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A Review of Spectrophotometric and Chromatographic Methods and Sample Preparation Procedures for Determination of Iodine in Miscellaneous Matrices

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1. Introduction

Why nearly 200 years after the accidental discovery of natural iodine by Bernard Courtois (Dijon, France, 1811) are researchers still intrigued by this element? Why do they constantly search for more sensitive and reliable methods of its determination? During the last 200 years the status of research into the role of iodine in living organisms and the environment has progressed through many phases, from rapture over its interesting properties and healing powers to even some kind of "iodophobia". According to the World Health Organization (WHO), an estimated 2 billion people, including 285 million school-age children, are iodine deficient. And among them, iodine deficiency disorders (IDD) affect some 740 million -- with almost 50 million of them suffering from some form of brain damage resulting from iodine deficiency (United Nations Administrative Committee on Coordination/ Sub-Committee on Nutrition, 2000). On the other hand, it is known that large amounts of iodine are able to block the thyroid's ability to make hormones and worsen infiltration of the thyroid by lymphocytes. According to Teng's studies (Teng et al., 2009) giving iodine to people who had adequate or excessive iodine intake increases the incidence of autoimmune thyroiditis.

It became evident that increasing familiarity with the role of iodine would translate into development and discovery of more and more powerful analytical methods and techniques. Present-day analytical techniques are capable of detecting extremely small quantities. Some of them have become routine ultra-trace measurement tools in analytical and clinical laboratories.

The aim of this review is to explore available information regarding iodine determination in various samples (mainly of biological and environmental origin) focusing on spectrophotometry and chromatography as sensitive and reliable analytical methods of its measurement.

2. Iodine species in nature

Iodine plays an integral role in a diverse array of processes. As such, it exists in a variety of forms reflecting either the environment in which it is found or its biological function. Water,

air, soil and food constitute the most common group of analyzed samples derived from our external environment.

2.1 Water

In water iodine is predominantly found in the iodide (I^-) or iodate (IO_3^-) form (Gilfedder et al., 2007; Schwehr & Santschi, 2003). Other forms of iodine species in water include: IO_4^- (periodate), IO^-(hypoiodite), CH_3I (methyl iodide), CH_2I_2 (methyl diiodide), C_2H_5I (ethyl iodide), C_3H_7I (propyl iodide), C_4H_9I (butyl iodide), and CH_2BrI (methyl iodide bromide) (Hou, 1999, Hou et al., 2009). Organic iodine concentrations may be especially high in fresh water (from rivers, lakes and rain).

2.2 Air

Generally, the air contains iodine in particulate form, as inorganic gaseous iodine (I_2, HIO) and as some forms of organic gaseous iodine (CH_3I, CH_2I_2). High iodine concentrations are found in urban areas due to the combustion of oil and coal. Coastal areas also have high iodine concentration due to the emission of gaseous I_2 from algae, seawater and sea spray, which varies with location, season and climate (Hou, 2009; Yoshida & Muramatsu, 1995). There are numerous pathways that may be responsible for transferring I_2 from the sea to air. Photochemical oxidation of I^- from seawater to elemental iodine has been recreated in the laboratory (Miyake & Tsunogai, 1963). Another means of obtaining elemental I_2 is through the reaction of I^- with ozone (O_3)(Garland & Curtis, 1981). The greatest source of atmospheric I_2 is thought to be from microbial activity within the oceans, through the transformation of I^- and IO_3^- into organic CH_3I, which has a residence time between 1.1-8 days (Cicerone, 1981). Lovelock et al. (Lovelock et al., 1973) measured the mean atmospheric CH_3I concentration above the Atlantic as 1.2 ppt (6.8 ng/m^3). Rasmussen et al. (Rasmussen et al., 1982) found the background level of CH_3I to vary between 1 and 3 ppt (5.7-17 ng/m^3) with measurements near oceans with high biomass productivity to be around 7-22 ppt (40-125 ng/m^3).

2.3 Soil

Strong evidence suggests that atmospheric transport from the oceans is responsible for the deposition of iodine in soil. Iodine exists in various forms in soil and varies largely with respect to its concentration. I^- (more mobile form) is believed to be the dominant species in acidic soils whilst IO_3^- (less mobile) will occur in alkaline soils. In low pH oxidizers, e.g. Fe^{3+} and Mn^{4+} convert I^- into molecular I_2. The activity of reducing bacteria impacts the form of iodine in the soil as well. CH_2I_2 and other volatile organic complexes of iodine are generated by microbial activity (Johnson, C.C. 2003). Generally, organic bound iodine is more abundant in soil samples. The secondary environment (soil) has high iodine content compared to the primary environment (parent rocks) from which it is derived as a result of weathering. Weathered rocks and soils are richer in iodine than the unweathered bedrocks (Fuge & Johnson, 1986). On average, the igneous rocks contain an average of 0.25 mg/kg of iodine, the sedimentary rocks have 2.3 mg /kg iodine and the metamorphic rocks have 0.81 mg/kg of iodine. Organic matter is the major concentrator of iodine in sedimentary basins (Mani et al., 2007). The highest values were found in soil samples from areas close to the coast, where there is high rainfall, and from areas with high soil organic matter. In one study, the iodine concentration in Japanese soils was found to range from 0.2 mg/kg to 150

mg/kg (Muramatsu, 2004). Retention of iodine in the soil is influenced by a number of factors, including the soil pH, moisture content, porosity and composition of the organic and inorganic components (Sheppard et al., 1995; Whitehead, 1984).

2.4 Food and plants

Geographic differences in topsoil iodine content and irrigation procedures determine food iodine levels. In most diets the mainstay sources of iodine are fish, shellfish, milk and iodinated salt. Food supplements constitute an alternative means of obtaining dietary iodine. Fish contain iodine in similar forms to those found in humans. Perhaps the widest assortment of forms is encountered in different species of seaweed. Brown seaweeds contain mostly I^-, however green seaweeds play host to a wide array of organic molecules to which iodine is bound, including numerous proteins and polyphenols. Dietary iodine is obtained from a variety of sources and individual dietary habits contribute to the wide disparity in iodine intake among populations. In 1993, the World Health Organization [WHO] published the first version of the WHO Global Database on Iodine Deficiency with global estimates on the prevalence of iodine deficiency based on total goitre prevalence (TGP), using data from 121 countries. Since the international community and the authorities in most countries where IDD was identified as a public health problem have taken measures to control iodine deficiency, in particular through salt iodization programmes – the WHO recommended strategy to prevent and control IDD (World Health Organization [WHO], 2004). Salt iodization programmes are carried out in more than seventy countries, including the United States of America and Canada. There is a wide variation in the scope of iodine supplement; almost 90% of households in North and South America utilize iodized salt while in Europe and the East Mediterranean regions this figure is less than 50%, with a worldwide figure about 70% (WHO, 2007). WHO, ICCIDD (International Council for the Control of Iodine Deficiency Disorders) and UNICEF (United Nations International Children's Emergency Fund) recommend that the term "iodized" be used to designate the addition of iodine to any substance, regardless of the form. Iodine is commonly added as the I^- or IO_3^- of potassium, calcium or sodium. 70% of salt sold for household use in the U.S.A. is iodized with 100 ppm KI (400 μg iodine per teaspoon) (U.S. Salt Institute, 2007). In Canada all salt must be iodized with 77 ppm KI. Mexico requires 20 ppm levels of iodization. Recommendations for the maximum and minimum levels of iodization of salt are calculated as iodine and determined by local national health authorities in accordance with regional variations in iodine deficiency. In Poland iodine deficiency prophylaxis was first started in 1935. Near the end of the 1940's and 80's, the practice of iodizing table salt was abandoned. A nonobligatory recommendation of iodizing salt took place in 1989. In 1991 the Polish Council for Control of Iodine Deficiency Disorders (PCCIDD) was established and an epidemiological survey performed in 1992-1993, defined Poland as an area with moderated – the seaside region as light – severity of iodine deficiency. In 1996 the production of table salt without the addition of KI was made illegal. An obligatory law was passed, mandating the addition of 30(+/-10) mg of KI per kilogram of salt (Szybiński, 2009). Iodization of salt in Turkey has been mandatory since 1998 and the recommended iodine concentration is 50-70 mg KI/kg or 25-40 mg KIO_3/kg (Gurkan et al., 2004). In Switzerland, iodization of salt was altered three times. Iodization was first introduced in 1922 at 3.75 mg/kg. In 1962 the concentration was doubled and in 1980 it was doubled again giving a present level of 15 mg/kg. Although it's use is voluntary, by 1988, 92% of retail salt and 76% of all salt for human consumption

(including food industry) was iodized. Most other countries add from 10 to 40 μg iodine per gram of salt (10-40 ppm) (Bürgi et al., 1990).

Bread (0.14 mg/kg), milk (0.32 mg/kg), eggs (0.48 mg/kg), meat (0.13 mg/kg), and poultry (0.1 mg/kg) constitute other important sources of iodine (figures in parentheses represent the average iodine content per fresh weight) (Food Standards Agency [FSA], 2000). In certain individuals, medications may contribute to the ingested daily iodine. Examples include amiodarone, an antiarrythmic agent (Fang et al, 2004), iodized intravenous radiographic contrast agents and certain topical antiseptics (Aiba et al., 1999).

When considering multivitamins and mineral supplements as a source of iodine, one can find that the majority of iodine they contain is in the KI or NaI forms. According to Zimmerman's research, iodine concentrations in plant matter can range from as little as 10 μg/kg to 1 mg/kg dry weight (Zimmermann, 2009). This variability is relevant because plant matter affects the iodine content of meat and animal products (Pennington et al., 1995). Iodine content of different seaweed species varies greatly (Teas et al., 2004). Japanese iodine intake from edible seaweeds is relatively high compared to the rest of the world. Having taken into consideration many factors, such as information from dietary records, food surveys, urinalysis and seaweed iodine content, Zava and Zava estimated that the daily iodine intake in Japan averages approximately 1,000 to 3,000 μg/day (Zava & Zava, 2011). In certain diets, seafood is a large source of iodine, containing 2 to 10 times more iodine than meat (Hemken, 1979). Saltwater seafood usually contains significantly more iodine than freshwater food, some edible seaweeds may contain up to 2500 μg iodine per gram (Teas et al., 2004).

Simon et al. (Simon et al., 2002) presented an example of the value of the determination of iodine compounds in fish. The authors analyzed whole-body homogenates of zebrafish (Danio rerio) and tadpoles of the African clawed frog (Xenopus laevis). They detected five previously unknown iodinated compounds and measured the concentrations of I^-, MIT, DIT, T4, T3 and rT3 in these species.

2.5 Human body

In relation to iodine determinations, in clinical practice the most frequent analytical samples include urine, serum, blood, and a variety of tissues. Therefore, some examples of research studies related to iodine determinations in the mentioned matrices are presented below. The bioavailability of organic iodine, especially associated with macromolecules, is low (Hou et al., 2009), whereas I^- and IO_3^- have high bioavailability. According to recent estimates, KI is almost completely absorbed in humans (96.4%) (U.S. Food and Drug Administration [FDA], 2009).

2.5.1 Thyroid

Iodine plays a key structural role in the thyroid hormones of humans and other mammals, primarily in the form of T3 (triiodothyronine) and T4 (thyroxine). In such samples precursor forms such as MIT (monoiodotyrosine) and DIT (diiodotyrosine) or isomer forms such as rT3 (reverse triiodothyronine) may also be measured. Iodine accounts for 65% of the molecular weight of T4 and 59% of the T3. 15–20 mg of iodine is concentrated in the thyroid and hormones with 70% distributed in other tissues. In the cells of these tissues, iodide enters via the sodium-iodide symporter (NIS).

According to Hou (Hou et al. 1997), the contents of iodine expressed as ng/g wet weight tissue±1SD) in five tissues, plus hair, averaged over 9–11 individuals were: the heart (46.6±14.9), liver (170±34), spleen (26±8.6), lung (33.3±10.6), muscle (23.5±14.3), and hair (927±528). In the U.S. population, Okerlund found a mean value of 10 mg iodine per thyroid, with a range of 4-19 mg. In 56 patients suffering from autoimmune thyroiditis but with normal thyroid function, a mean value of 4.8 mg/thyroid was reported. In 13 patients with autoimmune thyroiditis and hypothyroidism, the mean value was 2.3 mg/thyroid (Okerlund, 1997).

Zaichick and Zaichick (Zaichick & Zaichick, 1997) used instrumental neutron activation and X-ray fluorescent analyses to determine the concentration and total iodine content of iodine within thyroids. They obtained 90 samples (at autopsy) from subjects of a broad age spectrum, from 2 to 87 years old and calculated correlations between iodine concentration and age. All their thyroid samples were weighed, lyophilised and homogenised. Iodine was analyzed in approximately 50-mg samples. The mean intrathyroidal iodine concentration (mean +/- S.E.) of a normal subject aged 26-65 averaged 345 +/- 21 μg/g dry tissue in non-endemic goitre region with no obligatory salt iodination. Maximum iodine concentration was found to be 494 +/- 65 μg/g ($P < 0.05$) for the age of 16-25. For the elderly aged over 65 an increase in iodine of 668 +/- 60 μg/g was shown ($P < 0.001$). When comparing the right and left lobes, the authors found no variation in weight, iodine concentration or the total content. An inverse correlation was found between the thyroid weight and intrathyroidal iodine concentration (-0.32, $P < 0.01$).

Tadros et al. (Tadros et al., 1981) determined iodine in 48 normal thyroids obtained at autopsy. According to the authors' findings, the iodine concentration ranged from 0.02 to 3.12 mg/g of tissue with a mean value of 1.03 +/- 0.67 mg/g. In 91 surgical thyroid specimens with a variety of abnormalities they found that iodine concentration was much lower. The samples of thyroids with cancer had the lowest values. Sixteen (76%) of 21 analyzed malignant thyroid specimens had undetectable iodine (less than 0.02 mg/g), whereas 22 (96%) of 23 benign nodules had measurable iodine concentrations. Błażewicz et al. (Błażewicz et al., 2011) examined correlations between the content of iodides in 66 nodular goitres and 100 healthy human thyroid tissues. The authors presented an accurate assessment of the iodine content in the thyroids of patients with a nodular goitre (mean concentration was 77. 1 +/- 14.02 μg/g) and in the thyroids obtained at autopsy - considered as a control group (mean concentration 622.62 +/- 187.11 μg/g -for frozen samples and 601.49 +/- 192.11 μg/g- for formalin fixed samples). Statistical analysis showed approx. 8-fold reduction of iodine concentration in the pathological tissues in comparison with the control group.

Interesting research into iodine content in human thyroids was also conducted by Zabala et al. (Zabala et al., 2009). Their study focuses on the determination of iodine content in healthy thyroid samples on male population from Caracas in Venezuela. The authors aimed at establishing a baseline of iodine content in thyroid glands and hence to compare the iodine thyroid concentration of the Venezuelan population with other countries. Male post-mortem individual samples were analyzed using a spectrophotometric flow injection method, based on the Sandell-Kolthoff reaction. The median intrathyroidal iodine concentration was 1443+/-677 μg/g (wet weight), ranging from 419 to 3430 μg/g, which corresponds to a median of total iodine content of 15+/-8 mg (ranging from 4 to 37). These results were

higher than those values which were found in the literature. No correlation of iodine content with the age or weight of the healthy gland was observed.

2.5.2 Plasma

The inorganic form of iodine represents about 0.5 % of the total plasma iodine. The rest occurs in bound form with specific plasma protein (protein - bound iodine, PBI) which has gained wide use as an indicator of thyroid activity in humans. It has been reported that the total plasma iodine concentration in healthy subjects is between 40 and 80 µg/l. According to Allain's studies when plasma iodine concentrations are below 40 µg/l, hypothyroidism is highly likely, when they are between 80 and 250 µg/l, hyperthyroidism, particularly Graves' disease is probable. Above 250 µg/l – iodine overload is almost certainly indicated (Allain et al., 1993).

2.5.3 Brain

Despite the fact that iodine is one of the most important essential elements, the quantitative data on its concentration in the human brain is really scarce. The nature and site of iodine binding in the human brain is still unknown. The results of Andrasi et al. (Andrási et al., 2004) investigations on iodine distribution between the lipid fraction and in the brain tissue without lipid have indicated that its mean contents vary between 910 ± 147 ng/g dry weight and 281 ± 68 ng/g dry weight depending on the brain region (the highest content was found in susbstantia nigra and the lowest in vermis crebelli).

2.5.4 Hair

Levine et al. (Levine et al., 2007) presented a study on determining iodine concentration in tiny (less than 25 mg) human hair samples. Iodine concentrations from the blinded hair autism study samples ranged from 0.483 to 15.9 µg/g. In Adams' et al. studies (Adams et al., 2006) the mean concentration of iodine in the hair of autistic children has been reported to be lower than in the hair from the control group children. The low level of iodine in the hair of children with autism suggests that iodine could be important in the aetiology of autism, presumably due to its effect on thyroid function.

2.5.5 Human milk

Approximately 80% of iodine in human milk is present as I^-, while, mainly, another six high molecular weight iodine containing molecules (Braetter et al., 1998) account for the remaining 20%. European breast milk samples have been determined to contain 95 ± 60 µg/l total iodine. The total iodine content varied depending on the lactation state, and iodine was associated with fat at approximately 30% and 70% of the low molecular weight fraction (Michalke, 2006). A study of iodine species in milk samples obtained from humans from several different European countries and in infant formulas from different manufacturers was carried out by Fernández-Sanchez and Szpunar (Fernández-Sanchez & Szpunar, 1999). The authors also developed a method to determine iodine in human milk and infant formulas using ICP-MS. In the human milk the values found were between 144 ± 93.2 µg/kg, whereas in the infant formulas the values were 53.3 ± 19.5 (Fernández-Sánchez et al., 2007).

2.5.6 Urine

In urine, iodine occurs as I^-, but some organic species can also be found. Urinary iodine concentration is the prime indicator of nutritional iodine status and is used to evaluate population-based iodine supplementation. In 1994, WHO, UNICEF and ICCIDD recommended median urinary iodine concentrations for populations of 100- 200 μg/l, assuming the 100 μg/l threshold would limit concentrations <50 μg/l to </=20% of people (Delange et al., 2002). During the period between the years 1994-2002, the urinary iodine concentration was determined in 29,612 samples at the Institute of Endocrinology in the Czech Republic. The mean basal urinary iodine concentrations +/-SD were 115+/-69 μg/l. Out of all the samples, 0.7% were in severe (<20 μg/l), 9.6% in moderate (20-49 μg/l), 40.1% in mild (50-99 μg/l), 35.6% in adequate (100-200 μg/l), and 14.0% in more than adequate (>200 μg/l) subsets of iodine nutrition. A statistically significant ($p<0.00001$) difference was found between the mean male (127 μg/l) and female (112 μg/l) urinary iodine, and an inversely proportional trend also existed in the age-related data (Bílek et al., 2005). It is also known that patients with iodine induced hyperthyrosis have 10- to 100-fold more urinary iodide than healthy patients (Mura et al., 1995).

Delange et al. (Delange et al., 2002) determined the frequency distribution of urinary iodine in iodine-replete populations (schoolchildren and adults) and the proportion of concentrations <50 μg/l. The findings were as follows: nineteen groups reported data from 48 populations with median urinary iodine concentrations >100 μg/l. The total population was 55 892, including 35 661 (64%) schoolchildren. Median urinary iodine concentrations were 111-540 (median 201) μg/l for all populations, 100-199 μg/l in 23 (48%) populations and >/=200 μg/l in 25 (52%). The frequencies of values <50 μg/l were 0-20.8 (mean 4.8%) overall and 7.2% and 2.5% in populations with medians of 100-199 μg/l and >200 μg/l, respectively. The frequency reached 20% only in two places where iodine had been supplemented for <2 years. According to the authors' conclusions the frequency of urinary iodine concentrations <50 μg/l in populations with median urinary iodine concentrations >/=100 μg/l has been overestimated, and the threshold of 100 μg/l does not need to be increased. The main conclusion of the cited work was that in populations, median urinary iodine concentrations of 100-200 μg/l indicate adequate iodine intake and optimal iodine nutrition.

According to Verheesen and Schweitzer (Verheesen and Schweitzer, 2011) the threshold of 100 μg/l is only to make sure that severe iodine deficiency (beneath 50 μg/l) is not present in more than 20% of the population. Although the WHO is concerned about the negative effects of even mild iodine deficiency, the 100 μg/l threshold was never intended to prevent mild iodine deficiency. In order to combat mild deficiency the threshold should be reconsidered. The authors also emphasized the need to test for other biomarkers in individual cases in order to be able to adequately establish iodine deficiency. Since there is a lack of trusted biomarkers, thus far statistics have been used to estimate the percentage of the population being deficient, instead of showing prevalence figures. Furthermore, population figures are typically described only by a median; variables such as % being deficient, % being pregnant, % women, % men and age related figures should be thoroughly investigated.

3. Problems with analysis of iodine in biological matrices

Despite a wide choice of available analytical methodologies, determination of iodide in biological matrices remains a difficult problem. Biological samples belong to so-called

complex samples (with complex matrices). In such samples, the analyte content is usually much scarcer when compared with the accompanying macrocomponents. Aside from the necessity of choosing the appropriately sensitive method, it is equally important to comply with the sample preservation, pretreatment, and preparation conditions.

Historically, published values of the I_2/I^- concentration of both tissue and body fluids from healthy subjects have varied greatly. These great differences were attributed to numerous variables, such as age, sex, dietary habits, physiological conditions, environmental factors and numerous other X-factors. Given the delicate nature and the instability of biological samples, it has been concluded that improper sample collection methods and manipulation drastically affects the iodine content of biological matrices.

Analytical methods are often versatile in nature. Thus, in order to achieve successful and satisfactory results, the process of analysis needs to be carefully tailored to its needs. Before applying the appropriate method for a particular application, many factors have to be considered and some of them are discussed below.

It is well known that sources of errors that affect the final error of an analytical result are connected, among other things, with incorrect obtaining of the samples, their improper transport, storage and transformation, wrong methodology, wrong measurement (instruments, parameters) or human errors (Konieczka & Namieśnik, 2007). When it comes to quantitative evaluations of iodine concentrations (in all chemical forms), the proper storage of biological samples is of paramount importance. The tissues must be preserved in such a way that a potential loss of the analyte (i.e. iodine) is minimized. The choice of the tissue-fixing agents is quite wide. Formalin is a routinely used tissue-fixing agent after surgical procedures. Other recommended agents for tissue preservation include, e.g. a mixture of 50% glutaraldehyde, 16 % paraformaldehyde, and 0.2M sodium phosphate buffer solutions (i.e. original composition of Karnovsky fixative) or its modification. The other possibility to preserve the tissues is sample freezing.

Hansson at al. (Hansson et al., 2008) used X-ray fluorescence analysis (XRF) and secondary ion mass spectrometry (SIMS) for evaluation of a freezing technique for preserving samples (XRF analysis) and for evaluation of the efficacy of using aldehyde fixatives to prepare samples (SIMS analysis). There were no significant changes in the iodine content due to freezing. Freezing for 4 weeks produced no more than a 10% change in the iodine content. For all the samples fixed in an aldehyde, there was a loss of iodine. The decrease in iodine content from baseline was significant for samples fixed in aldehyde ($p < 0.05$). Karnovsky was the best fixative in this regard, yielding a mean 14% loss compared to 20% and 30% for glutaraldehyde and formaldehyde, respectively. For SIMS method, Fragu et al. (Fragu et al., 1992) recommended chemical fixation with a mixture of Karnovsky fixative, followed by embedding in methacrylate. This method, which was evaluated for iodine loss by Rognoni et al. (Rognoni et al., 1974), has proven suitable for preservation of substances bound to macromolecules (like iodine bound to thyroglobulin [Tg]).

The effect of sample preservation on determination of I^- in healthy and pathological human thyroids has also been studied (Błażewicz et al., 2011). It was pointed out that the way of tissue preservation (either in formalin or by freezing) had no significant effect on the iodine determination result ($\alpha = 0.1$) by ion chromatography combined with the pulsed amperometic detection method (IC-PAD). Sample decomposition is a critical step in iodides' analysis as well. All reported methods have a digestion or ashing step prior to the final determination of

iodine. The procedure usually requires the use of alkaline media and a high temperature (Moxon & Dixon, 1980). A catalytic spectrophotometric method based on the Sandell-Kolthoff reaction together with many modifications and improvements of this method is a low-cost assay of iodine, however, it is not free of possible interferences (especially for foodstuffs with low range of iodine levels). Most iodine in biological media is covalently bonded and there are some substances that interfere with the determination reaction (eg. SCN^-, NO_3^-, or Fe^{2+}). A high lipid content in the sample (eg. milk) can cause problems in spectrophotometric readings, so a mineralization step is absolutely necessary before analysis.

When preparing a sample for analysis, it is necessary to take into consideration also the loss of analyte due to erroneous application of decomposition procedures. Some of them, e.g. "Schoeniger combustion", require a highly homogenous sample, which is sometimes difficult to obtain (Knapp et al., 1998). There are many options for biological sample preparations, among which alkaline digestion using tetramethylammonium hydroxide (TMAH) is the most common before the analysis of I^- (Fecher et al., 1998; Fecher & Nagengast, 1994; Schramel & Hasse, 1994). Alkaline conditions during the extraction procedure have some advantages in comparison with acidic media, where I^- may be oxidized into volatile forms (I_2 or HI). A destruction of the organic matrix using a typical digestion reagent, like HNO_3, is not possible because of the losses due to volatile iodine formation (therefore, no stable sample solution can be achieved). However, acid digestion procedures (by the use of mainly H_2SO_4, HNO_3, and $HClO_4$) have also been applied (Fischer et al., 1986). What is more, despite its obvious weak point (loss of analyte), the US Food and Drug Administration (FDA, 2009) still recommends such procedures.

Błażewicz et al. (Błażewicz et al., 2011) used the alkaline digestion with 25 % TMAH water solution for the thyroid glands` preparation before the IC method of analysis. A diluted TMAH solution has also been used for serum samples by Schramel and Hasse (Schramel & Hasse, 1994) to analyse iodine in the serum, milk, plants and tissues by using the ICP-MS method.

Unfortunately, despite the abovementioned advantages, the use of TMAH solution for the digestion of samples has some disadvantages as well. Since for all modern sample pretreatment methods time is a very important factor, the long procedure time still remains a huge problem. As reported in the literature, digestion of biological materials with TMAH usually requires up to 6 hours (Gamallo-Lorenzo et al., 2005). However, the assistance of microwaves significantly shortens the time of the sample preparation step (less than 20 minutes). Such microwave-assisted alkaline digestion has been developed before the IC analysis of thyroids' samples (Błażewicz et al., 2011). It is important to monitor all conditions of the digestion procedure, especially temperature, in order to avoid the decomposition of TMAH and bursting of the closed vessels (therefore a temperature lower than 100 ^{0}C is recommended). Each time the vessels must be thoroughly cleaned with a digestion mixture in order to avoid memory effects (adsorption by the walls of containers) and consequently the loss of analyte.

4. Spectrophotometry and chromatography as tools for iodine assessment in miscellaneous matrices

It is known that the choice of the proper analytical method depends on the intended application, the number of samples, the cost of analysis and the technical capability.

Currently, there are multiple distinctive analytical methods for determining concentrations of iodine species. The methods vary in principle, reliability, accuracy, precision, availability, detection limit, sample throughput, time and reagent consumption, ease of performance and cost of analysis. These factors all play a role in the choice of the most suitable method but ultimately the purpose of the analysis determines the method, e.g., whether the analysis is routine or if an analysis of a reference material is necessary. For any given purpose, one of the first factors taken into account is whether the method's detection limit is adequately low. Several methods of iodine determination have been proposed, including catalytic methods (with LOD=0.1 µg/ l) (Kamavisdar & Patel, 2002), chromatography in various modes (eg., IC with LOD = 0.1-0.8 µg/l (Hu et al., 1999; Bichsel & Von-Gunten, 1999), (chromatographic methods are especially useful for iodine speciation when coupled with ICP-MS or elecrochemical detection), GC-EC: gas chromatography with electron capture detection (0.11µg/l) (Maros et al., 1989), GC–MS: gas chromatography–mass spectrometry(0.010 µg/l) (Das et al., 2004), FAAS: flame atomic absorption spectrometry (2.75 µg/l) (Yebra & Bollaín, 2010), NAA (0.1-0.2 µg/l) (Hou et al., 1999), ETAAS: electrothermal atomic absorption spectrometry (1.2 -3.7 µg/l) (Bermejo-Barrera et al., 1999), inductively coupled plasma mass spectrometry ICP-MS (1.0-9.0 µg/l) (Fernandez-Sanchez & Szpunar 1999), ICP-AES (40.0-470.0 µg/l) (Anderson & Markowski, 2000), inductively coupled plasma optical emission spectrometry (ICP- OES) (2 µg/l) (Naozuka et al., 2003), ion selective electrodes (1.96 µg/l) (Kandhro et al., 2009), X-rayfluorescence (XRF) (180 µg/L) (Varga, 2007), VG-ICP-OES: vapour generation inductively coupled plasma optical emission spektrometry (20 µg/l) (Niedobová at al., 2005). The iodine content can also be measured by the use of titrimetric methods usually combined with potentiometric measurements. They are also used for verifying other methods (Gottardi, 1998). The titrimetric method is mainly used for samples without complex matrices (i.e. water or salt). Generally such methods involve acidification of the sample solution and adding an excess of KI solution to determine the liberated iodine by titration with sodium thiosulphate. Despite numerous advantages of the above-mentioned methods, very few of them are widely used due to very high costs of instrumentation, software, and maintenance. Spectrophotometric and chromatographic methods are used very frequently for the analysis of iodine and its various chemical forms. Chosen examples of applications of iodine determinations are presented below.

4.1 Spectrophotometric methods

4.1.1 Water samples

Spectrophotometric analysis continues to be one of the most widely used analytical techniques available. Kinetic spectrophotometric methods, which are based on the reaction, found by Sandell and Kolthoff (1934) set the foundation for the development of different methods for the determination of iodine in environmental samples (mostly water). The said reaction proceeds according to the following equation (1):

$$2\ Ce^{4+} + As^{3+} \rightarrow 2\ Ce^{3+} + As^{5+} \quad (1)$$

By adding an arsenious acid (H_3AsO_3) solution and an ammonium cerium sulfate ($(NH_4)_2Ce(SO_4)_3$) solution as reagents to I^- in a specimen, yellow Ce^{4+} is reduced to produce colorless Ce^{3+} ((2) and (3)).

$$2Ce^{4+} + 2I^- \rightarrow 2Ce^{3+} + I_2 \quad (2)$$

$$I_2 + As^{3+} \rightarrow 2I^- + As^{5+} \quad (3)$$

Iodine has a catalytic effect upon the course of reaction (1), i.e., the more iodine is present in the preparation to be analyzed, the more rapidly proceeds the reaction (1). The speed of reaction is proportional to the iodine concentration. In this manner it is possible to determine iodine even in the nanogram range. Sandell and Kolthoff found that Os and Ru catalyse this reaction in the same manner as I_2, while Mn and MnO_4^- do so in the presence of Br^-. Among substances reducing Ce^{4+} they listed NO_2^-, SCN^-, Fe^{2+}, while BrO_3^-, MnO_4 were classed by them as oxidising As^{3+}. These authors also pointed out that certain substances, such as F^-, form compounds with Ce^{4+} giving a stable complex. Ag^+, CN^-, and Hg^+ react with I^- as well. The effect of various concentrations of NaCl, NaF, KH_2PO_4, $ZnSO_4$, KCl, $MgSO_4$, KBr and of $CuSO_4$ on the described reaction was studied by Stolc (Stolc, 1961). According to the author the substances studied may be grouped into two categories, i.e. reaction inhibiting (NaF, KH_2PO_4, $ZnSO_4$, KCl) and reaction stimulating agents (NaCl, $MgSO_4$, KBr, $CuSO_4$).

The method is achieved in the following manner: a measured amount of an arsenous oxide (As_2O_3) solution in concentrated H_2SO_4 is combined with the test solution. This mixture is then adjusted to its reaction temperature, usually between 20 and 60 degree C. Cerium (IV) sulfate in sulfuric acid is then added, after which the solution is able to react for a limited time at the set temperature. The reaction time ranges from 10 to 40 minutes, and subsequently the content of the test solution of cerium (IV) ions is photometrically determined. The lower the determined concentration of cerium (IV) ions, the faster the reaction, thus a larger amount of catalyzing agent, i.e., iodine. By these means it is possible to directly and quantitatively measure the iodine concentration of the test solution, though execution of such processes is complicated and demands extensive measuring times (Sandell & Kolthoff, 1934, 1937). The above-described method was modified in various ways, for example by replacing H_2SO_4 with HNO_3 (used for acidifying the reaction mixture). It was found that the catalytic activity of iodine in HNO_3 solution is 20 times that in H_2SO_4 and is also far less sensitive towards accompanying ions, making the system far more useful for the determination of traces of iodine (Knapp & Spitzy, 1969). The reaction mixture's change in composition multiplies the sensitivity of the reaction by twenty. Consequently, test solutions of an iodine content that, according to the conventional catalytic reaction method utilizing sulfuric acid, required a reaction time of approximately 20 minutes in order to display a notable decrease in cerium (IV) ion concentration need only 1 minute to produce the same result. These results were achieved while operating at the same reaction temperature. Rodriguez and Pardue (Rodriguez & Pardue, 1969) studied the effect of H_2SO_4, $HClO_4$, Ag(I), Hg(II), Cl^- and temperature on the aforemetioned kinetic reaction. Their studies utilized the catalytic action of iodide on the decomposition of the $FeSCN^{2+}$complex ion. This indicator reaction is characterized by an induction period, the length of which depends on the reagent concentration, pH and temperature. The mentioned method was adopted as a standard method for iodide determination in natural and waste waters as well as in food and biological samples. However, high inter-laboratory relative standard deviations have frequently been reported for this method. Some authors have suggested that this might be partly attributed to the limitations of the method to quantitatively detect or tolerate IO_3^- that are found in natural waters (Heckwan, 1979).

An alternative flow injection spectrophotometric method for the determination of I^- in the ground and surface water was reported by Kamavisdar and Patel (Kamavisdar & Patel, 2002). The method was based on the catalytic destruction of the colour of the Fe(III)–SCN^-–CP^+–$_nBP_y$ quarternary complex. The detection limit of the method was reported to be 0.1 ng ml^{-1} of iodide. Another redox reaction between chloramine-T and N,N'-tetramethyldiaminodiphenylmethane (Feigl's Catalytic Reaction) was applied for the determination of traces of iodine in drinking water (Jungreis & Gedalia, 1960).

An alternative to the Sandell-Kolthoff method was developed by Gurkan et al., (Gurkan et al., 2004). Iodides were determined in waters by inhibition kinetic spectrophotometric method based on the inhibitory effect of I^- on the Pd(II)-catalyzed reduction of Co(III)-EDTA by the hypophosphite ion in a weak acid medium. The main advantage of this method was related to the pretreatment step of the analysis which would be omitted (a time-consuming alkaline ashing preparative procedure is necessary in order to apply the standard method). The sensitivity of the method allowed determinations in the range of 2-35 ng/ml of I− (LOD=1.2 ng/ml). Koh et al. (Koh et al., 1988) separated I^- from other chemical species by its oxidation and subsequent extraction into carbon tetrachloride. The proposed spectrophotometric method was based on the extraction of the back-extracted iodide into 1,2-dichloroethane as an ion pair with methylene blue. The authors applied that method to determine various amounts of iodide in natural water samples (at the 10^{-6} mol l^{-1} level). Spectrophotometric determination of the total dissolved sulfide in natural waters allowed also simultaneous determination of other UV-absorbing ions, including I^- (Guenther et al., 2001).

4.1.2 Soil and plant samples

Different analytical techniques have been developed to extract and measure iodine concentration from the soil. The reduction of Ce (IV) by As (III) catalyzed by iodine can be used to determine the low concentration of iodine in plant and soil samples. The sample preparation requires a specialized combustion apparatus and trapping systems for iodine. For plant samples and biological materials, halogen extraction using TMAH under mild conditions has proved to be effective (Knapp et al., 1998).

Kesari et al. (Kesari et al., 1998) developed a simple and sensitive spectrophotometric method for the determination of iodine in tap water, sea water, soil, iodized salt and pharmaceuticals samples. The said method was based on oxidation of I^- to IO_3^- with bromine water and liberation of free I_2 from IO_3^- by addition of KI in acidic medium. I_2 is then reacted with leuco crystal violet and the crystal violet dye liberated shows maximum absorbance at 591 nm. Beer's law is obeyed over the concentration range from 0.04 to 0.36 mg/l of iodine in a final solution volume of 25 ml. The method is free of interference of other major toxicants.

Lu et al. (Lu et al. 2005) applied the arsenic-cerium redox method for assessment of iodine content in soils and waters. Mean iodine concentration in soil samples was found to be 1.32 ± 0.14 mg/kg, and its content correlated positively with the water iodine content. In association with the photometric analytical technique, the alkaline dry ashing method (adding KOH and $ZnSO_4$), along with digestion via the calorimetric bomb and the utilization of the Schoniger digestion arc, provide a means for obtaining reliable results. For this investigation, the influence of iodine fertilisation on the iodine concentration of cress

(Lepidium sativum) was determined by an experiment in which different amounts of iodine were added to the potted plants. The iodine fertiliser used was natural caliche. The results show a very close correlation between the iodine supply and iodine concentration in the cress which increased to more than 30 mg/kg dry matter (Jopke et al., 1996).

4.1.3 Foodstuffs

A semi-automated method for determination of the total iodine in milk was described by Aumont (Aumont, 1982). The method involved destruction of organic matter by alkaline incineration and automated spectrophometric determination of iodide based on the Sandell and Kolthoff's reaction. The recoveries of the added iodide before calcination were between 90.05 +/- 7.36% and 97.14 +/- 4.56% (mean +/- S.D.). The coefficient of variation ranged from 2.15 to 7.21% depending on the iodine content in the milk. The limit of detection was estimated to be around 2 μg/kg.

The iodide-catalyzed reaction between As(III) and Ce(IV) stopped by the addition of diphenylamine-4-sulfonic acid was used for the development of a sensitive kinetic procedure for determining iodides with a detection limit of 2 ng/mL. The developed procedure was suitable for the determination of the total iodine in foodstuffs (Trokhimenko & Zaitsev, 2004).

Another modification of the catalytic kinetic spectrophotometric method has been established for the determination of iodine using the principle that potassium periodate oxidize rhodamine B (RhB) to discolor and I^- has a catalytic effect on the reaction. The absorbance difference (ΔA) is linearly related with the concentration of iodine in the range of 0 – 2.6 μg/mL and fits the equation ΔA = 0.1578 C(C: μg/mL) + 0.0052, with a regression coefficient of 0.9965. The detection limit of the method is 7.10 ng/mL. The method was used to determine iodine in kelp, potato, tap water, and rain water samples. The relative standard deviation of 13 replicate determinations was 1.81–2.10%. The recovery of the standard addition of the method was 96.2–99.2% (Zhai et al., 2010).

Some researchers reported that the spectrophotometric methods for the determination of IO_3^- are based on its reaction with the excess I^- to liberate I_2 which forms tri iodide (Afkhami & Zarei 2001; Ensafi & Dehaghi, 2000).

Balasubramanian and Nagaraja (Balasubramanian & Nagaraja, 2008) described a sensitive spectrophotometric method for the determination of multiple iodine species such as I^-, I_2, IO_3^- and IO_4^-. The method involved oxidation of iodide to ICl_2^- in the presence of iodate and chloride in an acidic medium. The formed ICl_2^- bleaches the dye methyl red. The decrease in the intensity of the colour of the dye is measured at 520 nm. Beer's law is obeyed in the concentration range 0-3.5 μg of iodide in an overall volume of 10 ml. The relative standard deviation was 3.6% (n=10) at 2 μg of iodide. The developed method can be applied to the samples containing iodine, iodate and periodate by prereduction to iodide using $Zn/H^{(+)}$ or $NH_2NH_2/H^{(+)}$. The effect of interfering ions on the determination was pointed out. The described method was successfully applied to determine iodide and iodate in salt samples and iodine in pharmaceutical preparations.

Silva *et al. (*Silva et al., 1998) outlined a new method for the determination of iodate in table salt. KIO_3, after being converted to I_3 by reacting with iodide in the presence of phosphoric

acid, was spectrophotometrically determined at two well defined UV absorption maxima of 352 and 288 nm. The results were comparable with a standard, ranging from 37.39 (±0.15) to 63.67 (±0.16) mg KIO_3 per kg of salt with samples of 0.15-0.21 g.

A flow injection method based on the catalytic action of iodide on the colour-fading reaction of the $FeSCN^{2+}$ complex was proposed and applied in order to determine iodine in milk. At pH 5.0, temperature 32°C and measurements at 460 nm, the decrease in absorbancy of Fe^{3+}-SCN (0.10 and 0.0020 mol /l) in the presence of NO_2^- (0.3 mol/ l) is proportional to the concentration of iodide, with a linear response up to 100.0 µg/l. The detection limit was determined as 0.99 µg/l and the system handles 48 samples per hour. Organic matter was destroyed by means of a dry procedure carried out under alkaline conditions. Alternatively, the use of a Schöninger combustion after the milk dehydration was evaluated. The residue was taken up in 0.12 mol/l KOH solubilization. For typical samples, recoveries varied from 94.5 to 105%, based on the amounts of both organic matter destroyed. The accuracy of the method was established by using a certified reference material (IAEA A-11, milk powder) and a manual method. The proposed flow injection method is now applied as an indicator of milk quality on the Brazilian market (de Araujo Nogueira et al., 1998).

Another spectrophotometric flow injection method for the determination of I^- and based on the catalytic effect of this ion on the oxidation of pyrocatechol violet by potassium persulphate has been developed. The method allows the determination of 0.5–5 mg/l I^- at a rate of 60 samples per hour and is subject to very little interference. It was successfully applied to the determination of iodide in table salt (Cerda et al., 1993).

4.1.4 Biological fluids and tissues

Due to the noninvasive way of sampling, urine is the most commonly analysed biological fluid. Efficient management of national salt iodization programmes depends on quality data on iodine concentrations in the urine and salt samples. These data are crucial in the evaluation of iodine interventions. Most of the analytical methods for urinary iodine concentration are based on the manual spectrophotometric measurement of Sandell-Kolthoff reduction reaction catalyzed by iodine using different oxidising reagents in the initial digestion step (Jooste & Strydom, 2010). Bilek et al. (Bilek et al., 2005) used a method which was based on alkaline ashing of urine specimens preceding the Sandell-Kolthoff reaction using brucine as a colorimetric marker. The detection limit was 2.6 µg/l and the limit of quantification was 11.7 µg/l, with intra-assay precision of 4% and inter-assay precision of 4.9%.

Another study described simple photometric determination of the iodine concentration in the thyroid tissue of small animals. Again, the method was based on the well-known catalytic Sandell-Kolthoff reaction. Prior to the analysis, the tissue was digested in a mixture of sodium chlorate and perchloric acid at 100 degrees C. Using this manner of digestion between 94 and 110% of iodine in the sample was recovered. Comparison with the neutron activation analysis showed excellent agreement of the obtained values (Tiran et al., 1991).

4.2 Chromatographic methods

While the main advantage of catalytic spectrophotometric methods is low cost of the needed equipment, chromatography is arguably the most widely used separation technique in the

modern analytical laboratory. Fast, simple, reliable and sensitive chromatographic systems coupled with various detectors became the basic tool in many analytical laboratories. Routine analysis of iodine compounds can be carried out by means of gas chromatography (GC) and high performance liquid chromatography (HPLC). Analysis of inorganic iodine species in waters is mainly carried out with the use of ion chromatography (IC) or IC inductively coupled-mass spectrometry (IC-MS). Separation methods enable direct determination of various species of iodine in the presence of various kinds of complex components with the detection limit in the range of sub µg/l or µg/l (Hu et al., 1999; Schwer & Santschi, 2003). The IC method can separate I^- directly by using anion-exchange column, while HPLC method usually uses the reverse phase column modified by an ionpairing reagent in the mobile phase. Both spectrophotometric and electrochemical detectors are commonly used. Pulsed amperometric detection (PAD) typically utilizes gold, silver, platinum and glass carbon electrodes.

It has to be emphasized that both spectrophotometric and chromatographic methods are not applicable to a wide range of matrices. As far as complex matrices are concerned (e.g. seawater with high content of Cl^- and Br^- and relatively small of I^-) IC and HPLC are useful tools for iodine determination. Unfortunately, none of these methods are flexible enough to measure all iodine species, including organo-iodine in biological samples. The oxidative pretreatment of biological materials limits the application of the described methods (IO_3^- and I^- can be converted to I_2 under acidic conditions). In order to analyse IO_3^- , I^-, and organic forms of iodine in the same sample, IC is often coupled with ICP-MS. What is more, the coupling of highly efficient IC to multi-dimensional detectors such as MS or ICP/MS significantly increases sensitivity, while simultaneously reducing possible matrix interference to the absolute minimum.

4.2.1 Water samples

Liang et al. (Liang et al., 2005) applied the disposable electrode for the determination of iodide in soil and seawater samples with the spiked recovery ranging from 96–104% and the detection limit of 0.5 µg/L. Rong et al. (Rong et al., 2005) performed a direct determination of iodide and thiocyanate ions in seawater collected from the coasts of Japan. No sample pretreatment was needed. Liquid chromatography (LC) with a UV detection of 220 nm was applied. The separation was achieved on a C_{30} column of conventional size (150 mm × 4.6 mm i.d.) modified with poly(ethylene glycol). Such stationary phase enables the determination of I^- in seawater without any interference. Anions such as NO_3^-, NO_2^-, Br^- which absorb in the UV region do not interfere because the I^- peak is well resolved from the others. An aqueous solution of 300 mM sodium sulfate and 50 mM sodium chloride was used as the mobile phase. Detection limits (S/N=3) were obtained by injecting a 20-µL sample with 0.5 and 6 ng /ml for iodide and thiocyanate, respectively.

Buchberger (Buchberger, 1988) determined I^- (among other ions) in water samples using an anion-exchange stationary phase (Vydac 302-IC) and methanesulphonic acid solution as the mobile phase. A post-column reaction detector was developed based on the reaction between iodide or bromide, chloramine-T and 4,4′ bis (dimethylamino)diphenylmethane. The detection limit was *ca*. 20 pg iodide injected.

A non-suppressed ion chromatography (IC) with inductively coupled plasma mass spectrometry (ICP-MS) was developed for simultaneous determination of trace IO_3^- and

iodide in seawater. An anion-exchange column (G3154A/101, Agilent) was used for the separation of IO_3^- and I^- with an eluent containing 20 mM NH_4NO_3 at pH 5.6. NH_4NO_3 used in mobile phase minimizes salt deposition on the sampler and skimmer cones of mass spectrometer. Linear plots were obtained in a concentration range of 5.0–500 µg/l and the detection limit was 1.5 µg/L for IO_3^- and 2.0 µg/l for I^-. The proposed method was used to determine IO_3^- and I^- in seawaters without sample pre-treatment (with exception of dilution) (Chen et al., 2007).

Using IC-ICP-MS, Tagami and Uchida (Tagami & Uchida, 2006) measured concentrations of halogens (Cl, Br and I) in 30 Japanese rivers. Cesium was used as an internal standard during I counting. The typical detection limit was calculated as three times the standard deviation of the blank, between 0.01–0.04 µg/l. The ranges of geometric means of I in each river were 0.18-8.34 µg/l.

Bruggink et al. developed an anion-exchange chromatography method in combination with the pulsed amperometric detection (PAD) for the analysis of dissolved I^- in surface water and in absorption solutions obtained from adsorbable organic iodide (AOI) determination. The development of the amperometric waveform for a selective detection using a silver-working electrode together with the optimization of the injection volume and digital signal smoothing was performed. This method exhibited a detection limit of 0.02 µg/L, without any need of sample treatment other than micro-filtration. The results of AOI determination of the method described in this article were compared with results obtained with a different ion chromatography approach utilizing UV detection (Bruggink et al., 2007).

4.2.2 Seaweed

A gas chromatography (GC) method was reported for the trace analysis of I^- in processed seaweed by Lin et al. (Lin et al., 2003). The method is based on the derivatization of aqueous iodide extracted from seaweed with 2-(pentafluorophenoxy)ethyl 2 (piperidino) ethanesulfonate in toluene using tetra-*n*-hexylammonium bromide as a phase-transfer catalyst.

4.2.3 Food

GC method has been developed for determination of total iodine in food, based on the reaction of iodine with 3-pentanone. Organic matter of a sample was destroyed by an alkaline ashing technique. Iodide in a water extract of the ash residues was oxidized in order to free I_2 by adding $Cr_2O_7^{2-}$ in the presence of H_2SO_4. Liberated iodine reacted with 3-pentanone to form 2-iodo-3-pentanone, extracted into n-hexane, and then determined by gas chromatography with an electron-capture detector. Recoveries of I^- from spiked food samples ranged from 91.4 to 99.6%. Detection limit for iodine was 0.05 µg/g (Mitsuhashi & Kaneda Y, 1990).

Two methods were described for the preparation of samples for total iodine measurement in milk and oyster tissue. In the first method, the samples were combusted in a stream of oxygen to release iodine that, subsequently, was trapped in a solution as iodide. The second method used a new approach in which the samples were oxidized in a basic solution of peroxydisulfate. In this case, iodine was retained in the solution as an iodate. Total iodine

was measured by means of the GC analysis of the 2-iodopentan-3-one derivative. The methods were tested using Standard Reference Materials (SRMs) 1549 Non-Fat Milk Powder, and 1566a and 1566 Oyster Tissue. Also, KI and KIO_3 were used for testing the procedures. The results obtained for the SRMs, given as average +/- standard deviation in µg/l, were: 3.39 +/- 0.14 and 3.40 +/- 0.23 for SRM 1549; 4.60 +/- 0.42 and 4.51 +/- 0.45 for SRM 1566a; and 2.84 +/- 0.16 and 2.76 +/- 0.06 for SRM 1566; values corresponding to combustion and wet oxidation, respectively. Overall, the absolute recoveries varied between 91 and 103% (Gu et al., 1997).

Cataldi and Ciriello (Cataldi & Ciriello, 2005) described a sensitive method based on anion-exchange chromatographic separation coupled with amperometric detection at a modified platinum electrode under constant applied potential (+0.85 V vs. Ag AgCl). An experimental setup with an in-line and very effective method of electrode modification was proposed using an amperometric thin-layer cross-flow detector and a flowing 300 mg/l solution of iodide. The working electrode was polarized to the limiting current for oxidation of iodide to iodine in acidic solutions with the consequent formation of an iodine-based film. The results confirmed that the modified electrode exhibits high analytical response for iodide electro-oxidation with a good stability and long-life. The detection limit of iodide was estimated to be 0.5 µg/l (S/N=3) with an injection volume of 50 µL. This method was applied successfully to quantify the iodide content of milk samples, wastewaters, common vegetables and solutions containing high chloride levels. The iodide peak was always observed without interferences from the excess of coexisting anions (e.g. Cl^-, SO_4^{2-} or Br^-). Chloride (the main component of marine samples) exhibited no effect upon the separation and detection of iodide. The same method (RP ion pair HPLC with an electrochemical detector and a silver working electrode) was considered by the International Organization for Standardization (the determination of iodide content of pasteurized whole milk and dried skimmed milk when present at levels from 0.03 µg/g to 1 µg/g and from 0.3 µg/g to 10 µg/g) (International Standard ISO, 2009).

Xu et al. (Xu et al., 2004) described a method for determination of iodate developed by RP-HPLC with UV detection. Iodate was converted to iodine, which was separated from the matrix using a reversed-phase Ultrasphere C18 column (250×4.6 mm, 5 µm) with methanol (1M) H_3PO_4 (1:4) as the mobile phase at 1.00 ml/min and UV detection at 224 nm. The calibration graph was linear from 0.05 µg/ml to 5.00 µg/ml for iodine with a correlation coefficient of 0.9994 (n=7). The detection limit was 0.01 µg/ml. The recovery was from 96% to 101% and the relative standard deviation was in the range of 1.5% to 2.9%.

A method based on the coupling of size-exclusion chromatography (SEC) with on-line selective detection of iodine by ICP MS was developed allowing determination of iodine species in milk and infant formulas. Iodine species were quantitatively eluted with 30 mM Tris buffer which was prepared by dissolving 30 mM of tris [tris(hydroxymethyl)-aminomethane] in water and adjusting the pH to 7.0 by the addition of hydrochloric acid (1 : 10, v/v) within 40 min and detected by ICP MS with a detection limit of 1 µg l^{-1} (as I). A systematic study of iodine speciation in milk samples of different animals (cow, goat) and humans, of different geographic origin (several European countries) and in infant formulas from different manufacturers was carried out. When obtained after centrifugation of fresh milk or reconstituted , milk powders contained more than 95% of the iodine initially present in the milk of all the investigated samples with the exception of the infant formulas in which

only 15-50% of the total iodine was found in the milk whey. Adding sodium dodecyl sulfonate (SDS) improved considerably the recovery of iodine from these samples (in case of the natural milk samples, this increase was ca. 10±20% but for infant formula samples the amount of iodine recovered in the supernatant was more than twice that in the samples not incubated with SDS). Iodine was found to be principally present as iodide in all the samples except infant formulas. In the latter, more than half of iodine was bound to a high molecular (>1000 kDa) species. The sum of all the species recovered from a size-exclusion column accounted for more than 95% of the iodine present in a milk sample. For the determination of total iodine in milk, a rapid method based on microwave-assisted digestion of milk with ammonia followed by ICP MS was optimized and validated using CRM 151 Skim Milk Powder (Fernandez-Sanchez & Szpunar, 1999).

4.2.4 Biological fluids and tissues

Odink et al. (Odink et al., 1988) presented a simple method for the routine analysis of iodide in urine. Iodide was separated by means of ion-pair reversed phase chromatography (RP-HPLC) and detected electrochemically with a silver electrode after a one-step sample clean-up. The coefficient of variation of a single analysis of iodide in a pooled urine sample (530 nmol/l) was 7.6%. The detection limit was 3 pmol (S/N 3), corresponding to 0.06 µmol/l. The recovery of iodide added to urine was 96±7 %.

There are also studies that compare spectrophotometric and RP-HPLC determinations of iodine concentrations in urine (Bier et al., 1998). In the first one ammonium persulfate was used as an oxidant in the modified ceric arsenite method. With the use of this sensitive method iodine concentrations can be determined in very small specimens (50 µL). A Technicon Autoanalyzer II and a paired-ion-RP HPLC were the basic analytical equipment. The authors found that the precision of this optimized ammonium persulfate method yielded inter assay CVs of <10% for urinary iodine concentrations >10 µg/dL. The detection limit was 0.0029 µg iodine. There was a high correlation between all three methods ($r > 0.94$ in any case) and the interpretation of the results was consistent. The authors suggested that the manual ammonium persulfate method could be performed in any routine clinical laboratory for urinary iodine analysis. Another benefit of the described methods is a possibility to process a large number of samples with high accuracy and minimal technician`s time.

When using the HPLC assay method, contaminations from the protein bound iodine do not interfere with the determination of the serum inorganic iodide (SII), making it the method of choice for detection in the serum. Although the clinical relevance of the measurement of SII is limited, it allows calculation of the absolute iodine uptake , which has a great value in certain pathophysiological studies *(*Rendl et al., 1998).

Błażewicz et al. (Błażewicz et al., 2011) examined correlations between the content of iodides in 66 nodular goitres and 100 healthy human thyroid tissues (50 - frozen and 50 formalin - fixed). A fast, accurate and precise ion chromatography method on the IonPac AS11 chromatographic column (Dionex, USA) with a pulsed amperometric detection (IC-PAD) followed by alkaline digestion with tetramethylammonium hydroxide (TMAH) in a closed system and with the assistance of microwaves was developed and used for the comparative analysis of two types of human thyroid samples (healthy and pathological). A good correspondence (for 10 additional determinations) between the certified (3.38 ± 0.02 ppm with variation coefficient /V.C. / of 0.59 % for Standard Reference Material (SRM) NIST 1549- non-fat milk powder) and the

measured iodine concentrations (3.52 ± 0.29 ppm; V.C. = 10 %) was achieved. Suitability of the developed IC method was supported by validation results.

Ion chromatography coupled with electrospray ionization tandem mass spectrometry was applied for quantifying iodide, as well as perchlorate and other sodium-iodide symporter (NIS) inhibitors in the human amniotic fluid. The use of selective chromatography and tandem mass spectrometry decreased the need to clean up samples, leading to a quick and rugged method that is capable of the routine analysis of 75 samples per day. Along the physiologically relevant concentration range for the analytes, the analytical response was linear. The analysis of a set of 48 samples of amniotic fluid identified the range and median levels for iodide as: 1.7–170, 8.1µg/l (Blount & Valentin-Blasini, 2006).

5. Conclusion

There are many analytical methods available for detecting, and/or measuring iodine and its various species in complex matrices. Unfortunately, there is no perfect method which would be accurate, sensitive, cheap, fast, simple, and free of interferences at the same time. This review has been focused mainly on applications of spectophotometric and chromatographic methods of iodine analysis because they are widely used in practice, and relatively cheap. What is more, to achieve lower detection limits, they can also be coupled with other more sophisticated techniques (eg. ICP-MS). Although, these two methods have their own limitations, connected mainly with sample preatretment step (often timeconsuming), the literature data show continuous progress in the search for the best spectrophotometric and chromatographic conditions in iodine determinations. Reduction of time necessary for sample preparation still remains a challenge for analysts. Summarizing, future directions of iodine analysis lie rather in the simplification of methodologies and their extensive accessibility rather than in the tendency to decrease the limit of detection. Some recently published papers on the determination of iodine include: the evaluation of urinary iodide by the use of micro-photometric method compared to ICP-MS results (Grimm et al., 2011); determination of iodine and its species in plant samples using IC-ICP/MS (Lin et al., 2011); spectrophotometric determination of I^-, IO_3^-, IO_4^- in table salt, pharmaceutical preparations and sea water (George et al., 2011); investigation of the concentration-dependent mobility, retardation, and speciation of iodine in surface sediment from the river (Zhang et al., 2011); comparison of Sandell-Kolthoff reaction with potentiometric measurements of urinary iodide in female thyroid patients (Kandhro et al., 2011). One of the newest studies concerns the analysis of food samples by ICP-MS after alkaline digestion with TMAH (Tinggi et al., 2012). As it turns out, the newest published works utilize the most common already existing methods.

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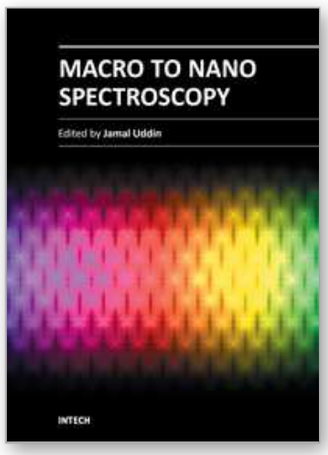
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In the last few decades, Spectroscopy and its application dramatically diverted science in the direction of brand new era. This book reports on recent progress in spectroscopic technologies, theory and applications of advanced spectroscopy. In this book, we (INTECH publisher, editor and authors) have invested a lot of effort to include 20 most advanced spectroscopy chapters. We would like to invite all spectroscopy scientists to read and share the knowledge and contents of this book. The textbook is written by international scientists with expertise in Chemistry, Biochemistry, Physics, Biology and Nanotechnology many of which are active in research. We hope that the textbook will enhance the knowledge of scientists in the complexities of some spectroscopic approaches; it will stimulate both professionals and students to dedicate part of their future research in understanding relevant mechanisms and applications of chemistry, physics and material sciences.

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