what and how much they feed their infants (Ziegler et al., 2006).

No data about day-to-day variation of iodine intake in infants were found in literature.

2.4.2.2.2. Estimation of breast milk intake

“The golden standard” for measuring daily breast milk intake is weighing infants before and after each breast-feeding during 24 hours. This method was used, for example, in the German DONALD study (Alexy et al., 1998) and the

Copenhagen Cohort study (Michaelsen et al., 1994).

Two options for estimation of breast milk intake without weighing are given in literature. Two British studies on infant nutrition assessed dietary intake of 6 – 12-month-old infants by a 3-day unweighed dietary record and asked mothers to record number of daily breast-feeds and minutes per feed (Emmett et al., 2000; Mills and Tyler, 1992). These studies used the following method for estimation of breast milk intake. The estimated amount of breast milk per full feed was 135 g for 6 – 7-month-old infants and 100 g for 8 – 12-month-olds (the amounts were estimated based on the study of Paul et al. (Paul et al., 1988)). A feed of 10 minutes or longer was assumed a full feed. For feeds of shorter duration, the amount of BM was calculated proportionally (Emmett et al., 2000; Mills and Tyler, 1992).

In the national US FITS study, dietary intake of infants and toddlers (4 – 24 months of age) was assessed by telephone-interviewed 24-hour dietary recall. In this study, a daily breast milk intake of 780 ml was assumed for exclusively breast-fed infants < 7 months of age. If the infants were fed breast milk and formula, the volume of formula was subtracted from 780 ml to obtain the quantity of consumed breast milk. For infants ≥ 7 months a daily quantity of 600 ml breast milk was assumed and the corresponding volume of consumed formula or cow milk was subtracted from 600 ml (Devaney et al., 2004). The assumed breast milk quantities (780 ml, 600 ml) were estimated from the DARLING study, in which infants were weighed before and after feeding (Heinig et al., 1993). The authors of the FITS study pointed out the problem of overestimating the breast milk intake in infants who already consumed more non-milk foods than other infants (Devaney et al., 2004).

A recent study in 7 – 24-month-old children compared the results of dietary assessment from a single telephone 24-hour dietary recall with a 3-day weighed food record (Fisher et al., 2008). This study used the weighing method for food records and combined both estimation methods mentioned above for the 24-hour recall. For 7 – 11-month-old infants an intake of 600 ml breast milk was assumed and other types of milk were subtracted. For children above 12-months of age a breast milk intake of 29.6 ml (1 fluid ounce) for every 5 min of

feeding was assumed. The evaluation of both questionnaire types revealed that breast milk intake was overestimated by 24-hour recall. However, it was concluded that the extent of the overestimation was small regarding the total sample and that the method used in the 24-hour recall still delivered good estimates (Fisher et al., 2008).
Other studies excluded breast-fed infants from data evaluation. In a study from New Zealand, which assessed dietary intake of 6 – 24-month-old infants using a 3-day weighed food record, breast-fed infants were excluded from questionnaire evaluation as breast milk intake was not quantified (Soh et al., 2002). Breast milk intake was also not assessed in the Euro-Growth study and not quantified for data evaluation (Freeman et al., 2000).

In a WHO publication in 2002, measured daily breast milk intake from several studies was compared. The studies were conducted in developed countries and used the test-weighing method. The mean ± SD daily breast milk intake in these studies was 854 ± 118 ml for 6-month-old exclusively breast-fed infants respectively 612 ± 180 ml for 6-month-old partially breast-fed infants and 497 ± 238 ml for 12-month-old partially breast-fed infants (intake volumes weighted for sample size of studies) (Butte et al., 2002).

2.4.2.2.3. Measurement of iodine content in formula and infant food

Hammer and Andrey recently gave a short overview of published methods for iodine determination in food products. These are based on X-ray fluorescence, spectrophotometry, HPLC, GC, ion-selective electrode (ISE) or ICP-MS (Hammer and Andrey, 2008). In 2007, the “European Committee for Standardization” had adopted ICP-MS as EN15111:2007 for determination of iodine in foodstuffs (European Committee for Standardization, 2007; Hammer and Andrey, 2008). Hammer and Andrey recently compared ICP-MS (internal standard, TMAH extraction; see method section) and ISE by measuring formula products and whole milk reference material. They found that the results were accurate for both methods. However, ICP-MS was more precise. Therefore, they also recommended the ICP-MS technique as international standard for controlling labeled iodine concentration in milk-based nutritional products

(Hammer and Andrey, 2008).

Earlier, Rädlinger and Heumann had already tested an ICP-MS method that was similar to the one used in the present study (isotope dilution analysis with TMAH extraction, see method section) and showed accurate results in measuring iodine in infant food and milk powder reference samples (Radlinger and Heumann, 1998). Sturup and Buchert (Sturup and Buchert, 1996) (standard addition calibration, samples diluted in TMAH/KOH solution) and Fernandez-Sanchez et al. (Fernandez-Sanchez et al., 2007) (standard addition, digestion with ammonia solution) measured formula milk samples with ICP-MS. They showed good accuracy of the method by measuring the certified iodine concentration of milk powder reference samples (Fernandez-Sanchez et al., 2007; Sturup and Buchert, 1996).

Haldimann et al. measured iodine in Swiss foods (Haldimann et al., 2005) and in infant formulae (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000) using ICP-MS (isotope dilution analysis with nitric acid digestion). They found that the method was accurate according to the results of reference materials and in comparison with measurement by neutron activation analysis (Haldimann et al., 2005; Haldimann et al., 2000). For the present study, a modification of Haldimann's method was applied (the same as used for the breast milk). This modification also showed accurate results by determination of certified iodine concentration in milk powder reference material (Crnkic et al., 2006). A description of the isotope dilution ICP-MS method with TMAH extraction is given in the method section (chapter 3.6.2).

Reference material is available for infant formula (Wise and Watters, 2007), but not for cereal-based infant food.

In 1999, the Swiss Federal Office of Public Health measured iodine in Swiss formula products (n = 31, bought in 1997 and 1999) to check if the minimum level of required iodine was present. 13% of the products (one on cow milk basis and three on soy milk basis) had an iodine content below the required minimum level (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000). Some of the measured iodine values were as much as 10 times lower than the labeled value and others were as much as

five times higher (unpublished data, personal communication M. Haldimann).
A US study also compared labeled with measured iodine contents in eight formula products (spectrophotometrical method). Slightly higher iodine contents were measured in the samples compared with the labeled contents. In two samples a four to seven times higher iodine content was observed (Pearce et al., 2004).

2.5. Urinary iodine concentration in infants – previous studies

No representative Swiss studies on UIC in infants are available. In fact, only a few studies at all have examined UIC in infants (excluding newborns) worldwide.

A list of studies which examined UIC in infants in the age range of our study infants is given in the Appendix 3. The list includes data on country, date and level of study (local, regional, national), studied age group, sample description (e.g. gender, sub-groups), sample size, median/mean UIC [µg/l], prevalence below/above specified UIC levels [%], UIC of mothers [µg/l] (if available), UIC analysis method, comments concerning the study and classification of iodine intake in the country (see below).
The studies were carried out or published between 1989 and 2009. In total, 23 studies were found (all in Pubmed), which were carried out in 19 different countries. The majority were performed in Europe (12 studies: one in Switzerland, Armenia, Austria, Belgium, Czech Republic, Italy and Turkey, two in Germany and three in France), followed by the Western-Pacific area (4 studies: one in Malaysia and New Zealand and two in China). Studies in two countries of the Americas (Mexico and Venezuela), Africa (Nigeria and Reunion Island) and South-East Asia (India and Indonesia) were found and one in an Eastern-Mediterranean country (Sudan). In Switzerland, only one small regional study was carried out in our studied age group (Als et al., 2000b), see also chapter 2.7 “Iodine in Switzerland”.
Just one study (in Indonesia) included only infants of our studied age groups/range (Wijaya-Erhardt et al., 2007). However, the study included only

boys and it was an intervention study (data taken from baseline). All other studies also included either younger or older children than our target group. In most of the studies the exact age of the participating children was not indicated or UIC values were only given for a wider age range or for the full sample.
Only three studies were performed on a national level, in Armenia (Rossi and Branca, 2003), in Czech Republic (Bilek et al., 2005) and in Germany (Thamm et al., 2007). The other studies were carried out on a local or regional level. Sample sizes ranged from 18 to about 2500. Most studies, however, had small sample sizes.

The lowest measured median UIC value was 10.6 µg/l in 0- to 6-year-old Malaysian children living in a goitrous area (Foo et al., 1996). The highest median UIC was found in 1- to 12-month-old French infants 328 µg/l (Pouessel et al., 2008).
In seven studies, a median/mean UIC < 100 µg/l was found either in the full sample or in a specified subgroup (Akanji et al., 1996; Elnour et al., 2000; Foo et al., 1996; Manz et al., 1993; Rapa et al., 1999; Skeaff et al., 2005; Thamm et al., 2007).

Only three studies looked at differences in UIC depending on infant feeding practices (Manz et al., 1993; Pouessel et al., 2003; Skeaff et al., 2005).

In two studies, it was clearly stated that UIC of matched pairs of mother and infant were examined (Akanji et al., 1996; Gupta et al., 2006). Some studies also looked at women of childbearing age or lactating women but it was not clear whether these women were the mothers of the examined infants in the studies (Foo et al., 1996; Jaffiol et al., 1997; Rapa et al., 1999; Wang et al., 2009; Yan et al., 2005).

The studies measured iodine in spot urine samples. None of the studies indicated that pads were used for urine collection in infants. Most of the studies used a method based on the Sandell-Kolthoff reaction for UIC analysis.

Appendix 3 further includes the WHO classification of iodine intake of the above

mentioned countries (de Benoist et al., 2008; WHO Nutrition, 2008a; WHO Nutrition, 2008b). Twelve studies were performed in countries which were classified as having adequate or more than adequate iodine nutrition (Switzerland, Austria, Czech Republic, Germany, Mexico, Venezuela, Nigeria, India, Indonesia and China). One study was carried out in a country with "excessive" iodine intake (Armenia). In 11 of these studies a median/mean UIC ≥ 100 µg/l was measured in the infants (Switzerland, Armenia, Austria, Czech Republic, in one of the German studies (Thamm et al., 2007), Mexico, Venezuela, India, Indonesia, China). Nine studies were performed in countries that were classified as having insufficient iodine nutrition (Belgium, France, Italy, Turkey, Sudan, Malaysia and New Zealand). Only in three of these studies was a median/mean UIC < 100 µg/l measured in the infants (Italy, Malaysia and New Zealand). Reunion Island was not classified by the WHO (WHO Nutrition, 2008b).

2.6. Breast milk iodine concentration – previous studies

In 2001, Semba and Delange reviewed existing studies on BMIC that were performed between 1926 and 1999 (Semba and Delange, 2001). In those studies, very low mean BMICs were found in women living in goitrous areas (9 – 32 µg/l) and in women with goiter (13 – 18 µg/l). Summarized BMICs from areas with a salt iodization program were higher ranging from 90 – 150 µg/l. The authors pointed out that most of the studies had too small a sample size to determine adequate iodine intake and to interpret the data (n = 2 - 143). They suggested that the well baby visit/vaccination appointment of the child (at a pediatric practice or clinic) would be a good occasion to come into contact with women and to select them for studies (Semba and Delange, 2001).

Another review was performed by Dorea (Dorea, 2002). In those studies, BMIC ranged from 5 µg/l in Ethiopia to 660 µg/l in Japan (the Japanese population is known to have a high seaweed intake, which is rich in iodine). In studies which were performed in a goitrous area, BMIC was between 17.5 and 40 µg/l. No sample size was given for the studies (Dorea, 2002).

The most recent review was done by Azizi and Smyth in 2009 (Azizi and Smyth,

2009). This review added four studies performed between 2005 and 2007 and included only studies with a sample size > 40. A recent study in China had the largest sample size (n = 710) (Yan et al., 2005). The four new studies were all conducted in regions with a salt iodization program and measured a median BMIC between 117 and 155 µg/l (Azizi and Smyth, 2009).

In Switzerland, four small regional studies on BMIC have been performed so far. See chapter 2.7 “Iodine in Switzerland” and Appendix 4: Studies on BMIC – in Switzerland and worldwide (selection) - conducted between 1998 and 2009.

In Appendix 4 an overview of studies on BMIC which were performed between 1998 and 2009 is given. This is not a complete overview of studies in this time frame, but a selection. The following information about the studies is listed: country, date and level of study, age of women, description of BM samples, sample size, median/mean BMIC [µg/l] or [µg/kg], BM analysis method, comments and the country’s classification of iodine intake (WHO Nutrition, 2008a; WHO Nutrition, 2008b). If available, median/mean UIC of women and their infants was also added.
Besides the four Swiss studies, 17 studies are listed, which were conducted in 9 different countries. Five were performed in Europe (in Belgium, Denmark, Germany (two) and Spain), five in the USA, two in Iran, two in China, one in Australia and one in New Zealand. All studies were conducted either on a local or a regional level. Most studies had a small sample size (n = 14 - 710). Only in five studies was it stated that the BM was mature (> 12^{th} day postpartum). All other analyses were done in colostral or transitory milk. The lowest BMIC was measured in New Zealand (mean 22 µg/l) (Skeaff et al., 2005), the highest in China (median 163 µg/l) (Wang et al., 2009). New Zealand is classified by the WHO as iodine insufficient and China as more than adequate (WHO Nutrition, 2008a).
In the countries that the WHO classified as iodine-sufficient (iodine nutrition adequate or more than adequate: Switzerland, Germany, Spain, USA, Iran, Australia and China) (WHO Nutrition, 2008a), the studies measured a median/mean BMIC between 43 and 163 µg/l. In the countries that the WHO

classified as iodine-deficient (iodine nutrition insufficient: Belgium, Denmark, New Zealand) (WHO Nutrition, 2008a), the studies measured a median/mean BMIC between 22 and 78 µg/l.

The studies used various different methods for analysis of BMIC; some did not indicate the method. Five studies used a method based on ICP-MS.

Eight studies also measured UIC in the women (Bazrafshan et al., 2005; Chan et al., 2003; Dasgupta et al., 2008; Laurberg et al., 2004; Ordookhani et al., 2007; Pearce et al., 2007; Wang et al., 2009; Yan et al., 2005) and seven studies included UIC of the infants or newborns (Ciardelli et al., 2002; Hoang Truong et al., 1997; Laurberg et al., 2004; Ordookhani et al., 2007; Skeaff et al., 2005; Wang et al., 2009; Yan et al., 2005).

2.7. Iodine in Switzerland

Before the introduction of iodized salt, Switzerland was severely iodine-deficient due to its geographical situation in the iodine-deplete Alp region of Europe (Clugston and Hetzel, 1994; Zimmermann, 2008c). Many people had goitres; some infants were born as cretins (Bürgi et al., 1990). In 1922 a Swiss Goiter Committee was formed and recommended iodization of Swiss salt to cantons first at a quite low level from 1.9 to 3.75 mg/kg salt and sale of it on a voluntary basis (Bürgi et al., 1990; Zimmermann, 2008c). By 1952 iodized salt was available nationwide and the level of iodization was adapted continuously (see Table 7) (Bürgi, 2005; Bürgi et al., 1990). The former Goiter Commission has now been replaced by the Fluorine-Iodine Commission of the Swiss Academy of the Medical Sciences which meets annually to discuss further adaptations of salt iodization (Bürgi, 2005). The last elevation of salt iodization was carried out in 1998 to the current level of 20 mg/kg (Bürgi, 2005) because in 1997 it was recognized that UIC in SAC had started to fall (Zimmermann et al., 1998).

Table 7: Salt iodine concentration (ppm) and UIC in SAC in Switzerland from 1923 to 2004 (Bürgi, 2005)

Date	Before 1924	1924-61	1962-79	1980-97			1998-	
Salt iodine concentration (ppm)	0	3.75	7.5	15			20	
Year of iodine survey	1932	No data	1974-79	1981-88	1994	1997	1999	2004
Urinary iodine concentration(µg)	18[1]	No data	79-93[2]	127-160[2]	118[3]	96[3]	115[3]	141[3]
	a		b	b	c	c	c	c

[a] µg/day; [b] µg/g creatinine; [c] µg/l

Many surveys showed that the iodization of salt has been the reason for eradication of goitre and cretinism in Switzerland (Bürgi et al., 1990). Over 90% of Swiss households use iodized salt, which is provided by only two producers (Schweizer Rheinsalinen and saline de Bex) (Bürgi et al., 1990; Zimmermann et al., 2005).

Since 1999, an iodine monitoring program on UIC of SAC and pregnant women is performed every five years in Switzerland (Bürgi, 2005). In the first two national monitoring studies in 1999 and 2004, the median UIC of SAC showed a sufficient iodine status (115 respectively 141 µg/l). Additionally, the frequency of UIC values < 50 µg/l in SAC showed iodine sufficiency (8.5% respectively 5%). Pregnant women had a marginal status in 1999 (138 µg/l) but had a clearly sufficient status in 2004 (249 µg/l) (Hess et al., 2001; Zimmermann et al., 2005). Newborn TSH levels showed iodine sufficiency in both monitoring studies (< 3% of newborns with TSH > 5 mU/l) (Hess et al., 2001; Zimmermann et al., 2005).
Based on these study results and the long-standing Swiss salt iodization program which covers nearly all households (Zimmermann, 2008c), Switzerland is categorized as a country with optimal iodine nutrition by WHO (Andersson et al., 2007; de Benoist et al., 2008).
Parallel to our infant study, the next national monitoring study on iodine status in SAC and pregnant women was started in 2009. First results showed a sufficient iodine status for school age children (n = 916) with a median UIC of 120 µg/l. Pregnant women seemed to have a marginal sufficient iodine status (interim analysis, n = 318) with a median UIC of 151 µg/l (personal communication I Henschen and A Piacenza, ETH Zurich, 2009).

Between 2005 and 2007, a nationally representative study to set reference values for spot urinary iodine concentrations in newborns was conducted. Two urine samples were collected from newborns (on day 0 – 5, n = 634) and their median UIC showed a value of 77 µg/l (Dorey and Zimmermann, 2008). Even though the value was below the current WHO cut-off for iodine sufficiency (≥ 100 µg/l), it was stated as sufficient because TSH levels in the newborns showed iodine sufficiency (Dorey and Zimmermann, 2008). Moreover, pregnant

women had a sufficient iodine status in the monitoring study which was performed in Switzerland in 2004 (Zimmermann et al., 2005). The authors suggested that the current WHO cut-off might be set too high for newborns (Dorey and Zimmermann, 2008).
In three earlier regional Swiss studies on newborns conducted in 1984, 1985 and 1994 (n total = 237), similar median UIC values were found (62 µg/l, 70 µg/l, 66 µg/l) (Hoang Truong et al., 1997).

No study has analyzed UIC in 6- and 12-month-old infants in Switzerland, except one regional study in 1997 which looked at 31 children aged between 0 and 5 years (Als et al., 2000b). No information about the exact age of the children was given. Their median UIC was 108 µg/l.

Iodine status in women was investigated in a regional Swiss study in 1997 (Bernese region). The median UIC of women from 13 – 20 years (n = 13), 21 – 35 years (n = 31) and 36 – 50 years (n = 35) was 90 µg/l, 91 µg/l and 93 µg/l. In this study SAC (6 – 12 yr) had a UIC of 110 µg/l (n = 47) (Als et al., 2000b).
A longitudinal study was conducted between 1996 and 2000 including 11 women between 35 – 65 years of age. UIC before and after increase of salt iodization in year 1998 was measured (2128 urine samples). A median UIC of 92 µg/l was measured before the increase of salt iodine level and a median of 93 µg/l was measured after the increase. In comparison, children (3 – 15 yr, n = 12) had a median UIC of 141 µg/l before salt iodine increase and after 1998 their median UIC increased to a value of 162 µg/l (Als et al., 2004).
Two recent Swiss studies on UIC in non-pregnant, non-lactating women showed a median UIC of 79.1 µg/l in women from Zurich area (n = 567, 18-42 yr) (personal communication, M Andersson, 2007) and a median UIC of 81.0 µg/l (n = 144) in women from several regions in Switzerland (personal communication, M Kammermann, 2009).

No studies on UIC in lactating women have been performed in Switzerland.

Four small regional studies on the iodine concentration in breast milk have been carried out in Switzerland: 1992/93 in Berne median BMIC 98 µg/l (n = 38, 5th –

12th day after birth); 1993/94 in Basel median BMIC 82 µg/l (n = 23, 5th – 12th day after birth); 1998/99 in Basel median BMIC 68 µg/l (n = 52, > 12th day after birth, ICP-MS analysis method, personal communication M. Haldimann) (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000). Another study was carried out in 1994 in Solothurn with a mean BMIC of 78 ± 59 µg/l (n = 30, 3 – 6 days after birth) (Hoang Truong et al., 1997).

No direct dietary assessment to determine the iodine intake in the Swiss population or in one of our examined population groups has been performed. Only per capita exposure to iodine has been estimated based on the food consumption statistics (Camenzind-Frey et al., 2005; Haldimann et al., 2005; Jacob, 2005; Schlotke and Sieber, 1998). In the most recent estimation of Haldimann et al., who also measured the iodine contents in Swiss foods, it was estimated that the overall dietary iodine exposure to (average) consumers was 140 µg/day. The use of iodized kitchen salt was excluded from the estimation (Haldimann et al., 2005).

3. SUBJECTS & METHODS

3.1. Study population

The study was conducted in 6- and 12-month-old infants (± 6 weeks) and their mothers. The study subjects were enrolled at pediatric practices.

The inclusion criteria were: 1) Full-term birth of the infant (between the 38th and 42nd week of pregnancy); 2) No infantile or maternal history of recent thyroid disorders; 3) Intact health of infant; 4) No application of iodine-containing disinfectants in the infant within the last month and no use of (iodine-containing) contrast media in the infant since birth; 5) Mother resident in Switzerland for at least 12 months before and since the infant's birth (together with the infant); 6) No intake or injection of (iodine-containing) radiologic/CT-contrast media or drugs (amiodarone [anti-arrhythmic]) by the mother since pregnancy.

Based on earlier studies in Switzerland that were carried out in school age children, pregnant women and newborns (Dorey and Zimmermann, 2008; Hess et al., 2001; Zimmermann et al., 2005) (see chapter 2.7.) it was assumed that the infants should be iodine-sufficient, which is an essential condition to be fulfilled to develop reference values. Nevertheless, to prove this assumption, iodine status in mothers was also assessed by measuring UIC and BMIC.

3.2. Study design

The study was designed as a national cross-sectional survey. A 2-stage population-based cluster sampling was performed to obtain a representative sample of infants. In the first stage, 20 pediatric practices (clusters) had to be selected distributed throughout the seven "greater Swiss regions" (Swiss Federal Statistical Office, 2008a). The selected number of pediatric practices per region had to be proportional to the number of annual births in the regions (% live births in relation to all annual births in Switzerland) (see Table 8). In the second stage, pediatricians at the selected practices had to enroll infants and their mothers.

For the selection, pediatricians were initially contacted by letter and invited to participate in the study (addresses from "Forum für Praxispädiatrie", "Swiss pediatric society" and phone book). Out of all positive answers, a convenience

selection of the pediatric practices (single or group practices) was made according to the required number of practices per “greater Swiss region” (see above and Table 8) with specific regard to the practices with the greater number of infants visiting the practice per week. This method was chosen in order to reach the required number of infants within good time under the assumption that the iodine intake is uniform across the country (Hess et al., 2001; Zimmermann et al., 2005).

Table 8: Population data, live births and number of pediatric practices per greater Swiss region

Greater Swiss regions	Swiss population (31.12.2006) [a]	% population per region	Live births (2006) [a]	% live births per region	Required clusters (practices) per region
Total	**7'508'739**	**100**	**73'371**	**100**	**20**
Lake Geneva region	1'389'988	18.5	14'868	20.3	**4.1**
Espace Mittelland	1'703'966	22.7	15'909	21.7	**4.3**
Northwestern Switzerland	1'026'801	13.7	9'388	12.8	**2.6**
Zurich	1'284'052	17.1	13'533	18.4	**3.7**
Eastern Switzerland	1'065'253	14.2	9'659	13.2	**2.6**
Central Switzerland	713'828	9.5	7'222	9.8	**2.0**
Ticino	324'851	4.3	2'792	3.8	**0.8**

[a] Source: (Swiss Federal Statistical Office, 2006)

The enrollment of mother-infant pairs at the pediatric practices took place at the “routine check-up”/vaccination occasion of the infants. The routine check-ups/vaccinations are not mandatory in Switzerland, but they are covered by the health insurance. 85% to 95% of infants and children in Switzerland are vaccinated depending on the kind of vaccination (Lang et al., 2008).

At each pediatric practice, 30 mother-infant pairs of each age group had to be enrolled. The pediatricians were allowed to perform a convenient sampling of the study subjects, but were asked to enroll every eligible subject when possible. As the pediatric practices had varying numbers of infants per week, no fixed timeframe was defined to reach the required number of subjects at the beginning of the study.

The study was approved by the ethical committee of the Swiss Federal Institute of Technology Zurich (ETH) [reference number EK 2008-08]. The participating mothers provided written consent before the study started and had the option to withdraw from the study at any time. Study participants and doctors were not remunerated for study participation.

The study was financed by the “Swiss Foundation of Nutrition Research” of the ETH Zurich, Switzerland. The obtained funding was dedicated to material costs for the study. The Laboratory of Human Nutrition (ETH, Zurich) provided equipment/chemicals for urine sample analysis and for breast milk analysis, equipment/chemicals were supplied by the Swiss Federal Office of Public Health (FOPH, Liebefeld).

3.3. Sample size calculation

The estimation of the sample size was based on currently available data on iodine-sufficient infants (Zimmermann, 2007b). A standard deviation (SD) of UIC of 40 µg/l was used to estimate the length of the total reference range for UIC (4 x SD). The required relative precision at the upper and lower limit of the reference range was specified as 3% of this range. The required sample size was calculated using the formula: $n > 7.14 \times \sigma^2 / \varepsilon^2$, where σ^2 is the variance of UIC and ε^2 the specified precision for the 97.5th percentile being estimated (Armitage et al., 2002). Based on this calculation, a sample size of at least 1200 infants was required to obtain the specified precision level. This calculation was originally meant for a study population including infants from 6 - 12 months of age. Due to the fact that healthy infants visit the pediatric practice only at 6 and at 12 months of age (and not in between) for routine check-up/vaccination, it was decided to split the sample size into two age groups and include 600 infants of each age group (6 and 12 months).

3.4. Data collection

3.4.1. Overview

The required personal data of infants and mothers (including infant feeding practices) were gathered using individual registration forms. A spot urine sample was collected from each infant and each mother and in addition, a breast milk sample was obtained from lactating mothers. Furthermore, a dietary questionnaire (self-administered), which assessed the infants' food intake on the day before sample collection, was filled out by the mothers on the sampling day (retrospective) and a second dietary questionnaire was filled out three to four days afterwards.

3.4.2. Study procedure at pediatric practices

All participating pediatric practices were visited once by the study coordinator of the ETH to instruct them personally about the study procedure and to give them written study instructions (see Appendix 5 - German).

The eligible mothers were informed about the study at the pediatric practice by a written information sheet (see Appendix 6 - German) which was handed out to them at the day of the routine check-up or during an earlier visit. The information sheet outlined the study purposes and objectives, the study procedure, the required inclusion criteria and included information about the risks, financing, insurance, withdrawal option, the anonymity of the data and the study contacts. Mothers were also orally informed about the study by the pediatrician or the pediatrician's medical assistant. The pediatrician ensured the fulfillment of the inclusion criteria and the subscription of the consent form.

An individual registration form for each mother-infant pair was filled out by the pediatrician (see 3.4.3 Individual registration form and Appendix 7 - German). Mothers could optionally provide their phone numbers so that ETH could contact them for any further questions. It was also possible to participate anonymously in the study. The registration and consent form always had to be filled out at the pediatric practice.

The practices had the option either to collect the samples in the practice or to instruct the mother about sample collection at home. If the sampling was done

at home, the mother additionally received a detailed information leaflet explaining in simple instructions how to collect the samples (see Appendix 9 - German). Mothers were advised to do the sample collection if feasible on the same day they visited the pediatric practice or as soon as possible after the visit. A phone number of ETH was indicated on the leaflet for any questions.
The dietary questionnaires were handed to the mothers with a short explanation on the purpose and usage (see also 3.4.8).
Ten minutes were estimated in total for registration and instruction of each participating mother-infant pair at the pediatric practice.
Each practice listed their study participants on a practice registration form in which the place of sample collection was also documented.
All required study materials and forms were provided to the pediatric practices/mothers. They were pre-labeled and packed in plastic bags (one bag per mother-infant pair) to allow an easy and rapid handling for the pediatric practices and for the mothers.
After the study was completed by a pediatric practice, the doctor received a short questionnaire with some questions about the selection of mother-infant pairs and the study procedure at the practice (see Appendix 10 - German).

3.4.3. Individual registration form

On the individual registration form, fulfillment of the inclusion criteria (see 3.1.), subject characteristics and infant feeding practices were documented from each mother-infant pair (see Appendix 7: Individual registration form – German).

3.4.3.1. Subject characteristics

The following subject characteristics were registered.

Infant: gender, date of birth, mode of delivery, body weight and length.
Weight and length were measured in the pediatric practice on the day of study registration using routine measuring instruments of the practice. The weight was recorded to the nearest 10 g, the length to the nearest 0.5 cm.

Mother: place of residence, date of birth, body weight and height (indication

made by mother), nationality, intake of vitamin/mineral or algae/kelp supplements, use of iodized salt.

3.4.3.2. Infant feeding practices

The following questions were included on the individual registration form to obtain an overview of the feeding practices of the infants (in case a mother had not filled out the dietary questionnaire):

- Ever/still breast-fed (exclusively, predominantly or partially; definition according to WHO et al. (WHO et al., 1998; WHO et al., 2008)) - times per day
- Ever/still formula-fed (breast milk substitutes including infant-formula, follow-on formula, junior milk) - times per day/week/month
- Already fed (semi-)solid foods/nutritious fluids (excl. fruit juices, sweetened drinks) in addition to or instead of breast milk/formula; either especially prepared for the infant or from the family table - times per day.
  In this diploma thesis, these meals were named complementary/family foods (CF/FF).
- Kinds of (semi-)solid foods/nutritious fluids (milk-cereal porridge/bottle with FM or cow milk, diluted/undiluted cow milk (w/o cereals), vegetable-carbohydrate-(meat)-meals (w/o milk), fruit-(cereal)-meals (w/o milk)) - times per day/week
- Already fed family food (= food given from the family table)
- Use of (iodized) salt in home-made/ready meals for the infant

Some doctors addressed questions to us about the part on infant feeding after the study instruction. Therefore, we provided an explanation sheet to all doctors; see Appendix 8 (German).

3.4.3.3. Comparison with WHO child growth standards

The height and weight of the study infants were compared with the WHO child growth standards. These were developed from the growth data of 8440 healthy breastfed infants and young children from diverse ethnic and cultural backgrounds living in an environment that promotes normal growth in 6 different

countries (WHO Multicentre Growth Reference Study Group, 2006). Based on weight, length, age (birth date – study registration date) and sex of the study infants, the following mean z-scores were calculated with the aid of the "WHO Anthro" Software (WHO, 2009): Weight-for-age, length-for-age, weight-for-length, BMI-for-age. Based on this, we identified the percentage of underweight (weight-for-age < -2SD (= z-scores) of the reference median), stunting (length-for-age < -2SD of the reference median), wasting (weight-for-length, BMI-for-age < -2SD of the reference median) and overweight (weight-for-length, BMI-for-age > +2 SD of the reference median) of the studied population in comparison with the WHO reference population. The reference population is expected to have infants with z-scores < -2 and > +2 with a prevalence of 2.3% (WHO Expert Committee on Physical Status, 1995; WHO Statistical Information System, 2008; World Health Organization, 2008).

3.4.4. Spot urine sample of infants

A spot urine sample of 3 ml was collected from each participating infant using the "pad collection" method (Euron Uricol Set, sterile, art. no. 310019, Sterisets Int. B.V., Oss, NL). This method was chosen because it is simple, fast and not painful or uncomfortable for the infant (Crofton et al., 2008; Liaw et al., 2000). The method was successfully used for urine collection in the Swiss newborn study (Dorey and Zimmermann, 2008).

The urine sample was collected at the pediatric practice by the pediatrician/medical assistant or at home by the mother (as described above).

Collection procedure: The infant's genital area was cleaned without using any cream or powder. The pad was then placed in the nappy which was turned inside out to make sure that the urine was not absorbed by the nappy. The pad was regularly checked if it had become wet. The mother was instructed to breast-feed the infant or to give it something to drink to encourage urination. If the pad became soiled with feces, it was replaced by the second pad. As soon as the pad was wet with urine, it was removed and laid on a clean surface, with the wet side facing up. With a syringe (in the Uricol set; positioned at 45° on the pad) the urine was extracted from the pad by slowly pulling up the plunger and

emptying the urine into the specially labeled transport-tube (PS 15 ml, art. no. 2276, Semadeni AG, Switzerland). This procedure was repeated until the tube contained at least 3 ml urine (mark on the tube).
An illustration of the urine extraction was provided to the mothers, see Figure 4.

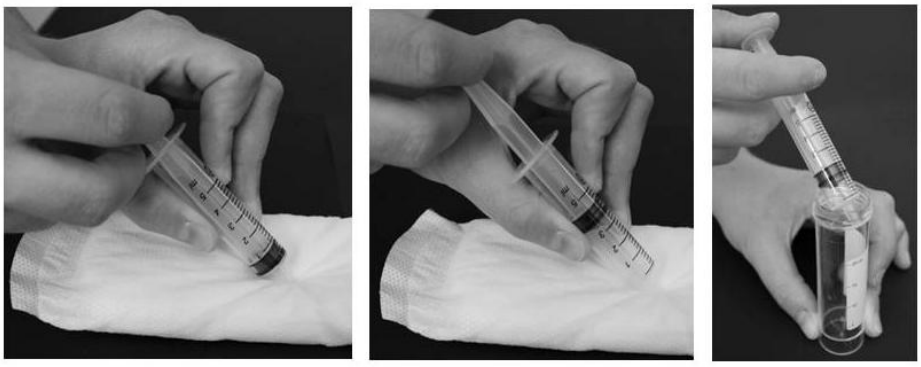


Figure 4: Illustration of “pad collection method”

The doctors were told that it was very important to avoid direct or even indirect (e.g. open disinfectant close to the sample) contact of iodine-containing disinfectants with the urine samples.

3.4.5. Spot urine sample of mothers

A spot urine sample of 10 ml was collected from the mothers either at the pediatric practice or at home.
The urine was collected with a urine collection cup (PP 125 ml, art. no. 5664, Semadeni AG, Switzerland) and 10 ml were filled into a specially labeled transport-tube (PS 15 ml, art. no. 2276, Semadeni AG, Switzerland).

3.4.6. Breast milk sample

A breast milk sample of 10 ml was obtained from breastfeeding mothers either at the pediatric practice or at home. The mother had the option to collect the breast milk sample either manually or by breast-pump. A description of the method for manually collecting breast milk was handed out to the mothers (provided by the “Swiss Foundation for the Promotion of Breastfeeding”), see Figure 5.

Mothers were instructed to discard the first few milk drops because of possible differences in composition. Therefore, disposable bra pads (Medela AG, Medical Technology, Switzerland) were provided. Then, 10 ml of breast milk was collected in a collection cup (PP 125 ml, art. no. 5664, Semadeni AG, Switzerland) and filled into a specially labeled transport-tube (PS 15 ml, art. no. 2276, Semadeni AG, Switzerland).

Figure 5: Description of the method for manual breast milk expression - German
Source: (Swiss Foundation for the Promotion of Breastfeeding, 2008) (with permission)

3.4.7. Storage and transport of samples

In the pediatric practices urine and breast milk were kept refrigerated at 2 to 8°C until they were transported to ETH Zürich (to avoid unpleasant odor). The samples were sent to ETH by (priority) mail enclosed in plastic bags and in special soft envelopes on a weekly basis. If the samples were collected at home, mothers were asked to keep them refrigerated and to send them to ETH as soon as possible. The pediatric practices/mothers were provided with all transport material (pre-stamped). As it was shown that there is no iodine loss in well sealed samples (Sullivan et al., 2000), it was not problematic to transport the samples to ETH at ambient temperature.

When arriving at ETH, the samples were instantly refrigerated at 4°C. Within the same or next day they were aliquoted into Eppendorf tubes (2 x 1.5 ml for urine,

5 x 2 ml for breast milk; Clicklock Microcentrifuge tubes, Simport, Canada) and frozen at -25°C until analysis.

If breast milk samples became coagulated during transport, the tubes were placed in an ultrasound bath (Fisher Scientific FB 15061, Germany) for 10 to 15 minutes to dissolve the coagulation and were subsequently aliquoted.

3.4.8. Dietary questionnaires and social demographics of mothers

More detailed information about the structure and development of the dietary questionnaire is given in chapter 3.7. “Dietary assessment” and the questionnaire is shown in Appendix 11 (German).

The first dietary questionnaire was filled out by the mothers either directly at the pediatric practice or at home and sent to ETH. At the practice, a folder with brochures of commercial infant food products was provided to help mothers remember the correct product names. It was emphasized in the questionnaire that the mother should try to remember the food intake of her infant as precisely as possible. If she had not spent the day before sample collection together with her infant, she was asked to fill out the questionnaire on the next possible day. If the sample collection took place at home, the mother was instructed to fill out the first questionnaire at the day of sample collection.

The second dietary questionnaire had to be filled out at home three to four days after sample collection and was sent to ETH in a pre-stamped envelope.

The pediatrician had the option to leave out the dietary questionnaires if the mother seemed to be incapable of completing the questionnaires because of poor language skills.

The questionnaire also included sociodemographic questions about the mother: age, nationality, canton of residence, number of children, single parent, smoker, professional activity and education/profession. Contact data of mother for further inquiry of ETH was optional.

Mothers’ education and profession were classified in nine super groups of occupation according to the “Schweizer Berufsnomenklatur, SBN 2000” (Bundesamt für Statistik, 2000) (see Appendix 14). They were also categorized

according to the UNESCO “International Standard Classification of Education” (ISCED) levels (UNESCO Institute for Statistics, 2006). These levels (see Appendix 14) are also used by the Swiss Federal Statistical office to classify professional education in Switzerland (Bundesamt für Statistik, 2007/2008).

3.4.9. Formula and infant food product samples

The labeled iodine concentration of formula and commercial infant food products was compared with the analyzed concentration. Formula products (infant formulae 2x, follow-on formulae 9x, soy-based formula 1x; all instant powders) and baby cereal products (10x; 9 instant powders, 1 ready-to-eat product) of the eight most common infant food brands in Switzerland were bought in several retail stores, pharmacies and health food shops located in Zürich, Berne and Sargans. We made a convenient selection of each available brand on the Swiss market and particularly of the products that were frequently consumed by the infants of our study (as indicated in the dietary questionnaires).

3.5. Time schedule

The estimated time schedule for the study was:

- April to July 2008: Study preparation and recruitment of pediatric practices
- August 2008 to August 2009: Data collection
- January 2009 until study completion: Ongoing data input and laboratory analysis
- September to November 2009: Statistical analysis and data evaluation

3.6. Laboratory analyses

3.6.1. Urinary iodine concentration - modified Sandell-Kolthoff method

The analysis of the urinary iodine concentration (UIC) was performed by a modified Sandell-Kolthoff method at the Laboratory of Human Nutrition, Institute of Food Science and Nutrition, ETH Zürich.

3.6.1.1. Principle

This colorimetric method was first described in detail by E.B. Sandell and I.M. Kolthoff (Sandell and Kolthoff, 1937) and modified by Pino et al. (Pino et al., 1996).

The method is based on the reduction of cerium(IV) ion *(yellow)* to the colorless cerous(III) ion in the presence of arsenious acid (Sandell and Kolthoff, 1937):

$$2\ Ce^{4+} + As^{3+} \rightarrow 2\ Ce^{3+} + As^{5+}.$$

This reaction proceeds slowly in the absence of a catalyst in dilute sulfuric acid medium at room temperature. If only a few micrograms of iodide are added, it causes a decolorization of the solution from yellow to colorless within a few minutes. No other relevant elements were found which also distinctly catalyze the reaction (the only elements found were osmium, ruthenium). Iodine must be present as iodide (I^-) to catalyze the reaction (Sandell and Kolthoff, 1937). Iodide is also the main chemical form of iodine in urine (Gnat et al., 2003). If iodine is present as iodate (IO_3^-), this is reduced to iodide in the presence of sulfuric acid and arsenite solution (Sandell and Kolthoff, 1937). For the measurement of the iodine concentration, the ceric solution (Ce^{4+}) needs to be added to an excess of arsenite solution (As^{3+}) which contains the iodide. The amount of iodide is than directly proportional to the rate of decolorization. The reaction must take place in a fairly acid medium (dilute sulfuric acid) to prevent the precipitation of ceric arsenate (Sandell and Kolthoff, 1937).

This original method had no digestion step so that interfering substances in urine (such as oxidizing and reducing substances) could affect the reaction (Sandell and Kolthoff, 1937). Therefore, Pino et al. modified the method in order to obtain exact measurements by eliminating interfering substances and the

natural color of urine. For this purpose, urine samples are digested by ammonium persulfate, an oxidizing agent, before the colorimetric analysis is performed (Pino et al., 1996).

3.6.1.2. Acid-washing

To avoid iodine contamination, all glassware required for the analysis was acid washed with the following procedure: The objects were filled in a PE-container and washed three times with nanopure water (18MΩ, Nanopure Cartrige System, Skan AG, Switzerland). Concentrated nitric acid (HNO_3 (65%) pro analysi, Merck, Germany) was diluted with nanopure water to a concentration of 22% and filled in the container with the objects. After shaking the container over night on a lab shaker (K5501, IKA Labortechnik, Germany) the acid was emptied out and the objects washed three times with nanopure water. Then the container was again filled with nanopure water and shaken over night. After that, the objects were again washed three times with nanopure water and put in an oven (WTC Binder, Germany) at 65°C for drying.

3.6.1.3. Test of collection materials

Before sample collection, urine collection pads (Euron Uricol Set (sterile), art. no. 310019, Sterisets Int. B.V., NL) were tested for iodine contamination and iodine recovery. All other materials for the study were also tested for iodine contamination: syringes (in Euron Uricol Set, see above), urine collection cups (PP 125 ml, art. no. 5664, Semadeni AG, Switzerland), urine transport-tubes (PS 15 ml, art. no. 2276, Semadeni AG, Switzerland), disposable bra pads (Medela AG, Medical Technology, Switzerland) and the bottle with nanopure water that was used during the iodine analysis (Art. no 1165, Semadeni AG, Switzerland). As one pediatric practice insisted on using urine collection bags instead of pads, two brands of bags were also tested for iodine contamination (Pediatric urine collectors (sterile), Ref: PEDUB100, Romed, NL; U-bag pediatric (sterile), Urine collectors No. 7511 (Single Specimen), Hollister, Illinois, USA). All other plastic materials used for the study had already been assessed to have no iodine contamination at an earlier point of time by the laboratory and are regularly used for iodine analyses (Eppendorf tubes, Pasteur pipettes and

pipette tips).

Test of the urine collection pads: To verify the absence of iodine contamination, the pad was soaked with 10 ml of nanopure water. After half an hour, the water was extracted from the pad with a syringe (from the Uricol set) and aliquoted into three Eppendorf tubes. This was done for three pads. As a control for iodine contamination in the nanopure water, another three Eppendorf tubes were filled with nanopure water without extracting it from a pad. Then, all aliquots were analyzed in duplicate by the modified Sandell-Kolthoff method in the same way as urine samples, see chapter 3.6.1.7.
The same procedure was applied to control for iodine recovery from the pads. Therefore, an iodine solution [100 µg/l] was used instead of nanopure water.

Test of the other collection materials: To verify the absence of iodine contamination, 10 ml of nanopure water was filled in the urine collection cups, transport tubes, disposable bra pads and urine bags (each in triplicate), 5 ml of nanopure water in the syringes (in triplicate) and one plastic bottle was filled completely with nanopure water. All materials were shaken well for 5 minutes. After half an hour, three samples of each piece of material were aliquoted into Eppendorf tubes (with disposable Pasteur pipettes). To check whether the nanopure water that was used for analysis was contaminated, three Eppendorf tubes were filled with nanopure water. Then, all aliquots were analyzed in duplicate by the modified Sandell-Kolthoff method in the same way as urine samples, see chapter 3.6.1.7.
It was not possible to extract the water after half an hour from the disposable bra pads because they contained a super-absorbent gel. Medela assured that the disposable bra pads did not contain any iodine (personal communication).
After analysis, all aliquots were frozen at -25°C for repeat analysis.

3.6.1.4. Reagents

All reagents that were used for the modified Sandell-Kolthoff method are listed in Table 9. For all analyses, nanopure grade water purified by reverse osmosis was used (18MΩ, Nanopure Cartrige System, Skan AG, Switzerland).

Table 9: Reagents for the modified Sandell-Kolthoff method

Reagent	Chem. formula	Art. no	Supplier
• Sodium hydroxide (pellets)	NaOH	puriss. p.a., 71695	Fluka Chemie, Switzerland
• Arsenic (III) oxide	As_2O_3	puriss. p.a., 11100	Fluka Chemie, Switzerland
• Concentrated sulfuric acid (95 -97%)	H_2SO_4	puriss. p.a., 84720	Fluka Chemie, Switzerland
• Sodium chloride	NaCl	puriss. p.a., 71379	Fluka Chemie, Switzerland
• Ammonium cerium (IV) sulfate Dihydrate	$Ce(NH_4)_4(SO_4)_4$ *$2H_2O$	puriss. p.a., 22269	Fluka Chemie, Switzerland
• Ammonium peroxodisulfate	$H_2N_2O_8S_2$	puriss. p.a., 09915	Fluka Chemie, Switzerland
• Potassium iodate	KIO_3	puriss p.a., 60390	Fluka Chemie, Switzerland

3.6.1.5. Equipment/materials

All equipment and materials that were used for the modified Sandell-Kolthoff method are listed in Table 10.

Table 10: Equipment/materials for the modified Sandell-Kolthoff reaction

Equipment/material	Model	Supplier
• Analytical scale	AT 200	Mettler-Toledo, Switzerland
• Fume hood		Renggli, Switzerland
• Biohazard-box	Skanair VFV 90	Skan AG, Switzerland
• Heating/Magnetic stirrer	FB 15001	Fisher Scientific, Germany
• Vortex	Genie 2™	Bender & Hobein, Switzerland
• Timer		
• Heating block		Bioblock Scientific, Switzerland
• Borosilicate glass test tubes	12 x 100 mm	Schott Duran®, Germany
• Micro-pipette (25 µl)	single channel, Finnpipette	Thermo Labsystems, Germany
• Micro-pipette (50-200 µl)	single channel	Socorex, Switzerland
• Micro-pipette (100-1000 µl)	single channel	Eppendorf reference, Germany
• Multichannel-pipette (20-200 µl)	Acura 855	Socorex, Switzerland
• Disposable pipette tips	graduated	Starlab, Germany

Continuation of Table 10:

Equipment/material	Model	Supplier
• 96-well micro-plates (PS)	Polystyrene, flat bottom	Greiner-bio-one, Germany
• Micro-plate shaker	Titramax 100	Bioblock Scientific/Heidolph, Switzerland
• MRX Micro-plate Reader	MR1200	Dynatech Laboratories, Germany
• Various glassware (acid washed)	Volumetric flasks, beakers, reagent containers, measuring cylinders, glass measuring pipettes	Schott Duran/Pyrex/Hirschmann, Germany

3.6.1.6. Solutions

Sodium hydroxide solution (8.0 mol/l):

159.4 g of NaOH pellets were dissolved in 300 ml of nanopure water in a volumetric flask (500 ml) in an ice bath. After cooling, the solution was adjusted to 500 ml with nanopure water. The solution is stable for months.

Sodium hydroxide solution (0.875 mol/l):

21.8 g of NaOH solution (8 mol/l, see above) was weighed into a volumetric flask (200 ml) and diluted with nanopure water to a volume of 200 ml.

Arsenious acid solution (0.05 mol/l):

9.8 g of arsenic (III) oxide (As_2O_3) was dissolved in 200 ml of NaOH solution (0.875 mol/l, see above) in a volumetric flask (1000 ml). In an ice bath under a fume hood, 32 ml of concentrated sulfuric acid (H_2SO_4) was slowly added. After cooling to room temperature, 25 g of sodium chloride (NaCl) was dissolved in the solution and nanopure water was added to a volume of about 800 ml. The solution was heated under stirring (magnetic stirrer) at 85-90°C until complete dissolution (about 1 h, flask covered with aluminum foil). After cooling to room temperature, the solution was adjusted to 1000ml with nanopure water.

Stored away from light at room temperature, the solution is stable for at least three months.

Sulfuric acid solution (1.75 mol/l):

Under a fume hood in an ice bath, 94.5 ml of concentrated sulfuric acid (H_2SO_4) was slowly added to about 700 ml of nanopure water in a volumetric flask (1000 ml). After cooling to room temperature, the solution was adjusted to 1000 ml with nanopure water.

Ceric ammonium sulfate solution (0.019 mol/l):

Under a fume hood, 6 g of ammonium cerium (IV) sulfate dihydrate ($Ce(NH_4)_4(SO_4)_4*2H_2O$) was dissolved in 400 ml of sulfuric acid solution (1.75 mol/l) in a volumetric flask (500 ml). The solution was covered with aluminum foil and stirred on a magnetic stirrer. When the solution became clear, it was adjusted to a final volume of 500 ml with the sulfuric acid solution (1.75 mol/l, see above). Stored away from light at room temperature, the solution is stable for at least 3 months.

Ammonium persulfate solution (1.0 mol/l):

57.05 g of ammonium peroxodisulfate ($H_2N_2O_8S_2$) was dissolved in approximately 180 ml of nanopure water in a volumetric flask (250 ml). The solution was stirred on a magnetic stirrer until it became clear. Finally, it was filled to a volume of 250 ml with nanopure water. The solution was prepared freshly every week.

Iodine stock solution (1 g iodine/l):

168 mg of potassium iodate (KIO_3) was dissolved in nanopure water in a volumetric flask (100 ml) and adjusted to 100 ml with nanopure water.

Covered with aluminum foil, the stem solution is stable for at least 3 months at room temperature.

Iodine standard solution A (0.5 mg iodine/l):

50 µl of iodine stock solution (1 g iodine/l, see above) was pipetted into a volumetric flask (100 ml). Nanopure water was added to a final volume of 100 ml. The iodine standard solution A was freshly prepared every day.

3.6.1.7. Experimental procedure

For each experiment 26 urine samples (aliquots of 1.5 ml) and two urine control samples (X and Z, aliquots of 1.5 ml) were defrosted to room temperature and

vortexed to dissolve sediments. In a biohazard-box, 2 x 250 µl of each sample (duplicate), 250 µl of each control sample (no duplicate) and 250 µl of nanopure water (= blank, no duplicate) were pipetted into borosilicate glass test tubes (totally 55 tubes). As the color reaction has no specific endpoint a standard curve is required (Pino et al., 1996). For the standard curve the iodine standard solution A was pipetted into glass tubes according to the following scheme (no duplicate) (S1 – S5 = standard solutions 1 - 5):

						Iodine conc. [µg/l]
S1	25 µl	iodine standard solution A	+	225 µl	H_20 *	**50**
S2	50 µl	iodine standard solution A	+	200 µl	H_20	**100**
S3	100 µl	iodine standard solution A	+	150 µl	H_20	**200**
S4	150 µl	iodine standard solution A	+	100 µl	H_20	**300**
S5	200µl	iodine standard solution A	+	50 µl	H_20	**400**

*(H_20 always refers to nanopure water)

1 ml of ammonium persulfate solution (1.0 mol/l) was added to each glass tube. All tubes were vortexed. Then, the tubes were heated to 95°C for 60 min in a heating block under a fume hood. Heating time and temperature had to be identical for all tubes (time stopped). After one hour, the tubes were taken out of the heating block and cooled to room temperature (approximately 30 min). Subsequently, the glass tubes were vortexed. Then, 50 µl from each tube were pipetted into the corresponding well/wells of a 96-well micro-plate according to the pipetting scheme in Table 11 (finally, each well on the micro-plate contained 50 µl of the respective solution/sample).

Table 11: Pipetting scheme on 96-well micro-plate

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
A	0	0	0	0	0	0	0	0	0	0	0	0
B	S1	S5	S5	S5	S5	S5	S5	S5	S5	S5	S5	S1
C	S2	U1a	U3a	U5a	U8a	U11a	U14a	U17a	U20a	U23a	U25a	S2
D	S3	U1b	U3b	U5b	U8b	U11b	U14b	U17b	U20b	U23b	U25b	S3
E	S4	U2a	U4a	U6a	U9a	U12a	U15a	U18a	U21a	U24a	U26a	S4
F	S5	U2b	U4b	U6b	U9b	U12b	U15b	U18b	U21b	U24b	U26b	S5
G	X	X	X	U7a	U10a	U13a	U16a	U19a	U22a	X	X	X
H	Z	Z	Z	U7b	U10b	U13b	U16b	U19b	U22b	Z	Z	Z

Legend: 0 = blank; S1-5 = standard solutions; X and Z = urine control samples; U1-26 = urine samples in duplicate (a, b), plate filled column-wise; (A - H = lines; 1 – 12 = columns of the micro-plate)

100 µl of arsenious acid solution (0.05 mol/l) was added to each well of the micro-plate with a multichannel-pipette (from left to right, column 1-12). The plate was shaken on a micro-plate shaker for 15 min (time stopped). Then, 50 µl of ceric ammonium sulfate solution (0.019 mol/l) was pipetted to each well of the micro-plate within 60 sec using a multichannel-pipette (from left to right, column 1-12) and the plate was shaken on the micro-plate shaker for exactly 28 min (time stopped). The micro-plate was placed in the micro-plate reader and the absorbences were measured photometrically at a wavelength of 405 nm, against air (settings of micro-plate reader are shown in Table 12).

Table 12: Settings of the micro-plate reader MRX 1.2

MRX 1.2	Description	Setting
Photometer	Test filter	1: λ= 405nm
	Reference filter	0
	Blank (Air/Kavit.)	AIR
	Control well	A1
	Shaking time (sec)	0
Periphery	RS-232-C (COMx:)	1
	Baudrate	9600
	Pieps	2

Data processing was performed by the associated MRX-software. The absorbences were transferred to a computer for the evaluation with Excel (Microsoft, Seattle, WA, 2003).

3.6.1.8. Calculations

Urinary iodine concentrations were calculated with the help of a standard curve by linear regression.

A “control” standard curve was calculated with the log transformed absorbances of the standards in the first and last column (column 1 and 12, see Table 11) of the micro-plate (y-axis) versus the standard iodine concentrations (x-axis) according to the following regression equation: $y = a * x + b$ (y = log absorption, x = iodine concentration [µg/l], a = slope, b = intercept). An example can be seen in Figure 6. The coefficient of determination (R^2) of the standard curve had to be ≥ 0.99 to accept the measurements.

To compensate for the slight time difference of the color reaction, when the

ceric ammonium sulfate solution was pipetted from column 1 to 12 of the micro-plate, the blank and standard 5 (400 µg/l) were pipetted in each column of the micro-plate (see Table 11). The sample concentrations were not calculated with the "control" standard curve (Figure 6), but with two-point standard curves (using blank and standard 5) for each single column of samples (columns 2-11) on the micro-plate.

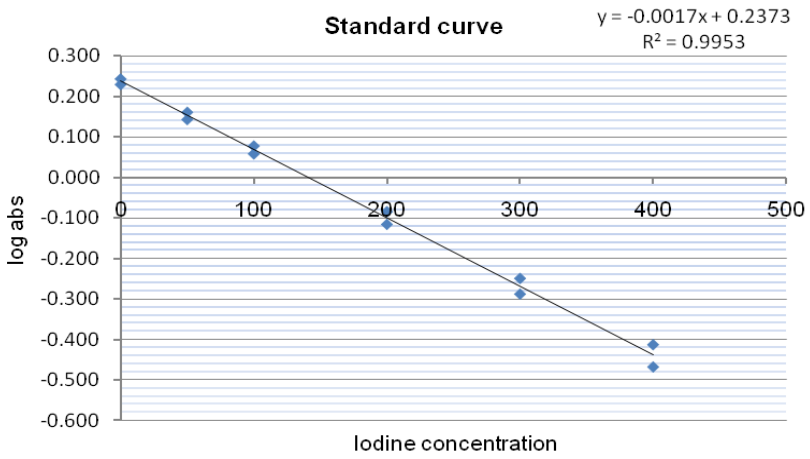


Figure 6: Example of standard curve

For each sample the difference of UIC [in %] between the duplicate was determined. A sample was accepted, if the difference was:

≤ 15% for iodine concentrations < 50 µg/l,

≤ 10% for iodine concentrations between 50 - 150 µg/l,

≤ 5% for iodine concentrations > 150 µg/l.

Otherwise, the sample was repeated until the difference fell in the above-mentioned range.

For the data analysis, the average of both measured UI concentrations of a duplicate was used.

3.6.1.9. Quality control

3.6.1.9.1. Internal quality control

As internal control, two control samples (X and Z) were included in each run (= on each micro-plate). The control samples were from a urine pool, one with low (X) and one with high (Z) iodine concentration. Before they were set as control

samples, they were measured on 20 plates in duplicates against the former controls to determine their mean and SD. It was defined for all future measurements that a measurement was only accepted if both control samples were within 3 SD of the control mean:

X control sample: 34.1 ± 3.34 µg/l; CV% 9.80; acceptable range 24-44 (3 SD)

Z control sample: 218 ± 7.05 µg/l; CV% 3.24; acceptable range 197-239 (3 SD)

X and Z values were also validated by measuring the concentration by ICP-MS at FOPH in Berne, Switzerland. See chapter 3.6.2.10.

X and Z were also used to assess the inter-assay precision of the measurements. To assess the intra-assay precision a urine sample was measured in several tubes in one single assay (see results).

3.6.1.9.2. External quality control

For a constant control of the quality of urinary iodine measurements the laboratory takes part in a worldwide program “to ensure the quality of urinary iodine procedures” (EQUIP) developed by the Centers for Disease Control and Prevention (CDC). Currently, more than 80 iodine laboratories in more than 30 countries participate in the program. In this program, urine specimens with unknown iodine concentration are analyzed by the participating laboratories three times a year. CDC defines the EQUIP target values of the urine specimens by taking the mean of nine individual measurements with ICP-DRC-MS on at least three different days. Each participating laboratory has to report data for each specimen measured three times in duplicate (on three different plates) (Caldwell et al., 2005). During our analyses we participated in one round and measured four EQUIP samples of different iodine concentrations.

3.6.2. Breast milk iodine concentration & iodine in formula and infant food - ICP-MS method

All breast milk, formula and infant food samples were measured by an inductively coupled plasma mass spectrometry (ICP-MS) method at the Swiss Federal Office of Public Health (FOPH, Liebefeld) in the laboratory of the Consumer Protection Directorate in collaboration with M. Haldimann and A. Blanc.

3.6.2.1. Principle

Several modifications of the ICP-MS method for the determination of iodine exist. The method which was applied here was developed by Haldimann at FOPH based on Adriaens et al., Fecher at al. and Haldimann et al. (Adriaens et al., 1993; Fecher et al., 1998; Haldimann et al., 2000; Haldimann et al., 1998). It was used before for the analysis of iodine in cow milk samples at the same laboratory (Crnkic et al., 2006).

First, iodine has to be quantitatively extracted from the samples and brought into solution. Therefore, tetramethylammonium hydroxide (TMAH), a strong alkaline reagent, was used at an elevated temperature (90°C) (Fecher et al., 1998). Furthermore, the measuring of iodine in alkaline solution suppresses the development of volatile iodine species such as HI and I_2 (Haldimann et al., 2000).

In breast milk (BM), iodine is mainly found as iodide (I^-) in the aqueous phase (milk whey) (Dorea, 2002; Fernandez-Sanchez et al., 2007). Organic iodine like thyroid hormones and metabolites is also reported in BM however with large concentration differences (Dorea, 2002). In infant and follow-on formula it is allowed to add iodine as potassium iodide, sodium iodide and potassium iodate and in complementary foods sodium iodate is also allowed (EDI, 2005b). With ICP-MS the total concentration of soluble iodine of a sample is measured regardless of the chemical form as all molecules are atomized and ionized (I^+) in the plasma of the spectrometer (Fecher et al., 1998; Thomas, 2001a).

After the extraction, iodine concentration is measured with ICP-MS using isotope dilution analysis (IDA) with ^{129}I (Haldimann et al., 1998). In the method

of IDA the sample is spiked with an isotope of the element that is to be determined. It must be either an isotope that does not naturally exist in the sample or else a low abundance isotope that is enriched (Adriaens et al., 1993). In the case of iodine only one stable isotope, ^{127}I, exists naturally in samples and its concentration is the searched variable. ^{129}I is a radioactive, β emitting isotope of iodine (half-life: 1.57 x 10^7 years) (Platzner, 1997) and its natural abundance is negligible (Muramatsu and Yoshida, 1995). ^{129}I is added to the samples as a spike (= tracer) (Haldimann et al., 1998). The ratio of these two isotopes is directly measured by ICP-MS. Knowing the ^{129}I concentration in the added spike, the ^{127}I concentration in the sample can be determined (Adriaens et al., 1993; Haldimann et al., 1998). The method of IDA (in contrast to an external standard) is ideal to compensate for plasma fluctuations during ICP-MS measurement and to erase matrix effects of the sample such as suppressions by other ions (like Ca^{2+}, Mg^{2+} and Cl^-), which play an important role in biological samples. The isotope ratio is not affected because the degree of modification is the same for both isotopes (Haldimann et al., 1998; Horlick and Montaser, 1998). For the principle of the ICP-mass spectrometer, see below.

3.6.2.2. Reagents/reference materials

All reagents and reference materials used for the ICP-MS analysis are listed in Table 13.

Ultrapure water was used (18.2MΩ, Ultra-pure, Purelab ultra, Elga, UK) for all analyses.

3.6.2.3. Equipment/materials

All equipment/materials used for the ICP-MS analysis are listed in Table 14.

Table 13: Reagents/reference material for iodine analysis with ICP-MS

Reagents/reference material	Art. no	Supplier
• Tetramethylammonium Hydroxide (TMAH) 25% $(CH_3)_4NOH$	Tamapure-AA, Lot. No. Z826N01K, UN No. 1835, Ultrapure analytical reagent, Specification (on certificate of analysis) < 1000 ppt iodine (pg/mL)	Tama Chemicals, Japan
• Iodine-129 radioactivity standard (Gills, 1995)	Standard reference material 4949C	NIST, Gaithersburg, USA
• Natriumhydroxid-Monohydrat $NaOH * H_2O$	Suprapur, 99.99%, art. no. 1.06466	Merck, Darmstadt, Germany
• Whole milk powder (Gills, 1993)	Reference Material 8435	NIST, Gaithersburg, USA
• Infant formula (powder) (Wise and Watters, 2007)	Standard Reference Material 1846	NIST, Gaithersburg, USA

Abbreviation: ICP-MS = Inductively Coupled Plasma Mass Spectrometry

Table 14: Equipment/materials for iodine analysis with ICP-MS

Equipment / material	Model	Supplier
• Heat cabinet	Thermocenter TC40	SalvisLab, Switzerland
• (Drying) oven	Durocell 55	MMM, Germany
• Analytical balance	XP205	Mettler Toledo, Switzerland
• Precision balance	PR8002 Delta Range	Mettler Toledo, Switzerland
• Pipette	0.5 – 5 ml	Socorex, Switzerland
• Disposable pipette tips	100 – 5000 µl	Eppendorf, Germany
• Automatic pipette	EDOS 5222	Eppendorf, Germany
• Combitips plus (disposable)	1 ml, 5 ml, 10 ml	Eppendorf, Germany
• PP-tubes with red screw cap (HD-PE) (disposable)	50 ml, conical skirted base	Sarstedt, Germany
• PP-tubes with push cap (disposable)	12 ml, round base	Sarstedt, Germany
• Ultrasound bath	TPC-40, Telesonic	Ultrasonics Steckmann GmbH, Germany
• Polycarbonate bottles (500 ml)	Narrow-mouth square bottle, Lexan	Nalgene, USA
• Laboratory mixer	B-400, titan blades	Büchi, Switzerland
• Mixer sample vessels	Borosilicate glass	Büchi, Switzerland

Abbreviation: ICP-MS = Inductively Coupled Plasma Mass Spectrometry

3.6.2.4. Spiking solution

Preparation of the ^{129}I spiking solution (1.41 ppm):

254.3 mg of the iodine-129 radioactivity standard (189.9 mg/L, (Gills, 1995)) was weighed and filled up to 34.16 g with ultrapure water. 134 mg of NaOH (hydrate) was then added. This resulted in 1.41 ng/µl (ppm) iodine-129 in a 0.26% NaOH solution. The ^{129}I spiking solution was stored at 8°C.

3.6.2.5. Experimental procedure

The samples were generally analyzed once. Some samples were repeated (another aliquot) in a second run to test the repeatability of the analysis and preparation as well as the homogeneity of the samples.

3.6.2.5.1. Preparation for measurement

See also preparation scheme, Table 15:

***Preparation of breast milk samples*:**

The BM samples were transported to Berne for analysis in frozen conditions (with dry ice). For the analysis, the desired number of samples (aliquots of 2 ml, the number of samples per run varied between 35 and 40) was equilibrated to room temperature for about one hour. The samples were agitated carefully to homogenize the BM and 1.5 ml of each sample was pipetted into 50ml-PP-tubes on an analytical scale. The exact weight of each pipetted sample was noted and each tube was closed with a cap. If an aliquot contained less than 1.5 ml, the maximum volume was taken for analysis. The pipetted amount and weight were noted. Some BM samples were coagulated to different extents. To dissolve the coagulated particles - presumably mainly consisting of fat – the corresponding samples were placed in an (drying) oven at 40°C for 15 - 30 minutes depending on the extent of coagulation. After cooling for 5 minutes, they were pipetted in the same way as the rest of the samples. Subsequently, 0.5 ml of TMAH solution (25%) was added to each PP-tube using an automatic pipette (5 ml tip, DISP mode). The tubes were closed again with the caps and swayed slightly. The samples were heated in the heat cabinet for 3 hours at 90°C to extract the iodine. After that, the samples were taken out of the heat

cabinet and left to cool to room temperature for 45 minutes. The tubes were filled up to the 50 ml mark with ultrapure water, closed with the caps, shaken well and left over night for sedimentation at room temperature. The next morning, the tubes were handled carefully and not shaken to avoid dispersing of sediments. Aliquots of 10 ml were pipetted from the middle of the tubes into 12ml-PP-tubes using an automatic pipette (10 ml tip, PIP mode). Care was taken not to take up any sediment from the bottom of the tube or parts of the fat fraction floating on top of the solution as this would have interfered with the ICP-MS measurement. Then, 25 µl of the ^{129}I spiking solution (shaken well and equilibrated to room temperature; 25 µl spiking solution contains 35.25 ng ^{129}I) was added to each sample using an automatic pipette (1 ml tip, DISP mode). The 12ml-PP-tubes were closed with caps and shaken well.

***Preparation of formula and infant food samples*:**

The infant food sample packages were stored at room temperature in dry ambiance. Before taking out a sample, the package was shaken well to homogenize the content. We always reconstituted full portions of the products for the analyses to control for a possible inhomogeneous distribution of iodine in the dry product. Some products were additionally analyzed in powder form. The number of formula/infant food samples that was included per run varied (depending on the time required for sample preparation and the number of included BM samples in the same run).

Preparation of formula and infant food samples in powder form: About 0.25 g of a product (powder) was weighed into a 50ml-PP-tube on an analytical scale. The exact weight was noted and the cap was closed. 2 ml of ultrapure water was added to the tube using an automatic pipette (10 ml tip, DISP mode). Subsequently (continuing with the addition of TMAH), the samples were prepared for the ICP-MS measurement in the same way as the BM samples (see also Table 15).

Preparation of reconstituted formula: The formula (FM) was prepared freshly on the day of experiment according to the instructions described on the package. The portion size for an infant of about six months of age was used (between

200 and 260 ml depending on the product). The amount which had to be prepared was calculated precisely based on the indicated standard resolution of the product [g/vol] (defined as: amount of powder (g) + 90 ml of water = 100 ml of FM). Polycarbonate bottles were used for the preparation because they are commonly used as baby bottles. Before usage, the bottles were rinsed three times with ultrapure water and dried. The required amount of ultrapure water was weighed directly into a polycarbonate bottle on a precision balance, the cap was closed and the bottle heated in the heat cabinet for about one hour at the required temperature for preparation (between 40 – 50°C depending on the product). After that, the required amount of powder was directly added to the water and simultaneously weighed, the bottle closed again and shaken to dissolve the powder. After cooling and shaking again, about 40 ml of the preparation was transferred to a 50 ml PP-tube (for storage after the analysis at -25°C). From this, 1.5 ml was pipetted into another 50ml-PP-tube on an analytical scale. The exact weight was noted and the tube was closed with a cap. Subsequently (continuing with the addition of TMAH), the reconstituted FM samples were prepared for the ICP-MS measurement in the same way as the BM samples (see also Table 15).

Preparation of reconstituted baby cereal porridge: The porridge (one portion per product) was prepared freshly on the day of experiment according to the instructions described on the package. Ultrapure water was heated in a polycarbonate bottle in the heat cabinet for about one hour at the required temperature (between 40 – 50°C depending on the product). Then, according to the instruction on the package, either firstly the water, then the powder, or vice versa were weighed in a borosilicate mixer vessel and the exact weights were recorded. The vessel was fixed in the mixer and the porridge was mixed twice for about 10 sec. If the porridge was homogeneous, an aliquot of about 40 ml was transferred to a 50ml-PP-tube (for storage after the analysis at -25°C). 1.5 – 2.0 g of the sample was weighed into another 50ml-PP-tube on an analytical scale. The exact weight was noted and the tube was closed with a cap. Subsequently (continuing with the addition of TMAH), the porridge samples were prepared for the ICP-MS measurement in the same way as the BM

samples (see also Table 15).

Before and after usage, the borosilicate vessels were first cleaned with hot water and rinsing agent and then rinsed with ultrapure water. They were then filled with nitric acid (5%, HNO_3 (65%) pro analysi, Merck, Germany) for a few minutes and rinsed again three times with ultrapure water and finally left for drying. In between mixing different porridges, the mixing blades were rinsed well with ultrapure water. Finally, the blades were soaked overnight in 1% RBS 50 concentrate (art. no. 83462, Fluka Chemie, Switzerland) and then rinsed with ultrapure water.

***Preparation of the blank*:**

The blank solution was freshly prepared for each ICP-MS measurement series.

For the blank, 2 ml of ultrapure water was pipetted into a 50ml-PP-tube using an automatic pipette (10 ml tip, DISP mode) and the cap was closed. Afterwards (continuing with the addition of TMAH), the blank was prepared in the same way as the BM samples, except that no ^{129}I spiking solution was added (see also Table 15).

***Preparation of the whole milk powder/infant formula reference samples*:**

One to three whole milk/infant formula (IF) reference samples were included in each ICP-MS measurement (depending on kind and number of measured samples).

About 0.2 g of whole milk reference powder or 0.25 g of IF reference powder was weighed into a 50ml-PP-tube on an analytical scale. The exact weight was recorded and the cap was closed. 2 ml of ultrapure water was added to the tube using an automatic pipette (10 ml tip, DISP mode). As the IF reference powder did not dissolve well, the PP-tubes with the IF reference were put in an ultrasound bath for 20 min at 40°C. In the following (continuing with the addition of TMAH), the reference samples were prepared in the same way as the BM samples, except that after the sedimentation an aliquot of 5 ml was taken from the middle of the 50ml-PP-tube (instead of 10 ml for the BM samples) (see also Table 15).

Table 15: Preparation scheme: Measurement of iodine concentration by ICP-MS

	BM/FM (reconst.)	**Baby cereal** (reconst.)	**Baby cereal** (powder)	**Whole milk/IF reference**	**Blank**	
Pipetted/ weighed sample	*1.5 ml*	*1.5 - 2.0 g*	*0.25 g*	*0.2/0.25 g*	*--*	50ml-PP-tube
Water (Nanopure)	*--*	*--*	*2 ml*	*2 ml*	*2 ml*	
TMAH (25%)	*0.5 ml*	*0.5 ml*	*0.5 ml*	*0.5 ml*	*0.5 ml*	
	Swayed slightly					
Heat cabinet	*3 h, 90°C*					
Equilibration to RT	*45 min*					
Water (Nanopure)	*Filled up to 50 ml*					
	Shaken well					
	Sedimentation over night (at RT)					
Aliquot from 50 ml PP-tube	*10 ml*	*10 ml*	*10 ml*	*5 ml*	*10 ml*	12ml-PP-tube
^{129}I spiking solution	*25 µl*	*25 µl*	*25 µl*	*25 µl*	*--*	
	Shaken very well					

Abbreviations: ICP-MS = Inductively Coupled Plasma Mass Spectrometry; reconst. = reconstituted; BM = breast milk; FM = formula; IF = infant formula; TMAH = tetramethylammonium hydroxide; RT = room temperature

***Preparation of the spike ratio solution*:**

The spike ratio solution was freshly prepared for each ICP-MS measurement series.

About 30 ml of the prepared blank solution (see above) was transferred from the 50ml-PP-tube into another 50ml-PP-tube. 75 µl of ^{129}I spiking solution was added to the blank solution in the new tube using an automatic pipette (1 ml tip, PIP mode).

3.6.2.5.2. Measurement

The measurements were performed with a double focusing magnetic sector-field ICP-MS (Finnigan™ ELEMENT 2, Thermo Scientific, USA).

For the measurement, the 12ml-PP-tubes were placed on a special rack in a defined order. The programmed sequence was started and the samples were

taken up and measured automatically at fixed operating conditions (Table 16).

A typical sample sequence of the ICP-MS measurements is shown in Table 17.

Table 16: Operating conditions of ICP-MS

Operating conditions of ICP-MS		
• Sample flow rate	ml/min	0.3
• Sample take-up time	min	2
• Sample measuring time	sec	25
◦ Radio frequency power	W	1300
◦ Resolution	m/Δm	Low = 300
◦ Mode		1
◦ Runs/passes		9 * 9
◦ Settling time	sec	0.001
◦ Sample time	sec	0.010
◦ Samples per peak		30
◦ Spectrum range	u	126.8060 - 129.0050
◦ Segment duration	sec	0.150
◦ Scan type		E-Scan (electric)
◦ Detection mode		Analog + counting
◦ Integration type		Average
• Wash time with TMAH	min	3
• Monitored ions	m/z	^{127}I, ^{129}I, ^{129}Xe (impurity)
• Quantification type	cps	Intensities

Abbreviations: ICP-MS = Inductively Coupled Plasma Mass Spectrometry;
TMAH = tetramethylammonium hydroxide

Table 17: Typical sample sequence of ICP-MS measurements (e.g. breast milk)

Sample definition	**No. of measurement in the sequence**
Blank (TMAH 0.25%)	Start
Spike ratio solution	Start
Whole milk reference	1
Breast milk samples	1 - 5
Spike ratio solution	1
Breast milk samples	6 - 10
Spike ratio solution	2
Breast milk samples	11 - 15
Spike ratio solution	3
Whole milk reference	2
Breast milk samples	…
Spike ratio solution	…
Whole milk reference	3
Blank (TMAH 0.25%)	End
Spike ratio solution	End

Abbreviations: ICP-MS = Inductively Coupled Plasma Mass Spectrometry;
TMAH = tetramethylammonium hydroxide

The washing solution - in between each sample - was TMAH (0.25%, Tama Chemicals, Japan). For aerosol generation and sample introduction a Burgener Mira Mist nebulizer (low flow, inert Teflon capillaries, Burgener Research Inc., Canada) and a Cinnabar spray chamber (20 ml cyclonic, borosilicate glass, Glass Expansion P/L., Australia) were used. The plasma gas was argon (Alphagaz 1 Argon, ≥ 99.999% mol, Carbagas, Switzerland; cool gas flow ca. 15.4 l/min, sample gas flow ca. 1.07 l/min and auxiliary gas flow ca. 0.66 l/min, argon pressure: middle ca. 2.6 bar, max. ca. 5.8 bar; daily optimized). Instrument control and data acquisition was performed by the associated Finnigan ELEMENT2 software.

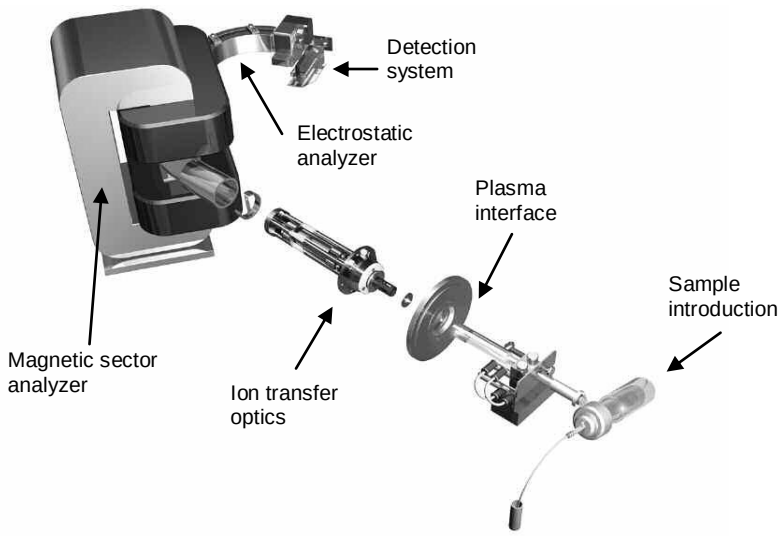


Figure 7: Schematic sector field inductively coupled plasma mass spectrometer (Source: (Thermo Electron Corporation, 2004))

The measurement principle of the sector field ICP-MS is the following (see Figure 7): The liquid sample is introduced into the plasma with a nebulizer that forms an aerosol and with a spray chamber that selects small droplets (carried by argon gas) (Montaser et al., 1998; Thomas, 2001b). In the inductively coupled plasma (plasma gas: argon) the sample is atomized and then positively ionized predominantly by collisions with energetic argon electrons at 6000-7000 K (Thomas, 2001c; Turner and Montaser, 1998). Then, the ions are transported through the interface region (sampler and skimmer metallic cone with very small orifices) from the plasma (atmospheric pressure) to the high vacuum of the MS-

analyzer (Thomas, 2001d; Turner et al., 1998). Before entering the analyzer, electrostatic ion optics focus and accelerate positive ions onto the entrance slit and stop particulates, neutrals and photons (reduction of background noise) (Turner et al., 1998). In the MS-analyzer the mass separation is performed by a magnetic field which disperses ions according to their mass and energy. After this, the ions enter an electrostatic analyzer for energy focusing. The combination of the magnetic and electrostatic sector fields result in the double focusing, high-resolution properties of the analyzer. The ions are detected with a discrete dynode detector system in which ions generate electrons that are quantified simultaneously by analog collection (for high ion concentrations) and pulse counting (for low ion concentrations) (Thermo Electron Corporation, 2004; Thomas, 2002; Turner et al., 1998). The measured signals are collected and they result in a MS-spectrogram with relative abundance (intensity) [cps] versus mass to charge ratio [u]. The analyzer constantly switches rapidly between measuring ^{127}I- and ^{129}I-signals. An example of the MS-spectrogram is shown in Figure 8.

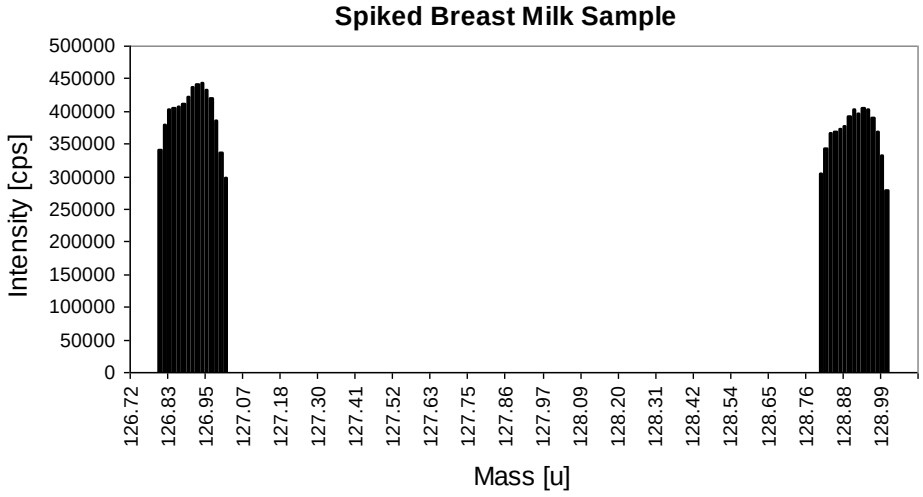


Figure 8: Example of a MS-spectrogram of a spiked breast milk sample

3.6.2.6. Calculations

The formula to calculate the iodine content in the samples was derived from Adriaens et al. (Adriaens et al., 1993) and adapted by Haldimann (personal communication, used in (Crnkic et al., 2006)): $\mathbf{m = n*(R_M - R_S)*M}$

m is the unknown total mass of ^{127}I in the sample (BM, FM or infant food) [ng]; **n** is the number of moles of ^{129}I in the added spike: n [nmol] = mass of added iodine spike [ng]/molar mass of ^{129}I [128.905 ng/nmol] (mass of added iodine spike [ng] = ^{129}I concentration of spiking solution [ng/µl] * volume of added spiking solution [µl]) ; $\mathbf{R_M}$ is the molar $^{127}I/^{129}I$ – ratio in the resulting mixture in the sample [calculated from measured mean cps (relative) of ^{127}I and ^{129}I in the sample: ^{127}I [cps]/^{129}I [cps] = ratio in sample]; $\mathbf{R_S}$ is the molar $^{127}I/^{129}I$ – ratio in the spike solution (measured in the spike ratio solution) [calculated from measured mean cps (relative) of ^{127}I and ^{129}I in the spike ratio solution: ^{127}I [cps]/^{129}I [cps] = ratio in spike]. R_S was measured at the beginning of each measurement sequence and after about five samples it was measured again on a regular basis. The R_S which was measured closest prior to the sample was used for the calculation (see Table 17, spike ratio solution); **M** is the molar mass of ^{127}I [126.904 ng/nmol]. An illustration of the formula can be seen in Figure 9. To determine the iodine concentration [ng/g = µg/kg] in the sample, **m** was divided by the weight of the sample [g] in the 12ml-PP-tube (e.g. weighed sample amount in 50ml-PP-tube divided by 5 to calculate the sample weight in the 10 ml aliquot in the 12ml-PP-tube).

Calculations were performed with spreadsheet software (Excel, Microsoft, Seattle, WA, 2003).

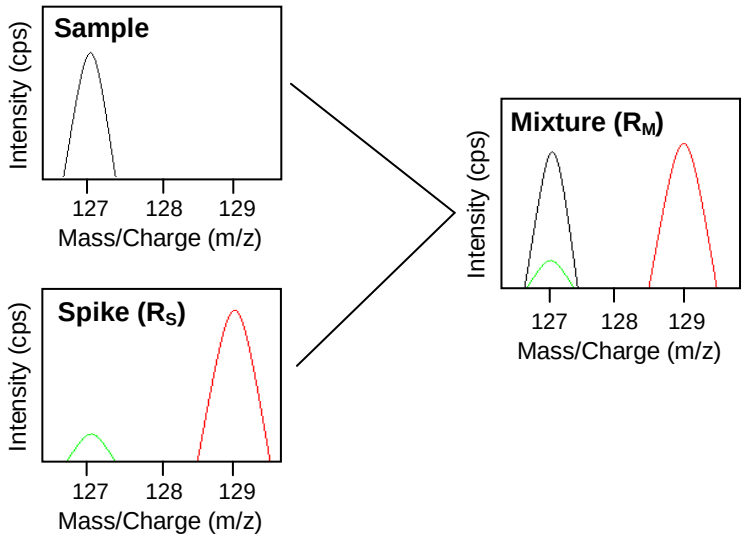


Figure 9: Calculation of ^{127}I concentration with $^{127}I/^{129}I$ – ratio (adapted from M. Haldimann, personal communication)

3.6.2.7. Limit of detection & limit of quantification

The limit of detection (LOD) and the limit of quantification (LOQ) for the IDA were calculated on the basis of the spike ratio measurements (Heumann, 1988).

LOD: $R_{LOD} > (^{127}I/^{129}I)_{Spike} + 3s$

LOQ: $R_{LOQ} > (^{127}I/^{129}I)_{Spike} + 10s$

^{127}I and ^{129}I are the measured intensities [cps] of the iodine isotopes in the spike ratio solution; s is the SD of the spike ratio measurements.

3.6.2.8. Quality control

3.6.2.8.1. Blank

The blank was used as a control for possible iodine contamination in the used solutions and materials. It was always measured at the beginning and end of each measurement sequence.

3.6.2.8.2. Reference samples

One to three whole milk (powder) reference samples with certified iodine concentration were included in each run of BM samples as a control for the accuracy of the method. BM reference material does not exist.

Certified iodine content in whole milk reference: mg/kg ± 95% CI: 2.3 ± 0.4	(Gills, 1993)

In each run of FM/infant food samples three to four IF (powder) reference samples with certified iodine concentration were included as a control for the accuracy of the method.

Certified iodine content in infant formula reference: mg/kg ± 95% CI: 1.11 ± 0.17	(Wise and Watters, 2007)

The reference samples were placed at the beginning, in the middle and at the end of a measurement sequence (see Table 17).

The reference powders were stored at room temperature.

3.6.2.8.3. Spike ratio solution

The spike ratio solution was measured regularly during each run to check for possible iodine memory effects which could be caused by accumulation of iodine in the spray chamber of the ICP-MS (Haldimann et al., 1998).

3.6.2.9. Test of iodine stability in cow milk

Some BM samples contained coagulated particles when they arrived at ETH. Most of the particles disappeared after heat treatment and before ICP-MS measurement. Therefore, we concluded that the particles might have mainly consisted of fat. However, they could also originate from acidification of the milk. Haldimann et al. (Haldimann et al., 2000) reported that a low pH is attributed to the formation of volatile iodine species from iodide. To test if there had been an iodine loss during the transport of BM samples, a milk iodine stability test was performed with pasteurized cow milk (organic whole milk, bought at Migros, March 2009) as cow milk has a very similar matrix to BM. The cow milk was measured in triplicate on the day of purchase and then remeasured after seven days storage at ambient temperature. After this week the milk smelled sour and contained coagulations. The measurement procedure was the same as for BM.

3.6.2.10. Validation of X and Z urine reference samples

The two urine reference samples X and Z, which were used as internal control for the Sandell-Kolthoff method at ETH Zurich (see chapter 3.6.1.9.1), were measured by ICP-MS for validation. Each sample was analyzed in triplicate (from three different aliquots).

1 ml of urine sample was pipetted into a 50ml-PP-tube on an analytical scale (three tubes for X and for Z). The exact weight was noted. Then, 25 µl of ^{129}I spike solution was added to the X samples and 50 µl of ^{129}I spike solution was added to the Z samples using an automatic pipette (1 ml tip, DISP mode). The tubes were then filled up to 25 ml with TMAH solution (0.1%), shaken well and directly measured with ICP-MS.

3.7. Dietary assessment of infants

The purpose of the dietary questionnaire was to assess the infants' iodine intake, to get a broader insight into the major iodine sources in infancy in Switzerland, to examine if iodine intake varies by feeding habits such as breastfeeding or formula feeding and to evaluate if fortified industrial infant foods are necessary for an adequate iodine intake of infants.

The first questionnaire assessed the infant's food and consequently iodine intake on the day before urine sample collection. As UIC is an indicator of short-term iodine intake (World Health Organization et al., 2007), it was assumed that iodine intake on the day before urine collection would be most comparable with UIC.

The day-to-day variability of food and iodine intake was examined by a second dietary questionnaire which had to be filled out 3-4 days after the first questionnaire.

3.7.1. Development of the dietary questionnaire

The aim was to develop a self-administered dietary questionnaire which could be filled out by mothers at once without detailed oral instructions from the pediatric practices or by ETH, but which asked the mothers precisely about their infant's food intake on the previous day. Mothers had the option to fill out the dietary questionnaire at the pediatric practice if the samples were collected there or could fill it out at home on the same day as the sampling was performed. It was assumed that mothers normally know well what they feed to their infants and that food intake in infants is less variable compared with adults. Therefore, it was concluded that a retrospective questionnaire (in terms of a 24-hour recall) was accurate to assess the infants' food intake. In any case, it was not possible to use a prospective dietary protocol as it was not feasible to give the questionnaires to the mothers before they were recruited for the study at the routine-check up in the pediatric practice. The questionnaire had to be well-structured and use precise questions in order to lead the mothers to provide the required information without the help of an interviewer. Furthermore, the mothers needed to be able to complete the questionnaires within a reasonable

time frame.

Before the questionnaire was developed, usual consumer wording and recommendations of the most important foods and meals for infants were evaluated. Therefore, information brochures about infant feeding designated for parents were used. Such brochures were available from the Swiss Society for Nutrition (SGE) (Dähler et al., 2007) and the Research Institute of Child Nutrition in Dortmund (FKE) (Forschungsinstitut für Kinderernährung, 2007). It was also examined what kind of commercial infant food was currently available on the Swiss market (in retail shops, pharmacies, health food shops and on web pages of infant food producers). Furthermore, the kind of food and meal patterns which were observed in previous studies on food intake of infants were examined (Fox et al., 2004; Freeman et al., 2000; Kersting et al., 1998; Kudlova and Rames, 2007; Merten et al., 2005; Noble and Emmett, 2001; Stocker, 2001; Thomson et al., 2008) (see also chapters 2.3.3.1 and 2.3.3.2).
We had the support of Dr. M. Wälti, a nutrition scientist and in charge of the Swiss version of EBISpro (see 3.7.3). She also had an infant at the age of the study infants at that time.
With the help of all this information, a questionnaire consisting of eight sections was developed between April and July 2008. The questionnaire was pre-tested for comprehension with a group of 22 mothers some who attended public mother-child meetings and others who were from a circle of friends (see also (Münger, 2008)). Specified problems and unclarities were used to ameliorate the questionnaire. Appendix 11 presents the final version of the questionnaire (German).

3.7.2. Structure of the dietary questionnaire

The complete questionnaire (German version) can be found in Appendix 11.
In the introductory section of the questionnaire, the mother was instructed to record foods and drinks that her infant had consumed the previous day (in the first questionnaire: the day before the samples were collected). She was informed about the importance of mentioning all foods and drinks and was

asked to fill out the questionnaire as precisely as possible. In case the mother did not know what her infant had eaten the day before (e.g. because the infant was in a nursery), she was asked to fill out the questionnaire on the next possible day (as a questionnaire with missing or vague data would not be possible to evaluate). To help the mother remember the day before, she was asked what day that had been and where respectively with whom the infant had spent the previous day (from morning through evening; options to cross: at home or outside the home with mother, father, grandparents, at nursery, day mother/family or other). Furthermore, the mother was asked at what time the infant had been fed the first and the last time and she was informed that "yesterday" meant 0h to 24h.

After the introduction, the mother had to fill out what she had fed her infant in five sections with different meal types. All sections were built up in a similar way but with specific adaptations which allowed the collection of particular information about each meal type. All sections started with a question about how often the infant had received a certain meal type the day before. If the infant had not been fed the meal type the day before, the mother could directly continue with answering the next section. If the infant had received the meal type, the mother was asked to fill out the frequency of consumption on a vertical line in which the day was divided into six periods (morning to night). This would help the mother to reconstruct the day before and make her think of her infant's food intake. See Figure 10 (in German) as an example.

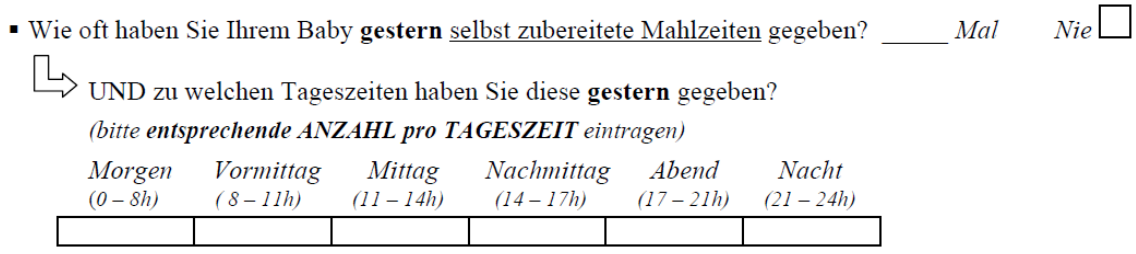


Figure 10: Example of dietary questionnaire section about frequency of meal consumption by the infant (German)

The following information about the different meal types was collected in the five sections of the questionnaires:

1. *Breast milk*: The number of breast-feeds per day, the duration per breast-feed in minutes or the quantity of breast milk fed to infant per feed (if the mother expressed the breast milk manually or by pump).
2. *Formula* (infant, follow-on and other types of formula; in a bottle or drinking cup): The brand and point of purchase of the products, the exact product names, number of spoons used for each preparation (if it was a dry powder) as well as type and quantity [ml] of fluid for preparation and the fraction or amount the infant had actually consumed (from each prepared formula).
3. *Purees/porridges, (semi-)solid food* (eaten with a spoon):

3.1. *Home-made meals and snacks* (such as fruit, vegetables, bread, biscuits or rusks): All ingredients used to prepare the meals with, including the quantity and variety/brand of the ingredients, use of salt for the meals, method of preparation (e.g. cooked, pureed) and amount (fraction) of the prepared meal the infant had actually consumed.

To help the mothers estimate the quantities of foods, pictures of bread and cheese were provided (for weight definition of foods on pictures, see Appendix 12) and a list of household measurements that could be used for estimation (such as spoon, cup or size). The option for exact quantity indication [g or ml] was also mentioned.

In a separate question, mothers were asked if the salt they had used was iodized, non-iodized or unknown and which brand of salt they had used.

3.2. *Ready meals:*

3.2.1. *Ready-to-eat meals* (e.g. in jars, cups): The brand and point of purchase of the products, the exact product names including weight/size of the products and age level, the quantity consumed by the infant and additional ingredients (added by mother).

To illustrate and help with the estimation of sizes of available jars in Switzerland, a photo with jars and their weight (incl. a yoghurt jar as object of comparison) was provided on the questionnaire.

In a separate question, mothers were asked if the meals contained salt.

3.2.2. *Dry powders prepared with fluid* (e.g. baby cereals): The brand and point of purchase of the products, the exact product names including number

of spoons as well as kind and quantity of fluid used for preparation, additional ingredients and the actual quantity (fraction) consumed by the infant.

In sections 2 and 3, an example of each meal type was given to show how the meals should be indicated in the questionnaire (see Figure 11 as example).

We always asked first for the quantity of ingredients the mother had used for the meal preparation and then how much the infant had actually consumed of the whole prepared meal. This method was chosen as it was assumed to be a good way to receive accurate data on the consumed quantities of the infant.

▪ Welche Art und Menge Schoppen/Trinkbecher mit Säuglingsmilchnahrung *oder* anderer Milchnahrung haben Sie Ihrem Baby **gestern** gegeben? *(bitte so genau wie möglich in die Tabelle eintragen)*

Tages-zeit	**Marke** + gekauft bei…	**PRODUKTbezeichnung** (möglichst genau!) + **Anzahl** zur Zubereitung verwendete **Mess-/Ess-/Teelöffel**	**Zubereitet mit:** *z.B. Wasser, Kuhmilch, Säuglingsmilch etc.* → genaue **Bezeichnung, Marke** + verwendete **Menge [ml]**	**davon getrunkener Anteil**
Beispiel: *Morgen*	*HIPP (Coop)*	*Bio-Folgemilch, HIPP 2, 7 Messlöffel*	*Wasser, 200 ml*	*alles (220ml)*

Figure 11: Example of dietary questionnaire (German)

4. *Other foods*: Foods and meals which could not be allocated to the other sections including all necessary information on type and quantity consumed.
5. *Drinks:* Other drinks than breast milk/formula consumed by the infant, the type of drinks, the consumption frequency and the approximate consumption quantity [ml or dl].

   The following drinks could be chosen: tap water, mineral water, tea, juice, diluted and undiluted cow milk, others (indication of type of drink).

Following these questions, the mothers were asked if the reported day had been a usual day for the infant and if not, the reasons for not being so were

inquired on.

The questionnaire finished with some sociodemographic questions about the mother (see 3.4.8).

The second questionnaire was identical to the first one with the instruction that it should be filled out three to four days after the first questionnaire. Mothers should choose a day they had spent together with their infant for the second questionnaire.

3.7.3. EBISpro and SwissFIR

For analysis of dietary data the Swiss version of the nutrition software EBISpro for windows (version 8.0, Dr. J Erhardt, University of Hohenheim, Stuttgart, Germany) is available at the laboratory of human nutrition at ETH. This software can translate the food intake into daily iodine intake. The program contains about 680 foods commonly consumed in Switzerland from the Swiss Food Composition Database (Version 2003, ETH/BAG, Switzerland (Infanger, 2004)) complemented by about 450 foods from the German Food and Nutrition Database (BLS 2.3, Federal Health Department, Berlin, Germany) as well as about 360 Swiss recipes and products (www.ebis-schweiz.ch).
The Swiss Food Composition Database is constantly updated by the project group SwissFIR, ETH Zürich (SwissFIR, 2008), and is available online (www.swissfir.ethz.ch). In one of the next versions of EBISpro, an updated Swiss Food Composition Database will be incorporated in the software (personal communication M. Wälti).

The iodine content is not available for all foods in the databases (in EBISpro: indicated as “0 µg/100g”, which can mean either that the food has no iodine or that the iodine content is not available (personal communication, M. Wälti, 2008); in SwissFIR: if not available, the content is not listed). In such a case a similar food with known iodine content needs to be chosen and documented. Variations in iodine content of foods and products also need to be considered and can depend on where the food crops were grown, seasonality (e.g. milk) or

preparation/production (e.g. use of iodized salt or not). EBISpro software does not give any information about the sources of the nutrient values; SwissFIR indicates the data sources (see www.swissfir.ethz.ch). The mentioned issues need to be taken into account for questionnaire analysis and data interpretation.
As iodine content of some foods have been updated by SwissFIR (version V 2.11, data retrieved 7.4.09) by iodine measurements in Swiss foods (Haldimann et al., 2005), the updated values were adapted in the EBISpro version for the questionnaire analysis (changes were documented).

Data entry and evaluation of the dietary questionnaires was not part of this diploma thesis, but partly the preparation for data entry, see following chapters.

3.7.4. Infant food database

Commercial infant food products, which our study population used, as well as breast milk had to be entered manually in the database of EBISpro software. For data-input, most recent detailed product information of producers was ordered or, in case they did not have any (e.g. Coop), the information was directly taken from product packages.
During set-up of the infant food database, it was recognized that producers regularly change and improve their formula and infant food products. Therefore, iodine content of some infant products could have changed during the study; especially because the legislation of iodine content in formula/infant foods had been changed in 2008 (see chapter 2.3.3.3). The parents were not asked to indicate the date of purchase or charge number of products. This needs to be taken into account for data interpretation and has the effect that the database regularly needs to be updated for further use.
Within this thesis, 148 products were entered into the database.

3.7.4.1. Products with labeled iodine concentration

If the iodine content of a product was labeled on its package or indicated in the detailed product information of the producer, the product was directly entered into EBISpro as a new food item with all available nutrient data. The iodine content was labeled for all products which were fortified with iodine, except for

some products with iodized salt. For 72 of the entered products the iodine content was labeled.

3.7.4.2. Products without iodine labeling

For products without iodine labeling the iodine content was calculated with EBISpro using the following method:

- First, all ingredients were listed with their percentage in the product (if available) in quantitatively downward order.
- Percentages were then directly transformed to g/100g.
- For ingredients without the percentage value, the quantity [g] per 100 g was estimated based on the rule that ingredients have to be listed on the product in quantitatively downward order (decisive is the mass fraction at time of processing) (EDI, 2005a) and in total, the ingredients should not exceed 100 g per 100 g of the product. Ingredients of very small quantity and containing practically no iodine (e.g. food additives or vitamins) were ignored.
- Then the ingredients of the product were entered into EBISpro as a recipe. The summarized nutrient content of the product was displayed and if necessary quantities [g] of estimated ingredients were adapted to obtain a similar content of macro-/micronutrients as labeled on the product.
- Finally, the product was entered into EBISpro as a new food item using the nutrient contents that were labeled on the product and adding the iodine content that was calculated with the recipe.

The iodine content of 73 of the entered products had to be calculated in this way. The iodine content of three products was measured with ICP-MS and in this case the measured value was used.

3.7.4.3. Breast milk

Breast milk was entered as a new food item into EBISpro with nutrient composition from Souci et al. (Souci and Deutsche Forschungsanstalt für Lebensmittelchemie (Garching), 2008). The iodine content was replaced by the measured median iodine concentration of breast milk from the present study.

3.7.4.4. Infant food categories

Special codes in EBISpro were chosen for the newly entered infant food products to categorize them into the following eight food groups for data analysis:

- Infant and follow-on formula, junior-milk (to prepare with water or ready to drink)
- Instant milk-cereal mixtures (already containing dry FM or cow milk to prepare porridges by adding water)
- Dry/instant milk-free cereal based products and cereal mixtures (to prepare porridges by adding water or milk)
- Ready-to-eat cereal-milk-(fruit/vegetable)-porridges, "Trinkmahlzeiten", baby yoghurts and desserts (containing milk) in jars, cups or drink cartons
- Vegetable and fruit purees in jars or cups (simple recipes, just containing fruits/vegetables/potatoes and maybe some cereal/starch/oil, no milk)
- Baby ready meal menus (vegetable-carbohydrate-(meat)) in jars or cups (more complicated recipes, labeled as "menu" by producer)
- Biscuits, rusks and bars
- Baby pasta

The categories were chosen according to existing product categories on the Swiss market and other studies were therefore considered as well (Kersting et al., 1998; Noble and Emmett, 2001). The category codes also showed if a product was fortified with iodine or not.

3.7.5. Definition of food measurement units

As infants often consume small amounts of food, the standard amounts and portion sizes given by EBISpro are usually too large. Therefore, measurement units for foods, which were indicated by the mothers in the questionnaires, and their weight were defined for data entry (e.g. average weight for a tea-/tablespoon of foods or weight for a piece of pasta or slice of sausage). Small measurement units for some foods were available in EBISpro and some were taken from Infanger, Wachtel and Zacharias et al. (Infanger, 2004; Wachtel,

1990; Zacharias and Deutsche Gesellschaft für Hauswirtschaft, 1992). Some were weighed by us at ETH. To define the weight of a measurement unit for a food, we weighed a food ten times with the same measurement unit and then took the average weight. 128 different measurement units for various foods were defined so far of which 46 were weighed by us (see Appendix 13).

3.7.6. Definition of standard portion sizes

As we recognized that in some questionnaires the quantities of eaten foods were not indicated by parents, it was necessary to define standard portion sizes for data entry to make it possible to estimate the food intake of the infant. Of course these portion sizes can differ greatly from the actual food intake. For the definition, recommended standard recipes and quantities of ingredients for home-made purees and porridges may be used from SGE and FKE (Dähler et al., 2007; Forschungsinstitut für Kinderernährung, 2007) and adapted with the actually used ingredients in each case. SGE and FKE recommend very similar portion sizes ranging from 140 to 240 g per meal. The standard meals they defined are: vegetable-potato-puree, vegetable-potato-meat-puree, milk-cereal-porridge and fruit-cereal-porridge (Dähler et al., 2007; Forschungsinstitut für Kinderernährung, 2007).

Another option is to use portion sizes of ready-meal products which contain the same or a similar type of meal that was fed to the infant and which are intended for the respective age group.

3.7.7. Estimation of breast milk intake

It was not decided in this diploma thesis which method is best for the estimation of breast milk intake in the present study. An overview of possible calculation methods can be found in the background section (chapter 2.4.2.2.2). The golden standard method, which is individual weighing of infants before and after each breast-feed during 24 hours, was not applicable in this study for practical reasons.

The method used by Emmett et al. and Mills and Tyler (Emmett et al., 2000; Mills and Tyler, 1992) would probably give imprecise results and would over- or

underestimate breast milk intake of infants, as mothers in our study only had to indicate the approximate breast-feeding duration of each feed on the day before assessment. Therefore, the methods applied in the US FITS study (Devaney et al., 2004) or by Fisher et al. (Fisher et al., 2008) might be more suitable. As assumption of basic daily breast milk intake, the amounts published by Butte et al. could be used (Butte et al., 2002). More details are given in chapter 2.4.2.2.2.

3.7.8. Comparison with energy requirement, over-/underreporting

A recent study found an overestimation of energy and nutrient intake in infants comparing 24-hour dietary recalls with weighed food records (Fisher et al., 2008). Therefore, it is important to compare the calculated energy intake of the questionnaires with the predicted energy requirement for the infants.

In a British study on infant food intake (Noble and Emmett, 2001), predicted energy expenditure was compared with observed energy intake and based on that, infants were categorized as potential under- or over-reporters. The following formula was used to calculate the predicted energy expenditure (PEE): PEE = body weight (kg) * energy requirement (kJ/kg) (Noble and Emmett, 2001). Energy requirements for infants aged six and twelve months can be found in publications of Butte and the Joint FAO/WHO/UNU Expert Consultation of 2004. Estimated daily energy requirements for boys and girls are 337 respectively 341 kJ/kg at 6 months of age and 337 respectively 331 kJ/kg at 12 months of age (Butte, 2005; Joint FAO/WHO/UNU Expert Consultation, 2004).

3.8. Statistical analyses

Data processing and statistical analyses were performed using the statistics program SPSS (SPSS inc., Chicago, IL, version 16.0) and Excel (Microsoft, Seattle, WA, 2003).

Kolmogorov-Smirnov (K-S) test (with Lillifores significance correction) was used to check for the normality of the data. Normally distributed data were presented as mean ± SD, non-normally distributed data were presented as median (95% CI or range). UI and BM iodine concentrations were not normally distributed.

Mann-Whitney U (MWU) test was used to calculate the difference between two groups of continuous, non-normally distributed data.

Kruskal-Wallis (K-W) test was used for group comparisons of continuous, non-normally distributed variables (with Bonferroni corrected post-hoc tests).

Pearson's chi-square test was performed to compare categorical variables.

Correlations between continuous, normally distributed data were tested using correlation analysis of Pearson (r) and correlations between continuous, non-normally distributed variables were analyzed using Spearman correlation analysis (r_s).

P values < 0.05 were considered significant.

Box plots: the line in the middle of the box represents the median, the lower end of the box the 25^{th} percentile and the upper end the 75^{th} percentile. The whiskers represent the lowest/highest value that is not yet an outlier. The maximum length of the whiskers is 1.5-fold the height of the box, values outside this range are shown as outliers.

4. RESULTS

4.1. Selection of the pediatric practices

Invitation letters for study participation were sent to 441 pediatricians all over Switzerland. The biggest part of the doctors' addresses was provided by the pediatricians' association "Forum für Praxispädiatrie" (n = 411, mainly German-speaking Switzerland), some by the "Swiss pediatric society" (n = 9, French-speaking Switzerland) and some were taken from the phone book (n = 21, Italian-speaking Switzerland). As there was no positive answer from the region "Ticino" to the invitation letter, a reminder letter was sent to the doctors of this region. In the Lake Geneva region only one doctor agreed to participate in the study. Because of time and translational reasons, it was decided to postpone contacting more pediatricians in the French-speaking part of Switzerland ("Lake Geneva region"). The total response rate by pediatricians was 30.6% [n=135]. 13.8% [n=61, in 50 pediatric practices] were positive responses (see Table 18 for distribution to regions). The number of infants visiting the pediatric practice for routine check-up/vaccination per week ranged from < 1 to < 25 for each age group. Eighteen pediatric practices were selected and sequentially visited for study instruction starting from the end of July to November 2008. Table 18 lists the responses and participating pediatric practices (state of May 2009) and Figure 12 shows the geographical distribution.

Table 18: Overview of pediatric practices

Greater Swiss regions	**Required pediatric practices** [n]	**Positive responses** [n] (by practice)	**Participating practices** [n] (May 2009)	**Drop-outs** [n]	**Need for search/ replacement** [n]
Total	**20**	**50**	**15**	**3**	**5**
Lake Geneva region	3	1	**1**	0	2
Espace Mittelland	4	12	**2**	2	2
Northwestern Switzerland	3	12	**3**	0	0
Zurich	4	11	**3**	1	1
Eastern Switzerland	3	6	**3**	0	0
Central Switzerland	2	5	**2**	0	0
Ticino	1	3	**1**	0	0

At the beginning of May 2009, fifteen pediatric practices were still participating

in the study. Two of them had already completed the study (located in Eastern and Central Switzerland) and thirteen were still collecting samples. Three pediatric practices decided to quit the study. The reason for drop-outs were either relocation (one practice) or too few German-speaking mothers (two practices). Due to time constraints their replacement was postponed and is not reported in the diploma thesis (Table 18 lists the drop-outs).

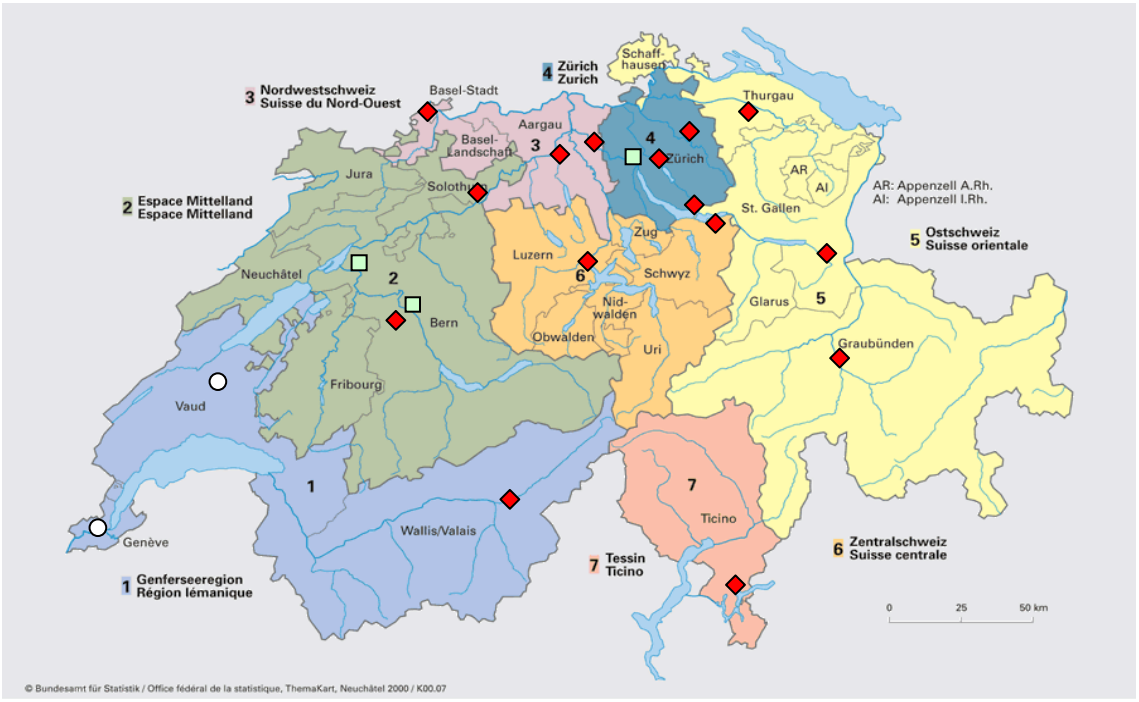


Figure 12: Geographic distribution of pediatric practices

Legend: Red rhombus: participating practices (state May 2009); White circle: need to be selected; green rectangle: drop-outs (Picture source: (Swiss Federal Statistical Office, 2008a))

4.2. Status of the study

The results presented here are an interim evaluation of the study with data collected from August 2008 to May 2009. The study is continued until the desired number of infants is accomplished. The sampling took a longer time than expected, therefore the originally planned time period needed to be expanded. Based on communication with the still participating pediatric practices and the final questionnaire for the practices, the main reasons for the above mentioned issue were: small weekly patient numbers, often a huge work load in the practice and therefore they did not always have time to recruit

infants, language problems with the parents and therefore it was not possible to include all eligible infants. The two pediatric practices having completed the study reported to have asked approximately 75% of the mothers of all eligible infants for study participation. As a main reason for preliminary study exclusion, the two pediatricians indicated non-term birth of the infant (10% of all infants in both age groups). One pediatric practice reported that 5% of mothers declined study participation and the other practice specified that 15% and 10% of mothers of 6- and 12-month-old infants, respectively, refused to participate in the study. The main reason mentioned by the mothers was lack of interest in the study (data from final questionnaire of the two finished practices).

4.3. Subject description

4.3.1. Sample size

The subjects of the interim study evaluation were enrolled for the study from mid August 2008 to the beginning of May 2009. The total number of mother-infant pairs who agreed to participate in the study was n = 379 (6-mo: n = 193, 12-mo: n = 186, these numbers are based on the number of subscribed consent forms we received). Out of those, 40 infants and 36 mothers had to be excluded from the study due to the following reasons:

Twenty-seven mother-infant pairs were excluded because they had not provided any samples (6-mo: n = 7; 12-mo: n = 20). One mother withdrew her study consent. In four cases, we only received a sample of the infant (12-mo: n = 2) or mother (12-mo: n = 2) and included the subject with the sample. Five mother-infant pairs had to be excluded because they did not fulfill the following inclusion criteria: the mother had not been resident in Switzerland for more than one year before the infant's birth (6-mo: n = 1), recent history of thyroid disorder of the mother (12-mo: n = 1), missing data concerning use of contrast media/iodine containing drugs (6-mo: n = 2), various missing data for inclusion criteria (6-mo: n = 1). One infant (12-mo) was excluded because the pediatrician indicated that its health was not intact (recurrent urinary tract infection). Another infant had an unexpected surgery after study consent (12-mo) and was therefore excluded. The mothers of these two infants were still included.

Two infants (6- and 12-mo) were excluded from the analysis as their UI values were considered as outliers. They had a concentration > 1000 µg/l (1504 µg/l, 1691 µg/l). This was suspected as either contamination of the collection material (e.g. by iodine containing disinfectants at the pediatric practice) or contamination during the collection (e.g. due to application of iodine containing disinfectants to the infant). Their mothers were included.
One mother-infant pair (6-mo) was excluded because the BM sample was considered as outlier. Its iodine concentration was 512 µg/kg (measured twice), which was much higher than all other BM samples. The reason for this could be a contamination (e.g. by an iodine containing disinfectant), an unusually high iodine intake (e.g. iodine tablets or algae) or some metabolic disorder. The UIC of this mother was 63 µg/l and the UIC of her infant was 873 µg/l. It was decided to exclude mother and infant since the UIC of the infant was also very high and their high values could have a metabolic reason. The responsible pediatrician was informed.

Finally, 337 mother-infant pairs, two single infants and six single mothers were included in the present analysis. 52.8 % of all infants belonged to the 6-mo age group (infants n = 179; mothers n = 180) and 47.2% to the 12-mo age group (infants n = 160; mothers n = 163). An overview of the included infants in each region and pediatric practice is given in Table 19 (if there is no comment, the numbers are the same for mothers).
The mother-infant pairs were enrolled in all seven regions by 17 pediatric practices. The practices which dropped out during the study, but had enrolled some subjects, were also included in the analysis (practice no. 7 and 13; practice no. 15 (Espace Mittelland) did not collect any samples before drop-out and was therefore not counted).
The mean (± SD) number of included infants per pediatric practice was eleven (± nine) 6-month-old and nine (± nine) 12-month-old infants (ranging from 0 to 32 infants). Two practices (no. 4 and 6) had already enrolled the desired number of thirty infants per age group (see Table 19).
Most of the practices were located in urban areas (13 practices). In total, 287 of the included urine samples of infants came from practices in urban areas. Only

four practices were located in rural areas and they collected 52 urine samples from infants (see Table 19; “urban/rural area” was defined according to the Swiss Federal Statistical office (Bundesamt für Statistik, 2009a)).

Table 19: Included infants (and mothers) in each region and pediatric practice

Region	**Practice ident. no.**	**Urban/ rural**	**Infants 6-mo** [n] [a]	**Infants 12-mo** [n] [a]	**Total** of **infants per region** [n] [a]	[% of total]
Lake Geneva	12	u	3	1	4	1.2
Espace Mittelland	13	r	4	1	35	10.3
	14	r	10	6		
	17	u	10	4		
Northwestern Switzerland	2	u	9 [b]	5 [b]	54 [e]	15.9
	3	u	13	18 [c]		
	16	u	5	4		
Zurich	1	u	14	11	46	13.6
	5	u	8	5		
	7	u	2	0		
	11	u	2	4		
Eastern Switzerland	4	u	31	30 [d, b]	92 [d, b]	27.1
	9	r	3	11		
	18	r	8	9		
Central Switzerland	6	u	30	32 [d]	91 [d]	26.8
	10	u	19	10		
Ticino	8	u	8	9 [b]	17 [b]	5.0
TOTAL infants	**17 [f] practices**		**179**	**160**	**339**	100
TOTAL mothers	**17 [f] practices**		**180**	**163**	**343**	

Abbreviations: practice ident. no. = identification number of practice; u = urban, r = rural
[a] If there is no comment, the number is the same for mothers
[b] Additionally one single mother
[c] Additionally two single mothers
[d] Includes one single infant
[e] Additionally four single mothers
[f] Including 2 drop-out practices (no. 7 + 13), the third drop-out practice did not collect any samples and was therefore not listed (no. 15, Espace Mittelland)

In relation to the number of annual births in Switzerland, the sample included about every 180th infant in Switzerland (approximately 1:360 per age group). For this calculation the Lake Geneva region was excluded from the number of annual births as most pediatric practices were not recruited from there (average number of annual births in Switzerland in 2007/08: n = 75’593; excl. Lake Geneva region n = 60’443 (Swiss Federal Statistical Office, 2008b)).

4.3.2. Subject characteristics – Infants and their mothers

4.3.2.1. Inclusion criteria

The included study subjects fulfilled the inclusion criteria. All infants had a term birth. None had a history of thyroid disorders and the pediatricians indicated intact health of the infants. All mothers had lived in Switzerland for at least one year before the birth of their infant and since the infant's birth, together with the infant. No mother had a history of recent thyroid disorders and none had received contrast media or iodine-containing drugs since pregnancy. Two infants (8.2 month-old and 13.8 month-old) were above the indicated age range (± 6 weeks), but it was still decided to include them.

4.3.2.2. Infant characteristics

Table 20 shows the characteristics of the infants included in the study.

The age of infants in the 6-mo group ranged from 5.2 to 8.2 months (mean 6.3 mo). In the 12-mo group, age ranged from 11.4 to 13.8 months (mean 12.3 mo). In the 6-mo group there were slightly more girls (51%) and in the 12-mo group more boys (58%). Overall, 47% of participants were girls, 53% were boys.

Table 20: Characteristics of the infants

Infants	**Age group**		**Total**
	6-mo	**12-mo**	
n	*179*	*160*	*339*
Age [mo]	6.3 ± 0.4 [a]	12.3 ± 0.4	9.3 ± 3.0
Sex ratio [n girls/boys]	91/88	67/93	158/181
Body weight [kg]	7.67 ± 0.86	9.73 ± 1.17	8.65 ± 1.45
Body length [cm]	67.4 ± 2.5	75.7 ± 3.0	71.3 ± 5.0
Age-specific z-scores [b]			
WHZ-score	- 0.10 ± 0.96	0.24 ± 0.97	0.06 ± 0.98
HAZ-score	0.12 ± 1.04	0.13 ± 1.08	0.12 ± 1.06
WAZ-score	- 0.09 ± 0.90	0.23 ± 0.94	0.06 ± 0.93
BAZ-score	- 0.21 ± 0.96	0.22 ± 0.99	0.00 ± 1.00
Delivery mode [n]			
Vaginal	136	118	254
Cesarean	43	42	85

[a] mean ± SD (all such values)
[b] Abbreviations: WHZ-score = Weight-for-height z-score; HAZ-score = Height-for-age z-score; WAZ-score = Weight-for-age z-score; BAZ-score = BMI-for-age z-score

To ensure the fulfillment of normal growth criteria of the study infants, their age specific z-scores were calculated (see Table 20) and compared to the WHO child growth standards (see 3.4.3.3 Child growth standards). The calculated mean z-scores ranged between - 0.21 and 0.12 in the 6-month-old[6] infants and between 0.13 and 0.24 in the 12-mo group, which means that the z-scores were all very close to the WHO standard median 0.00. All z-scores were normally distributed (K-S test). The SDs of all z-scores were either < 1 or slightly > 1 indicating accurately conducted measurements (WHO, 2009). Figure 13 shows the z-score curves for all four indicators and compares the study infants with the WHO standard population (displayed by WHO Anthro (WHO, 2009)). All curves of the study infants were close to the curves of the standard population.

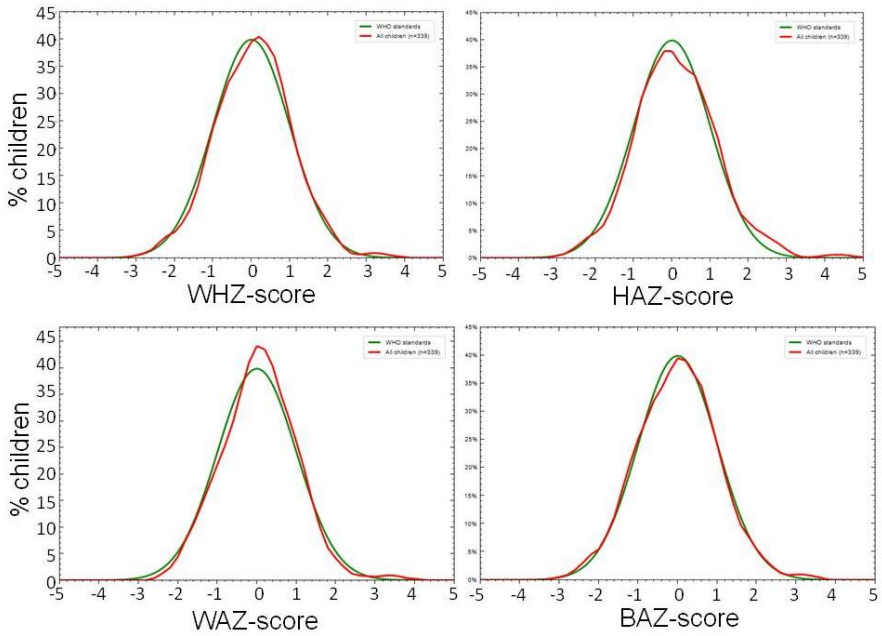


Figure 13: Z-score curves of all study children (n = 339, red curves) and WHO standards (green curves): WHZ = Weight-for-height; HAZ = Height-for-age; WAZ = Weight-for-age; BAZ = BMI-for-age z-scores

For the four anthropometric indicators, the prevalence of infants with z-scores under - 2 or over + 2 (WHO cut-off) was ≤ 2.3% (2.3% = expected prevalence in the reference population (WHO Expert Committee on Physical Status, 1995)) for 6-month/12-month-old boys and girls, with the following exceptions:

[6] 6-month-old/12-month-old always refers to the age group and is not an exact age statement.

- *WHZ-score*: 3% of 12-month-old girls < - 2 and 3.3% of 6-month-old girls > + 2
- *HAZ-score:* 3% of 12-month-old girls < - 2
- *WAZ-score:* 3% of 12-month-old girls < - 2
- *BAZ-score:* 4.5% of 12-month-old boys and 3% of 12-month-old girls < - 2, 3.2% of 12-month-old boys > + 2 and 3.3% of 6-month-old and 3% of 12-month-old girls > + 2.

This means that a very low percentage of infants in the present study population were considered at risk of being underweight, stunted, wasted or was overweight and we could assume that the study infants were growing normally according to the WHO child growth standards (WHO Multicentre Growth Reference Study Group, 2006). Detailed z-score values are given in Appendix 15.

4.3.2.3. Maternal characteristics

Table 21 shows the characteristics of the included mothers.

Table 21: Characteristics of the mothers

Mothers	**Age group of infants**		**Total**
	6-mo	**12-mo**	
n	*180*	*163*	*343*
Age [yr]	32.4 ± 4.2 [a]	32.6 ± 5.0	32.5 ± 4.6
Body weight [kg]	64.6 ± 11.5 [b]	64.7 ± 12.5 [c]	64.6 ± 12.0 [d]
Height [m]	1.68 ± 0.06	1.66 ± 0.06 [c]	1.67 ± 0.06 [c]
BMI [kg/m^2]	22.9 ± 3.8 [b]	23.3 ± 4.2 [c]	23.1 ± 4.0 [d]
Lactating [n]			
Yes	102	29	131
No	78	134	212
Nationality [n]			
Swiss	158	132	290
Foreign	22	31	53

[a] mean ± SD (all such values);
[b - d] Missing data/values: [b] n = 4; [c] n = 3; [d] n = 7

57% of the mothers of 6-month-old infants were lactating and 18% of the mothers of 12-month-old infants (mean of all mothers 38%).

85% of all mothers were Swiss and 15% had a foreign nationality (4% German, 2% Italian, 1% Kosovar, 8% various nationalities).

Table 22 shows the supplement and salt use of mothers by infant age group and in total.

Table 22: Supplement/salt use of mothers

Mothers	**Age group of infants**		**Total**
	6-mo	**12-mo**	
n	*180*	*163*	*343*
Use of multivitamin/mineral supplements [n]		[a]	[a]
Yes, with iodine	6	7	13
Yes, unclear if with iodine or not	7	8	15
Yes, but without iodine	48	31	79
No	119	114	233
Use of iodized salt at home [n]	[b]	[c]	[a]
Yes	157	138	295
No	9	11	20
Unknown	12	13	25

[a – c] Missing data/values: [a] n = 3; [b] n = 2; [c] n = 1

In total, about one third of the mothers reported taking multivitamin/mineral supplements (Table 22). Of these only 12% specified iodine-containing supplements and in 14% of cases, it was unclear if their supplement contained iodine. The other supplement users named supplements without iodine.

Looking at lactating (n = 131, missing data concerning supplement use n = 1) and non-lactating mothers (n = 212, missing data concerning supplement use n = 2), 40% (*n = 52*) and 26% (*n = 55*) were taking a supplement. Nevertheless, among these supplement users only 10% (*n = 5*) and 15% (*n = 8*) of the lactating and non-lactating mothers were taking an iodine-containing supplement. For 14% of the supplement users it was unclear if their supplement contained iodine (lactating n = 6, non-lactating n = 9) based on the information received from them. Five of those users were taking a vitamin/mineral supplement containing some kind of algae (mainly sweet water or no clear information was available). However, iodine was not displayed in the nutrition facts of these products and therefore they were allocated the “unclear” group.

None of the mothers answered the question concerning the use of algae supplements with “yes” (data not displayed).

The most frequently used supplement was Elevit pronatal (Bayer (Schweiz) AG, Zürich), which is especially meant for pregnant and lactating women or for women with the wish to have a child. 56% (n = 29) of lactating and 33% (n = 18) of non-lactating supplement users took Elevit pronatal. However, it does not contain any iodine.

The iodine containing supplements that were used by mothers (n) were:

Allsan (Biomed AG, Dübendorf, Switzerland; 34 µg iodine (as KI) per dragée; lactating n = 3, non-lactating n = 2), Gynéfam (EFFIK SA, Nyon, Switzerland; 150 µg iodine (as KI) per capsule; lactating n = 1, non-lactating n = 1), Multivitamin Complex (Herbalife, Darmstadt, Germany; 25 µg iodine (as KI) per tablet; non-lactating n = 2), Supradyn (Bayer (Schweiz) AG, Zürich; 75 µg iodine per tablet; non-lactating n = 1), Adapta Maman (Adapta, Lenzburg, Switzerland; 52 µg iodine per daily portion, lactating n = 1), Centrum (Whitehall-Much GmbH, Münster, Germany; 100 µg iodine (as KI) per tablet; non-lactating n = 1), Green Source (Puritan, UK; 50 µg iodine (as kelp) per tablet; non-lactating n = 1).

87% of the mothers reported use of iodized salt and only 6% acknowledged not using iodized salt at home. Seven percent did not know if they were using iodized salt or not (three mothers did not answer the question, excluded from percentage calculation) (Table 22).

4.3.3. Infant feeding practices

The results regarding infant feeding practices are based on the data indicated on the individual registration forms. If some dietary data was missing on a form, we made use of the dietary questionnaire (documented). The indicated percentages in the text were always calculated with the total number of valid data. Missing data was not included in the percentage calculations (see respective tables for number of missing data). Percentages were always rounded up or down to integers.

4.3.3.1. Breast milk and formula

Table 23 gives an overview of the breast milk (BM) and formula (FM) intake of the infants (questions 1 and 2 on the individual registration form, Appendix 7).

Table 23: Intake of breast milk and formula

	Age group		Total
	6-mo	12-mo	
n	*179*	*160*	*339*
Breast milk			
BM at some time [a] [n]		[g]	[g]
Yes	173	141	314
No	6	17	23
Currently BM			
Yes - Exclusively [n] [b]	9	0	9
(times/day) [e]	(6.7 ± 1.6)		(6.7 ± 1.6)
- Predominantly [n] [c]	2	0	2
(times/day)	(6.5 ± 2.1)		(6.5 ± 2.1)
- Partially [n] [d]	91	29	120
(times/day)	(4.3 ± 1.7)	(2.6 ± 1.5)	(3.9 ± 1.8)
No (incl. never BM)	77	131	208
Formula			
FM at some time [a] [n]	[f]	[g]	[h]
Yes	116	135	251
No	62	23	85
Currently FM			
Yes - Exclusively [n]	2	0	2
(times/day) [e]	(4.8 ± 0.4)		(4.8 ± 0.4)
- Daily [n]	100	88	188
(times/day)	(3.4 ± 1.4)	(2.0 ± 0.9 [f])	(2.7 ± 1.3)
- Occasionally: weekly	8	4	12
monthly	0	1	1
No (incl. never FM)	69	67	136

Abbreviations: BM = breast milk; FM = formula
[a] Infant had at some time received BM/FM since the birth
[b] Defined as: Only breast milk, no other drinks or foods (except drugs)
[c] Defined as: Predominantly breast milk, but also water (-based) fluids/fruit juice, no formula or other foods
[d] Defined as: Mixed feeding of breast milk and other sources of energy and nutrients
[e] Mean ± SD (all such values); [f-h] Missing data: [f] n = 1; [g] n = 2; [h] n = 3

Ninety-three percent of the infants had at some time received BM (6-mo: 97%; 12-mo: 89%) and only 75% had at some time received FM (6-mo: 65%; 12-mo: 85%) since they were born (see also Table 23).

At the time of study participation only 6% of the 6-month-old and none of the 12-month-old infants were still being exclusively or predominantly breast-fed. 51% of the 6-month-old infants were partially breast-fed at an average of four breast-feeds per day and 18% of the 12-month-old infants still received BM at an

average of 3 times daily. 40% of the 6-month-old infants and 71% of the 12-month-old infants, who were at some time breast-fed, were not receiving BM anymore when the study was carried out (see also Table 23).

Two 6-month-old infants (1%) received FM as their only food source. About 55% of the infants in both age groups received FM on a daily basis when the study was carried out and 4.5% of the 6-month-old respectively 3% of the 12-month-old infants received FM occasionally. The 6-month-old infants received FM on average three times a day and the 12-month-old infants just two times a day. Forty percent (6-mo: 39%; 12-mo: 42%) of the infants were not fed FM at the time of study participation (see also Table 23).

4.3.3.2. (Semi-)solid foods & fluids with nutritional value (CF/FF)

Table 24 gives an overview of the (semi-)solid foods and fluids with nutritional value (other than BM/FM) which were consumed by the infants (questions 3 - 5 on the individual registration form, Appendix 7). These foods were categorized as complementary/family foods here (CF/FF). The data should give an insight into the types of food and meals infants already received in addition or instead of BM/FM and if they already received them on a daily basis or not. As CF/FF intake was suspected to show greater daily variability than BM/FM intake, the "frequency per day" was not taken into account for UIC analysis, especially as it might not reflect the intake of the day before the urine collection. Therefore, the frequency of CF/FF intake per day should give a more general insight into current CF/FF feeding habits. Moreover, it might not necessarily correlate with the amount the infants actually ate. For more detailed analysis, the data of the dietary questionnaires would be required.

During data input it was recognized that the indicated total number of daily CF/FF meals (question 3 on the individual registration form, Appendix 7) was often not consistent with the accumulated number of the individual types of CF/FF meals (question 4). Reasons for this could be: 1) the infant also ate other foods which were not listed, 2) in case a food was only given as snack, it was not counted as a meal, 3) the consumption of cow milk was not taken into account by some doctors. In some cases the same number of daily eaten/drunk

FM-cereal porridges/bottles was reported in the question about CF/FF (question 4.a) as the daily number of FM in the question about FM (question 2.1). This indicated a double reporting of FM if any cereal was added to the FM bottle.

88% and 100% of the 6-month-old and 12-month-old infants already received CF/FF. Most infants in both age groups were fed the different types of CF/FF either daily or did not receive them. Few mothers reported feeding certain types of CF/FF on a weekly basis (see Table 24).

Most of 6-month-old infants already received vegetable-carbohydrate-(meat)-meals (80%) on a daily basis. About half (48%) of 6-month-old infants were fed daily a fruit-(cereal)-meal. 28% already received milk-cereal porridges/bottles with FM on a daily basis. As mentioned before, there might be a certain percentage of double reporting with FM intake in this 28% when the mother added some cereal to the FM bottle. Just six 6-month-old infants received daily milk-cereal porridges/bottles with cow milk. Ninety-six percent of mothers indicated that their 6-month-old infant was not yet fed porridges containing cow milk. Only one 6-month-old infant was fed diluted cow milk (w/o cereals) once a week and none received undiluted cow milk (see also Table 24).

All 12-month-old infants daily ate vegetable-carbohydrate-(meat)-meals and nearly all (93%) consumed fruit-(cereal)-meals on a daily basis. 16% of 12-month-old infants daily received diluted and 28% even undiluted cow milk (w/o cereals). Twenty-six percent of mothers of 12-month-old infants reported feeding their infant a milk-cereal porridge/bottle with cow milk daily and 31% specified giving a milk-cereal porridge/bottle with FM on a daily basis (see also Table 24).

Only few 6-month-old infants already received food from the family table - meaning food that was prepared for the whole family -, one daily and twelve occasionally (missing data n = 3). At the age of 12 months however, only ten infants had not yet received family food. 79% of the 12-month-old infants ate family food daily (n = 125) and 15% occasionally (n = 23) (missing data n = 2) (data not reported in the table).

Table 24: Intake of (semi-)solid foods & fluids with nutritional value (CF/FF) by infants

(Semi-)solid foods & fluids with nutritional value (CF/FF) [a] (excl. fruit juices, sweetened drinks)	**Age group**		**Total**
	6-mo	**12-mo**	
n	*179*	*160*	*339*
Already CF or FF [n]			
Yes [b]	158	160	318
(times/day)	(1.7 ± 0.7) [c]	(3.5 ± 1.2 [d])	(2.6 ± 1.4 [d])
No	21	0	21
Types of CF/FF			
Milk-cereal porridge/bottle with FM		[e]	[e]
Yes - Daily [n] (times/day)	51 (1.5 ± 1.0 [e])	49 (1.4 ± 0.9)	100 (1.5 ± 0.9 [e])
- Weekly [n] (times/week)	4 (1.4 ± 0.5)	1 (2.0 ± 0.0)	5 (1.5 ± 0.5)
No [n]	124	108	232
Milk-cereal porridge/bottle with cow milk (+ water)	[d]	[e]	[f]
Yes - Daily [n] (times/day)	6 (1.3 ± 0.5)	41 (1.3 ± 0.8 [d])	47 (1.3 ± 0.8 [d])
- Weekly [n] (times/week)	0	1 (2.0 ± 0)	1 (2.0 ± 0)
No [n]	172	116	288
Diluted cow milk (w/o cereals)		[e]	[e]
Yes - Daily [n] (times/day)	0	26 (1.5 ± 0.7 [d])	26 (1.5 ± 0.7 [d])
- Weekly [n] (times/week)	1 (1.0 ± 0)	2 (3.5 ± 2.1)	3 (2.7 ± 2.1)
No [n]	178	130	308
Undiluted cow milk (w/o cereals)		[e]	[e]
Yes - Daily [n] (times/day)	0	44 (1.7 ± 0.7)	44 (1.7 ± 0.7)
- Weekly [n] (times/week)	0	2 (2.0 ± 1.4)	2 (2.0 ± 1.4)
No [n]	179	112	291
Vegetable-carbohydrate-(meat) -meals (w/o milk)		[d]	[d]
Yes - Daily [n] (times/day)	143 (1.0 ± 0.2)	159 (1.5 ± 0.6 [d])	302 (1.3 ± 0.5 [d])
- Weekly [n] (times/week)	1 (2.0 ± 0)	0	1 (2.0 ± 0)
No [n]	35	0	35
Fruit-(cereal)-meals (w/o milk)		[e]	[e]
Yes - Daily [n] (times/day)	86 (1.0 ± 0.2 [d])	147 (1.3 ± 0.5)	233 (1.2 ± 0.4 [d])
- Weekly [n] (times/week)	3 (3.2 ± 1.3)	3 (3.2 ± 0.3)	6 (3.2 ± 0.8)
No [n]	90	8	98

[a] In this thesis these were defined as complementary foods (CF) and family foods (FF).
[b] Even if the infant already ate completely with the family, he/she was also included in "yes" here.
[c] Mean ± SD (all such values)
[d - f] Missing data: [d] n = 1; [e] n = 2; [f] n = 3

4.3.3.3. Summary infant feeding practices

Table 25 summarizes the current infant feeding practice by grouping the infants into seven different feeding patterns.

Table 25: Summarized current infant feeding practices

Σ infant feeding practice	**Age group**				**Total**	
	6-mo		**12-mo**			
n	*179*		*160*		*339*	
	%	(n)	%	(n)	%	(n)
Only BM (exclusively or predominantly)	6	(11)	0	--	3	(11)
Only FM	1	(2)	0	--	1	(2)
Only BM & FM	4	(8)	0	--	2	(8)
BM & CF/FF	32	(58)	11	(17)	22	(75)
FM & CF/FF	42	(75)	51	(81)	46	(156)
BM & FM & CF/FF	14	(25)	8	(12)	11	(37)
No BM, no FM, but CF/FF	0	--	31	(50)	15	(50)

Abbreviations: BM = breast milk; FM = formula milk; CF = complementary food; FF = family food

At the age of 6 months, the majority of infants received a combination of FM and CF/FF (42%), followed by infants who received BM and CF/FF (32%). Only few infants were fed a combination of BM, FM and CF/FF (14%). All 6-month-old infants received either BM or FM and a low percentage of 6-month-old infants did not yet receive CF/FF (12%).

At the age of 12 months, about half of the infants received a combination of FM and CF/FF. Nearly one third of them received neither BM nor FM anymore (31%). All except two of those infants, however, received either porridges containing FM/cow milk or cow milk as a drink (diluted or undiluted) on a daily basis (data not shown in table). A rather low percentage (18%) of the 12-month-old infants still received BM in combination with either CF/FF or FM and CF/FF. All 12-month-old infants received CF/FF.

4.3.3.4. Salt use for infants

Table 26 shows the use of salt in home-made and ready meals.

Table 26: Salt use for infants [n]

Use of salt for infants	Age group		Total
	6-mo	12-mo	
n	*179*	*160*	*339*
• in home-made meals [n]	[a]	[b]	[c]
Yes - iodized	14	111	125
- not iodized	3	6	9
- unknown if iodized	5	20	25
No salt	127	20	147
No home-made meals	6	2	8
No CF/FF yet	21	0	21
• in ready meals (e.g. jars) [n]	[c]	[d]	[e]
Yes	24	35	59
No	93	74	167
Unknown	5	8	13
No ready meals	32	33	65
No CF/FF	21	0	21

Abbreviations: CF = complementary food; FF = family food
[a - e] Missing data: [a] n = 3; [b] n = 1; [c] n = 4; [d] n = 10; [e] n = 14

Home-made meals

12.5% of the mothers of 6-month-old infants reported already using salt in home-made meals for their infants. 64% of those indicated using iodized salt, 14% used non-iodized salt and the rest did not know if the salt was iodized or not. Most of the mothers specified not yet adding salt to their 6-month-old infant's home-made meals (72%) or not giving home-made/CF/FF at all (15%) (Table 26).

86% of the mothers of 12-month-old infants on the other hand, indicated already adding salt to home-made meals, of which 81% specified using iodized salt and only six mothers (4%) acknowledged not using iodized salt. 15% did not know which salt they use for their infant. Only 14% of the 12-month-old infants did not yet receive salt in home-made meals (Table 26).

Ready meals

14% of 6-month-old infants were fed ready meals containing salt (either added by producer or mother) and 23% of 12-month-old infants. 53% and 49% of mothers of 6-month-old infants and 12-month-old infants reported not giving ready meals with salt to their infants. The rest of the infants either did not receive ready meals (20% of all infants) or CF/FF or the mother did not know if the ready meals they used contained salt (4%). Fourteen mothers in total did

not answer the question (not considered in %-calculation) (Table 26).

General salt use

It was concluded whether or not the infants generally already received salt based on the salt use in home-made and ready meals and the feeding of family food, which usually contains a certain amount of salt. About 22% (n = 39) of the 6-month-old infants already received salt, about 74% did not (n = 132) and for 4% (n = 8) it was unclear if they received salt or not. For the 12-month-old infants, it was concluded that nearly all (96%, n = 153) already received salt and that only 2.5% (n = 4) did not. For three 12-month-old infants, we could not make a conclusion (data are not reported in the table).

4.3.4. Social demographics of mothers

As an additional characterization of the mothers, Table 27 presents the sociodemographic data, which was obtained from the mothers through the dietary questionnaires. The percentages in the table and text are in relation to the number of mothers who answered the question in the questionnaire.

Table 27: Social demographics of mothers (from dietary questionnaires)

Social demographics of mothers [i]	**Age group of infants**		**Total**
	6-mo	**12-mo**	
Mothers [n]	*180*	*163*	*343*
Questionnaire [n]	*175*	*148*	*323*
Number of children [n]	1.8 (1 - 4) [a, b]	1.6 (1 - 4) [e]	1.7 (1 - 4) [f]
Single parent [%]	[b]	[e]	[f]
Yes	2	2	2
No	98	98	98
Smoker [%]	[c]	[e]	[g]
Yes	7	12	9
No	93	88	91
Professional activity [%]	[d]	[e]	[h]
Full time (90-100%)	3	4	4
Part time (20-80%)	39	53	46
By the hour	13	15	14
Not working	44	28	37

[a] mean (range) (all such values)
[b - e] Data from: [b] n = 175; [c] n = 173; [d] n = 174; [e] n = 147; [f] n = 322; [g] n = 320; [h] n = 321.
Percentages are in relation to number of answers in questionnaire (not in relation to all mothers), rounded up or down to integers.
[i] Data if possible taken from 1st questionnaire, if missing there from 2nd.

The average number of children per mother was 1.7. Fifty-three percent of the mothers had more than one child.

Only 2% of the mothers were single parents. Nine percent acknowledged being a smoker. More mothers of 12-month-old infants smoked (n = 18, one of those lactating) compared with mothers of 6-month-old infants (n = 12, four of those lactating).

44% and 28% of mothers of 6-month-old infants respectively 12-month-old infants did not work. The others worked either full, part time or by the hour.

In Table 28, mothers were classified into eight different occupational categories.

Table 28: Classification of occupation of the mothers

Classification of occupation [a] [%] (n)	**Age group of infants**				**Total**	
	6-mo		**12-mo**			
Mothers [n]	*180*		*163*		*343*	
Questionnaire 1./2. [n]	*175 / 163*		*148 / 143*		*323 / 306*	
	% [e]	(n) [b]	%	(n) [c]	%	(n) [d]
1. Agriculture, forestry, stock-breeding	2	(4)	1	(2)	2	(6)
2. Production in industry & commerce (excl. construction)	2	(4)	3	(5)	3	(9)
3. Technical & computer science	3	(5)	3	(5)	3	(10)
4. Construction industry & mining	0	(0)	0	(0)	0	(0)
5. Trade and transport	7	(12)	11	(16)	9	(28)
6. Hotel/restaurant industry & provision of personal services	8	(14)	9	(13)	8	(27)
7. Management & administration, banking & insurance industry & legal system	29	(49)	26	(39)	28	(88)
8. Health, education & culture, scientists	48	(81)	45	(67)	47	(148)
9. Non-classifiable data	1	(1)	1	(1)	1	(2)

[a] The educations/professions indicated by the mothers on the questionnaire were classified in different occupational categories (see methods).
[b - d] Data from: [b] n = 170; [c] n = 148; [d] n = 318 (total missing n = 25)
[e] The percentages indicated are related to the total number of valid data, missing data were not included in the %-calculation. Percentages were rounded up or down to integers.

Nearly half of all mothers in each infant age group had an occupation in the category 8 “health, education & culture, scientists”, followed by 28% in the category 7 “management & administration, banking & insurance industry & legal

system". Minor percentages were distributed between the other categories (see Table 28).

Classifying mothers according to their educational background, about half of the mothers had a compulsory school/secondary education level, about one quarter had a higher vocational education and one quarter had a university education (see Table 29).

Table 29: Educational background of the mothers

Educational background [a] [%] (n)	**Age group of infants**				**Total**	
	6-mo		**12-mo**			
Mothers [n]	*180*		*163*		*343*	
Questionnaire 1./2. [n]	*175 / 163*		*148 / 143*		*323 / 306*	
	% [e]	(n) [b]	%	(n) [c]	%	(n) [d]
Compulsory school/secondary education level	52	(88)	53	(78)	52	(166)
Higher vocational education	24	(41)	26	(38)	25	(79)
University level	24	(41)	22	(32)	23	(73)

[a] Definition of the ISCED-levels: Compulsory school/secondary education level (ISCED 1-4); Higher vocational education ("Höhere Berufsbildung") (ISCED 5B); University/university of applied sciences ("Hochschule") (ISCED 5A,6) (see also methods).
[b - d] Data from: [b] n = 170; [c] n = 148; [d] n = 318 (total missing n = 25)
[e] The percentages indicated are related to the total number of valid data, missing data were not included in the %-calculation. Percentages were rounded up or down to integers.

4.4. Urinary iodine concentration

4.4.1. Collection materials

The iodine concentration in the pads, urine bags and other collection materials was below the detection limit of the method (≈ 2 µg/l). They were therefore not considered to be contaminated with iodine.

In the iodine recovery test, with an iodine concentration of 100 µg/l, no change in iodine concentration was found in the urine collection pads compared to the "no-pad" reference. For detailed results see the B.Sc. thesis of C. Piccapietra (Piccapietra, 2008).

4.4.2. Sample collection

The samples for this interim study evaluation were collected between mid August 2008 and beginning of May 2009 (according to dates of study registration).

The main place of sample collection differed from practice to practice. The majority of pediatricians instructed parents to carry out sample collection at home. Some doctors collected practically all samples in the practice. Some doctors did both. The relation based on currently available information was about 2 **:** 0.5 **:** 1. More detailed information about the sample collection location was not available for this evaluation as the required data was on the practice registration form, which was not returned to us from the pediatric practices before study completion.

The approximate median (range) number of days between the registration of the infant and the sample arrival at ETH (date of postmark) was 3 (0 - 53) days. 76.3% of samples (infants) arrived at ETH (by post) within one week after study registration and 91% arrived within two weeks. For 5.4% and 3% of the samples it took more than three and four weeks until arrival at ETH. It is possible however, that those samples were collected earlier but not sent to us directly after collection.

The pad collection method was applied for the first time for urine collection in all pediatric practices. Earlier, the practices used urine bags for collection. The pediatricians were generally content with this new urine collection method even

if most found it time consuming to extract the urine from the pad (oral communication). One of the two pediatric practices which had already finished sampling could imagine using this method regularly for urine collection in infants; the other still preferred using urine bags (final questionnaire to doctors). One pediatric practice insisted on using urine bags for the study sample collection because they considered the pad collection method too time consuming (region Ticino; bags tested for iodine contamination, see methods). None of the parents reported any problems with the method; also, the doctors did not mention any problems encountered by parents.

4.4.3. Infants - Overview

Table 30 gives an overview of the measured urinary iodine concentrations of the infants by age group and for the total sample.

The UIC values of the infants (total sample and both age groups separately) were not normally distributed, but positively skewed (mean ± SD = 122.4 ± 102.5 µg/l; median = 93.2 µg/l). Figure 14 shows the UIC distribution of all infants.

The median (95% CI) UIC of infants together (n = 339, total sample) was 93.2 µg/l (85.6, 104.3). This is just below the currently available WHO cut-off for iodine sufficiency of 100 µg/l (World Health Organization et al., 2007).

For 6-month-old infants, the median UIC of 88.4 µg/l was clearly below 100 µg/l. 12-month-old infants had a median UIC of 104.0 µg/l. Nevertheless, the two age groups were not significantly different (MWU, p = 0.078). Box plots of UIC of both age groups are shown in Figure 15. Furthermore, infant age [months] did also not significantly correlate with UIC (all n = 339: r_S = .10, p = 0.06; 6-mo n = 179: r_S = -.02, p = 0.75; 12-mo n = 160: r_S = 0.13, p = .11).

In the total sample, the included UICs ranged from 6.4 to 763.1 µg/l. The interquartile range was 104.0 µg/l (from 53.4 to 157.4 µg/l). Ninety-five percent of all UICs lay between 20.3 and 371.6 µg/l.

53% of all infants had a UIC below the WHO cut-off 100 µg/l and 23% < 50 µg/l. In school age children or adults this would indicate mild iodine deficiency (World Health Organization et al., 2007). In 5.3% of all infants a UIC ≥ 300 µg/l (6.1%

6-mo, 4.3% 12-mo) was measured. In school age children or adults a UIC ≥ 300 µg/l indicates an excessive iodine intake (World Health Organization et al., 2007). Three 6-month-old and one 12-month-old infant even had a UIC ≥ 500 µg/l.

Table 30: Overview of urinary iodine concentrations [µg/l] of infants

UIC [a] ***of infants***	**Age group**		**Total**	
	6-mo	**12-mo**		
n	*179*	*160*	*339*	
Median [µg/l]	88.4 (67.8, 99.8) [b]	104.0 (88.1, 125.5) [b]	93.2 (85.6, 104.3) [b]	
Minimum [µg/l]	10.9	6.4	6.4	
Maximum [µg/l]	763.1	504.0	763.1	
Percentiles [µg/l]				
2.5th	20.6	18.5	20.3 (11.4, 22.6) [c]	
25th	49.4	61.4	53.4	
50th	88.4	104.0	93.2	
75th	153.1	161.0	157.4	
97.5th	434.6	347.0	371.6 (329.9, 550.5) [c]	
Prevalence of UIC	*%*	*n*	*%*	*n*	*%*	*n*
< 20 µg/l	1.7 [d]	(3)	2.5 [d]	(4)	2.1 (0.5, 3.6) [e]	(7)
< 50 µg/l	25.7 (19.2, 32.1)	(46)	20.0 (13.7, 26.3)	(32)	23.0 (18.5, 27.5)	(78)
< 100 µg/l	58.7 (51.4, 65.9)	(105)	46.9 (39.1, 54.7)	(75)	53.1 (47.8, 58.4)	(180)
≥ 100 µg/l	41.3 (34.1, 48.6)	(74)	53.1 (45.3, 60.9)	(85)	46.9 (41.6, 52.2)	(159)
≥ 300 µg/l	6.1 (2.6, 9.7)	(11)	4.4 (1.2, 7.6)	(7)	5.3 (2.9, 7.7)	(18)
≥ 500 µg/l	1.7 [d]	(3)	0.6 [d]	(1)	1.2 [d]	(4)

[a] Abbreviation: UIC = urinary iodine concentration
[b] 95% CI, calculated with SPSS 16
[c] 95% CI, calculation after (Campbell and Gardner, 1988). Calculating CI for the single age groups gave no reasonable results with this method (non-existing observations required).
[d] Here the number of cases below/above the defined limit was too small for the used calculation for the 95% CI, see [e].
[e] 95% CI, calculation: $p \pm 1.96 * \sqrt{p(1-p)/n}$; p = proportion of cases below/above the defined limit, n = sample size (Altman, 1999), p. 230; (all such values in this section).

The proportion of UIC < 100 µg/l and ≥ 100 µg/l was significantly different between the two age groups (chi-square, $p < 0.05$). A significantly higher percentage of 12-month-old infants (53%) had a UIC ≥ 100 µg/l compared to the

6-month-old infants (41%). All other proportions were not significantly different between the age groups.

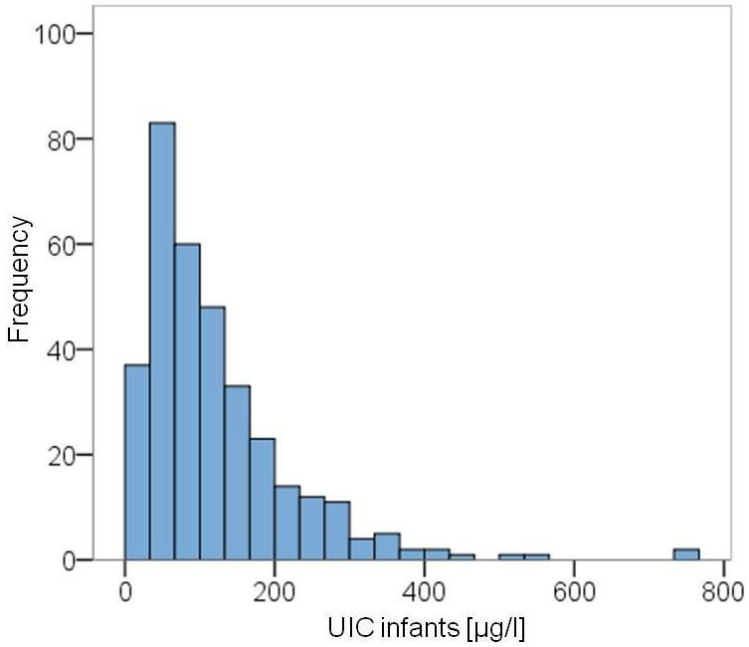


Figure 14: Distribution of urinary iodine concentrations (UIC) of the infants (n = 339, both age groups together)

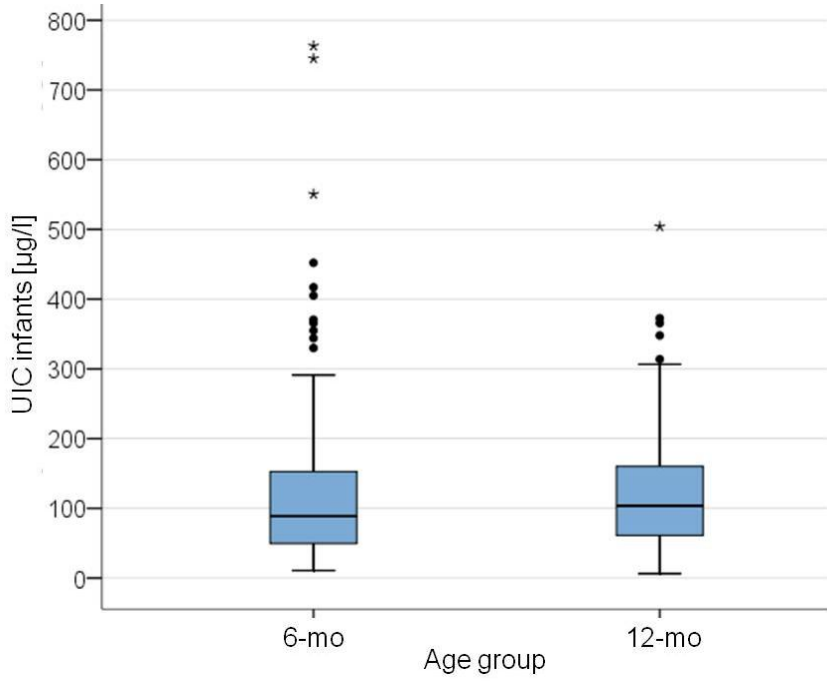


Figure 15: Box plots of urinary iodine concentrations (UIC) in infants by age group (6-months: n = 179; 12-months: n = 160) (MWU, p = 0.08)

4.4.3.1. Gender

Table 31 shows median UIC (95% CI) in girls and boys. Comparing UIC between boys and girls in the total sample, there was no significant difference (MWU, p = 0.59). 6-month-old boys had the lowest median UIC.

UIC between boys and girls was not significantly different within each age group, even if there was a strong tendency towards a significance in the 6-mo group (MWU, 6-mo: p = 0.053; 12-mo: p = 0.22).

Comparing girls and boys between the age groups, 12-month-old boys had a significantly higher median UIC than 6-month-old boys (MWU, p < 0.05) and among girls, there was no significant difference in UIC (MWU, p = 0.73).

Table 31: Urinary iodine concentration (UIC) [µg/l] of infants by gender

UIC of infants	**Age group**				**Total**	
	6-mo		**12-mo**			
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Girls	*91*	94.7 [a] (83.6, 114.6)	*67*	103.7 (71.2, 125.5)	*158*	99.8 (86.7, 112.7)
Boys [1]	*88*	68.2 (56.2, 93.2)	*93*	104.3 (84.8, 140.7)	*181*	90.0 (71.0, 104.7)

[a] Median (95% CI) (all such values)
[1] Boys significantly different between age groups (p < 0.05)

4.4.3.2. Weight and length

No significant correlations were found between UIC and body weight or length of infants including the total sample (weight: r_s = .11, p = 0.05; length: r_s = .06, p = 0.25). The correlations were even weaker after controlling for gender and age in months (weight: r_s = .04, p = 0.46; length: r_s = .01, p = 0.85).

Looking at age groups, no significant correlations were found for body weight/length in the 6-mo group (weight: r_s = -.08, p = 0.30; length: r_s = -.15, p = 0.05) and no correlation was found with body length in the 12-mo group (r_s = .09, p = 0.25). In contrast, there was a significant positive correlation between UIC and body weight in the 12-mo group (r_s = .21, p < .01), which however, became non-significant after controlling for gender and exact age in months (r = .15, p = 0.06).

4.4.3.3. Nationality

Table 32 shows median UICs (95% CI) of Swiss infants and infants with foreign nationality (85% vs. 15%, based on the nationality of the mother).

Table 32: Urinary iodine concentration (UIC) [µg/l] of Swiss and foreign infants

UIC of infants	**Age group**				**Total** [1]	
	6-mo		**12-mo** [1]			
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Swiss	*158*	87.5 [a] (66.5, 99.8)	*131*	100.6 (74.6, 114.8)	*289*	90.0 (75.4, 102.4)
Foreign nationality	*21*	93.2 (54.8, 162.5)	*29*	138.6 (90.5, 196.2)	*50*	123.8 (90.5, 145.4)

[a] Median (95% CI) (all such values)
[1] Swiss < foreign nationality: significantly different, $p < 0.05$

Looking at the total sample, infants with foreign nationality were found to have a significantly higher median UIC than Swiss infants (MWU, $p < 0.05$). Figure 16 shows the box plots of UIC of Swiss and foreign infants.

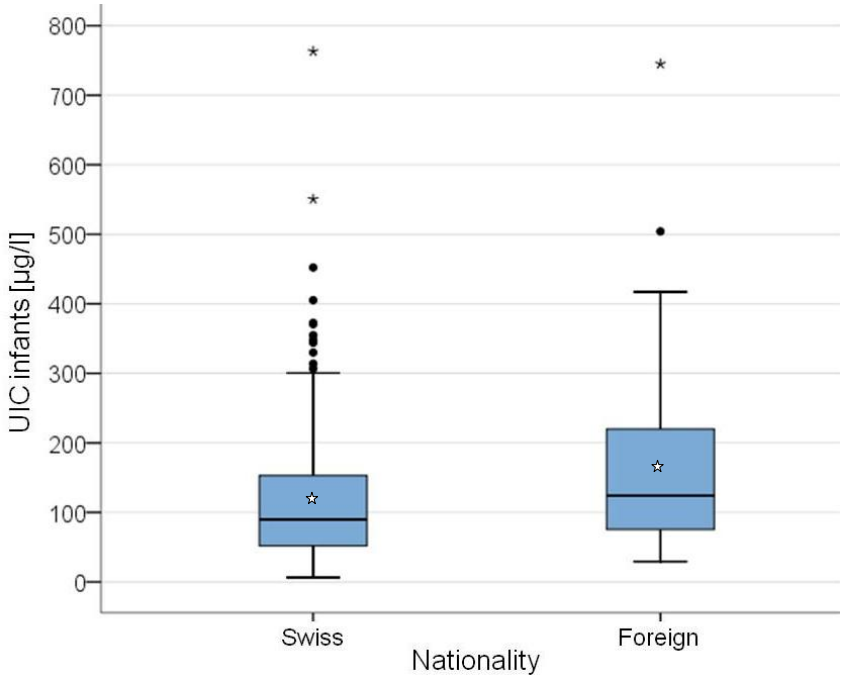


Figure 16: Box plots of urinary iodine concentration (UIC) [µg/l] in Swiss (n = 289) and foreign infants (n = 50) (☆ Swiss < foreign: $p < 0.05$)

Examining both age groups separately, foreign infants in the 6-mo group were found to have a slightly higher median UIC than Swiss infants, but the

difference in UIC was not significant (MWU, p = 0.39). In the 12-mo group, UICs of foreign infants were significantly higher compared to Swiss infants (MWU, p < 0.05).
12-month-old Swiss infants had a higher median UIC compared to 6-month-old Swiss infants, but the difference in UIC was not significant (MWU, p = 0.25). The same holds true for infants with foreign nationality (MWU, p = 0.23).

4.4.3.4. Pediatric practice/region

As the number of infants per pediatric practice (n = 2 to 62) and region (n = 4 to 92) was variable, the data were not evaluated separately for each pediatric practice and region. Indeed, the study was not planned to be representative for single practices or geographic regions, but for the country as a whole.
The median (range) UIC of infants in each practice can be found in Appendix 16. There was no significant difference in UIC of infants between pediatric practices (K-W, p = 0.20). Median UICs of practices ranged from 67.4 to 184.3 µg/l (all infants).

Table 33 lists the median UICs of infants in the seven Swiss regions. Median UICs of regions ranged from 67.8 to 184.3 µg/l (total sample).
Within each region, there was no significant difference in UIC between the two age groups (MWUs, all p > 0.05), except for Central Switzerland where UIC of 12-month-old infants was significantly higher compared with 6-month-old infants (MWU, p < 0.05).
There was a significant difference in UIC between the regions (total sample, K-W, p < 0.05). Post-hoc tests (MWU with Bonferroni correction p < 0.005) showed that UIC in Ticino was significantly higher than UIC in Espace Mittelland and Eastern Switzerland (p < 0.005). The Lake Geneva region probably had too small a sample size (n = 4) to detect a significant difference to Ticino.
Due to a very small sample size in some regions, a comparison between regions was not performed separately for the age groups.
Looking at the box plots of the regions (total sample, Figure 17), Ticino tended to have the highest UICs.

Table 33: Urinary iodine concentration (UIC) [µg/l] of infants arranged by the seven Swiss regions

UIC of infants	**Age group**				**Total [2]**	
	6-mo		**12-mo**			
Regions	*n*	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Lake Geneva region (1)	*3*	61.6 (47.3 – 91.1) [a]	*1*	110.7	*4*	76.3 (47.3 – 110.7)
Espace Mittelland (2)	*24*	69.4 (21.9 – 291.3)	*11*	64.0 (36.7 – 205.8)	*35*	67.8 **°** (21.9 – 291.3)
Northwestern Switzerland (3)	*27*	90.5 (11.4 – 763.1)	*27*	140.2 (18.5 – 296.4)	*54*	92.9 (11.4 – 763.1)
Zurich (4)	*26*	97.0 (17.4 – 452.1)	*20*	99.4 (51.5 – 225.3)	*46*	98.5 (17.4 – 452.1)
Eastern Switzerland (5)	*42*	83.0 (10.9 – 370.6)	*50*	82.3 (6.4 – 306.6)	*92*	82.5 ***** (6.4 – 370.6)
Central Switzerland (6) [1]	*49*	88.6 (21.8 – 417.1)	*42*	133.8 (15.8 – 372.6)	*91*	100.0 (15.8 – 417.1)
Ticino (7)	*8*	152.9 (51.9 – 405.1)	*9*	184.3 (75.6 – 504.0)	*17*	184.3 *** °** (51.9 – 504.0)
TOTAL	*179*	88.4 (10.9 – 763.1)	*160*	104.0 (6.4 – 504.0)	*339*	93.2 (6.4 – 763.1)

[a] Median (range) (all such values)
[1] 6-mo vs. 12-mo $p < 0.05$ (MWU)
[2] Significant difference between regions, K-W, $p < 0.05$; * ° $p < 0.005$ (MWU)

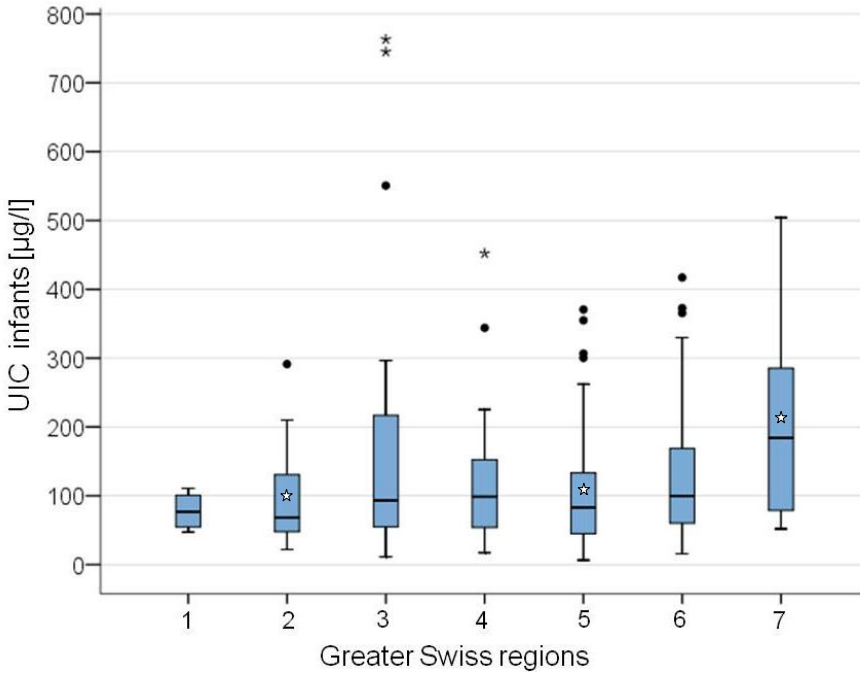


Figure 17: Box plots of urinary iodine concentration (UIC) [µg/l] of all infants (n = 339) in each greater Swiss region (K-W, $p < 0.05$; ☆ 2 < 7 and 5 < 7: $p < 0.005$)
Legend: Names of regions (numbers in brackets) and [n] per region can be found in Table 33

4.4.3.5. Urban – rural area of pediatric practice

In the total sample the median UIC (95% CI) of samples collected from pediatric practices in urban areas (96.6 (88.1, 109.0) µg/l, n = 287) was higher compared to the median of samples from pediatric practices in rural areas (73.2 (57.3, 105.1) µg/l, n = 52) (see also Table 19). Nevertheless, there was no significant difference in UIC (MWU, p = 0.06). There was also no significant difference when looking at the age groups separately (MWU, 6-mo: p = 0.08 (median UIC *urban*: 90.3 µg/l, *rural*: 71.0 µg/l), 12-mo: p = 0.28 (median UIC *urban*: 104.7 µg/l, *rural*: 87.6 µg/l)). The proportion of breast-fed infants was about the same in urban and rural areas (39% and 36.5%).

Pediatric practices in rural areas were located only in Espace Mittelland and Eastern Switzerland (see Table 19). Therefore, we analyzed these regions separately and found no significant difference between UIC of infants (both age groups together) from practices in urban and rural areas (MWU, Espace Mittelland: p = 0.46 (median UIC *urban*: 67.4 µg/l, *rural*: 71.0 µg/l) and Eastern Switzerland: p = 0.81 (median UIC *urban*: 82.6 µg/l, *rural*: 75.4 µg/l)).

4.4.3.6. Month of study registration/sample collection

Table 34 lists median UIC (range) by month of sample collection (= month of registration for study) and box plots of UIC (all infants) are shown in Figure 18.

When including the total sample, there was no significant difference in UIC of infants between the months of sample collection (K-W, p = 0.42). The lowest median UIC was found in February ’09 (62.2 µg/l, n = 24) and the highest in May ’09 (180.4 µg/l, n = 3).

In 6-month-old infants no significant difference in UIC was detected between the months of sample collection (K-W, p = 0.14). The lowest median UIC was found in February ’09 (36.5 µg/l, n = 10) and the highest in Sept ’08 (114.4 µg/l, n = 34).

In 12-month-old infants UIC also did not differ significantly between the months of sample collection (K-W, p = 0.69). The lowest median UIC was found in April ’09 (68.8 µg/l, n = 7) and the highest in May ’09 (180.4 µg/l, n = 3).

Table 34: Urinary iodine concentration (UIC) of infants [µg/l] by month of study registration/sample collection

UIC of infants	**Age group**				**Total**	
	6-mo		**12-mo**			
Month	*n*	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Aug '08	*6*	72.5 (11.4 – 216.3) [a]	*6*	76.5 (20.2 – 224.4)	*12*	76.5 (11.4 – 224.4)
Sept '08	*34*	114.4 (10.9 – 763.1)	*25*	111.9 (23.3 – 504.0)	*59*	112.0 (10.9 – 763.1)
Oct '08	*34*	85.8 (21.8 – 417.1)	*27*	102.4 (28.8 – 365.5)	*61*	89.3 (21.8 – 417.1)
Nov '08	*24*	73.9 (21.8 – 329.9)	*30*	127.3 (18.5 – 306.6)	*54*	105.5 (18.5 – 329.9)
Dec '08	*31*	88.4 (21.9 – 291.3)	*20*	97.8 (6.4 – 300.4)	*51*	91.2 (6.4 – 300.4)
Jan '09	*10*	70.0 (35.9 – 171.7)	*14*	136.9 (47.4 – 200.0)	*24*	113.6 (35.9 – 200.0)
Feb '09	*10*	36.5 (17.4 – 184.4)	*14*	78.1 (36.7 – 225.3)	*24*	62.2 (17.4 – 225.3)
March '09	*30*	99.9 (40.8 – 550.5)	*14*	83.1 (33.1 – 245.9)	*44*	96.9 (33.1 – 550.5)
April '09	*0*	--	*7*	68.8 (30.8 – 265.2)	*7*	68.8 (30.8 – 265.2)
May '09	*0*	--	*3*	180.4 (87.6 – 372.6)	*3*	180.4 (87.6 – 372.6)

[a] Median (range) (all such values)

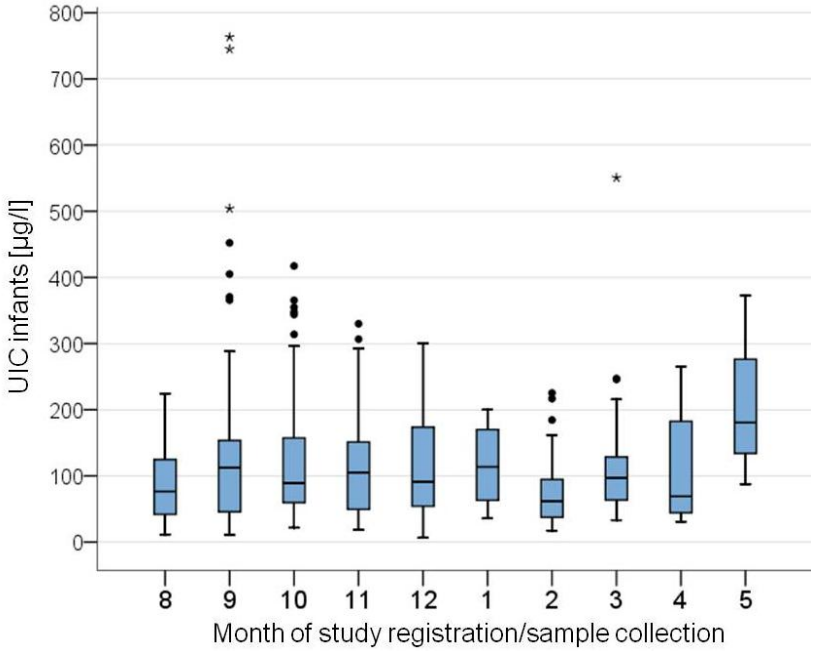


Figure 18: Box plots of urinary iodine concentration (UIC) [µg/l] of infants (n = 339) by month of study registration/sample collection (K-W, p = 0.42)

Legend: Numbers in x-axis = months 8/2008 – 12/2008, 1/2009 – 5/2009; n per month see Table 34

4.4.3.7. Current infant feeding practices

4.4.3.7.1. Breast-fed - not breast-fed

Median UICs of breast-fed and not breast-fed infants are shown in Table 35.

Table 35: Urinary iodine concentration (UIC) [µg/l] of breast-fed vs. not breast-fed infants

UIC of infants	**Age group**				**Total** [1]	
	6-mo [1]		**12-mo**			
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Breast-fed	*102*	70.7 [a] (56.6, 93.2)	*29*	105.4 (78.7, 140.2)	*131*	83.8 (65.2, 99.8)
Not breast-fed	*77*	96.6 (86.3, 125.5)	*131*	103.1 (84.9, 128.8)	*208*	101.4 (90.0, 120.6)

[a] Median (95% CI) (all such values)
[1] Significant difference between breast-fed vs. not breast-fed infants ($p < 0.01$)

Figure 19 shows box plots of UIC of breast-fed and not breast-fed infants, subdivided by age group.

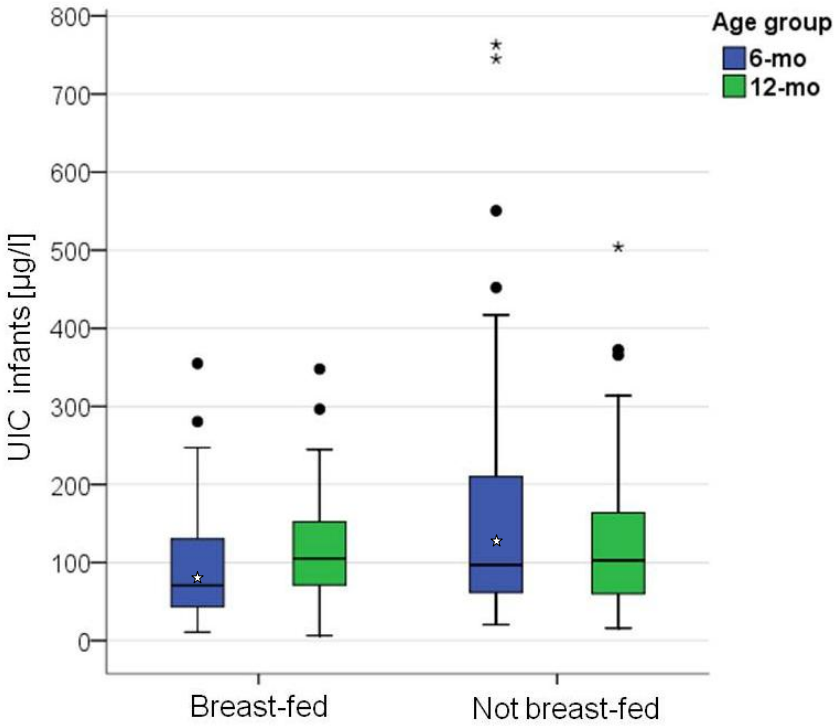


Figure 19: Box plots of urinary iodine concentration (UIC) [µg/l] of breast-fed and not breast-fed infants, subdivided by age group (⭐ 6-mo: BF < not BF: $p < 0.01$)
Legend: breast-fed (BF): 6-mo n = 102, 12-mo n = 29;
not breast-fed (not BF): 6-mo n = 77, 12-mo n = 131

When including the total sample, median UIC in currently breast-fed infants was

17% lower compared with not breast-fed infants. The difference in UIC was significant (MWU, $p < 0.01$). This significant difference was also detected in the 6-month-old infants (MWU, $p < 0.01$). In the 12-month-old infants, there was no difference in UIC between not breast-fed and breast-fed infants (MWU, $p = 0.99$).

Breast-fed infants in the 6-mo group had a 33% lower median UIC compared with breast-fed infants in the 12-mo group, but the difference in UIC was not significant (MWU, $p = 0.087$). UICs of not breast-fed infants in the 6-mo group also did not differ significantly from UICs of not breast-fed infants in the 12-mo group (MWU, $p = 0.72$).

4.4.3.7.2. Exclusively/predominantly - partially breast-fed

There was no significant difference in UIC between exclusively/predominantly breast-fed (n = 11, median UIC (range) = 68.7 (21.8 – 233.8) µg/l) and partially breast-fed infants (n = 120 (both age groups), median UIC (range) = 84.3 (6.4 – 355.0) µg/l) (MWU, $p = 0.99$). However, the number of exclusively/ predominantly breast-fed infants was too small to make an accurate comparison.

There was no significant correlation between UIC of breast-fed infants and the number of daily breast-feeds (data from registration form) (all BF infants: $r_s = -.052$, $p = 0.56$; exclusively/predominantly BF: $r_s = .48$, $p = 0.13$; partially BF: $r_s = -.088$, $p = 0.34$).

4.4.3.7.3. Formula – no formula

Median UICs of infants currently fed formula and infants not fed formula are given in Table 36.

Infants who currently received formula had a higher median UIC than infants not receiving formula (total sample and both age groups). The difference in UIC was however, only significant when all infants were included in the comparison (MWU, $p < 0.001$, see also Figure 20) and when only the 6-month-old infants were included (MWU, $p < 0.001$). In the 12-month-old infants, the difference in UIC was not significant (MWU, $p = 0.08$).

Table 36: Urinary iodine concentration (UIC) [µg/l] of infants currently fed formula vs. infants not fed formula

UIC of infants	**Age group**				**Total [1]**	
	6-mo [1]		**12-mo**			
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Formula	*110*	102.5 [a] (90.0, 125.5)	*93*	111.9 (91.2, 132.1)	*203*	105.4 (94.7, 121.5)
No formula	*69*	64.1 (53.5, 85.6)	*67*	89.3 (68.8, 126.1)	*136*	72.5 (63.3, 88.6)

[a] Median (95% CI) (all such values)
[1] Significant difference between formula-fed vs. not formula-fed infants ($p < 0.001$)

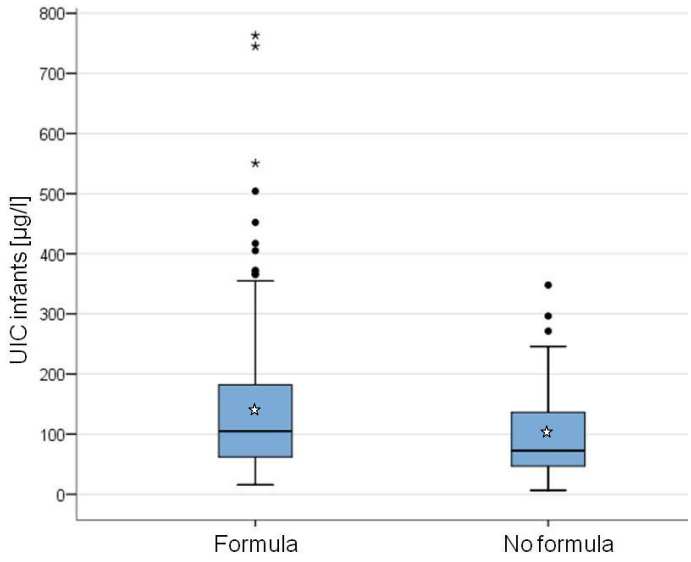


Figure 20: Box plots of urinary iodine concentration (UIC) in infants fed formula (n = 203) and not fed formula (n = 136) (☆ formula > no formula: $p < 0.001$)

There was no significant correlation between UIC of formula-fed infants and the number of daily FM feeds (data from registration form) ($r_s = .076$, $p = 0.30$).

4.4.3.7.4. Breast feeding - formula feeding

The number of infants who did not yet receive complementary/family food (CF/FF) (= exclusively/predominantly breast-fed, formula-fed or breast- and formula-fed) was very small (see Table 25). Therefore, those infants were added to the respective groups of infants who already received CF/FF and the infants were grouped into four feeding groups for comparison based on their current consumption of BM/FM (1. BM with or without CF/FF, no FM; 2. FM with or without CF/FF, no BM; 3. BM and FM with or without CF/FF; 4. No BM and

no FM, but CF/FF). Table 37 shows the four groups and the median UICs of the infants by age group and for the total sample.

Table 37: UIC [µg/l] of infants subdivided into four groups of different feeding practices

UIC of infants	**Age group**				**Total** [1]	
	6-mo [2]		**12-mo**			
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
BM	*69*	64.1 *** °** (53.5, 85.6) [a]	*17*	95.9 (65.2, 152.1)	*86*	69.6 *** °** (55.0, 86.7)
FM	*77*	96.6 ***** (86.3, 125.5)	*81*	112.8 (88.1, 134.6)	*158*	103.1 ***** (90.5, 125.5)
BM & FM	*33*	114.6 **°** (59.6, 165.8)	*12*	108.5 (82.6, 183.3)	*45*	112.0 **°** (83.6, 140.2)
No BM, no FM	*0*	---	*50*	82.5 (61.4, 135.8)	*50*	82.5 (61.4, 135.8)

Abbreviations: UIC = Urinary iodine concentration; BM = breast milk; FM = formula milk
[a] Median (95% CI) (all such values)
[1] Significant difference between groups (K-W, $p < 0.001$), ***** $p < 0.0001$, **°** $p < 0.0083$
[2] Significant difference between groups (K-W, $p < 0.005$), ***** $p < 0.001$, **°** $p < 0.017$

When including the total sample, a comparison of the four feeding groups showed a significant difference in UIC (K-W, $p < 0.001$). The lowest median UIC was found in the BM group (69.6 µg/l), the highest in the BM & FM group (112.0 µg/l). Post-hoc tests (MWU with Bonferroni correction $p < 0.0083$) showed that median UIC of the BM group was significantly lower compared with the FM group ($p < 0.0001$) and BM & FM group ($p < 0.0083$). The other groups were not significantly different from each other.

All 6-month-old infants received either BM or FM. A comparison of UIC between the three groups showed that they were significantly different (K-W, $p < 0.005$). Post-hoc tests (MWU with Bonferroni correction $p < 0.017$) showed the same result as for the total sample. Median UIC of the BM group was significantly lower compared with the FM group ($p < 0.001$) and the BM & FM group ($p < 0.017$). There was no significant difference in UIC between the BM & FM and FM group.

A comparison between the feeding groups in 12-month-old infants showed no significant difference in UIC (K-W, $p = 0.37$). The lowest median was found in the group not receiving any BM or FM (82.5 µg/l), the highest was in the FM

group (112.8 µg/l).

Figure 21 shows the box plots of UIC by feeding group in each age group.

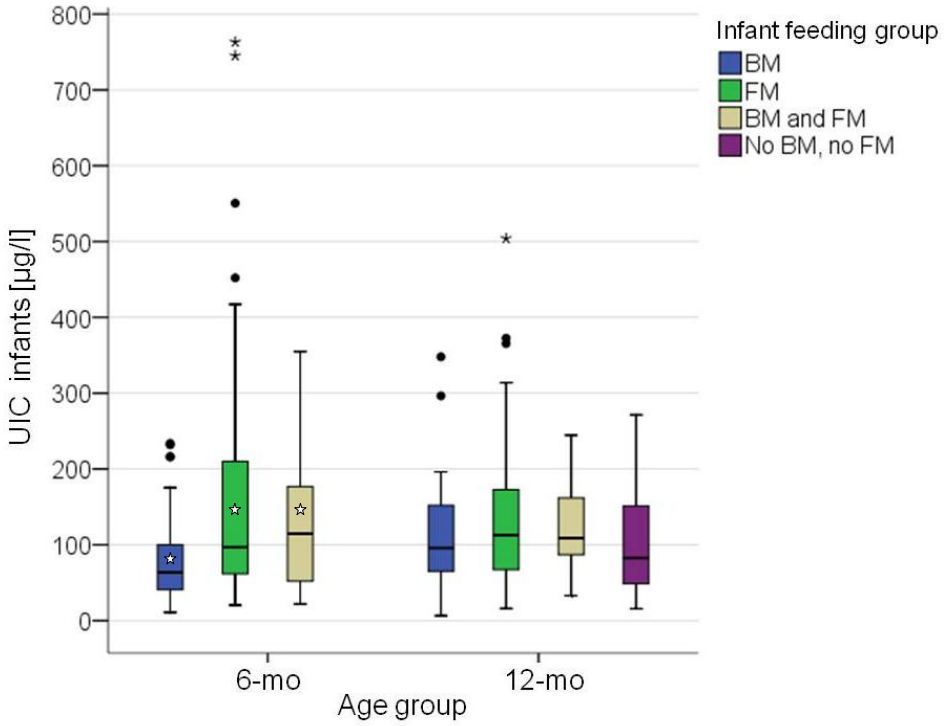


Figure 21: Box plots of urinary iodine concentration (UIC) in infants (6-mo and 12-mo) in different feeding groups (☆ 6-mo: BM < FM: $p < 0.001$; BM < BM & FM: $p < 0.017$)
Legend: BM = breast milk; FM = formula milk; n per box plot see Table 37

Within each feeding group, UICs in 6-month-old infants did not significantly differ from 12-month-old infants (MWU, all $p > 0.05$).

A significant positive correlation was found between UIC of infants only fed BM (with or without CF/FF, no FM) and the number of daily breast-feeds (data from individual registration form) (total sample: $r_s = .26$, $p < 0.05$; 6-mo: $r_s = .41$, $p < 0.01$; 12-mo: $r_s = .49$, $p < 0.05$). The number of daily FM feeds did not correlate with UIC of infants only fed FM (with or without CF/FF, no BM) (total sample: $r_s = .11$, $p = 0.19$; 6-mo: $r_s = .21$, $p = 0.07$; 12-mo: $r_s = .22$, $p = 0.05$). UIC of infants fed BM and FM (with or without CF/FF) and the number of daily breast-feeds (total sample: $r_s = -.27$, $p = 0.08$) or daily FM meals (total sample: $r_s = -.07$, $p = 0.70$) also did not correlate.

However, the number of daily feeds does not necessarily correlate with the

amount of BM or FM that was drunk, and iodine content in BM/FM varies between infants. Moreover, mothers just had to indicate average numbers of daily feeds, which most probably does not allow any causality of the correlations between UIC and daily feeds.

4.4.3.7.5. Complementary and family food

All 12-month-old infants already received CF. In the 6-mo group, there was no significant difference in UIC between infants who already received CF (n = 158, median (range) = 85.9 (10.9 – 763.1) µg/l) and those who did not (n = 21, median (range) = 114.7 (21.8 – 355.0) µg/l) (MWU, p = 0.083).

Very few 6-month-old infants already consumed FF. In contrast, nearly all 12-month-old infants already ate foods from the family table. Therefore, a comparison in UIC between infants eating FF and infants not eating FF was not done as it would be equal to comparing the age groups (see 4.3.3).

Types of complementary/family food (CF/FF):

There was no significant difference in UIC between users and non-users of the following CF/FF types: milk-cereal porridge/bottle with FM, milk-cereal porridge/bottle with cow milk, diluted cow milk (w/o cereals), undiluted cow milk (w/o cereals) (in both age groups); fruit-(cereal)-meals (w/o milk) (6-mo group). All $p > 0.05$ (detailed data not shown).

In the 6-mo group, non-consumers of vegetable-carbohydrate-(meat)-meals (w/o milk) (n = 35, median (range) = 135.1 (21.8 – 763.1) µg/l) had a 61.4% higher median UIC than consumers (n = 144, median (range) = 83.0 (10.9 – 745.0) µg/l). The difference in UIC was significant (MWU, $p < 0.001$). About one third of the non-consumers was breast-fed (no FM, n = 13, median UIC = 68.7 µg/l), one third was formula-fed (no BM, n = 11, median UIC = 263.9 µg/l) and another third was breast- and formula-fed (n = 11, median UIC = 176.9 µg/l). All 12-month-old infants ate vegetable meals.

In the 12-mo group, there was a significant difference in UIC between consumers (n = 150, median (range) = 102.5 (6.4 – 504.0) µg/l) and non-consumers (n = 8, median (range) = 170.4 (69.1 – 271.5) µg/l) of fruit-(cereal)-meals (w/o milk) ($p < 0.05$).

No significant correlation was found between UIC and number of daily meals in

any type of CF/FF (total sample and both age groups, all $p > 0.05$).

The questions about the consumption of CF/FF were rather general and we did not know from the registration form if the amounts and types of CF/FF given to the infants varied much from day-to-day. Therefore, we did not go deeper into this data. Furthermore, the average number of meals of CF/FF consumed per day lay between one and two and therefore the contribution of each of those foods to the total iodine intake is probably rather small compared with BM or FM.

For more detailed analyses, data from the dietary questionnaires would be required.

4.4.3.8. Use of salt for infants

Home-made meals

As the subgroups in each age group were rather small for comparisons (see 4.3.3, Table 26) we only looked at the total number of infants.

Just looking at infants who received salt in home-made meals (n = 159), there was no significant difference in UIC between infants who received iodized salt (n = 125 (6-mo: n = 14, 12-mo: n = 111), median UIC = 112.0 µg/l), who received non-iodized salt (n = 9, median UIC = 67.3 µg/l) and for whom it was unclear which kind of salt they received (n = 25, median UIC = 94.7 µg/l) (K-W, $p = 0.57$).

There was however, a significant difference in UIC between infants who received salt (any kind) in home-made meals (n = 159 (6-mo: n = 22, 12-mo: n = 137), median UIC = 103.7 µg/l) and infants who did not receive salt in home-made meals (n = 147 (6-mo: n = 127, 12-mo: n = 20), median UIC = 75.4 µg/l) (MWU, $p < 0.01$). Examining both age groups separately, no difference in UIC was detected (MWU, both $p > 0.05$) although infants who did not receive salt showed a lower median UIC in both age groups (*6-mo*: salt: 110.8 µg/l, no salt: 75.4 µg/l; *12-mo*: salt: 103.7 µg/l, no salt: 75.8 µg/l). Infants who did not receive CF/FF (n = 21, median UIC = 114.7 µg/l) or home-made meals (n = 8, median UIC = 159.3 µg/l) were excluded from the comparison. Data were missing in four cases.

Ready meals

There was no significant difference in UIC between infants (total sample) who received salt in ready meals (n = 59 (6-mo: n = 24, 12-mo: n = 35), median = 105.1 µg/l), who did not receive salt in ready meals (n = 167 (6-mo: n = 93, 12-mo: n = 74), median = 88.6 µg/l) and for whom it was unclear if they received salt (n = 13, median = 120.6 µg/l) (K-W, p = 0.28). Infants not receiving CF/FF (n = 21) or ready meals (n = 65) were excluded from the comparison.

General salt use

All except four 12-month-old infants received salt. Therefore, no comparison was made. In 6-month-old infants, UIC in infants who received salt (n = 39, median UIC = 91.6 µg/l), who did not receive salt (n = 132, median UIC = 86.5 µg/l) and for whom it was unclear if they received salt (n = 8, median UIC = 104.4 µg/l) did not significantly differ (K-W, p = 0.64).

4.4.3.9. Social demographics of mothers

Professional activity of mothers

Professional activity of the mother had no significant influence on UIC of the infants (both age groups together, K-W, p = 0.34; see Table 38), also not when looking at age groups separately (data not shown).

Table 38: Professional activity of mother and UIC of infants (total sample)

Professional activity	**UIC of infants**	
	n [a]	[µg/l]
Full time (90-100%)	*10*	116.2 (58.0, 200.0) [b]
Part time (20-80%)	*146*	98.5 (84.9, 111.2)
By the hour	*45*	78.7 (54.9, 113.5)
Not working	*120*	92.1 (71.2, 116.2)

UIC = Urinary iodine concentration;
[a] Missing data of n = 18 infants; [b] Median (95% CI) (all such values)

Classification of mothers' occupation

There was no significant difference in UIC of infants between different

occupational categories of the mothers (total sample, K-W p = 0.07, and age groups separately, both n.s., detailed data not shown; for categories see Table 28). As nearly 50% of the participating mothers had an occupation belonging to the "8. Health, education & culture, scientists" category, we examined if UIC in the infants of those mothers differed from UIC in infants of mothers from other categories (total sample and both age groups). A comparison showed no significant difference (total sample (n = 315, missing data of 24 infants), MWU, p = 0.34). Table 39 shows the medians.

Table 39: Classification of mothers' occupations and UIC of infants (total sample)

Classification of occupations	**UIC of infants**	
	n [a]	[µg/l]
Health, education & culture, scientists (category 8)	*146*	89.7 [b] (70.9, 104.7)
Other occupational category	*169*	96.6 (84.8, 111.9)

UIC = Urinary iodine concentration
[a] Missing data of n = 24 infants; [b] Median (95% CI) (all such values)

Educational background of mother

There was no significant difference in UIC between the infants of mothers with different educational background (all infants together (n = 315, missing data of 24 infants), K-W, p = 0.24, and age groups separately, both p > 0.05). Table 40 shows the medians.

Table 40: Educational background of mother and UIC of infants (total sample)

Educational background	**UIC of infants**	
	n [a]	[µg/l]
Compulsory school/secondary education level	*166*	97.5 [b] (85.6, 114.4)
Higher vocational education	*77*	93.4 (62.1, 111.6)
University level	*72*	85.7 (62.9, 105.4)

UIC = Urinary iodine concentration
[a] Missing data of n = 24 infants; [b] Median (95% CI) (all such values)

4.4.4. Mothers - Overview

An overview of the measured UICs of the mothers is given in Table 41.

The UIC values of mothers were not normally distributed, but positively skewed (mean ± SD = 93.3 ± 60.2 µg/l; median = 81.1 µg/l). Figure 22 shows the distribution of UICs.

Table 41: Overview of urinary iodine concentrations [µg/l] of mothers (total sample)

	UIC [a] of mothers	
n	*343*	
Median [µg/l]	81.1 (74.3, 92.7) [b]	
Minimum [µg/l]	6.4	
Maximum [µg/l]	403.0	
Percentiles [µg/l]		
2.5th	13.0 (9.7, 18.8) [c]	
25th	46.8	
50th	81.1	
75th	127.9	
97.5th	237.0 (213.3, 310.1) [c]	
Prevalence of UIC	%	n
< 20 µg/l	5.8 (3.4, 8.3) [d]	(20)
< 50 µg/l	26.5 (21.9, 31.2) [d]	(91)
< 100 µg/l	58.0 (52.8, 63.2) [d]	(199)
≥ 100 µg/l	42.0 (36.8, 47.2) [d]	(144)
≥ 300 µg/l	1.2 [e]	(4)

[a] Abbreviation: UIC = Urinary iodine concentration
[b] 95% CI, calculated with SPSS 16
[c] 95% CI, calculation after (Campbell and Gardner, 1988)
[d] 95% CI, calculation: $p \pm 1.96 * \sqrt{p(1-p)/n}$; p = proportion of cases below/above the defined limit, n = sample size (Altman, 1999), p. 230.
[e] Here the number of cases below/above the defined limit was too small for the used calculation for the 95% CI, see [d].

Median (95% CI) UIC of mothers (n = 343) was 81.1 (74.3, 92.7) µg/l. UIC between mothers of both age groups (median (95% CI) 6-mo = 78.5 (68.4, 92.7) µg/l; 12-mo = 86.6 (74.3, 102.4) µg/l) showed no significant difference (MWU, p = 0.42). Therefore, data for all mothers together are given in Table 41.

The UICs ranged from 6.4 to 403.0 µg/l. The interquartile range was 81.0 µg/l (from 46.8 to 127.9 µg/l). 95% of all UICs lay between 13.0 and 237.0 µg/l.

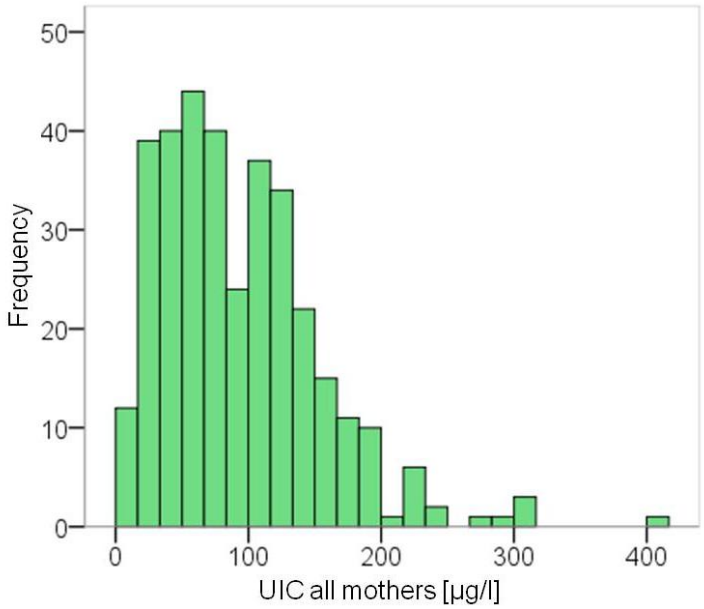


Figure 22: Distribution of urinary iodine concentrations (UIC) in mothers (n = 343)

4.4.4.1. Lactation

Table 42 gives an overview of UIC of non-lactating (n = 212) and lactating (n = 131) mothers.

The median UIC of non-lactating mothers was 34.3% higher than the median UIC of lactating mothers. The difference in UIC was significant (MWU, $p < 0.01$). The box plots are shown in Figure 23.

The median UIC of non-lactating mothers (95.5 µg/l) was below 100 µg/l, which is the WHO cut-off for iodine sufficiency in SAC and adults (World Health Organization et al., 2007). 50.9% of the non-lactating mothers had a UIC below 100 µg/l and 23.1% < 50 µg/l. According to WHO references, this would just indicate mild iodine deficiency (World Health Organization et al., 2007).

In lactating mothers the median UIC (71.1 µg/l) was clearly below 100 µg/l. 69.5% had a UIC < 100 µg/l, indicating mild ID (World Health Organization et al., 2007). Nearly one third of the lactating mothers had a UIC < 50 µg/l.

Only four mothers in total had a UIC ≥ 300 µg/l (the cut-off for excessive iodine intake (World Health Organization et al., 2007)).

Table 42: UIC [µg/l] of non-lactating and lactating mothers

UIC of mothers	**Non-lactating**		**Lactating**	
n	*212*		*131*	
Median [µg/l] [1]	95.5 (80.7, 106.1) [a]		71.1 (60.4, 79.9) [a]	
Minimum [µg/l]	9.7		6.4	
Maximum [µg/l]	403.0		305.4	
Percentiles [µg/l]				
2.5th	13.5		11.8	
25th	51.5		41.4	
50th	95.5		71.1	
75th	137.2		110.5	
97.5th	267.1		193.2	
Prevalence of UIC	%	n	%	n
< 20 µg/l	4.2 (1.5, 7.0) [b]	(9)	8.4 (3.6, 13.1) [b]	(11)
< 50 µg/l	23.1 (17.4, 28.8)	(49)	32.1 (24.1, 40.1)	(42)
< 100 µg/l	50.9 (44.2, 57.7)	(108)	69.5 (61.6, 77.4)	(91)
≥ 100 µg/l	49.1 (42.3, 55.8)	(104)	30.5 (22.6, 38.4)	(40)
≥ 300 µg/l	1.4 [c]	(3)	0.8 [c]	(1)

Abbreviation: UIC = Urinary iodine concentration
[a] Median (95% CI)
[b] 95% CI, calculation: $p \pm 1.96 * \sqrt{p(1-p)/n}$; p = proportion of cases below/above the defined limit, n = sample size (Altman, 1999), p. 230; (all such values in this section).
[c] Here the number of cases below/above the defined limit was too small for the used calculation for the 95% CI, see [b].
[1] Significant difference non-lactating vs. lactating (MWU, $p < 0.01$)

The proportion of UIC < 100 µg/l and ≥ 100 µg/l was significantly different between non-lactating and lactating mothers (chi-square, $p < 0.001$) indicating that a significantly higher percentage of non-lactating mothers (49.1%) had a UIC ≥ 100 µg/l compared to lactating mothers (30.5%). Figure 24 shows these proportions. All other proportions were not significantly different from each other.

The median UIC in lactating mothers of 6-month-old infants (n = 102, median (95% CI) = 66.4 (57.8, 79.1) µg/l) was lower, but not significantly different from the median UIC in lactating mothers of 12-month-old infants (n = 29, median

(95% CI) = 79.9 (65.9, 117.3) µg/l) (MWU, p = 0.30). In non-lactating mothers, UIC was also not significantly different between mothers of both age groups (6-mo group: n = 78, median (95% CI) = 101.0 (80.7, 116.7) µg/l; 12-mo group: n = 134, median (95% CI) = 91.9 (74.7, 107.1) µg/l) (MWU, p = 0.23).

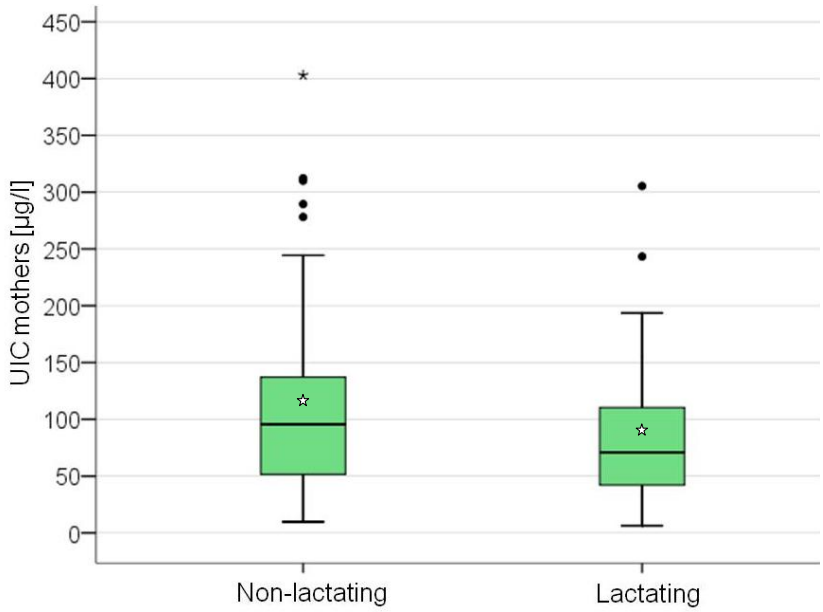


Figure 23: Box plots of urinary iodine concentration (UIC) [µg/l] of non-lactating (n = 212) and lactating mothers (n = 131) (☆ MWU, p < 0.01)

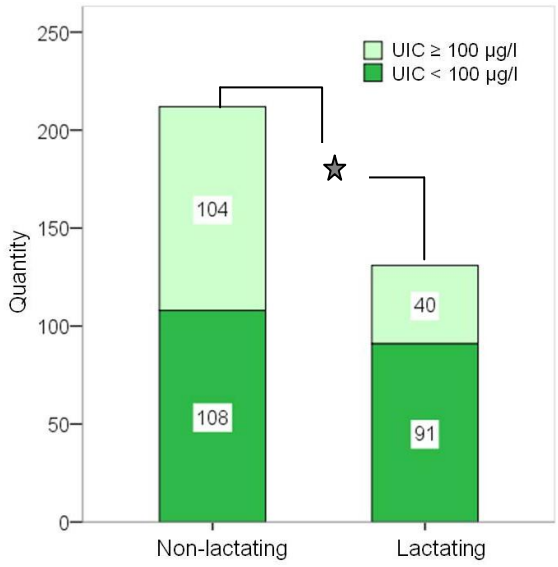


Figure 24: Proportion of urinary iodine concentrations (UIC) below/above 100 µg/l for non-lactating (n = 212) and lactating mothers (n = 131) (significant difference ☆ in proportions, p < 0.001)

There was no significant correlation between UIC of lactating mothers and number of breastfeeds per day (r_s = -.098, p = 0.26; data about breast-feeds from individual registration form).

There was no significant difference in UIC comparing mothers who indicated a daily number of breastfeeds between 1 and 5 (n = 99; median (95% CI) = 72.7 (65.9, 82.2) µg/l) with mothers who indicated between 6 and 10 breast-feeds per day (n = 32; median (95% CI) = 53.4 (40.6, 100.2) µg/l) (MWU, p = 0.20). However, there was a tendency for lower UICs in the mothers with the higher number of breastfeeds per day.

Looking at UIC of exclusively/predominantly breastfeeding mothers (n = 11; median (95% CI) = 47.3 (16.7, 123.2) µg/l) and partially breastfeeding mothers (n = 120; median (95% CI) = 71.8 (64.0, 81.1) µg/l), no significant difference in UIC was detected either (MWU, p = 0.17). However, there was also a tendency for lower UICs in exclusively/predominantly breastfeeding mothers. Box plots are shown in Figure 25.

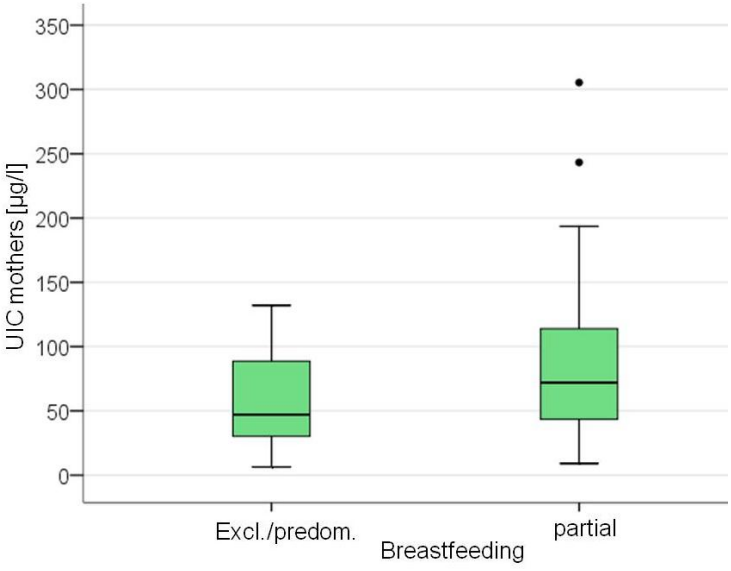


Figure 25: Box plots of urinary iodine concentration (UIC) [µg/l] of exclusively/predominantly (n = 11) and partially breastfeeding mothers (n = 120) (MWU, p = 0.17)

4.4.4.2. BMI

There was a significant positive relationship between UIC [µg/l] and BMI [kg/m^2] of mothers (r_s = .15, p < 0.01).

Figure 26 shows the scatter plot of the correlation.

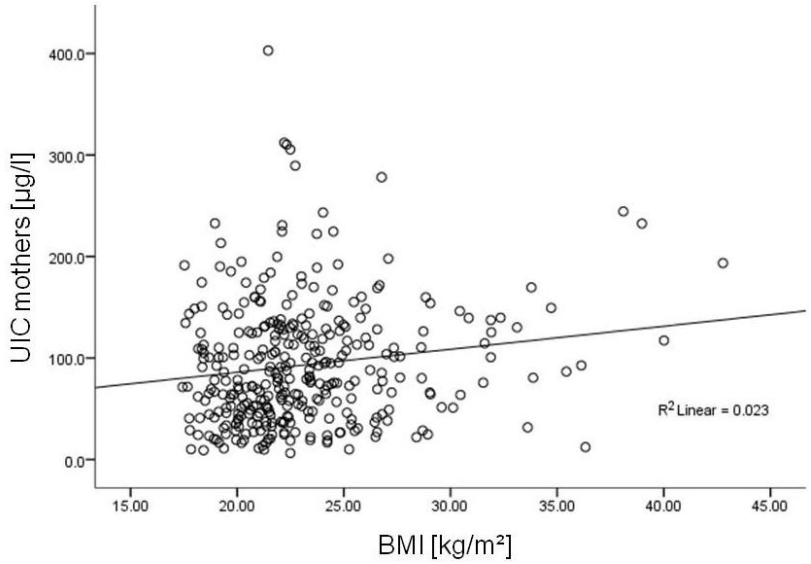


Figure 26: Scatter plot of BMI and UIC of mothers (n = 336, missing data on BMI n = 7) (r_s = .15, correlation p < 0.01)

4.4.4.3. Nationality

There was no significant difference between UIC of Swiss and foreign mothers (MWU, p = 0.29) (for medians see Table 43).

40% of the Swiss mothers were lactating compared to 28% of the foreign mothers. Looking at lactating and non-lactating mothers separately, no significant differences were found comparing UIC of Swiss and foreign mothers in both groups (*Lactating mothers:* Swiss vs. foreign p = 0.82; *Non-lactating mothers:* Swiss vs. foreign p = 0.55; for medians see Table 43).

Table 43: Urinary iodine concentration [µg/l] of Swiss and foreign mothers

UIC of mothers	**Lactating**		**Non-lactating**		**Total**	
	n	[µg/l]	*n*	[µg/l]	*n*	[µg/l]
Swiss [1]	*116*	69.3 (58.5, 80.1) [a]	*174*	97.5 (75.4, 108.7)	*290*	79.4 (69.5, 94.8)
Foreign nationality	*15*	77.3 (41.3, 102.7)	*38*	94.1 (77.6, 111.9)	*53*	88.3 (74.3, 92.7)

Abbreviation: UIC = urinary iodine concentration
[a] Median (95% CI), all such values
[1] Significant difference lactating vs. non-lactating (p < 0.05)

In Swiss mothers, non-lactating women had a 41% higher median UIC

compared to lactating women. The difference in UIC was significant (MWU, $p < 0.05$, see Table 43). In foreign mothers, there was also a trend of higher UICs in non-lactating mothers compared to lactating mothers, but the difference in UIC was not significant (MWU, $p = 0.08$).

4.4.4.4. Pediatric practice/region

The median (range) UIC of mothers in each pediatric practice is given in Appendix 17. There was no significant difference in UIC of mothers between pediatric practices (K-W, $p = 0.12$). Median UICs of practices ranged from 50.6 to 146.2 µg/l.

Table 44 lists the median (range) UICs [µg/l] of mothers in the seven Swiss regions. A comparison between the regions did not show a significant difference in UIC of mothers (K-W, $p = 0.27$). Box plots of UIC [µg/l] of mothers in each greater Swiss region are shown in Figure 27. Lake Geneva region and Ticino had a tendency for lower respectively higher UICs than the other regions, but their sample sizes were very small (n = 4 respectively 18) for comparisons.

Table 44: Urinary iodine concentration [µg/l] of mothers in the seven Swiss regions

	UIC of mothers	
Regions	*n*	[µg/l]
Lake Geneva region (1) [a]	*4*	50.6 (16.7 – 143.7) [b]
Espace Mittelland (2)	*35*	94.8 (16.6 – 310.1)
Northwestern Switzerland (3)	*58*	83.3 (6.4 – 403.0)
Zurich (4)	*46*	88.2 (20.5 – 232.5)
Eastern Switzerland (5)	*92*	71.7 (9.1 – 312.1)
Central Switzerland (6)	*90*	80.9 (11.0 – 213.3)
Ticino (7)	*18*	104.8 (64.3 – 142.7)
TOTAL	*343*	81.1 (6.4 – 403.0)

Abbreviation: UIC = urinary iodine concentration
[a] Numbers in brackets correspond to the numbers in the box plot figure
[b] Median (range) (all such values)

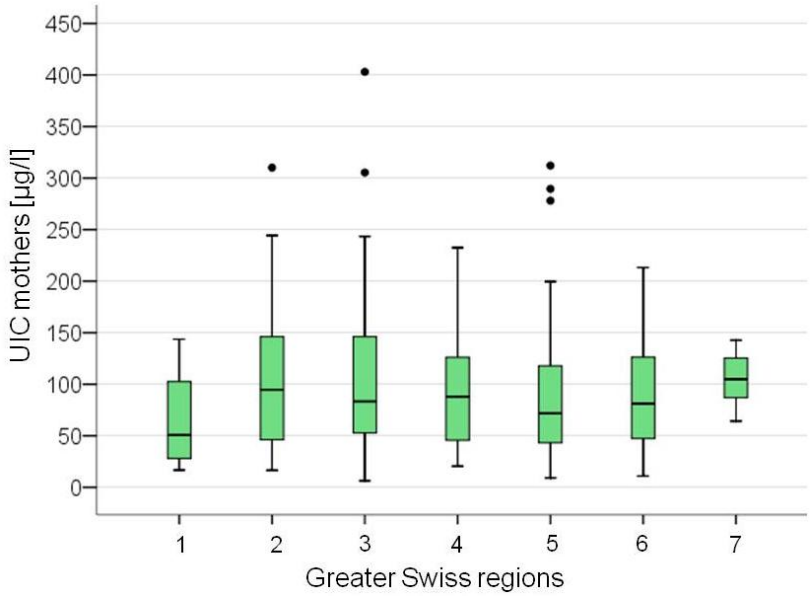


Figure 27: Box plots of urinary iodine concentration (UIC) [µg/l] of mothers in each greater Swiss region (K-W, p = 0.27)
Legend: The names of the regions (numbers in brackets) and [n] per region can be found in Table 44

4.4.4.5. Urban – rural area of pediatric practice

There was no difference in maternal UIC between samples collected from pediatric practices in urban and rural areas (MWU, p = 0.94; median UIC urban areas = 81.1 µg/l (n = 291); median UIC rural areas = 85.8 µg/l (n = 52)).

UIC of mothers in urban areas also did not differ significantly from rural areas, when non-lactating (*urban*: n = 179, median UIC = 95.0 µg/l; *rural:* n = 33, median UIC = 100.3 µg/l) and lactating mothers (*urban*: n = 112, median UIC = 71.8 µg/l; *rural*: n = 19, median UIC = 62.6 µg/l) were analyzed separately (MWU, p = 0.63 respectively p = 0.66).

Pediatric practices in rural areas were located only in Espace Mittelland and Eastern Switzerland (see Table 19). Therefore, we analyzed these regions separately. UIC of mothers from practices in urban areas was not significantly different from practices in rural areas in both regions (MWU, Espace Mittelland: p = 0.27 and Eastern Switzerland: p = 0.96).

4.4.4.6. Month of study registration/sample collection

Table 45 lists median (range) UIC of mothers by month of sample collection (= month of registration for study) and Figure 28 shows the box plots.

Table 45: UIC of mothers [µg/l] by month of registration/sample collection (n = 343)

	UIC of mothers	
Month	*n*	[µg/l]
Aug '08	*12* [a] *(9 / 3)*	69.0 (32.6 – 305.4) [b]
Sept '08	*60* *(38 / 22)*	75.3 (10.1 – 312.1)
Oct '08	*61* *(37 / 24)*	99.5 (11.1 – 289.5)
Nov '08	*55* *(34 / 21)*	77.3 (9.7 – 310.1)
Dec '08	*51* *(26 / 25)*	86.1 (6.4 – 244.4)
Jan '09	*25* *(16 / 9)*	108.7 (16.6 – 232.5)
Feb '09	*25* *(17 / 8)*	86.9 (18.6 – 230.7)
March '09	*44* *(25 / 19)*	61.3 (12.2 – 403.0)
April '09	*7* [c]	64.1 (20.2 – 155.2)
May '09	*3* [c]	149.4 (71.9 – 191.4)

Abbreviation: UIC = urinary iodine concentration
[a] All mothers (non-lactating/lactating) (all such values)
[b] Median (range) (all such values); [c] No lactating mothers in this month

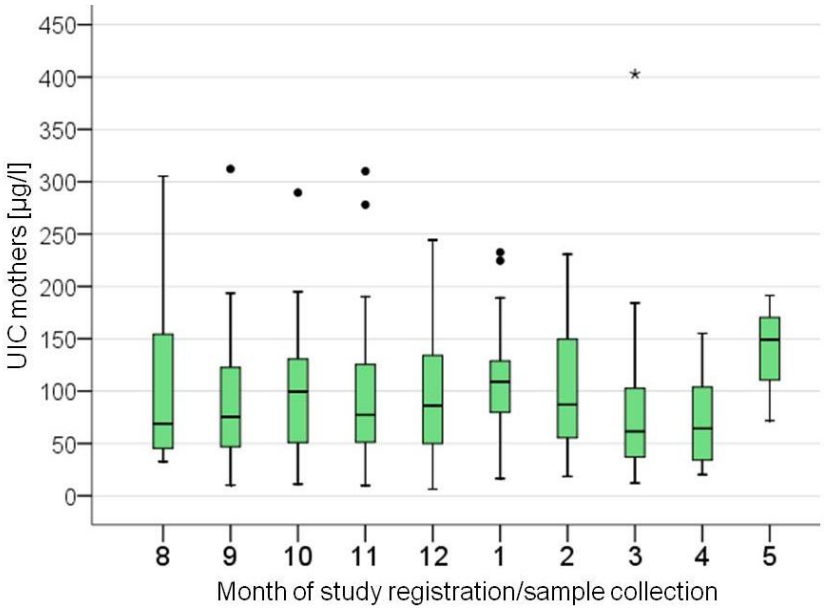


Figure 28: Box plots of urinary iodine concentration (UIC) [µg/l] of mothers (n = 343) by month of study registration/sample collection (K-W, p = 0.3)

Legend: Numbers in x-axis = months 8/2008 – 12/2008, 1/2009 – 5/2009; n per month see Table 45

No significant difference in UIC of mothers was detected between the months of sample collection (K-W, p = 0.31). The lowest median UIC was found in March ’09 (61.3 µg/l, n = 44) and the highest in May ’09 (149.4 µg/l, n = 3) (Table 45).

4.4.4.7. Supplements

No significant difference was found in UIC comparing mothers who took an iodine-containing supplement, those who did not take any iodine-containing supplement (incl. mothers not taking any supplements at all) and those who took a supplement where it was unclear if it contained iodine (K-W, p = 0.81). Table 46 shows the medians.

However, the number of mothers taking an iodine-containing supplement was very small for a comparison (n = 13, of which 5 lactating and 8 non-lactating).

Table 46: Use of supplement and UIC [µg/l] of mothers

Supplements	**UIC of mothers**	
	n [a]	[µg/l]
Taking an **iodine-containing** supplement	*13* [b] (8 / 5)	66.8 (29.0 – 403.0) [c]
Unclear if supplement contained iodine	*15* (9 / 6)	78.2 (24.7 – 173.2)
Not taking any **iodine-containing** supplement/no supplement	*312* (193 / 119)	81.6 (6.4 – 312.1)

Abbreviation: UIC = urinary iodine concentration
[a] Missing data of 3 mothers
[b] All mothers (non-lactating/lactating) (all such values)
[c] Median (range) (all such values)

4.4.4.8. Iodized salt

There was no significant difference in UIC between mothers using iodized salt, not using iodized salt and mothers who indicated not knowing if they used iodized salt (K-W, p = 0.35). However, median UIC of mothers answering “unknown” was about 40 – 50% higher compared to the other two groups. Nevertheless, interquartile ranges (IQR) of all three groups were very close to each other and the number of mothers with answers “no” or “unknown” was rather small for comparison. Table 47 gives medians and IQRs.

83% of the non-lactating mothers (n = 177) and 90% of the lactating mothers (n

= 118) answered “yes”. Numbers of mothers answering “no” or “unknown” were equally distributed in non-lactating and lactating mothers (see Table 47).

Table 47: Use of iodized salt and UIC of mothers [µg/l]

Use of iodized salt	**UIC of mothers**		
	n [a]	[µg/l]	IQR
Yes	*295* [b] (177 / 118)	80.7 (6.4 – 403.0) [c]	46.8 – 126.7
No	*20* (14 / 6)	75.7 (10.0 – 289.5)	39.1 – 131.8
Unknown	*25* (19 / 6)	113.8 (19.3 – 230.7)	49.9 – 144.1

Abbreviations: UIC = urinary iodine concentration; IQR = interquartile range
[a] Missing data of 3 mothers
[b] All mothers (non-lactating/lactating) (all such values)
[c] Median (range) (all such values)

4.4.4.9. Social demographics

Smoking

There was no difference in UIC between smokers and non-smokers (MWU, p = 0.69). Medians are shown in Table 48.

Table 48: Smoking and UIC [µg/l] of mothers

Smoking	**UIC of mothers**	
	n [a]	[µg/l]
Yes	*30* [b] (25 / 5)	81.0 (28.4 – 224.6) [c]
No	*293* (171 / 122)	81.1 (6.4 – 403.0)

Abbreviation: UIC = urinary iodine concentration
[a] Missing data of 20 mothers (of which 4 lactating)
[b] all mothers (non-lactating/lactating) (all such values); [c] Median (range) (all such values)

Professional activity

No significant difference in UIC was detected comparing professional activity of mothers (full time, part time, by the hour, not working) (K-W, p = 0.46).

As we saw no reason why professional activity should influence the mothers’ UIC, we did not examine this association in more detail.

Classification of occupation

There was no significant difference in UIC between different occupational categories of the mothers (K-W, p = 0.23, detailed data not shown).

Almost 50% of participating mothers had an occupation belonging to the "8. Health, education & culture, scientists" category. Therefore, we examined if UIC of those mothers was different from mothers belonging to the other categories (all together, see Table 49). Comparison showed a significantly lower median UIC in mothers belonging to the occupation category "Health, education & culture, scientists" (MWU, p < 0.05). The percentage of lactating mothers compared to non-lactating mothers was 47% in the category 8 and only 34% in the other occupational categories. Analyzing lactating and non-lactating mothers separately, there was no significant difference in UIC between category 8 and other categories in non-lactating mothers (p = 0.45, median cat. 8 = 88.1 µg/l; median other cat.: 101.2 µg/l), but there was a significance in lactating mothers (p = 0.0496, median cat. 8 = 65.1 µg/l; median other cat. = 77.3 µg/l) (for numbers see Table 49).

Table 49: Classification of mothers' occupations and UIC of mothers [µg/l]

Classification of occupations	**UIC of mothers [1]**	
	n [a]	[µg/l]
Health, education & culture, scientists (category 8)	*148* [b] (79 / 69)	74.3 (64.1, 85.3) [c]
Other occupational category	*170* (113 / 57)	94.7 (77.4, 105.8)

Abbreviation: UIC = urinary iodine concentration
[a] Missing data of 25 mothers (of which 5 lactating)
[b] All mothers (non-lactating/lactating) (all such values)
[c] Median (95% CI) (all such values)
[1] Significant difference between categories (MWU, p < 0.05)

Educational background of mothers

There was no significant difference in UIC between mothers with different educational background (K-W, all mothers: p = 0.092; non-lactating: p = 0.47; lactating: p = 0.57). Table 50 shows the medians (all mothers).

Table 50: Educational background of mothers and UIC of mothers [µg/l]

Educational background	**UIC of mothers**	
	n [a]	[µg/l]
Compulsory school/secondary education level	*166* [b] (111 / 55)	88.4 (75.7, 106.1) [c]
Higher vocational education	*79* (48 / 31)	75.9 (64.4, 100.3)
University level	*73* (33 / 40)	76.0 (59.0, 92.5)

Abbreviation: UIC = urinary iodine concentration
[a] Missing data of 25 mothers (of which 5 lactating)
[b] all mothers (non-lactating/lactating) (all such values)
[c] Median (95% CI) (all such values)

4.4.4.10. UIC of breast-fed infants and UIC of mothers

There was no correlation between the UIC of breast-fed infants (n = 131) and the UIC of their mothers (r_s = .024, p = 0.78).

4.4.5. Quality control of Sandell-Kolthoff method

4.4.5.1. Measurement repeats

Eight percent (infants n = 19, mothers n = 34) of the samples had to be measured twice because the difference of the duplicate was greater than the allowed difference (see methods). Of these, six had to be measured a third time and one a fourth time (always in duplicate).

As control, another eight percent of the samples (infants n = 18, mothers n = 38) were measured twice even if the first measurement was acceptable (both measurements in duplicate). In this case, the average UIC of both measurements was taken for data analysis.

4.4.5.2. Internal quality control

The intra- and inter-assay precision tests of the method showed good results. The results are given in Table 51, which also shows the results of the validation of the X and Z controls with ICP-MS. The ICP-MS validation showed good agreement with the Sandell-Kolthoff values.

Table 51: Intra-/inter-assay precision of modified S-K method and ICP-MS validation

	Intra-assay precision S-K (n = 12) [a]	Inter-assay precision S-K		ICP-MS validation (intra-assay precision)	
		X – reference [b] (n = 37)	Z – reference [c] (n = 37)	X – reference (n = 3)	Z – reference (n = 3)
Mean [µg/l]	104.9 ± 3.3 [d]	33.1 ± 2.1	214.9 ± 6.6	31.2 ± 0.8	211.4 ± 1.5
CV [%]	3.2	6.4	3.1	2.7	0.7

Abbreviations: S-K = Sandell-Kolthoff method; ICP-MS = inductively coupled plasma mass spectrometry; CV = coefficient of variation

[a] Spot urine sample of NW

[b/c] Laboratory reference values: X = 34.1±3.34 µg/l (CV% 9.80); Z = 218±7.05 µg/l (CV% 3.24)

[d] mean ± SD (all such values)

Two plates with urine samples of mothers had to be excluded because in one case the X-reference was above the allowed limit and in the other case the standard curve was below R = 0.99. All of these samples were measured again.

4.4.5.3. External quality control

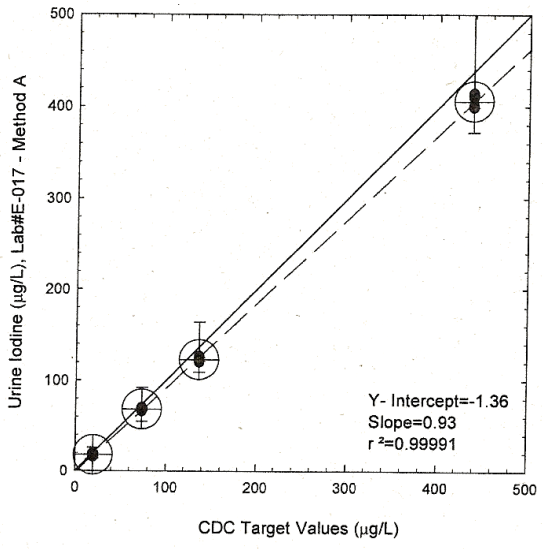
The four EQUIP urine control specimens were measured in three different runs

in duplicate on three different days. All measured means were within the acceptable range (defined by EQUIP) with a slight drift towards the lower end of the range with increasing iodine concentration. This drift could have been due to several reasons and should be considered in future experiments. As all EQUIP results were in the acceptable range, the results of the urinary iodine analysis can be considered as accepted. Table 52 lists the EQUIP results and Figure 29 shows the regression of the measured UICs for EQUIP at ETH and the CDC target values.

Table 52: Results EQUIP round 21

EQUIP round 21	**Urine specimen**			
	060489	060439	060404	060414
UIC, ETH [µg/l]	17.7 ± 2.0 [a]	68.1 ± 1.1	122.7 ± 1.7	406.0 ± 1.8
CV, ETH [%]	10.6	2.5	1.8	1.7
Mean all labs [b] [µg/l]	18.8 ± 6.5	68.7 ± 11.5	134.1± 22.5	428.7 ± 48.9
CDC target value [µg/l]	19.9 (13.9-25.9) [c]	73.4 (55.0-91.7)	136.3 (109.0-163.6)	438.5 (372.7-504.3)
% Error (measured vs. CDC target)	-11.1	-7.2	-10.0	-7.4

Abbreviations: ETH = Federal Institute of Technology, Zurich; UIC = urinary iodine concentration; CV = coefficient of variation (%); CDC = Center for disease control
[a] Mean ± SD (all such values)
[b] All labs which participated at the current EQUIP round
[c] CDC target value (acceptable range)



Legend:
Solid line = line of identity
Dashed line = linear regression of ETH values
Error bars = acceptable range
Black circles = measured values at ETH (individual points)
Center of large circle = mean of ETH data

Figure 29: Regression of urinary iodine concentration ETH (Lab#E-017) and CDC target values [µg/l]

4.5. Breast milk iodine concentration

4.5.1. Sample collection

The BM samples included in this thesis were collected between mid August 2008 and end of March 2009 (date of study registration). The numbers of included samples per month were (BM total n = 119): Aug ’08 n = 3, Sept ’08 n = 18, Oct ’08 n = 23, Nov ’08 n = 19, Dec ’08 n = 23, Jan ’09 n = 9, Feb ’09 n = 6, Mar ’09 n = 18.

All BM samples were collected at home, by which collection technique is not known.

Some of the BM samples showed coagulations when they arrived at ETH, therefore those were treated in a special way before storage and analysis (see respective chapters).

4.5.2. Overview of breast milk iodine concentration

An overview of the measured breast milk iodine concentrations (BMIC) in total and by age group of infants is given in Table 53.

The overall median BMIC was 51.2 µg/kg (n = 119). As breast milk was weighed and pipetted for the measurement, BMIC was available as µg/kg and µg/l (see 1 and 2 in Table 53). Weighing the samples on the analytical scale was more precise than pipetting; therefore, BMIC in µg/kg was used for comparisons. BMIC [µg/kg] multiplied with the specific density (1.031 kg/l) of breast milk (Neville and Jensen, 1995) is also a possible way of transforming BMIC to the unit µg/l (see 3 in Table 53). As the specific gravity of BM is close to the one of water (0.998 kg/l), all three medians were very close to each other.

Figure 30 shows the distribution of the BMICs [µg/kg] (n = 119). The BMICs were not normally distributed (K-S test), but skewed to the right (mean ± SD = 56.6 ± 28.7 µg/kg; median = 51.2 µg/kg).

The median BMIC of mothers of 6-month-old infants (53.3 µg/kg) was 26% higher than that of mothers of 12-month-old infants (42.3 µg/kg). Nevertheless, there was no significant difference in BMIC between the two age groups (MWU, p = 0.29, see also Figure 31). There was also no significant correlation between BMIC and age of infant [months] (r_s = -.086, p = 0.35). However, the sample

size of BM in the 12-mo group was very small (n = 24) compared with the 6-mo group (n = 95). Therefore, further analysis of BMIC was done for both age groups together.

Even though the sample size of BMIC was much smaller (n = 119) compared with maternal UIC (n = 343), the BMIC range was much narrower (10.7 – 147.7 µg/kg). 95% of all BMICs lay between 18.0 and 128.2 µg/kg.

The major part of the samples (89.1%) had an iodine concentration < 100 µg/kg and nearly half of the samples (47.9%) had a concentration < 50 µg/kg.

Table 53: Overview of breast milk iodine concentrations

	BMIC [a]	**Age group of infants**		**Total**
		6-mo	**12-mo**	
	n	*95*	*24*	*119*
1)	Median [µg/kg]	53.3 (45.1, 59.8) [b]	42.3 (35.6, 62.2) [b]	51.2 (44.3, 58.9) [b]
	Minimum [µg/kg]	10.7	19.6	10.7
	Maximum [µg/kg]	147.7	127.1	147.7
	Percentiles [µg/kg]			
	2.5^{th}	16.5	19.6	18.0
	25^{th}	38.2	33.0	37.2
	50^{th}	53.3	42.3	51.2
	75^{th}	68.9	62.2	68.4
	97.5^{th}	138.3	127.1	128.2
	Prevalence of BMIC	*% (n)*	*% (n)*	*% (n)*
	< 20 µg/l	5.3 (5)	4.2 (1)	5.0 (6)
	< 50 µg/l	46.3 (44)	54.2 (13)	47.9 (57)
	< 100 µg/l	89.5 (85)	87.5 (21)	89.1 (106)
	≥ 100 µg/l	10.5 (10)	12.5 (3)	10.9 (13)
2)	Median BMIC [µg/l]	56.2	44.0	53.9
3)	Median (BMIC [µg/kg] * specific gravity) [µg/l]	55.0	43.6	52.8

[a] Abbreviation: BMIC = Breast milk iodine concentration
[b] 95% CI, calculated with SPSS 16

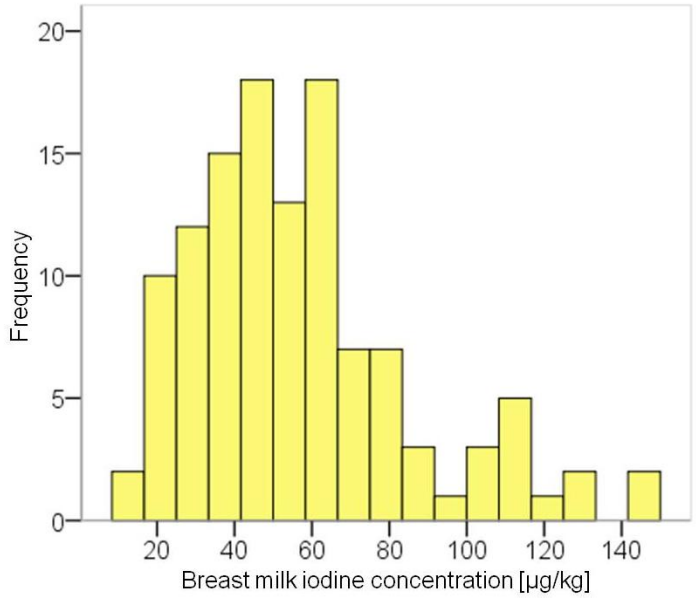


Figure 30: Distribution of breast milk iodine concentrations (n = 119)

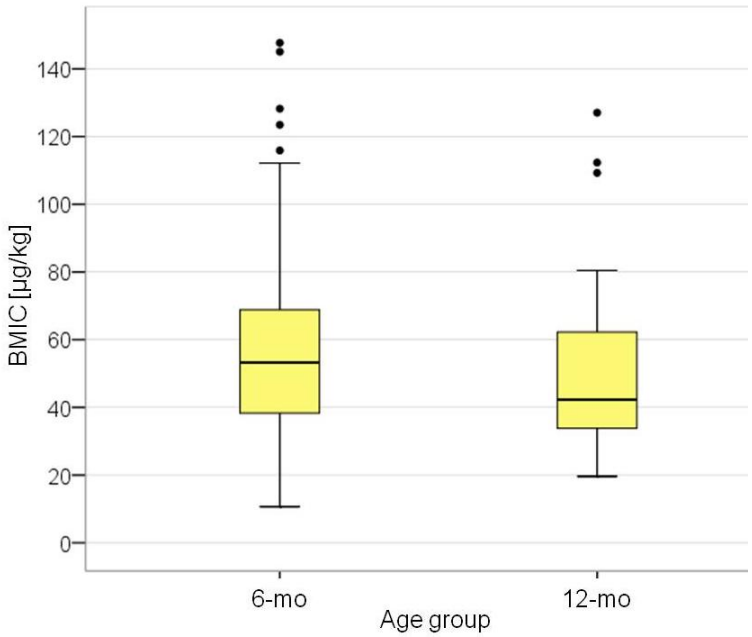


Figure 31: Box plots of breast milk iodine concentration (BMIC) [µg/kg] by infant age group (6-mo: n = 95, 12-mo: n = 24; MWU, p = 0.3)

4.5.2.1. Body weight & BMI

No significant correlations were found between BMIC and body weight of mothers (r_s = -.031, p = 0.75) and between BMIC and BMI of mothers (r_s = -.085, p = 0.36).

4.5.2.2. Nationality

Only 10% (n = 12) of the BM samples came from mothers with foreign nationality and 90% (n = 107) from Swiss mothers. No significant difference was detected comparing BMIC of Swiss mothers (n = 107, median (range) = 53.3 (10.7 – 147.7) µg/kg) to that of foreign mothers (n = 12, median (range) = 41.2 (19.6 – 112.3) µg/kg) (MWU, p = 0.72). The number of foreign mothers was very small for a comparison.

4.5.2.3. Pediatric practice/region

The median (range) BMIC in each pediatric practice can be found in Appendix 18. There was no significant difference in BMIC between pediatric practices (K-W, p = 0.60). Median BMICs of practices ranged from 31.3 to 64.6 µg/kg.

Table 54: BMIC [µg/kg] arranged by the seven Swiss regions

		BMIC
Regions	*n*	[µg/kg]
Lake Geneva region (1) [a]	*2*	58.8 (57.8 – 59.8) [b]
Espace Mittelland (2)	*16*	50.5 (18.5 – 112.3)
Northwestern Switzerland (3)	*17*	55.3 (18.6 – 147.7)
Zurich (4)	*12*	44.1 (10.7 – 74.3)
Eastern Switzerland (5)	*32*	52.3 (15.5 – 128.2)
Central Switzerland (6)	*35*	49.5 (21.2 – 123.5)
Ticino (7)	*5*	64.6 (24.9 – 145.1)
TOTAL	*119*	51.2 (10.7 – 147.7)

Abbreviation: BMIC = breast milk iodine concentration
[a] Numbers in brackets correspond to the numbers in the box plot figure
[b] Median (range) (all such values)

No significant difference was detected comparing BMIC between the seven Swiss regions (K-W, p = 0.45, medians shown in Table 54), also not if the regions 1 and 7 were excluded from the comparison due to their very small

sample size (n = 2 resp. 5) (K-W, p = 0.38). The median BMICs of the regions ranged from 44.1 µg/kg (Zurich) to 64.6 µg/kg (Ticino). The median BMICs in the seven regions are given in Table 54 and box plots are shown in Figure 32.

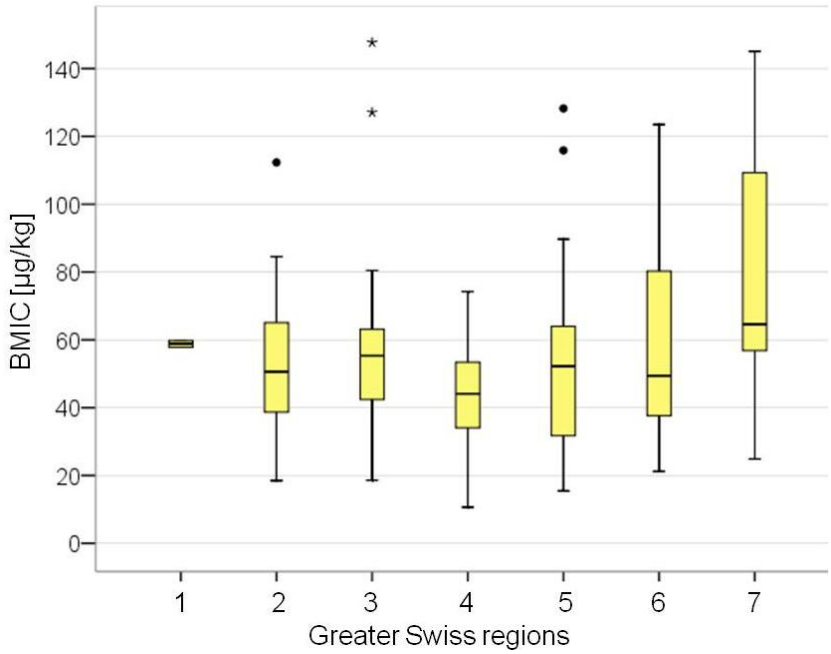


Figure 32: Box plots of breast milk iodine concentration (BMIC) [µg/kg] by the greater Swiss regions (K-W, p = 0.45)
Legend: The names of the regions and n per region are given in Table 54, see numbers in brackets

4.5.2.4. Urban – rural area of pediatric practice

The median BMIC from samples collected in urban areas was 34% higher compared to the median BMIC from samples collected in rural areas (*urban areas*: median (95% CI) BMIC = 55.9 (45.1, 60.0) µg/kg, n = 100; *rural areas*: median BMIC = 41.8 (29.6, 56.8) µg/kg, n = 19). The difference in BMIC was significant (MWU, p < 0.05).

Pediatric practices in rural areas were located only in Espace Mittelland and Eastern Switzerland (see Table 19). If only these regions were examined, there was no significant difference in BMIC between mothers from practices in urban and rural areas in both regions (MWU, *Espace Mittelland*: p = 0.27 (*urban*: median BMIC = 56.7 µg/kg, n = 7; *rural*: median BMIC = 44.1 µg/kg, n = 9); *Eastern Switzerland*: p = 0.14 (*urban*: median BMIC = 57.7 µg/kg, n = 22; *rural*:

median BMIC = 37.1 µg/kg, n = 10)).

4.5.2.5. Month of study registration/sample collection

Table 55 lists the median (range) BMICs by month of sample collection (= month of registration for study) and Figure 33 shows the box plots.

BMIC did not differ significantly between different months of sample collection (K-W, p = 0.76). The lowest median BMIC was measured in November '08 (44.1 µg/kg, n = 19) and the highest in August '08 (63.1 µg/kg, n = 3).

Table 55: BMIC [µg/kg] by month of study registration/sample collection (n = 119)

		BMIC
Month	*n*	[µg/kg]
Aug '08	*3*	63.1 (55.3 – 68.8) [a]
Sept '08	*18*	47.8 (15.5 – 127.1)
Oct '08	*23*	56.8 (10.7 – 108.3)
Nov '08	*19*	44.1 (21.8 – 81.4)
Dec '08	*23*	49.5 (18.6 – 128.2)
Jan '09	*9*	56.8 (19.6 – 147.7)
Feb '09	*6*	60.7 (18.5 – 145.1)
March '09	*18*	56.2 (18.0 – 123.5)
April '09	*0*	--
May '09	*0*	--

Abbreviation: BMIC = breast milk iodine concentration
[a] Median (range) (all such values)

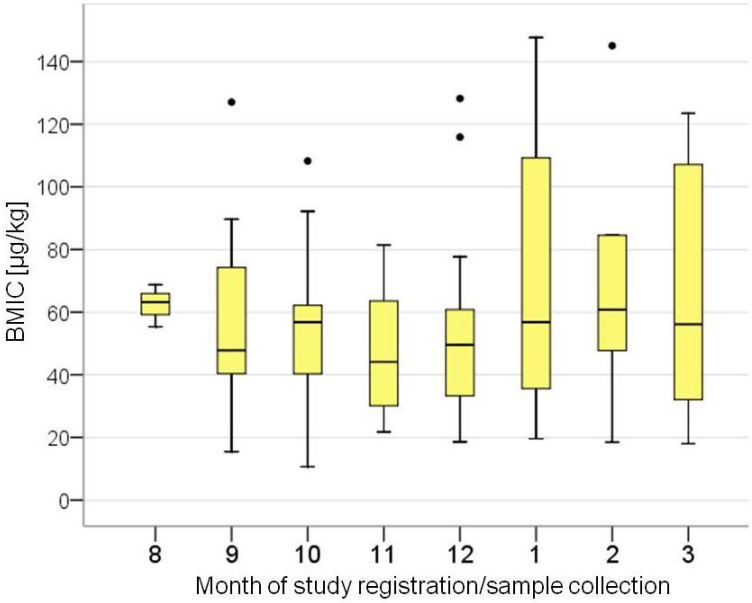


Figure 33: Box plots of breast milk iodine concentration (BMIC) [µg/kg] (n = 119) by month of study registration/sample collection (K-W, p = 0.8)

Legend: Numbers in x-axis = months 8/2008 – 12/2008, 1/2009 – 3/2009; n per month are given in Table 55

4.5.2.6. Breast feeding practice

There was no difference in BMIC between mothers who breast-fed exclusively/predominantly and mothers who breast-fed partially (MWU, p = 0.17). Table 56 shows the medians. However, the number of mothers who breast-fed exclusively/predominantly was very small for comparison (n = 11).

Table 56: BMIC [µg/kg] by breast feeding practice

Breast feeding		**BMIC** [µg/kg]		
	n	Median	Min	Max
Exclusive/predominant	*11*	51.2 (41.7, 72.2) [a]	37.3	115.9
Partial	*108*	52.1 (43.7, 58.9)	10.7	147.7

Abbreviation: BMIC = breast milk iodine concentration
[a] Median (95% CI) (all such values)

A significant positive correlation was observed between BMIC and number of daily breast-feeds (data from individual registration form) (r_s = .24, p < 0.01). A scatter plot of the correlation is shown in Figure 34.

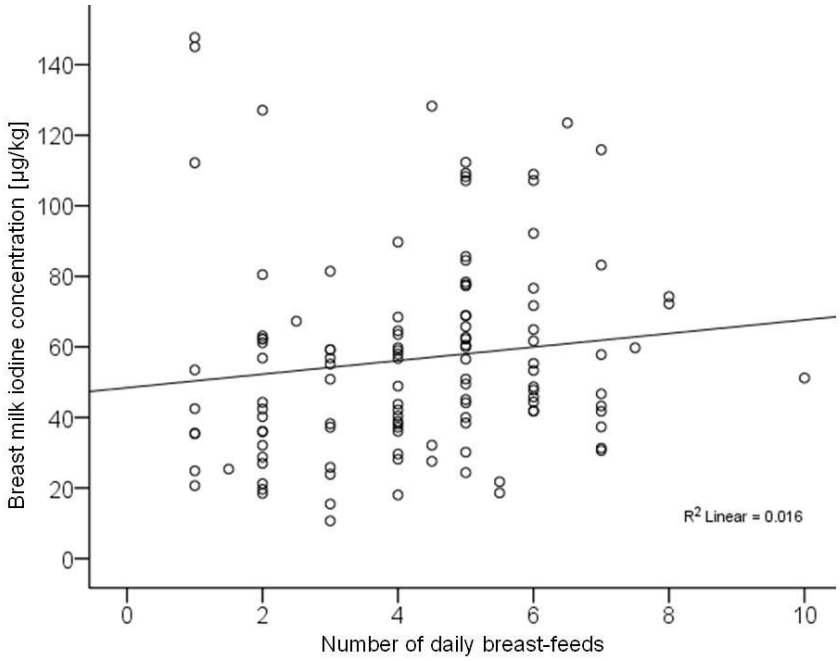


Figure 34: Scatter plot of breast milk iodine concentration [µg/kg] and number of daily breast-feeds (n = 119) (p < 0.01)

4.5.2.7. Supplements

Only 3% (n = 4) of mothers who provided a breast milk sample were taking an iodine-containing supplement. This percentage was very small for a comparison. The median BMIC of mothers taking an iodine-containing supplement was about 48% higher compared to the median BMIC of mothers not taking an iodine-containing supplement, but the range was very wide (27.0 - 145.1 µg/kg). Table 57 gives the medians and Figure 35 shows the box plots.

Table 57: Use of supplements by lactating mothers and their BMIC [µg/kg]

Supplements		**BMIC**
	n [a]	[µg/kg]
Taking an **iodine-containing** supplement	*4*	75.0 (27.0, 145.1) [b]
Unclear if supplement contains iodine	*5*	51.2 (10.7, 147.7)
Not taking any **iodine-containing** supplement/no supplement	*109*	50.8 (43.7, 57.9)

Abbreviation: BMIC = breast milk iodine concentration
[a] Missing data of one mother
[b] Median (95% CI) (all such values)

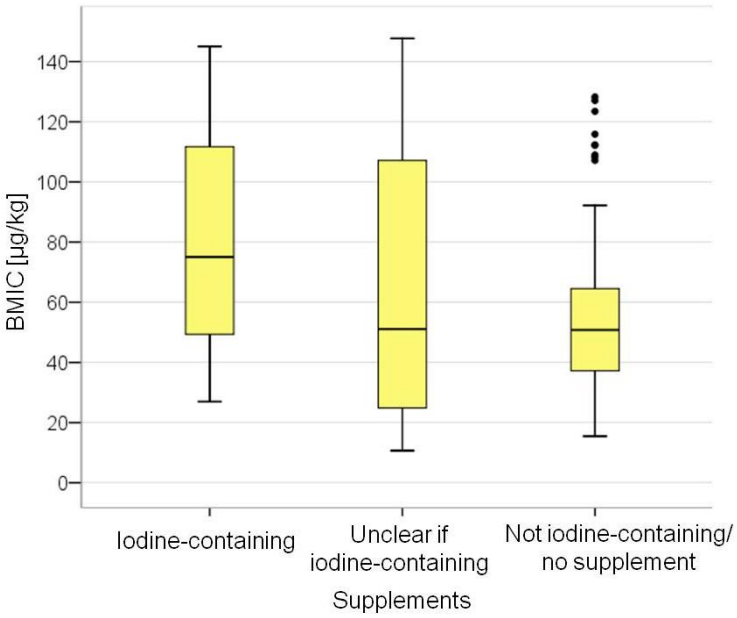


Figure 35: Box plots of maternal supplement intake and breast milk iodine concentration (BMIC) [µg/kg]: iodine-containing (n = 4), unclear if iodine-containing (n = 5), not iodine-containing/no supplement intake (n = 109) (K-W, p = 0.4)

No significant difference was found in BMIC comparing lactating mothers who took an iodine-containing supplement, those who did not take any iodine-containing supplement (incl. mothers not taking a supplement at all) and those who took a supplement where it was unclear if it contained iodine (K-W, p = 0.44; medians are given in Table 57).

4.5.2.8. Iodized salt

Ninety-one percent of mothers who provided a BM sample indicated using iodized salt at home. The number of mothers answering “no” or “unknown” was therefore very small for comparison of UIC (see Table 58).

Table 58 shows the median BMICs of the different groups of salt users. The median BMIC of mothers who did not use iodized salt was 28.5% lower compared to mothers who used iodized salt (MWU, p = 0.28). The median BMIC of mothers who did not know if they used iodized salt or not was in between the other groups. However, there was no significant difference in BMIC among the three groups (K-W, p = 0.56).

Table 58: Use of iodized salt and BMIC [µg/kg]

Use of iodized salt		**BMIC**
	n [a]	[µg/kg]
Yes	*107*	53.3 (10.7 – 147.7) [b]
No	*6*	38.1 (25.9 – 80.5)
Unknown	*5*	44.1 (21.8 – 115.9)

Abbreviation: BMIC = breast milk iodine concentration
[a] Missing data of one mother
[b] Median (range) (all such values)

4.5.2.9. Social demographics

Smoking

The median BMIC of smoking mothers was 50% lower compared to non-smokers. Table 59 shows the medians. However, as just four mothers indicated that they smoked this number was very small for comparison. The BMIC values were 10.7, 18.5, 37.2, 115.9 µg/kg. There was no significant difference in BMIC between smokers and non-smokers (MWU, p = 0.18).

Table 59: Smoking and BMIC [µg/kg] of mothers

Smoking		**BMIC**
	n [a]	[µg/kg]
Yes	*4*	27.8 (10.7 – 115.9) [b]
No	*110*	54.3 (15.5 – 147.7)

Abbreviation: BMIC = breast milk iodine concentration
[a] Missing data of 5 mothers
[b] Median (range) (all such values)

Professional activity

No significant difference in BMIC was found when comparing professional activity of mothers (full time, part time, by the hour, not working) (K-W, p = 0.094). As we saw no reason why professional activity should influence the mother's BMIC, we did not look at this in more detail.

Classification of occupation

There was no significant difference in BMIC between different occupational categories of the mothers (K-W, p = 0.43, detailed data not shown). Fifty-five percent (n = 63) of BM samples were provided from mothers with an occupation belonging to the category "8. Health, education & culture, scientists". Therefore, we examined if median BMIC of those mothers was different compared with mothers from other categories. Comparison showed no significant difference in BMIC between mothers belonging to the occupation category "Health, education & culture, scientists" and the other categories (MWU, p = 0.34). Medians are given in Table 60.

Table 60: Classification of mothers' occupations and BMIC [µg/kg]

Classification of occupations		**BMIC**
	n [a]	[µg/kg]
Health, education & culture, scientists (category 8)	*63*	51.2 (43.2, 57.9) [b]
Other occupational category	*51*	56.7 (42.5, 62.2)

Abbreviation: BMIC = breast milk iodine concentration
[a] Missing data of 5 mothers; [b] Median (95% CI) (all such values)

Educational background

BMIC did not differ significantly between mothers with different educational background (K-W, p = 0.47). Table 61 shows the medians. Even though the median BMIC of mothers with a compulsory school/secondary educational level was around 20% lower compared to the two higher education levels, IQR was rather similar in all groups (see Table 61).

Table 61: Educational background of mother and BMIC [µg/kg]

Educational background		**BMIC**	
	n [a]	[µg/kg]	IQR
Compulsory school/secondary education level	*50*	44.7 (40.2, 60.0) [b]	35.7 – 64.7
Higher vocational education	*26*	59.2 (40.0, 74.3)	34.7 – 79.9
University level	*38*	54.3 (44.1, 61.2)	38.8 – 66.1

Abbreviations: BMIC = breast milk iodine concentration; IQR = interquartile range
[a] Missing data of 5 mothers; [b] Median (95% CI) (all such values)

4.5.2.10. Maternal UIC and BMIC

No correlation was detected between maternal UIC and BMIC (r_s = -.062, p = 0.50 (n = 119); exclusive/predom. BF: r_s = .036, p = 0.92 (n = 11); partial BF: r_s = -.058, p = 0.55 (n = 108)).

4.5.2.11. UIC of breast-fed infants and BMIC

A significant positive correlation was found between UIC of breast-fed infants and BMIC (r_s = .22, p < 0.05, n = 119). The correlation was even stronger when log transforming UIC of infants and BMIC (r_s = .25, p < 0.01).

This significant correlation also existed if only partially breast-fed infants were examined (r_s = .21, p < 0.05, n = 108). For exclusively/predominantly breast-fed infants (n = 11) a positive correlation was observed as well, but it was not significant (r_s = .27, p = 0.42). Figure 36 shows the correlations.

Examining both infant age groups separately, the correlation was significant for the 6-month-old infants (r_s = .23, p < 0.05, n = 95), but not for the 12-month-old infants (r_s = .39, p = 0.062, n = 24).

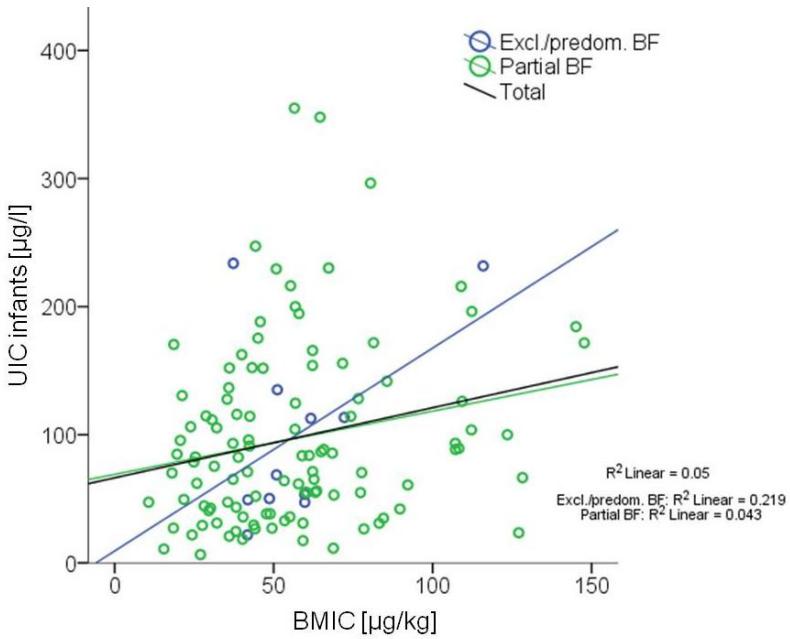


Figure 36: Scatter plot of breast milk iodine concentration (BMIC) [µg/kg] and urinary iodine concentration (UIC) of infants [µg/l] (total n = 119, excl./predom. BF n = 11, partial BF n = 108) (BF = breast feeding)

4.5.3. Limit of detection & limit of quantification of ICP-MS

The average ± SD of spike ratios ($(^{127}I/^{129}I)_{Spike}$) was 0.1518 ± 0.0044 (n = 54, measured in spike ratio solutions). Based on this value the R_{LOD} was > 0.1651 and the R_{LOQ} was > 0.1960. The usual sample weight per 12ml-tube was about 0.31 g. Therefore, the LOD for iodine with ICP-MS was ~ 1.5 µg/kg and the LOQ was ~ 4.9 µg/kg. All BM samples had a higher iodine concentration than the LOQ (minimal BMIC was 10.7 µg/kg).

4.5.4. Quality control of ICP-MS

4.5.4.1. Blank

At *m/z* 127 no elevated blank levels were measured. The signal intensities corresponded to the basic instrumental noise. Blank variations introduced by memory effects (e.g. due to contamination) were not observed.

At *m/z* 129 the blank intensities were higher by at least a factor of 4.5. This was accredited to the interference by ^{129}Xe which was however expected. Xenon is found as a trace contaminant in the plasma gas argon (Haldimann et al., 2000). It has, however, no influence on the iodine measurement as the interference is the same in blank, samples and spike ratio solution.

The measured blank levels were as expected. Therefore, they showed that the materials and chemicals used for the analysis were not contaminated with iodine.

4.5.4.2. Whole milk reference

The measured iodine concentrations [mg/kg] of the whole milk reference samples are shown in Figure 37. The mean ± SD of all measured reference samples (n = 18) in seven runs was 2.37 ± 0.15 mg/kg powder (= 237 ± 15 µg/100 g). The values ranged from 1.98 to 2.53 mg/kg. The measured mean was close to the certified mean (2.3 mg/kg) and all measured values were within the certified 95% CI of the mean (1.9, 2.7 mg/kg).

The CV% between the seven runs was 6.3% and the mean intra-run CV% was 2.9%. The measured whole milk reference samples showed that the BMIC measurements were reliable.

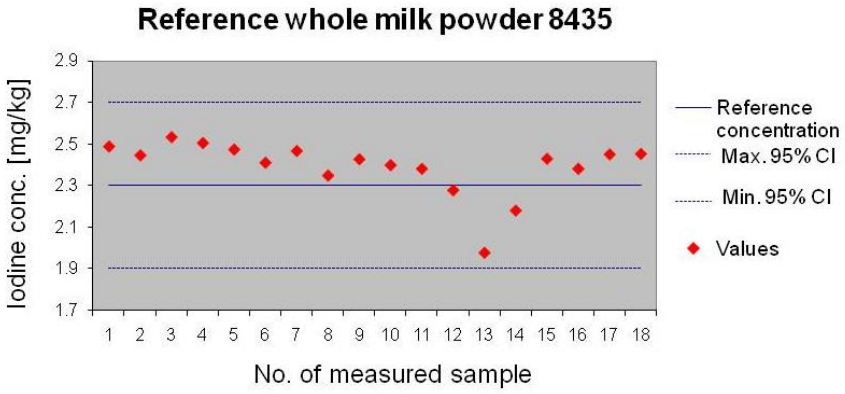


Figure 37: Iodine concentration of whole milk reference samples [mg/kg] measured with ICP-MS

4.5.5. Test of iodine stability in cow milk

There was no significant difference in the mean iodine concentration of cow milk (n = 3) which was measured on the day of purchase (mean ± SD: 86.133 ± 1.893 µg/kg) and again after seven days storage at ambient temperature having coagulations (mean ± SD: 83.733 ± 0.850 µg/kg) (p = 0.173, paired samples t-test; performed at FOPH using SYSTAT 12).

Based on this, we concluded that probably no iodine loss in breast milk occurred in the time between sample collection and freezing, even if some samples stayed at ambient temperature for a few days and had coagulations.

4.6. Iodine in formula and infant food

4.6.1. Formula

The labeled iodine contents of formula products are compared with the measured iodine concentrations in Table 62, which shows the difference between the values for each analyzed product. The twelve analyzed products were a convenient selection of products that were frequently indicated in the dietary questionnaires including at least one product of each available brand in Switzerland. The products were purchased in February 2009. Ten products were bought in pharmacies and two in retail stores.

Four products had labeled iodine concentrations lower than required by the new Swiss regulation, which was however not yet mandatory by the time of product purchase (all products with iodine concentration < 10 µg/100 kcal; regulation changed in March 2008, implementation in March 2010 (EDI, 2005b), see also chapter 2.3.3.3). The other products were consistent with the new regulations. None of the measured iodine contents was below the required iodine content of the still valid previous Swiss regulation (minimum iodine content of 5 µg/100 kcal, see also chapter 2.3.3.3). None of the products exceeded the allowed iodine content of 50 µg/100 kcal (EDI, 2005b).

The mean ± SD abs. difference [%] between labeled and measured values was 13.1 ± 7.7%. The range of abs. difference was 3.4% to 29.3 %. In absolute, the measured iodine concentrations differed between 0.2 and 2.6 µg/100 ml from the labeled values. Seven of the analyzed formula products had a slightly lower iodine concentration (- 7.2 to - 17.0%; - 0.2 to - 1.9 µg/100 ml) than labeled and five, a slightly higher one (5.6 to 29.3%; 0.6 to 2.6 µg/100 ml) (Table 62).

In the products Holle 2, Milumil 2 and Aptamil HA 2 the iodine concentration was also measured in the instant product (without reconstitution of one portion). The results corresponded well to the iodine contents measured in the reconstituted products:

- *Holle 2*: instant: 58.2 µg /100 g powder, reconst.: 62.8 µg/100 g powder
- *Milumil 2*: instant: 76.1 µg/100 g powder, reconst.: 78.9 µg/100 g powder
- *Aptamil HA 2*: instant: 79.5 µg/100 g powder, reconst.: 75.3 µg/100 g powder.

Table 62: Comparison of labeled and measured (ICP-MS) iodine concentrations in different brands of formula

Brand/ Product specification	Iodine concentration [1] Labeled [2] [µg/100 kcal]	Labeled [3] [µg/100 ml]	Measured [4] [µg/100 ml]	Difference [%] [5]
Infant formulae [6]				
Bimbosan [a]	7.1	4.8	4.6	-3.4
Bimbosan Bio [a]	7.7	5.2	4.4 [4a]	-17.0
Follow-on formulae [6]				
Adapta 2 [b]	14.5	10	9.1	-9.2
Coop Naturplan Bio Galactina 2 [c]	14.7	10	12.6	23.4
HiPP Folgemilch 2 [d]	14.3	11	11.6	5.6
Holle Bio 2 [e]	9.3	7	9.4 [4b]	29.3
Milupa Aptamil 2 [f]	17.6	12	13.2	9.2
Milupa Aptamil HA 2 [f]	19.1	13	11.1 [4a]	-15.5
Milupa Milumil 2 [f]	19.1	13	11.5 [4b]	-12.1
Nestlé Beba 2 [g]	23.9	16	14.8	-7.9
Nestlé Beba HA 2 [g]	14.9	10	9.3	-7.2
Soy-based formula				
Bimbosan Bisoja [a]	9.8	6.5	7.8	17.8

[1] Refers to product as prepared ready-to-drink
[2] Calculated based on energy and iodine content per 100 ml ready-to-drink product
[3] Values as they were indicated on the product packages or medical product documentation
[4] Measured in reconstituted products; [4a + 4b] Measured twice as a control, mean of both measurements given; [4a] new package, [4b] same package, but second bag
[5] Based on µg/100 ml; Difference % = $(x_1 - x_2)/((x_1 + x_2)/2)*100$; ($x_1$ = measured iodine concentration, calculated with the exact value, not with the rounded one that is indicated in the table; x_2 = labeled iodine content)
[6] Cow milk-based, HA = partially hydrolyzed milk proteins
[a – g] Products of [a] Bimbosan Ltd. (Welschenrohr, Switzerland); [b] Adapta (Lenzburg, Switzerland); [c] Coop (Basel, Switzerland); [d] HiPP GmbH (Sachseln, Switzerland); [e] Holle baby food GmbH (Riehen, Switzerland); [f] MILUPA SA (Domdidier, Switzerland); [g] Nestlé Suisse S.A. (Vevey, Switzerland).

4.6.2. Infant cereals

The iodine content was not labeled on many infant cereal products as many of them were not fortified with iodine. Still, the products often contained cow milk and therefore were thought to have a relevant amount of iodine. The ten analyzed products were a convenient selection of products that were often indicated in the dietary questionnaires (purchased in February and April 2009). On five of the products the iodine content was not labeled. Iodine was measured in the dry and reconstituted products. Table 63 compares the labeled and measured iodine contents of the five labeled products. The results of the measurements in the reconstituted products are shown as this reflects the form of product intake.

None of the products exceeded the maximum allowed iodine content of 35 µg/100 kcal (EDI, 2005b) (Table 63).

For the four instant products, the mean ± SD abs. difference [%] between labeled and measured values was 4.6 ± 2.8%. The range of abs. difference was 1.6% to 7.2%. Two products had a slightly higher and two a slightly lower iodine concentration than labeled (Table 63). The three instant milk-cereal products were fortified with iodine and contained skimmed milk and whey powder (partially demineralized). The “Galactina Ceralino Milchzusatz” was fortified with iodine but did not contain any milk.

For the ready-to-eat HiPP “Gute-Nacht Brei” the difference between labeled and measured value was 46% (Table 63). The product was not fortified with iodine but contained cow milk.

In two products the iodine concentrations measured in the reconstituted instant products were very similar to the iodine concentrations measured directly in the instant products (without reconstitution of one portion): *Milupa “Miluvid plus”*: reconstituted: 74.3 µg/100g powder, instant: 73.6 µg/100g powder; *Nestlé Baby Cereals “Vollkorn mit Früchten“*: reconstituted: 36.6 µg/100g powder, instant: 32.6 µg/100g powder. In the Nestlé Baby menu "Milchgriess” the measured iodine concentrations differed considerably. In the first measurement the iodine concentration was approximately twice as high for the reconstituted product as

for the instant product (46.2 vs. 19.9 µg/portion). The measured iodine concentration in the reconstituted product corresponded very well to the labeled concentration (45 µg/portion). Therefore, the low iodine content measured in the instant product was suspected to be an error in sample preparation or measurement. To check this, the measurement of the instant powder was repeated (using the second bag in the package). In the second measurement the iodine concentration of the instant powder (20.9 µg/portion) was still very different from the labeling (45 µg/portion), but very similar to the first measurement (19.9 µg/portion).

Table 63: Comparison of labeled and measured (ICP-MS) iodine concentrations of iodine-labeled infant cereals

	Iodine concentration [1]			
Brand/ Product specification	Labeled [2] [µg/100 kcal]	Labeled [µg/portion] [3]	Measured [µg/portion] [3]	Difference [%] [4]
Instant milk-cereals, *preparation with water*				
Milupa "Miluvid plus" [a]	19.1	36	33.5	-7.2
Nestlé Baby Cereals "Vollkorn mit Früchten" [b]	8.5	18	18.3	1.6
Nestlé Baby menu "Milchgriess" [b]	21.4	45	46.2	2.7
Instant cereals, *preparation with milk & water*				
Galactina "Ceralino Milchzusatz Getreide&Ovomaltine" [c]	10.7	40 [5]	37.4 [5]	-6.7
Ready-to-eat milk-cereal				
HiPP Gute-Nacht Brei "Griessbrei Früchte" (jar) [d]	4.6	7.6	4.8	-46.0

[1] Refers to product as prepared ready-to-eat
[2] Calculated based on energy and iodine content per 100 g dry product, except for "HiPP": based on ready-to-eat product
[3] Standard portion as indicated on the package, varying from 175 to 200g.
[4] Based on µg/portion; Difference % = $(x_1 - x_2)/((x_1 + x_2)/2)*100$; ($x_1$ = measured iodine concentration, calculated with the exact value, not with the rounded one that is indicated in the table; x_2 = labeled iodine content)
[5] Here µg/100g instant powder, as the iodine content per portion (on the package) was indicated for the preparation with milk and water. We used just water.
[a – d] Products of [a] MILUPA SA (Domdidier, Switzerland); [b] Nestlé Suisse S.A. (Vevey, Switzerland); [c] Adapta (Lenzburg, Switzerland); [d] HiPP GmbH (Sachseln, Switzerland).

In the five non-iodine-labeled products the following iodine contents were measured:

- Bimbosan "Bio-Hirsana" and "Bio-Prontosan" (Bimbosan Ltd., Welschenrohr, Switzerland): These two products mainly consisted of cereals (*Bio-Hirsana*: 99.99% millet flour; *Bio-Prontosan*: 80% flour from barley, millet, rice, wheat and rye). They were not fortified with iodine and did not contain any cow milk. The purpose of the measurement was to check if pure cereals were a source of iodine. The measured iodine concentrations were between the iodine detection and quantification limit (LOD ~ 1.5 µg/kg, LOQ ~ 4.9 µg/kg, see 4.5.3; *Bio-Hirsana*: 1.9 µg/kg; *Bio-Prontosan*: 4.3 µg/kg), therefore, it could be concluded that these products contained virtually no iodine.
- Milupa "Brei mit Früchten" (MILUPA SA, Domdidier, Switzerland): This product was not fortified with iodine but it contained skimmed milk and whey powder (demineralized). The measured iodine content in the reconstituted product was 14.3 µg per standard portion (120 ml of water and 40 g of powder). The same amount was measured in the powder.
- Holle Bio "Dinkel-Milchbrei" and "Hirse-Milchbrei" (Holle baby food GmbH, Riehen, Switzerland): These products were not fortified with iodine but they contained skimmed milk and whey powder (partially demineralized). The measured iodine content in the reconstituted product was 10 µg respectively 7.1 µg per standard portion (130 ml water and 40g powder). In the powder 9.3 µg respectively 6.7 µg per standard portion were measured.

4.6.3. Quality control of ICP-MS

4.6.3.1. Infant formula reference

The measured iodine concentrations [mg/kg] of the infant formula reference samples are shown in Figure 38.

The mean ± SD iodine concentration of the measured samples (n = 14) in four runs was 1.02 ± 0.10 mg/kg powder (= 102 ± 10 µg/100 g). The values ranged from 0.85 to 1.20 mg/kg. The measured mean was close to the certified mean (1.11 mg/kg) and 10 out of 14 iodine values were within the certified 95% CI (= 0.94, 1.28 mg/kg). Three values were slightly below the lower boundary of the certified 95% CI (values: 0.91, 0.91, 0.93 mg/kg). Only one value was clearly below the 95% CI (value: 0.85 mg/kg). This was suspected to be due to an error in preparation or measurement. All intra-run means were within the certified 95% CI (means: 0.99 mg/kg (sample no. 1-4), 1.04 mg/kg (no. 5-7), 1.07 mg/kg (no. 8-11) and 0.97 mg/kg (no. 12-14)). The CV% between the four runs was 4.2% and the mean intra run CV% was 9.7%.

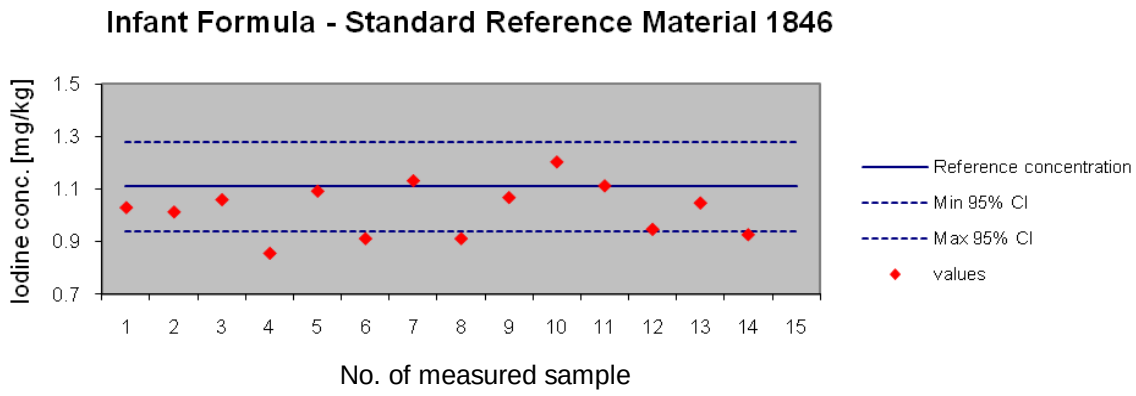


Figure 38: Infant formula reference samples measured with ICP-MS

4.7. Dietary assessment of infants

The data entry and evaluation of the dietary questionnaires were not part of this thesis and will be reported elsewhere.

4.7.1. Questionnaire response rate

Table 64 shows the response rate of the first and second dietary questionnaire. Overall, the response rate was > 89% in both age groups and for both the first and second questionnaire. A slightly higher percentage of first questionnaires was returned compared to the second.

Table 64: Response rate of dietary questionnaires (%)

Dietary questionnaires	**Age group**		**Total**
	6-mo	**12-mo**	
Included infants [n]	*179*	*160*	*339*
1st questionnaire % (n)	97.8% (175)	92.5% (148)	95.3% (323)
2nd questionnaire % (n)	91.1% (163)	89.4% (143)	90.3% (306)

4.7.2. Infant food database

Within this diploma thesis, 148 products were entered into the infant food database. An overview of the number of products per food category and their iodine content can be found in Table 65 (for an explanation of the categories see also chapter 3.7.4.4).

All formula products were fortified with iodine as required by law (EDI, 2005b). The mean ± SD iodine content of the instant formula products (n = 39) per 100 ml reconstituted product was 11.8 ± 3.5 µg/100 ml and ranged from 4.0 to 18.2 µg/100 ml.

Only 28% of the complementary food products were fortified with iodine. The highest percentage (67%) of fortified products was observed in the instant milk-cereal mixtures. In contrast, of the ready-to-eat cereal-milk products, only 1% was fortified with iodine. Milk-free instant cereal products were fortified in 29% of cases. 50% of the baby menus contained iodized salt (see Table 65).

Table 65: Iodine content of formula/infant food in infant food database sorted by food category

Food category	*n*	**Brands** [n]	**Energy** [kJ/100g] Mean ± SD	**Iodine** [µg/100g] [b] Mean ± SD	Min	Max	**Lab./ calc./ meas.** [c]
Infant/follow-on formula, junior-milk *(inst.)* [a]							
- fortified with iodine	39	8	2022 ± 73	**81 ± 25**	**30**	**140**	l
Junior-milk *(ready.)* [a]							
- fortified with iodine	2	2	288 ± 11	**16**	**11**	**21**	l
Instant milk-cereal mixtures							
- fortified with iodine	14	5	1768 ± 50	**76 ± 21**	**40**	**120**	l
- not fortified with iodine	6	4	1731 ± 93	**25 ± 7**	**17**	**36**	c/m[e]
Milk-free cereal based products or cereal mixtures *(inst.)*							
- fortified with iodine	8	3	1635 ± 73	**52 ± 28**	**11**	**100**	l
- not fortified with iodine	20	7	1580 ± 83	**2 ± 1**	**2**	**4**	c
Cereal-milk-(fruit/vegetable) porridge/drink meal, baby yoghurts/ desserts *(ready.)*							
- fortified with iodine	1	1	401	**20**	**--**	**--**	l
- not fortified with iodine	10	4	366 ± 73	**5 ± 1**	**4**	**7**	c/l[f]
Vegetable/fruit purees *(ready.)*							
- not fortified with iodine	22	6	244 ± 70	**1 ± 0**	**1**	**2**	c/l[f]
Baby menus *(ready.)*							
- fortified with iodine	7 [d]	1	305 ± 46	**8 ± 4**	**5**	**16**	l/c[g]
- not fortified with iodine	7	4	286 ± 42	**2 ± 2**	**1**	**6**	c
Biscuits/rusks/bars							
- not fortified with iodine	11	8	1726 ± 123	**5 ± 2**	**2**	**8**	c
Baby pasta *(dry)*							
- not fortified with iodine	1	1	1459	**1**	**--**	**--**	c

[a] Product in: inst. = instant condition; ready. = ready-to-eat condition
[b] 100g is related to the product as it is in the package either instant/dry or ready-to-eat
[c] l = iodine labeled on package; c = iodine calculated by EBISpro (see also chapter 3.7.4.2); m = iodine measured (ICP-MS)
[d] Fortified via iodized salt
[e] Three products; [f] Two products; [g] One product

None of the vegetable/fruit-purees, biscuits/rusks/bars and pasta products was fortified with iodine or contained iodized salt. Therefore, all these food items had a low iodine content.

Mean iodine content of fortified products was clearly higher than iodine content of non-fortified products in all food categories [µg/100g] (see Table 65).

5. DISCUSSION

5.1. Overview

The present study was designed to obtain data on UIC of 6- and 12-month-old Swiss infants in a nationally representative sample and to establish a reference range for UIC in infants. An iodine-sufficient population is an obvious precondition to be able to establish a reference range. Switzerland has a long existing salt iodization program which is regularly monitored. The national surveys which monitored the iodine status of SAC, pregnant women (UIC) and newborns (TSH) in 1999 and 2004 showed iodine sufficiency (Hess et al., 2001; Zimmermann et al., 2005). In addition, a recent study of Swiss newborns (UIC and TSH) concluded that they were iodine-sufficient (Dorey and Zimmermann, 2008). Therefore, infants in Switzerland were assumed to be iodine-sufficient. To confirm this assumption, the present study measured UIC and BMIC in the infants' mothers. Furthermore, the labeling of iodine content on infant food was checked and dietary iodine intake of infants was examined by a dietary questionnaire.

The interim analysis of UICs and BMICs in the present diploma thesis showed lower medians of UIC (81.1 µg/l) and BMIC (51.2 µg/kg) in mothers than expected. This finding was in agreement with two other recent regional studies in Switzerland on UIC in non-pregnant, non-lactating women who also showed low median UICs (1) median UIC = 81.0 µg/l (n = 144) (M Kammermann, ETH Zurich, 2009, personal communication) and (2) median UIC = 79.1 µg/l (range: 0-1193) (n = 567, young Swiss women 18-42 years old) (M Andersson, ETH Zurich, 2007, personal communication). Median UICs were below the recommended cut-off of 100 µg/l (World Health Organization et al., 2007) for women in the mentioned studies. Furthermore, in the new 2009 Swiss iodine monitoring study, pregnant women had a marginally sufficient iodine status (interim analysis of 318 women, median UIC = 151 µg/l; A Piacenza, ETH Zurich, 2009, personal communication). School age children showed a sufficient iodine status in the new monitoring study (n = 916, median UIC = 120 µg/l; I Henschen, ETH Zurich, 2009, personal communication). They had, however, a lower median UIC compared to the survey in 2004 (median UIC = 141 µg/l)

(Zimmermann et al., 2005). Thus, the above data indicate that the precondition of iodine-sufficiency in Swiss infants might not be met for the use of the final study data to establish a reference range.

The present study was the first national study on iodine status in infants and women of childbearing age in Switzerland. Within the framework of the diploma thesis, the study set-up, execution and data analysis of the first part of samples was performed and the iodine status of infants and mothers was evaluated and discussed. The focus of the discussion is on the iodine status of infants; mothers were mainly taken as comparison.

5.2. Selection of pediatric practices

The WHO recommends cross-sectional surveys with “probability proportion to size” cluster sampling for monitoring iodine status of a country using 30 clusters (World Health Organization et al., 2007). For practical reasons we decided to perform a cross-sectional survey with 20 clusters in the study. The clusters were selected proportionately to the percentage of annual live births in the seven “greater Swiss regions”. Within the regions convenient sampling of the clusters was performed. This was justified as iodine intake has been reported as uniform across the country (Hess et al., 2001; Zimmermann et al., 2005). The study was not planned to be representative for each region or cluster, but for the whole country.

Pediatric practices were regarded as the best place to reach the population group of 6- and 12-month-old infants as they attend pediatric practices in healthy condition for the 6-month and 12-month routine check-up/vaccination appointment. The pediatrician knows about the medical history of the infants and is able to confirm their health and absence of thyroid disorders. Routine check-ups/vaccinations for infants are, to our knowledge, not offered by hospitals in Switzerland.

We had a rather high positive response rate for study participation in the German speaking part of Switzerland, but a very low one for the French (Lake Geneva Region) and Italian speaking parts (Ticino). The reason for this is unclear, but the same difficulties occurred in the SAC and pregnant women

monitoring study of 2009 (I Henschen and A Piacenza, 2009, personal communication). The recruitment of pediatric practices was postponed for the French speaking part. The pediatric practice that agreed to participate sent only five samples. Therefore, in the present interim analysis the French speaking part of Switzerland was mainly not included (Lake Geneva Region). The participating pediatric practice in the Ticino region only returned a small number of samples (n = 17). Thus, this interim analysis of the study cannot be regarded as nationally representative.

5.3. Recruitment and sample collection

For this interim analysis a total of 379 mother-infant pairs were recruited during a time period of 10 months. After exclusions, 339 infants (53% 6-mo, 47% 12-mo) and 343 mothers were included for the analysis. This number is much lower than the estimated required sample size of 600 per age group. Therefore, it was not possible to discuss the data in terms of setting reference values. However, the results provide a first evaluation of the iodine status of infants and mothers in Switzerland.

The WHO recommends determining UIC in 30 urine specimens from a defined sampling group to compensate for varying degrees of hydration in subjects (World Health Organization et al., 2007). Therefore, we aimed to collect 30 urine samples per age group at each pediatric practice. At the time point of data evaluation only two pediatric practices had accomplished this target. The other practices had enrolled between 0 and 19 mother-infant pairs per age group. Therefore, it was not possible examine single pediatric practices. In terms of regions, all except Ticino and Lake Geneva region had collected more than 30 urine samples.

Usually, after analyzing more than 100 urine samples of a population group, the median UIC does not substantially change (personal communication, M Zimmermann). More than 100 samples per age group were available for the present evaluation (see above).

The recruitment of study subjects took more time than expected. Several reasons for this observation were communicated to us by the pediatric

practices, of which the most important were: not always enough time to recruit infants due to workload and language problems with non-German speaking parents. 10% of infants had to be pre-excluded due to not term birth, which is a rather high percentage but which was also confirmed by the Swiss Federal Statistical Office (Bundesamt für Statistik, 2007). Probably the most important reason for the rather slow sampling was the low weekly visiting frequency of infants for routine check-ups/vaccinations at the pediatric practices even though we aimed to select the practices with the highest weekly visiting frequencies. There are about 700 pediatric practices in Switzerland (personal communication, FFP) and the annual birth number is about 75'000 (Swiss Federal Statistical Office, 2008b), of which 10% preterm infants need to be excluded. Based on these numbers and estimating that the pediatric practices are open 48 weeks a year, this would result in about two infants per age group visiting a practice for routine check-up per week. Considering that each infant can only participate in the study once, the number of eligible infants is further reduced. This finally results in a rather small weekly number of infants and additionally including the fact that not every eligible infant is enrolled due to the above-mentioned reasons, it seems clear that a large time span for sample collection is required.

Urine collection in infants is more complicated than in children or adults and this is also regarded as a main problem for using UIC in iodine status assessment of infants (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). The "pad collection" method was already tested in the Swiss newborn study (Dorey and Zimmermann, 2008). In the present study the method was generally well accepted by pediatricians with the exception of one practice in the Ticino region which insisted on using urine bags for collection. The pad method was also considered as a good method for sample collection by the parents, by whom most of the samples were collected. No problems with the method were reported to the study team at ETH. Most of the samples arrived at ETH within a short time (median three days) and all infants provided a sufficient amount of urine for analysis. Furthermore, our iodine recovery tests with the pads showed accurate results and, as a comparison, Crofton et al. recently

showed reliable quantitative results in routine biochemistry tests with urine extracted from pads of the same brand as used for the present study (Crofton et al., 2008). The “pad collection” method can be thus recommended for urine collection in infants in further studies on UIC.

Another important point was to avoid sample contamination (directly or indirectly) with iodine-containing disinfectants or contrast media. Therefore, pediatricians and their assistants were specifically made aware of this problem and the samples suspected of contamination (due to extremely high iodine concentration, see results) were excluded from the study. Iodine-containing disinfectants are not to be applied to infants under 6 months of age and only with medical prescription in the following years (till 6 years of age) (information retrieved from http://www.kompendium.ch/, accessed July 2008). The two pediatric practices which had already finished sampling confirmed in the final questionnaire not having used any iodine containing disinfectants where the samples were collected or the urine was extracted.

5.4. Subject characteristics

In order to provide data for reference values it was important to include healthy and normally growing and developing infants in the study.

All included infants had a term birth, were healthy, did not have any thyroid disorders and had not had any treatment with iodine-containing contrast media or disinfectants (confirmed by the pediatricians). The included infants had a mother who had neither a recent thyroid disorder nor was treated with contrast-media or iodine-containing drugs during pregnancy or lactation as this could have had negative impacts on the health or iodine status of the infants.

The infants included in the present analysis were growing normally when compared with the WHO reference population with mean z-score values close to zero (World Health Organization, 2008) (see also result section).

The data should represent the population living in Switzerland. Therefore, all included mothers had already lived in Switzerland for at least one year before the infant’s birth and all mother-infants pairs had lived in Switzerland since the infant was born.

The other subject characteristics are discussed together with the urine and breast milk analysis data.

The two pediatric practices which had already finished the study reported in the final questionnaire that they had the impression that the mothers/parents did not have much knowledge about the importance of iodine for their infants' healthy development.

5.5. Iodine status in infants and mothers

5.5.1. Comparison with cut-offs and recommendations

Infants are particularly sensitive to ID because the iodine content of their thyroids is still low, but they have a fast intrathyroidal iodine turnover (Brown et al., 2005). Furthermore, ID has the worst consequences in the fetal period and infancy (Zimmermann, 2009).

The currently available cut-off for median UIC which indicates iodine-sufficiency in infants and adults is ≥ 100 µg/l (World Health Organization et al., 2007). In 2007, a technical consultation of the WHO recommended revising this cut-off for infants (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). The present study was planned to contribute to the revision. The data included in the diploma thesis are an interim analysis of the study and provide a first insight on the direction of the final study results. Looking at infants and mothers, both groups were found to have a median UIC below the cut-off (93.2 µg/l infants, 81.1 µg/l mothers) which would indicate iodine deficiency. Using the classification for SAC and adults, the medians indicate mild ID because they are between 50 and 99 µg/l (World Health Organization et al., 2007). Examining both age groups separately, the median UIC of 12-month-old infants (104.0 µg/l) was just above 100 µg/l. The 95%CI of the median, however, was 88.1, 125.5 µg/l which indicated that also for the 12-month-old infants the measured median above 100 µg/l was not assured. 6-month-old infants were clearly below 100 µg/l with a median UIC of 88.4 µg/l. The 95%CI (67.8, 99.8 µg/l) did not even reach the cut-off. Even if the 12-month-old infants showed a tendency towards a higher median UIC, UIC was not significantly different between the

two age groups. This was further supported by the fact that age (in months) did not correlate with UIC, indicating that there was no overall tendency for an increasing UIC with age. Pouessel et al. who also examined infants in the first year of life also did not find any relation between age and UIC in infants; however they examined hospitalized infants (Pouessel et al., 2008). Nevertheless, in our study, the proportion of 12-month-old infants with UICs ≥ 100 µg/l was significantly greater than in 6-month-old infants (see results).

The UICs of the infants in the present study were compared with the UICs of the Swiss newborn study which was carried out between 2005 and 2007 at ETH (n = 634 newborns, which provided 1224 spot urine samples) (Dorey and Zimmermann, 2008). The newborns had a median UIC of 77 µg/l. The authors of the newborn study suggested that this median indicated a sufficient iodine intake which was supported by the fact that the newborns had low TSH values (Dorey and Zimmermann, 2008). It is possible however, that the iodine status in newborns is not comparable with that of older infants due to the recent metabolic changes in newborns from birth.

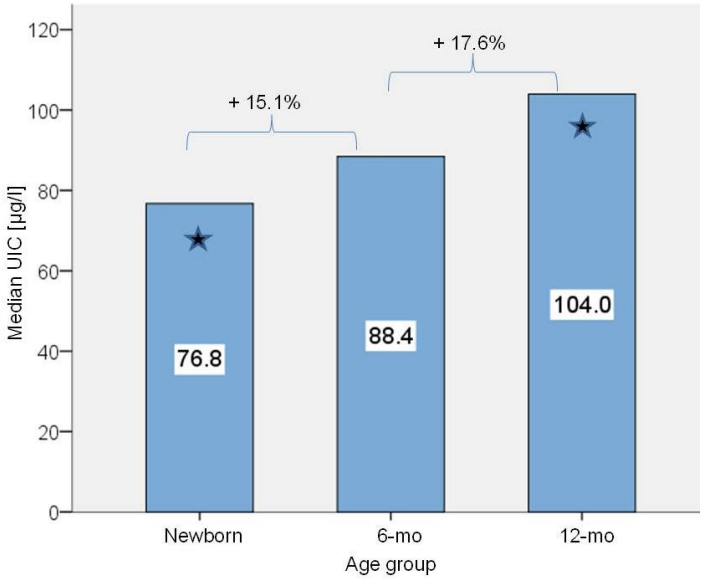


Figure 39: Bar diagrams showing median UIC [µg/l] of newborns (n = 1224) (Dorey and Zimmermann, 2008), 6- (n = 179) and 12- (n = 160) month-old infants (significant difference between ✦, $p < 0.0001$) (UIC = urinary iodine concentration)

Comparison of newborns and 6- and 12-month-old infants showed a significant

difference in UIC between the three groups (K-W, $p < 0.0001$). Post-hoc tests revealed that only the 12-month-old infants had a significantly higher median UIC than the newborns (MWU, $p < 0.0001$). UIC of the 6-month-old infants did not differ significantly from the newborns (MWU, $p = 0.15$). Looking at the three age groups together, a constant increase in median UIC could be observed during the first year of life. This is shown in Figure 39. However, all samples of the present study must be first analyzed before drawing firm conclusions about such an increase.

Reasons for the increase could be, for example, changes in metabolism or in feeding practice of infants during the first year of life. While 92% of the newborns were exclusively breast-fed (Dorey and Zimmermann, 2008), the breast-feeding rate decreased to 57% (6% exclusively/predominantly, 51% partially) in 6-month-old infants and to 18% in 12-month-old infants in the present study. Exclusive breast-feeding is recommended during the first six months of life by WHO (Butte et al., 2002). In Switzerland, the recommendation is exclusive breast-feeding or exclusive feeding with infant formula in the first 4 to 6 months of life (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008). After this period, complementary foods should be sequentially introduced while feeding with BM or FM is continued (Ernährungskommission der Schweizerischen Gesellschaft für Pädiatrie, 2008; World Health Organization, 2001). By the end of the first year, infants then start to eat family foods as well. Almost all infants in our study (88%) already received complementary foods by the age of 6 months. At 12 months most of the infants had already started to eat family foods. This indicates a constant change in iodine sources from foods. However, in literature the major iodine source for infants (at 6 and 12 months) is clearly milk (breast milk, formula, cow milk) contributing to about 70 - 90% of the daily iodine intake (Mills and Tyler, 1992; Murray et al., 2008; Thomson et al., 2008). Therefore, the determining factor for the iodine status of infants who are mainly breast-fed is breast milk. The iodine content of breast milk in turn is dependent on maternal iodine intake as reviewed by Semba and Delange (2001). BMIC was shown to be lower in goitrous areas compared to areas with efficient iodization of salt (Azizi and

Smyth, 2009). However, a recent US study found no correlation between BMIC and iodine intake, which was assessed by 24-h-dietary-recall. They used, however, only a sample size of 29 for the comparison (Hannan et al., 2009). The BMIC which was measured in 119 samples in the present study was 51.2 µg/kg (µg/kg is practically the same as µg/l for BM as the specific gravity of BM is nearly identical to water). No reference value exists for BMIC by WHO or other institutions as there is no agreement on the optimal iodine concentration of BM (Zimmermann, 2009). Semba and Delange recommended that the proportion of women with a BMIC ≥ 100 µg/l could be an indicator for the iodine status of a population (Semba and Delange, 2001). In our sample, only 10.9% of lactating women had a BMIC over 100 µg/kg, which is a rather low percentage. Bazrafshan et al. recently used a cut-off of ≥ 50 µg/l to indicate iodine sufficiency (Bazrafshan et al., 2005). The median BMIC of women in our study was slightly above this cut-off which would just indicate iodine sufficiency. Nevertheless, the iodine concentration was below 50 µg/kg in 48% of the BM samples. Zimmermann reported in a review that the mean or median BMIC found in iodine-sufficient countries ranged from 50 to 270 µg/l (Zimmermann, 2007b). Therefore, our measured median BMIC in women in Switzerland would be at the lower end. Azizi and Smyth suggested, on the contrary, that BMIC should be between 100 – 150 µg/l in iodine-sufficient countries and they proposed that values > 75 µg/l might be considered as an index of sufficient iodine nutrition (Azizi and Smyth, 2009). Compared with this, the median BMIC of Swiss women would clearly be categorized as too low.

Eleven infants of the present study relied solely on BM as their nutrient source. The median UIC of breast-fed infants (38.6% of all infants) was significantly lower than the median UIC of infants receiving no BM at all (83.8 µg/l vs. 101.4 µg/l). Examining both age groups separately, only the 6-month-old breast-fed infants had a significantly lower median UIC (70.7 µg/l) than the non-breast-fed. In the 12-month-old infants, no significant difference in UIC was observed between breast-fed and non-breast-fed infants. Subdividing the data by the consumption of different milk types (BM; FM; BM & FM; no BM & no FM), 6-month-old breast-fed infants who did not receive FM had the lowest median UIC

(64.1 µg/l) compared to all other feeding categories in both age groups. The median of these infants was significantly lower than the medians of 6-month-old infants who received FM or BM & FM, but not than the median UIC of 12-month-old infants in the same category (BM). This finding suggests that infants who are mainly breast-fed have a lower iodine supply than infants who receive FM or a relevant amount of complementary/family food as is normally the case at 12 months of age.

The mean ± SD of daily breast milk intake of 6-month-old exclusively and partially breast-fed infants was estimated to be 854 ± 118 ml and 612 ± 180 ml, respectively, as reported by Butte et al. (Butte et al., 2002). Based on this estimation and the assumption that 95% of BM iodine is absorbed (Zimmermann, 2009), 6-month-old exclusively or predominantly breast-fed infants would have a daily iodine intake of about 43 ± 6 µg. In partially breast-fed infants, an estimated daily quantity of 31 ± 9 µg of iodine originates from BM (both calculations made with the median BMIC of 53.3 µg/kg, measured in BM of mothers with 6-month-old infants). If the complementary food the infants receive additionally to the BM is low in iodine (like vegetable or fruit puree (Haldimann et al., 2005)), the quantity of iodine from BM might reflect the total iodine intake quite well. To accurately estimate the total iodine intake of infants who also receive other milk/foods than BM, it would be necessary to evaluate the dietary questionnaires.

As reported in the background section, UIC is a good indicator for recent iodine intake in adults as > 90% of dietary iodine is excreted in urine (Nath et al., 1992; Zimmermann, 2008b). This percentage might be different in infants as they also need iodine to build up iodine stores in the thyroid (van den Hove et al., 1999) and as their body grows and develops. However, the daily iodine retention for stores might be rather small as the thyroid weighs about 1 g at birth with an iodine store of 0.3 mg and increases to 15-20 g in adolescence with an iodine store of about 16 mg (annual increase of thyroid: about 1 g) (Brown, 2009; Brown et al., 2005). Therefore, the daily increase of the store could be estimated to be about 3 µg, which is a negligible amount. Infants also have a higher thyroid hormone turnover rate than adults (Brown, 2009), which could

also be responsible for a different urinary iodine excretion pattern. In the balance study of Delange et al. only about 57% of absorbed iodine was excreted through urine in one month old infants (iodine intake 20 µg/kg/day, body weight at one month of age about 4.5 kg) and 37% was kept in the body (Delange et al., 1988). Iodine metabolism is probably different in such young infants. If the infants would constantly retain such a high percentage of iodine in their body, body iodine content would increase by about 30 µg per day. Another study of Delange et al. in which 6 – 36-month-old infants were supplemented with 90 µg iodine per day showed indeed a urinary iodine excretion of about 90% after several weeks (Delange et al., 2001).

It was not clear from this data or studies how much the iodine excretion rate actually is in infants and further research is required. Therefore, the adults' excretion rate was relied on for the UIC based estimation of the iodine intake (Institute of Medicine et al., 2001). The average body weight for a 6-month-old infant is about 7.8 kg (mean BW of 6-mo study infants: 7.7 kg) and for a 12-month-old infant, 9.5 kg (mean BW of 12-mo study infants: 9.7 kg) (Butte, 2005). A daily urine volume of about 0.055 l/kg/day was estimated for infants (data from (Zimmermann, 2007b)). The iodine bioavailability was estimated to be 92% (Institute of Medicine et al., 2001). This resulted in the following estimation: daily iodine intake of infants = UIC [µg/l] : 0.92 * 0.055 l/kg/day * BW [kg].

Based on the measured median UIC, the iodine intake for 6-month-old infants was: 88.4 µg/l : 0.92 * 0.055 l/kg/day * 7.7 kg = 40.5 µg iodine per day. For 12-month-old infants the estimation was: 104.0 µg/l : 0.92 * 0.055 l/kg/day * 9.7 kg = 60.3 µg iodine per day. Taking both age groups of the present study together, the measured median UIC would suggest an average iodine intake between around 40 and 60 µg per day.

The iodine intake of 6-month-old breast-fed infants (no FM) estimated with the above formula would be 29.9 µg iodine per day (median UIC = 64.1 µg/l). This intake level is lower than when calculated with the BMIC for exclusively/predominantly BF infants, but it is very similar to the estimated quantity for partially BF infants (see above). Most of the breast-fed 6-month-old

infants (no FM) were partially BF (84%) and most of them (76%) did not receive additional CF with a potentially high iodine content (= milk-cereal porridge with cow milk/FM or cow milk). It is, however, difficult to draw conclusions about iodine intake from the calculations because they are just rough estimations. BM and CF intake and urine volume can vary and the true percentage of iodine excretion/retention is unclear. We observed however, a weak but significant correlation between UIC of breast-fed infants and BMIC.
For 6-month-old formula-fed infants (FM or FM & BM) the average daily iodine intake was estimated to be 47.2 µg (median UIC = 102.5 µg/l). In the 12-month-old infants, breast-fed infants (no FM; median UIC = 95.9 µg/l), formula-fed infants (FM or FM & BM; median UIC = 102.5 µg/l) and infants who did not receive any BM or FM (median UIC = 82.5 µg/l) had estimated daily iodine intakes of 55.6 µg, 64.9 µg and 47.8 µg, respectively.

Even if it seems clear that adequate iodine supply is essential for optimal child development (see background section), there are only a few studies on iodine in infants. The recommendations for iodine intake in infants are not based on well-controlled studies. The multiplicity of recommendations indicates a lack of data (see Table 2: Recommendations for iodine intake: Infants). Our estimated average iodine intake of 40 – 60 µg per day for 6- to 12-month-old infants was comparable with several of the recommendations such as: the D-A-CH recommendation for Switzerland (< 12 mo: 50 µg/day; ≥ 12 mo: 90 µg/day) (D-A-CH, 2008), the recommendation of the SCF of the European Commission (population reference intake 50-70 µg/day) (SCF (Scientific Committee for Food), 1993), the COMA (United Kingdom) reference nutrient intake (60 µg/day) (Thomson, 2002), the Nordic Nutrition Recommendations (50-70 µg/day) (Becker et al., 2004) and the AFSSA (France) recommendation (50 µg/day) (EU Scientific Committee on Food, 2003). The estimated iodine intake of 6-month-old infants (40 µg/day) in Switzerland would still be below the recommendations and that of 6-month-old breast-fed infants who do not receive FM (~ 30 µg/day) would even be clearly below the recommendations. 12-month-old infants (60 µg/day) would meet the above recommendations, which would suggest on average an adequate iodine supply for this age group. Except according to the

Swiss D-A-CH recommendation (D-A-CH, 2008), the 12-month-old infants would be just on the borderline between adequate and inadequate intake. The above recommendations were based either on estimated intakes from BM or extrapolations from adult values and for some, no explanation was found (see also background section, chapter 2.2.2).

The recommendation of the Spanish Dietetic and Food Science Association (35 µg/day) (EU Scientific Committee on Food, 2003) was even lower than our estimated average intake.

On the other hand, intake recommendations from UNICEF, ICCIDD, WHO (90 µg/day) (World Health Organization et al., 2007), D-A-CH Germany/Austria (< 12 mo: 80 µg/day; ≥ 12 mo: 100 µg/day) and Switzerland (≥ 12 mo: 90 µg/day) (D-A-CH, 2008), the US Institute of Medicine (130 µg/day) (Institute of Medicine et al., 2001) and CSH (Belgium) (90 µg/day) (EU Scientific Committee on Food, 2003) are higher than our estimation. They would thus indicate insufficient iodine intake. These intake recommendations should result in UIC levels between 150-220 µg/l (Delange, 2004; FAO and WHO, 2004), which is much higher compared to the median UICs measured in the present study. The new UNICEF, ICCIDD, WHO recommendation was revised in 2001 from the earlier recommendation (WHO et al., 1996) and the earlier RDAs (FAO and WHO, 2004). In fact, those earlier RDAs (50 µg/day), which were based on relative energy requirements of adults, were in the middle of our estimates (Subcommittee on the tenth edition of the RDAs et al., 1989). The revised recommendation of 90 µg/day was, on one hand, based on calculations from breast milk intake (90 µg/day is the mean of an estimated iodine intake from BM in Europe (60 µg/day) and the USA (120 µg/day)) and on the other hand, on Delange's balance study (FAO and WHO, 2004). If only the iodine intake from BM in Europe (60 µg/day) had been considered, this would have resulted in a similar recommendation compared to our estimation. The recommendation of the US Institute of Medicine, which is the highest of all recommendations, used BMICs of US women for the estimation and Delange's balance study (Institute of Medicine et al., 2001). Usually, higher iodine intakes and BM excretions were reported for the USA, compared to Europe. The reason for this observation is

the high iodine content in bread and cow milk in the USA, which mainly originates from iodophor disinfectants in the dairy industry and from iodate bread conditioners (Haldimann et al., 2005; Murray et al., 2008; Pearce, 2007; Pearce et al., 2004).

As mentioned before, two recent regional surveys on UIC in Swiss women of childbearing age showed medians below the WHO cut-off of 100 µg/l (World Health Organization et al., 2007). Therefore, we decided to analyze UIC of mothers as well, to check if they have a sufficient iodine status. Their median UIC was similar to the other studies below 100 µg/l. This was surprising as the last Swiss iodine monitoring study in 2004 showed an adequate iodine status in SAC and pregnant women (UIC) (Zimmermann et al., 2005). However, the UIC levels of the new 2009 monitoring study in SAC and pregnant women indicated lower levels than in 2004 with pregnant women (interim analysis) close to the cut-off of ID. SAC still had an adequate UIC (I Henschen, A Piacenza, 2009, personal communication). Based on this, the question was raised if mothers in Switzerland do have an adequate iodine intake or not. In the interim analysis of the present study, significantly lower UI values were measured in lactating mothers (median UIC = 71.1 µg/l) compared to non-lactating mothers (median UIC = 95.5 µg/l). This seems to support our concerns.

Similar to the present findings, other studies also found a higher UIC in SAC in comparison to women of childbearing age. In a Swiss longitudinal study (2 yr), Als et al. found a median UIC of 96 µg/l in women (n = 5, 30-46 yr) compared to 130 µg/l in SAC (n = 7, 6-10 yr) and 144 µg/l in pre-school children (n = 6, 3-5 yr). Men had the same median as SAC. The daily milk consumption was also assessed. The higher milk consumption of children (0.7-0.8 l/day) compared to adults was regarded as a reason for the lower UIC in women (0.3 l/day) (Als et al., 2003). In the NHANES I and III and 2003-2004 surveys, UIC was also higher in SAC than in adults (Caldwell et al., 2008; Hollowell et al., 1998). The reason for this could be not explained based on dietary iodine sources (Pearce et al., 2004).

A study in La Reunion found lower UICs in women of childbearing age (median UIC = 42 µg/l) compared to infants (median UIC = 120 µg/l) and SAC (median

UIC = 78 µg/l). In this study, infants had the highest UI values and the values decreased with age and with decrease in milk consumption. Goiter rate on the other hand increased with age (0% infants, 12% SAC, 38% women) (Jaffiol et al., 1997). In China, a similar picture was found in a recent multi-community study (Yan et al., 2005). Infants had the highest median UIC followed by SAC, women of childbearing age, lactating women and pregnant women, who had the lowest median UIC. However, all medians were above 150 µg/l. It has to be mentioned that salt iodization is mandatory in China (35 ppm) (Yan et al., 2005). Based on those study results, it seems common that women of childbearing age have lower UI values than SAC and infants. In contrast, the finding that infants have higher UICs than SAC was not encountered in the present Swiss study. There are, however, only a few studies available and further investigations are needed to decide why women have lower UICs than SAC (e.g. due to different food intake patterns or metabolic reasons) and whether they are at risk of ID. The iodine intake estimations from the US FDA Total Diet study would support the theory of different food intake patterns. In this study, SAC had a much higher estimated iodine intake which was mainly driven by the contribution of cow milk (70% of iodine intake versus only 49% in women) (Murray et al., 2008). As already mentioned, milk together with bread is the most important dietary iodine source also in Switzerland (use of iodized kitchen salt not included) (Haldimann et al., 2005).

Gowachirapant et al. explained their recent findings on higher UICs in SAC compared to pregnant women. They reported that SAC had a similar iodine intake compared to pregnant women, but that the daily urine volume of SAC is smaller compared to adults (Gowachirapant et al., 2009). The daily urine volume of a 26-kg child is about 600 ml based on a urine excretion of 0.9 ml/kg/h (Joint FAO/WHO/UNU Expert Consultation, 2004; Mattsson and Lindstrom, 1995) and the approximate daily urine volume in adults is 1.5 l (Larsson and Victor, 1988). This is the reason for a higher dilution of iodine in women's urine and therefore for their lower UI concentrations (Gowachirapant et al., 2009).

More studies are clearly required to ensure that women of reproductive age are

iodine-sufficient as ID in this population group can have detrimental effects during pregnancy and lactation.

For years, people have been encouraged to consume less salt due to health reasons and the WHO recommends a population average for salt intake of < 5 g/day (WHO, 2007). The Swiss Federal Office of Public Health reported in their "salt strategy" paper that between 2008 – 2012, a reduction of salt intake to < 8 g/day/person (this corresponds to a reduction of 16%) is aimed at and that the long-term goal is to achieve the WHO recommendation (EDI et al., 2009). This will consequently also lead to a reduced iodine intake, if the salt iodization level is not increased. The WHO and the Swiss FOPH both stated that this fact needs to be considered and appropriate measures must be taken (e.g. elevation of salt iodization level or different vehicle for iodine) (EDI et al., 2009; WHO, 2007).

A recent study in Switzerland estimated that about 35% (~ 2.8 g) of women's salt intake comes from discretionary salt consumption (Beer-Borst et al., 2009). Most of the women in our study used iodized salt at home (86%). However, the major part of salt intake comes from industrial food products (17% from bread, 10% from cheese, 7% from meat(-products), 9% from soups, 5% from ready-to-eat products) (Beer-Borst et al., 2009). Haldimann et al. stated that about 70% of salt used for the Swiss industrial food production is iodized (Haldimann et al., 2005). Bürgi, however, reported that export-orientated food producers in Switzerland are reluctant to use iodized salt as this could be disadvantageous for their markets. Furthermore, he pointed out that an increasing number of imported processed foods are not produced with iodized salt (Bürgi, 2005). This is supported by the salt producer "Swiss Salt Works on the Rhine", which confirms that decreasing amounts of iodized table salt (in bags) have been sold since 2006 (from about 1050 t in January 2006 to about 630 t in September 2009). In contrast, the sales of non-iodized salt has increased (about 250 t in January 2006 to about 590 t in September 2009) (personal communication by S Trachsel, Swiss Salt Works on the Rhine AG, Pratteln, September 2009). A personal communication (C Daeniker Roth, Migros-Genossenschafts-Bund, Zürich, February 2009) of the large Swiss retailer "Migros" affirmed that many

Swiss food producers have halted the use of iodized salt due to export reasons. France e.g. does not allow the import of food products with iodized salt (personal communication). FROMARTE (a Swiss association of cheese producers) have also restricted the use of iodized salt for cheese production due to export reasons (personal communication by C Daeniker Roth, Migros-Genossenschafts-Bund, Zürich, February 2009). This development could be a reason for the encountered decrease in UIC in the latest Swiss iodine monitoring study (2009) and should be carefully observed. The use of iodized salt at home did not change between the monitoring studies in 1999 and 2005 (82 - 86%) (Zimmermann et al., 2005) and the percentage use in the present study (87%).

An elevation of salt iodization will probably be necessary in the future in order to ensure a sufficient iodine supply for the Swiss population if the use of iodized salt by industries continues to decrease and the goal of a reduced salt intake of the population is achieved.

5.5.2. Comparison of infants' UIC and BMIC with previous studies

An overview of studies on UIC in infants that were carried out between 1989 and 2009 can be found in Appendix 3. Studies in newborns were not included as their iodine metabolism is probably not directly comparable with older infants. An overview of studies on BMIC within the last 10 years is given in Appendix 4.

5.5.2.1. Urinary iodine concentration in infants

In Switzerland, only one regional study on UIC examined 0 – 5-year-old children and women (Als et al., 2000b). The median UIC of 104 µg/l for 0-5 year old children was slightly higher than our overall median of 93.2 µg/l. However, most of the 31 children of Als et al.'s study were probably older than the infants in the present study. Exactly the same median UIC was found when looking only at the 12-month-old infants of our study. Women of reproductive age also had a very similar median UIC (90 µg/l) (Als et al., 2000b) compared to the mothers in the present study and the other two recent studies. This indicates that women in Switzerland have had a median UIC below 100 µg/l for several years now. The

study of Als et al., however, was carried out before the elevation of salt iodization from 15 to 20 ppm in 1998. Als et al. concluded that the iodine status measured in their study was not satisfactory (Als et al., 2000b).

Looking at worldwide studies on UIC, studies carried out in four countries found lower UIC values than we did: Germany (Manz et al., 1993), Italy (Rapa et al., 1999), Malaysia (Foo et al., 1996) and New Zealand (Skeaff et al., 2005). The medians in these studies ranged from 11 µg/l to 69 µg/l. All countries except Germany were currently classified by WHO as having an insufficient iodine intake (WHO Nutrition, 2008a; WHO Nutrition, 2008b). Thirteen studies found a mean or median UIC which was higher than our median UIC, ranging from 120 µg/l (Reunion Island) to 328 µg/l (France) (for references see Appendix 3). Six of those studies were carried out in countries that were classified as having a more than adequate or excessive iodine intake (Armenia, Mexico, Venezuela, Indonesia and China (2 studies)) (WHO Nutrition, 2008a). Two studies were performed in countries with an adequate iodine intake (Austria and India) (WHO Nutrition, 2008a). Three studies were carried out in France (Pouessel et al., 2003; Pouessel et al., 2008; Valeix et al., 1994) and in all study sites, very high median UICs for infants were measured even though France is classified as ID by WHO (WHO Nutrition, 2008a). Two other studies, one in Turkey (mean UIC = 130 µg/l) (Yilmaz et al., 2003) and one in Reunion Island (median UIC = 120 µg/l) (Jaffiol et al., 1997) measured higher UIC values compared to the present Swiss study, but the countries were classified as ID by WHO (WHO Nutrition, 2008a).

Only five studies found UIC medians close to the median UIC of our study. One was a local study in Belgium with 6-month- to 3-year-old children (n = 111). Their median UIC was 101 µg/l, which was classified by Delange et al. as ID (Delange et al., 2001). Belgium is also classified by WHO as having insufficient iodine intake (WHO Nutrition, 2008a).

A large national study in the Czech Republic measured a median UIC of 104 µg/l in 0- to 1-year-old infants and 114 µg/l in 1-5-year-old children. Measurements in SAC of the same study were 113 µg/l and for adults 98 µg/l (Bilek et al., 2005). Another large national study in Germany found higher

median UIC values for boys (113-133 µg/l) compared to our overall median, but identified the same or lower medians for girls (82-100 µg/l) between 0 and 2 years of age. The overall median UIC for children from 0-17 years was 117 µg/l (Thamm et al., 2007). The Czech Republic and Germany are classified as having an adequate iodine intake (WHO Nutrition, 2008a). Those two studies were probably the best comparable ones to our study as both were national and carried out in an iodine-sufficient European country.

One other local study was carried out in Nigeria, which is also classified as an iodine-sufficient country. A mean UIC of 99 µg/l (n = 68) was found there in 9- to 18-month-old infants. Mothers in this study had a mean UIC of 145 µg/l (Akanji et al., 1996). Nutrition habits in Africa are probably rather different from Europe and therefore this study is not ideal for comparison, especially as the study was carried out in a low socio-economic group (goiter-non-endemic area). This explanation might also be used for the study in Sudan, which was carried out in a goitrous area where no iodized salt was used. Still, a median UIC of 100 µg/l was measured in the study in 1 – 6-year-old children (n = 191) (Elnour et al., 2000). However, all of those infants were probably older than the infants in the present study.

In summary, it was difficult to draw conclusions about the iodine status in Swiss infants based on the reported earlier studies on UIC in infants because they usually did not include the same age range, were carried out in countries with different WHO iodine classification or in other cultures, were just regional/local or used different study settings. It was striking that median UIC in infants varied greatly by countries and sometimes was not consistent with the overall WHO country classification (e.g. France). However, the two only European national studies (Germany and Czech Republic) and the only earlier regional Swiss study were probably most comparable to the present study and reported UIC values which were slightly higher, but close to the median UIC of infants in the present Swiss study. Nevertheless, those studies found median UICs above the WHO cut-off of 100 µg/l (except for two sub-groups of girls in the German study, see above) (Als et al., 2000b; Bilek et al., 2005; Thamm et al., 2007), in contrast to our median in the total sample. This could indicate that Swiss infants are on

the borderline between adequate and inadequate iodine nutrition, especially the younger ones.

5.5.2.2. Breast milk iodine concentration

Even though infants rely on an adequate BMIC especially during exclusive or predominant breast-feeding and despite the importance of iodine for normal growth and brain development in infants, only a few studies have examined BMIC (Azizi and Smyth, 2009). No studies carried out between 1998 and 2009 (summarized in Appendix 4) were performed on a national level.

Four small studies on BMIC were carried out in Switzerland before the present study. Three of them examined colostral or transitory milk and observed a BMIC range between 78 and 98 µg/l (mean/median) (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000; Hoang Truong et al., 1997). Semba and Delange reported in a review that the highest BMIC is found in colostrum and that the concentration then decreases and remains steady in mature milk (> 12th day post-partum) (Semba and Delange, 2001). The BMICs measured in colostral/transitory milk samples in the earlier Swiss studies were therefore probably higher than we could expect for the mature BM we analyzed in the present study. The fourth Swiss study measured BMIC in mature BM samples (n = 52) and found a median BMIC of 68 µg/l (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000). This value was still about 30% higher compared to the value measured in the present study.

Comparing the median BMIC of the present Swiss study (51.2 µg/kg) with international studies, nine of the sixteen reported studies measured a higher mean or median BMIC than ours (listed in Appendix 4). All except one (Belgium) of those studies were carried out in countries that were classified by WHO as having an adequate or more than adequate iodine intake (Germany, Spain, USA, Iran, Australia and China) (WHO Nutrition, 2008a).
Only two studies observed a BMIC that was lower than ours. A study in New Zealand, which is classified as an ID country, found a mean BMIC of only 22

µg/l (n = 39) in mature BM. The study also measured UIC in 6- to 24-month-old infants and their UIC was also lower compared to our results (Skeaff et al., 2005). The other was a US study which reported a median BM iodide concentration of 33.5 µg/l. As they only measured iodide, the iodine content might actually have been higher (Kirk et al., 2005).

In a study in Belgium (classified as an ID country by WHO), a median BMIC of 78 µg/l was measured in transitory milk (Ciardelli et al., 2002). Laurberg et al. found a (geometric) mean BMIC of 53.8 µg/l in transitory milk of Danish women (n = 90). Denmark is also classified as ID by WHO and the study was carried out before the introduction of iodized salt into the market. (Geometric) mean UIC in those women was only 40.8 µg/l and 50.4 µg/l in infants (Laurberg et al., 2004). A recent German study measured a median BMIC of 52 µg/l in colostral/transitory milk. Women were supplemented with iodine (150 µg KI/day) during pregnancy. No data on sample size was given (Gärtner and Arbeitskreis Jodmangel, 2009). Another quite recent German study observed, however, a median BMIC of 156 µg/l in colostral/transitory milk (Bader et al., 2005) and a small Spanish study (a country classified as iodine-sufficient) reported a mean BMIC of 144 ± 93 µg/l (Fernandez-Sanchez et al., 2007). These recent European studies leave it unclear whether our measured median BMIC shows iodine-sufficiency or deficiency in women and thus in infants in Switzerland, but rather point to an inadequate iodine supply.

In non-European countries, median/mean BMICs in the review of studies in Appendix 4 ranged from 43 µg/l (USA) to 163 µg/l (China) in countries with adequate or more than adequate iodine intake. Three recent US studies measured a mean/median BMIC between 43 - 55.2 µg/l (Dasgupta et al., 2008; Hannan et al., 2009; Kirk et al., 2007), which was close to our median BMIC. On the other hand, a US study in Boston women observed a median BMIC of 155 µg/l (Pearce et al., 2007). Studies performed in Iran, Australia and China found higher median BMICs than we did, ranging from 84 µg/l (Australia) to 163 µg/l (China).

Taking into account earlier reviews, a median BMIC of 50 µg/l has been reported from iodine-sufficient and from deficient countries (Dorea, 2002;

Semba and Delange, 2001; Zimmermann, 2007b).

To draw conclusions on BMIC from all those studies is rather difficult as most of them included small sample sizes or were regional and used different methods to determine iodine in BM. It is, however, uncertain, based on the earlier studies, whether the measured BMICs in the present Swiss study indicate iodine-sufficiency, as the median concentration is at the lower end of observed concentrations in other studies of iodine-sufficient countries and as it is lower than in the earlier Swiss studies.

In the next subchapters, possible factors that might have an influence on UIC and BMIC of infants and mothers are discussed and compared with results of earlier studies. It has to be mentioned however, that the number of subjects was often below thirty in the compared sub-groups of the present interim analysis (see results). Due to the small sample sizes, it is possible that some comparisons in the final study evaluation will lead to different results.

5.5.3. Gender

We did not detect significant gender differences in UIC between infants. Even though there was a strong tendency towards a difference in 6-month-old infants. 6-month-old boys had the lowest median UIC (68.2 µg/l) and compared to 12-month-old boys it was even significantly lower. The reason for this is unclear. There was equal breast-feeding prevalence in 6-month-old boys and girls (50% each).

Gender differences in infants of our studied age groups were also not shown in several other studies (Pouessel et al., 2003; Pouessel et al., 2008; Skeaff et al., 2005). In the Swiss newborn study no gender differences were observed either (Dorey and Zimmermann, 2008).

Gender differences however, have been shown in older population groups.

A study in Sudan with 1- to 6-year-old children showed a significantly higher

median UIC in boys compared to girls (Elnour et al., 2000). Those infants were generally older than the infants in our study were and suffered from various deficiencies. Therefore, those are not ideal for comparison.

Thamm et al. examined UIC in German children between 0 and 17 years of age (n = 17'641). Girls showed slightly lower median UICs at all ages with values below 100 µg/l at one and two years. The publication did, however, not indicate any significances regarding UIC between genders (Thamm et al., 2007). At the age of one year, in contrast, girls and boys of our study group showed nearly the same median UIC (girls = 103.7 µg/l; boys = 104.3 µg/l).

In a small regional Swiss study on UI excretion (total n = 412; subjects between 0 to > 65 yr) women showed significantly lower UI values compared to men (Als et al., 2000b). Women of child-bearing age (13-35 yr) had the lowest values with a median UIC of 90 µg/l. Men in the same age group had a median UIC of around 150 µg/l. The researchers wondered whether the reason for this could lie in: 1) different iodine intakes in analogy to different proteo-caloric intakes between genders, 2) a qualitatively different diet of women, 3) smaller urine volumes in young men due to their higher perspiration (because of higher physical activity) (Als et al., 2000b).

5.5.4. Weight/length/BMI

In our study infants, there were no significant correlations between body weight or length and UIC.

In two French studies, no relation between nutritional status and UIC in infants was found either (Pouessel et al., 2003; Pouessel et al., 2008).

In the regional Swiss study of Als et al., UIC did not correlate with weight or BMI in the examined age groups (0 to > 65 yr) (Als et al., 2000b). In our study, however, we found a weak but significant correlation between UIC of mothers and their BMI. This resulted perhaps from a higher energy and nutrient intake of mothers who had a higher BMI.

No correlations were found between weight and BMIC as well as BMI and BMIC.

5.5.5. Nationality

Most of the mother-infant pairs participating in the study were Swiss (85%; nationality of the mother). The percentage of Swiss versus foreign nationalities in the present study was close to the overall distribution in Switzerland (21.7% foreign nationalities (Bundesamt für Statistik, 2008a)).

Looking at the total sample and then only at the 12-mo group, foreign infants had a 37% higher median UIC compared to Swiss infants (significant). In 6-month-old infants, foreign infants also had a higher median UIC than Swiss infants, but the difference was not significant. Reasons for the higher UI values in foreign infants could be different feeding practices or food choices.

According to the indications that mothers gave about feeding practices on the individual registration forms, Swiss and foreign infants were fed rather similarly concerning milk types (chi-square, $p = 0.31$):

Swiss: BM: 26.0%, FM: 46.4%, BM & FM: 14.2%, no BM and no FM: 13.5%;

Foreign: BM: 22.0%, FM: 48.0%, BM & FM: 8.0%, no BM and no FM: 22.0%.

The percentage of breast-fed Swiss infants (40%) was 10% higher compared to foreign infants (30%), but the association was not significant (chi-square, $p = 0.17$). All foreign infants received CF/FF compared to 93% of the Swiss infants. A higher percentage of foreign infants was fed milk-cereals with FM (39%) or cow milk (25%) compared to Swiss infants (30% and 13%, respectively; chi-square, $p = 0.21$ and $p < 0.05$). Diluted/undiluted cow milk was fed to approximately the same percentage of infants in both groups (Swiss: 22%, foreign: 25%; chi-square, $p = 0.30$). A higher percentage of foreign infants received vegetable-carbohydrate (98%) and fruit meals (84%) as well as meals from the family table (58%) compared with Swiss infants (88%, 69% and 46%, respectively; chi-square, $p < 0.05$, $p < 0.05$ and $p = 0.27$). Moreover, the percentage of infants who already received salt was higher in foreigners (70%) compared with Swiss (54%) (chi-square, $p = 0.09$). There was no significant difference in the percentage use of iodized salt in Swiss and foreign households (87% and 82%, respectively; chi-square, $p = 0.13$).

Therefore, some differences in feeding practices between Swiss and foreign infants living in Switzerland seem to exist, which might have an influence on

UIC. The evaluation of the dietary questionnaires could provide more information about this topic.

Two French studies also observed significant differences between UIC of infants from different ethnic/geographic origins, but no explanation for this was given by the authors (Pouessel et al., 2003; Valeix et al., 1994).

UICs and BMICs did not significantly differ between Swiss and foreign mothers.

5.5.6. Pediatric practice/region

No significant differences between pediatric practices were found for all three parameters. We did not expect differences and the study was not designed to compare single pediatric practices with each other.

There was a significant difference in UIC of infants between the seven Swiss greater regions, but not in UIC or BMIC of mothers. In the previous monitoring studies in Switzerland, no significant differences were observed between regions (Hess et al., 2001; Zimmermann et al., 2005). We also did not expect a difference. However in infants, the median UIC in the Ticino region was significantly higher compared to two other regions. The median UIC in infants in Ticino was 184.3 µg/l (n = 17). The medians of all other regions varied between 67.8 and 100.0 µg/l. Ticino represents the Italian speaking part of Switzerland. The mothers there might also buy infant foods from Italy. Perhaps the iodine content of Italian infant food products differs from Swiss products. However, this could be clarified with the questionnaires.
Interestingly, the median UIC and BMIC of mothers were also highest in the Ticino region (not significant). Such a tendency (not significant) for higher median UIC in Ticino was already seen in SAC in the 2004 iodine monitoring study (Zimmermann, 2005) and in the new 2009 monitoring study (personal communication, I Henschen, ETH Zurich, 2009). The investigators of these studies suspected that soil or water in Ticino might have a different iodine concentration compared to the German part of Switzerland, which could lead to different iodine excretion. This presumption needs to be further explored.

5.5.7. Urban - rural area of pediatric practice

Only 15% (n = 52) of infants were recruited from pediatric practices in rural areas (in total four practices). In Switzerland, 26% of the population lived in rural areas in 2008 (Bundesamt für Statistik, 2008b). Consequently, subjects from urban areas were probably overrepresented in the present study. However, some of the subjects who had their pediatrician in an urban area, maybe actually lived in rural areas. We suspected that people living in rural areas might have different dietary habits compared to people from urban areas and thus, they might have different iodine intakes. Proportions of breast-feeding mothers were quite similar between urban and rural areas (39% and 36.5%; chi-square, $p = 0.74$). The percentage of formula-fed infants was higher in urban areas than in rural areas, but the difference was not significant (61% and 52%; chi-square, $p = 0.20$). Furthermore, the feeding practices of different types of CF, family food and salt use did not differ significantly on a percentage basis between urban and rural areas (data not shown; chi-square, all $p > 0.05$).

We did not detect significant differences in UIC of infants and mothers between urban and rural areas, even though the median UIC of infants from urban areas (97 µg/l) was 33% higher than the median UIC in infants from rural areas (73 µg/l). However, median BMIC in urban areas (56 µg/kg) was significantly higher than in rural areas (42 µg/kg). Nevertheless, there was no significant difference in UIC between lactating mothers from urban (median UIC = 72 µg/l) and rural areas (median UIC = 63 µg/l).

In the regional Swiss study of Als et al. (2000) no significant difference in UIC between suburban and rural areas was found in all the examined age groups (0 - > 65 yr).

In a study in Sudan in 1 – 6-year-old children, no significant difference in UIC was found between urban and rural areas either (Elnour et al., 2000).

An Armenian study found that UIC of infants in rural areas was lower compared to urban areas, even though the percentage use of iodized salt was higher in rural areas. No explanation was given for this finding (Rossi and Branca, 2003).

Rapa et al. (1999) also detected a significantly higher median UIC in SAC of

urban areas compared to SAC of rural areas in Italy. UIC of newborns had a positive correlation with UIC of SAC. Therefore, the authors concluded that UIC of people living in the same environment showed similar trends (Rapa et al., 1999).

5.5.8. Month of study registration/sample collection

Seasonal variations in UIC were observed in previous studies. Lower UI values were found in summer compared to winter in a national Czech study (Bilek et al., 2005) as well as in an earlier Swiss study (Als et al., 2003). In the Swiss study only children and not adults had lower UI values in summer (Als et al., 2003). The investigators of both studies attributed the variations in UIC to seasonal variations of iodine concentration in cow milk and dietary habits (see also background section 2.3.1) (Als et al., 2003; Bilek et al., 2005). In the Swiss study, milk was a more important iodine source for children than for adults for what reason probably the variations were only observed in children (Als et al., 2003).

In the interim analysis of the present study, UI and BM samples that were collected between August 2008 and May 2009 were included. However, no significant differences and no patterns were observed in UIC of infants and mothers or BMIC between different months of sample collection.

5.5.9. Supplement use

A low percentage of mothers from the present study was taking an iodine-containing supplement, five lactating mothers and eight non-lactating mothers. Perhaps due to this low percentage, we did not observe significantly higher UICs or BMICs in mothers taking an iodine-containing supplement.

In their recent study, Laurberg et al. detected that the intake of iodine supplements was positively associated with UIC of mothers and infants and with BMIC (Laurberg et al., 2004).

Iodine supplementation during pregnancy and lactation is not recommended by Swiss Nutrition Society (SGE) (Schweizerische Gesellschaft für Ernährung

SGE, 2008), the Swiss Gynecologist Society (SGGG) (oral communication, May 2009) or the Swiss Federal Office of Public Health (Camenzind-Frey and Hesse-Lamm, 2008).
The widest used multivitamin/mineral supplement of Swiss pregnant and lactating women is Elevit (Bayer (Schweiz) AG, Zürich) which does not contain iodine.

According to WHO recommendations, Switzerland is not a country that needs iodine supplementation for lactating women because it is classified as iodine-sufficient by WHO (WHO Nutrition, 2008a; WHO Secretariat on behalf of the participants to the Consultation et al., 2007). This classification is however, based on the iodine monitoring studies in 1999/2004 (Hess et al., 2001; Zimmermann et al., 2005). Taking into account the present study and the pregnant women in the latest Swiss monitoring study (2009), Switzerland would already rather belong to the category of countries for which WHO suggests iodine supplementation for women of reproductive age, pregnant and lactating women (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).

Bazrafshan et al. recently measured a median BMIC of 93.5 µg/l in 100 Iranian mothers, who showed a high median UIC of 259 µg/l. However, the authors concluded that some breast-fed infants were at risk of ID as 19% of BMICs were below their applied cut-off of 50 µg/l. They proposed iodine supplements for lactating mothers (Bazrafshan et al., 2005). Also, other studies which measured even higher BMICs than we did in the present study, suggested supplementation of lactating mothers in order to ensure a sufficient iodine intake in infants (Ciardelli et al., 2002; Pearce et al., 2007; Yan et al., 2005). The American Thyroid Association recommends supplementation with 150 µg iodine/day for pregnant and lactating women in the USA and Canada (Becker et al., 2006). Iodine supplementation with iodine tablets (100 - 150 µg iodine/day) is also recommended by the German “Arbeitskreis Jodmangel” for pregnant and lactating women in Germany (Arbeitskreis Jodmangel, 2006).

Therefore, iodine supplementation of lactating mothers would also probably be a good means for Switzerland, especially as the median UIC of mothers was below the WHO cut-off and as lactating mothers showed significantly lower UICs compared to non-lactating mothers. Furthermore, BMICs measured in the present study were low and breast-fed infants had a significantly lower median UIC than non-breast-fed infants. In addition, the overall median UIC of infants was also below the current WHO cut-off. By iodine supplementation of lactating mothers, breast-fed infants would consequently also receive more iodine through BM (WHO Secretariat on behalf of the participants to the Consultation et al., 2007).

5.5.10. Iodized salt

Only 6% of the mothers acknowledged not using iodized salt at home and 7% did not know what kind of salt they used. The high percentage of iodized salt users in the present study is in accordance with earlier monitoring studies (Dorey and Zimmermann, 2008; Zimmermann et al., 2005). This is consequently not suggested to be the reason for the decreasing tendency of UI values in Switzerland.
No significant differences were detected in UIC or BMIC between mothers using iodized salt and non-iodized salt. We had, however, very small numbers in the subgroups of non-iodized salt for comparison.

Also, no significant difference in BMIC was found between users and non-users of iodized salt in the Boston study of Pearce et al. (Pearce et al., 2007).

Even if salt should be avoided during the first year of life (Swiss pediatric society, 2002), 12% and 86% of mothers reported using salt in home-made meals for their 6-month-old and 12-month-old infants. The percentage of mothers who indicated using iodized salt was only 64% in the 6-mo group and 81% in the 12-mo group. No significant differences were found between the infants who received iodized salt, non-iodized salt or for whom the kind of salt was unknown. Nevertheless, the median UIC was higher in infants who received iodized salt compared to the other infants. In addition, infants who

already received salt in home-made meals had higher UICs compared to infants who did not yet receive any salt (only significant when examining both age groups together). The reason for this is unclear. As most infants probably received very small amounts of salt, other iodine sources presumably overlapped the influence of (iodized) salt on iodine excretion. No clear differences in feeding patterns could be detected between the different groups of salt users based on the data from the individual registration forms.

In a New Zealand study with infants and toddlers, there was no significant difference in mean UIC between children whose caregivers used iodized salt and those whose caregivers did not (Skeaff et al., 2005).

5.5.11. Social demographics

Smoking

Smoking is suspected to have a negative influence on BMIC as thiocyanate from smoke inhibits iodine uptake by the mammary gland (Laurberg et al., 2004). Nine percent (n = 30) of the mothers who filled in the sociodemographic questions in the dietary questionnaire indicated that they are smokers. Five of those were lactating. Median UIC was the same between smokers and non-smokers. Median BMIC of smoking mothers (27.8 µg/kg) was 50% lower compared to non-smokers (54.3 µg/kg). However, as just four smoking mothers provided a breast milk sample, this number was probably too small to detect a significant difference.

Pearce et al. found no significant difference in UIC between lactating women who smoked and who did not smoke (Pearce et al., 2007). The same finding was also observed by Laurberg et al., but they found that smoking mothers (n = 50) had significantly lower BMICs (geometric mean = 26 µg/l) compared to non-smoking mothers (n = 90; BMIC = 54 µg/l). In addition, the neonates of smoking women had significantly lower UI values (geometric mean = 33 µg/l) compared to the neonates from non-smoking women (geometric mean = 50 µg/l) (Laurberg et al., 2004). Pearce et al. also found a highly significant lower mean BMIC in smokers (62 µg/l) compared to non-smokers (221 µg/l) (p = 0.0005)

(Pearce et al., 2007).

This topic remains interesting and for the final data evaluation, more data about BMIC of smoking mothers will be available. However, it is strictly recommended not to smoke during lactation in order to protect the infants from the risk of developing ID and of course from the overall detrimental effects of smoking.

Occupational/educational background of mother

Nearly 50% of the mothers who participated in the study had an occupation in the category “health, education & culture, scientists”. The connection with their occupation to health questions and consequently a high interest in nutrition, could be a reason for this incidence. We assumed that these mothers might have a better knowledge about iodine nutrition. Therefore, we compared this occupational category with the others. We discovered however, that mothers with a “health, education & culture, scientists” occupation had a lower median UIC (74.3 µg/l) compared to others (94.7 µg/l) (difference significant). This could be interpreted by the fact that 47% of mothers with a “health, education & culture, scientists” occupation were lactating and only 34% were lactating in the other categories (chi-square, $p < 0.05$). They might also have a healthier lifestyle using less salt or ready meals with salt and this might have resulted in a lower iodine intake. BMICs were however, not significantly different between those categories. There was also no significant difference in UIC between the infants.

It is often the case that a high percentage of people with higher educational levels participate in scientific studies. According to the Swiss Federal Statistical office (BFS), 16.8% of women have a lower than secondary level education (no post-compulsory education), 57.6% have a secondary level education, 6.7% have a higher vocational education and 18.9% a university level education (Bundesamt für Statistik, 2009b). Compared to this data, the mothers of the present study had a higher education level than the population average (52% compulsory school/secondary level, 25% higher vocational education, 23% university level).

However, we did not detect significant differences in UIC of infants and in UIC and BMIC of mothers between the different education levels.

Other studies have also found no differences in UIC between infants of mothers/parents with different education levels or occupation categories (Pouessel et al., 2003; Pouessel et al., 2008; Valeix et al., 1994).
A recent Iranian study observed no association between educational level or occupational status and iodine status in mothers (based on UIC and BMIC of lactating mothers, n = 100) (Bazrafshan et al., 2005).

5.5.12. Correlations of UIC and BMIC between infants and mothers

There was no correlation detected between UIC of breast-fed infants and UIC of their mothers and no significant association was observed between maternal UIC and BMIC. However, UIC of breast-fed infants was significantly positively related to BMIC in the present study.

A recent Indian study also observed no significant relationship between UIC of exclusively breast-fed infants and UIC of their mothers (Gupta et al., 2006). In contrast, Akanji et al. found a significant positive correlation between UIC of (almost) exclusively breast-fed infants (9-18 months old) and UIC of mothers (n = 68 each, r = 0.47). Mothers in the study had a 46% higher mean UIC compared to their infants (mean mothers: 145 µg/l, infants: 99 µg/l) (Akanji et al., 1996).
As in the present study, BMIC and UIC of lactating women were not significantly correlated in a Boston (mature milk, n = 57) (Pearce et al., 2007) and Australian study (transitory milk, n = 49) (Chan et al., 2003). In contrast, in two recent Iranian studies, including 100 and 142 lactating iodine-sufficient mothers, a moderate but significant relationship between BMIC and UIC of mothers was shown (mature milk) (Azizi and Smyth, 2009; Bazrafshan et al., 2005).
Similarly to the present Swiss study, there was also a significant positive correlation found between UIC of infants and BMIC in a recent Chinese study (> 90% of households in the studied area used iodized salt since 2000) (Wang et

al., 2009).

Ordookhani et al. recently examined Iranian neonates and their mothers (n = 42) and detected significant positive correlations between maternal and neonatal UIC, neonatal UIC and BMIC and maternal UIC and BMIC (Ordookhani et al., 2007).

The varying findings of the earlier studies in comparison with the present study indicate that there are no clear relationships between UIC and BMIC in infants and mothers.

5.6. Influence of infant feeding practices on urinary iodine concentration

The influence of infant feeding on UIC was examined based on the data about feeding practices on the individual registration forms.

It was not possible to compare general infant feeding patterns of the present study with the previous study on infant feeding in Switzerland of Dratva et al. and Merten et al. (see background) as they indicated feeding prevalence of milk and CF for other age subgroups than ours and as the prevalence changed quickly from one to the next age subgroup (Dratva et al., 2006; Merten et al., 2005).

Milk is the most important iodine source for infants (Mills and Tyler, 1992; Murray et al., 2008) and its intake was assumed to be more stable from day to day compared to complementary/family foods. Therefore, we subdivided the infants according to the pattern of BM and FM intake for the analysis. UIC differences according to the milk feeding practice were already discussed above (see chapter 5.5.1).

Similar findings concerning the difference in UIC according to milk feeding pattern were also found in two earlier studies. In the New Zealand study (including 6 - 24 month old children, n = 230) formula-fed children had a significantly higher (geometric) mean UIC (105 µg/l) compared to breast-fed children (40 µg/l), formula- and breast-fed children (56 µg/l) and children who

did not receive BM or FM at all (56 µg/l) (Skeaff et al., 2005). FM was the only feeding mode that was significantly different from the others. BMIC in the New Zealand study was very low with a mean of 22 µg/l. The reported mean iodine concentration of FM in New Zealand was 95 µg/l (range 30 - 270 µg/l) (Skeaff et al., 2005). Manz et al. also observed that breast-fed infants had significantly lower UICs compared to infants fed with FM (age: 3 – 5 mo, total n = 78) (Manz et al., 1993).

Pouessel et al. found in France (n = 160, children 10 days - 6 years old) that the only significant risk factor for UIC below 100 µg/l was the consumption of FM (median UIC = 165 µg/l; 29% < 100 µg/l) compared to the consumption of BM (exclusive), cow milk or no milk at all at the time of study (breast milk consumers (exclusive): median UIC = 206 µg/l; cow milk consumers: median UIC = 220 µg/l; together 19% < 100 µg/l) (Pouessel et al., 2003). This finding about FM is in contrast to the results of the present study. A reason for this could be that their study population included a wider age range (34% 0-6 mo, 36% 6 – 24 mo, 30% > 24 mo) (Pouessel et al., 2003). Older children have a different eating pattern compared to younger children, e.g. the older ones probably consume more iodized salt. The investigators found however, no significant difference in UIC between age groups. Pouessel et al. did not measure BMIC or iodine content of FM/cow milk which are probably different in France compared with Switzerland (Pouessel et al., 2003). The much higher median UIC of exclusively breast-fed infants in this French study compared to the present Swiss study points out that BMICs are also much higher in France compared with Switzerland.

It seems clear that the median UIC in (exclusively/predominantly) breast-fed infants is only lower than in formula-fed infants when the iodine concentration in BM is lower than in FM. In the new Swiss regulation, which should be implemented by March 2010, the allowed iodine concentration in FM is between 6.5 µg/100ml and 32.5 µg/100ml (EDI, 2005b). This is higher compared to the measured BMIC of 5.1 µg/100ml in the present study. The mean ± SD iodine content of formula products in our infant food database was 11.8 ± 3.5 µg/100

ml and ranged from 4.0 to 18.2 µg/100 ml. This mean is about twice as high as the measured median BMIC. This supports our finding that infants receiving FM have a higher median UIC than breast-fed infants (no FM).

The reported average iodine content of cow milk (whole milk, pasteurized) in Switzerland is 7.6 µg/100 g (SwissFIR, 2008) which is in-between BM and FM.

In Switzerland, fortification with iodine is only mandatory for FM and not for complementary foods such as cereals or purees (EDI, 2005b).

At 6 months of age, complementary foods are usually recently introduced and rather small quantities are eaten in addition to BM/FM. Therefore, they might not have any substantial influence on the total iodine intake and nearly all iodine comes from BM/FM. Most of the 6-month-old infants in the present study received vegetable or fruit purees, which were probably often home-made and therefore not fortified with iodine. Only 8% of the mothers reported using iodized salt for their infants' meals. Interestingly, 6-month-old non-consumers of vegetable-carbohydrate(-meat) meals had significantly higher UICs than consumers. The reason for this is unclear. The distribution of the non-consumers to the milk-feeding categories (BM, FM and BM & FM) was about equal.

At 12 months of age, CF/FF such as milk-cereal-porridges, cow milk and other dairy products along with bread, maybe fish, eggs and iodized salt usually contribute to a higher percentage of the total iodine intake than in younger infants. This might be a reason why no significant difference in UIC of 12-month-old infants was detected between the four feeding groups which were only based on BM/FM feeding practice. Nevertheless, 12-month-old infants who received FM or BM & FM had higher median UICs than infants who only received BM or neither BM nor FM, which indicates that FM still had a high influence on iodine intake compared with CF/FF. It was not possible to further subdivide the infants according to their CF consumption as this would have resulted in too small sample sizes per group. As mentioned before, milk (BM, FM, cow milk) and dairy products have been shown to have the highest contribution to the daily iodine intake in infants (Mills and Tyler, 1992; Murray et al., 2008) and therefore, the amount of iodine in these foods will anyway mainly

influence the iodine status in both age groups.

An evaluation of the dietary questionnaires could show whether infants who mainly receive non-iodine-fortified home-made meals have a significantly lower iodine supply compared to infants who are fed with fortified industrial foods. This was supposed by some German and Swiss authors (Alexy et al., 2009; Dähler et al., 2007; Kersting, 2001) (see also chapter 2.3.3.3). All FM products that were added to the infant food database so far were fortified with iodine as required by law (EDI, 2005b). Only 28% of commercial complementary foods were fortified with iodine. Most of the fortified CF products were instant milk-cereals (47%). The assumption of the above mentioned German and Swiss authors is already partially supported by the presently available study results looking at the consumption of FM. Formula-fed infants had a higher median UIC than non-formula-fed infants. However, the difference in UIC was only significant in 6-month-old infants and not in 12-month-olds.

5.7. Iodine measurements in infant food

5.7.1. Formula

In 1999, the Swiss FOPH measured iodine content in formulae at the same laboratory as we did. They found high variations between labeling and measurement results and four products even did not fulfill the legal requirements of iodine (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000).

None of our measured iodine concentrations in formula products differed much from the labeled concentration (mean abs. difference 13%). None of the products had a concentration below the legally required 5 µg/100kcal. According to the new regulation (effective from March 2010), the measured iodine content of two products (Bimbosan and Bimbosan Bio) would have been below the required minimum content (10 µg/100kcal). No product exceeded the allowed 50 µg/100kcal (EDI, 2005b). Our results indicate that the producers label their products correctly in terms of iodine content.

The measured differences could have occurred due to natural variations of

iodine in the product. On some packages there is an indication concerning natural variations of the product (Bimbosan products). The main part of iodine in the products comes from fortification. An additional amount of iodine may originate from the cow milk, which shows seasonally varying iodine concentrations depending on the amount of iodine in the fodder. Winter milk has higher iodine concentrations compared to summer milk (Haldimann et al., 2005). The kinds of milk used were: skimmed milk (Milumil 2), skimmed milk and partially demineralized whey powder (Galactina 2, HiPP 2, Holle 2, and Beba 2), partially demineralized whey powder (Beba HA 2), skimmed milk and demineralized whey powder (Bimbosan (Bio), Adapta 2, Aptamil 2). The variations could also have partly occurred during preparation of the FM samples or the ICP-MS measurement.

Pearce et al. measured iodine content in US formula milk and found much higher iodine contents than the labeled ones in many of the products (sometimes 7x higher) (Pearce et al., 2004). No explanation for this finding was given. In another more recent study, Pearce et al. again measured iodine concentrations in US formula milk products that were significantly higher compared to the labeled values (Pearce et al., 2007).

5.7.2. Infant cereals

The comparison of labeled and measured iodine contents of reconstituted infant cereals showed only small differences, indicating that the labeling was correct.
For the ready-to-eat HiPP product the measured iodine content was only about half of the labeled content. A reason for the large difference could be that this product was not iodized, but contained 50% whole milk. Therefore, the actual iodine content could differ from the labeled one due to natural variances (Haldimann et al., 2005).
For one Nestlé product (“Baby Menu Milchgriess”), the measurement in the instant powder showed a large difference compared to the measurement in the reconstituted product. The quantity of iodine per portion measured in the instant powder was about 50% lower (see also results). The reason for this needs to be

further investigated. However, it could be that the particles in this product are too roughly textured and are not digested well enough with TMAH in the dry product and therefore interfere with the measurement. This problem was also recognized by Fecher et al. who showed that iodine associated with larger sample particles (> 300 µm) was not extracted with TMAH and therefore not all iodine was determined with ICP-MS (Fecher et al., 1998). Visually, the products did not show much difference between each other. All infant cereals were rather smooth, homogeneous powders. Nevertheless, they were less smooth than the formula products.

5.7.3. Infant formula reference

The measurement of the infant formula reference samples showed that our FM and infant food measurements were reliable as the products have very similar matrices to the reference.

If the infant formula reference would have been measured in the reconstituted form instead of in the powder form, the measured concentrations might have been even closer to the certified mean. The powder did not dissolve well in the tubes (therefore ultrasound bath treatment was applied) and the solutions showed some small residues on the tube wall after the TMAH digestion of which probably not all iodine went into solution. This needs further investigation.

In accordance with the present measurements, Fecher et al. showed in a round-robin test with 15 laboratories that the determination of iodine in an infant milk porridge and a soy diet (artificially enriched with iodide, both from Milupa, Germany) was accurate and precise with the TMAH-extraction ICP-MS method (procedure very similar to ours) in dry and reconstituted samples (Fecher et al., 1998).

5.8. Limitations of the study

Several limitations should be pointed out in the current study.

The selection of pediatric practices and study subjects was not random, which could have had an influence on the results. The pediatricians were asked to try

to enroll every eligible mother-infant pair, if feasible. It is however possible that some pediatricians chose mothers from whom they expected good cooperation e.g. when they had a high workload in the practice. The pediatricians had to keep just a list of the subjects who agreed to participate in the study and not of all eligible subjects who visited the pediatric practice during the study period. It is possible that in general, more mothers who were interested in nutrition and who had time to be engaged in the study participated. This is an often experienced problem with scientific studies. However, mothers of young children are probably more interested in health and nutrition (especially of their infant) compared with other population groups.

Most of the mothers collected the samples at home. This may have led to less standardization of the study even if we provided clear instructions for the sample collection at home in order to standardize as far as possible. Pediatricians were also instructed to ask mothers to do the sample collection ideally on the same day as the practice visit or as soon as possible. Most, but not all mothers, followed this instruction. The best standardization would have been to have a large enough well-instructed study team from ETH instructing parents about sample collection and questionnaires, filling in forms and directly doing the sampling. This was not possible due to limited human, financial and time resources. Therefore, the best solution was seen in a cooperation with the pediatricians who were instructed as well as possible.

The study information was provided in the three national languages (depending on the language of the region). We did not have the resources to translate the information into more languages. Therefore, mothers living in Switzerland for more than one year before and after the infant's birth, but who were not able to speak German, French or Italian, might have been under-represented in the study.

A small sample size in some group comparisons was a limitation of this interim analysis of the study.

6. CONCLUSION

For many years, Switzerland has successfully eliminated the adverse health consequences of ID by iodization of salt. Therefore, Switzerland has been classified as a country with adequate iodine intake by WHO (de Benoist et al., 2008). The need for a reliable reference range for UIC in infants based on new studies was recently addressed by the WHO (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). UIC of newborns was already measured in a previous national study in Switzerland (Dorey and Zimmermann, 2008). The first aim of the present study was to collect nationally representative data on UIC in 6- and 12-month-old infants to obtain the entire range of UIC of infants in the first year of life. This data was then planned as basis to set a UIC reference range with the precondition that infants in Switzerland are iodine-sufficient. This should be confirmed by determination of UIC and BMIC in the infants' mothers and by assessment of the infants' dietary iodine intake with dietary questionnaires. The estimated required sample size for setting the reference range was 600 infants per age group. During the diploma thesis, the study was set up (including development of the self-administered dietary questionnaire) and it was executed in the first months of sampling. In an interim study analysis, the iodine excretion of infants and mothers was examined and their iodine status was evaluated based on the first urine samples of infants (n = 339) and mothers (n = 343), breast milk samples (n = 119), formula and infant food samples (n = 22) and the obtained data on the individual registration forms (including current infant feeding practices).

In the interim analysis, lower UI values of infants and their mothers than expected were found. The overall medians of infants and mothers were below the currently available cut-off of 100 µg/l as defined by WHO (World Health Organization et al., 2007) and the median of infants was even far below the range proposed by Delange of 180 – 225 µg/l (Delange, 2007). 6- and 12-month-old infants did not differ significantly in UIC although the median UIC of 12-month-old infants, which was just above the WHO cut-off, was higher than the median of 6-month-old ones. Furthermore, the 2009 Swiss iodine monitoring study in SAC and pregnant women showed lower UI values than in the

monitoring study five years ago (Zimmermann et al., 2005) with pregnant women on the border of mild ID (personal communication, I Henschen and A Piacenza, ETH Zurich, 2009). As with mothers in the present study, women of childbearing age in two other recent local studies in Switzerland showed median UICs below 100 µg/l (personal communication, M Andersson and M Kammermann, ETH Zurich, 2009). It could not be concluded from currently available data whether women in Switzerland are mildly iodine-deficient or their median UIC is naturally lower than in SAC who were the basis for the WHO cut-off. About 50% of the mothers in the present study had an occupation in the health/education/science sector and their median UIC was significantly lower compared to the other mothers.

Median BMIC was lower than in earlier regional studies carried out in Switzerland. It was just above 50 µg/kg which was used as cut-off for ID by Bazrafshan et al. (Bazrafshan et al., 2005) and about 50% below the cut-off of 100 µg/l which was proposed by Semba and Delange (Semba and Delange, 2001). Median BMIC was about 50% lower than the mean iodine content of FM products consumed by the study infants.

Breast-fed infants and lactating mothers were found to have significantly lower UICs compared to non-breast-fed infants respectively non-lactating mothers. These subgroups could therefore have an insufficient supply of iodine along with the rather low median BMIC. UIC of breast-fed infants correlated significantly positively with BMIC. 6-month-old infants who received only breast milk (as milk source) were at greatest risk of having a low UIC (based on median UIC) probably because of the low BMIC. The estimated average daily iodine intake of these infants (based on BMIC and UIC) was below all available recommendations for iodine intake.

Including all infants, the estimated average daily iodine intake was close to most of the European intake recommendations, but it was much lower than the recommendations of the WHO (World Health Organization et al., 2007) and the US institute of medicine (Institute of Medicine et al., 2001).

A conclusion about the infants' iodine status based on a comparison to earlier studies was difficult due to the varying study settings and as the measured UICs

and BMICs varied considerably between the studies. The medians of the present study were among the lower measured medians. The median UIC of infants (total sample) was, however, close to the measured median UICs in the two only national studies in iodine-sufficient European countries (Bilek et al., 2005; Thamm et al., 2007). Nevertheless, those two studies found median UICs slightly above 100 µg/l.

Infants with foreign nationality, living in Ticino region, receiving FM, no BM or receiving salt in home-made meals showed significantly higher median UICs compared to their respective counterparts (total sample). No significant differences in UIC of infants were detected among groups in comparison of genders, anthropometry, pediatric practices, urban/rural areas (sig. difference in BMIC), months of sample collection, consumption of CF/iodized salt and social demographics of mothers (total sample).

Based on the interim study results and the comparisons to earlier studies and recommendations, it is questionable whether infants in Switzerland, especially breast-fed infants, generally are iodine-sufficient or not and if the final study data will be applicable to define a UIC reference range for infants. To be able to make a clearer statement on this it remains to wait for all UIC and BMIC data and for the evaluation of the dietary questionnaires, which could help to draw conclusions also from the point of view of iodine intake from different foods. As there is not much data available on the percentage of iodine excretion in urine in infants and as it is unclear what the actual daily needs for iodine in infants are and how much of daily-ingested iodine is required for build-up of iodine stores and for growth, a well-controlled iodine balance study with infants could be helpful to broaden this knowledge. Such a study is, however, rather difficult to carry out.

To our knowledge, no visible signs of ID are recognizable in Switzerland and data on TSH from newborn screenings give no hint of a possible inadequate supply of iodine during fetal period (Dorey and Zimmermann, 2008; Zimmermann et al., 2005). Furthermore, anthropometric measurements (weight, length) in the present study showed normal growth of the infants. Further research would be necessary to investigate if any mild, unapparent

developmental impairment in infants occurs in Switzerland due to a possible mild ID, e.g. by performing development tests (Velasco et al., 2009).
Despite a high percentage use of iodized salt in Swiss homes (~ 90%), attention should be paid to the indicated trend of decreasing use of iodized salt by the food industries in Switzerland and importing countries as well as to the "salt strategy" of the Swiss Federal Office of Public Health to reduce salt intake in Switzerland (EDI et al., 2009). An elevation of the salt iodization level might be necessary in the future.

A second aim of the study was to assess the infants' dietary intake to evaluate if infants who are mainly fed with home-made meals have a lower iodine intake compared to infants mainly fed with commercial infant products. This question can only be clearly answered after evaluating the dietary questionnaires. However, the higher median UICs of infants who were formula-fed compared to breast-fed infants indicates that this could be the case (significant difference in the total sample and in 6-month-old infants), especially as BMIC was found to be low. In Switzerland, it is only mandatory to fortify FM with iodine at a minimum level and not commercial complementary foods (EDI, 2005b). Within the diploma thesis, commercial formula and infant food products were tested for their iodine labeling and it was found that the products were labeled correctly. However, only a low percentage of the CF products consumed by the study infants was fortified with iodine (28%). This could pose a risk for breast-fed infants in Switzerland (who do not receive FM) if they are fed only home-made CF without iodized salt or non-fortified commercial CF, especially during the weaning period in the second half of the first year when salt and cow milk (particularly undiluted) are not yet recommended (Dähler et al., 2007; Swiss pediatric society, 2002). By 12 months of age and afterwards, most infants start to receive small amounts of salt and many consume cow milk, dairy products and bread which are important iodine sources (Dratva et al., 2006; Haldimann et al., 2005) and therefore they do not rely solely on the iodine content of BM anymore. However, 12-month-old breast-fed infants in the present study still had a lower median UIC than formula-fed ones (n.s.) and when 12-month-old infants did not receive BM or FM at all, they even showed the lowest median

UIC compared to the others (n.s.), which indicates that they did not receive many foods with a comparably high iodine content to FM.
A possibility to reduce the risk for ID in infants might be to also mandate the fortification of commercial CF with iodine in Switzerland. The fortification of CF was also recommended by Dunn (Dunn, 2003) and the WHO (WHO Secretariat on behalf of the participants to the Consultation et al., 2007). This measure would however still not reach breast-fed infants who exclusively receive home-made CF.

To ensure that women of childbearing age, lactating and pregnant women and consequently infants have an adequate iodine intake, it is necessary to make them aware of the importance of iodine for themselves and their infants and to inform them about major dietary iodine sources (see background) e.g. by gynecologists, pediatricians or public counseling centers for mothers using information material that could be provided by the FOPH. Furthermore, it might be recommendable to advise pregnant and lactating women to take an iodine-containing supplement, which is not yet common in Switzerland (< 1% of lactating mothers in the present study) (Zimmermann and Delange, 2004; Zimmermann et al., 2005), to provide them and thus their fetuses and infants (through breast milk) with an adequate daily iodine supply. An iodine supplementation has even been proposed by researchers who have found higher UICs and BMICs than we did in the present study (Bazrafshan et al., 2005; Becker et al., 2006; Ciardelli et al., 2002; Pearce et al., 2007; Yan et al., 2005) . It would also be advisable to include infants and women of childbearing age in regular iodine monitoring, especially as ID can have severe health consequences for fetuses and infants (see background). More studies on UIC in infants of the same age groups and on UIC and BMIC in women are necessary from iodine-sufficient countries to be able to set reference ranges and to allow a reliable monitoring of the iodine status in the vulnerable population groups.

7. SUMMARY

Iodine is crucial for optimal mental and physical development of infants. Insufficient iodine intake leads to so called iodine deficiency (ID) disorders and may cause irreversible damage in infants. As > 90% of ingested iodine is finally excreted in urine, median urinary iodine concentration (UIC) is the recommended indicator for assessing a population's iodine status. However, the median UIC indicating iodine sufficiency (IS) in infants (< 2 yr) was questioned by the WHO in 2007. More studies are required from IS countries to establish a reliable reference range for monitoring UIC in infants. In Switzerland iodine nutrition was classified as optimal by the WHO.

Therefore, the aim of the present study was to assess UIC in healthy 6- and 12-month-old infants and their mothers in Switzerland in a nationally representative cross-sectional sample enrolled at pediatric practices. Another aim was to examine the infants' dietary iodine intake and the influence of different feeding practices on the UIC of infants. To achieve these aims, iodine concentration was measured in: spot urine samples of infants and their mothers (modified Sandell-Kolthoff method), breast milk (BMIC) and formula/infant food (both ICP-MS). Iodine intake of infants was recorded retrospectively by a 24h-dietary questionnaire (DQ) (self-administered by mothers). This diploma thesis presents the study set-up and execution, the interim analysis of urine samples from 339 infants and 343 mothers, 119 breast milk and 22 formula/infant food samples and their examination in different aspects (such as gender, anthropometry, nationality, region, season, dietary habits, social demographics) as well as the development of the DQ and an infant food database.

Median UIC was 93 µg/l in infants (88 µg/l at 6 months, 104 µg/l at 12 months) and 81 µg/l in mothers (71 µg/l in lactating, 96 µg/l in non-lactating mothers). Median BMIC was 51 µg/kg. Formula/infant food iodine content was found to be accurately labeled. Breast-fed (BF) infants/lactating mothers had significantly lower UICs compared to the other infants/mothers. Significantly higher UICs were found in infants receiving formula or salt (in home-made meals) and in infants with foreign nationality or from Ticino. UIC of BF infants was positively related to BMIC (sig.).

The overall interim study results were lower than proposed values from literature for an IS country. According to the current WHO cut-off of ≥ 100 µg/l the median UICs would indicate mild ID. This was the first Swiss national study on UIC in infants/mothers and BMIC. Comparisons to previous studies in other countries were difficult. Based on the interim study results and recent Swiss studies in other population groups, it is questionable if infants, especially BF ones, and mothers in Switzerland have an adequate iodine intake. It remains to evaluate the final study results and to do further research to ensure that Swiss infants and mothers are iodine-sufficient and in order to define a UIC reference range in infants. Mothers should be well informed about the important role of iodine for themselves and their infants and about its dietary sources. In addition, iodine supplementation may be recommended to lactating mothers.

8. ZUSAMMENFASSUNG

Jod ist essentiell für eine optimale geistige und körperliche Entwicklung von Säuglingen/Kleinkindern. Eine ungenügende Jodaufnahme verursacht so genannte Jodmangel-Störungen und kann bei Säuglingen/Kleinkindern zu irreversiblen Schädigungen führen. Da > 90% des mit der Nahrung aufgenommenen Jods über die Niere ausgeschieden werden, ist der Median der Jodkonzentration im Urin (JKU) der empfohlene Indikator zur Bestimmung des Jodstatus einer Bevölkerung. Allerdings wurde derjenige Median der JKU, welcher auf eine ausreichende Jodzufuhr bei unter 2-Jährigen hinweist, 2007 von der WHO in Frage gestellt. Zur Etablierung eines verlässlichen Referenzbereichs für das Monitoring der JKU bei Säuglingen/Kleinkindern, sind mehr Studien von Ländern mit optimaler Jodversorgung erforderlich. In der Schweiz wurde die Jodversorgung von der WHO als optimal eingestuft. Daher war das Ziel der vorliegenden Studie die JKU bei gesunden 6- und 12-monatigen Kindern sowie deren Müttern in einer national repräsentativen Querschnittstudie in der Schweiz zu untersuchen (Rekrutierung in Kinderarztpraxen). Ein weiteres Ziel war die Ermittlung der Jodzufuhr der Kinder sowie die Untersuchung des Einflusses unterschiedlicher Ernährungsweisen auf die JKU der Kinder. Um diese Ziele zu erreichen wurde die Jodkonzentration in Spoturinproben von Kindern und deren Müttern (modifizierte Sandell-Kolthoff Methode) sowie in Muttermilch und Säuglingsnahrung (beide ICP-MS) gemessen. Die Jodaufnahme der Kinder wurde mit einem, von den Müttern selbständig auszufüllenden, 24h-Ernährungsfragebogen retrospektiv erfasst. Die vorliegende Diplomarbeit beinhaltet den Aufbau und die Durchführung der Studie, die Zwischenauswertung von Urinproben von 339 Kindern und 343 Müttern, von 119 Muttermilchproben und 22 Säuglingsnahrungsproben sowie deren Betrachtung unter verschiedenen Aspekten (wie Geschlecht, Anthropometrie, Nationalität, Region, Jahreszeit, Ernährungsweise und Soziodemographie) und die Entwicklung des Ernährungsfragebogens und einer Säuglingsnahrungs-Datenbank.

Der Median der JKU der Kinder war 93 µg/l (6-monatige: 88 µg/l, 12-monatige:

104 µg/l) und derjenige der Mütter war 81 µg/l (Stillende: 71 µg/l, Nicht-Stillende: 96 µg/l). Der Median der Jodkonzentration in Muttermilch betrug 51 µg/kg. Der Jodgehalt der Säuglingsnahrungsprodukte war korrekt deklariert. Gestillte Kinder/stillende Mütter hatten signifikant niedrigere JKU im Vergleich zu den anderen Kindern/Müttern. Signifikant höhere JKU wurden bei Kindern festgestellt, welche Säuglingsmilchnahrung oder Salz (in selbstgemachter Beikost) erhielten und bei Kindern mit ausländischer Nationalität oder aus der Region Tessin. Die JKU von gestillten Kindern korrelierte positiv mit der Jodkonzentration in Muttermilch (sig.).

Die Zwischenresultate der Studie waren niedriger als in der Literatur vorgeschlagene Werte für ein Land mit optimaler Jodversorgung. Gemäss dem derzeitigen WHO Cut-off von ≥ 100 µg/l würden die gemessenen medianen JKU auf einen leichten Jodmangel hinweisen. Dies war die erste nationale Studie in der Schweiz zur Jodversorgung von Säuglingen/Kleinkindern und Müttern. Vergleiche mit früheren Studien aus anderen Ländern waren schwierig. Anhand der Zwischenresultate der Studie und kürzlich durchgeführten Studien bei anderen Personengruppen in der Schweiz ist es fragwürdig, ob Säuglinge/Kleinkinder, besonders gestillte, und deren Mütter in der Schweiz eine ausreichende Jodzufuhr haben. Es bleibt die Auswertung der Endergebnisse der Studie abzuwarten und es bedarf weiterer Untersuchungen, um sicher zu stellen, dass Säuglinge/Kleinkinder und Mütter in der Schweiz ausreichend mit Jod versorgt sind und um einen Referenzbereich für die JKU bei Säuglingen/Kleinkindern festlegen zu können. Mütter sollten gut informiert werden über die bedeutende Rolle von Jod für sie selbst und ihr Kind und über dessen Nahrungsquellen. Zusätzlich könnte stillenden Müttern eine Supplementation mit Jod empfohlen werden.

9. REFERENCES

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10. APPENDIX

Appendix 1: „Verordnung des EDI über Speziallebensmittel“ (817.022.104) (from 25.11.2005, state 01.01.2009) (EDI, 2005b)

Definition of infant formula („Säuglingsanfangsnahrung“):

„**Art. 17**[28] Säuglingsanfangsnahrung: Definition und Anforderungen

[1] Säuglingsanfangsnahrung sind Lebensmittel, die für die besondere Ernährung von gesunden Säuglingen (Kinder unter zwölf Monaten) während der ersten Lebensmonate bestimmt sind und für sich allein den Ernährungsbedürfnissen dieser Säuglinge bis zur Einführung angemessener Beikost genügen.“

Definition of follow-on formula („Folgenahrung”):

„**Art. 18**[32] Folgenahrung: Definition und Anforderungen

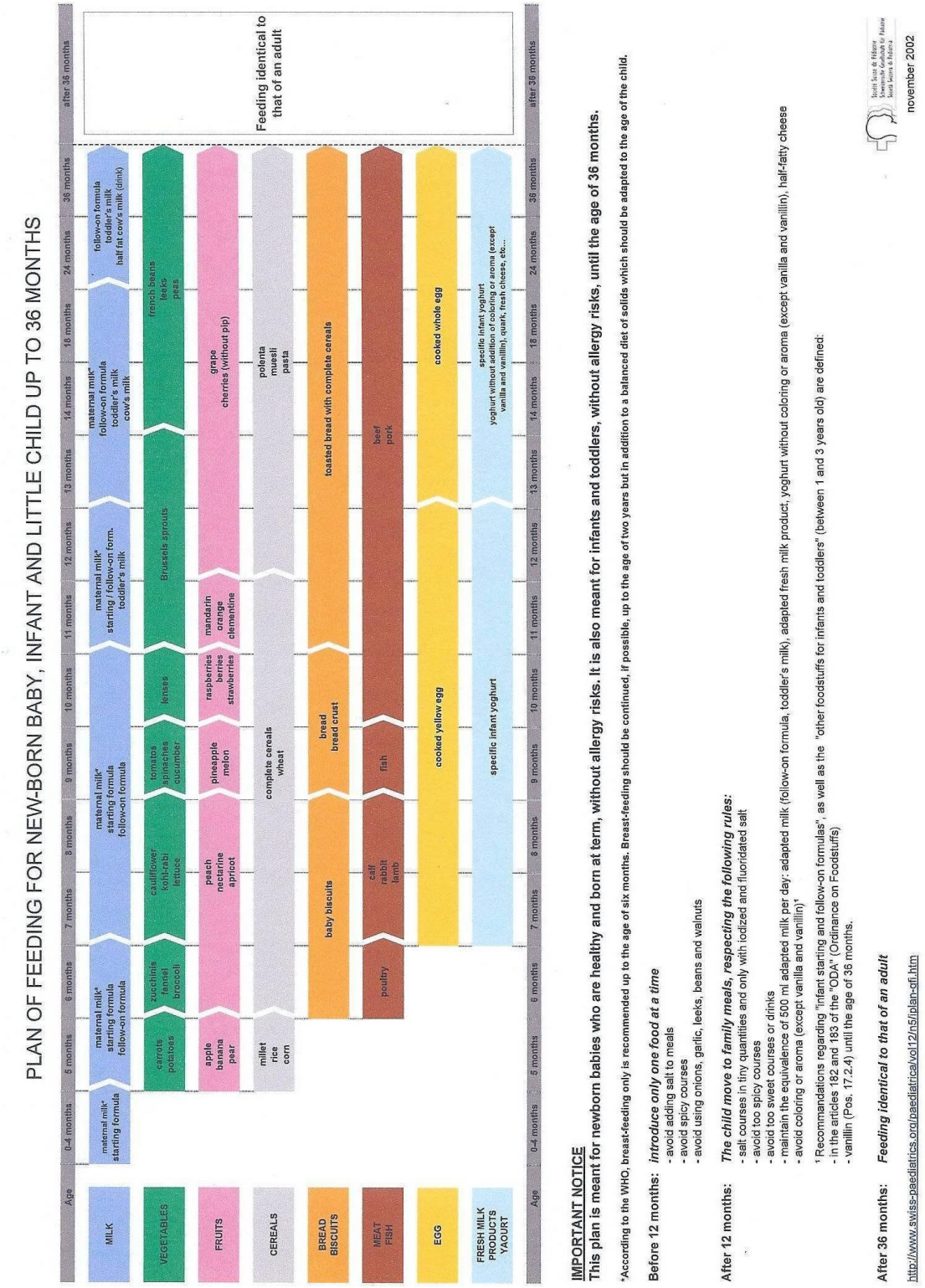
[1] Folgenahrung sind Lebensmittel, die für die besondere Ernährung von gesunden Säuglingen, die älter als sechs Monate sind, ab Einführung einer angemessenen Beikost, und für Kleinkinder (Kinder zwischen einem und drei Jahren) bestimmt sind und den grössten flüssigen Anteil einer nach und nach abwechslungsreicheren Kost dieser Säuglinge darstellen.“

Definition of cereal-based and other complementary food

„**Art. 19** Getreidebeikost und andere Beikost für Säuglinge und Kleinkinder

[1] Getreidebeikost und andere Beikost für Säuglinge und Kleinkinder sind Lebensmittel, die den besonderen Ernährungsbedürfnissen von gesunden Säuglingen und Kleinkindern zwischen vier Monaten und drei Jahren entsprechen und bestimmt sind:
a. während der Entwöhnungsperiode der Säuglinge;
b. als Beikost für Kleinkinder; oder
c. für deren allmähliche Umstellung auf normale Kost. 35
[2] Nicht als andere Beikost gilt Milch, die für Säuglinge und Kleinkinder bestimmt ist.
[3] Getreidebeikost darf angeboten werden als:
a. einfaches Getreideprodukt, das mit Milch oder anderen geeigneten nahrhaften Flüssigkeiten zubereitet ist oder damit zubereitet werden muss;
b. Getreideprodukt mit zugegebenen proteinreichen Lebensmitteln, das mit Wasser oder anderen proteinfreien Flüssigkeiten zubereitet ist oder damit zubereitet werden muss;
c. Teigwaren, die nach dem Kochen in siedendem Wasser oder anderen geeigneten Flüssigkeiten verzehrt werden;
d. Zwiebacks und Biskuits (Kekse), die entweder direkt oder nach dem Zerkleinern unter Zusatz von Wasser, Milch oder anderen geeigneten Flüssigkeiten verzehrt werden.“

Appendix 2: Plan of feeding for new-born baby, infant and little child up to 36 months. Source: (Swiss pediatric society, 2002)



Appendix 3: Studies on UIC in infants and young children – worldwide – conducted between 1989 and 2009

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20 µg/l	< 50 µg/l	< 100 µg/l	< 200 µg/l	> 300 µg/l	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
EUROPE																	
Switzer-land	1997	R (Bernese Region)	0-5 y (random selection)	All	31	**108**	-	-	9	41	-	-	-	S-K	Salt iodization 15 ppm. Women are not mothers of children in the study.	Ade-quate (2004) SAC: 141 µg/l	(Als et al., 2000 b)
				Boys	14	**110**		-	-	-	-	-					
				Girls	17	**105**		-	-	-	-	-					
			6-12yr	All	47	110		-	8	40	-	-					
			13-20yr	women	24	90		-	-	-	-	-					
			21-35 yr	women	44	91		-	-	-	-	-					
			36-50 yr	women	72	93		-	-	-	-	-					
Armenia	1997	N	0-5 y	All	2559	**139.5** (73, 250 [a])	-	-	-	31.7	-	-	- Goiter rate: 33% thyroid palpable, 6% goiter	Commer cial colorime tric kit by Dunn et al., 1993	66% of study household s used iodized salt	Exces-sive (2005) SAC: 313 µg/l	(Ross i and Branc a, 2003)
				6-24 mo				-	-	37.5	-	-					
				25-59 mo				-	-	28.8	-	-					

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20 µg/l	< 50 µg/l	< 100 µg/l	< 200 µg/l	> 300 µg/l	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
Austria	1989 P	R (Vienna area)	4 wk - 16 y	All	124 (68/56)	-	-	-	-	-	-	-	-	S-K	** Values are declared as **µg iodine/g creatinine**.	Ade-quate (1994) SAC: 111 µg/l	(Blum el et al., 1989)
				1-12 mo		400** (156,635[b])		-	-	-	-	-					
				1-3 y		177** (135,409 [b])		-	-	-	-	-					
Belgium	2001 P	L (Brussel)	6 mo - 3 y	All (healthy)	111 (58/53) Urine samples: 244	**101**	-	3	21	49	81	-	-	S-K	Intervention Study: Values from baseline; Delange classified this value as iodine-deficient	In-sufficient (1998) SAC: 80 µg/l	(Delange et al., 2001)
Czech Republic	1994 -2002	N	0-8 y	0-4 y	1050 (550/ 500)	-	-	-	-	-	-	-	-	S-K	All values read from graphs. In the same study UIC of SAC was around: 113 µg/l, adults 98 µg/l	Ade-quate (2000 P) SAC: 199 µg/l Since 1997 table salt iodization 20-34 ppm (voluntary)	(Bilek et al., 2005)
				4-8 y	1300 (600/ 700)	-	-	-	-	-	-	-					
				0-1 y		**104**	129	-	-	-	-	-					
				1-5 y		**114**	136	-	-	-	-	-					

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
France	1994 P	R (Paris area)	10 mo - 4 y	10 mo	456	**181** *(64,390 [c])*	-	0	0.7	18.0	-	-	-	Method of Riley and Gochman, 1964	UI > 600 µg/l excluded	Insufficient (1996) Adults: 85 µg/l	(Valeix et al., 1994)
				2 y	368	**134** (54,345 [c])		0	3.5	31.7							
				4 y	398	**116** (57,291 [c])		0	2	37.2							
France	2000, 2001	R (Nord-Pas-de-Calais)	10 d - 6 y (healthy)	All	160 (93/67)	**196** (4-1042 [d])	-	2	7	24	-	-	-	Spectro-photo-metric	10 % of infants UI > 400 µg/l. Feeding mode: 50% cow milk, 42 % FM, 6% BM, 1% no milk;	Insufficient (1996) Adults: 85 µg/l	(Pousset et al., 2003)
				0-6 mo	54	**183**		2	4	17	-	-					
				6-24 mo	58	**160**		3	10	31	-	-					
				24-6 y	48	**261**		2	8	23	-	-					
				BM (excl.)	10	**206** (124,296 [b])	234 ± 47	-	-	20	-	-					
				FM	68	**165** (87,244 [b])	175 ± 81	-	-	29	-	-					
				Cow milk	80	**220** (110,327 [b])	224 ± 80	-	-	15	-	-					

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
France	2005	R (Nord-Pas-de-Calais)	1 mo – 1y	All 6 mo (1.5-12mo) Hospitalized infants, not healthy. 93% FM, 3% BF, 2% cow milk, 2% n/a.	95 (59/36)	**328** (12-1580 [d])	338	5	11	20	-	-	-	Specto-photo-metric	25 % of infants UI > 400 µg/l. TSH > 5 mU/l: 12%, no correlation with UI.	Insufficient (1996) Adults: 85 µg/l	(Pouessel et al., 2008)
Germany	1993	L (Düssel-dorf)	4.-5. mo (healthy)	All	78 (44/34)	**-**	-	-	-	-	-	-	-	Cer-arsenit-method by Wawschinek et al., 1985	Not all FM were fortified with iodine.	Ade-quate (1999) SAC: 148 µg/l	(Manz et al., 1993)
				Breastmilk	29	**36** (2-550 [d])		-	-	-	-	-					
				Hypoaller-genic formula	23	**64** (11-780 [d])		-	-	-	-	-					
				Commer-cial formula	26	**60** (7-590 [d])		-	-	-	-	-					

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
Germany	2003 - 2006	N	0-17y	All	17'641 (8985/8656)	**117**	-	-	-	-	-	-	-	S-K	UI data read from bar chart UI > 600 µg/l excluded. * < 25 µg/l 80-90% of German households use iodized salt.	Ade-quate (1999) SAC: 148 µg/l	(Thamm et al., 2007)
				0-2 y	-	**-**		12.7 *	24.5	47.7	-	7.3					
				Boys 0 y	-	**133**		-	-	-	-	-					
				Girls 0 y	-	**100**		-	-	-	-	-					
				Boys 1 y	-	**117**		-	-	-	-	-					
				Girls 1 y	-	**82**		-	-	-	-	-					
				Boys 2 y	-	**113**		-	-	-	-	-					
				Girls 2 y	-	**92**		-	-	-	-	-					
Italy	1999 P	R (Hill, seas, mountain & plain area)	1 mo	All	241 (132/109)	**69** (12,21[e])	-	-	34	63	-		Within same study: women after delivery: median 55 µg/l	S-K	UI > 600 µg/l excluded.	Insufficient (1992-1999) SAC: 94 µg/l	(Rapa et al., 1999)
			3-5 d	All	384	68 (10, 192 [e])			35.9	67.7							
			8-10 y	All	847	121 (39, 244 [e])			13.9	47.8							

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
Turkey	2003 P	L (Ankara)	Infants	All	50			-	-	-	-	-	-	Modified S-K	Intervention study: UI values from baseline. No life-threat.diseases, malnutr., major congen. abnorm., thyroid affect. Drugs	Insufficient (2002) SAC: 75 µg/l	(Yilmaz et al., 2003)
				Group 1		-	**128.4** ± 34.8	-	-	-	-	-					
				Group 2		-	**130.0** ± 18.7	-	-	-	-	-					
			Newborns (full term)	All	40			-	-	-	-	-					
				Group 1		-	120.5	-	-	-	-	-					
				Group 2		-	126.0	-	-	-	-	-					
EASTERN MEDITERRANEAN																	
Sudan	1994	R (Blue Nile area)	1-6 y	All (4.7 ± 1.6 yr)	191	**100.3** (88,124 [e])	-	-	-	-	80.7	-	-	Method described in Bourdoux, 1988	Goiter rate (all): 22.3%; high anemia and vitamin A deficiency prevalence; high goitrogen consumption (millet)	Insufficient (1997) SAC: 75 µg/l ---------- no iodized salt	(Elnour et al., 2000)
				Boys	96	**119.3** (91,160 [e])	-	-	-	-	76.0	-					
				Girls	95	**91.4** (69,116 [e])	-	-	-	-	82.6	-					

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20 µg/l	< 50 µg/l	< 100 µg/l	< 200 µg/l	> 300 µg/l	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
AMERICAS																	
Mexico	1999	R (North, Center, Mexico City and South)	0.5-4 y	All	18	No data	-	0	0	17	-	-	-	S-K	Table salt iodization mandatory by law since > 50 yr	More than ade-quate (1999) SAC: 235 µg/l	(Villalpando et al., 2003)
Vene-zuela	1999	R (Mérida (Zone of the Andes))	1 mo – 4 y	Healthy	116	-	**308** ± 155	0	0	0	-	-	-	S-K	-	More than ade-quate (2000/1) SAC: 286 µg/l	(Paoli-Valeri et al., 2003)

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
AFRICA																	
Nigeria	1996 P	L (Ibadan, South-western Nigeria)	9-18 mo (almost excl. BF, healthy)	All	68 (38/30)	-	**99** ± 7	-	-	-	-	-	Mean: 145 ± 14 (n = 68)	Alternative A of S-K (Dunn et al, 1993)	Study in a goiter-non-endemic area (<5%). Low socio-economic group.	Ade-quate (2004/5) SAC: 130 µg/l	(Akanji et al., 1996)
				MUAC * > 13.5cm	47	-	**99** ± 7	-	-	38.3	-	-					
				MUAC < 13.5cm	21	-	**97** ± 7	-	-	38.1	-	-					
				* MUAC = mid-upper arm circumference													
Reunion Island	1997	R (Cirque de Salazie, mountainous area)	6-30 mo	All	28	**120**	-	-	14.8	40.7	-	-	Women of childbearing age in same study: median 42 µg/l (n = 52)	S-K auto-analyzer	Goiter rate: infants 0%, SAC 12%, women 38%. Low iodization level in analyzed salt samples.	No WHO data. Median SAC in present study: 78 µg/l (n = 91)	(Jaffiol et al., 1997)

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20 µg/l	< 50 µg/l	< 100 µg/l	< 200 µg/l	> 300 µg/l	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
SOUTH-EAST ASIA																	
India	2006 P	L (New Delhi)	-	Exclusively breast-fed, healthy	175	**162**	-	-	-	21	-	-	Median: 124 µg/l (n =175)	No data	Only abstract. 96% of analyzed salt samples were adequate. iodized > 15 ppm	Ade-quate (1993-2002) SAC: 133 µg/l	(Gupta et al., 2006)
Indo-nesia	2007 P	R (Central Java)	6-12 mo	All	133 (133/0)	-	174	0	6.8	24.1	-	11.3		S-K	Intervention study: UI values from baseline. 92.5% of infants are breast-fed > 4 times per day, one third received FM	More than ade-quate (2003) SAC: 229 µg/l	(Wijaya-Erhardt et al., 2007)
			(infants deficient in multiple micronutrients)	Group 1	31	**138**	169 ± 109	-	-	-	-						
				Group 2	32	**171**	180 ± 102	-	-	-	-						
				Group 3	39	**168**	182 ± 109	-	-	-	-						
				Placebo group	31	**170**	164 ± 79	-	-	-	-						

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20 µg/l	< 50 µg/l	< 100 µg/l	< 200 µg/l	> 300 µg/l	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
WESTERN-PACIFIC																	
China	2005 P	R (11 provinces)	0-2 y	Urban sites Rural sites	1295 1258	**235.5** **247.3**	- -	- -	- -	- -	- -	- -	Median lactating mothers: 188.6 (urban), 192.1 (rural) µg/l	Modified S-K	Mandatory salt iodization 35 ppm	More than ade-quate (2005) SAC: 246 µg/l	(Yan et al., 2005)
China	2009 P	R (regions where iodized salt since 2000)	0-1 y	All	n/a	**233**	-	-	-	-	-	-	Lactating women: BF < 6 mo: 126 µg/l; BF > 6 mo: 145 µg/l	No data	Only abstract; Universal salt iodization program in place > 90% coverage since 2000	More than ade-quate (2005) SAC: 246 µg/l	(Wang et al., 2009)
Malaysia	1996 P	L (Menjiling Mengkak, rural, goitrous area)	0-6 y	From Menjiling From Mengkak	32 33	**10.6** **28.1**	-	87.5 12	100 70	100 97	0 -	0 -	Median women 15-40 yr: 11.3 resp. 36.8 µg/l (n = 53 resp. 48)	S-K	Intervention study: UI values from baseline Prevalences read from bar chart	Insufficient (1995) SAC: 91 µg/l	(Foo et al., 1996)

Continuation of Appendix 3

Country	Date of study	Level of study [1] (Location)	Age group	Sample description	Sample size (M/F)	Median UIC infants [µg/l]	Mean UIC infants [µg/l]	Prevalence % < 20	< 50	< 100 µg/l	< 200	> 300	UIC mothers [µg/l]	UIC analysis [2]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
New Zealand	1998 -1999	L (Christ-church, Dunedin, Invercar-gill: 3 cities)	6-24 mo (healthy)	All	230 (131/99)	**67** (37-115 [d])		11.7	37.0	67.4	-	-	-	S-K	* geometric mean Mean UIC of formula-fed children sig. higher than other feeding groups. BMIC mothers: 22 µg/l	Insufficient (2002) SAC: 66 µg/l	(Skeaff et al., 2005)
				Breast-fed	43	**44** (23-82 [d])	40 *	-	51.2	83.7	-	-					
				Formula-fed	51	**99** (68-167 [d])	105	-	13.7	51.0	-	-					
				BF and FM	17	**59** (39-103 [d])	56	-	47.1	70.6	-	-					
				No BM, no FM	119	**59** (36-112 [d])	56	-	39.5	66.4	-	-					

[1] L = local, R = regional, N = national
[2] S-K = (modified) Sandell-Kolthoff reaction
[3] Classification of the country according to the WHO Global Database on Iodine Deficiency and median UIC of the age group that was reported together with the classification in the WHO database (de Benoist et al., 2008; WHO Nutrition, 2008a; WHO Nutrition, 2008b).
[a] 20th percentile, 80th percentile; [b] Quartile 1 and quartile 3; [c] 5th percentile, 95th percentile; [d] Highest and lowest value of UI (range); [e] 10th percentile, 90th percentile; [f] 95 % CI

Appendix 4: Studies on BMIC – in Switzerland and worldwide (selection) - conducted between 1998 and 2009

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
EUROPE													
Switzer-land	1992/ 93	L (Berne)	n/a	5th – 12th day after birth	38	**98**	-	-	-	-	-	Ade-quate (2004) SAC: 141 µg/l	4
Switzer-land	1993/ 94	L (Basel)	n/a	5th – 12th day after birth	23	**82**	-	-	-	-	-		4
Switzer-land	1994	L (Solothurn)	n/a	3 – 6 days after birth	30	**-**	78 ± 59	Modified S-K	-	66 ± 33 * (newborns)	* mean ± SD		(Hoang Truong et al., 1997)
Switzer-land	1998/ 99	L (Basel)	n/a	> 12th day after birth	52	**68**	-	ICP-MS (personal comm. M. Haldiman n, FOPH)	-	-	-		4
Belgium	1999-2000	L (Brussels)	n/a	Day 5 after delivery	58	**78**	98 ± 5	n/a	-	86 (newborns)	Newborns concluded as iodine-deficient	In-sufficient (1998) SAC: 80 µg/l	(Ciarde lli et al., 2002)

Continuation of Appendix 4

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
Denmark	2004 P	R (5 cities in Denmark)	Mean 27 yr	5 days after delivery	Non-smoker (n = 90) Smokers (n = 50)	-	53.8 [b] * (49.4-58.5 [d]) 26.0 [b] * (23.2-29.1 [d]) * p < 0.001	S-K after alkaline ashing	40.8 [b] (6-665 [a]) 40.1 [b] (9-143 [a])	50.4 [b] * (46.0-55.1 [d]) 33.3 [b] * (29.9-37.2 [d]) * p = 0.005 (neonates)	Healthy women, study before introduction of iodized salt, majority of women from moderately iodine-deficient areas	In-sufficient (1997-8) Adults: 61 µg/l	(Laurberg et al., 2004)
Germany	2005 P	L (Jena)	18-39 y	1st – 5th day (n =24), 6th – 10th day (n = 8)	32	**156** (33–348 [a])	169 ± 88	ICP-MS	-	-	* supplements during pregnancy: 175 µg I/day (average)	Adequate (1999) SAC: 148 µg/l	(Bader et al., 2005)
				Iodine supplement *	20	**151**	160 ± 91						
				No iodine supplement	12	**176**	184 ± 84						
Germany	2009 P	-	-	3rd – 7th day after birth	-	**52** (20-230 [a])	-	S-K	-	-	All women supplemented with 150 µg I /day during pregnancy	Adequate (1999) SAC: 148 µg/l	(Gärtner and Arbeitskreis Jodmangel, 2009)

Continuation of Appendix 4

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
Spain	2007 P	L (Santiago)	-	Collected in hospital after delivery	14	**-**	144 ± 93.2	ICP-MS	-	-	-	Ade-quate (1995-2002) SAC: 109 µg/l	(Fernandez-Sanchez et al., 2007)
AMERICAS													
USA	2003	R (15 US states)	-	-	23	**33.5 ***	63.3 * (4.5-184.5 [a])	Chromatography/ ICP-MS	-	-	* Iodide Also perchlorate assessed Healthy lactating volunteers	More than adequate (2001-02) SAC: 249 µg/l	(Kirk et al., 2005)
USA	2007 P	R (6 US states)	-	-	108 of 10 women	**55.2 *** (3.1-334)	87.9 ± 80.9 *	Ion-chromatography-MS	-	-	* Iodide Non-smokers. Also perchlorate/thiocyanate assessed	More than adequate (2001-02) SAC: 249 µg/l	(Kirk et al., 2007)

Continuation of Appendix 4

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
USA	2002-2006	R (Boston-area)	19-45y	10-250 days postpartum	57	**155** (2.7-1968 [a])	205 ± 271	Spectrophotometrical, modified method of Benotti et al.	114 [c] (25-920 [a])	-	Healthy lactating volunteers	More than adequate (2001-02) SAC: 249 µg/l	(Pearce et al., 2007)
USA	2008 P	L (Arlington)	24-34 y	55-253 days postpartum	447 samples of 13 women	**43** (1-1200 [a])	120 ± 75	ICP-MS	110 [c] (26-630 [a]) (n = 117 24-h urine samples)	-	Non-smokers.	More than adequate (2001-02) SAC: 249 µg/l	(Dasgupta et al., 2008)
USA	2009 P	R (Rio Grande Valley, Texas)	20-38 y	30-45 days postpartum 75-90 days postpartum	30 17	**-**	47.8 ± 17.1 42.3 ± 8.71	NAA	-	-	Healthy, Mexican-American, low-income; 24-h recall: iodine intake 34 – 50% of DRI	More than adequate (2001-02) SAC: 249 µg/l	(Hannan et al., 2009)

Continuation of Appendix 4

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
EASTERN-MEDITERRANEAN													
Iran	2003	L (City of Gorgan)	Mean 25.6 y	30-180 days postpartum	100	**93.5** (17-696 [a])	117 ± 101 (97.3,137.2 [e])	S-K	259 [c] (35-519 [a])	-	Iodine-sufficent area, salt iodized; Healthy women, non-smokers	Ade-quate (2000-1) SAC: 165 µg/l	(Bazrafshan et al., 2005)
Iran	2004-05	L (Teheran)	18-36 y	12 ± 4 days postpartum	42	**148** (45-750 [a])	176 ± 120	S-K	107 [c] (20-710 [a])	271 (57-800 [a]) (newborn)	Healthy women, non-smokers; Exclusively BF		(Ordoo khani et al., 2007)
WESTERN-PACIFIC													
Australia	2000	L (Sydney)	33 ± 4.5	3-9 days postpartum	49	**84** (25-234 [a])	103.6 ± 59.5	ICP-MS	46.0 [c] (4-140 [a])	-	TSH infants measured 6% > 5mU/l BMIC considered as moderately ID	Ade-quate (2003-4) SAC: 104 µg/l	(Chan et al., 2003)

Continuation of Appendix 4

Country	Date of study	Level of study [1] (Location)	Age women	BM sample description	Sample size	Median BMIC [µg/l] or [µg/kg]	Mean BMIC [µg/l] or [µg/kg] (± SD)	BMIC analysis [2]	UI Lactating women [µg/l]	Median UI infants [µg/l]	Comment	Country class. iodine intake (1993 – 2006) [3]	Ref
China	2005 P	R (11 provinces)	n/a	All from mothers with infants 0-2 y Urban sites Rural sites	710 364 346	**145.7** **135.9** **157.5**	-	S-K	 188.6 [c] 192.1	 235.5 247.3	Mandatory salt iodization 35 ppm	More than ade-quate (2005) SAC: 246 µg/l	(Yan et al., 2005)
China	2009 P	R (regions where iodized salt since 2000)	n/a	All BF < 6 mo BF > 6 mo	n/a	**163**	-	n/a	 126 [c] 145 [c]	233	Only abstract; Universal salt iodization program in place > 90% coverage since 2000	More than ade-quate (2005) SAC: 246 µg/	(Wang et al., 2009)
New Zealand	1998 - 1999	L (Christ-church, Dunedin, Invercar-gill: 3 cities)	n/a	With children aged 6-24 mo	39	**-**	22 (18, 26 [e])	S-K	-	**67** (37-115 [a]) BF: **44** (23-82 [a]) FF: **99** (68-167 [a])	Healthy infants Mean UIC of formula-fed children sig. higher than other feeding groups.	Insufficie nt (2002) SAC: 66 µg/l	(Skeaff et al., 2005)

[1] L = local, R = regional, N = national
[2] S-K = (modified) Sandell-Kolthoff reaction; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; NAA = neutron activation analysis

[3] Classification of the country according to the WHO Global Database on Iodine Deficiency and median UIC of the age group that was reported together with the classification in the WHO database (de Benoist et al., 2008; WHO Nutrition, 2008a; WHO Nutrition, 2008b).
[4] Ref: (Facheinheit Lebensmittel und Gebrauchsgegenstände des Bundesamtes für Gesundheit, 2000)
[a] Highest and lowest value of UI (range); [b] geometric mean; [c] median; [d] SEM range; [e] 95 % CI

Appendix 5: Instruction about materials and study procedure for the pediatric practices – German

„ETABLIERUNG VON REFERENZWERTEN FÜR DIE JODKONZENTRATION IM URIN VON 6- UND 12-MONATIGEN SCHWEIZER KINDERN“

Materialien & Durchführung

Das Ziel dieser Studie ist die Gewinnung neuer Erkenntnisse zur optimalen Jodversorgung von Säuglingen. Diese dienen als Basis für die Etablierung von Referenzwerten für die Jodkonzentration im Urin von Säuglingen.

Für die Gewinnung einer repräsentativen Stichprobe werden in jeder Praxis **pro Altersgruppe (6 und 12 Monate) je 30 Säuglinge** in die Studie einbezogen.

Von jedem teilnehmenden Mutter-Säuglings-Paar wird eine Urinprobe des Säuglings, eine Urinprobe der Mutter und von stillenden Müttern eine Muttermilchprobe gesammelt, sowie ein Fragebogen zur Säuglingsernährung ausgefüllt.

1. Unterlagen zur Information, Registrierung

1.1 Materialien

- Informationsblatt für die Eltern *(100x)*
- Schriftliche Einverständniserklärung für die Eltern *(100x)*
- Persönliches Registrierungsformular für 6- bzw. 12-monatige Säuglinge *(je 50 Stk.)*
- Praxis-Registrierungsformular für 6- bzw. 12-monatige Säuglinge *(je 1x)*
- Selbstklebende Codierungs-Etiketten *(pro Säugling je 7 Stk.)*
- Übersichtsblatt der Einschlusskriterien *(1x)*
- Kontaktdatenblatt der ETH Zürich *(1x)*

1.2 Durchführung

a) Information der Eltern mittels schriftlichem Informationsblatt und kurze mündliche Erklärung des Studienablaufs
b) Unterschrift der Einverständniserklärung zur Studienteilnahme durch die Eltern
c) Beurteilung der intakten Gesundheit des Säuglings durch den Arzt/ die Ärztin und Abklärung der Erfüllung aller Einschlusskriterien (siehe Übersichtsblatt Einschlusskriterien)
d) Ausfüllen des persönlichen Registrierungsformulars für jeden Säugling durch den Arzt/ die Ärztin
e) Bei Erfüllung aller Einschlusskriterien und definitiver Studienteilnahme – Vergabe des Codes für den Säugling und Aufkleben der Etiketten *(siehe 3. Etiketten)*
f) Eintragung des teilnehmenden Säuglings auf dem jeweiligen Praxis-Registrierungsformular (diese bleiben bis zum Ende der Studie in der Praxis)
g) Nach Abschluss der Probennahme eines Säuglings auf dem Praxisregistrierungsformular und dem persönlichen Registrierungsformular ankreuzen, welche Proben gesammelt bzw. Formulare/ Fragebogen ausgefüllt wurden und was mit nach Hause gegeben wurde

1

2. Probensammlung: Materialien und Durchführung

2.1 Materialien

- Pro Säugling je ein Plastikbeutel mit voretikettiertem Material zur Probensammlung *(40 Beutel pro Altersgruppe)*:
  - Uricol-Set: - 2 Pads
    - 1 Einwegspritze à 5 ml
    - (1 Ersatzröhrchen)
  - 1 Versandröhrchen (à 15 ml) für Urin Baby
  - 1 Versandröhrchen (à 15 ml) für Urin Mutter
  - 1 Versandröhrchen (à 15 ml) für Muttermilch
  - 3 kleine Plastikbeutel für die Röhrchen
- Becher mit Schnappdeckel zum Sammeln von Urin und Muttermilch *(130x)*
- Beschreibung zum Ausstreichen von Muttermilch *(60x)*
- Einweg-Stilleinlagen *(1 Packung)*
- Ersatz-Uricol-Sets *(10x)*

Versandröhrchen in Originalgrösse

2.2 Sammlung der Urinprobe des Babys

a) Genitalbereich und After des Babys reinigen, keine Crème oder Puder verwenden.
b) Den Pad *(aus dem Uricol-Set)* so auf die umgekehrte Windel (Innenseite nach aussen) legen, dass er den Urin gut absorbieren kann.
c) Regelmässige Kontrolle des Pads. Bei Verunreinigung mit Kot Verwendung des Ersatzpads.
d) Sobald der Säugling uriniert hat, den Pad entnehmen und auf eine saubere Fläche legen.
Hinweis: Um das Urinieren des Säuglings auszulösen, kann die Mutter den Säugling stillen oder ihm ein Getränk geben.
e) **3 ml Urin** mit der Einwegspritze *(aus dem Uricol-Set)* vom Pad abnehmen (Spritze im 45° Winkel auf dem Pad ansetzen, mehrmals langsam aufziehen bis genug Urin extrahiert ist) und in das entsprechende Versandröhrchen (*aus dem Plastikbeutel)* mit dem Etikett «Urin Baby» füllen (mind. bis zum unteren Rand der Etikette).
f) Röhrchen gut verschliessen!

2.3 Sammlung der Urinprobe der Mutter

a) Abgabe der Urinprobe der Mutter in einen Urinbecher *(siehe 2.1)*.
b) **10 ml Urin** in das entsprechende Versandröhrchen (*aus dem Plastikbeutel)* mit dem Etikett «Urin Mutter» einfüllen (ca. bis zur Rille unterhalb des Deckels).
c) Röhrchen gut verschliessen!

2.4 Sammlung der Muttermilchprobe

a) Abgabe der Muttermilchprobe durch Ausstreichen. Beschreibung für die Mutter, *siehe Materialien*.
b) Die ersten paar Tropfen Milch werden mit der Einweg-Stilleinlage *(siehe 2.1)* abgenommen, danach werden mindestens 10 ml Milch in einem Becher *(siehe 2.1)* aufgefangen.
c) **10 ml Muttermilch** in das entsprechende Versandröhrchen (*aus dem Plastikbeutel)* mit dem Etikett «Muttermilch» einfüllen (ca. bis zur Rille unterhalb des Deckels).
d) Röhrchen gut verschliessen!

Desinfektionsmittel (z.B. Betadine) können **Jod** enthalten. Um eine Kontamination der Proben zu verhindern, vermeiden Sie bitte jeglichen Kontakt jodhaltiger Desinfektionsmittel mit den Proben.

2

3. Fragebogen zur Säuglingsernährung

3.1 Materialien

- 1. Fragebogen zur Ernährung des Säuglings *(80x)*
  (voretikettiert, im Plastikbeutel mit zugehörigen Materialien zur Probensammlung, *siehe 2.*)
- 2. Fragebogen zur Ernährung des Säuglings
  (inkl. vorfrankiertem Rückantwortkuvert an die ETH Zürich) *(80x)*
  (voretikettiert, im Plastikbeutel mit zugehörigem Material zur Probensammlung *siehe 2.*)
- Mäppchen mit Produktbroschüren für Säuglingsnahrung *(2x),* Schreibunterlage *(1x)*
- Ersatz-Fragebogen (1.) *(10x)*

3.2 Durchführung

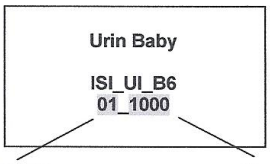
a) **1. Fragebogen** zur Ernährung des Säuglings am Vortag: auszufüllen von der Mutter (in der Praxis oder zuhause). Das Mäppchen mit den Produktbroschüren kann als Hilfe zur Erinnerung der korrekten Produktnamen dienen. Das genaue Ausfüllen des Fragebogens ist sehr wichtig für die Berechnung der Jodaufnahme des Säuglings.

b) **2. Fragebogen** zur Ernährung des Säuglings zum Ausfüllen 3-4 Tage nach der Probennahme: der Mutter mit nach Hause geben (inkl. vorfrankiertem Antwortkuvert an die ETH Zürich).

4. Etiketten

4.1 Beschreibung

Beispiel:



Code der Praxis **Code des Babys** bzw. **seiner Mutter**

Abkürzungen

ISI	= Iodine Status Infants, *Name der Studie*
UI	= Urinary Iodine, *Probenmaterial*
BM	= Breastmilk, *Probenmaterial*
B6	= Baby 6 Monate alt
B12	= Baby 12 Monate alt
M6	= Mutter von 6-monatigem Baby
M12	= Mutter von 12-monatigem Baby

Farbcode
Gelb: 6 Monate
Blau: 12 Monate

Code Baby / Mutter
Identisch auf allen Etiketten des jeweiligen Säuglings bzw. seiner Mutter

4.2 Anwendung

- **Fragebögen** und **Probenröhrchen** sind bereits **voretikettiert** in den Plastikbeuteln. Diese sind geordnet nach Alter, 6 Monate *(gelbe Etiketten)* und 12 Monate *(blaue Etiketten).*
- Bei Teilnahme des Säuglings: Auf die **Einverständniserklärung**, das **persönliche Registrierungsformular** und das **Praxisregistrierungsformular** die entsprechende **Codierungs-Etikette aufkleben** (*Etiketten im Ordner*).

Bitte gut überprüfen, ob auf allen Formularen, Proben, Fragebögen des Säuglings und seiner Mutter der **gleiche Code** ist!

3

4. Aufbewahrung der Proben

- Jedes Röhrchen in einen kleinen Plastikbeutel *(siehe 2.1)* geben.
- Bis zum Versand alle Proben im Kühlschrank bei 2 bis 8 °C aufbewahren.

5. Versand an die ETH Zürich

5.1 Materialien

- Adressierte und vorfrankierte Luftpolsterkuverts *(40x)*
- Adressierte und vorfrankierte C4 Kuverts für Fragebögen und Formulare *(8x)*

5.2 Durchführung

a) Bitte überprüfen, dass alle Probenröhrchen und die Beutel sehr gut verschlossen sind.
b) Pro Luftpolsterkuvert die **Proben** von **2 Säuglingen** (je 3 Röhrchen) zum Versand einpacken (max. Dicke: 5 cm, max. Gewicht: 250 g).
c) **Formulare** und **Fragebögen** von je ca. **9 Säuglingen** zusammen in ein C4 Kuvert geben (berechnet für persönliches Registrierungsformular, Einverständniserklärung, 1. Fragebogen; max. Dicke: 2 cm, max. Gewicht: 500g).
d) Name der Praxis auf dem Umschlag vermerken.
e) Regelmässige Rücksendung an die ETH Zürich, sobald genug Proben/Formulare pro Kuvert vorhanden sind (**Proben mindestens 1x pro Woche**).
f) Das Praxisregistrierungsformular wird nach Abschluss der Studie an die ETH Zürich gesendet.

6. Bei Probensammlung der Mutter/Eltern zu Hause

6.1. Materialien

- Anleitung für die Eltern zur Probensammlung zu Hause *(80x)*
- Zusätzliche adressierte Luftpolsterkuverts und Briefmarken *(30x)*
- Zusätzliche C5 Rückantwort-Kuverts (für Fragebogen) *(60x)*

6.2. Durchführung

a) Information über die Studie, Unterschrift auf der Einverständniserklärung, Ausfüllen des persönlichen Registrierungsformulars und Praxisregistrierungsformulars für alle Säuglinge in der Praxis.
b) Entsprechende Materialien/Fragebögen mitgeben und die Mutter/Eltern kurz über die Anwendung instruieren.
c) Überprüfung der Übereinstimmung der Codierung!
d) Eine Anleitung für die Probensammlung zu Hause mitgeben und auf das Antwortformular auf Seite 1 der Anleitung die Etikette des Säuglings aufkleben.
e) Ein vorfrankiertes und adressiertes Luftpolsterkuvert für die Proben bzw. je ein C5 Kuvert für den 1. und/oder 2. Fragebogen zur direkten Sendung an die ETH Zürich mitgeben *(ein C5 Kuvert befindet sich bereits im grossen Plastikbeutel, ein zweites in der kleinen Kartonschachtel)*.
f) Auf dem persönlichen Registrierungsformular und dem Praxisregistrierungsformular ankreuzen, welche Teile der Studie zu Hause gemacht werden.

Appendix 6: Information sheet for the parents – German

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Institut für Lebensmittel- und Ernährungswissenschaften
Labor für Humanernährung
Schmelzbergstr. 7
CH-8092 Zürich

Informationsblatt für die Eltern

„Festlegung von Referenzwerten für die Jodkonzentration im Urin von Säuglingen“

Was möchten wir untersuchen?

Jod ist ein wichtiger Nährstoff, welcher jedoch oft nur in sehr geringer Menge in unseren Nahrungsmitteln vorkommt. Speisesalz wird daher in der Schweiz mit Jod angereichert. Bei Jodmangel fühlt sich eine Person müde, antriebslos und hat Konzentrationsschwierigkeiten.

Während der Schwangerschaft wird der Fötus durch seine Mutter mit Jod versorgt. Nach der Geburt wird Jod über die Muttermilch an den Säugling weitergegeben oder er nimmt dieses aus Säuglingsmilch sowie später aus Beikost und Familienkost auf. Zu wenig Jod während der Schwangerschaft und der frühen Kindheit kann die körperliche und geistige Entwicklung des Kindes beeinträchtigen.

Das Ziel dieser Studie ist es die Jodversorgung Ihres Kindes zu bestimmen. Dies erfolgt, indem die Jodmenge im Urin Ihres Babys gemessen wird, da die Menge an Jod im Urin einen wichtigen Indikator für die Jodversorgung darstellt. Um ein vollständiges Bild zu bekommen, messen wir auch den Jodgehalt in der Muttermilch und berechnen mit Hilfe eines Ernährungsfragebogens die Jodmenge in der Nahrung Ihres Babys. Zusätzlich messen wir den Jodgehalt im Urin der Mütter und vergleichen ihn mit dem Jodgehalt im Urin der Kinder.

Wegen der Jodierung von Lebensmitteln erwarten wir, dass Kinder in der Schweiz genug Jod aufnehmen. Die Schweiz eignet sich daher optimal um anhand der Studienergebnisse internationale Referenzwerte für Jod festzulegen.

Wie ist der Ablauf der Studie?

Zur Sammlung der Urinprobe Ihres Babys dient eine weiche, sterile Stoffeinlage, die in die umgedrehte Windel Ihres Kindes eingelegt wird. Die Einlage saugt den Urin Ihres Kindes auf. Sie wird dann wieder herausgenommen und der Urin von der Einlage abgenommen.

Über die Ernährung Ihres Babys wird von Ihnen ein Fragebogen ausgefüllt. Von der Mutter ist eine kleine Menge Urin erforderlich und von stillenden Müttern zusätzlich ein wenig Muttermilch (10 ml).

Aus welchen Gründen ist die Teilnahme Ihres Babys an der Studie nicht möglich?

Ihr Kind kann nicht an der Studie teilnehmen, wenn

1) er/sie vor der 38. oder nach der 42. Schwangerschaftswoche auf die Welt kam.
2) er/sie nicht gesund ist (die Entscheidung darüber trifft der Kinderarzt/-ärztin in der Praxis).
3) bei ihm/ihr Schilddrüsenstörungen vorhanden sind/ waren.
4) die Mutter während den 12 Monaten vor der Entbindung ausserhalb der Schweiz gelebt hat.
5) die Mutter und Ihr Kind seit der Geburt ausserhalb der Schweiz gelebt haben.
6) mütterlicherseits Schilddrüsenstörungen vorhanden sind/ waren.
7) die Mutter seit der Schwangerschaft Kontrastmittel (für Röntgen oder Computertomografie) oder jodhaltige Medikamente (Amiodaron [Antiarrhytmikum]) eingenommen hat/ injiziert bekam.

Risiken der Studie

Die Sammlung des Urins Ihres Babys sowie des Urins der Mutter und der Muttermilch bringen keine Risiken mit sich. Die Studie wird die geplante Vorsorgeuntersuchung/ Impfung nicht beeinträchtigen.

Finanzierung der Studie

Die Studie wird von der ETH Zürich finanziert.

Rücktritt von der Studie

Ihre und die Teilnahme Ihres Babys an der Studie sind vollkommen freiwillig und frei von Kosten. Sie können jederzeit und ohne Angabe von Gründen von der Studie zurücktreten.

Was geschieht mit den Daten Ihres Babys?

Ihr(e) Kinderarzt(-ärztin) wird die Ergebnisse der Studie erhalten und mit Ihnen persönlich die Resultate der Messungen besprechen. Niemandem ausser Ihnen werden die Daten mitgeteilt.

Ausserhalb der Arztpraxis werden die erhobenen Daten mit einer Nummer gekennzeichnet. Der Name Ihrer Tochter/ Ihres Sohns sowie Ihr Name werden nicht verwendet. Die Daten werden absolut vertraulich behandelt und ausschliesslich für wissenschaftliche Zwecke verwendet.

Versicherung

Es besteht eine allgemeine Haftpflichtversicherung der ETH Zürich (Police Nr. 100.001 der Schweizerischen Mobiliar Versicherungsgesellschaft), die im Rahmen der gesetzlichen Vorschriften Gesundheitsschäden, falls solche im Zusammenhang mit der Studie auftreten, abdeckt.

Wenn ich noch Fragen habe?

Für weitere Fragen stehen wir Ihnen selbstverständlich jederzeit zur Verfügung.

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Mit freundlichen Grüssen,

Prof. Dr. med. M.B. Zimmermann M. Andersson N. Wüst

Appendix 7: Individual registration form – German

„ETABLIERUNG VON REFERENZWERTEN FÜR DIE JODKONZENTRATION IM URIN VON 6- UND 12-MONATIGEN SCHWEIZER KINDERN"

PERSÖNLICHES REGISTRIERUNGSFORMULAR
6 – monatige Säuglinge

Säugling (Etikette): ☐ **Erfassungsdatum**: I__I__I / I__I__I / I__I__I **Praxis Nr.:** I__I__I

Praxis Dr.: ..... PLZ, Ort Praxis: .....

Wohnort Eltern: ..... Name, Telefonnr. Eltern: .....
(optional, für Rückfragen der ETH Zürich)

SÄUGLING	☐ w ☐ m
Geburtsdatum:	I__I__I / I__I__I / I__I__I (T M J)
Körpergewicht:	I__I__I,__I__I kg
Körpergrösse:	I__I__I__I cm
Termingerechte Geburt *: (zw. 38. und 42. Schwangerschaftswoche)	☐ Ja * ☐ Nein
Entbindungsart:	☐ natürlich ☐ Kaiserschnitt
Vorgeschichte mit Schilddrüsenproblemen *:	☐ Ja ☐ Nein *
Wenn JA, bitte erklären:	....
Intakte Gesundheit *:	☐ Ja * ☐ Nein
Bemerkungen:	

MUTTER	
Geburtsdatum:	I__I__I / I__I__I / I__I__I (T M J)
Körpergewicht:	I__I__I__I,__I kg
Körpergrösse:	I__I__I__I cm
Nationalität:	I_____I
Wohnhaft in der Schweiz seit:	
- mindestens 1 Jahr vor der Geburt des Säuglings*	☐ Ja * ☐ Nein
- seit der Geburt des Säuglings (gemeinsam mit dem Säugling) *	☐ Ja * ☐ Nein
Vorgeschichte mit Schilddrüsenproblemen *:	☐ Ja ☐ Nein *
Wenn JA, bitte erklären:	....
Einnahme von (aktuell) - Multivitamin-/mineralstoff-supplementen	☐ Ja ☐ Nein
- Algen-/Tangsupplementen	☐ Ja ☐ Nein
Wenn JA, bitte erklären:	....
Seit der Schwangerschaft: Einnahme/Injektion von - Röntgen-/CT-Kontrastmitteln *	☐ Ja ☐ Nein *
- jodhaltigen Medikamenten * (Amiodaron, [Antiarrhytmikum])	☐ Ja ☐ Nein *

Einschlusskriterien erfüllt (siehe *):	☐ Ja	☐ Nein	Studien-teilnahme nicht möglich
Schriftliches Einverständnis der Mutter:	☐ Ja	☐ Nein	

Urinprobe des Säuglings:	☐ Ja ☐ Nein ☐ Zusendung direkt an die ETH durch die Mutter	Brustmilchprobe der Mutter:	☐ Ja ☐ Nein ☐ Zusendung direkt an die ETH durch die Mutter
1. Ernährungs-fragebogen:	☐ Ja ☐ Nein ☐ Zusendung direkt an die ETH durch die Mutter	Urinprobe der Mutter:	☐ Ja ☐ Nein ☐ Zusendung direkt an die ETH durch die Mutter

ERNÄHRUNG DES SÄUGLINGS

Muttermilch (Stillen, Ausstreichen, Brustpumpe)

1. Hat der Säugling jemals Muttermilch bekommen?		☐ Ja ☐ Nein
1.1. Wenn JA: Bekommt der Säugling immer noch Muttermilch?	☐ Ja, ausschliesslich [1] ☐ Ja, voll [2] ☐ Ja, teilweise [3]	I___I Mal pro Tag *(24h)*
	☐ Nein	

[1] keine andere Flüssigkeit oder Nahrung als Muttermilch
[2] Muttermilch und zusätzlich Wasser/ Flüssigkeiten auf wässeriger Basis/ Fruchtsaft, keine Säuglingsmilchnahrung oder andere Nahrung
[3] Muttermilch, Muttermilchersatzpräparate und andere Flüssigkeiten/Nahrungsmittel

Säuglingsmilchnahrung

2. Hat der Säugling jemals Säuglingsmilchnahrung bekommen?		☐ Ja ☐ Nein
2.1. Wenn JA: Bekommt der Säugling derzeit Säuglingsmilchnahrung?	☐ Ja, ausschliesslich (ausser evt. Flüssigkeiten auf wässeriger Basis) ☐ Ja, täglich	I___I Mahlzeiten pro Tag *(24h)*
	☐ Ja, ab und zu	I___I Mahlzeiten pro Woche; I___I Mahlzeiten pro Monat
	☐ Nein	

Halbfeste, feste Nahrung sowie **Flüssigkeiten mit Nährwert** (ausgenommen Fruchtsäfte, Süssgetränke)

3. Bekommt der Säugling bereits halbfeste, feste Nahrung sowie Flüssigkeiten mit Nährwert (zusätzlich zu/ anstelle von Muttermilch/Säuglingsmilch)?		☐ Ja	I___I Mahlzeiten pro Tag		
		☐ Nein			
4. Bekommt der Säugling:		Ja	I___I Mal pro Tag	I___I Mal pro Woche	Nein
a) Milch – Getreide – Breie / Fläschchen	mit Säuglingsmilch				
	mit Kuhmilch (+ Wasser)				
b) Kuhmilch (ohne Getreidezusatz)	verdünnt				
	unverdünnt				
c) Gemüse - Kohlenhydrat (- Fleisch) – Mahlzeiten (ohne Milch)					
d) Obst (- Getreide) – Mahlzeiten (ohne Milch)					

5. Bekommt das Kind bereits Speisen vom Familientisch? ☐ Ja, täglich ☐ Ja, ab und zu ☐ Nein

6. Erhält der Säugling bereits Salz in:

a) selbst zubereiteten Mahlzeiten	☐ Ja ⇨ ☐ jodiert ☐ unjodiert ☐ Nicht bekannt ☐ Nein ☐ bekommt keine selbst zubereiteten Mahlzeiten
b) Fertigprodukten (z.B.Gläschen)?	☐ Ja ☐ Nicht bekannt ☐ Nein ☐ bekommt keine Fertigprodukte

7. Verwendet die Mutter im Haushalt Jodsalz zum Kochen? ☐ Ja ☐ Nein ☐ Nicht bekannt

Bemerkungen

Appendix 8: Explanation sheet for individual registration form (infant feeding) – German

„ETABLIERUNG VON REFERENZWERTEN FÜR DIE JODKONZENTRATION IM URIN VON 6- UND 12-MONATIGEN SCHWEIZER KINDERN“

ERLÄUTERUNGEN
zu den Fragen über die „Ernährung des Säuglings“ auf dem persönlichen Registrierungsformular:

- zu **Frage 1.1** und **2.1.:**
  Diese Fragen beziehen sich auf die im Moment aktuelle Form der Ernährung des Säuglings. Die Angabe der Mahlzeiten pro Tag ist die durchschnittliche Anzahl der Gaben von Muttermilch bzw. Säuglingsmilchnahrung, welche der Säugling im Moment erhält.

- zu **Säuglingsmilchnahrung:**
  Darunter verstehen wir Milchnahrungen, die speziell zur Ernährung von Säuglingen bestimmt sind (Muttermilchersatzpräparate d.h. Säuglingsanfangs- und Folgenahrungen sowie Junior-/Wachstumsmilchen).

- zu **Frage 3.:**
  Die Anzahl der Mahlzeiten pro Tag bezieht sich auf alle Mahlzeiten (ausser Muttermilch und Säuglingsmilchnahrung), welche der Säugling aktuell im Durchschnitt täglich erhält. Dies können sowohl speziell für den Säugling zubereitete Mahlzeiten sein als auch Speisen, die er/sie vom Familientisch bekommt.

- zu **Frage 4. a) „Milch – Getreide – Breie/Fläschchen <u>mit Säuglingsmilch</u>:**
  Hierzu zählen sowohl Milch – Getreide – Breie/Fläschchen, bei welchen die Säuglingsmilch zugefügt wird als auch solche, bei welchen die Säuglingsmilch bereits in Pulverform enthalten ist und die nur noch mit Wasser anzurühren sind.

- zu **Frage 4. a) - d):**
  Die genannten Speisen können speziell für den Säugling zubereitet sein oder dem Säugling vom Familientisch gegeben werden.

- zu **Frage 5.:**
  Diese Frage ist separat von Frage 4. zu betrachten und dient uns als Zusatzinformation, ob das Kind bereits einen Teil der Mahlzeiten vom Familientisch erhält.

- zu **Frage 6. a) und b):**
  Hier möchten wir erfragen, ob der Säugling bereits Salz erhält:
  a) in selbst zubereiteten Speisen d.h. in speziell für den Säugling zubereiteten Speisen und/oder solchen, die er vom Familientisch erhält
  b) in Fertigprodukten d.h. das Salz ist bereits im Fertigprodukt enthalten oder wird zugefügt.

- zu **Frage 7.:**
  Kochen ist hier im weiteren Sinne zu verstehen als allgemeine Verwendung von jodiertem Salz im Haushalt durch die Mutter, einerseits zum eigentlichen Kochen, aber auch zum Würzen von Speisen am Tisch.

Appendix 9: Manual for the parents for the sample collection at home – German

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Institut für Lebensmittel- und Ernährungswissenschaften
Labor für Humanernährung
Schmelzbergstr. 7
CH-8092 Zürich

Anleitung für die Eltern zur Probensammlung zu Hause

„Festlegung von Referenzwerten für die Jodkonzentration im Urin von Säuglingen"

Liebe Mutter, liebe Eltern

Im Folgenden möchten wir Ihnen eine Anleitung zur Probensammlung geben.
Die Probensammlung und das Ausfüllen des 1. Fragebogens sollten unbedingt am gleichen Tag erfolgen und nach Möglichkeit am gleichen Tag wie der Arztbesuch.
Wenn Sie Fragen zur Probensammlung haben, können Sie uns gerne jederzeit kontaktieren:

Nadja Wüst
Tel: 044 632 83 93
Natel: 079 340 75 09
Email: nwuest@ethz.ch

Maria Andersson
Tel: 044 632 80 51
Email: maria.andersson@ilw.agrl.ethz.ch

Nach der Probensammlung bitte dieses Antwortformular ausfüllen und mitschicken:

✂----------

Etikette Säugling: ☐
(in der Praxis aufgeklebt)

Im Kuvert befinden sich folgende Proben:

☐ Röhrchen mit Urin des Babys → *Datum der Probensammlung:* .....
☐ Röhrchen mit Urin der Mutter → *Datum der Probensammlung:* .....
☐ Röhrchen mit Muttermilch → *Datum der Probensammlung:* .....

Name Ihres Kinderarztes/-ärztin:.....

PLZ und Ort der Praxis:.....

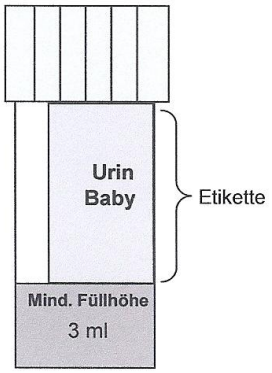
Ihr Name, Telefon-Nummer und E-Mail-Adresse für Rückfragen der ETH Zürich *(optional)*:

.....

1

Sammlung der Urinprobe des Babys

1. Bitte reinigen Sie den Genitalbereich und den After des Babys ohne eine Crème oder Puder zu verwenden.
2. Legen Sie die weisse Stoffbinde *(aus dem mitbekommenen Uricol-Set)* auf die umgekehrte Windel (Innenseite nach aussen) Ihres Babys. Platzieren Sie die Stoffbinde so, dass sie den Urin Ihres Babys gut auffangen kann. Verschliessen Sie die Windel gut.
3. Kontrollieren Sie regelmässig, ob die Stoffbinde bereits nass ist. Sollte sie durch Kot verschmutzt sein, entfernen Sie die Stoffbinde und legen die Ersatzbinde (wie bei 2.) ein.
4. Ist die Stoffbinde nass, entnehmen Sie diese und legen sie mit der nassen Seite nach oben auf eine saubere Fläche.
5. Mit der Plastikspritze aus dem mitgegebenen Uricol-Set nehmen Sie bitte 3 ml Urin *(siehe Graphik, rechts)* wie folgt ab:
   - Halten Sie die Spritze im 45° Winkel und drücken Sie die Spritze in den nassen Teil der Stoffbinde *(siehe Bild 1, unten)*.
   - Ziehen Sie den Kolben der Spritze langsam nach oben *(siehe Bild 2, unten)*. Der Urin wird so aus der Stoffbinde gesaugt.
   - Entleeren Sie die Spritze vorsichtig ins Röhrchen mit dem Etikett **«Urin Baby»** durch langsames Runterdrücken des Kolbens *(siehe Bild 3, unten)*. Achtung, dass das Röhrchen dabei nicht umkippt!
   - Bitte wiederholen Sie diesen Vorgang an verschiedenen nassen Stellen der Stoffbinde solange bis der Urin im Röhrchen bis mindestens zum unteren Rand der Etikette reicht (3 ml) *(siehe Graphik, rechts)*.



Röhrchen in Originalgrösse

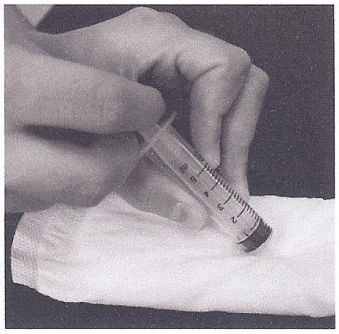


Bild 1: Spritze auf der Stoffbinde aufsetzen (im 45° Winkel)

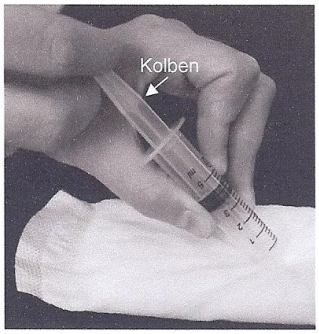


Bild 2: Kolben der Spritze langsam aufziehen

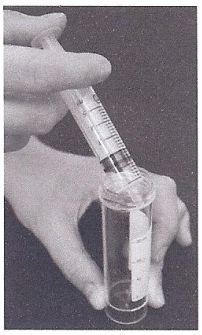


Bild 3: Inhalt ins Röhrchen entleeren. Dieses dabei festhalten!

6. Zum Schluss verschliessen Sie das Röhrchen bitte gut und stellen es bis zum Versand in den Kühlschrank!

2

Sammlung der Urinprobe der Mutter

1. Bitte füllen Sie den mitgegebenen Becher ca. bis zur ersten Markierung (25 ml) mit Ihrem Urin.
2. Den Becher können Sie mit dem roten Schnappdeckel verschliessen.
3. Schneiden Sie dann den vorstehenden Auslauf des Deckels mit einer Schere auf.
4. Danach füllen Sie den Urin in das Röhrchen mit dem Etikett **«Urin Mutter»** bis zur Rille unterhalb des geschlossenen Deckels (10 ml) (*siehe Graphik, rechts*).
5. Zum Schluss verschliessen Sie das Röhrchen bitte gut und stellen es bis zum Versand in den Kühlschrank!

Röhrchen in Originalgrösse

Sammlung der Muttermilch

- Sammeln Sie bitte eine kleine Menge Muttermilch durch **Ausstreichen**: Eine Beschreibung der Technik des Ausstreichens finden Sie auf dem Informationsblatt, welches Ihnen mitgegeben wurde.

1. Die ersten paar Tropfen Milch nehmen Sie bitte mit einem Tuch oder einer (Einweg-)Stilleinlage ab.
2. Anschliessend streichen Sie Muttermilch in den mitgegebenen Becher ca. bis zur Hälfte der ersten Markierung (bei 25ml) aus.
3. Den Becher mit der Milch können Sie mit dem roten Schnappdeckel verschliessen.
4. Schneiden Sie dann den vorstehenden Auslauf des Deckels mit einer Schere auf.
5. Danach füllen Sie die Muttermilch in das Röhrchen mit dem Etikett **«Muttermilch»** bis zur Rille unterhalb des geschlossenen Deckels (10 ml) (*siehe Graphik, rechts*).
6. Zum Schluss verschliessen Sie das Röhrchen bitte gut und stellen es bis zum Versand in den Kühlschrank!

Röhrchen in Originalgrösse

- Falls Sie eine **Brustpumpe** haben, so können Sie auch diese zur Gewinnung der Muttermilch verwenden.

3

Fragebögen

1. Bitte füllen Sie im **1. Fragebogen** möglichst genau aus, was Ihr Baby **am Tag vor der Sammlung der Urinprobe** gegessen hat *(siehe Erklärung auf dem Fragebogen).*

2. **3 - 4 Tage nach der Sammlung der Urinprobe** bitten wir Sie im **2. Fragebogen** auszufüllen, was Ihr Baby **am Vortag gegessen** hat.

Versand an die ETH Zürich

Senden Sie bitte die Röhrchen bzw. die Fragebögen so bald wie möglich mit den vorfrankierten und adressierten Kuverts an die ETH Zürich.
Werden die Röhrchen nicht gleich verschickt, können diese gut verschlossen bis zum Versand im Kühlschrank gelagert werden!

1. Versichern Sie sich bitte, dass alle Röhrchen gut verschlossen sind.
2. Geben Sie jedes Röhrchen in einen kleinen Plastikbeutel (befinden sich im grossen Plastikbeutel) und verschliessen Sie alle Beutel gut.
3. Schneiden Sie bitte das **Antwortformular auf Seite 1** ab und füllen es aus. Das Datum der Probensammlung bitte nicht vergessen!
4. Geben Sie das Antwortformular und die Beutel mit den Röhrchen in das adressierte und vorfrankierte Luftpolsterkuvert und senden dieses an die ETH Zürich.
5. Die Fragebögen (1. und/oder 2.) geben Sie bitte in die adressierten und vorfrankierten C5 Kuverts und schicken diese an die ETH Zürich.

4

Appendix 10: Questionnaire to the pediatrician after study completion – German

„ETABLIERUNG VON REFERENZWERTEN FÜR DIE JODKONZENTRATION IM URIN VON 6- UND 12-MONATIGEN SCHWEIZER KINDERN“

Fragen zur Studiendurchführung nach Abschluss der Studie

(Bitte füllen Sie die grau hinterlegten Felder direkt in Word aus)

Dr. med. **Praxis Nr.:** **Datum Studienstart:** **/ -ende:**

1. Auswahl der Mutter-Säuglingspaare:

a. Wie viele Vorsorgeuntersuchungen hatten Sie etwa insgesamt im Zeitraum der Studie?

bei 6-monatigen Säuglingen, bei 12-monatigen Säuglingen.

b. Wie viel Prozent dieser Säuglinge mussten circa aufgrund der Nicht-Erfüllung der Einschlusskriterien von vornhinein von der Studie ausgeschlossen werden?

% 6-monatige Säuglinge, % 12-monatige Säuglinge

☐ Es wurde *keine* vorangängige Abklärung der Einschlusskriterien vorgenommen.

Welches war diesbezüglich das wichtigste Kriterium für einen Ausschluss (gemäss zu erfüllender Einschlusskriterien)?

c. Welchen Anteil der Mütter/Eltern der (geeigneten) Säuglinge haben Sie etwa gefragt, ob sie an der Studie teilnehmen möchten?

☐ Alle ☐ Fast alle (90%) ☐ etwa 75% ☐ etwa 50% ☐ etwa 25% ☐ < 20%

Wenn nicht alle gefragt wurden, aus welchen Gründen? (*mehrere Antworten möglich)*

☐ Keine Zeit um alle zu fragen
☐ Sprachliche Verständigungsschwierigkeiten
☐ Vermutete schlechte Kooperation (z.B. Nicht-Rücksenden der Proben)
☐ Andere Gründe:

→ *Hauptgrund*:

d. Wie viel Prozent der Mütter/Eltern, welche Sie für eine Studienteilnahme gefragt haben, wollten etwa nicht teilnehmen?

% Mütter/Eltern von 6-monatigen Säuglingen, % Mütter/Eltern von 12-monatigen Säuglingen

Welche Gründe für eine Nicht-Teilnahme hatten diese Mütter/Eltern?

☐ Sprachliche Verständnisschwierigkeiten ☐ Keine Zeit für eine Teilnahme
☐ Inhaltliche Verständnisschwierigkeiten ☐ Zu aufwendig
☐ Allg. kein Interesse an der Studie ☐ Andere Gründe:

→ *Hauptgrund*:

e. Wie viel Prozent der Säuglinge, deren Mütter/Eltern grundsätzlich für eine Teilnahme bereit waren, mussten im Laufe der Studienbesprechung aufgrund einer Nicht-Erfüllung der Einschlusskriterien (mütterlicher-/ säuglingsseits) von der Studie ausgeschlossen werden?

% 6-monatige Säuglinge, % 12-monatige Säuglinge

Welches war diesbezüglich das wichtigste Kriterium für einen Ausschluss (gemäss zu erfüllender Einschlusskriterien)?

2. Information der Mütter/Eltern:

a. Zu welchem Zeitpunkt wurden die Mütter normalerweise über die Studie informiert (mittels Informationsblatt und/oder mündlich)?

- ☐ Mitgabe des Informationsblattes bei einer vorangängigen Untersuchung
- ☐ Bei Ankunft in der Praxis am Tag der Vorsorgeuntersuchung
- ☐ Während der Vorsorgeuntersuchung
- ☐ Anderer Zeitpunkt:

b. Bei einer Zusage der Mutter/Eltern zur Studienteilnahme, wann bzw. durch wen wurde dieser/n die konkrete Durchführung der Studie erklärt?

☐ vor ☐ während ☐ nach der Vorsorgeuntersuchung

durch ☐ Arzt/Ärztin ☐ MPA ☐ anderes Vorgehen:

c. Welchen Zeitaufwand benötigten Sie in etwa für die Erklärung der Studiendurchführung und das Ausfüllen des persönlichen Registrierungsformulars? Minuten

3. Durchführung der Studie

a. Wie war im Allgemeinen Ihr Eindruck von der Studiendurchführung?

Für Sie: ☐ gut machbar/einfach ☐ in Ordnung/machbar ☐ aufwendig/kompliziert

Für die Mutter/Eltern: ☐ gut machbar/einfach ☐ in Ordnung/machbar ☐ aufwendig/kompliziert

Kommentare:

b. Wer hat in der Regel das persönliche Registrierungsformular mit der Mutter ausgefüllt?

☐ Arzt/Ärztin ☐ MPA ☐ Mutter allein ☐ anderes Vorgehen:

c. Wo hat die Probensammlung stattgefunden?

	Am häufigsten	manchmal	nie
- In der Praxis:	☐	☐	☐
- Bei den Eltern zu Hause & direkte Sendung an die ETH:	☐	☐	☐
- Bei den Eltern zu Hause & Proben/Pad in die Praxis gebracht:	☐	☐	☐

Kommentare:

d. Bei hauptsächlicher Probensammlung zu Hause: Weshalb hat diese zu Hause stattgefunden?

- ☐ Zu viel Zeitbeanspruchung in der Praxis
- ☐ Zu viel Platzbeanspruchung in der Praxis
- ☐ Den Eltern war die Probensammlung zu Hause lieber
- ☐ Andere Gründe:

e. Wie ist Ihr Eindruck von der „Pad"-Methode zur Urinsammlung bei Säuglingen?

☐ sehr gut ☐ gut ☐ in Ordnung ☐ mässig brauchbar ☐ unbrauchbar

Begründung Ihrer Antwort:

f. Könnten Sie sich die „Pad"-Methode als Alternative zur Urinsammlung mit dem Urinbeutel vorstellen? ☐ Ja, auf jeden Fall ☐ Ja, eventuell ☐ Eher nicht ☐ Nein

g. Haben Sie den Eindruck, dass die „Beschreibung zum Ausstreichen von Muttermilch" nützlich war?
☐ Ja ☐ Nein

h. Wo wurde der 1. Fragebogen zur Ernährung des Säuglings hauptsächlich ausgefüllt?
☐ in der Praxis ☐ zu Hause
Wurden beim Ausfüllen in der Praxis die Broschüren zur Säuglingsnahrung angewendet?
☐ Ja, immer ☐ meistens ☐ manchmal ☐ selten ☐ Nie

4. Messung des Körpergewichts / der Körpergrösse der Säuglinge

a. Haben Sie immer die direkt am Tag der Vorsorgeuntersuchung gemessenen Werte des Körpergewichts/-grösse des Säuglings angegeben?
☐ Ja ☐ Nein Wenn nein, weshalb nicht?

b. Welchen Typ/Hersteller von Waage haben Sie verwendet?

c. Welchen Typ/Hersteller des Messgerätes für die Körpergrösse haben Sie verwendet?

5. Jodhaltige Desinfektionsmittel

a. Welche jodhaltigen Desinfektionsmittel/-salben etc. haben Sie in der Zeit der Studie in der Praxis verwendet?
☐ keine

b. Haben Sie diese im Zimmer der Vorsorgeuntersuchung für Säuglinge oder am Ort, wo der Urin vom Pad abgesaugt wurde, angewendet? ☐ Ja ☐ Nein

6. Wissen der Mütter/Eltern zu Jod

a. Wie ist Ihrem Eindruck nach im Allgemeinen das Wissen der Mütter/Eltern über die Bedeutung von Jod für die Entwicklung Ihres Kindes?
☐ sehr gut ☐ gut ☐ in Ordnung ☐ eher schlecht ☐ schlecht
Kommentare:

7. Haben Sie Reaktionen der Mütter/Eltern auf die Studie bekommen? Wenn ja, welche?

8. Anmerkungen zu bestimmten Fragen/allgemeine Bemerkungen/Verbesserungstipps zur Studie:

Herzlichen Dank, dass Sie sich Zeit genommen haben für die Beantwortung der Fragen.

Appendix 11: Dietary questionnaire (first) – German

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Etikette:

Datum: _____

1. Fragebogen zur Ernährung des Säuglings am Vortag

Vorname des Babys: _____ **Geburtsdatum:** | | | | | | | | |

Kinderarzt/-ärztin: _____ **m** | **w**

Wir möchten Sie gerne fragen, was Ihr Baby **GESTERN** gegessen und getrunken hat.
Bitte versuchen Sie sich an ALLE LEBENSMITTEL UND GETRÄNKE zu erinnern, die Sie Ihrem Baby GESTERN gegeben haben. Es ist wichtig, dass Sie den Fragebogen so genau wie möglich ausfüllen, damit wir die Nährstoffaufnahme Ihres Babys richtig berechnen können.

Wenn Sie gestern nicht den ganzen Tag mit Ihrem Baby verbracht haben und daher vielleicht nicht über alles Bescheid wissen, was Ihr Baby GESTERN gegessen hat (z.B. weil es in der Krippe war), füllen Sie den Fragebogen bitte am nächstmöglichen Tag aus.

- Wochentag und Datum von **gestern**: _____
- Wo bzw. bei wem hat Ihr Baby **gestern** den Tag verbracht? *(bitte ankreuzen)*

	Zuhause		Ausser Haus		Gross-eltern	Kinder-krippe	Tagesmutter-/familie	Anderes? (bitte angeben)
	Mutter	Vater	Mutter	Vater				
Morgen								
Vormittag								
Mittag								
Nachmittag								
Abend								

- Um welche Uhrzeit etwa haben Sie Ihrem Baby **gestern** das ERSTE Mal [____:____h] / das LETZTE Mal [____:____h] etwas gefüttert (Stillen/ Schoppen/ Brei/ feste Nahrung)? [*Gestern von 0h bis 24h*]

I. MUTTERMILCH (Stillen/Abpumpen/Ausstreichen)

- Wie oft haben Sie Ihrem Baby **gestern** Muttermilch gegeben? _____ *Mal* *Nie* ☐

  ↳ UND zu welchen Tageszeiten haben Sie **gestern** Muttermilch gegeben?

  *(bitte **entsprechende ANZAHL pro TAGESZEIT** eintragen)*

Morgen (0 – 8h)	*Vormittag* (8 – 11h)	*Mittag* (11 – 14h)	*Nachmittag* (14 – 17h)	*Abend* (17 – 21h)	*Nacht* (21 – 24h)

Bei STILLEN: *Trink**dauer pro Stillmahlzeit** in* [**Minuten**]

Bei ABPUMPEN/AUSSTREICHEN: ***pro Mahlzeit** getrunkene **Menge Muttermilch*** in [**ml**]

1

II. SÄUGLINGSMILCHNAHRUNG & andere MILCHNAHRUNG im SCHOPPEN/TRINKBECHER

- Wie oft haben Sie Ihrem Baby **gestern** einen Schoppen/Trinkbecher mit Säuglingsmilchnahrung *oder* anderer Milchnahrung gegeben? _____ *Mal* *Nie* ☐

  ↳ UND zu welchen Tageszeiten haben Sie dies **gestern** gegeben?
  *(bitte **entsprechende ANZAHL pro TAGESZEIT** eintragen)*

Morgen (0 – 8h)	*Vormittag (8 – 11h)*	*Mittag (11 – 14h)*	*Nachmittag (14 – 17h)*	*Abend (17 – 21h)*	*Nacht (21 – 24h)*

- Welche Art und Menge Schoppen/Trinkbecher mit Säuglingsmilchnahrung *oder* anderer Milchnahrung haben Sie Ihrem Baby **gestern** gegeben? *(bitte so genau wie möglich in die Tabelle eintragen)*

Tages-zeit	**Marke** + gekauft bei…	**PRODUKTbezeichnung** (möglichst genau!) + **Anzahl** zur Zubereitung verwendete **Mess-/Ess-/Teelöffel**	**Zubereitet mit:** *z.B. Wasser, Kuhmilch, Säuglingsmilch etc.* → genaue **Bezeichnung, Marke** + verwendete **Menge [ml]**	**davon getrunkener Anteil**
Beispiel: *Morgen*	*HIPP (Coop)*	*Bio-Folgemilch, HIPP 2, 7 Messlöffel*	*Wasser, 200 ml*	*alles (220ml)*

III. BREIE, HALBFESTE/FESTE NAHRUNG (mit dem Löffel gegeben)

A) SELBST ZUBEREITETE MAHLZEITEN: - aus **gekochten** Lebensmitteln z.B. Gemüse-Kartoffel-Fleisch-Brei
Nudeln mit Gemüse
& kleine Zwischenmahlzeiten
- aus **rohen** Lebensmitteln z.B. Früchte-Brei
Gemüse + Käse + Brot

▪ Wie oft haben Sie Ihrem Baby **gestern** selbst zubereitete Mahlzeiten gegeben? _____ *Mal* *Nie* ☐

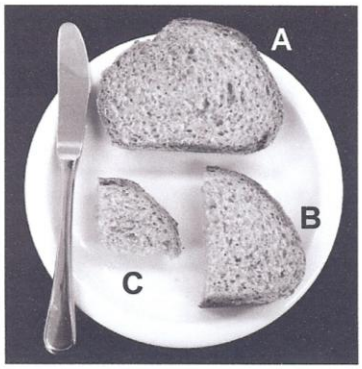
↳ UND zu welchen Tageszeiten haben Sie diese **gestern** gegeben?
*(bitte **entsprechende ANZAHL pro TAGESZEIT** eintragen)*

Morgen (0 – 8h)	*Vormittag (8 – 11h)*	*Mittag (11 – 14h)*	*Nachmittag (14 – 17h)*	*Abend (17 – 21h)*	*Nacht (21 – 24h)*

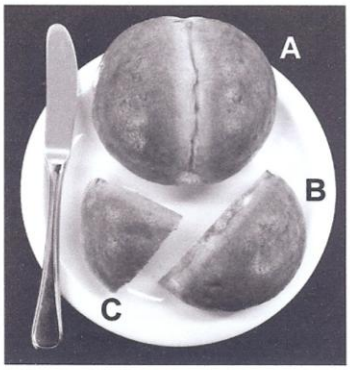
▪ Haben Sie Ihrem Baby **gestern** kleine Zwischenmahlzeiten wie ein Stück frisches Obst/Gemüse oder Brot/ Biskuit/ Zwieback etc. gegeben? *Ja* ☐ *Nein* ☐

⇨ Gebrauchen Sie bitte folgende **Mengenangaben** beim Eintragen der selbst zubereiteten Mahlzeiten bzw. kleinen Zwischenmahlzeiten auf der **nächsten Seite (Seite 4):**

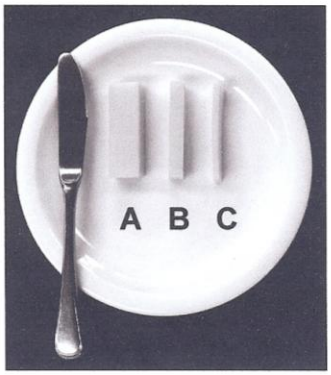
☆ - Mengenangabe bei Brot, Käse: *Wenn ihr Baby gestern Brot oder Käse gegessen hat, tragen Sie bitte den Buchstaben der zutreffenden Grösse auf Seite 4 ein.*



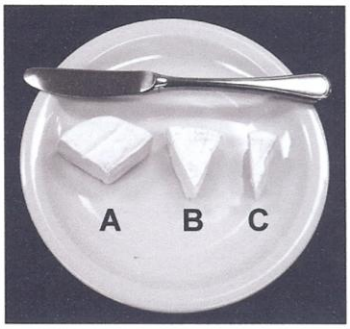
Brot, Scheibe: Grösse A, B, C



Brötchen, Stück: Grösse A, B, C



Halbhart-/Hartkäse, Stück: Grösse A, B, C



Weichkäse, Stück: Grösse A, B, C

3

Fortsetzung von Seite 3:

☆ - Für die Zubereitung der selbst zubereiteten Mahlzeiten **verwendete Zutaten** wenn möglich in **g** bzw. **ml** angeben oder bei:

Obst/ Gemüse/ Kartoffel:	klein / mittel / gross
Flüssigkeiten/ Öl:	Esslöffel / Teelöffel
Butter:	Teelöffel
Griess/ Flocken/ Reis/ Mais:	Esslöffel / Teelöffel
Nudeln:	Esslöffel / Stückzahl
Fleisch/ Fisch/ Geflügel:	Esslöffel / mundgerechte Stückchen
Joghurt/ Quark:	Esslöffel / Teelöffel / Becher
Käse:	→ ***Foto!** (siehe **Seite 3**)*
Brot:	→ ***Foto!** (siehe **Seite 3**)*

- Falls Sie die angegebene Menge für mehrere Mahlzeiten gekocht haben, geben Sie bitte an für wie viele.
- *Breie aus Pulver zum Anrühren*: bitte im Fragebogen auf Seite 7 eintragen!

▪ Beschreiben Sie bitte mit Hilfe der obigen Mengenangaben möglichst genau alle verwendeten Zutaten (einzelne Lebensmittel) der SELBST ZUBEREITETEN MAHLZEITEN, die Sie Ihrem Baby **gestern** gegeben haben UND geben Sie bitte auch kleine ZWISCHENMAHLZEITEN an z.B. ½ Apfel, Scheibe Brot.

⇨ **!Vor dem Ausfüllen!:** Beachten Sie bitte die **Angabe der MENGEN** ☆ oberhalb und auf Seite 3!

Tageszeit	**ALLE ZUTATEN** der Mahlzeit (bei der Zubereitung verwendete einzelne Lebensmittel/ Produkte) + zur Zubereitung verwendete **MENGEN** (so genau wie möglich → *siehe oben & Seite 3!)* + **SORTE / MARKE** des Lebensmittels ☆	**Speise gesalzen** (ja/nein)	**Zubereitung**	**davon gegessener Anteil**
Beispiel: *Mittag*	*- ½ grosse Karotte* *- 1 mittlere Kartoffel* *- 1 Esslöffel Rapsöl* *- 1 kleines Stück Ruchbrot → Grösse: ½ C*	*nein*	*gekocht, püriert*	*3/4*

▪ WENN Sie **gestern** Salz zur Zubereitung verwendet haben: ☐ *jodiertes* ☐ *nicht jodiertes* ☐ *weiss nicht*

Marke oder Aussehen (Farbe) der Verpackung *(gekauft bei...)*: _____

4

B) FERTIGPRODUKTE

(1) DIREKT ESSFERTIGE Fertigprodukte (z.B. im Gläsli, Becher):

- Wie oft haben Sie Ihrem Baby **gestern** direkt essfertige Fertigprodukte gegeben? ____*Mal* *Nie* ☐

  ↳ UND zu welchen Tageszeiten haben Sie **gestern** direkt essfertige Fertigprodukte gegeben?
  *(bitte **entsprechende ANZAHL pro TAGESZEIT** eintragen)*

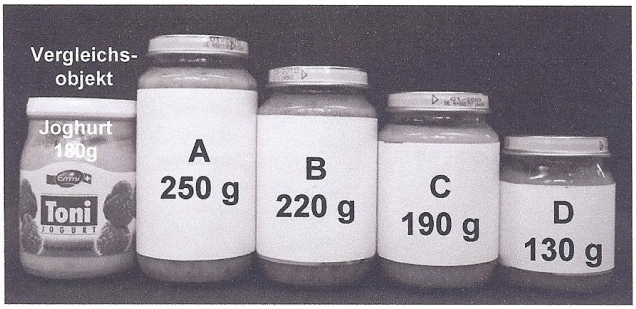
Morgen (0 – 8h)	*Vormittag* (8 – 11h)	*Mittag* (11 – 14h)	*Nachmittag* (14 – 17h)	*Abend* (17 – 21h)	*Nacht* (21 – 24h)

- Welche direkt essfertigen Fertigprodukte haben Sie Ihrem Baby **gestern** gegeben
  z.B. im Gläsli, Becher (kein Anrühren mit Flüssigkeit nötig)? *(bitte so genau wie möglich in die Tabelle eintragen)*

Tageszeit	**Marke** + gekauft bei…	**PRODUKTNAME** (möglichst genau) + **Gewicht/Grösse** des Produkts → *Angaben Gläschen siehe **Foto** (unten)!* + auf dem Produkt angegebene **Altersstufe**	**davon gegessener Anteil**	Zusätzlich ergänzt mit (eventuell):
Beispiel: *Nachmittag*	*Galactina (Coop)*	*Apfel-Banane mit Reis, Gläschen, 190 g → Grösse: C, nach 4 Monaten*	*2/3*	*2EL Joghurt, nature*

- Haben Sie Ihrem Baby **gestern** direkt essfertige Fertigprodukte gegeben, welche Salz enthalten? *Ja* ☐ *Nein* ☐ *weiss nicht* ☐

⇨ **Hilfe zur Mengenangabe bei Gläschen:**



Gläschennahrung, im Handel erhältliche Grössen A, B, C, D

Bitte tragen Sie den Buchstaben der zutreffenden Grösse des Gläschens in der Tabelle (oben) ein.

5

(2) BREIE aus PULVER zum ANRÜHREN mit Flüssigkeit**:**

- Wie oft haben Sie Ihrem Baby **gestern** Breie aus Pulver zum Anrühren gegeben? ____ *Mal* *Nie* ☐

  ↳ UND zu welchen Tageszeiten haben Sie **gestern** Breie aus Pulver zum Anrühren gegeben?

  *(bitte **entsprechende ANZAHL pro TAGESZEIT** eintragen)*

Morgen (0 – 8h)	*Vormittag (8 – 11h)*	*Mittag (11 – 14h)*	*Nachmittag (14 – 17h)*	*Abend (17 – 21h)*	*Nacht (21 – 24h)*

- Welche Breie aus Pulver zum Anrühren haben Sie **gestern** gegeben?

  (bitte so genau wie möglich in die Tabelle eintragen)

Tages-zeit	**Marke** + gekauft bei…	**PRODUKTbezeichnung** (möglichst genau!) + **Anzahl** zur Zubereitung verwendete **Mess-/Ess-/Teelöffel**	**Zubereitet mit:** *z.B. Wasser, Kuhmilch, Säuglingsmilch etc.* → genaue **Bezeichnung, Marke** + verwendete **Menge** [Mess-/Ess-/Tee**löffel** bzw. **ml**]	Ergänzt mit (eventuell)	**davon gegessener Anteil**
Beispiel: *Abend*	*Milupa (Apotheke)*	*Drei Korn Brei, 7 Messlöffel*	*Säuglingsmilch, BEBA 1 pro, 6 Messlöffel + 180 ml Wasser*	*1/2 Apfel*	*alles*

IV. WEITERE LEBENSMITTEL

- Hat Ihr Baby **gestern** weitere Lebensmittel gegessen, welche Sie bisher noch nicht genannt haben? *Ja* ☐ *Nein* ☐

  ➢ Wenn JA: Bitte beschreiben Sie diese möglichst genau in der Tabelle:

Tageszeit	**Marke** + gekauft bei…	**Produktname** (möglichst genau)	**Gegessene Menge**	*Anmerkungen:*

V. GETRÄNKE

▪ Hat Ihr Baby **gestern** andere Getränke ausser Muttermilch/Säuglingsmilch getrunken? *Ja* ☐ *Nein* ☐

➢ Wenn JA:
Welche Getränke hat Ihr Kind **gestern** getrunken?
(falls bereits bei Frage zu Milchnahrungen im Schoppen (II.) genannt, bitte hier nicht wiederholen!)

Leitungs-wasser	*Mineral-wasser*	*Früchte-/ Kräutertee*	*Frucht-/ Gemüsesaft*	*Kuhmilch **un**verdünnt*	*Kuhmilch verdünnt*	*Anderes (Was?)*
☐	☐	☐	☐	☐	☐	----------

Wie oft hat Ihr Baby vom jeweiligen Getränk getrunken? ***[Anzahl]***

☐	☐	☐	☐	☐	☐	----------

Wie viel hat Ihr Baby vom jeweiligen Getränk **insgesamt** getrunken? *[ungefähre **Menge** in **mL** oder **dL**]*

☐	☐	☐	☐	☐	☐	----------

(Total: Milch + Wasser)

Verdünnungsverhältnis: ☐

▪ Hat Ihr Baby **gestern** gegessen/getrunken wie an einem durchschnittlichen Tag? *Ja* ☐ *Nein* ☐

➢ Wenn NEIN: Wieso? _____

VI. FRAGEN AN DIE MUTTER

Alter: _____ *Jahre* Nationalität: _____ Kanton des Wohnorts: _____

Anzahl Kinder: _____ Alleinerzieherin: *Ja* ☐ *Nein* ☐ Raucherin: *Ja* ☐ *Nein* ☐

Berufstätigkeit: *Vollzeit (90-100%)* ☐ *Teilzeit (20-80%)* ☐ *Stundenweise* ☐ *Nicht berufstätig* ☐

Ausbildung/ Beruf: _____

Optional: Name: _____ Telefonnummer: _____
(für Rückfragen der ETH Zürich) Email-Adresse: _____

WIR BEDANKEN UNS HERZLICH FÜR IHRE TEILNAHME!

BEMERKUNGEN zu bestimmten Fragen (bitte genau beschreiben zu welcher Frage):

.....
.....
.....
.....
.....
.....
.....

KONTAKTDATEN der ETH Zürich bei Fragen zum Ausfüllen des Fragebogens:

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Appendix 12: Defined quantities of foods on pictures in the dietary questionnaire (see dietary questionnaire, page 3)

Kind of food	Measuring unit	Defined quantity [g]	*Data source* [a]
• **Bread ("Ruchbrot")**	A (= medium slice)	40	*1*
	B (= ½ medium slice)	20	*2*
	C (= ¼ medium slice)	10	*2*
• **Bread roll ("Weggli")**	A (= medium slice)	60	*1*
	B (= ½ medium slice)	30	*2*
	C (= ¼ medium slice)	15	*2*
• **Hard / Semi-hard cheese**	A (= medium slice)	25	*1*
	B (= ½ medium slice)	12.5	*2*
	C (= ¼ medium slice)	6.25	*2*
• **Soft cheese**	A (= medium slice)	30	*1*
	B (= ½ medium slice)	15	*2*
	C (= ¼ medium slice)	7.5	*2*

[a] *Data source: 1 = Quantity definitions in EBISpro*
2 = Calculated from measuring unit A

Appendix 13: Defined measurement units for data entry of dietary questionnaires

Type of food	Food	Measuring unit	Defined weight [g]	*Data source*
Bread/ rusks/ biscuits	Bread	→ see Appendix 12		
	Microc (Migros)	slice	**5**	*1*
	Pancroc Weizen (Roland)	slice	**6**	*Producer*
	Rice cake	piece	**9**	*1*
	Rusk (Stück)	piece	**5**	*1, 2*
	Crispbread	piece	**9**	*2*
	Biscuit (Petit Beurre)	piece	**7**	*5*
Cereal-products	Cereal	teaspoon, medium	**3**	*5*
		tablespoon, medium	**8.5**	*3*
	Cereal, instant	tablespoon, level	**2.5**	*3*
	Semolina (raw)	teaspoon, medium	**4**	*5*
		tablespoon, medium	**12**	*5*
	Semolina (cooked)	teaspoon	**8**	*5*
		tablespoon	**24**	*5*
	Semolina porridge	ladle	**100**	*1*
	Rice (raw)	teaspoon	**5**	*2*
		tablespoon	**15**	*2*
	Rice (cooked)	teaspoon, medium	**6**	*5*
		tablespoon, medium	**20**	*5*
	Egg spaetzle	piece	**2**	*5*
		tablespoon	**16**	*5*
	Elbow pasta (raw)	tablespoon	**11**	*5*
	Elbow pasta (cooked)	tablespoon	**13**	*5*
	100g raw elbow pasta	→ cooked	**230**	*4*
	Penne pasta	piece, small, raw	**1.2**	*5*
		piece, small, cooked	**2.2**	*5*
		tablespoon, raw	**9.5**	*5*
		tablespoon, cooked	**13**	*5*
	100g raw penne pasta	→ cooked	**260**	*4*
Vegetables	String beans	tablespoon	**20**	*1*
	Fennel	piece, small	**175**	*3*
		piece, medium	**200**	*1*
	Cucumber	slice, thin	**3**	*1*
		slice, medium	**12**	*5*
		slice, thick	**18**	*1*
	Carrot	piece, small	**50**	*5*
		piece, medium	**80**	*2*
	Carrot (fresh, cooked)	tablespoon	**28**	*1*
	Potato (cooked, peeled)	piece, small	**70**	*2*
		piece, medium	**90**	*2*
	Potato puree	teaspoon, medium heaped	**9.5**	*5*
		tablespoon, medium heaped	**27**	*5*
		tablespoon, heaped	**35**	*3*
		tablespoon, level	**15**	*3*
	Vegetable puree	teaspoon, medium	**8**	*5*
		tablespoon, medium heaped	**22**	*5*

Type of food	Food	Measuring unit	Defined weight [g]	*Data source*
Vegetables	Vegetable puree	tablespoon, heaped	**35**	*3*
		tablespoon, level	**15**	*3*
	Kohlrabi	piece, medium	**160**	*3*
	Sweet corn	tablespoon, heaped	**25**	*1*
	Beet root	piece, medium/normal	**150**	*1*
	Spinach	tablespoon	**30**	*1*
	Tomato puree	tablespoon	**20**	*1*
	Tomato sauce	tablespoon	**20**	*1*
	Zucchini	slice, medium, raw	**10**	*5*
		tablespoon, raw	**20**	*5*
		tablespoon, cooked	**25**	*1*
	Onion	teaspoon	**5**	*2*
Fruits	Apple/pear	piece, small	**90**	*1*
		piece, medium	**135**	*1*
		piece, large	**180**	*1*
		slice, medium	**21**	*5*
	Banana (mini)	piece	**40**	*1*
	Banana	piece, medium/normal	**125**	*Mean of 1, 2*
	Banana (cooked)	tablespoon	**30**	*1*
	Blueberry	piece	**3**	*1*
	Raspberry	piece	**5**	*1*
	Mandarin	piece, medium	**50**	*Mean of 1, 2*
		slice	**6**	*Deduced form piece*
	Orange	piece, medium	**150**	*1*
	Raisin	teaspoon	**7**	*2*
		tablespoon	**20**	*2*
	Grape	piece	**4.5**	*Mean of 1, 2*
	Plum	piece, medium	**35**	*1*
	Apricot	piece, medium	**45**	*1*
	Peach	piece, medium	**110**	*1*
	Orange/apple juice	teaspoon	**5**	*5*
		tablespoon	**10**	*5*
	Fruit puree	teaspoon, medium	**9.5**	*5*
		tablespoon, small/level	**18**	*5*
		tablespoon, medium	**25**	*5*
		tablespoon, heaped	**35**	*3*
Nuts	Walnut	piece	**3**	*Mean of 1, 2*
Milk-products	Hard/semi hard cheese	see → Appendix 12		
	Cheese (grated)	teaspoon	**3**	*2*
		tablespoon	**9**	*2*
	Soft cheese	see → Appendix 12		
	Cream cheese/curd	teaspoon, medium	**12.5**	*2*
		teaspoon, heaped	**15**	*5*
		tablespoon, medium	**25**	*2*
		tablespoon, heaped	**30**	*1*
		spread, medium	**15**	*1*
	Cottage cheese	teaspoon, heaped	**10.5**	*5*
		tablespoon, heaped	**26**	*5*
	Yoghurt	teaspoon, medium	**8.5**	*5*
		tablespoon, medium	**22**	*5*
		cup/jar	**180**	*1*
	Curd	cup, small	**125**	*1*

Type of food	**Food**	**Measuring unit**	**Defined weight [g]**	*Data source*
Milk-products	Curd	cup, large	**140**	*1*
	Petit Suisse (low fat curd)	cup	**100**	*Producer (Coop)*
	Fruchtzwerge/Danonino	cup	**50**	*Producers*
	Cream	teaspoon	**5**	*2*
		tablespoon	**13**	*2*
Fat/oil	Butter	teaspoon	**5**	*1*
		tablespoon	**10**	*2*
		spread, thin	**5**	*1*
	Oil	teaspoon	**5**	*1, 3*
		tablespoon	**10**	*1, 3*
Egg	Egg	medium	**55**	*1*
Meat (-products)	Meat (braised, pureed)	tablespoon	**8.5**	*3*
		piece	**22.5**	*3*
	Bratwurst	piece	**120**	*5*
		slice	**8**	*5*
Sauces	Meat sauce	tablespoon	**20**	*1*
	Curry sauce	tablespoon	**12**	*1*
Sugar/ sweets	Jam/honey	teaspoon	**10**	*2*
		tablespoon	**20**	*2*
	Sugar	teaspoon	**5**	*2*
		tablespoon	**15**	*2*
Salt	salt	pinch of salt	**0.25**	*5*

[*] *Data sources: 1 = EBISpro; 2 = Swiss Food Composition Database (Infanger, 2004); 3 = (Wachtel, 1990); 4 = (Zacharias and Deutsche Gesellschaft für Hauswirtschaft, 1992); 5 = defined by ETH Zürich*

Appendix 14: “Schweizer Berufsnomenklatur, SBN 2000” & UNESCO “International Standard Classification of Education” (ISCED)

“Schweizer Berufsnomenklatur, SBN 2000” (Bundesamt für Statistik, 2000)

The SBN classifies professions into the following 9 groups of occupation:

1. Agricultural and forestry occupations, professions of stock-breeding
2. Production occupations in industry and commerce (excl. construction)
3. Technical and computer science professions
4. Professions of the construction industry and mining
5. Trade and transport professions
6. Professions of the hotel/restaurant industry and for the provision of personal services
7. Occupations of management and administration, banking and insurance industry and the legal system
8. Health, educational and cultural professions, scientists
9. Non-classifiable data

UNESCO “International Standard Classification of Education” (ISCED)

(UNESCO Institute for Statistics, 2006)

The levels are defined as following:

1 = Primary education or first stage of basic education (compulsory school)
2 = Lower secondary or second stage of basic education (I) (compulsory school)
3 = (Upper) secondary education (II): 3A: „Matura“, 3B: „Fachmittelschule“, 3C: Vocational education
4 = Post-secondary non-tertiary education
5 = First stage of tertiary education: 5A: University/university of applied sciences (“Hochschule”), 5B: Higher vocational education (“Höhere Berufsbildung”),
6 = Second stage of tertiary education (doctorate)

Appendix 15: Z-scores of child growth references (calculated with WHO Anthro program)

Z-scores

Boys and girls	**Age groups**	**n**	**% < -3SD**	**% < -2SD**	**% > +1SD**	**% > +2SD**	**% > +3SD**	**Mean**	**SD**
Weight-for-length/height **(WHZ) (%)**	Total	339	0	2.1	14.7	2.1	0.6	0.06	0.98
	6-mo	179	0	2.2	10.6	2.2	0.6	-0.1	0.96
	12-mo	160	0	1.9	19.4	1.9	0.6	0.24	0.97
Length/height-for-age **(HAZ) (%)**	Total	339	0	2.1				0.12	1.06
	6-mo	179	0	1.7				0.12	1.04
	12-mo	160	0	2.5				0.13	1.08
Weight-for-age **(WAZ) (%)**	Total	339	0	0.9				0.06	0.93
	6-mo	179	0	0.6				-0.09	0.9
	12-mo	160	0	1.3				0.23	0.94
BMI-for-age **(BAZ) (%)**	Total	339	0	2.7	13	2.7	0.6	-0.01	1
	6-mo	179	0	3.4	7.8	2.2	0.6	-0.21	0.96
	12-mo	160	0	1.9	18.8	3.1	0.6	0.22	0.99
Boys									
Weight-for-length/height **(WHZ) (%)**	Total	181	0	1.7	16	1.7	0.6	0.05	0.99
	6-mo	88	0	2.3	10.2	1.1	0	-0.21	0.95
	12-mo	93	0	1.1	21.5	2.2	1.1	0.3	0.97
Length/height-for-age **(HAZ) (%)**	Total	181	0	1.7				0.16	1.1
	6-mo	88	0	1.1				0.11	1.05
	12-mo	93	0	2.2				0.21	1.16
Weight-for-age **(WAZ) (%)**	Total	181	0	0				0.08	0.97
	6-mo	88	0	0				-0.17	0.89
	12-mo	93	0	0				0.32	0.98
BMI-for-age **(BAZ) (%)**	Total	181	0	2.8	15.5	2.2	0.6	-0.01	1.01
	6-mo	88	0	4.5	8	1.1	0	-0.31	0.95
	12-mo	93	0	1.1	22.6	3.2	1.1	0.27	0.99
Girls									
Weight-for-length/height **(WHZ) (%)**	Total	158	0	2.5	13.3	2.5	0.6	0.06	0.97
	6-mo	91	0	2.2	11	3.3	1.1	0	0.96
	12-mo	67	0	3	16.4	1.5	0	0.15	0.98
Length/height-for-age **(HAZ) (%)**	Total	158	0	2.5				0.08	1
	6-mo	91	0	2.2				0.13	1.03
	12-mo	67	0	3				0	0.97
Weight-for-age **(WAZ) (%)**	Total	158	0	1.9				0.04	0.89
	6-mo	91	0	1.1				-0.01	0.9
	12-mo	67	0	3				0.11	0.88
BMI-for-age **(BAZ) (%)**	Total	158	0	2.5	10.1	3.2	0.6	0	0.99
	6-mo	91	0	2.2	7.7	3.3	1.1	-0.11	0.97
	12-mo	67	0	3	13.4	3	0	0.14	1

Appendix 16: UIC [µg/l] of infants by pediatric practice

Region	Practice No.	6-mo [n]	12-mo [n]	Total [n]	UIC of infants [µg/l]		
					Median	Min	Max
Lake Geneva	**12**	3	1	4	**76.3**	47.3	110.7
Espace Mittelland	**13**	4	1	5	**85.6**	26.6	112.7
	14	10	6	16	**67.5**	21.9	210.0
	17	10	4	14	**67.4**	34.8	291.3
Northwestern Switzerland	**2**	9	5	14	**110.9**	32.4	745.0
	3	13	18	31	**94.7**	11.4	763.1
	16	5	4	9	**71.2**	18.5	271.5
Zurich	**1**	14	11	25	**101.7**	17.4	219.9
	5	8	5	13	**112.0**	20.4	452.1
	7	2	0	2	**182.9**	21.8	344.0
	11	2	4	6	**76.4**	26.8	180.8
Eastern Switzerland	**4**	31	30	61	**82.6**	6.4	370.6
	9	3	11	14	**112.6**	31.0	306.6
	18	8	9	17	**68.8**	30.8	190.8
Central Switzerland	**6**	30	32	62	**97.5**	15.8	417.1
	10	19	10	29	**101.2**	42.7	372.6
Ticino	**8**	8	9	17	**184.3**	51.9	504.0
TOTAL		179	160	339	**93.2**	6.4	763.1

Appendix 17: UIC [µg/l] of mothers by pediatric practice

Region	**Practice No.**	**Non-lactating** [n]	**Lactating** [n]	**Total** [n]	**UIC of mothers [µg/l]**		
					Median	Min	Max
Lake Geneva	**12**	2	2	4	**50.6**	16.7	143.7
Espace Mittelland	**13**	1	4	5	**58.5**	32.3	310.1
	14	11	5	16	**117.2**	33.1	230.7
	17	7	7	14	**91.2**	16.6	244.4
Northwestern Switzerland	**2**	14	2	16	**100.1**	6.4	403.0
	3	22	11	33	**69.1**	25.2	305.4
	16	4	5	9	**146.2**	10.0	243.3
Zurich	**1**	15	10	25	**88.3**	20.5	232.5
	5	7	6	13	**55.4**	24.5	159.8
	7	1	1	2	**146.0**	132.1	159.9
	11	6	0	6	**112.6**	28.6	149.6
Eastern Switzerland	**4**	38	23	61	**71.5**	9.1	312.1
	9	9	5	14	**101.7**	9.7	138.9
	18	12	5	17	**51.1**	20.2	174.6
Central Switzerland	**6**	37	24	61	**100.2**	11.0	213.3
	10	14	15	29	**64.1**	12.2	191.4
Ticino	**8**	12	6	18	**104.8**	64.3	142.7
TOTAL		212	131	343	**81.1**	6.4	403.0

Appendix 18: BMIC [µg/kg] of mothers by pediatric practice

Region	**Practice No.**	**6-mo** [n]	**12-mo** [n]	**Total** [n]	**BMIC [µg/kg]**		
					Median	Min	Max
Lake Geneva	**12**	2	0	2	**58.8**	57.8	59.8
Espace Mittelland	**13**	4	0	4	**52.9**	25.9	68.4
	14	4	1	5	**41.8**	18.5	112.3
	17	5	2	7	**56.7**	35.6	84.5
Northwestern Switzerland	**2**	2	0	2	**44.1**	37.3	50.8
	3	6	4	10	**58.8**	36.1	127.1
	16	3	2	5	**60.0**	18.6	147.7
Zurich	**1**	8	1	9	**46.7**	10.7	74.3
	5	2	0	2	**34.1**	28.1	40.0
	7	1	0	1	**41.7**	41.7	41.7
	11	0	0	0	**--**	--	--
Eastern Switzerland	**4**	19	3	22	**57.7**	15.5	128.2
	9	3	2	5	**38.2**	32.1	65.8
	18	5	0	5	**31.3**	18.0	55.1
Central Switzerland	**6**	17	3	20	**44.0**	23.9	108.3
	10	13	2	15	**63.5**	21.2	123.5
Ticino	**8**	1	4	5	**64.6**	24.9	145.1
TOTAL		95	24	119	**51.2**	10.7	147.7

Curriculum vitae

Personalien

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Geburtsdatum:	22.02.1982	Geburtsort:	Zürich
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Ausbildung

• *04/2008-05/2010*	Diplomarbeit: *„Assessment of iodine status in 6- and 12-month-old infants and their mothers in Switzerland"* ausgeführt an der Eidgenössischen Technischen Hochschule (ETH) Zürich
• *03/2005-03/2008*	Zweiter Studienabschnitt mit Schwerpunkt „Ernährung & Ökonomie"
• *02/2005*	Abschluss erster Studienabschnitt - 1. Diplomzeugnis
• *10/2002*	Beginn Studium Ernährungswissenschaften, Universität Wien
• *2001/2002*	Architekturstudium, ETH Zürich
• *1994-2001*	Gymnasium, Literargymnasium Rämibühl Zürich, Matura Typus B (Latein)
• *1988-1994*	Grundschule, Zürich

Berufserfahrung

• *04/2008-09/2009*	Labor für Humanernährung, ETH Zürich, Aufbau und Durchführung einer nationalen Studie zur Jodversorgung von Säuglingen und Müttern in der Schweiz
• *Sommer 2007*	Labor für Humanernährung, ETH Zürich, 7 Wochen Praktikum im Bereich Mikronährstoffe
• *05-07, 10/2007*	„HELENA-Projekt", Medizinische Universität Wien, Mitarbeit bei Datenerhebung in Schulen & Dateneingabe
• *01/2007-03/2007*	„Nutrition Day 2007", AKE Wien, Mitarbeit bei Datenerhebung & -auswertung
• *Herbst 2005-Sommer 2006*	Novartis Oncology Wien, laufende Mitarbeit im Produkt-Management
• *Herbst 2005*	Beratung auf der „Fem Vital"-Messe für Nestlé, Wien

• *Sommer 2005*	Institut für Ernährungsbiologie, ETH Zürich, 5 Wochen Unterstützung bei einer Humanstudie (Praktikum)
• *Sommer 2005/ 2006*	Beratung auf der Baby-Expo für Nestlé Alété/Beba, Wien und Graz
• *Sommer 2004 - Sommer 2005*	Application Group, Nestlé Wien, laufende Mitarbeit
• *Sommer 2004*	Application Group, Nestlé Wien,1 Monat Praktikum
• *Sommer 2002*	Klinik Bethanien Zürich, 2 Monate Spitalpraktikum
• *Frühling 2002*	Ernährungsberatung, Bethanien/ Triemli Spital Zürich, 2 mal 3 Tage Schnupperpraktikum
• *Sommer 2001*	Architekturbüro, Vasconi Associés Architectes Paris, 3 Monate Praktikum
• *Winter 2001*	Architekturbüro, atelier ww Zürich, 3 Monate Praktikum

Weiterbildung

• *Ernährung:*	Theorie und Praxis der Lebensmittelsensorik, April 2010, VEÖ-success-Workshop, Wien
	„Richtig essen von Anfang an“, Januar 2010, Tagung, AGES-Akademie, Wien
	XII. Dreiländertagung, September 2008, SGE, DGE, ÖGE, Zürich
	Theory and Practice of Nutritional Science, SS 2008, ETH Zürich
	Nutrition and Chronic Disease, SS 2008, ETH Zürich
• *Englischkurse:*	Universität für Bodenkultur Wien, WS 2007, Englisch Kommunikationskurs
	Englisch Language Centre Boston, 1 Monat Sommer 2006
	Australienaufenthalt, 6 Wochen Herbst 2001
	Interlingua Jersey, 2 Wochen Juli 1999
• *Französischkurse:*	Institut Français de Vienne, WS 2003, Konversationskurs
	Alliance Française Paris, 3 Monate Sommer 2001 ‚Diplôme de Langue Française’

Zusatzqualifikationen

Fremdsprachen	• Englisch: sehr gut (mündlich und schriftlich)
	• Französisch: sehr gut (mündlich und schriftlich)
	• Italienisch: gute Grundkenntnisse
EDV-Kenntnisse	• Word, Excel, Outlook, PowerPoint, SPSS, Endnote, EBISpro

Wien, 2010