AN ASSESSMENT OF IODINE-129 AND IODINE 127 IN HUMAN BIOLOGICAL MATERIALS WITH MODELLING OF DIETARY IODINE INTAKE AND EXCRETION

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Dedication

To Jack Cornett (1954-2017), the captain who passed away

Acknowledgment

This is an essences of six years higher education adventure toward my philosophy degree. Gaining a Ph.D. is a start of a new journey that aim to join the communities of human whom standing on the shoulders of giants. Science used to be a pleasure, now it has become an industry. Modern scientific research is characterized by research team led by a scientist who specialize in a very specific field. Therefore, I must conclude by saying that the merits of this thesis are largely due to the helpful support and guidance of my research team.

I am so grateful to my supervisor, **Dr. Matthew Herod** who guided me during this research where I gained a lot of knowledge and useful experience. This project would not be nearly as good without his trust and support. A very special thanks to my co-supervisor **Dr. Liam Kieser** and to the thesis advisory committee members **Dr. Ian D Clark** and **Dr. Maxim Berezovski** for their helpful comments and feedback.

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My deepest emotions will not be sufficient to express my gratitude and love to my wife **Fadia Saad**, my son **Faisal**, my daughter **Sara,** and my youngest son **Sami** who stood beside me throughout my journey and particularly at the time of discouragement. To my older brother **Faisal Awwadh** who always there whenever I needed him. Finally, a heart-felt thank is to my parents **Awwadh Marzooq** and **Madawi Hanas** for their countless sacrifices to set a smooth road for me to reach this point. Proudly now, I can say your planting has been harvested and here I am as you always love to see me.

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List of Abbreviation

A	
AMS	Accelerator Mass Spectrometry
AgI	Silver iodide
$AgNO_3$	Silver nitrate
AgCl	Silver Chloride
AI	Adequate Intake
B	
Bq	Becquerel
BM	Breastmilk
BMIC	Breastmilk iodine concentration
C	
CHMS	Canadian Health Measures Survey
D	
DNA	Deoxyribonucleic acid
DRI	The Dietary Reference Intake
DFO	Dairy Farmers of Ontario
E	
EAR	Estimated Average Requirement
ESMP	Elementary School Milk Program
F	
FFQ	food frequency questionnaire
G	
GIT	Gastrointestinal tract
H	
HNO_3	Nitric acid
H_2O_2	Hydrogen peroxide
HCl	Hydrochloric acid
HATM	Human Alimentary Tract Model
HC	Health Canada
I	
^{123}I-MIBG	iodine-123 metaiodobenzylguanidine
IDD	Iodine deficiency disorder
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IDI	Iodine daily intake

K	
$K_2S_2O_8$	Potassium persulfate
L	
LSC	Liquid scintillation counting
LOAEL	Low Observed Adverse Effect Level
N	
NFRP	Nuclear fuel reprocessing plants
NPP	Nuclear power plant
NIS	Sodium/iodide symporter
NAA	Neutron Activation Analysis
NH_4OH	Ammonium hydroxide
NaI	Sodium iodide
NOAEL	No Observed Adverse Effect Level
P	
pH	Potential of hydrogen
R	
RDA	Recommended Dietary Allowance
S	
SPECT	Single-Photon-Emission-Computing-Tomography
Sv	Sievert
T	
T4	Thyroxine
T3	Triiodothyronine
U	
UIC	Urinary iodine concentration
UIE	Urinary iodine Estimation
Ul	Tolerable Upper Intake Level
W	
WHO	World Health Organization

Abstract

This thesis concerned with iodine status, sources in human body, and measurements especially here in Canada, where iodine status for the Canadian population is not well known. With the recent re-emergence of iodine deficiency among individuals in other industrial countries, understanding the main sources of iodine to the Canadian population is necessary to ensure fortification strategies are justified and effective. Uncertinaty has arisen to the importance of iodized salt recently, along with medical warnings to reduce salt consumbtion. This conflicts give rise to improve scientific research and hone thier methods with new applications.

The research question here is that: Can we benefit from the existence of long-lived radioiodine-129 in the environment and explore its potential as a tracer? To answer this question, the study was divided into an introductory chapter contains a review about the topic, then three research chapters. The second chapter was devoted to study the possibility of extracting ^{129}I from human urine. As for third chapter of the thesis, it was about refining a method that already established, and use it to extract ^{129}I from breastmilk using combustion, then determine the radiological dose of ^{129}I in infants' thyroid. While the fourth chapter was devoted to investigate the main sources of ^{127}I and ^{129}I in the Canadian diet based on daily food consumption and modelling the urinary iodine concentration for adults and infants through the novel application of a well-established compartment model implemented in AMBER.

The path of this thesis was crowned with a set of results, which are detailed in the end of each chapter as follow:

1- The advantage of accelerator mass spectrometry (AMS) helps to measure ^{129}I in human urine for the first time. The result for 25 participants from Ottawa ranged from 3.3 x 10^6

atoms/L to 884 x 10^6 atoms/L with a median of 108.7 x 10^6 atoms/L, and the $^{129}I/^{127}I$ ratio ranged from 7.38 x 10^{-12} to 3.97 x 10^{-10} with a mean of 1.3 x 10^{-10}.

2- The concentration of ^{127}I and ^{129}I in Ottawa urine samples were significantly correlated and generally similar to the ^{129}I concentrations and $^{129}I/^{127}I$ ratios from environmental samples collected around Ottawa.

3- This correlation suggests that ^{129}I could be a potential nutritional tracer of dietary iodine.

4- In chapter 3, the ^{129}I in breastmilk ranged from $1.26\text{x}10^8$ atoms/L to $6.64\text{x}10^8$ atoms/L with a median of 2.10 $\text{x}10^8$ atoms/L, and the $^{129}I/^{127}I$ ratio ranged from $1.27\text{x}10^{-10}$ to $9.9\text{x}10^{-10}$ with a median of $2.13\text{x}10^{-10}$.

5- A correlation was also observed between ^{127}I and ^{129}I concentrations in breastmilk.

6- The isotopic ratios in breastmilk were similar to Canadian cow's' milk, indicating that the milk of both cows and humans is a reflection of the ^{129}I concentration of their local environment and the food ingested.

7- Result from chapter 3 confirms that humans are exposed to the ^{129}I from birth through their mother breastmilk, giving them an average dose of 1.10 $\text{x}10^{-4}$ Bq/year and thyroid dose rate equal to 5.92 $\text{x}10^{-10}$ Sv/year.

8- In fourth chapter, the daily milk consumption was measured for 78 mother-infants' pairs, and ranged from 275 -1202 g/day, with a mean of 731 g/day. This value agrees well with global infant milk intake which estimated at 730g/day.

9- The daily iodine intake from breastmilk ranged from 11.2 µg/day to 476.2 µg/day with a median of 127.9 µg/day.

10- The urinary iodine concentrations were estimated without urine collection using iodine biokinetic model, giving a median urinary iodine concentration (n=78) at 304.7 µg/L. The result was compared to those measured by Health Canada (median= 398.7 µg/L), showing a moderate correlation (r= 0.496).

11- A further comparison of the results was made based on gender shows that the difference between UIC in male and female infants measured by Health Canada and those estimated by AMBER is non-significant.

12- Through AMBER software, the influence of seven common diets on UICs was assessed to determine which foods play an important role in ensuring iodine adequacy. We observed that the main source of iodine in a vegan diet is grain products providing up to 70%, while in remaining diets the main source of iodine was dairy products (50-69%) when they are consumed.

13- The contribution of iodized salt to all Canadian diets was ranked second, after dairy, unless the diet is vegan or ovo-vegetarian, where dairy is not consumed, iodized salt was ranked first.

14- Among 23 scenarios for seven different diets, the urinary iodine-129 concentrations ranged from 1.4 $\times 10^{-7}$ to 3.3 $\times 10^{-7}$ µg/L with a median of 3.1 $\times 10^{-7}$ µg/L, and the isotopic $^{129}I/^{127}I$ ratio ranged from 1.1 $\times 10^{-9}$ to 1.2 $\times 10^{-8}$ with a median of 2.8 $\times 10^{-9}$.

15- In contrast to stable iodine, the highest isotopic ratio was observed in vegan diet, while the lowest was observed in ketogenic diet. This suggests that grain products are the main contributor of ^{129}I to humans.

16- Despite being the primary contributors of stable iodine (^{127}I), salt and dairy show a lower contribution of ^{129}I. Based on this we can qualitatively predict the source of iodine 127 using isotopic ratio $^{129}I/^{127}I$. For example, in cases where the isotopic ratio was between 10^{-8} and 10^{-9}, therefore, the main sources of iodine in this person may be from grains products, vegetables, and fruits; and in cases where the isotopic ratio was between 10^{-10} and 10^{-11}, therefore, the main sources of iodine in this person may be from dairy products and some contribution from salt.

This study has shown the capability of ^{129}I to be used in biomedical fields. In this thesis ^{129}I used as a nutritional tracer where it helps to detect the sources of stable iodine in human body based on isotopic ratio. The extraction method invented in Chapter 2 can be used to evaluate ^{129}I exposure directly in the human body for those who live nearby nuclear fuel reprocessing plants. An additional application for this method can be in assessing ^{129}I in human to investigate ^{131}I uptake in the event of a nuclear emergency using ^{129}I in urine as a proxy. Moreover, the extraction technique used Chapter 3, can be extended to other biological samples such as thyroid or brain. Furthermore, Chapter 4 shows that with the right estimation of daily iodine intake and urine volume, a biokinetic model of iodine, built in the AMBER software, can predict urinary iodine concentration with a high degree of accuracy without collecting urine samples.

1 Chapter 1: Literature review, scope and objectives

1.1 Overview of iodine

Iodine (Fig.1.1) is derived from the products of nucleosynthesis that occurred ~10 billion years ago in stars-supernova explosions, which dispersed the dust that formed planet Earth (Venturi 2011). Iodine is a minor component on Earth (10 ppb for the bulk silicate crust) and is mostly concentrated in oceans and sediments because it is highly soluble and biophilic. It is found in nature as iodide (I^-), iodate (IO_3^-), elemental iodine (I_2), and multiple organic iodine species (Chauvel 2018). Iabstodine is a non-metallic, grayish-black element of the halogen group of the periodic system with symbol **I** (Considine 1995) and was discovered by French chemist Bernard Courtois in 1811 A.D. and named iode from the Greek "ioeides" which means violet because of the strong violet colour of iodine vapour (Chauvel 2018). The chemical and the physical properties of iodine are summarized in Table (1.1).

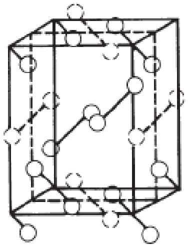


Figure 0.1 Iodine (I_2) crystal structure. Adapted from (Hibbert et al. 1987).

Table 1.1 Chemical and physical properties of iodine

Property	
Atomic mass	126.9054 g/mol
Atomic number	53
Boiling point	184.4 C
Density (at 25C)	4.93g/cm^3
Isotopes	37
Melting point	113.5
Oxidation state	−1, +1, +3, +5, +7
Solubility (at 25C)	0.34g/L
Vapour pressure (at 25C)	40 Pa

1.2 Function of iodine and its uses

Iodine is the second heaviest element to be essential in living organisms (Chauvel 2018). Inside the human body, iodine is required to form thyroid hormones (T3) and (T4) which are critical for metabolism and growth (ATSDR 2004). Iodine may also play a vital role in protecting protein and DNA molecules in animal cells from oxidation as iodide is an antioxidant (Sebastiano and Begin 2010). Moreover, iodide is related to the activity of enzymes that acts as antioxidants such as catalase, glutathione peroxidase, and superoxide dismutase (Soriguer et al. 2011). Commercially, iodine is frequently used as a local anti-infective agent for skin wounds as well as a disinfecting agent in the form of tablets, for water treatment, or solutions for surfaces in hospitals, surgical tools, and laboratories (Backer and Hollowell 2000).

1.3 Sources of iodine in the environment and humans

Iodine occurs naturally in the environment and can be found in all environmental reservoirs including the hydrosphere, biosphere, atmosphere, and geosphere (Fig 1.2) In addition, iodine is a mobile, redox-sensitive element that distributes readily in the environment due to its high affinity for aqueous fluids (Chauvel 2018). Iodine exists in the atmosphere as particulate iodine, organic and inorganic gaseous iodine. Its concentration in the atmosphere ranges from 1 ng/m^3 to 100 ng/m$^{3.}$ In the hydrosphere, iodine ranges from 1 ng/ml to 60 ng/ml. In the geosphere, iodine is often associated with organic matter and its concentration varies based on location and organic matter content. In the biosphere, iodine enters plants through absorption from the surrounding environment and enters the body of mammals through ingestion (Hou et al. 2009). Most of the iodine in the environment is derived from volatilization from the ocean while relatively little is derived from weathering of the lithosphere (Fuge 2013). As shown in Figure 1.2, geochemical studies of iodine indicate that iodine is volatilized from oceans, carried overland by winds, and deposited on the soil by rain (Considine 1995).

Food is the primary source of iodine to humans. An additional source of iodine may come through taking medications (e.g., amiodarone) or multivitamins as supplemental sources of iodine. Most dietary iodine is absorbed by small intestine and transferred into blood and then transported to the thyroid, where it is concentrated (Hays 1984). Table 1.2 summarizes the content of iodine in some of the most commonly consumed food in Canada.

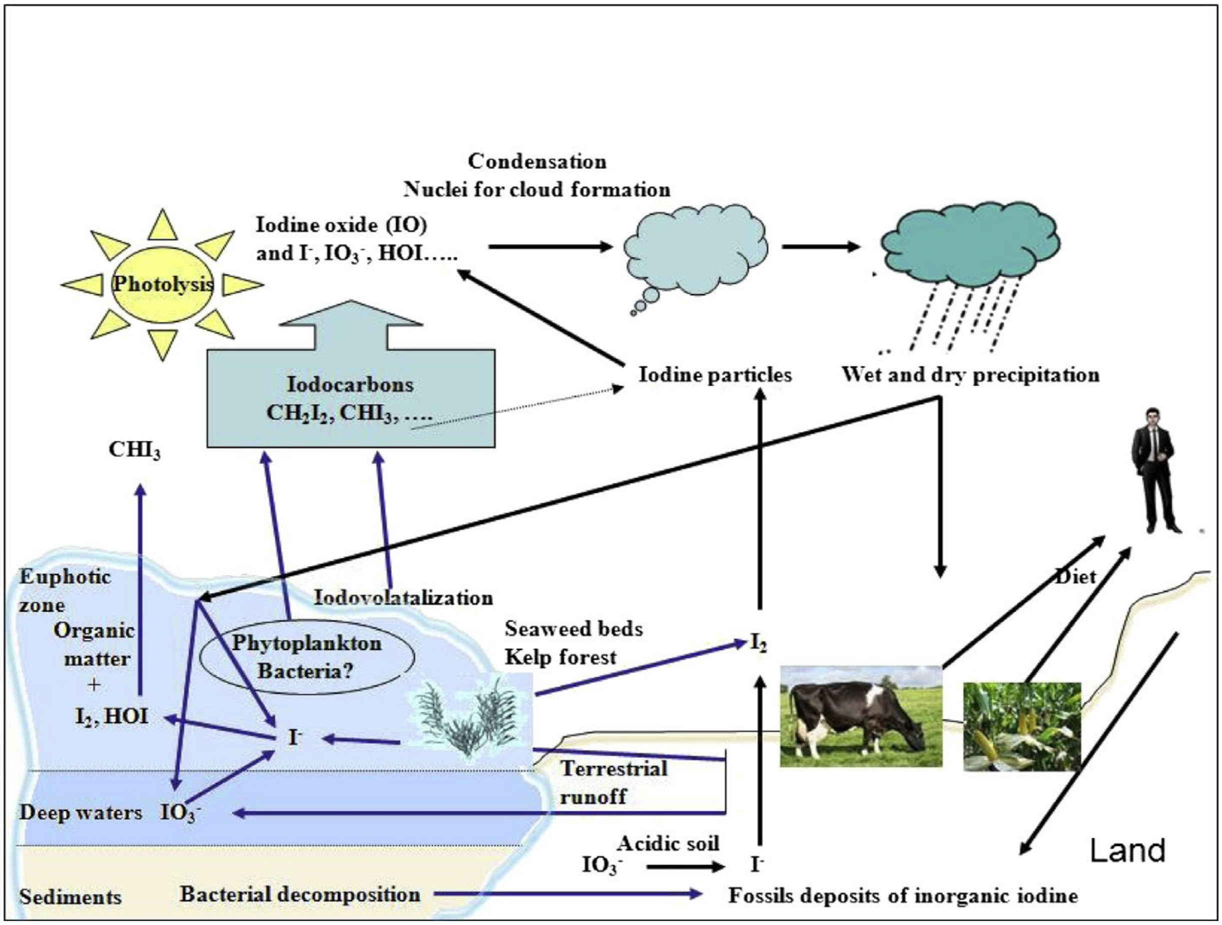


Figure 0.2 Iodine distribution through different chemical forms in the environment. Source from (Jabbar, Wallner, and Steier 2013).

Table 1.2 Average iodine content (µg/g) in most consumed Canadian food. Modified from (Benkhedda et al. 2009).

	Food type	***Iodine Concentration µg/ g***
1	Tea, coffee, and water	0.028
2	Grain products	0.164
3	Fruits and Vegetables	0.028
4	Milk	
	whole	0.268
	2%	0.317
	1%	0.301
	skimmed	0.258
	raw milk	0.160
5	Yoghurt	0.493
6	Beef	0.105
7	Chicken	0.346
8	Cheese	1.163
9	Fish	0.640
10	Eggs	0.727
11	Iodized Salt	50.89

1.4 Isotopes of iodine

Thirty-seven isotopes of iodine have been identified, beginning with ^{108}I up to ^{145}I. The only iodine isotope that is stable is ^{127}I. All of the other isotopes are radioactive. Iodine isotopes ^{123}I, ^{125}I, ^{129}I, and ^{131}I are of interest (Table 1.3) (Hou and Ding 2009).

Table 1.3 Nuclear prosperities and application of some radioiodine, modified from (Coenen, Mertens, and Maziere 2006).

	Mode of decay	Half life	Application
^{123}I	Electron Capture	13.2 hours	Nuclear medicine diagnostic tests such as scintigraphy and SPET “single-photon emission tomography”.
^{125}I	Electron Capture	59.4 days	Radioimmunoassay “RIA”, and as tracer in lab experiments
^{129}I	**β-**	16.14 million years	dating tool, oceanography, and groundwater tracer
^{131}I	**β-**	8.02 days	Therapy

1.4.1 Iodine-123

^{123}I is a short-lived radioisotope with a half-life of 13.2 hours (Hupf, Eldridge, and Beaver 1968) and decays by electron capture, followed by the emission of a 159 keV gamma ray and low energy Auger electrons (Narra et al. 1992). It is produced anthropogenically from a nuclear reaction in a cyclotron and there have been about 25 nuclear reactions proposed, the most common one is from Tellurium-123 $^{123}Te\ (p,n)\ ^{123}I$ (Coenen et.al 2006). Due to its unique short half-life and low energy emissions that decrease the radiation risk, iodine 123 is used mainly in nuclear medicine as a diagnostic tool and imaging. For example, iodine-123 has been used to study thyroid gland uptake, iodine metabolism in the human body, and imaging studies for the brain (Myers 1973; Narra et al. 1992). Moreover, iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) is considered by many physicians as a non-invasive tool for the diagnosis of ventricular arrhythmias and other cardiovascular risks in cardiac patients (Van Vickle and Thompson 2015; Stefanelli, Treglia, and Giordano 2012)

1.4.2 Iodine-125

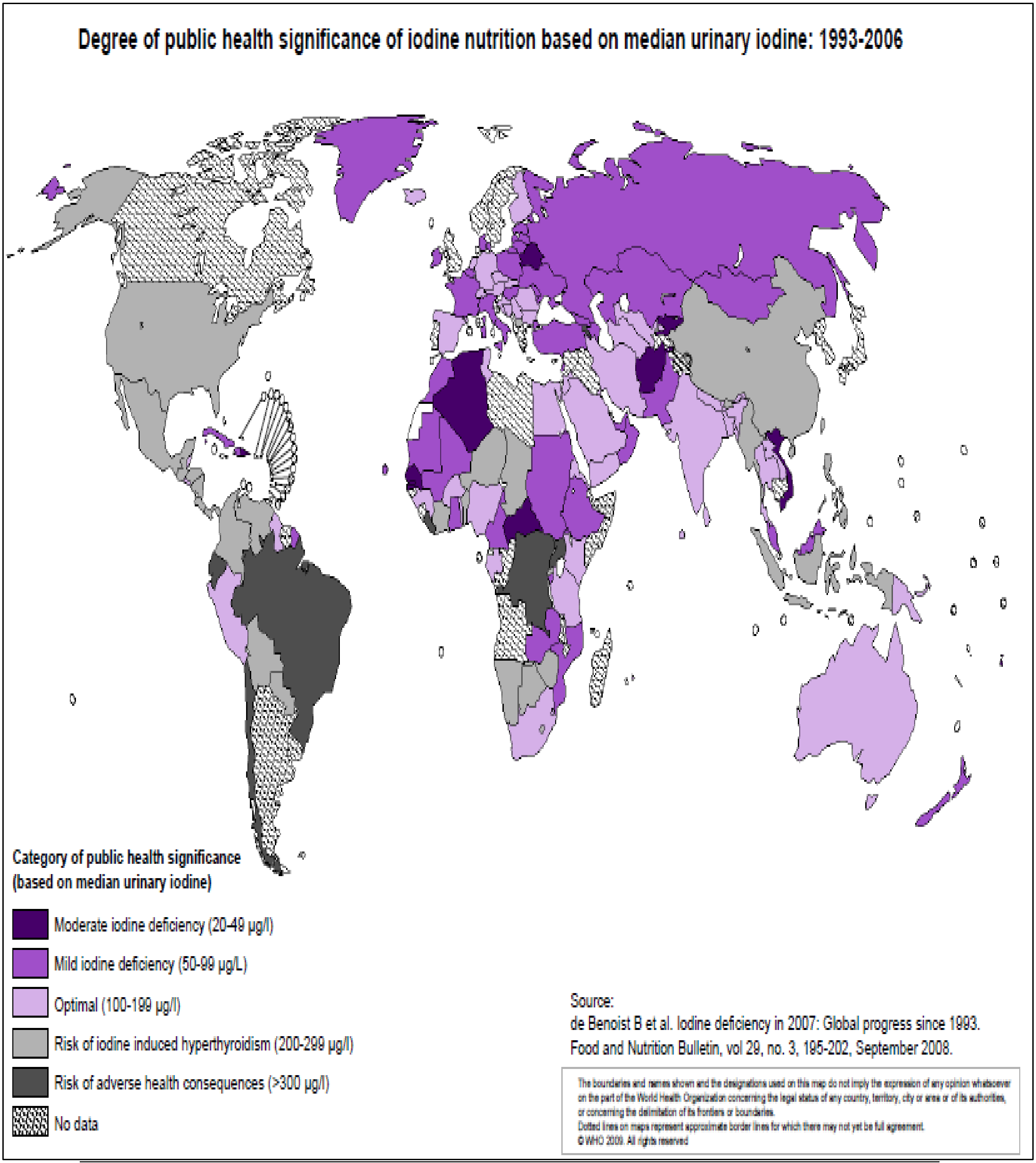
^{125}I is a short-lived radioisotope discovered by Reid and Keston in 1946 in a tellurium solution that had been bombarded with deuterium (Baker and Gerrard 1972). It has a half-life of 59.4 days and decays by electron capture, followed by a 35.5 keV gamma ray from the resulting ^{125}Te nucleus, as well as low energy Auger electron. (Coenen et.al 2006). ^{125}I is produced anthropogenically from the nuclear reaction of tellurium-125 in a cyclotron $^{125}Te\ (p,n)\ ^{125}I$ or from reactor irradiation of xenon-124 (Baker and Gerrard 1972). There are many applications of ^{125}I primarily in scientific research and chemical compound labelling, such as methotrexate (Paxton, Rowell, and Cree 1978; Baker and Gerrard 1972). Attempts to use it in cancer therapy for colorectal adenocarcinoma and brain tumor gave promising results (Gutin et al. 1984; Martinez-Monge et al. 1999). In terms of medical radiography, ^{125}I was used for Single-Photon-Emission-Computing-Tomography (SPECT) imaging but its low energy emissions (35.5 keV) makes it only suitable for small animals (Cavina et al. 2017).

1.4.3 Iodine-127

^{127}I is the stable isotope of iodine that is an essential element for the formation of thyroid hormones which are critically important for metabolism and growth in humans and animals (ATSDR 2004). The World Health Organization (WHO) recommends that daily iodine intake should be 90-120 μg for children less than twelve, 150 μg for children above twelve and adults, and 250 μg for pregnant and lactating women (ATSDR 2004). If the daily intake is below these recommended levels; iodine deficiency occurs (Mannar and Dunn 1995). Iodine deficiency has had significant attention from the WHO since 1945 and it is believed that approximately two billion individuals have insufficient daily iodine intake (Zimmermann 2009). Iodine deficiency is classified into moderate and mild deficiencies, and is linked to many health disorders such as autism, hypothyroidism, brain damage, psychomotor impairment, and goitre (Table 1.4). According to the WHO data (Fig 1.3), 47 countries have iodine deficiency; 10 were classified as moderate iodine deficiency and the remaining 37 were classified as mild (de Benoist et al. 2004). According to the Canadian Health Measures Survey (CHMS) , the median urinary iodine concentration in Canada was 151 µg/L which is within the range of the optimal intake recommended by the WHO (Statistics Canada 2012).

Table 1.4 Health disorders linked with IDD

Physiological groups	***Iodine Deficiency Disorders***
All Ages	*Goitre - Hypothyroidism*
Adult	*Impaired mental function*
Child and adolescent	*Impaired mental function - Delayed physical development*
Pregnant woman	*Abortion*



Source:
de Benoist B et al. Iodine deficiency in 2007: Global progress since 1993.
Food and Nutrition Bulletin, vol 29, no. 3, 195-202, September 2008.

Figure 0.3 3 Degree of iodine status worldwide based on urinary iodine concentration.

1.4.4 Iodine-129

^{129}I is a long-lived radioisotope with a half-life of 16.14 million years (García-Toraño et al. 2018). It is produced naturally by the nuclear interaction of cosmic rays with xenon in the upper atmosphere and by the spontaneous fission of uranium-238 in minerals (Raisbeck and Yiou 1999). The natural production of iodine 129 is estimated as 5.29x10^{5} Bq/y. Since 1945, the concentration of ^{129}I in the environment has increased sharply due to anthropogenic nuclear activities such as nuclear weapons testing, nuclear fuel reprocessing plants (NFRP), and a minor contribution from nuclear power plant (NPP) accidents and emissions (Fig.5). Anthropogenic production ranges from 3.7x10^{11} to 5.21x10^{11} Bq/y (Sunny et al. 2014a). Therefore, the I^{129}/I^{127} ratio in environmental samples ranges from 10^{-12} up to 10^{-4} depending on proximity to a point source of ^{129}I (Fig.4) (Zhang and Hou 2013). A study by Zhang et al. 2013 differentiated ^{129}I/^{127}I ratios into three categories: pre-nuclear era natural levels with ^{129}I/^{127}I ratios of 10^{-12}, modern background ^{129}I/^{127}I ratios ranging from 10^{-11} to 10^{-9}, and contaminated areas that have ^{129}I/^{127}I ratios of 10^{-8} or higher. As a mobile long-lived radioisotope in the hydrosphere and atmosphere, iodine is distributed throughout the environment and can easily enter the food chain through the hydrosphere, atmosphere, and geosphere (Jabbar, Wallner, and Steier 2013; Zhang and Hou 2013). Since ^{129}I is a fission product, it is a very good indicator of the global dispersion of nuclear emissions, without being itself a dangerous radioisotope. Owing to its high mobility ^{129}I is distributed through different chemical forms in the environment and can stay in oceans up to 10^{5} years and in the atmosphere up to 30 days (Jabbar, Wallner, and Steier 2013; Zhang and Hou 2013).

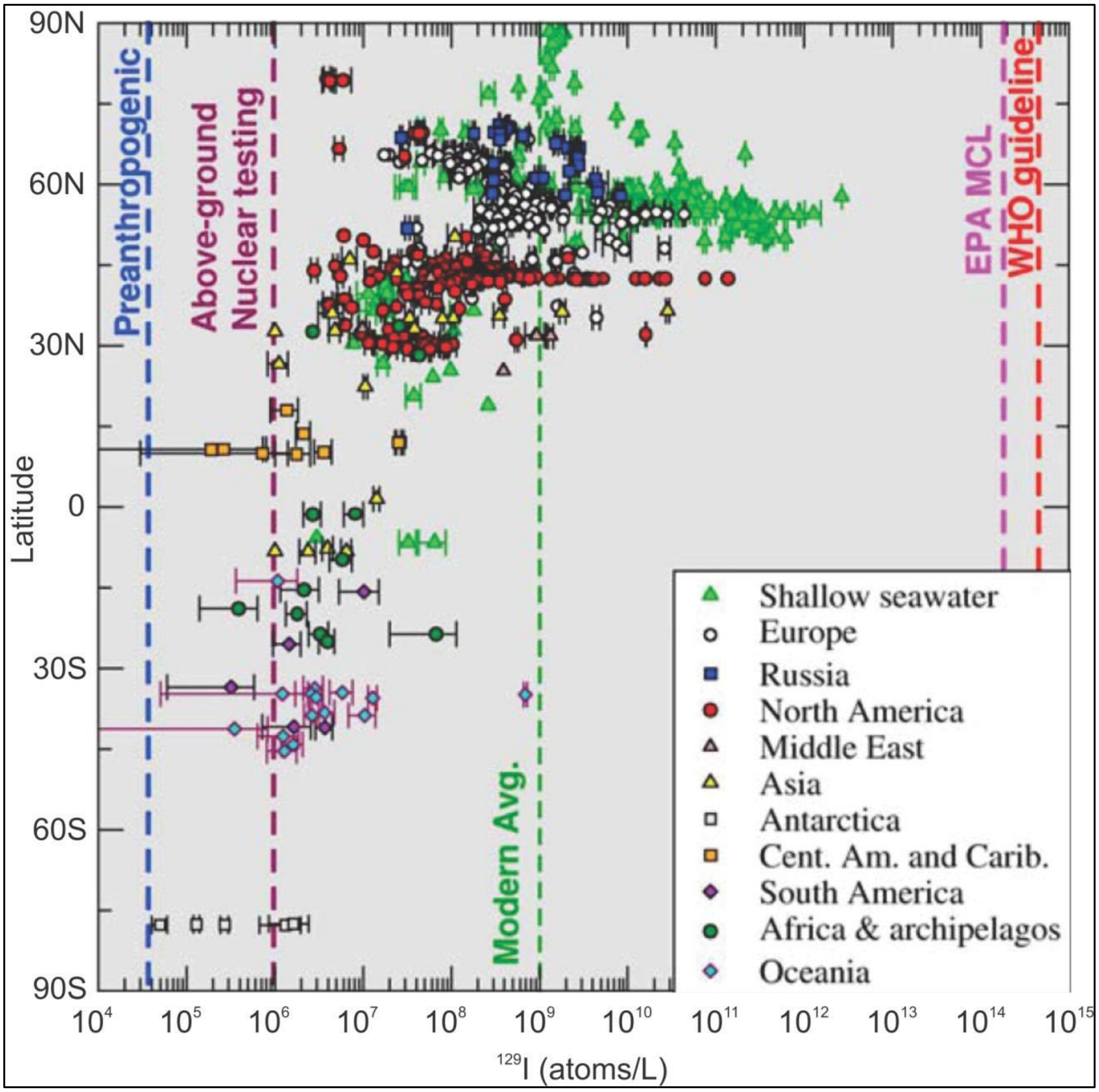

90N
60N
30N
0
30S
60S
90S
Latitude
10^4
10^5
10^6
10^7
10^8
10^9
10^{10}
10^{11}
10^{12}
10^{13}
10^{14}
10^{15}
^{129}I (atoms/L)
Preanthropogenic
Above-ground Nuclear testing
Modern Avg.
EPA MCL
WHO guideline
▲ Shallow seawater
○ Europe
■ Russia
● North America
△ Middle East
△ Asia
□ Antarctica
■ Cent. Am. and Carib.
◆ South America
● Africa & archipelagos
◆ Oceania

Figure 0.4 . Global distribution of ^{129}I/^{127}I ratios in shallow seawater, rivers and lakes. EPA MCL = the Maximum contaminant level that is allowed in water based on US Environmental protection Agency. adapted from (Matthew Noel Herod 2015).

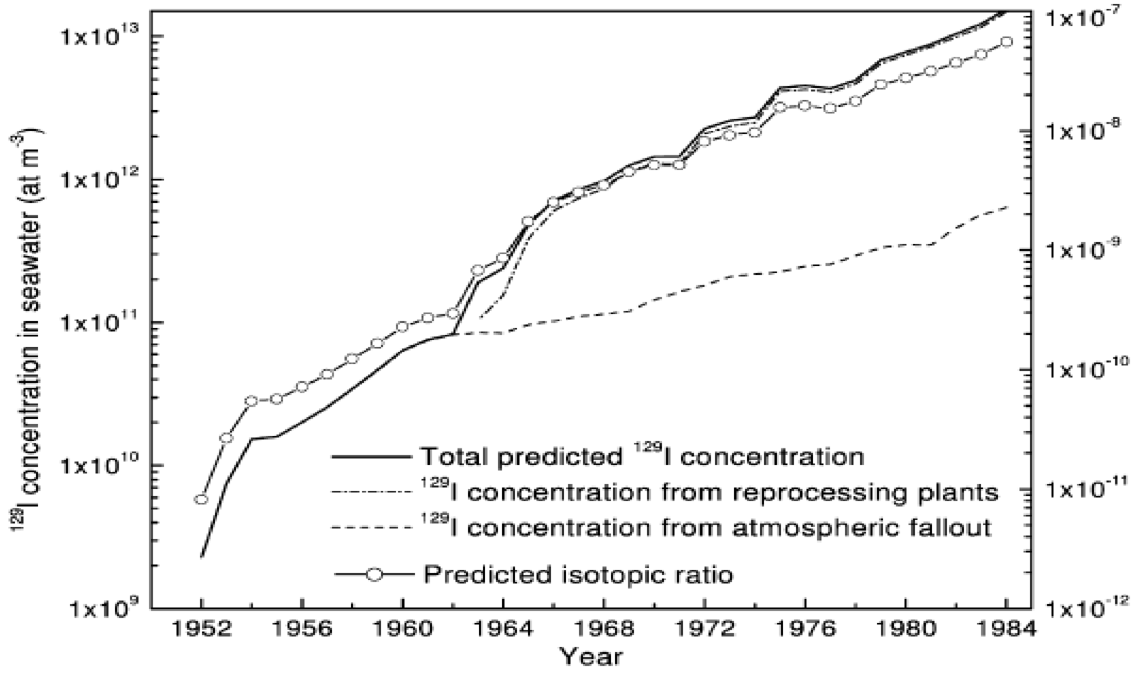


Figure 0.5 The impact of the reprocessing plants on ^{129}I concentration over time. adapted from (López-Gutiérrez et al. 2004).

1.4.5 Iodine-131

^{131}I is a highly radioactive isotope of iodine. It has a half-life of 8.02 days and decays by beta emission giving a 606 keV electron. (Mody et al. 2015; Cavina et al. 2017). It is produced as fission product of ^{235}U or a from nuclear reaction of Tellurium-130 in a cyclotron *^{130}Te (n,ɣ) ^{131}I* (Coenen et.al 2006). ^{131}I is considered the most dangerous radioactive contaminant of nuclear accidents. If released it can enter the human body through inhalation or ingestion (WHO 2017). Thyroid tumors are the moat common consequences observed after nuclear accidents or atomic bomb detonations, and higher rates of thyroid cancer were linked to radioactive iodine ^{131}I after the Chernobyl accident (Likhtarev et al. 1995). Children and adolescents are at higher risk of developing radiation-induced thyroid cancer, since their uptake rate is higher during the development, and their tissue dose also is relatively higher due to the small size of their thyroid glands. ^{131}I is the most common and widely used radioisotope in medical diagnosis and shows notable success in therapeutic purposes, such as radioimmunotherapy for thyroid cancer as well as neuroendocrine tumors and hematologic malignancies (Scott and Lee 2008). Although, ^{131}I from external radiation is linked to thyroid cancers, therapeutic ^{131}I causes fewer cancer cases (Hall, Mattsson, et al. 1996; Hall, Fürst, et al. 1996). (Hindié et al. 2002) suggested that the thyroid gland is increasingly sensitive to radiation with decreasing age. Therefore, (Hindié et al. 2002) recommended that the medical use of ^{131}I should not be performed in children. In addition, it was observed that the toxicity of ^{131}I when entering the organisms through inhalation is higher than ingestion (Luchanskii et al. 1988). Therefore, the route of exposure to ^{131}I could play a significant role in developing radiation-induced thyroid cancer.

1.5 Iodine toxicokinetics in humans

1.5.1 Absorption

The main route of iodine exposure is through ingestion, then inhalation, and very low quantity may be absorbed through the skin or eyes. Iodine is ingested in a number of chemical forms by gastrointestinal tract (GIT). However, these chemical forms are converted into the iodide ion in the stomach before it is absorbed (ATSDR 2004). The absorption rate of iodine in the gastrointestinal tract is reported to be similar in all ages above 18 years old (Sternthal1980). Once iodide is absorbed, it is transported in the bloodstream by binding to plasma and is quickly metabolized with half -life around 10 hrs. The active uptake of iodine is controlled by sodium/iodide symporter (NIS), that is located in the cells of the thyroid membrane. NIS pumps iodide into the thyroid based on the required amount. For prolonged iodine intake at several times, less than 10% of iodide is absorbed by thyroid, while in cases of severely deficient intake, the absorption reaches 80% (M. Li and Eastman 2012). Nonetheless, the presence of perchlorate, thiocyanates, isothiocyanates, and nitrates can decrease iodide absorption which may lead to a decrease in thyroid production (Prasad et al 2020).

1.5.2 Distribution/ Metabolism

Once iodine is absorbed into the bloodstream, it must be distributed to its site of action, i.e., the thyroid gland. The thyroid converts iodide into neutral iodine (I) or iodonium (I+) where it is added to its hormones. More than 80% of the iodine in the human body is stored in the thyroid gland with an amount ranging between 10-20 mg in healthy adults (Hou and Ding 2009; M. Li and Eastman 2012). The thyroid gland is an endocrine gland located on the front and sides of the trachea and produces three types of hormones: thyroxine (T4), triiodothyronine (T3), and calcitonin. Iodine is essential to the synthesis of T4 and T3. Thyroxine ($C_{15}H_{11}O_4I_4N$) has four atoms of iodine while triiodothyronine (T3) has three atoms of iodine. Both hormones function in the body to synthesize proteins, and to produce energy by increasing cellular respiration of carbohydrates, fatty acids, and amino acid molecules. In general, T4 and T3 contribute to the growth of body parts and organs such as the muscles, liver, and brain in mammals (Scanlon 2007). In order to adequately synthesize T4 and T3, the thyroid gland requires no more than 70 µg daily. The recommended daily allowance level of iodine 150 µg/day, which is double the thyroid gland required value, may be necessary for optimal function of other non-thyroidal tissues. Thus, further research and study of iodine beyond its role in thyroid hormones is needed (Venturi 2011).

1.5.3 Excretion

Iodine that is free in bloodstream or not stored in the thyroid gland leaves the body, primarily through urine and a small amount through sweat, saliva, and breast milk (ATSDR 2004), The concentration in urine is varies considerably among individuals and on a daily basis. Under condition of adequate intake, more than 90% of iodine is excreted in the urine as iodide, with limited re-absorption in the kidney (M. Li and Eastman 2012; ATSDR 2004; Nath et al. 1992; Rao, McCready, and Spathis 1986; Vought and London 1967). The excretion of iodine through faeces was reported and its concentration was negligible as <0.5% of ingested iodine (Hays 2001). The excretion half-life varies among individuals and has been reported to be between 15.1 -54.6 days with a mean of 31 days. In terms of dietary iodine, the Agency for Toxic Substances and Disease Registry (2004) reported that iodine leaves the body through urine in few weeks to months. Therefore, it recommended that patients with thyroid cancer begin a low iodine diet at least 2 weeks prior to performing a radioiodine scan, to eliminate dietary iodine and increase the absorption for radioiodine treatment (Burman 2016).

1.6 Research Rationale

To combat iodine deficiency, iodine is an essential component of the human diet that in many countries is supplemented though mandated addition to salt. Due to widespread iodine deficiency disorder the WHO recommends that iodine be added as a dietary supplement. Many types of food such as salt, milk, bread, and water have been considered as possible supplemental sources of iodine (de Benoist et al. 2004). Among these foods, salt has been internationally accepted, because it is widely used in culinary recipes. Therefore, it is recommended as a supplement to cure iodine deficiency disorder (IDD) internationally (Mannar and Dunn 1995). Consequently, many studies suggest that iodized salt is a very important source of iodine in humans. For example, (Gunnarsdottir and Dahl 2012) mentioned that iodized table salt is the main dietary source of iodine in the human diet and provides 50% of iodine intake Sweden. Other studies (Pandav et al. 2013) and (Fields and Borak 2009) mentioned the same concept indirectly by saying that avoiding iodized salt may increase the risk of iodine deficiency. Moreover, the WHO and the International Council for Control Iodine Deficiency Disorder (ICCIDD) believe that iodine fortification in salt is an important strategy for iodine deficiency elimination (Mannar and Dunn 1995)(de Benoist et al. 2004).

However, more recently some uncertinaty has arisen as to the importance of iodized salt for daily iodine intakes. For example, a study by (K. E. Charlton et al. 2013) shows that lower iodized salt intakes did not compromise iodine status in the study population in Cape Town, South Africa. In addition, (He et al. 2016) studied the effect of salt reduction on iodine status. Their findings indicate that reducing salt consumption by 30% of its recommended daily intake did not compromise iodine status. Moreover, (Nazeri et al. 2015) showed that iodine status was inadequate for a lactating woman, despite mandatory salt iodization. Furthermore, (K. Charlton et al. 2014) were concerned about the WHO recommendation to reduce salt intakes by 30% in 2025 and tested how far this reduction may compromise iodine status due to the fact that iodized salt is an established strategy to reduce IDD. Their study concludes that there is no difference in iodine status between women who are salt users and women how are non-salt users and that both groups had a mild iodine deficiency. Therefore, greater empirical knowledge of iodine sources in the human body is needed, in particular, which foods are the most important contributors of dietary iodine. Most studies consider that high iodine content in specific food reflects food importance as a source of iodine in the human diet, ignoring many factors such as daily intake, iodine loss during storage or cooking, and iodine absorption and metabolism in the presence of iodine inhibitors.

1.7 Thesis Statement

^{129}I exists in the environment and has been identified as potential tracer; however the applications of ^{129}I are typically limited to environmental investigations such as its use as a tracer in oceanography, groundwater dating or nuclear emissions (Jabbar, Wallner, and Steier 2013; Zhang and Hou 2013). Due to the sensitivity of AMS, there is an opportunity to expand the use of ^{129}I applications into new fields such as biomedical applications or nutrition. There is potential to use I^{129} to identify different sources of iodine in the human diet. The primary objective of this thesis is to expand the applications of the ^{129}I in biomedical and nutritional fields. This goal is addressed through several subsidiary objectives:

1- Extracting ^{129}I from human urine to establish a baseline ^{129}I concentration and ^{129}I/^{127}I ratio for the Ottawa area. Previously, one study, (Hou et al. 2003), measured ^{129}I in three urine samples by NAA (Neutron Activation Analysis). This research aims to measure iodine ^{129}I and ^{127}I in urine samples directly by accelerator mass spectrometry. To do this, a new rapid and efficient extraction technique was developed and 25 human urine samples were analyzed.

2- Extracting ^{129}I and ^{127}I from human breastmilk to determine its concentration to predict the concentrations inside human infant using the AMBER compartment model. To do this, a combustion extraction technique was developed to reliably extract iodine from breastmilk samples.

3- Applying a computational modelling tool used in the nuclear industry, called AMBER to investigate the main sources of ^{127}I and ^{129}I in the Canadian diet based on daily food consumption. This will include investigating the relative importance of different food items such as salt, milk, water, grains, meat and fish to urinary iodine concentrations and the $^{129}I/^{127}I$ ratio in urine. Moreover, the concentrations of ^{127}I in infant urine will be predicted based on their iodine intake from previously measured breastmilk using AMBER. The findings will be used to assess the adequacy of breastmilk iodine concentration thresholds for adequate iodine nutrition as well as the applicability of modelling in place of direct sampling of infant urine, which is challenging.

This is a novel application of the AMBER model to the field of nutrition.

1.8 Contributions by collaborators

The majority of the laboratory work, data collection and interpretation were done by the author (FA). The contributions of colleagues at the Andre E. Lalonde AMS Laboratory and other contributions are outlined below:

Chapter 2: The design of the iodine 129 extraction method was done in collaboration with Prof. Jack Cornett and Dr. Barbara Francisco.

Chapter 3: Breastmilk samples were collected by Health Canada and analysed for ^{127}I by Nimal DeSilva and Smita Mohanty.

Chapter 4: The compartment model software (AMBER) was provided by Dr. Laura Limer.

Some lab training or assistance was provided by other members of Andre E. Lalonde AMS Laboratory, specifically Monika Wilk, Normand St. Jean, and Sarah Murseli.

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2 Chapter 2: Rapid and efficient autoclave digestion for the extraction of iodine-129 from urine samples

2.1 Abstract

A new method was developed to extract ^{129}I from urine samples and measure it using accelerator mass spectrometry (AMS). The samples were pre-treated in an autoclave with hydrogen peroxide and were then acidified with nitric acid, followed by the precipitation of iodine as silver iodide (AgI) for measurement by AMS. This new procedure is substantially faster than previous methods for the extraction of iodine from urine and results in less chemical waste. The efficiency and reproducibility of this method were evaluated by using ^{125}I as a yield tracer, eventually giving a recovery above 99%. To achieve this, several iterations of the method were required. The method was then successfully applied to measure ^{129}I/^{127}I isotopic ratios and ^{129}I concentrations in 25 human urine samples. The AMS results for ^{129}I in urine ranged 3.3 x 10^6 atoms/L to 884 x 10^6 atoms/L and the isotope ratio (^{129}I/^{127}I) in human urine ranged from 7.38 x 10^{-12} to 3.97 x 10^{-10} with a median of 1.29 x 10^{-10}. This new method will be useful for investigations into the sources of iodine in the human diet and their relative importance for iodine sufficiency.

2.2 Introduction

^{129}I is a long-lived radioisotope with a half-life of 16.14 million years (García-Toraño et al. 2018). It is produced naturally by the nuclear interaction of cosmic rays with xenon in the upper atmosphere and by the spontaneous fission of uranium-238 in minerals (Raisbeck and Yiou 1999). Since 1945, the concentration of ^{129}I in the environment has increased sharply due to anthropogenic nuclear activities such as nuclear weapons testing, nuclear fuel reprocessing plants (NFRP), and a minor contribution from nuclear power plant (NPP) accidents and emissions. A study by Zhang et al. 2013 differentiated ^{129}I/^{127}I isotope ratios into three categories: pre-nuclear era natural levels with ^{129}I/^{127}I ratios of 10^{-12}, modern background ^{129}I/^{127}I ratios ranging from 10^{-11} to 10^{-9}, and contaminated areas that have ^{129}I/^{127}I ratios from 10^{-8} higher. As a mobile long-lived radioisotope in the hydrosphere and atmosphere, iodine is distributed throughout the environment and can easily enter the food chain through the hydrosphere, atmosphere, and geosphere (Zhang and Hou 2013; Jabbar, Wallner, and Steier 2013). As a fission product, ^{129}I is a good tracer of the global dispersion of nuclear emissions, without being itself a dangerous radioisotope.

High ^{129}I concentrations can be measured by activity counting methods such as liquid scintillation counting (LSC), γ-spectrometry, or neutron activation analysis (NAA) as well as mass spectrometry techniques such as Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) and Accelerator Mass Spectrometry (AMS). Of these methods, AMS is the only one that can measure ^{129}I in environmental and biological samples at the low abundances typically found in the environment.

Applications of ^{129}I are typically limited to environmental investigations such as its use as a tracer in oceanography, groundwater dating or nuclear emissions (Zhang and Hou 2013; Jabbar, Wallner, and Steier 2013). Due to the sensitivity of AMS, there is an opportunity to expand the use of ^{129}I applications into new fields such as biomedical applications or nutrition, which have been investigated less frequently. One hurdle to expanding ^{129}I applications is extracting ^{129}I from biological samples for AMS analysis. Due to its low concentration in the environment, ^{129}I analysis requires chemical separation that must consider many factors such as sample type, sample size, and iodine chemical species (Lu et al. 2010; Zhang and Hou 2013; Jabbar, Wallner, and Steier 2013). ^{129}I pre-treatment procedures such as UV-irradiation, caustic fusion, acid decomposition, oxidant decomposition, alkaline leaching, ashing, combustion, and microwave digestion have all been used with varying degrees of complexity and success, to prepare ^{129}I samples for AMS analysis (Matthew N. Herod et al. 2014; Gómez-Guzmán et al. 2011; Muramatsu et al. 2008; Lu et al. 2010; Zhang and Hou 2013).

Regarding ^{129}I in urine, there is only one study by (Hou et al. 2003) that measured ^{129}I in three urine samples, using neutron activation analysis (NAA). (Hou et al. 2003) used three to four liters of urine and compared ^{129}I in animal thyroid and human urine. To date, no studies have measured ^{129}I in urine by accelerator mass spectrometry.

Urine is a human waste product that is typically excreted in a range of 600 ml to 2000 ml daily and is a common clinical sample. In general, 95% of urine is water, and 5% is dissolved solutes (Strasinger.2008). Urine contains a high concentration of urea, organic substances such as creatinine, and inorganic elements, which are primarily chloride followed by sodium, potassium, and trace amounts of others (Strasinger.2008).

This paper aims to demonstrate a reliable and reproducible method for the measurement of ^{129}I in human urine, by using thermal-pressure digestion in an autoclave for AMS analysis and by relating the result to iodine sources in the diet in a preliminary sense. The initial results from the method are presented and compared to those of (Hou et al. 2003). The efficiency and reproducibility of this method were evaluated using ^{125}I as a tracer of recovery, and a discussion on the factors that affect the extraction efficiency and AMS measurements is presented. This study is a first step towards understanding the sources of ^{127}I and ^{129}I in the human diet using ^{129}I as a nutritional tracer. This procedure is envisaged to potentially expand the applications of ^{129}I into non-environmental fields.

2.3 Methods

2.3.1 Chemicals and Instruments

Urine samples were digested in 60 ml borosilicate glass tubes in an autoclave (Tuttnauer Brinkmann). ^{125}I tracer solution (37 MBq) was ordered from PerkinElmer and diluted in 14.9 M NH_4OH to give an activity of 20,000 Bq/ml for use as a recovery tracer. All solutions were prepared using 18 MΩ de-ionized water. The parameters used for autoclave digestion are given in Table 2.1.

A PerkinElmer Wizard 2 Automatic Gamma Counter (2470-0020) with two well type NaI detectors was used to measure ^{125}I to quantify the extraction efficiency. Using ^{125}I as a quantitative recovery tracer for ^{127}I and ^{129}I has been reported in detail elsewhere (Herod et al. 2014). Briefly, the method uses the coincidence sum gamma counting method to determine absolute sample activity without the need for a calibrated standard of ^{125}I (Horrocks and Klein 1974). Relative efficiencies were calculated for each sample according to the method of (Horrocks 1974; Horrocks and Klein 1974) and are reported in Table 7. A 3MV HVE tandem AMS system was used to measure the concentrations of ^{129}I in the AgI extracted from the urine at the Andre E. Lalonde Accelerator Mass Spectrometry Laboratory. The technical details of the ^{129}I measurement by AMS are described in (Francisco et al. 2020) and ion source parameters are given in Table 2.2. An Agilent 8800 ICP-MS triple quadrupole was used to measure the concentrations of ^{127}I.

Table 2.1 Autoclave parameters

Parameter	**Value**
Program	Wrapped Instruments and Porous Loads
Temperature	250°F (121°C)
Digestion Time	20 min
Dry time	60 min

Table 2.2 AMS ion source parameters (adapted from Francisco et al. 2020).

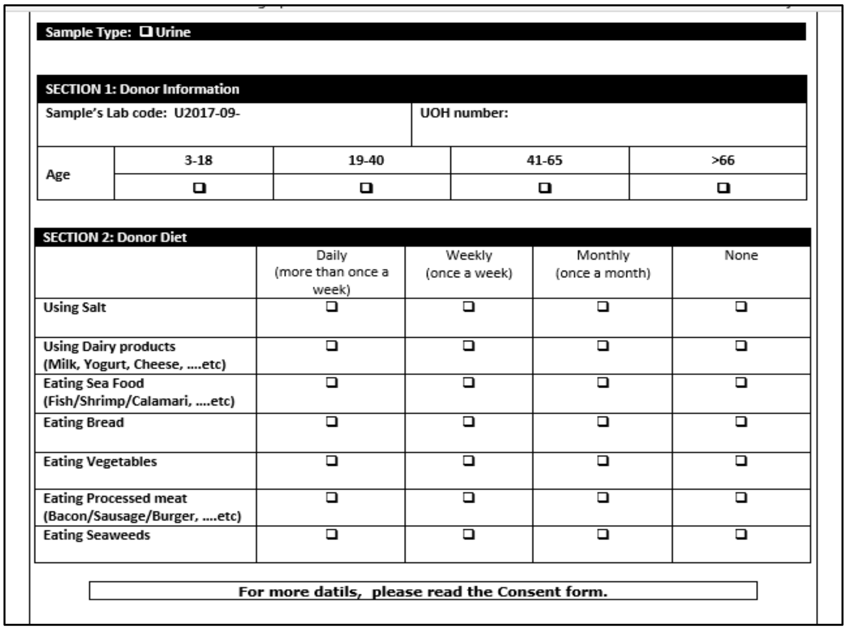
Parameter	**Value**
Cesium reservoir temperature	80 °C
Target Voltage	7.0 kV
Target current	0.5–1.5 mA
Extraction Voltage	28.0 kV
Extraction current	0.2 mA
Ionizer current	18 A
Vacuum (mbar)	0.5–1.0 mBar

2.3.2 ^{127}I analysis by inductively coupled plasma mass spectrometry

The most commonly used method to measure iodine in urine is direct dilution and ICP-MS analysis. In this procedure, we considered FDA guidelines for method validation (FDA 2018), and we applied a modified procedure of (Allen et al.1990) as follows: 1 g of urine sample was mixed with 9 grams of 1% 0.292 M ammonium hydroxide (NH_4OH) to obtain a 1/10 dilution. To avoid any sample memory during the analysis, the samples were diluted an additional 50 times with deionized water.

2.3.3 Sample collection and preparation

Human urine samples were collected in sterile, dry, 200 ml polypropylene, disposable containers from 27 individuals living in Ottawa, Ontario, Canada. Their ages ranged from 3 years old to more than 66 years old (Table 3). Ethics approval was obtained from the University of Ottawa, and participants were provided with consent forms and surveys about their eating habits (Figure 2.1). The participants were advised to fill the container in the early morning as morning urine typically has a higher specific gravity, i.e., less water and more solute than urine from other times of day (Strasinger 2008). The minimum urine volume required to perform the experiments was 100 ml.



Sample Type: ☐ Urine

SECTION 1: Donor Information

Sample's Lab code: U2017-09-		**UOH number:**		
Age	**3-18**	**19-40**	**41-65**	**>66**
	☐	☐	☐	☐

SECTION 2: Donor Diet

	Daily (more than once a week)	Weekly (once a week)	Monthly (once a month)	None
Using Salt	☐	☐	☐	☐
Using Dairy products (Milk, Yogurt, Cheese, ….etc)	☐	☐	☐	☐
Eating Sea Food (Fish/Shrimp/Calamari, ….etc)	☐	☐	☐	☐
Eating Bread	☐	☐	☐	☐
Eating Vegetables	☐	☐	☐	☐
Eating Processed meat (Bacon/Sausage/Burger, ….etc)	☐	☐	☐	☐
Eating Seaweeds	☐	☐	☐	☐

For more datils, please read the Consent form.

Figure 2.1 An example of the questionnaire given to all participants.

Table 2.3 Participants demographic information.

Age (years)	Number
3 to 18	4
19 to 40	14
41 to 65	8
> 66	1
Total number	**27**

2.3.4 Extraction of ^{129}I from urine for AMS analysis

Four progressive iterations were required to develop the optimal procedure to extract ^{129}I from the urine samples. In order to improve the yield of iodine and to minimize the chemical waste, the fourth iteration that used less HNO_3 and less NH_4OH was applied to all samples for the extraction to analyse the samples by AMS.

In the fourth, and final, extraction procedure, 25g of urine plus 5 g of hydrogen peroxide were treated in the autoclave. After digestion in the autoclave, twenty milligrams of sodium carbonate Na_2CO_3 was added and heated on a hot plate for 10 min to remove any residual hydrogen peroxide. The samples were then acidified using 0.2ml of 15.66M HNO_3 to lower the pH to around one, and two milligrams of iodine as NaI carrier with a $^{129}I/^{127}I$ isotope ratio of 1.4×10^{-14} was added. To precipitate a sample of AgI for AMS, 200 µl of 0.1M $AgNO_3$ was added. The samples were left for 12 hours in darkness to allow the precipitate to settle. The precipitate was collected and washed in de-ionized water and 1 ml of 14.99 M ammonium hydroxide, NH_4OH, was added to dissolve any co- precipitating AgCl. The samples were centrifuged and the supernatant removed. The precipitate was washed in de-ionized water and centrifuged. The samples were dried in the oven at 60°C for overnight. The AgI precipitate was then prepared for AMS analysis by mixing it with pure niobium powder in a ratio of 1:1 or 1:2 by volume and pressing the mixture into a copper cathode to make the AMS target. A flow chart of the method is shown in Fig 2.2.

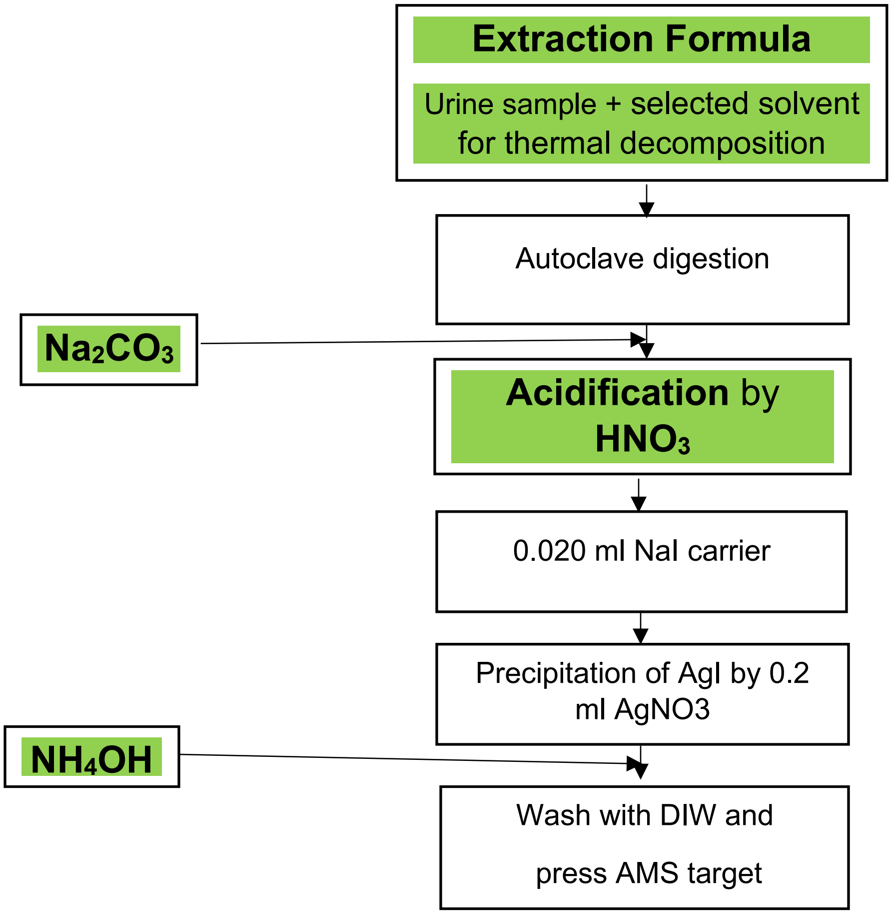


Figure 2.2 Flow chart showing the chemical extraction of 129I in urine. Steps in the bold were varied among the iterations.

2.3.5 Blanks, Standards and Duplicates

Deionized water was used as a process blank during the digestion and extraction procedure and analyzed on both AMS and ICP-MS. The blank had a ^{129}I concentration of 2.47 x 10^6 atoms/L and a ^{127}I concentration of 0.13 µg/L and a resulting ^{129}I/^{127}I isotope ratio of 4.01 x 10^{-9}. For the AMS analysis both sodium iodide (NaI) carrier, and niobium powder were used as blanks. The

NaI carrier had an average ratio of 1.5 x 10^{-14} (n=3). The ratio was not calculated for the niobium powder as it simply measures spurious counts in the gas ionization detector of the AMS and is not analyzed for ^{127}I. The counts recorded in the ^{129}I window for the Nb blank had a mean of 17 (n=3), which is extremely low and shows there were essentially no background counts recorded for ^{129}I during AMS analysis. In the ICP-MS run, 1% NH_4OH was also used as blank and its concentration averaged 0.063 µg/L (n=23).

For AMS analysis the ISO-6II standard was used which has a ^{129}I/^{127}I ratio of 5.717 x 10^{-12}. The ratio for the standard averaged 5.716 x 10^{-12} (n=3). For ICP=MS, Indium-115 and tellurium-205 were used as internal standards to obtain optimal precision and to determine the accuracy of the ICP-MS instrument. Seven standards (0ppb), (1.56ppb), (3.125ppb), (6.25ppb), (12.5ppb), (25ppb), and (50ppb) were used to develop a calibration curve to determine ^{127}I in urine. The limit of detection was 0.0445 ppb, and the limit of quantification was 0.148 ppb.

Duplicates were analyzed on both AMS and ICP-MS. For ICP-MS in almost all samples duplicated were within the error of their corresponding sample. For AMS some of the duplicated samples showed more variance and were slightly outside the error of the corresponding sample in a few instances.

2.4 Results and Discussion

2.4.1 Experimental optimization

2.4.1.1 Optimization of iodine extraction from urine

Biological samples, such as urine, contain variously abundant components and elements, generally termed matrix, which often affect extraction recovery and reproducibility for rare isotopes. In order to measure ^{129}I in urine samples by AMS, the sample preparation should recover sufficient iodine through reduction of these matrix effects. In the case of iodine in urine, sample matrix is usually eliminated either by acid digestion or alkaline ashing (May et al. 1997). In this method, autoclave pre-treatment is used as an alternative to the conventional extraction techniques for ^{129}I, which typically use strong acids or bases to digest the sample (May et al. 1997; Lu et al. 2010). For the digestion, autoclave and microwave provide the same outcome of thermal breakdown (C. R. Taylor et al. 1996). However, the autoclave is generally more affordable than lab microwaves. The ability of the autoclave to break down organic matter is well known and it can be used to digest organic matter and compounds such as urine, if it is used with a proper digestion solvent (Jeffries, Dieken, and Jones 1979; Crowther 1978; Navarrete-López et al. 2012). Using an autoclave to extract iodine from samples is uncommon in the literature (Haldimann, Eastgate, and Zimmerli 2000); therefore, the evaluation of this technique with respect to iodine recovery was necessary to ensure all iodine remained in the sample. The recovery of iodine during autoclave pre-treatment was tested using the addition of a known amount of ^{125}I to determine the efficiency of the procedure.

2.4.1.2 Chloride interference

In the first and second iterations, potassium persulfate was the digestion solvent used. For the first iteration, 0.4 g of urine was mixed with 1 g of potassium persulfate then dissolved in 20 g of de-ionized water and digested in the autoclave. The preliminary AMS results showed that ^{129}I concentration was low and too close to the AMS background to obtain reliable data. Therefore, a second iteration with increased sample volume was attempted to increase the AMS signal. A 4 g urine sample was mixed with 1 g potassium persulfate then dissolved in 200 g of de-ionized water and digested. The sample was precipitated using the method described above; however, the resulting precipitate was initially white and became gray over time. A portion of this gray precipitate was collected and analyzed using a scanning electron microscope which showed a significant amount of chlorine relative iodine, suggesting that AgCl was coprecipitating with AgI (Table 2.4). This resulted in poor currents in the AMS ion source (Brunzel 2013).

Table 2.4 Scanning Electron Microscope results show chloride interferences for two samples from iteration two. Units in %.

Sample 1	Al	Cl	Ag	I	O	K	S	Total %
Spectrum 1	0.48	**22.71**	66.01	**5.48**	5.32			100
Spectrum 2	0.00	**22.45**	67.20	**5.37**	4.98			100
Spectrum 3	0.00	**16.30**	72.06	**6.29**	5.34			100
Spectrum 4	19.27	**17.62**	42.79	**0.00**	20.31			100
Sample 2								
Spectrum 1		**18.74**	59.78	**3.22**	10.53	4.23	3.49	100
Spectrum 2		**18.74**	63.80	**3.23**	9.17	2.43	2.63	100

The results of these initial experiments raise questions regarding the efficiency of digestion solvent, the required sample volume and how to eliminate interference from coprecipitation of AgCl.

2.4.1.3 Iodine loss due to volatilization

To resolve the problems identified in the first two iterations, potassium persulfate was replaced with hydrogen peroxide as the solvent, and the ratio of sample volume to solvent was changed to 5 ml urine + 0.5 ml H_2O_2 (10:1) in order to reduce dilution. 20 mg sodium carbonate, Na_2CO_3, was added after the autoclave digestion to remove residual hydrogen peroxide (Tingting Wu and Englehardt 2012). 3 mL of ammonium hydroxide was added at intervals before drying to eliminate chloride. A portion of the precipitate was collected and analyzed using a scanning electron microscope which showed a large reduction in the chloride interference (Table 2.5). However, both gamma spectrometry of the ^{125}I tracer and ^{129}I results from AMS showed that there was poor recovery despite these changes. We hypothesize that the loss of iodine from samples was related to the addition of nitric acid after the autoclave pre-treatment, which oxidized the iodine into the volatile I_2 species. Therefore, the acid volume was decreased in the fourth iteration from 1 milliliter to 0.2 millilitres to reduce iodine volatilization.

Table 2.5 SEM results show the absence of chloride interferences in the precipitate. Units are %..

Sample	Al	Cl	Ag	I	O	C	Total %
Spectrum 1	0.00	0.00	39.29	**45.03**	2.62	13.06	100
Spectrum 2	0.00	0.00	38.85	**44.35**	3.11	13.69	100

2.4.1.4 Effect of autoclave digestion and solvent on ^{125}I recovery

In order to determine if there was any loss of iodine in the autoclave, ^{125}I was added as a yield tracer. The data in Table 2.6 confirms that heat and pressure in autoclave digestion has no effect on ^{125}I recovery and, therefore, is not expected to cause a loss of ^{129}I or ^{127}I from the samples. In the first iteration, potassium persulfate was used as a digestion solvent because the persulfate digestion is known as a safe oxidizing agent used in iodine analysis (Pino, Fang, and Braverman 1996) but it requires more water and produces substantial chemical waste. Thus, another safe oxidizing agent such as hydrogen peroxide was used as a solvent along with an increase in the volume of urine. The results of the ^{125}I yield tracer for each solvent after digestion in the autoclave show that the recovery obtained from H_2O_2 was superior to that of $K_2S_2O_8$. As a result, H_2O_2 was chosen as the solvent for the optimized procedure as it is both more efficient and produced less waste.

Table 2.6 Analytical results of ^{125}I yield for the two-solvents (n=3 each) used in the extractions following autoclave digestion.

Sample	**Total Activity (Bq)**	**Recovery %**
Blank(air)	0	N/A
Mean value of ^{125}I standards (n=4)	2390	N/A
Mean value of ^{125}I in urine with $K_2S_2O_8$ (n=3)	2157	90.3
Mean value of ^{125}I in urine with H_2O_2 (n=3)	2510	105

Results are compared to the mean value of a known activity of ^{125}I in water (n=4). The results show that heat and pressure in autoclave digestion has no effect on ^{125}I recovery.

2.4.1.5 Comparison of ^{125}I recovery for each iteration

The ^{125}I recoveries for each iteration were compared and the results are summarized in Table 2.7. The second iteration was not tested as it was identical to the first except for an increased volume of the sample and volume of solvent.

Table 2.7 A comparison table of the iterations in terms of ^{125}I recovery

Iteration	**Total activity (Bq)**	**Error (Bq)**	**Recovery (%)**	**Efficiency (%)**
First	8765.6	0.01	42.4	65
	8206.8	0.01	39.7	65
	8351.5	0.01	40.4	65
Third	584.6	0.03	2.8	79
	536.8	0.03	2.6	79
	555.2	0.03	2.7	79
Fourth	20739.9	0.01	100.4	80
	20718.1	0.01	100.3	77
	20667.2	0.01	100	63

The comparison table of the iterations in terms of ^{125}I recovery shows that the fourth extraction procedure has more sensitivity and reproducibility.

The first iteration had a poor recovery of ^{125}I of less than 50% due to the low sample volume and interference from chloride in the samples, while the third experiment had very poor recovery of ~3% due to volatilization of iodine from the sample during acidification. The loss of iodine from samples in the first and third iteration is not related to the autoclave digestion as the results in Table 6 showed no loss of ^{125}I this step. The fourth iteration decreased the amount of acid used and as a result an excellent recovery of ^{125}I, exceeding 99%, was obtained.

2.4.2 ^{129}I and ^{127}I concentrations in urine

The fourth iteration of the method was successfully applied to measure ^{129}I in urine samples from 25 people. The AMS results for ^{129}I in urine ranged from 3.3 x 10^6 atoms/L to 884 x 10^6

atoms/L with a median of 108.7 x 10^6 atoms/L. The results of ^{127}I in the urine sample ranged from 24.1 µg/L to 3544 µg/L with a median of 160.4 µg/L. The ^{129}I/^{127}I ratio ranged from 7.38 x 10^{-12} to 3.97 x 10^{-10} with a mean of 1.36 x 10^{-10} and a median of 1.29 x 10^{-10}. All results are summarized in Table 2.8.

Table 2.8 Concentration of ^{129}I and ^{127}I in human urine from ICP-MS and AMS (n=25)

Sample ID	^{127}I concentration µg/L with standard error ± 0.24	^{129}I Concentration 10^6 atm/L	Error of ^{129}I Concentration 10^6 atm/L	^{129}I/^{127}I ratio 10^{-10}
1	225.6	238.3	6.65	2.23
2	79.7	61.8	2.74	1.64
3	3543.9	884.0	20.22	0.56
4	85.0	109.5	2.56	2.72
5	94.4	3.3	2.33	0.07
6	1197.0	798.6	18.31	1.41
7	207.2	217.3	4.63	2.21
8	339.7	318.4	7.51	1.98
9	94.8	16.1	1.01	0.36
10	255.4	40.2	1.76	0.33
11	24.1	15.3	1.28	1.33
12	143.1	87.7	2.49	1.29
13	139.6	180.2	3.61	2.72
14	482.5	84.5	2.63	0.37
15	394.8	340.6	17.05	1.82
16	185.9	264.6	5.65	3.00
17	338.8	108.7	2.66	0.68
18	122.6	52.2	2.61	0.90
19	81.0	12.4	3.36	0.32
20	160.4	50.8	2.78	0.67
21	131.0	32.1	2.23	0.52
22	83.3	156.6	3.25	3.97
23	102.3	14.2	0.87	0.29
24	441.8	231.0	8.21	1.10
25	222.7	157.5	4.40	1.49

Urinary iodine concentrations are highly variable from day to day (Zimmermann 2008b). The results in Table 2.8 show the concentration of ^{127}I on the day of collection. Figure 2.3 shows the frequency distribution of ^{127}I in the samples. One sample had a very low ^{127}I concentration of 24.1 μg/L which could be related to the age of that particular participant, who was 3 years old. Six samples were within mild deficiency concentration range (50-99 μg/L), eleven samples were within the optimal concentration range (100-299 μg/L), and five samples were within the risk of hyperthyroidism concentration range (300-499 μg/L). There were two samples which significantly exceeded the high concentration range (^{127}I above 500 μg/L) and exceeded 1000 μg/L. It is likely these extremely high values are due to thyroid diseases or iodine supplements taken by those participants. The ^{127}I and ^{129}I concentrations were found to be positively correlated when these high samples were included, with a Pearson r = 0.84 (n=25). If we consider the ^{127}I values above 500 μg/L as outliers and eliminate those samples from correlation analysis, the variables ^{127}I and ^{129}I were still found to be significantly correlated with a Pearson r = 0.56 (n=23). In both scenarios, the ^{129}I concentration had a statistically significant correlation with the ^{127}I concentration (Fig 2.4). This positive correlation suggests that there may be a common source of ^{129}I and ^{127}I in the human body or iodine residence and the biokinetic transfer of iodine within the body is relating ^{129}I and ^{127}I irrespective of its source. In environmental samples, including those from other studies analysing ^{129}I in North America, ^{129}I and ^{127}I are rarely correlated due to their differing sources (Matthew N. Herod et al. 2016; Fehn 1999) as the majority of ^{129}I usually enters environmental reservoirs through atmospheric washout, while ^{127}I is naturally occurring, and part of the ongoing iodine cycle with few additional sources. Therefore, observing this correlation in human urine is surprising. This is the first time such a correlation has been measured in humans and suggests that ^{129}I could be a potential tracer of dietary ^{127}I as it appears the integration of these two iodine isotopes may be occurring in nature prior to their consumption by humans. Alternatively, further study on the biokinetic transfer of iodine isotopes and their residence time in the body is also warranted to potentially explain this correlation. Nutritional literature generally presumes that most ^{127}I in the human body is from iodized salt (Pandav et al. 2013; Fields and Borak 2009; Gunnarsdottir and Dahl 2012) and salt iodination programs have been extremely successful in reducing hypothyroidism due to lack of sufficient dietary iodine, particularly in developing nations (Mannar and Dunn 1995; de Benoist et al. 2004). However, these results could indicate that the source of iodine in humans is mixed as opposed to being solely from iodized salt and that whatever the principal sources of iodine to humans is, they include ^{129}I as well. It is clear from this data that additional dietary sources of iodine may be important contributors of both ^{129}I and ^{127}I and their importance as iodine sources should be the subject of further study.

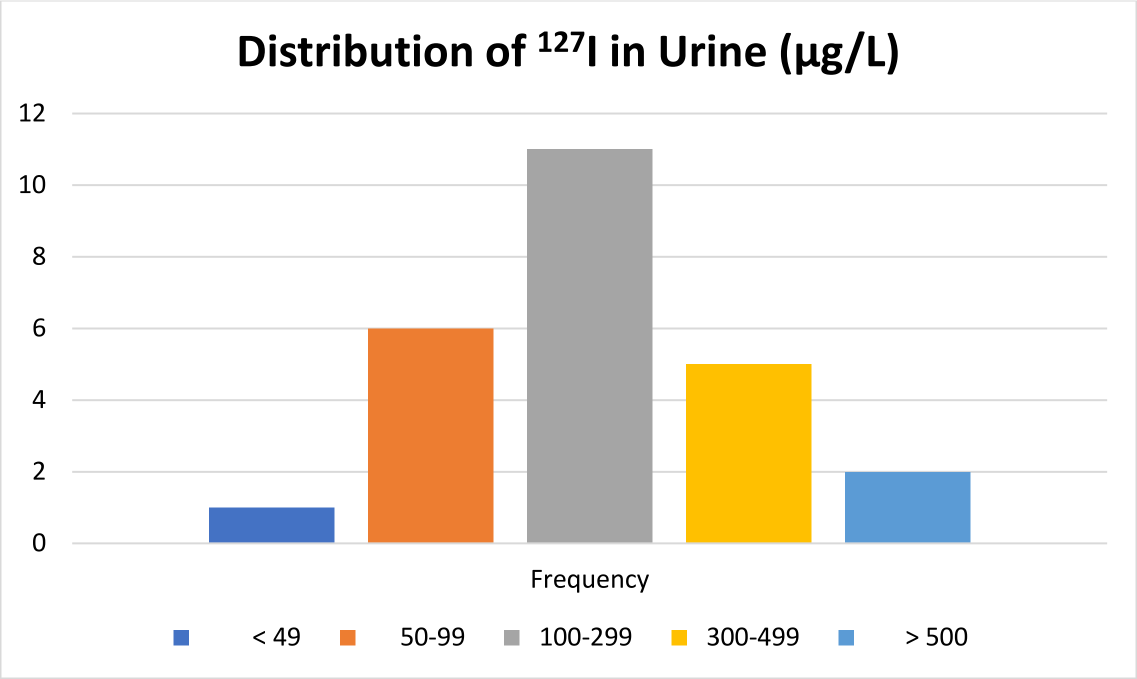


Figure 2.3 Frequency distribution of ^{127}*I concentration data based on 5 categories. Less than 49 is mild deficiency, 50-99 is moderate deficiency, 100-299 is optimal concentration, 300-499 is risk of hyperthyroidism concentration, and > 500 is high concentration.*

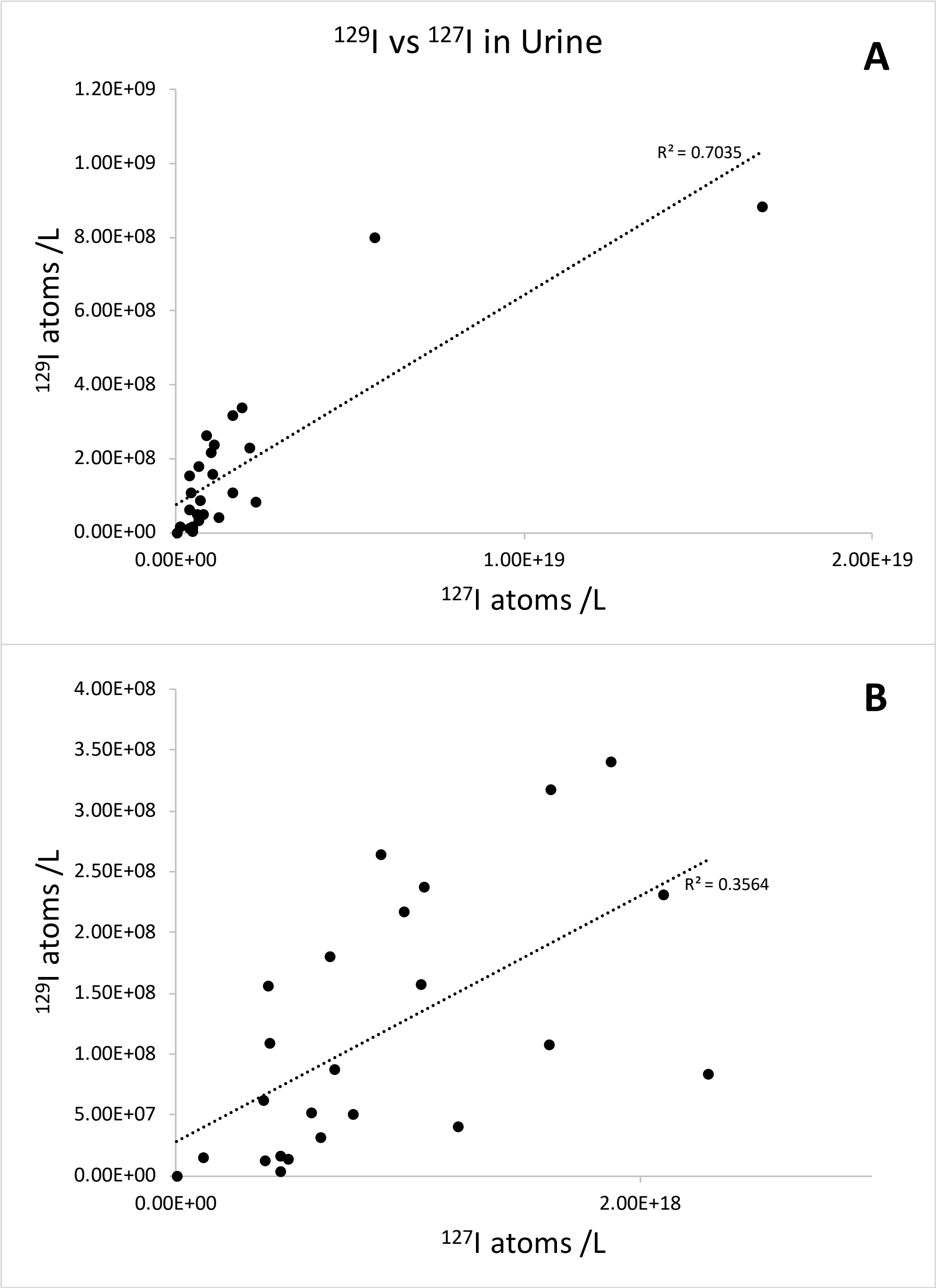


Figure 2.4 Linear regressions showing correlation of ^{129}I concentration expressed as atoms/L with ^{127}I atoms/L (A) $R^2 = 0.70$, $p < 0.01$, $n = 25$, (B) $R^2 = 0.36$, $p < 0.01$, $n = 23$.

The main sources of ^{129}I in the environment are from human nuclear activities specifically, nuclear fuel reprocessing plants in Europe and to a lesser degree, Asia. The release of ^{129}I from all sources, dominated by fuel reprocessing, is estimated at 5.21 x 10^{11} Bq/year, giving an estimated dose equal to 3.36 x 10^{-6} mSv/year, which is inconsequential compared to background (Sunny et al. 2014b). Although there is no radiation risk for human health at this current environmental dose level, the accumulation of ^{129}I in the human body should be investigated as it may be used as a tracer. To do so, it is helpful to establish a biological background level of ^{129}I and the ^{129}I/^{127}I ratio in humans as they may provide sensitive indicators of the key dietary sources of iodine isotopes. The ^{129}I/^{127}I ratios in our data ranged from 7.38 x 10^{-12} to 3.97 x 10^{-10} with median of 1.29 x 10^{-10}. These values all fall within the present environmental background level in the (Zhang and Hou 2013) study. Our ratios are considerably lower than those measured by Hou et al., 2003, where the median ratio in human urine was 1.87 x 10^{-8}. However, only 3 samples of urine were measured in (Hou et al. 2003) and cannot be used to establish a robust background level. Nevertheless, as the three urine samples were obtained from three males in Zealand, Denmark it highly probable that the source of these urine samples is responsible for the higher values of ^{129} I/^{127}I. In Denmark, the ^{129}I concentration is heavily influenced by nearby contributors of ^{129}I, such as atmospheric and liquid discharges from the nuclear fuel reprocessing plants at Sellafield and La Hague with a small contribution in the past from Chernobyl. Also, the concentration of ^{129}I in this area is influenced by a secondary emission of ^{129}I from surface seawater in the North Sea (Kadowaki et al. 2018). In comparison, the source of human urine samples in this study was from Ottawa, Canada, where the emission of ^{129}I is much lower. Indeed, the primary source of ^{129}I in North America today is wet deposition of ^{129}I from long-range atmospheric transport of ^{129}I from European fuel reprocessing, recycled ^{129}I from weapons testing and ocean volatilization (Wetherbee et al. 2012). As a result, the atmospheric deposition of ^{129}I in North America is much lower than western Europe, and the ^{129}I concentration in North American rivers and rain reflects this (Santschi and Schwehr 2004; Sheppard and Herod 2012). ^{129}I has been investigated in several sites in Ontario and around Ottawa. For instance, the ^{129}I concentration was measured in groundwater, snow, soil, and grass from Sturgeon Falls, Ontario, which is ~400 km from Ottawa. In these samples the ^{129}I concentration ranged from 1.5×10^5 atoms/L to 1.9×10^6 atoms/L in groundwater, 8.5×10^7 atoms/L in snow, 4.3×10^8 atoms/g in the soil, and 7.5×10^7 atoms/g in grass (Renaud et al. 2005). These ^{129}I concentrations are very similar to the data presented in this paper. The ^{129}I/^{127}I ratios reported for Sturgeon Falls groundwater, snow and soil are also very similar to those measured in human urine from Ottawa. This convergence between the Ontario environmental ^{129}I concentrations and urine of people who live in nearby supports the earlier hypothesis that the higher values of ^{129}I/^{127}I of urine in (Hou et al. 2003) compared to this study is related to the location and suggests that there is a strong influence on place of residence on the concentration of ^{129}I and the ^{129}I/^{127}I ratio in people. Furthermore, the convergence in urine values to the local environment also suggests that additional dietary sources, besides salt, may have an influence on the ^{129}I/^{127}I ratio in human urine and may indicate that ingestion of local food sources plays a key role in altering the ^{129}I/^{127}I ratio in people.

2.5 Conclusions

Iodine-129 was successfully extracted from human urine using hydrogen peroxide as a solvent and digested in an autoclave. Autoclave digestion was chosen because it is available in most labs and provides the same outcome, thermal breakdown, as a lab microwave (Taylor et al. 1996) with low cost. Inorganic ^{125}I was successfully used as a quantitative recovery tracer. Our extraction technique determined the optimal conditions needed to extract ^{129}I from urine efficiently. It was found that a smaller volume of acid (0.2 ml HCl) after autoclave digestion is critical to avoid loss of iodine by volatilization. After determining the optimal conditions for extracting ^{129}I from urine, 25 urine samples from Ottawa residents were analyzed. The concentration of ^{127}I and ^{129}I in Ottawa urine samples were significantly correlated and generally similar to the ^{129}I concentrations and $^{129}I/^{127}I$ ratios from environmental samples collected around Ottawa. The ability to measure ^{129}I in human urine expands the application of ^{129}I in the biomedical field and its use as a tracer. This new and reliable method will enable the investigation of the sources of iodine in the human diet and their relative importance for iodine sufficiency.

2.6 Conflict of Interests

The authors declare that they have no conflict of interest.

2.7 Human Rights:

All procedures followed were in accordance with the ethical standards of the Office of Research Ethics and Integrity committee in University of Ottawa, Canada. Informed consent was obtained from all participants for being included in the study.

2.8 Animal Rights:

This article does not contain any studies with animal subjects performed by the any of the authors.

2.9 Acknowledgment

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3 Chapter 3: Determination of ^{129}I in human breastmilk using combustion technique and AMS measurement to estimate its thyroid dose.

3.1 Introduction

The concentration of long-lived anthropogenic radionuclides has been increased in the environment by human nuclear activities. Most of these long-lived radionuclides are alpha and beta emitters and when they are ingested, they may pose a concern about their chronic effects on human health. One of these long-lived anthropogenic radionuclides is iodine 129. ^{129}I is a long-lived radioisotope with a half-life of 16.14 million years (García-Toraño et al. 2018). It is produced naturally by the nuclear interaction of cosmic rays with xenon in the upper atmosphere and by the spontaneous fission of uranium-238 in minerals, giving a natural world-wide production rate equal to 5.29x10^{5} Bq/y (Raisbeck and Yiou 1999) (Sunny et al. 2014b). However, since 1945, the concentration of ^{129}I in the environment has increased sharply due to anthropogenic nuclear activities. Therefore, the main sources of ^{129}I in the environment nowadays are specifically from, nuclear fuel reprocessing plants in Europe and to a lesser degree, Asia. A study by Zhang et al. 2013 differentiated ^{129}I/^{127}I ratios into three categories: pre-nuclear era natural levels with ^{129}I/^{127}I ratios of 10^{-12}, modern background ^{129}I/^{127}I ratios ranging from 10^{-11} to 10^{-9}, and contaminated areas that have ^{129}I/^{127}I ratios from 10^{-8} or higher. The release of ^{129}I from all sources, dominated by fuel reprocessing, is estimated at 5.21 x 10^{11} Bq/year, giving an estimated dose to world population equal to 3.36 x 10^{-6} mSv/year, which is inconsequential compared to background (Sunny et al. 2014b). Radiation exposure dose and health risks remain a crucial aspect of scientific understanding. Although there is no radiation risk for human health at this current environmental dose level, the accumulation of ^{129}I in a sensitive group of humans such as infants should be investigated. As a mobile long-lived radioisotope in the hydrosphere and atmosphere, iodine-129 is distributed throughout the environment and can easily enter the food chain through the hydrosphere, atmosphere, and geosphere.(Zhang and Hou 2013; Jabbar, Wallner, and Steier 2013). Due to the fact that the only source of food in infant up to 6 month of age is milk, estimating the ^{129}I daily intake, and determining ^{129}I concentration in infant urine through breastmilk, will be more accurate than other demographic groups.

This chapter aims to demonstrate a reliable and reproducible method for the measurement of ^{129}I in human breastmilk, by using a combustion technique for iodine extraction and subsequent AMS analysis of ^{129}I. The efficiency and reproducibility of this method were evaluated using ^{125}I as a tracer of recovery. This study is the second step towards establishing a primary concentration of ^{129}I in human. This procedure is envisaged to potentially expand the applications of ^{129}I into non-environmental fields.

3.2 Method

3.2.1 Sample collection, chemical, and instruments

Human breastmilk samples were collected by Health Canada in 20 ml borosilicate glass or polypropylene plastic tubes from breastfeeding mothers living in Canada. Ethics approval was obtained from the University of Ottawa to analyze them. The minimum breastmilk volume required to perform the analysis was 10 g. All samples were stored in a freezer upon arrival.

Breastmilk samples (n=14) were freeze-dried in a 2.5-liter benchtop freeze drier. The details of the freeze drier are given in Table 3.1. ^{125}I tracer solution (37 MBq) was ordered from Perkin-Elmer and diluted in 0.1 M NH_4OH to give an activity of 254.8 kBq/ml for use as a recovery tracer. All solutions were prepared using reverse osmosis (RO) water.

A pyrohydrolysis system that was used for the combustion of breastmilk samples was custom made and has been reported in detail elsewhere (Herod et al. 2014). Briefly, the system consists of a furnace with two heating zones, the temperature of which can be electronically controlled and programmed up to 900 ˚C. Both combustion line and sample tubes were custom manufactured quartz. The combustion line tube had an inner diameter of 2.1 cm, while the sample tubes were 15-20 cm long with an inner diameter of 0.8-1.2 cm. A trap solution (0.5% TMAH + 0.02M $NaHSO_3$ solution) was attached to the outlet of the combustion tube. The flow rate of input oxygen gas was adjusted to 800-900 mL/min.

A PerkinElmer Wizard 2 Automatic Gamma Counter (2470-0020) with two well type NaI detectors was used to measure ^{125}I to quantify the extraction efficiency. Using ^{125}I as a quantitative recovery tracer for ^{127}I and ^{129}I has been reported in detail elsewhere (Herod et al. 2014). Briefly, the method uses the coincidence sum gamma counting method to determine absolute sample activity without the need for a calibrated standard of ^{125}I (Horrocks and Klein 1974). Relative efficiencies were calculated for each sample according to the method of (Horrocks 1974; Horrocks and Klein 1974) and are reported in Table 3.3.

A 3MV HVE tandem AMS system was used to measure the concentrations of ^{129}I in the AgI extracted from the breastmilk at the Andre E. Lalonde Accelerator Mass Spectrometry Laboratory. The technical details of the ^{129}I measurement by AMS are described in (Francisco et al. 2020) and ion source parameters are given in Table 3.2. An Agilent 8800 ICP-MS triple quadrupole was used to measure the concentrations of ^{127}I.

Table 3.1 Freeze dry system details.

Parameter	
Refrigeration system	*Non-flammable refrigerant, HCFC/CFC-free*
Collector coil	*Cooled to -50° C*
Freeze drying samples	*Aqueous*
Operation	*On 115 volts, 60 Hz*
Dimensions	*12.6" w x 17.9" d x 16.9" h*
	(32.0 cm x 45.4 cm x 42.9 cm).
Vacuum pressure	*0.021 mBar*

Table 3.2 AMS ion source parameters (adapted from Francisco et al. 2020).

Parameter	**Value**
Cesium reservoir temperature	80 °C
Target Voltage	7.0 kV
Target current	0.5–1.5 mA
Extraction Voltage	28.0 kV
Extraction current	0.2 mA
Ionizer current	18 A
Vacuum (mbar)	0.5–1.0 x10^{-6} mBar

3.2.2 Extraction of ^{129}I from breastmilk for AMS analysis

The freeze-dried breastmilk powder sample (1 g) was weighed and placed in a quartz boat, more than 2000 Bq of ^{125}I tracer solution (as Na^{125}I) was pipetted on the sample. Samples were then placed in Zone 1 of the furnace tube and combusted at 900 degrees Celsius, under pure O_2 flow (800-900) mL/min, until the sample was fully combusted within 4-5 hrs. After the combustion, the trap solution was transferred to a separate 50 mL centrifuge tube and 2 mL of the sample was taken for ^{125}I counting via gamma spectrometry to calculate the recovery. The remaining trap solution was used for further separation of iodine for ^{129}I measurements by hexane extraction. A 15 ml of hexane and 0.1-0.3 ml of $NaNO_2$ (6M) were added to the sample and mixed on a shaker for 15 min. The sample was then transferred into a 250-ml separatory funnel. The hexane was collected into a 50-ml centrifuge tube and the aqueous phase was returned to the aliquot bottle. This step was repeated with fresh hexane (15, 10, 10 ml) but no $NaNO_2$ added, until the hexane became colorless. Hexane was collected in to the separatory funnel and 10 ml of RO water was added. A sufficient amount of 1M $NaHSO_3$ was added until both phases became colorless and the hexane was discarded. The aqueous layer was drained into a 20-ml scintillation vial and 100 µl of concentrated HNO_3 and two milligrams of iodine as NaI carrier with a $^{129}I/^{127}I$ isotope ratio of 1.4×10^{-14} were added. To precipitate a sample of AgI for AMS, 300 µl of 0.1M $AgNO_3$ was added. The samples were left for 12 hours in darkness to allow the precipitate to settle. The precipitate was collected and washed in RO water. The samples were centrifuged and the supernatant removed. The precipitate, for a second time was washed in RO water and centrifuged. The samples were dried in the oven at 60°C for overnight. The AgI precipitate was then prepared for AMS analysis by mixing it with pure niobium powder in a ratio of 1:1 or 1:2 by volume and pressing the mixture into a copper cathode to make the AMS target. A flow chart of the method is shown in Fig 3.1.

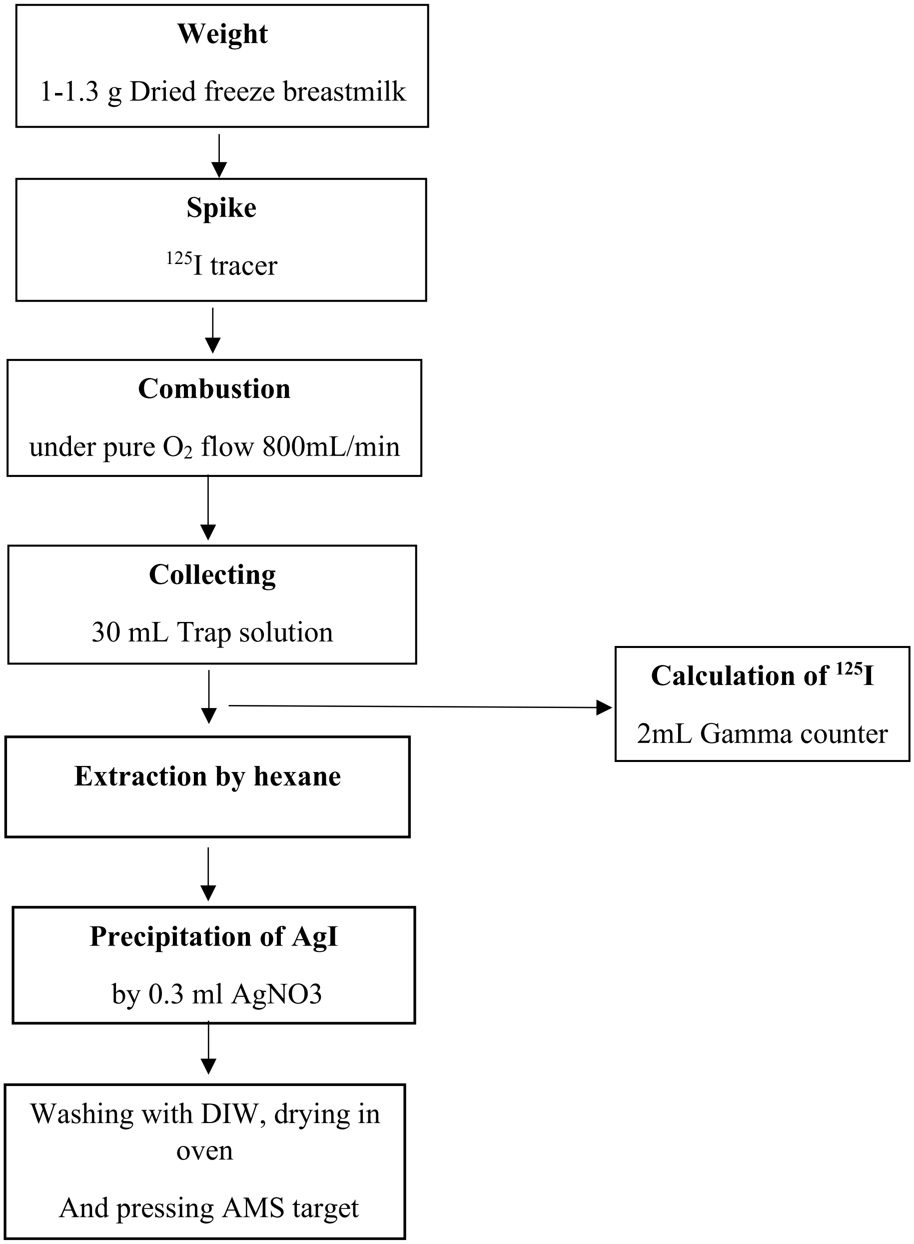

Figure 3.1 Flow chart showing the chemical extraction of ^{129}I in breastmilk.

3.2.3 Blanks, Standards and Duplicates

By combusting an empty tube with O_2 gas bubbling into 30 mL of trap solution, 4 process blanks were obtained. Then 2mL were transferred into the gamma counter to look for any memory effects. The AMS carrier was added; then hexane extraction was performed. The iodine was precipitated by 0.1M $AgNO_3$, targets produced and analyzed by AMS using the same procedure as for the unknowns.

For AMS analysis the ISO-6II standard was used which has a $^{129}I/^{127}I$ ratio of 5.717 x 10^{-12}. The ratio for the standard averaged 5.716 x 10^{-12} (n=3). One sample of cow's milk were used as duplicates and were analyzed on both AMS and ICP-MS.

3.3 Result and discussion

3.3.1 ^{125}I recovery for each sample

The ^{125}I recoveries for 18 samples vary between 50.5% recovery and 100% recovery. The four blanks result shows no memory effect. Nine samples out of eighteen gave an excellent recovery above 80%, seven samples gave a good recovery above 60%, and two samples above 50%. The results are summarized in Table 3.3.

Table 3.3 Analytical results of ^{125}I yield for each sample (n=22) used in the combustion following dry freeze.

	Sample ID	***sample weight (g)***	***^{125}I amount(g)***	***^{125}I activity (Bq)***	***Recovery***
1	*Blank1*	0		35	
2	*Cow milk1*	1.1263	0.1	4,843	103.9%
3	*BM1*	1.2238	0.4	16,050	87.8%
4	*BM2*	1.0558	0.4	15,478	84.5%
5	*BM3*	1.0011	0.4	15,085	82.4%
6	*BM4*	1.0202	0.1000	2,942	59.5%
7	*Blank2*	0		10	
8	*Cow milk2*	1.1240	0.2020	2,092	63.0%
9	*BM5*	1.0026	0.1015	2,986	77.4%
10	*BM6*	1.0121	0.1011	2,974	81.0%
11	*BM7*	1.0092	0.1020	3,000	83.8%
12	*BM8*	1.0040	0.1015	2,986	64.2%
13	*Blank3*	0		5	
14	*Cow milk3*	1.1333	0.2020	2,092	60.3%
15	*BM9*	1.0608	0.1015	2,986	62.6%
16	*BM10*	1.0085	0.1015	2,986	87.5%
17	*BM11*	1.0137	0.1021	3,003	90.6%
18	*BM12*	1.1100	0.1970	2,040	68.7%
19	*Blank4*	0		0	
20	*Cow milk4*	1.1596	0.2010	2,081	89.0%
21	*BM13*	1.0744	0.1950	2,019	50.5%
22	*BM14*	1.0222	0.2020	2,092	63.2%

Results are compared to the mean value of known activity of ^{125}I standards (n=2) equal 10,000 Bq/g.

3.3.2 ^{129}I and ^{127}I concentrations in Breastmilk

The AMS results for ^{129}I in breastmilk ranged from 1.26x10^{8} atoms/L to 6.64x10^{8} atoms/L with a median of 2.10 x10^{8} atoms/L. The results of ^{127}I in the breastmilk sample ranged from 97.7 µg/L to 472.7 µg/L with a median of 225.2 µg/L. The ^{129}I/^{127}I ratio ranged from 1.27x10^{-10} to 9.9x10^{-10} with a median of 2.13x10^{-10}. The correlation between ^{127}I and ^{129}I is significant in breastmilk ($p<0.05$, $r=0.54$) (Figure 3.2). The mean ^{129}I concentration in cow's milk equals 2.08 x10^{8} atoms/L and the mean ^{129}I/^{127}I ratio equals 1.6x10^{-10}. All results are summarized in Table 3.4.

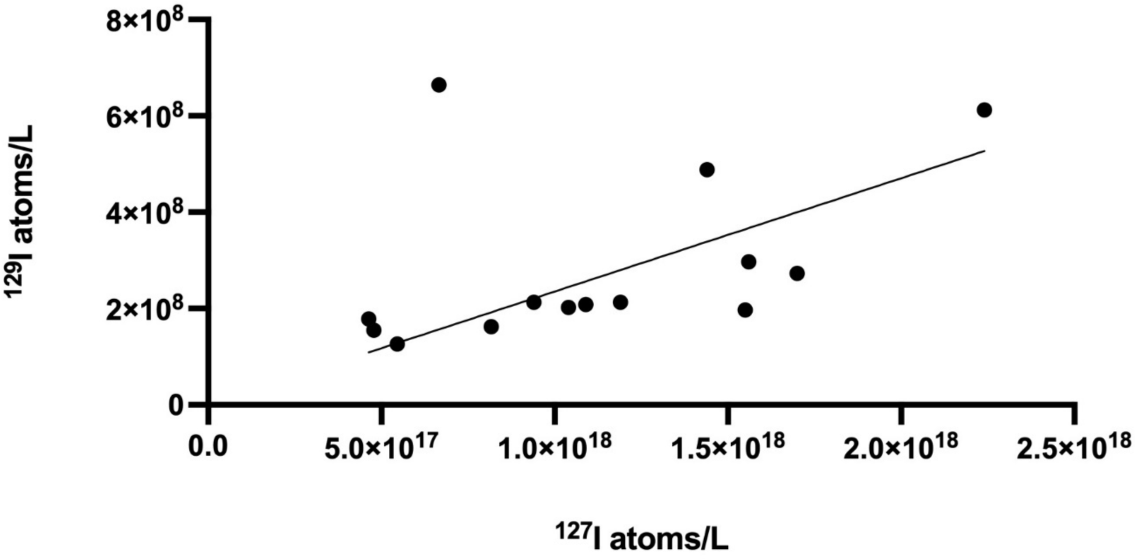

Figure 3.2 Linear regressions showing correlation of ^{129}I concentration expressed as atoms/L with ^{127}I atoms/L, $R=0.54$, $p < 0.05$, $n = 14$.

Table 3.4 Concentration of ^{129}I and ^{127}I in breastmilk (n=14) and cow milk (n=3) measured by ICP-MS and AMS.

Sample ID	^{127}I concentration (µg/L)	^{129}I Concentration (x10^8atoms/L)	Error of ^{129}I Concentration (x10^8atoms/L)	^{129}I/^{127}I ratio (x10^{-10})
Cow M2	379.5	2.22	0.04	1.23
Cow M3	238.1	2.7	0.03	2.39
Cow M4	238.6	1.31	0.04	1.16
BM1	172.2	1.62	0.04	1.98
BM2	327.3	1.97	0.04	1.27
BM3	230.3	2.08	0.04	1.9
BM4	100.8	1.55	0.05	3.24
BM5	472.7	6.12	0.03	2.73
BM6	302.7	4.88	0.09	3.4
BM7	358.3	2.73	0.08	1.61
BM8	328.2	2.97	0.05	1.91
BM9	97.7	1.78	0.04	3.85
BM10	140.5	6.64	0.03	9.97
BM11	115.2	1.26	0.09	2.31
BM12	220.2	2.02	0.03	1.93
BM13	198.2	2.13	0.03	2.27
BM14	251.9	2.13	0.03	1.78

The most important step in ^{129}I extraction is to remove unwanted matrices, such as water and organics, from the milk. The traditional method for evaporating water from milk is to heat the milk either by boiling it or by ashing; however, here we used freeze-drying because heat can cause iodine loss in milk samples (Milk et al. 1927). We observed that almost 88% of sample total weight was evaporated. At the time of preparation, all samples weighed 10 g, and then after freeze-drying, they weighed around 1.2 g. This confirms what previous studies have shown to be true about milk being 85% of it, is water (Lopez 2005; Robert G.,Jensen Marvin 1995). When compared to ashing, freeze-drying is preferred and does not alter the structure of milk or cause any iodine loss.

In order to determine if there is any loss of iodine during combustion, ^{125}I was added as a yield tracer (Table 3.3). One possible reason for the variability in the ^{125}I recoveries is due to the environment surrounding the combustion procedure. For example, sample BM13 was combusted the next day after the device was relocated. Moreover, after combusting samples BM8, BM9, and BM10, a crack was noticed in the combustion tube. We think the crack may have contributed to the loss of iodine in these samples. Another possibility for this change in recovery is likely due to the condensation of iodine on parts of line where the temperature changes. However, we believe this is less likely due to the fact that any exposed parts of the furnace tube were well wrapped in heating tape to maintain prevent condensation. In the end, 16 samples out of 18 yielded good recoveries above 60%. Any loss was counted in the final calculations for the AMS result.

To date, no studies have measured ^{129}I in breastmilk by accelerator mass spectrometry. All the measurements of ^{129}I in milk to date have been in cow's milk in order to estimate the internal radiation dose from ^{129}I in foodstuff or in order to detect the source of ^{129}I in the environment (Robens, Hauschild, and Aumann 1988; Parry et al. 1995). The concentration of ^{129}I in cow's milk varies based on the location. For instance, in Japan after Fukushima, the ^{129}I/^{127}I ratio in milk samples ranged between 1.2×10^{-10} to 3.4×10^{-7}, while in Canada the ^{129}I/^{127}I ratio in milk samples ranged between 7.3×10^{-10} to 1×10^{-10} (Satoh et al. 2019). The isotopic ratios presented here from breastmilk were not different from isotopic ratios in Canadian cow's' milk. Indicating that, broadly speaking, the milk of both cows and humans is a reflection of the ^{129}I concentration of their local environment and the food ingested. For example, one possible common source is water as both cow's and human consume water daily, the ^{129}I concentration in Canadian groundwater ranged from 1.5×10^{5} atoms/L to 1.9×10^{6} atoms/L and the average isotopic ratios in Canadian ground water range from 4.69×10^{-11} to 1.29×10^{-9} (Rogerson 2018). Another possible source is soil; the concentration of ^{129}I is accumulated in the soil through wet deposition. In North American, the primary source of ^{129}I in soil is wet deposition of ^{129}I from long-range atmospheric transport of ^{129}I from European fuel reprocessing, recycled ^{129}I from weapons testing and ocean volatilization (Wetherbee et al. 2012). Taking into consideration that the ^{129}I fallout over the past two decades has not noticeably changed (Herod et al. 2013), the ^{129}I concentration in the Canadian soil will theoretically remain roughly constant at 14.3x 10^8 atoms/g, and 7.5 x 10^7 atoms/g in grass (Renaud et al. 2005)

3.3.3 Radiation dose to infant from ingestion

The potential daily intake of ^{129}I is calculated by I= C_1 *C_2, where I is the intake (atoms/day), C_1 is the concentration (atoms/L), and C_2 is the consumption rate (L/day). Then the daily intake converted to (Bq/day), then to (Bq/year) in order to estimate thyroid dose in infant. The dose to the thyroid is then calculated by multiplying the intake by thyroid dose factor.

Dose= Intake (Bq/year) X Df_t (Sv/Bq). Dose factor $_t$ is a factor which converts iodine intake form becquerel to dose in sievert (Sv) to thyroid (t), and was calculated as $5.4x10^{-6}$(Robens and Aumann 1988). As a result, the dose rate in infant ranged from 0.14 $x10^{-10}$ to 7.77 $x10^{-10}$ Sv/year, with an average of 5.92 $x10^{-10}$ Sv/year. Table 9 shows these measurements.

Table 3.5 ^{129}I concentrations, intakes and their dose rate.

Infant	^{129}I Concentration (atoms /L) (x10^{8})	Breastmilk consumption rate per infant (L)	^{129} I daily intakes (atoms /day) (x10^{8})	^{129} I daily intakes (Bq/day) (x10^{-7})	^{129} I yearly intakes (Bq/ year) (x10^{-5})	Dose rate (Sv/year) (x10^{-10})
1	1.62	0.552	0.89	1.24	4.52	2.44
2	1.97	0.852	1.68	2.33	8.50	4.59
3	2.08	1.006	2.09	2.90	10.6	5.72
4	1.55	0.6379	0.99	1.37	5.00	2.70
5	6.12	0.852	5.21	7.24	26.4	14.3
6	4.88	0.582	2.84	3.94	14.4	7.77
7	2.73	0.860	2.35	3.26	11.9	6.42
8	2.97	0.510	1.51	2.10	7.67	4.14
9	1.78	0.760	1.35	1.88	6.86	3.71
10	6.64	0.824	5.47	7.59	27.7	15
11	1.26	0.730*	0.92	1.28	4.66	2.52
12	2.02	0.796	1.61	2.23	8.14	4.40
13	2.13	0.730*	1.56	2.16	7.89	4.26
14	2.13	0.855	1.82	2.53	9.22	4.98
Average		753	2.16	3.00	1.10E-04	5.92

* No data available for this sample, therefor, the consumption rate was calculated based of the mean of global breastmilk consumption.

Our data shows that humans are exposed to the ^{129}I since birth through breastmilk with an average concentration of 3 x10^{-7} Bq/day, giving an average intake of 1.10 x10^{-4} Bq/year leading to a dose rate equal to 5.92 x10^{-10} Sv/year. The dose from ^{129}I in infants will vary depending on the concentration of ^{129}I in mothers, which is affected by diet. In (Robens and Aumann 1988), the dose rate was calculated for German infants based on daily intake of cow's milk, and the result was 4.37 x10^{-8} Sv/year. Our dose rate in infant thyroid is considerably lower than those calculated by (Robens and Aumann 1988). We believe that the difference is related to the location. The ^{129}I concentration in European countries such as Germany, is heavily influenced by nearby emissions of ^{129}I, such as atmospheric and liquid discharges from the nuclear fuel reprocessing plants at Sellafield and La Hague with a small contribution in the past from Chernobyl. In addition, the ^{129}I concentration in German milk was measured by (Robens and Aumann 1988) at 3 x10^{-5} Bq/Kg, while in this study the ^{129}I concentration in Canadian milk measured at 3 x10^{-7} Bq/Kg. This lower concentration in cow's milk also supports the earlier explanation that the higher thyroid dose rate in German infant compared to this study is related to the location.

This method is not limited to milk; it can be extended to determine iodine 129 in other biological samples with complex matrices such as thyroid samples. Nonetheless, this method consumes a significant amount of time since the instrument combusts one sample per day. Developing an instrument to combust more than one sample at the same time will have a huge effect in reducing the time needed, to extract iodine 129, to be within two days and increase practicality for routine analysis.

3.4 Conclusion

This chapter highlights an analytical method that can be used to measure ^{129}I in breastmilk and the calculation of dose to infants from ^{129}I ingestion from breast milk. After freeze drying breastmilk, iodine-129 was successfully extracted from breastmilk using pyrohydrolysis and trapping iodine in an alkaline solution. Inorganic ^{125}I was successfully used as a quantitative recovery tracer showing a high recovery for the method. The concentration ^{129}I in breastmilk ranged from $1.26\text{x}10^{8}$ atoms/L to $6.64\text{x}10^{8}$ atoms/L with a median of $2.10\ \text{x}10^{8}$ atoms/L, and the ^{129}I/^{127}I ratio ranged from $1.27\text{x}10^{-10}$ to $9.9\text{x}10^{-10}$ with a median of $2.13\text{x}10^{-10}$. The concentrations of ^{127}I and ^{129}I in breastmilk samples were moderately well correlated and generally similar to the ^{129}I concentrations and ^{129}I/^{127}I ratios from cow's milk samples. This correlation indicates a similar source for both humans and animals in Canada reflective of the local environment. In addition, this method confirmed that humans are exposed to the ^{129}I from birth through their mother breastmilk giving them an average dose of $1.10\ \text{x}10^{-4}$ Bq/year and thyroid dose rate equal to $5.92\ \text{x}10^{-10}$ Sv/year. Furthermore, this method could be extended to determine iodine 129 in other biological samples with complex matrix such as thyroid. However, this method is labour-intensive. Therefore, improving the technique to combust more than one sample per day will have a large effect in reducing the time needed to extract iodine 129 and making the procedure more practical for routine analysis.

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4 Chapter 4: Assessment of ^{127}I and ^{129}I in different Canadian subpopulation by using biokinetic compartment model

4.1 Introduction

Iodine deficiency has been tracked by the WHO since 1945 and it is believed that approximately two billion individuals, ~25% of the global population, have insufficient iodine intake (Zimmermann 2009). In Canada, according to the Canadian Health Measures Survey (CHMS), the median concentration of urinary iodine was 151 µg/L which is within the optimal range of recommended by the WHO (Statistics Canada 2012). As a result, iodine deficiency is not seen as a serious public health concern in Canada; but certain sub-populations such as infants, vegans, and vegetarians may be vulnerable (Eveleigh, Coneyworth, and Welham 2021) and monitoring of the Canadian population is necessary to ensure ongoing sufficiency.

Iodine deficiency in the body can be detected through three main laboratory indicators: high thyroid stimulating hormone (TSH) concentrations in blood, high thyroglobulin, and low urinary iodine (Taixiang Wu et al. 2002; Andersen et al. 2017). Of these, the most commonly used method to estimate dietary iodine intake is through urine samples analysis and determination of the urinary iodine concentration. The typical procedures in which urine can be collected for iodine measurement are either 24-hour urine collection, termed urinary iodine estimation (UIE), expressed as µg/24hr or a spot urinary sample, and termed urinary iodine concentration (UIC), expressed as µg/L (Jolin and Escobardelrey 1965; Vejbjerg et al. 2009; König et al. 2011). The 24-hour urine collection is considered the gold-standard to determine iodine intake in an individual while spot urine collection is recommended in population-based research of iodine intake because 24-hour urine collection is difficult to obtain (Vejbjerg et al. 2009). Urine production varies during a 24 hour period, and it is estimated that the mean urine production for healthy individuals is 83 ml urine per hour during the day and 48 ml per hour during the night giving 1.6 L as a mean total urine volume per 24 hours (Huang Foen Chung and van Mastrigt 2009). Therefore, UIE (µg/day) can be calculated by multiplying the UIC of the samples (µg/L) by the volume of the corresponding 24-h urine excretion (Andersen et al. 2001; Vejbjerg et al. 2009,Laurberg et al. 2001).

The relationship between the level of dietary iodine consumption and the risk of thyroid disease is frequently shown in nutrition by U-shaped curves, which means both low (hypo) and high (hyper) intakes are associated with an increase in risk (Laurberg et al. 2001). It is well known and documented that low iodine intake is causes hypothyroidism and is strongly associated with many health disorders such as autism, neuropsychological disorders and learning disabilities in human infants, psychomotor impairment, abortions or stillborn in pregnant women, and endemic goitre (Delange et al. 2001,Venturi 2011). However, excess iodine intake is less frequently addressed. In addition to hyperthyroidism, it has been noticed that excess iodine intake is also associated with endemic goitre and hypothyroidism, similar to iodine deficiency (Laurberg et al. 2001).

The Dietary Reference Intake (DRI) for iodine includes 4 types of values that are distributed based on age and gender (C. L. Taylor and Meyers 2012). The first is **Estimated Average Requirement (EAR)** which is the average daily iodine intake level estimated to meet the *requirement of half* the healthy individuals. The second is **Recommended Dietary Allowance (RDA)** which is the average daily dietary iodine intake level sufficient to meet the iodine *requirement of almost all (98%)* of healthy individuals. Setting the Recommended Dietary Allowance (RDA) value depends on EAR and can be calculated as **RDA = 1.2 X EAR**. However, when RDA cannot be determined for specific ages of individuals, such as iodine for infants, the adequate intake is used. **Adequate Intake (AI)** is the recommended average daily intake level that is *assumed to be adequate* based on observed or experimentally determined approximations. For example, **the RDA** of iodine cannot be determined for infants due to insufficient data; therefore, **AI** is used and it reflects the mean of iodine intake that is observed in infants exclusively fed breast milk. The last value is **Tolerable Upper Intake Level (UL)** and reflects the highest average daily iodine intake level that is likely to pose no risk of adverse health effects in 98% of individuals in the general population. Toxicological studies that identified the No-Observed-Adverse-Effect-Level (**NOAEL)** and Low-Observed-Adverse-Effect-Level (**LOAEL)** of iodine, helped to determine the **UL** of iodine. The Tolerable Upper Intake Level (UL) of iodine can be calculated by dividing the LOAEL by the uncertainty factor of toxicological studies. Iodine **NOAEL** was estimated at 1000 -1200 µg/day, while **LOAEL** was estimated at 1700 µg/day, and the uncertainty factor used was 1.5.

The **Tolerable Upper Intake Level (UL)** of iodine $= \frac{\text{LOAEL}}{\text{uncertainty factor}} = \frac{1700}{1.5} = 1133.3\ \mu\text{g/day}$

Tolerable Upper Intake Level (UL) of iodine for adults was rounded to 1100 µg/day, and from this value, the UL for children was calculated and adjusted based on body weight. The values of all four (DRIs) for iodine are summarized in Table 4.1 (Otten, Hellwig, and Linda 2006)

Table 4.1 The Dietary Reference Intake (DRI) for iodine.

	EAR µg/day	RDA µg/day	AI µg/day	UL µg/day
Infant (months)				
0-6	Not possible	Not possible	110	Not possible
7-12			130	
Children (years)				
1-3	65	90		200
4-8	65	90		300
9-13	73	120		600
14-18	95	150		900
Adults (years)				
19 > 70	95	150		1100
Pregnancy (years)				
14-50	160	220		1100 unless age < 18, then 900
Lactation (years)				
14-50	209	290		1100 unless age < 18, then 900

Reference: (Otten, Hellwig, and Linda 2006).

Monitoring urinary iodine concentrations (UIC) is essential to assessing the effectiveness of fortification strategies (Abudo et al. 2021) especially in Canada, as Canada has no registered data about their iodine intake through UIC. Iodine status for the Canadian population is not well known, especially with the recent re-emergence of iodine deficiency among individuals in other industrial countries (Rayman and Bath 2015; M. Li et al. 2001). Therefore, understanding the main sources of iodine to the Canadian population remains poorly understood and is necessary to ensure fortification strategies are justified and effective. Various methods and measurements for estimating dietary iodine intake have been discussed in recent years (Montenegro-Bethancourt et al. 2015; Combet and Lean 2014; Zimmermann 2008a) . However, the quantitative measurement of dietary iodine intake guidelines remains challenging due to the need for very exacting oversight of foods and the quantities consumed. Despite these difficulties, all methods have advantages and disadvantages depending on the type of study and study conditions. Moreover, uncertainties remain regarding how much iodine Canadians consume, particularly which foods are key dietary sources of iodine. It is difficult to collect and analyze samples directly and requires significant effort on the part of participants to track their diet. In this paper, a novel approach using a compartment model, implemented in a software tool AMBER is used to overcome these obstacles. A biokinetic model of iodine transfer developed by Leggett 2017 has been implemented in AMBER and used to:

(1) estimate the daily dietary intake of iodine using best estimates of food consumption rates in Canada,
(2) determine the major food sources of iodine in Canadian diet,
(3) assess the urinary iodine concentration and $^{129}I/^{127}I$ ratio in different Canadian diets
(4) determine the urinary iodine 129 concentration in Canadian population based on dietary iodine intake and its association to specific food sources,
(5) determine the urinary iodine concentration in infants based on breastmilk iodine concentrations and intake rates,
(6) estimate iodine daily intake based on urinary iodine concentration.

4.2 Materials and Methods

4.2.1 Study populations

Several study populations were investigated in this research. These were divided into three groups. The first is Canadian infants aged one month. These infants were healthy, exclusively breastfed, and without complications during childbirth. Infants who consume milk formula or are older than one month were excluded. Breastmilk was sampled by Health Canada into sterile bottles, using an electric breast pump. Aliquots were stored frozen in 20 mL plastic scintillation vials until analysis. The second population consists of adults who consume various diets. Their iodine intake was estimated based on diet, and the details will be provided accordingly in section 4.2.8. The third population is composed of 25 individuals who are residents of Ottawa. Their urinary iodine concentrations were measured previously and this data was used in order to estimate their iodine intake. Data from these populations was applied as inputs to the iodine biokinetic model in AMBER.

4.2.2 AMBER software

AMBER is a software tool that enables users to build compartment models to represent the migration and fate of contaminants in a system; it can be accessed through a user-friendly graphical interface (Quintessa 2019). The system of interest can reflect the context being studied which can be homogenous, such as water, or heterogenous, such as waste. The system can also encompass whatever spatial scale is desired. AMBER has been used widely, particularly in the nuclear industry for assessments of impacts from radioactive waste management facilities, and applied to different projects; from radiological dose assessments to radioisotope migration and accumulation from radioactive waste sites (Jinescu and Dogaru 2009; R Klos 1996; Agüero et al. 2007).

A basic compartment model consists of a contaminant source and two compartments (Quintessa 2019) (Figure 4.1)**.** The migration of contaminants from one compartment to another at any given time is represented with a transfer/turnover rate per unit of time (second, day, month or year). The accumulating amount (mole/gram/Bq) of a contaminant N in compartment i and j can be calculated using a first order linear differential equation:

$$\frac{dN_i}{dt} = \sum_{j \neq i} \lambda_{ji} N_j + \lambda_M M_i + S_i(t) - \sum_{j \neq i} \lambda_{ij} N_i - \lambda_N N_i$$

Where:

i and j are the two compartments;

N and M are the amounts of contaminants N and M in a compartment; M also is precursor of N.

$Si(t)$ is a time dependent external source of contaminant N (amount/time);

λN is the decay/degradation rate for contaminant N (time);

λij is the transfer rate representing the loss of contaminants N from compartment i to j (time);

and λji is the transfer rate representing the loss of contaminants N from compartment j to i (time).

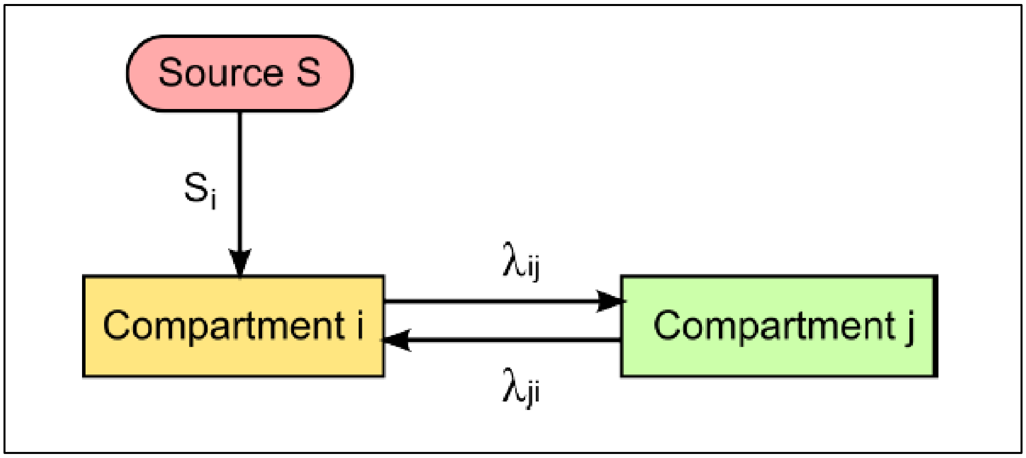


Figure 4.1 Basic compartment model structure showing source, compartments and transfers (Quintessa 2019).

Although, the distribution of contaminants within a single compartment in AMBER is considered to be uniform, the model can be split-up into a number of sub-models, in this case to enable multiple transfers within individual organ systems (Figure 4.2)

AMBER is generally used to evaluate the migration and fate of contaminants in environmental systems, but recently it has been used to evaluate migration and accumulation of contaminants such as radioiodine and lead in humans through the use of biokinetic transfer rates. One disadvantage of AMBER is that it is limited to set up as a one-directional donor-controlled compartment, i.e., a contaminant is moving in one direction. However, this limitation can be bypassed by setting up separate forward and backward transfer directions (Quintessa 2019). Table 4.2 shows the components of the iodine biokinetic model used in this study.

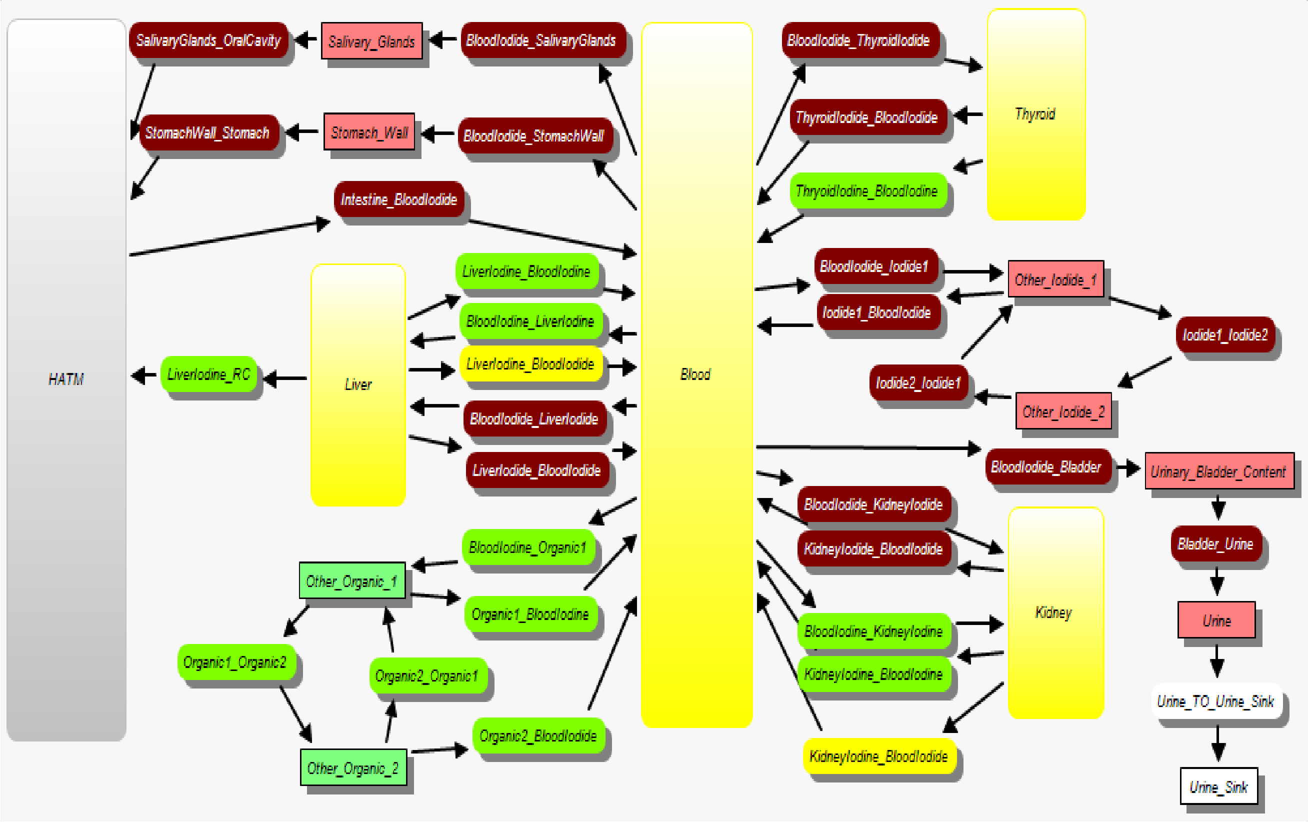


Figure 4.2 (A) The biokinetic model of iodine and sub-models implemented in AMBER(Leggett 2017). New compartments (in white color) named (urine to urine sink) and (urine sink) were added to the model.

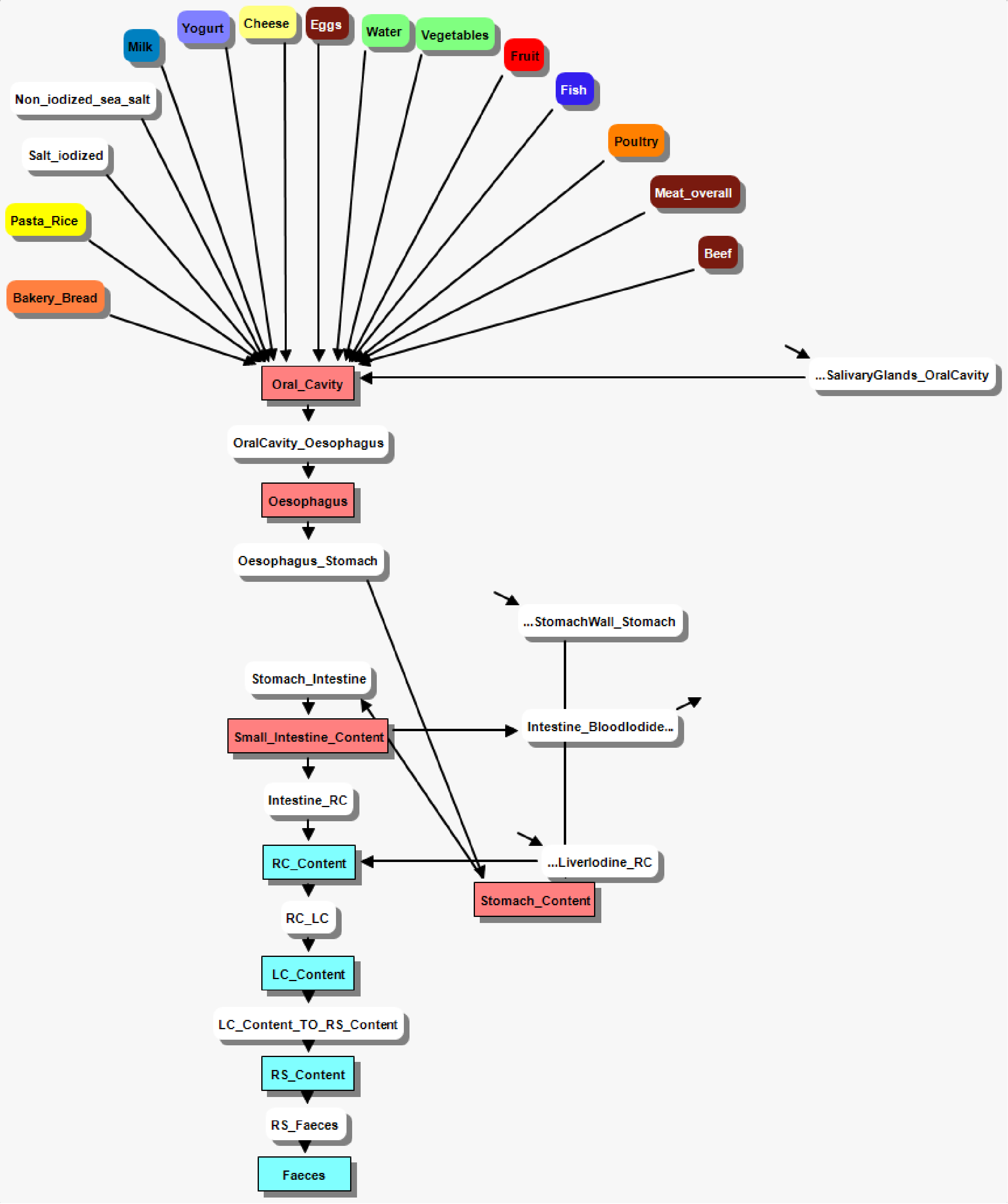


Figure 4.2 (B) AMBER Human Alimentary Tract Model (HATM) showing foods as sources to the Oral Cavity compartment.

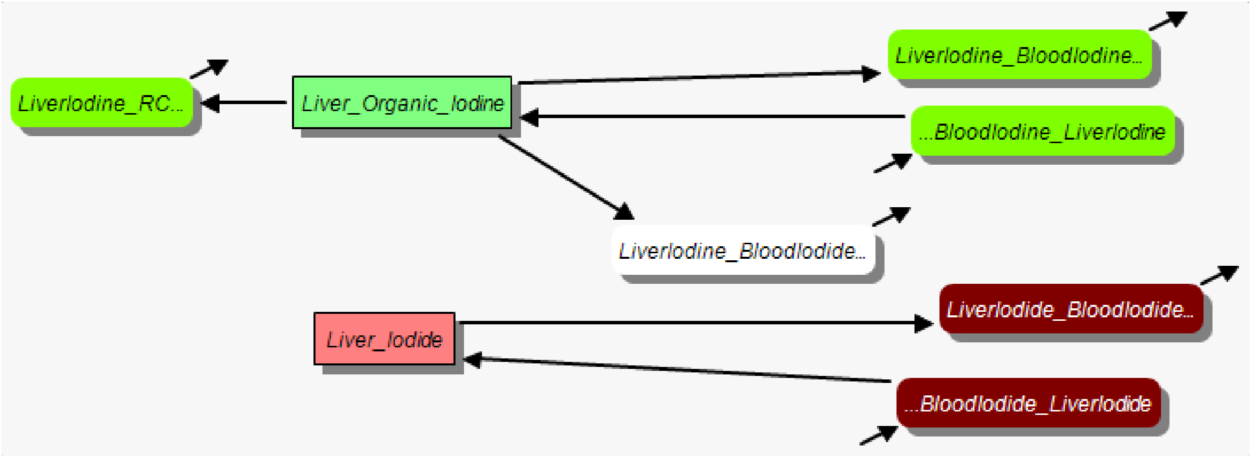


Figure 4.2 (C) AMBER Liver sub-model.

Figure 4.2 (D) AMBER Blood sub-model

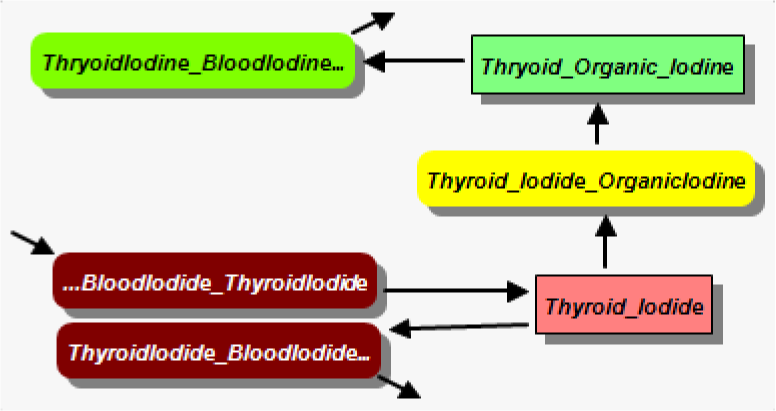


Figure 4.2 (E) AMBER thyroid sub-model

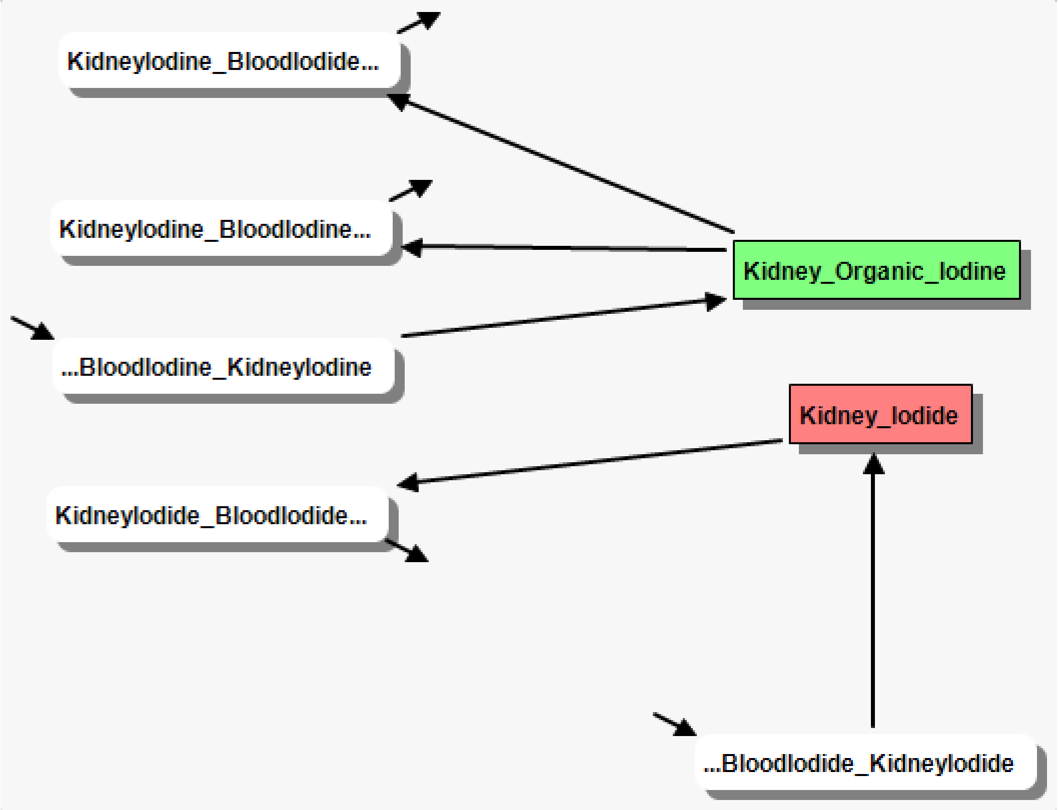


Figure 4.2 (F) AMBER Kidney sub-model

Table 4.2 Biokinetic model components in this study.

Number of compartments	25
Number of sub-models	5
Number of transfers	39
Number of contaminants	2
Number of parameters	44

4.2.3 AMBER input data

4.2.3.1 Iodine 127 and 129 inputs

Health Canada (2017) reported the consumption rates based on ages and gender for ten main food groups. These are: grain products include bread, wheat, rice, and pasta; dairy products; fat products include oils and butter; meats products; meat alternatives which includes eggs and nuts; vegetables; fruits; beverages; baby food; miscellaneous, which includes sugar, salt, sauces, and spices. The eleven most consumed food items in Canada were identified from the Canada Health survey (Health Canada 2017) and used in this study to calculate their contribution to daily iodine consumption (Table 4.3). Regarding salt, the consumption rate for salt was calculated from (Garriguet 2007). The daily consumption rate for table salt is also expressed in (Table 4.3).

Relatively few papers have been published on the iodine concentration in Canadian food. In (P. W. F. Fischer and L'Abbé 1980), iodine was measured in 8 samples of iodized salt and 10 samples of regular sea salt, while in (Benkhedda et al. 2009) iodine was measured in 9 groups of food similar to those used by (Health Canada 2017). Therefore, the iodine concentration in Canadian food was obtained from the most recent paper (Benkhedda et al. 2009). Then by multiplying consumption rates obtained from (Health Canada 2017) and iodine concentration (Benkhedda et al. 2009), the daily iodine intakes (μg/day) were calculated for each item (Table 4.4).

The concentration of ^{129}I in Canadian food has not been widely measured with data only existing for milk and water (Rogerson 2018). However, for European and Asian countries, there have been several studies that measured ^{129}I in different types of food such as vegetables and meat (Satoh et al. 2019; Parry et al. 1995; Robens, Hauschild, and Aumann 1988; Ueda et al. 2015). However, the values of ^{129}I in European and Asian countries cannot be used to ascertain the ^{129}I concentration in Canadian food as they were measured in regions that have been affected by liquid and atmospheric ^{129}I emissions from nuclear fuel reprocessing plants and to a much lesser degree, the Chernobyl accident; therefore these have much higher ^{129}I concentrations and ^{129}I/^{127}I ratios than would be expected in Canadian food (Rogerson 2018). For instance, the ^{129}I/^{127}I ratios measured in (Satoh et al. 2019) for Japanese milk samples were high compared to Canadian milk ranging between 1.2 x 10^{-10} to 3.4 x $10^{-7,}$ while Canadian milk measured by (Rogerson 2018) ranged between 7.3 x 10^{-10} to 1 x 10^{-10}. Today, the primary source of ^{129}I in North America is wet deposition of ^{129}I from the long-range atmospheric transport of ^{129}I from nuclear fuel reprocessing, ^{129}I recycled from weapons testing or ocean volatilization (Wetherbee et al. 2012). Therefore, the ^{129}I concentration in Canadian food in this study was estimated based on ^{129}I concentrations in Canadian soil, water and plants (Rogerson 2018; Herod et al. 2013; Renaud 2002). Specifically, Renaud 2002, reported ^{129}I concentration for soil, grass and cedar leaves from Sturgeon Falls, Ontario. In place of measured data, these values are being used for grains, vegetables, and fruits. Ottawa River water was measured by Sheppard and Herod and had a ^{129}I concentration of 2.79 x 10^{-8} (μg/L), this value is being used as the ^{129}I concentration for water in this study. Finally, cow's milk has been previously measured by (Rogerson 2018) and again in the previous chapter. A mean value 4.45x 10^{-8} (μg/L) (n=4) is being used as the ^{129}I concentration for all dairy products. Due to the fact that meat, chicken and eggs have ^{127}I concentrations close to milk, the ^{129}I concentration in milk is being used for meat, chicken and eggs as well. Table 4.5 shows ^{129}I input data used in AMBER.

Table 4.3 Food consumption rates in Canada (Health Canada 2017; Garriguet 2007).

	Most consumed food	The mean consumption rate for Canadian in all ages and gender (g/day)
1	Tea, coffee, and water	1253.75
2	Grain products overall	204.84
3	Vegetables overall	202.4
4	Cow's milk	193.26
5	Fruits overall	152.2
6	Red Meat include sausages, luncheon and liver	64.55
7	Chicken, Turkey, Birds	42.63
8	Yoghurt	27.8
9	Cheese	27.78
10	Eggs	23.67
11	Fish include shellfish	16.84
12	Salt	0.87349

Table 4.4 Iodine-127 daily intakes for each item of food.

Most consumed food	The mean consumption rate for Canadian in all ages and gender (g/day)	^{127}I concentration (µg/g)	^{127}I Daily Intake (µg/day)	Reference
Tea, coffee, and water	1253.75 ± 15.11	0.0025	3.13 ±0.04	(Rogerson 2018)
Grain products	204.84 ±2.19	0.164	33.59 ±0.36	(Benkhedda et al. 2009)
Vegetables	202.4 ±2.84	0.028	5.67 ±0.08	(Benkhedda et al. 2009)
Cow's milk	193.26 ± 3.39	0.304	58.75 ±1.03	(Borucki Castro et al. 2010)
Fruits	152.2 ±2.85	0.028	4.26 ±0.08	(Benkhedda et al. 2009)
Red Meat include sausages, luncheon and liver	64.55 ±2.96	0.274	17.69 ±0.81	(Benkhedda et al. 2009)
Chicken, Turkey, Birds	42.63 ±1.36	0.311	13.26 ±0.42	(Benkhedda et al. 2009)
Yoghurt	27.8 ±1.02	0.493	13.71 ±0.5	(Benkhedda et al. 2009)
Cheese	27.78 ±0.68	1.163	32.31 ±0.79	(Benkhedda et al. 2009)
Eggs	23.67 ±0.8	0.727	17.21 ±0.58	(Benkhedda et al. 2009)
Fish include shellfish	16.84 ±0.9	0.64	10.78 ±0.58	(Benkhedda et al. 2009)
Salt	0.87	76	66.12	(Dussault 1993)
	0.87	50.887	44.27	(Benkhedda et al. 2009)

Table 4.5 Iodine-129 daily intakes for each item of food.

Most consumed food	The mean consumption rate for Canadian in all ages and gender (g/day)	^{129}I concentration (µg/g)	^{129}I Daily Intake (µg/day)	Reference
Tea, coffee, and water	1253.75 ± 15.11	2.79E-11	3.5E-08	(Matthew Noel Herod 2015)
Grain products	204.84 ± 2.19	9.00E-10	1.8E-07	(Renaud 2002)
Vegetables	202.4 ± 2.84	9.00E-10	1.8E-07	(Renaud 2002)
Cow's milk	193.26 ± 3.39	4.45E-11	8.6E-09	Measured
Fruits	152.2 ± 2.85	9.00E-10	1.4E-07	(Renaud 2002)
Red Meat include sausages, luncheon and liver	64.55 ± 2.96	4.45E-11	2.9E-09	
Chicken, Turkey, Birds	42.63 ± 1.36	4.45E-11	1.9E-09	
Yoghurt	27.8 ± 1.02	4.45E-11	1.2E-09	
Cheese	27.78 ± 0.68	4.45E-11	1.2E-09	
Eggs	23.67 ± 0.8	4.45E-11	1.1E-09	
Fish include shellfish	16.84 ± 0.9	1.61E-09	2.7E-08	(Matthew Noel Herod 2015)
Salt	0.87	3.29E-09	2.9E-09	Measured
	0.87	3.29E-09	2.9E-09	Measured

4.2.3.2 AMBER transfer coefficients

Age-specific parameter values for the iodine model are adapted from (Leggett 2017). In (Leggett 2017), children and infants with normal thyroid function were included in the biological behavior of iodine. Unless there is clear evidence of an age dependence in a parameter value, the adult values measured in (R. W. Leggett 2010) were applied to all younger ages in (Leggett 2017). The age dependant values are limited to the biological half time of organic and extrathyroidal organic iodine, yielding 12 different transfer coefficients. Table 4.6 shows these different and values shared for both infants and adults.

Table 4.6 Age-specific parameter values (day^{-1}) for infant and adult.

Pathway	Infant	Shared value	Adult
Bladder to urine	32		12
Blood iodide to Bladder		11.84	
Blood iodide to Iodide 1		600	
Blood iodide to kidney iodide		25	
Blood iodide to Liver iodide		15	
Blood iodide to salivary glands		5.16	
Blood iodide to stomach wall		8.6	
Blood iodide to Thyroid iodide		7.26	
Blood iodide to kidney iodine	5.6		3.6
Blood iodide to Liver iodine	32.7		21
Blood iodide to organic 1	23.3		15
Intestine to Blood iodide		594	
Intestine to Right Colon		6	
Iodide 1 to blood iodide		330	
Iodide 1 to iodide 2		35	
Iodide 2 to iodide 1		56	
kidney iodide to blood iodide		100	
kidney iodine to blood iodide	0.218		0.14
kidney iodine to blood iodine	32.7		21
Left Colon content to Right Colon content	2.4		2
liver iodide to blood iodide		100	
liver iodine to blood iodide	0.218		0.14
liver iodine to blood iodine	32.7		21
liver iodine to Right Colon	0.124		0.08
Oesophagus to stomach		2160	
Oral cavity to oesophagus		7200	
Organic iodine pool 1 in other tissue to blood iodine	32.7		21
Organic iodine pool 1 in other tissue to Organic pool 2 in other tissue	1.87		1.2
Organic pool 2 in other tissue to blood iodide	0.218		0.14
Organic iodine pool 2 in other tissue to Organic pool 1 in other tissue	0.964		0.62
Right Colon to Left Colon	2.4		2
Rectosigmoid colon to Faeces		2	
Salivary glands to Oral cavity		50	
Stomach wall to Stomach		50	
Stomach to intestine		20.57	
Thyroid iodine to blood iodine	0.0462		0.0077
Thyroid iodide to blood iodide		36	
Thyroid iodide to organic iodine		95	
Urine to Urine sink	32		12

4.2.4 Determination of urinary iodine concentration

A new compartment named urine sink was added to the Leggatt model, and a modification to volume and transfer parameters was applied to determine the urinary iodine concentration (Figure 4.2 A). To enable this calculation, 1.6 L is being assumed as the total daily volume of urine excreted by an adult (Z. T. Li et al. 2020) which is then divided by the (urine to urine sink) transfer rate coefficient for adults (12 day^{-1}) which is an approximate value for the number of urination events per day, to yield a volume per urination event of 0.133 L. For infants, 0.378 L is being assumed as the total daily volume of urine excreted by an infant one month old (Mark H Goellner, Ekhard E Ziegler 1981) which is then divided by the (urine to urine sink) transfer rate coefficient for infant (32 day^{-1}) to yield a volume per urination event of 0.011813 L.

To obtain an approximate thyroid iodine concentration, a second addition was made to the Leggatt model to obtain a volume per transfer for iodide and iodine that equals a total volume of adult thyroid (0.01287L). For iodide, the total volume is divided by the transfer rate of iodide leaving the thyroid (36 day^{-1}): 0.01287/36 = 0.0003575 L. For iodine, the total volume is divided by the transfer rate of iodine leaving the thyroid (0.0077 day^{-1}): 0.01287/0.0077 = 1.6714L. The same equation was used for infants with respect to thyroid volume which is equal to 0.00044 L (Santiago et al. 2013). A volume per transfer for iodide in infant is 0.000012 L and the volume per transfer for iodine in infant is 0.0095 L.

4.2.5 Breastmilk

The total iodine concentrations in 105 samples of breastmilk were analyzed using an Agilent 8800 triple quadrupole ICP-MS. The daily iodine intakes for infants drinking this breastmilk were calculated for each sample. Using this information, the iodine concentration in infant urine was calculated in AMBER using the infant transfer parameter set.

4.2.6 Determination of daily iodine intake

In order to determine daily iodine intake using urinary iodine concentrations the direction of all transfer coefficients in AMBER were reversed. In essence, the total amount of iodine excreted in urine daily was considered the “source” function for the model that resulted in a total daily intake of iodine, taking into account that the daily volume of urine is 1.6 liters. When considering 9% non-urinary iodine loss, this loss was compensated through multiplying the results by a constant equal to 1.092 to estimate iodine daily intakes (Johner et al. 2013). Then the yielded iodine daily intakes were verified by re-entering them into the original model to obtain similar UIC.

4.2.7 Validation of AMBER results

In order to validate the AMBER results for urinary iodine concentrations, several studies that had measured urinary iodine in large populations and estimated their daily iodine intake were recalculated using AMBER. In these cases, the estimated daily iodine intake from the study was used as the daily iodine input for AMBER and the resulting UIC was compared to the measured value.

4.2.8 Simulation of dietary habits

To enhance comparisons between Canadian dietary habits, we have adopted the dietary terms and definitions outlined in (Dagnelie and Mariotti 2017; Tonstad et al. 2009; Paoli, Bianco, and Grimaldi 2015; Freeman et al. 2006; Fields and Borak 2009). Seven diet variation are investigated with additional variations regarding the consumption of iodized salt to investigate its importance for each type of diet (table 4.7). 1) A lacto-ovo-vegetarian refers to a diet that includes grains, vegetables, fruits, dairy products, and eggs but excludes all types of meat including fish. 2) Lacto-vegetarian refers to a diet that includes grains, vegetables, fruits, and dairy products, but excludes all types of meat and eggs. 3) Ovo- vegetarian refers to a diet that includes grains, vegetables, fruits, and eggs, but excludes all types of meat and dairy products. 4) Vegan refers to a diet that excludes all types of meat, dairy products, and eggs, but includes grains, vegetables, and fruits. 5) Regular diet refers to a diet without any restriction. 6) Ketogenic diet refers to a diet consists of high fat and protein, therefore, avoiding any carbohydrate from grain product and fruits. 7) Low carbohydrate diet in this study is similar to ketogenic; however, it does consider the addition of fruits. Using the consumption rates of the food eaten for each diet (Table 4.3), and the measured or estimated ^{127}I and ^{129}I concentrations, the daily intake of both iodine isotopes was calculated for each diet (Table 4.8).

Table 4.7 Type of diets.

Name of diet	Include	Exclude
Lacto-ovo-vegetarian	Grains, vegetables, fruits, dairy products, and eggs	Meat, chicken, and fish
Lacto-vegetarian	Grains, vegetables, fruits, and dairy products	Meat, chicken, fish, and eggs
Ovo-vegetarian	Grains, vegetables, fruits, and eggs	Meat, chicken, fish, and dairy products
Vegan	Grains, vegetables, and fruits	Meat, chicken, fish, eggs, and dairy products
Regular	Grains, vegetables, fruits, dairy products, eggs, all type of meat	Nothing
Ketogenic	Vegetables, meat, chicken, fish, eggs, and dairy products	Grains products and fruits
Low-carbohydrate	Vegetables, fruits meat, chicken, fish, eggs, and dairy products	Grains products

Table 4.8 Estimations of ^{127}I and ^{129}I daily intakes for different Canadian diets:

Diet	Daily ^{127}I intake (µg/day)	Daily ^{129}I intake (µg/day)	^{129}I/^{127}I ratio
Vegan diet using iodized salt	112.8	5.41E-07	4.80E-09
Vegan diet without using salt	46.7	5.38E-07	1.15E-08
Lacto-ovo-vegetarian diet using iodized salt	234.7	5.53E-07	2.36E-09
Lacto-ovo-vegetarian diet without using salt	168.6	5.50E-07	3.26E-09
Lacto-vegetarian diet using iodized salt	217.5	5.52E-07	2.54E-09
Lacto-vegetarian diet without using salt	151.4	5.49E-07	3.63E-09
Ovo-vegetarian diet using iodized salt	130.0	5.45E-07	4.19E-09
Ovo-vegetarian diet without using salt	63.9	5.42E-07	8.48E-09
Regular diet using iodized salt	276.5	5.85E-07	2.12E-09
Regular diet using iodized salt and eating meat only	252.4	5.56E-07	2.20E-09
Regular diet using iodized salt and eating chicken only	248.0	5.55E-07	2.24E-09
Regular diet using iodized salt and eating fish only	245.5	5.80E-07	2.36E-09
Regular diet without using salt	210.4	5.82E-07	2.77E-09
Regular diet using iodized salt but no Dairy	171.7	5.74E-07	3.34E-09
Regular diet using iodized salt but no milk	217.7	5.77E-07	2.65E-09
Regular diet without milk and salt	151.6	5.74E-07	3.78E-09
Regular diet without dairy and salt	105.6	5.71E-07	5.41E-09
ketogenic diet using iodized salt	238.6	2.64E-07	1.11E-09
ketogenic diet without using salt	172.5	2.61E-07	1.51E-09
ketogenic diet without using salt or dairy	67.7	2.50E-07	3.69E-09
low carb diet using iodized salt	242.9	4.01E-07	1.65E-09
low carb diet without using salt	176.8	3.98E-07	2.25E-09
low carb without using salt or dairy	72.0	3.89E-07	5.41E-09

4.3 Results and Discussion

4.3.1 Model Validation.

Model validation of the iodine biokinetic model used in AMBER, which checks the accuracy of the model results against measured data, is essential. To validate the AMBER model, four studies containing measured UIC's covering different genders, ages, and types of diets were used. These studies all provided estimated iodine daily intakes (IDI) for their respective populations. Using these data as the total daily iodine input in AMBER we predicted the resulting urinary iodine concentrations and compared them to the measured UIC (Table 4.9) reported in the papers discussed below. The results show no significant difference between the UIC calculated by AMBER and the measured UIC (Fig 4.3). Specifically, in the Japanese study (Fuse et al. 2021), the iodine daily intake IDI was estimated at 388.8 µg/day based on food frequency questionnaire (FFQ) and mean UIC was 213 µg/L. By using the same IDI in AMBER, the UIC was estimated to be 219.2 µg/L. In the Danish population study (Rasmussen et al. 2002), two different IDIs were estimated using a food frequency questionnaire, : the first IDI was 162 µg/day giving a UIC equal to 63 µg/L, while in AMBER the result was 91.3 µg/L. The second IDI estimation was 152 µg/day and UIC in the study was 61 µg/L while in AMBER it was 87.5 µg/L. One possible reason for these differences in UIC is the volume of urine, which was not provided in Japanese and Danish studies. As evidence for this, we found excellent agreement between the UIC in the Italian study (Iacone et al. 2021) and the UIC measured by AMBER when urine volume was provided. Similarly, excellent agreement was found in the UIC from pre-school children measured in (Johner et al. 2013) and the UIC measured by AMBER when daily urine volume was provided and implemented in AMBER.

The reverse model and its calculations were also validated by using urinary iodine concentrations data to predict the IDI, then the results were compared to the estimated IDI in these papers (Table 4.10). An excellent agreement was found in the Italian study (Iacone et al. 2021) where IDI was estimated for men at 111 µg/day, 85 µg/day for women, and 96 µg/day total. In the reverse model, the estimated IDI was 116.2 µg/day for men, 89 µg/day for women, and 97.2 µg/day total. Similarly, in the Japanese study (Fuse et al. 2021), the iodine daily intake IDI was estimated at 388.8 µg/day while in AMBER the IDI was 372 µg/day. A slightly difference, which is not significant, was observed between IDI in AMBER and IDI in (Johner et al. 2013); the reason for this is likely due to differing assumptions in the calculation of iodine intake for pre-school children. Specifically, in assessing intake in (Johner et al. 2013), the difference came from considering 15% non-renal iodine losses. However, we assumed the non renal iodine losses are 10% maximum, due to the fact that over 90% of dietary iodine appears in the urine (Nath et al. 1992; Rao, McCready, and Spathis 1986; Vought and London 1967).

Overall, the iodine biokinetic model implemented in the AMBER software was very accurate in determining urinary iodine concentrations when daily iodine intake is estimated correctly, particularly when the urine volume is known. The results of the validation show that AMBER is a useful and reliable tool to estimate the concentration of urinary iodine *in silico*, especially, when sampling urine is difficult, such as collecting urine from infants or from very large populations.

Table 4.9 Validation of UIC measured by AMBER.

Country & gender	Number of samples	Urine Volume (L)	Estimated iodine daily intake (IDI) (µg/day)	UIC (µg/L)	Reference	UIC by AMBER (µg/L)
Japan	334	NA	388.8	213	(Fuse et al. 2021)	219.21
Denmark	108	NA	162*	63*	(Rasmussen et al. 2002)	91.3
	4616		152*	61*		87.5
Italy					(Iacone et al. 2021)	
Men	1229	1.9	111	55		52.57
Women	1149	1.95	85	41		39.2
Total	2378	1.9	96	46		45.46
Germany					(Johner et al. 2013)	
Boys	106	0.5824	82	124.4		126.8
Girls	115	0.5791	75	105.3		115.99

*Median values

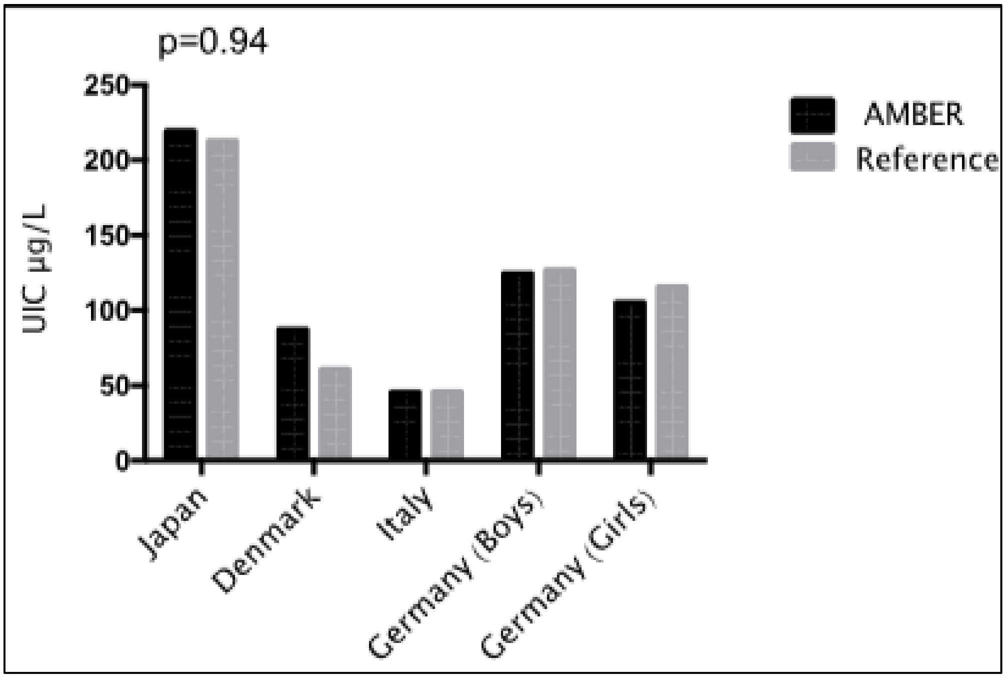


Figure 4.3 A comparison by using Mann-Whitney test shows no significant difference between the UIC measured in AMBER and the UIC measured in other references (p=0.94).

Table 4.10 Validation of AMBER reverse model results.

Country & gender	Urine Volume (L)	UIC (µg/L)	Estimated iodine daily intake (IDI) (µg/day)	Reference	Estimation of IDI by AMBER based on UIC in paper (µg/day)
Japan	NA	213	388.8	(Fuse et al. 2021)	372
Denmark	NA	63*	162*	(Rasmussen et al. 2002)	112
		61*	152*		108.4
Italy				(Iacone et al. 2021)	
Men	1.9	55	111		116.2
Women	1.95	41	85		89
Total	1.9	46	96		97.2
Germany				(Johner et al. 2013)	
Boys	0.5824	124.4	82		73.8
Girls	0.5791	105.3	75		67.17

*Median values

4.3.2 Breastmilk iodine and infant urinary iodine concentration.

Out of 105 breastmilk samples, 27 samples were excluded because the infant pair was also fed baby formula, complicating the estimate in AMBER as neither the volume of formula nor its iodine concentration are known. The remaining 78 breastmilk samples and their infant pairs were included. The breastmilk samples were obtained from mothers who used a multivitamin-mineral (MVM) supplement containing iodine during their pregnancy and lactating; 16 of MVM have 150 µg iodine and the remaining 62 MVM have a 220-µg. The daily milk consumption was measured by Health Canada for each infant, and ranged from 275 -1202 g/day, with a mean of 731 g/day and median of 747 g/day. These values of milk consumption are in agreement with those published in previous studies (Dewey and Lonnerdal 1986; Dewey et al. 1991; Arthur 1987; Michaelsen 1994; Cohen et al. 1994), indicating that the mean breastmilk intake globally is around 730 g/day. Infants' daily intakes of iodine were calculated for each mother-infant pair using the breastmilk consumption rate and breastmilk iodine concentration measured by ICP-MS. The daily iodine intake ranged from 11.2 µg/day to 476.2 µg/day with a median of 127.9 µg/day. This data was then used in AMBER as a source to estimate the urinary iodine concentration for each infant (Table 4.11). The median urinary iodine concentration calculated using AMBER (n=78) was 304.7 µg/L. Unfortunately, the volume of urine excreted for each infant was not measured. As a result an estimate was applied to all infants of 378 ml urine/day (Mark H Goellner, Ekhard E Ziegler 1981). Using this data, the urinary iodine estimation (UIE) was calculated, giving a median UIE of 115.2 µg/day.

As a further validation of the UIC estimates calculated using AMBER, a comparison of infant UIC values between Health Canada (HC) measurements and AMBER was made. The iodine intakes for each infant were used in AMBER enabling a comparison of the AMBER UIC result with the measured UIC for each of the 78 infants both individually and as a population. For the Health Canada data, the median UIC was 398.7 μg/L and the median UIE was 150.7 μg/day while for AMBER the median UIC was 304.7 μg/L and the median UIE was 115.2 μg/day. The measurement of UIC in infant is higher in the HC results than in AMBER (Figure 4.4). The results show that when sufficient data is provided, the iodine biokinetic model implemented in AMBER can be used to predict a trend in urinary iodine concentration of infants as a function of intake without collecting their urine. This comparison both validates the use of AMBER as a tool to estimate UIC on a sample-by-sample basis and for large populations of data. Despite the variability on a sample-by-sample basis, AMBER is a reliable predictor of urinary iodine concentrations in infants if the daily intake of iodine is known. One possible explanation for this difference between HC and AMBER with respect to individual samples is related to the analytical procedure used to measure iodine in the infant urine. Specifically, two different methods were used to measure iodine in breastmilk and urine. The Sandell-Kolthoff method was used for measurement of UIC, and the more accurate ICP-MS method was used to measure iodine in breastmilk. Although, the relationship between breastmilk intake and urinary iodine concentration in both AMBER and HC techniques was significantly correlated (Figure 4.5), the correlation between daily iodine intake and UIC for the mother infant-pairs had significant variability. This variability is not surprising given these are biological samples that represent complex biokinetic processes, however, this could account for some of the difference observed between the measured UIC data and AMBER for each sample. For instance, several infant samples have urinary iodine concentrations (UIC) higher than their corresponding breastmilk iodine concentrations (BMIC) and their iodine intakes which again implicates the complexity of the iodine biokinetics in real individuals relative to a model. The most likely reason for the difference between the AMBER and HC results for each sample pair is due to lack urine volume data. As mentioned earlier the same urine volume was used for every infant in the model. This has the effect of dampening real variability that exists with respect to the volume of urine excreted by each infant on the days the urine samples were collected. It is probable that if urine volume was known the AMBER model would perform better. Nevertheless, the Pearson correlation between the UIC measured by AMBER and the UIC measured by HC is moderately correlated (r= 0.496) and significantly different from zero (Figure 4.6), indicating that the AMBER results are reliable indicators of UIC in infants provided the daily intake of iodine is known. Variability is observed in the comparison between the measured Health Canada UIC's and the modelled UIC's, particularly for higher UIC values. This variability is possibly due to the complex biokinetics of iodine in people as well as the lack of data on urine volumes for the participants. Moreover, a comparison of the results based on gender shows that the difference between UIC in male and female infants measured by Health Canada is non-significant when compared to UIC measured by AMBER (Figure 4.7).

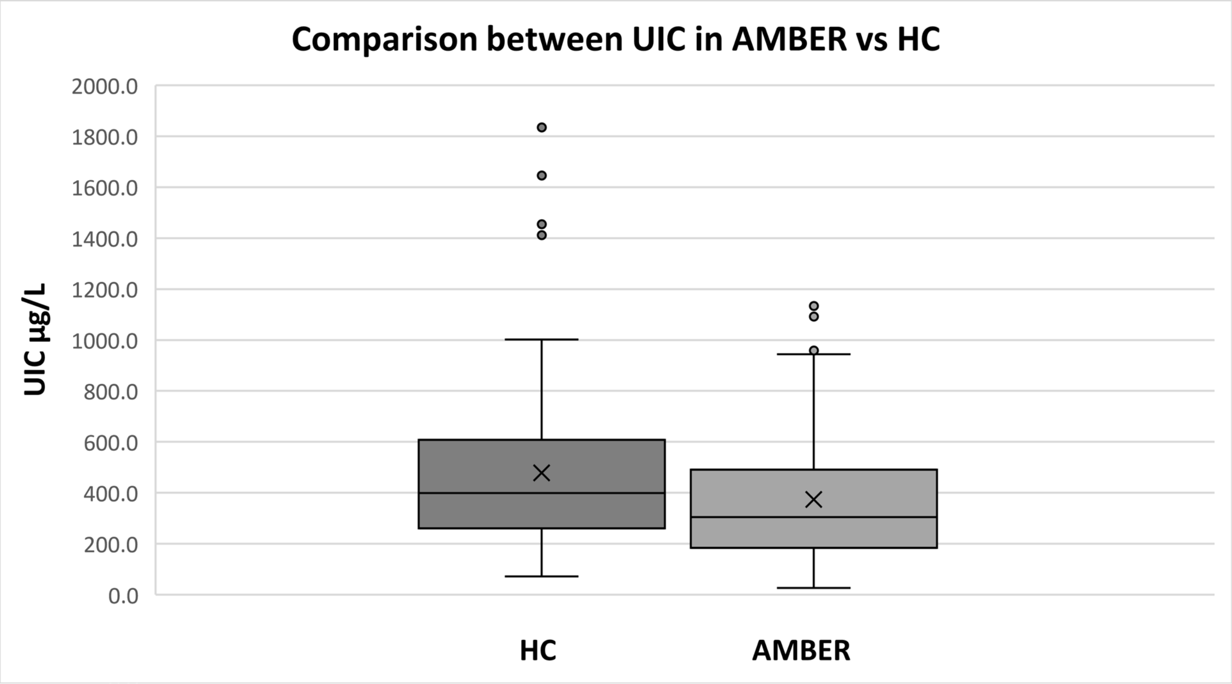


Figure 4.4The Comparison between urinary iodine concentration (UIC) results in infants based on AMBER Vs Health Canada (HC).

Sample size is (78); in (HC) the minimum: 71.7 µg/L, Q1:261.4 µg/L, median:398.75 µg/L, Q3:607.4 µg/L, and maximum:1833.9 µg/L. Mean (x):478.4 µg/L. The outliers in HC are: 1411 µg/L, 1454 µg/L, 1645 µg/L & 1833.9 µg/L. In AMBER the minimum: 26.8 µg/L, Q1:185.4 µg/L, median:304.65 µg/L, Q3:482.6 µg/L, and maximum:1133.9 µg/L. AMBER mean (x):374.4 µg/L. The outliers in AMBER are: 980 µg/L, 1091.4 µg/L, & 1133.9 µg/L.

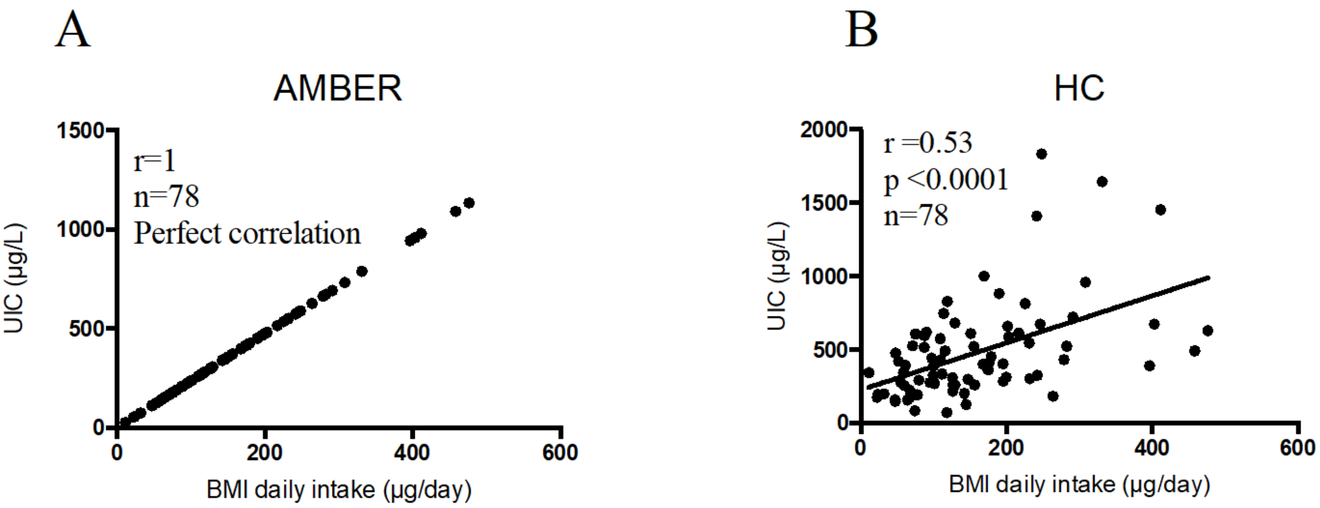


Figure 4.5 Spearman correlation shows the relationship between breastmilk iodine daily intake (BMI) (µg/day) and urinary iodine concentration (UIC) (µg/L) in Canadian infants.

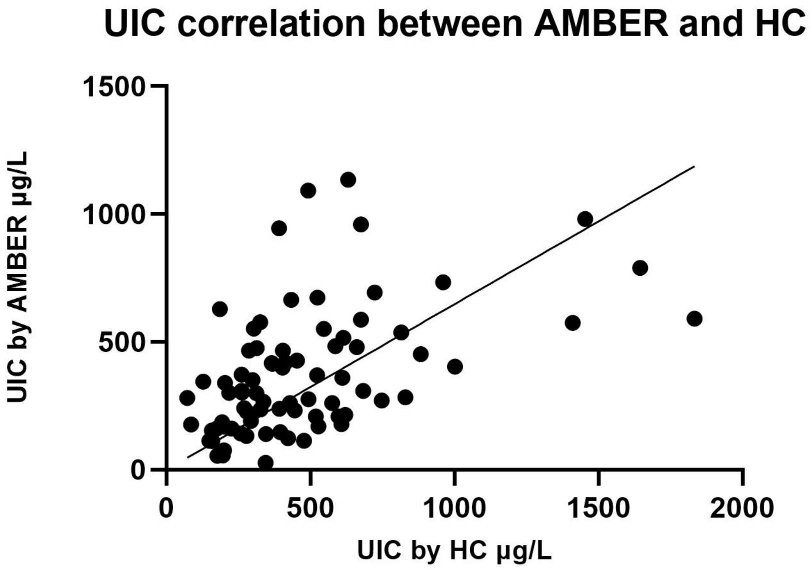


Figure 4.6 The correlation between urinary iodine concentration (UIC) in Canadian infants between AMBER and HC, r (78) =0.496, (p<0.05).

When the data is separated by the gender, the urinary iodine concentration estimated by AMBER for male infants (n=44) ranged from 26.8 µg/L to 1133.9 µg/L with a median of 371 µg/L, while the AMBER result for urinary iodine concentration for female infants (n=34) ranged from 53.9

µg/L to 980 µg/L with median of 253.6 µg/L. The urinary iodine concentration measured by HC for male infants (n=44) ranged from 127.4 µg/L to 1644.9 µg/L with median of 420.4 µg/L, while the urinary iodine concentration for female infants (n=34) ranged from 71.7 µg/L to 1833.9 µg/L with median of 335.8 µg/L; (Figure 4.8)**.** The null hypothesis is that would be no difference in UIC for males vs females. However, Mann-Whitney statistical analysis shows that there is indeed a difference in UIC for males vs females for the AMBER model results (p=0.02). The explanation for this difference is uncertain. However, it has been found that during pregnancy women consume about 10% more nutrients when they carry a male rather than a female (Tamimi et al. 2003) and this may explain why one month old infant males have higher UIC than females; however this difference is only observed in utero, and therefore it is uncertain if it would result in the observed difference a month after birth. Notwithstanding the difference in UIC between genders, the median UIC for both Canadian infant males and females reflects a sufficient iodine intake. The sufficient iodine intake indicates that Health Canada recommendation for pregnant and lactating women to take a multivitamin-mineral supplement (Health Canada 2009) is an important strategy to overcome iodine deficiency in both lactating women and infants.

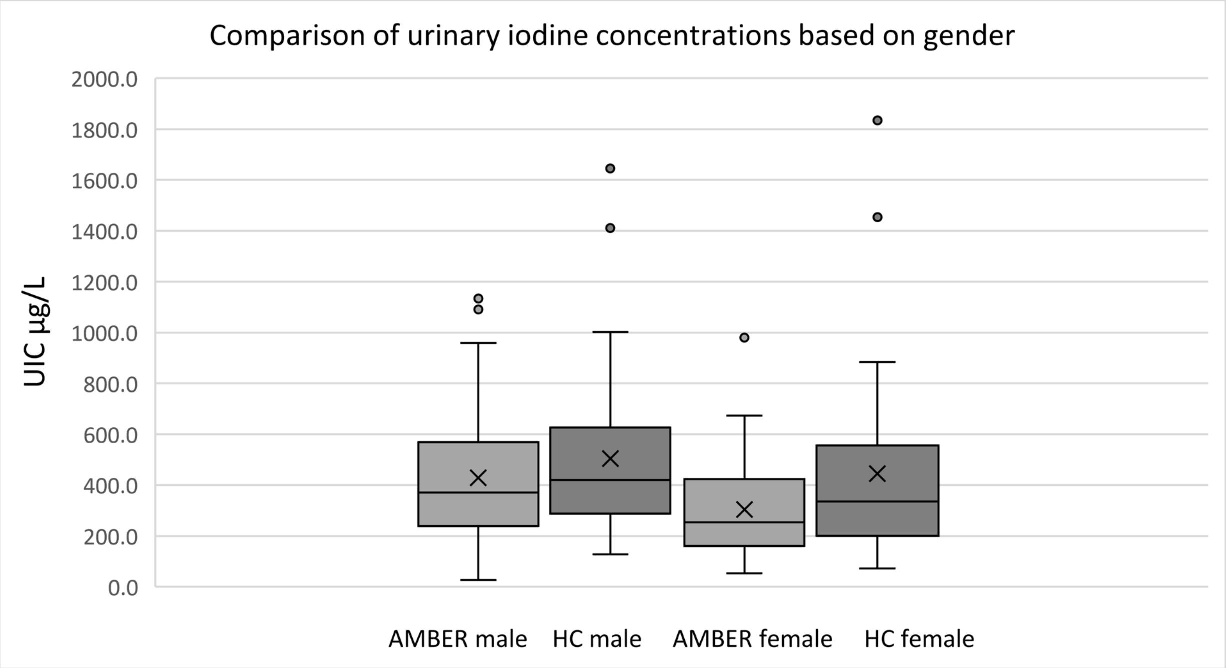


Figure 4.7 The comparison of urinary iodine concentration in Male vs Female Infants between AMBER and Health Canada using box and whisker.

For male, sample size (44). In HC minimum:127.4 µg/L, Q1:289.8 µg/L, median: 420.4 µg/L, Q3:622.2 µg/L, and maximum:1645 µg/L, with mean(X):504.1 µg/L. The outliers are: 1645 µg/L, & 1411 µg/L. In AMBER minimum: 26.8 µg/L, Q1:239.7 µg/L, median: 370.95 µg/L, Q3:563.3 µg/L, and maximum:1133.9 µg/L, with mean(X):428.6 µg/L. The outliers are: 1091.4 µg/L, & 1133.9 µg/L. For Female, sample size (34). In HC minimum:71.7 µg/L, Q1:202.9 µg/L, median: 335.8 µg/L, Q3:545.7 µg/L, and maximum:1833.9 µg/L, with mean(X):445 µg/L. The outliers are: 1454 µg/L & 1833.9 µg/L. In AMBER minimum: 53.9 µg/L, Q1:160.2 µg/L, median:253.6 µg/L, Q3:414.1 µg/L, and maximum:980.2 µg/L, with mean(X):304.3 µg/L. The outlier is 980.2 µg/L.

Table 4.11 Iodine 127 concentrations in urine infant measured by AMBER and Health Canada.

	Iodine in breastmilk (ppb)	Infant milk intake (g/day)	Infant daily intake of iodine (µg/day)	UIC by AMBER (µg/L)	UIE calculated for AMBER (µg/day)	UIC by HC (µg/L)	UIE* calculated for HC (µg/day)
1	123.96	808	100.2	238.5	90.1	391.9	148.2
2	303.53	658	199.6	475.4	179.7	313	118.3
3	186.72	610	113.9	271.2	102.5	747.4	282.5
4	124.62	947	118.0	281.0	106.2	71.7	27.1
5	446.71	1026	458.3	1091.4	412.5	491.8	185.9
6	533.41	621	331.2	788.8	298.2	1645	621.8
7	233.95	645	150.9	359.4	135.8	610.9	230.9
8	109.39	645	70.6	168.0	63.5	203.3	76.8
9	270.14	746	201.5	479.9	181.4	660.8	249.8
10	122.92	388	47.7	113.6	42.9	477.2	180.4
11	306.29	788	241.4	574.7	217.2	1411	533.3
12	169.16	575	97.3	231.6	87.5	444.6	168.1
13	202.28	967	195.5	465.7	176.0	286.6	108.3
14	300.28	301	90.2	214.9	81.2	620.2	234.4
15	587.86	810	476.2	1133.9	428.6	631	238.5
16	196.67	445	87.5	208.4	78.8	597.6	225.9
17	176.17	714	125.9	299.7	113.3	311.5	117.7
18	82.25	275	22.6	53.9	20.4	176.1	66.6
19	14.89	755	11.2	26.8	10.1	343.5	129.8
20	207.57	914	189.7	451.8	170.8	883.1	333.8
21	395.52	584	231.0	550.0	207.9	545.7	206.3
22	162.41	731	118.7	282.7	106.9	829.1	313.4
23	197.72	744	147.1	350.3	132.4	298.8	113
24	71.61	661	47.3	112.7	42.6	147.8	55.8

25	175.01	1116	195.3	465.1	175.8	403.4	152.5
26	185.45	837	155.3	369.7	139.8	522.7	197.6
27	199.38	784	156.3	372.2	140.7	260.6	98.5
28	349.32	710	248.2	591.0	223.4	1833.9	693.2
29	89.95	748	67.3	160.2	60.6	173.6	65.6
30	289.80	618	179.1	426.5	161.2	452.9	171.2
31	239.02	458	109.5	260.7	98.5	428.4	161.9
32	538.80	764	411.6	980.2	370.5	1454	549.6
33	312.99	787	246.3	586.6	221.7	674.7	255.1
34	75.86	774	58.7	139.8	52.8	345.1	130.5
35	197.67	856	169.2	402.9	152.3	1002.1	378.8
36	271.41	1041	282.5	672.8	254.3	524.1	198.1
37	95.86	643	61.6	146.7	55.4	394.9	149.3
38	124.21	418	51.9	123.6	46.7	421.9	159.5
39	357.05	568	202.7	482.6	182.4	585.7	221.4
40	143.20	385	55.2	131.4	49.7	276.8	104.6
41	329.97	1202	396.6	944.5	357.0	390.9	147.7
42	197.78	730	144.4	343.8	130.0	127.4	48.2
43	172.21	552	95.1	226.4	85.6	277.8	105
44	327.35	852	278.9	664.1	251.0	432.9	163.7
45	142.31	500	71.2	169.4	64.0	527.6	199.4
46	47.78	665	31.8	75.7	28.6	198.9	75.2
47	169.45	748	126.8	301.8	114.1	261.4	98.8
48	203.27	700	142.3	338.8	128.1	202.9	76.7
49	125.09	639	79.9	190.3	71.9	292.9	110.7
50	230.28	1006	231.8	551.9	208.6	302.9	114.5
51	107.68	810	87.2	207.7	78.5	518	195.8
52	100.81	638	64.3	153.1	57.9	157.6	59.6
53	472.69	852	402.7	959.0	362.5	674.6	255

54	302.70	582	176.2	419.5	158.6	412.4	155.9
55	136.96	798	109.3	260.3	98.4	575.1	217.4
56	260.67	1117	291.2	693.3	262.1	723	273.3
57	190.39	680	129.5	308.3	116.5	260.3	98.4
58	172.92	645	111.5	265.6	100.4	335.7	126.9
59	146.61	512	75.1	178.7	67.6	607.4	229.6
60	358.27	860	308.1	733.7	277.3	960.8	363.2
61	328.18	510	167.5	398.8	150.7	402.6	152.2
62	97.66	760	74.2	176.7	66.8	84.9	32.1
63	140.48	824	115.8	275.6	104.2	492.6	186.2
64	251.23	964	242.2	576.7	218.0	325.4	123.0
65	220.16	796	175.2	417.3	157.7	364.8	137.9
66	262.84	824	216.7	516.0	195.1	613.4	231.9
67	125.19	1006	126.0	300.0	113.4	217.4	82.2
68	91.46	516	47.2	112.4	42.5	158.6	60
69	203.41	855	173.9	414.1	156.5	367	138.7
70	73.58	913	67.2	160.0	60.5	226.4	85.6
71	69.23	859	59.5	141.6	53.5	257.4	97.3
72	115.57	875	101.1	240.8	91.0	269.4	101.9
73	120.97	819	99.1	236.0	89.2	326.5	123.4
74	116.12	671	77.9	185.4	70.1	193	72.9
75	187.16	690	129.1	307.5	116.2	683.2	258.3
76	253.29	890	225.4	536.8	202.9	814.7	308
77	76.12	309	23.5	56.0	21.2	195.1	73.8
78	276.38	955	263.9	628.5	237.6	184.7	69.8

*Urinary iodine estimation was calculated by multiplying 0.378L with UIC.

4.3.3 Urinary iodine concentration.

4.3.3.1 Influence of diets on urinary iodine concentration.

Using AMBER, it is possible to investigate the influence of diet on UIC to determine which foods play an important role in ensuring iodine adequacy. The UIC results for seven diets (vegan, lacto-ovo-vegetarian, lacto-vegetarian, ovo-vegetarian, regular, keto, and low carb) were modelled in AMBER. In addition, sub-scenarios where iodized salt was excluded were analyzed to investigate the importance of iodized salt relative to other foods. Using AMBER, urinary iodine-127, iodine-129 concentrations and the $^{129}I/^{127}I$ ratio were calculated for people following these differing diets (Figure 4.9). The UIC's calculated in AMBER are best estimates derived using consumption rates (Health Canada 2017) and iodine concentrations (Benkhedda et al. 2009) to calculate daily iodine intakes for each food group (Table 4.8). The results presented here would likely vary greatly on an individual basis due to differing food consumption habits, day-to-day variation in food choices, the sources of the food consumed and differing consumption rates among a population. However, on a population basis the results presented here for each diet represent a reasonable and well-supported best-estimate for an individual consuming a particular diet.

A baseline is established for all regular diets, which had an iodine daily intake of 210.4 µg/day. This yielded a urinary iodine concentration of 118.6 µg/L. The relative contributions of each food item were quantified with 29.7% of the iodine intake derived from milk, followed by 15.9% from grain products, 15% from cheese, 8% from meat, 8% from eggs, 7% from yogurt, 6% from chicken, and only 5% from fish. When iodized salt is included the daily intake of iodine reached 276.5 µg/. This resulted in a UIC of 155.9 µg/L, which reflects an optimal concentration. In the regular diet, salt (23.9%) still contributed less iodine than dairy products, which made up 38%. (Figure 4.8, A).

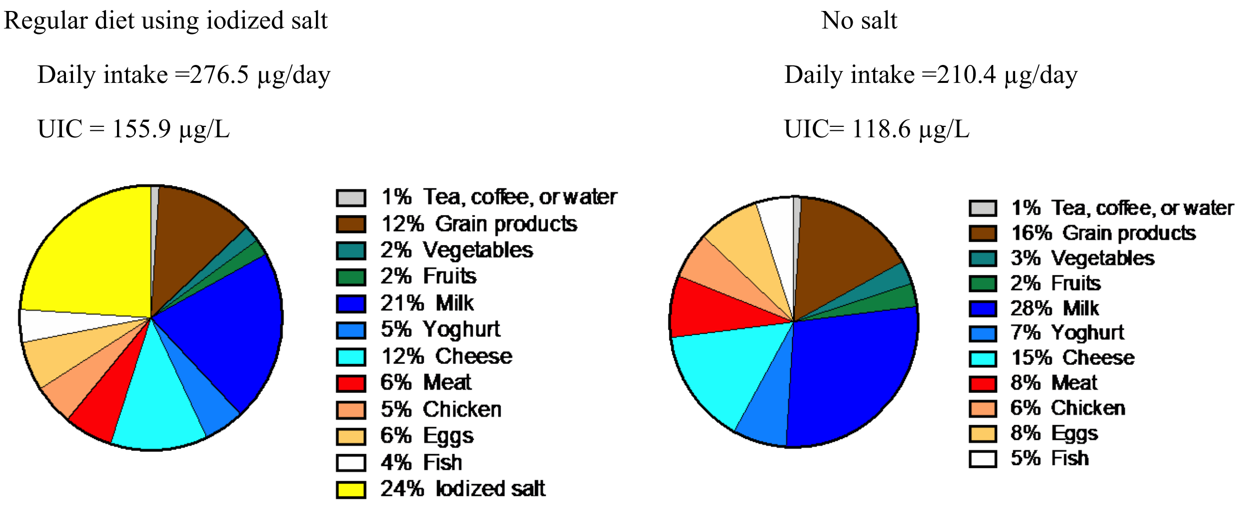


Figure 4.8(A) a comparison between regular diet using iodized salt and regular diet without salt in term of salt contribution shows that adding salt has a minor effect in iodine status.

Those who exclude grains and fruits from their diets (ketogenic diet) or exclude grains only (low carbohydrate diet) may begin to exhibit signs of moderate iodine deficiency. The iodine daily intake dropped to 172.5 µg/day for the ketogenic diet, and 176.8 µg/day for the low carbohydrate diet, yielding urinary iodine concentrations of 97.3 µg/L and 99.7 µg/L. For these diets, the majority of iodine intake is from consuming dairy products including milk, cheese, and yogurt, and some from meat and eggs. However, iodized salt can boost daily intake substantially for the ketogenic and low carbohydrate diet; if added, the daily iodine intake increased to 238.6 µg /day for the ketogenic diet and 242.9 µg /day for the low carbohydrate diet. Similarly, the UIC increased to 139.6 µg/L and 137 µg/L, which are both within the optimal concentration range. The contribution of iodized salt to both the ketogenic diet and low carbohydrate diet is (28%) while the contribution of dairy products was over 40% (Figures 4.8, B and C).

Ketogenic diet using iodized salt

Daily intake =238.6 µg/day

UIC = 134.5 µg/L

No salt

Daily intake =172.5 µg/day

UIC= 97.3 µg/L

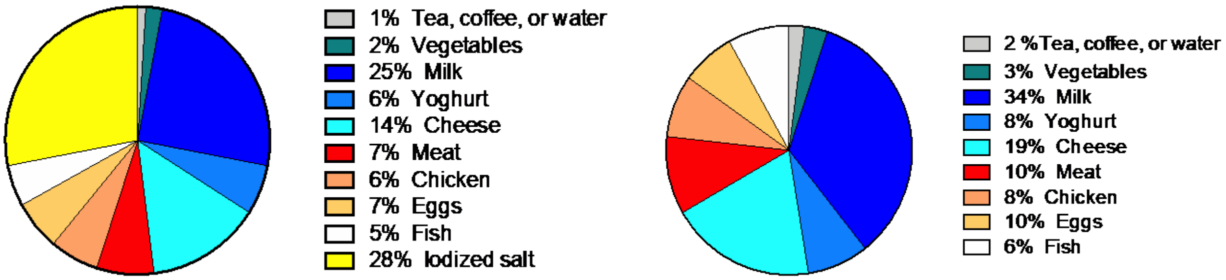


Figure 4.8 (B) a comparison between ketogenic diets in term of using iodized salt shows a significant improvement in UIC status among salt user.

Low carb diet using iodized salt

Daily intake =242.9 µg/day

UIC = 137 µg/L

No salt

Daily intake =176.8 µg/day

UIC= 99.7 µg/L

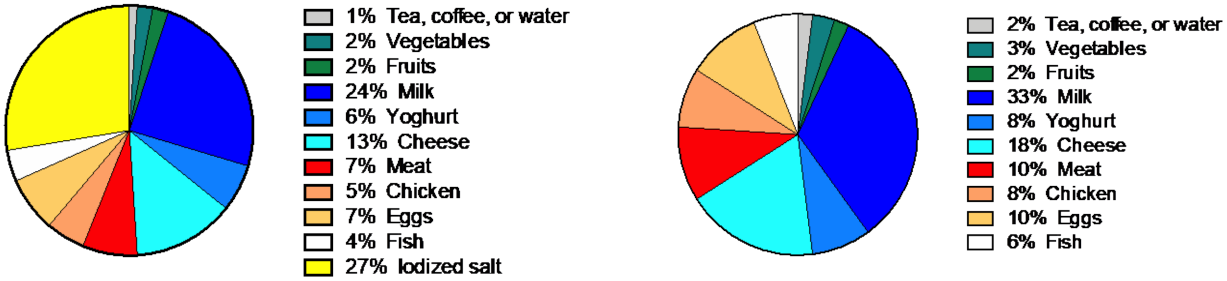
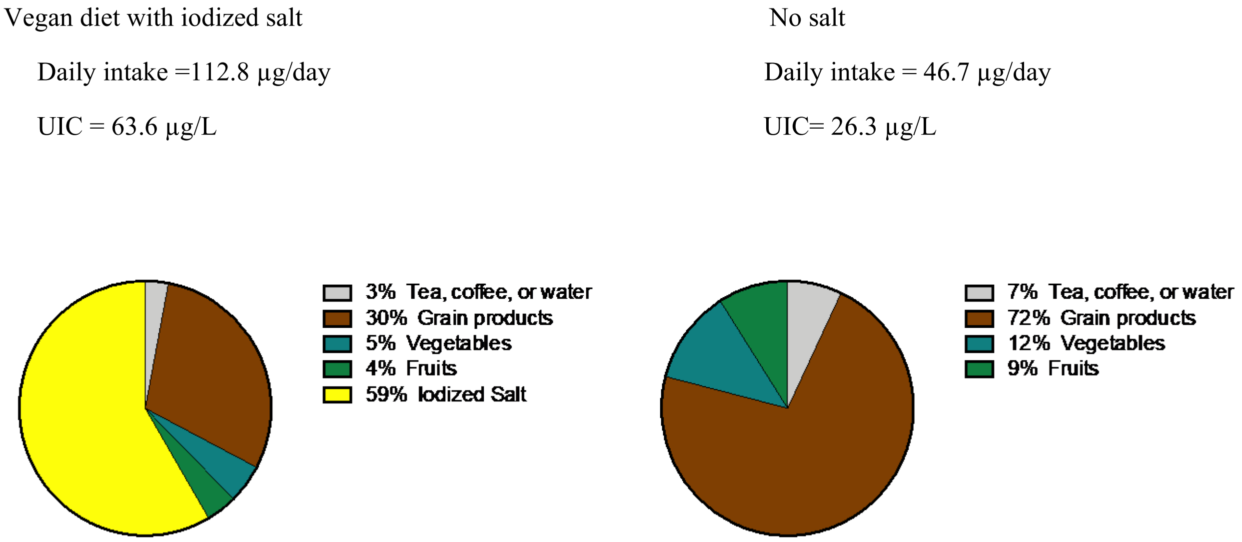


Figure 4.8 (C) a comparison between low carbohydrate diets in term of using iodized salt shows a significant improvement in UIC status among salt user.

For a vegan diet, the daily iodine intake was estimated at 46.7 µg/day, 72% of which is derived from the consumption of grain products. The modelled UIC was 26.3 µg/L, which reflects a mild-severe iodine deficiency. However, when iodized salt is added to vegan diet, the daily intake doubles to 112.8 µg/day, 58.6 % of which is from iodized salt and 29.8% from grain products. The resulting UIC for vegans when consuming iodized salt was 63.6 µg/L, which reflects a mildly deficient intake (Figure 4.8 D).



Vegan diet with iodized salt

Daily intake =112.8 µg/day

UIC = 63.6 µg/L

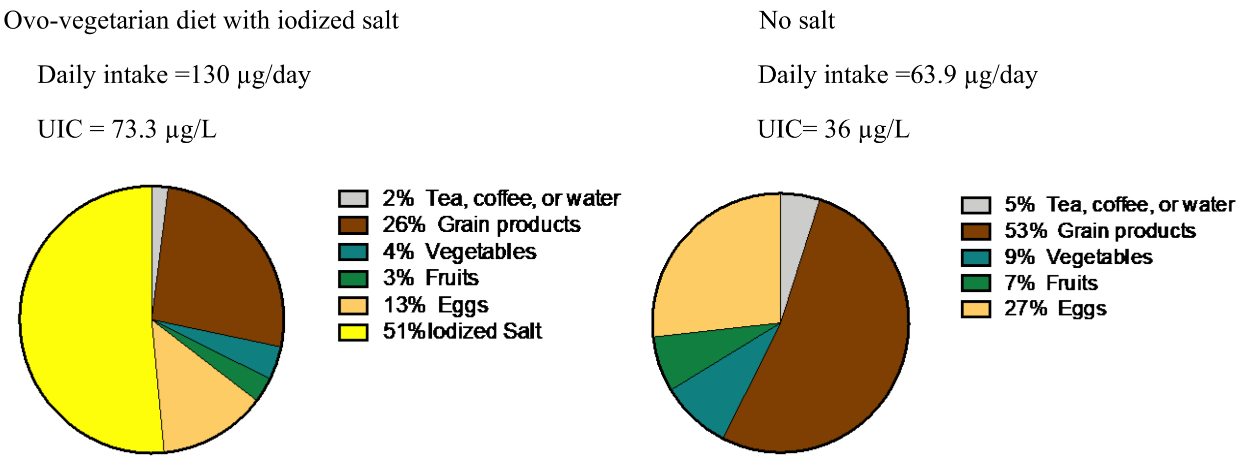
No salt

Daily intake = 46.7 µg/day

UIC= 26.3 µg/L

Figure 4.8 (D) a comparison shows significant difference between vegan diet using iodized salt and vegan diet without salt.

When eggs are included in the vegan diet (ovo-vegetarian), the daily iodine intake increased by 17.2 µg, totalling 63.9 µg of iodine per day. The majority (52.6%) of iodine, was derived from consuming grain products while the remainder (26.9%) came from eating eggs. The urinary iodine concentration, 36 µg/L, is still in the mild deficiency spectrum, Nevertheless, when iodized salt is included in the ovo-vegetarian diet, the daily intake doubled to 130 µg/day, 50.9 % of which was from iodized salt, 25.8% from grain products, and 13.2% from eggs. The UIC for an ovo-vegetarian when consuming iodized salt was 73.3 µg/L, which still reflects a moderate iodine deficiency (Figure 4.8, E).



Ovo-vegetarian diet with iodized salt

Daily intake =130 µg/day

UIC = 73.3 µg/L

No salt

Daily intake =63.9 µg/day

UIC= 36 µg/L

Figure 4.8 (E) a comparison shows significant difference between ovo-vegetarian diet using iodized salt and ovo-vegetarian diet without salt.

If vegans include dairy products only (milk, yogurt, and cheese) in their diet (lacto-vegetarian), their daily iodine intake jumps by 104.7 µg, meaning they consume 151.4 µg of iodine per day with dairy products; milk, cheese, yogurt, representing 38.8%, 21.3%, and 9% respectively with an additional 22% from grains. Their urinary iodine concentration increased to 85.4 µg/L. Moreover, when iodized salt is added to lacto-vegetarian diet, the daily intake increased to 217.5 µg/day, 48.1 % from dairy products, while iodized salt contributed 30.3% and grain products 15.4%. The UIC for lacto-vegetarians when consuming iodized salt reached 122.6 µg/L, which is within the optimal concentration range (Figure 4.8, F).

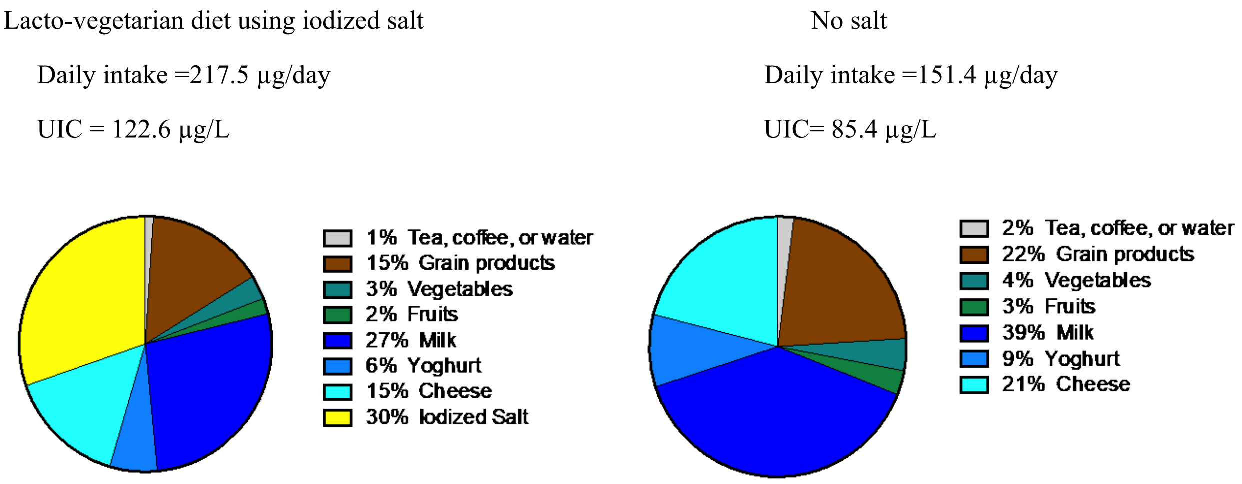
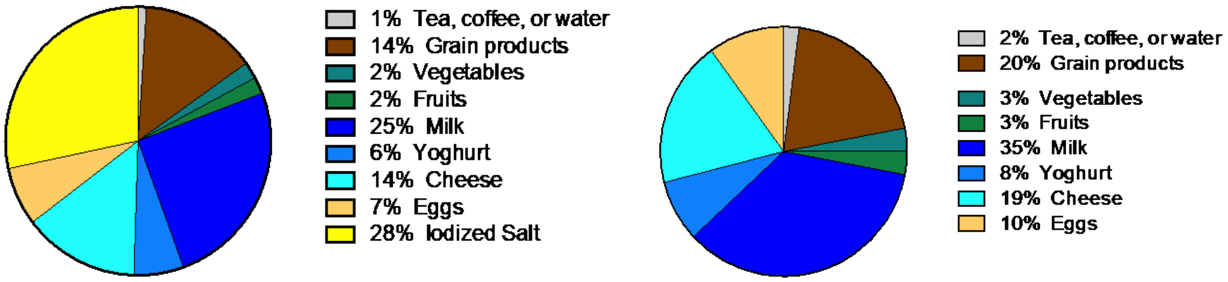


Figure 4.8 (F) a comparison shows difference between lacto-vegetarian diet using iodized salt and lacto-vegetarian diet without salt.

Lacto-ovo-vegetarians have no restrictions in their diet besides meat, resulting in a daily iodine intake of 168.6 µg/day. The key iodine sources are dairy products; milk, cheese, yogurt, (34.8%, 19.2%, 8%) respectively, 20% from grains and 10% from eggs with a urinary iodine concentration of 95.1 µg/L, reflecting a moderate iodine deficiency. However, when iodized salt is added to lacto-ovo-vegetarian diet, the daily intake reached 234.7 µg/day with important contributions from iodized salt (28%) and dairy products (45%). When consuming iodized salt, the UIC reached 132.3 µg/L, which is within the optimal concentration range (Figure 4.8, G).



Lacto-ovo-vegetarian diet using iodized salt

Daily intake =234.7 µg/day

UIC = 132.3 µg/L

No salt

Daily intake =168.6 µg/day

UIC= 95.1 µg/L

Figure 4.8 (G) a comparison shows significant difference between lacto-ovo-vegetarian diet using iodized salt and lacto-ovo-vegetarian diet without salt.

In 1987, a representative diet study (P. Fischer and Giroux 1987) estimated the daily iodine intake for Canadians at 1046 µg/day. However, based on our calculation of daily iodine intakes we find that it is less than 300 µg/day. One reason for this difference may be related to significantly different estimates of food consumption rates. For example, in (Fischer 1987), the Canadian consumption rate for salt was reported as 11.5 g/day while we calculated it as 0.89 g/day. Moreover, the estimation of iodine intake was not supported by any analysis of urinary iodine to verify this high daily intake. Currently, individuals follow many different types of diet; thus, a representative diet should consider these differences in food consumption. A strength of this study, and the AMBER model, is that it considers the high variability between different dietary choices and is capable of readily investigating the influence of different foods.

A vegetarian diet may lead a loss of important vitamins and minerals such as iodine if alternative sources are not added (Fields and Borak 2009). In this study, we observed that the main source of iodine in a vegan diet is grain products such as wheat, cereal, pasta, and rice, providing up to 70% of the daily iodine intake. Generally speaking, grains are not a good source of iodine due to their low iodine concentration. Indeed, consumption of 1 gram of a grain product provides only ~0.16 µg of iodine. Therefore, when not using iodized salt, the modelled result showed that the urinary iodine concentration in vegans shows a state of severe deficiency (<30 µg/L). However, when iodized salt is added to a vegan diet, a very large improvement in their daily iodine intake is predicted. Iodine daily intake increases when an increased variety of food items are included in a diet as the model consumption rates were not changed when omitting a food for a particular dietary subgroup. For example, when adding eggs, we observed an increase of 50% in urinary iodine concentration in vegetarians eating eggs (ovo-vegetarian). Eggs are a very rich natural source of iodine, as their iodine concentration varies between 25 to 104 µg/egg, with an average of 52 µg/egg (Daugeras-Bernard and Lachiver 1980). In addition, when dairy products are added to a vegetarian diet, iodine concentrations improved by 400%. Indeed, dairy products are the main source of dietary iodine in industrialized countries (Lee et al. 1994). In this study, the average consumption of dairy products, according to the Canadian total diet study was 249 g/day(Health Canada 2017), and this consumption, as indicated here, shows that dairy products represent 38-48% of daily dietary iodine, for diets that also included iodized salt. These percentages agree with those in other countries that have similar consumption rates. In the UK, for instance, people consume 239 gram of dairy products per day, with dairy products contributing 34% of iodine daily intake. In addition, in Ireland, 38% of iodine daily intake is from dairy products, with a daily consumption of 268 g/day (van der Reijden, Zimmermann, and Galetti 2017).

For diets that did not use iodized salt, we observed that dairy products are the primary source of iodine in most diet variations. The highest contribution (69%) was observed in the lacto-vegetarian diet, while in the lacto-ovo-vegetarian, ketogenic, and low carbohydrate diets the contribution was around 60%. The lowest contribution from dairy was in the regular diet, where dairy products provide 50% of iodine daily intake when iodized salt is not consumed. The recommended daily dairy intake in North America is 2-3 serving/day which is equal to 400g-600g/day (Comerford et al. 2021). Nevertheless, this recommendation was not achieved for Canada based on Health Canada (2017) where the mean daily dairy intake is less than 300g/day. Several studies have observed decreasing dairy intakes with increasing age (van der Reijden, Zimmermann, and Galetti 2017) and Canada shares many similarities with other industrialized countries. Recently, milk and dairy consumption has also declined among children and adolescents in many European countries such as France, Germany, Ireland, Spain, and the U.K (van der Reijden, Zimmermann, and Galetti 2017). If dairy consumption continues to decline it is important that other sources of iodine be added to an individual diet. In Canada, however, the Dairy Farmers of Ontario (DFO) created a free program in 1986 called the Elementary School Milk Program (ESMP) that distributes milk to elementary school students in the province of Ontario. This program encourages schools to join and recommends they to distribute milk at least 3 times a week. Based on the finding of this study, in which dairy is observed to play a very important role in iodine status, this strategy helps to maintain iodine status, and if adopted by other provinces, it will improve iodine status among children.

Salt iodination programs have long been a critical part of ensuring sufficient iodine status in many nations around the world. In term of iodized salt, the amount of iodine to be added to salt for a given population is determined by the severity of iodine-deficiency disorders, and the average salt consumption per capita (Diosady et al. 1998). In Canada, Health Canada regulations mandate that table salt producers add 76 µg of iodine per gram of salt (Dussault 1993). Potassium iodide (KI) is the most common compound used to meet this requirement. However, as KI easily oxidises to iodine by heat or humidity, it is unstable and loss occurs during storage (Waszkowiak and

Szymandera-Buszka 2008). Therefore, the measured concentration of iodine in salt tends to be less than mandatory requirement as shown in (Benkhedda et al. 2009) and (P. W. F. Fischer and L'Abbé 1980). In this study, it was assumed that all iodine in salt met the requirement, in order aim to assess the importance of this mandatory value. Although P. Fischer and Giroux (1987) estimated Canadians salt consumption at 11.5 g/day, Canadians presently consume less than one gram of iodized salt per day (Garriguet 2007). As a result, the contribution of iodized salt to all Canadian diets assessed here was ranked second, after dairy, unless the diet is vegan or ovo-vegetarian, where dairy was not consumed meaning the contribution of iodized salt was ranked first. Nevertheless, iodized salt plays an important role in ensuring sufficient iodine status as it ranged from 24 to 59% of daily iodine intake.

4.3.3.2 Influence of diets on urinary iodine-129 concentration.

Among 23 scenarios for seven different diets, the urinary iodine-129 concentrations ranged from 1.4×10^{-7} to 3.3×10^{-7} µg/L with a median of 3.1×10^{-7} µg/L. The isotopic $^{129}I/^{127}I$ ratio ranged from 1.1×10^{-9} to 1.2×10^{-8} with a median of 2.8×10^{-9} (Table 4.12). In contrast to stable iodine, the result shows that urinary iodine-129 concentrations ($U^{129}IC$) are similar among all diets. Nevertheless, a small change in ^{129}I concentration should be considered carefully, due to the fact that ^{129}I concentrations in the environment are small. In contrast to stable iodine, the highest isotopic ratio was observed in vegan diet, while the lowest was observed in ketogenic diet. This suggests that grain products are the main contributor of ^{129}I to humans. As observed in the difference between ketogenic diet and low carb diet, fruits also have a big influence on ^{129}I contribution. Salt and dairy show a lower contribution of ^{129}I despite being the primary contributors of stable iodine. This result is surprising given the importance of salt and dairy. However, it is possible that despite the authors best efforts to find reliable sources for ^{129}I in foods that the assumptions made for the concentration of ^{129}I in grains and other sources were too high as they were derived from samples of cedar leaves as no direct measurements of grains or several other food items were available. As a result, this interpretation could likely be improved if further direct measurements of ^{129}I in food are made.

Table 4.12: Urinary iodine-129 concentration and ratio based on diets.

Diet	Daily ^{129}I intake (µg/day)	UIC ^{129}I (µg/L)	UIC ^{129}I (atoms/L)	^{129}I/^{127}I ratio
Vegan diet using iodized salt	5.4E-07	3.1E-07	1.45E+09	4.8E-09
Vegan diet without using salt	5.4E-07	3.0E-07	1.40E+09	11.5E-09
Lacto-ovo-vegetarian diet using iodized salt	5.5E-07	3.1E-07	1.45E+09	2.4E-09
Lacto-ovo-vegetarian diet without using salt	5.5E-07	3.1E-07	1.45E+09	3.3E-09
Lacto-vegetarian diet using iodized salt	5.5E-07	3.1E-07	1.45E+09	2.5E-09
Lacto-vegetarian diet without using salt	5.5E-07	3.1E-07	1.45E+09	3.6E-09
Ovo-vegetarian diet using iodized salt	5.4E-07	3.1E-07	1.45E+09	4.2E-09
Ovo-vegetarian diet without using salt	5.4E-07	3.1E-07	1.45E+09	8.5E-09
Regular diet using iodized salt	5.9E-07	3.3E-07	1.54E+09	2.1E-09
Regular diet using iodized salt and eating meat only	5.6E-07	3.1E-07	1.45E+09	2.2E-09
Regular diet using iodized salt and eating chicken only	5.6E-07	3.1E-07	1.45E+09	2.2E-09
Regular diet using iodized salt and eating fish only	5.8E-07	3.3E-07	1.54E+09	2.4E-09
Regular diet without using salt	5.8E-07	3.3E-07	1.54E+09	2.8E-09
Regular diet using iodized salt but no Dairy	5.7E-07	3.2E-07	1.49E+09	3.3E-09
Regular diet using iodized salt but no milk	5.8E-07	3.3E-07	1.54E+09	2.7E-09
Regular diet without milk and salt	5.7E-07	3.2E-07	1.49E+09	3.8E-09
Regular diet without dairy and salt	5.7E-07	3.2E-07	1.49E+09	5.4E-09
ketogenic diet using iodized salt	2.6E-07	1.5E-07	7.00E+08	1.1E-09
ketogenic diet without using salt	2.6E-07	1.5E-07	7.00E+08	1.5E-09
ketogenic diet without using salt or dairy	2.5E-07	1.4E-07	6.54E+08	3.7E-09
low carb diet using iodized salt	4.0E-07	2.3E-07	1.07E+09	1.7E-09
low carb diet without using salt	4.0E-07	2.2E-07	1.03E+09	2.3E-09
low carb diet without using salt and dairy	3.9E-07	2.2E-07	1.03E+09	5.4E-09

4.3.4 Estimation of iodine daily intake based on urinary iodine.

4.3.4.1 Estimation of stable iodine daily intake.

It is challenging to estimate with any accuracy the daily iodine intake due to significant uncertainty around foods consumed. Food recall surveys provide general data at best and the only accurate means of measuring daily iodine intake is through the use of controlled conditions where participants are provided with food. In order to address this challenge, the AMBER model was modified to calculate iodine daily intakes using urinary iodine concentrations as the data source. UIC values are relatively easy to obtain, and a correction factor to account for iodine absorption in the body can be applied. Daily iodine intakes were estimated for two datasets of Canadian urine samples. The first dataset was for 25 urinary iodine concentration samples from individuals that were measured previously (Alotaibi et al. 2021). The second was for population level urinary iodine concentrations for Canadians according to their age. In the 25 individual samples (Table 4.13), one individual has a severe deficiency where the iodine intake was calculated as 42.8 µg/day, 3 individuals have a sub-optimal daily intake below 150 µg/day, 9 samples were in the optimum daily intake range, which is below 300 µg/day, and -10 individuals were over the optimum daily intake which is higher than 300 µg/day but below 1000 µg/day. Finally, 2 individuals were at-risk to induce hyperthyroidism where daily intake is above 1000 µg/day. Based on the food recall survey distributed to the participants during urine collection, the deficient sample (11) was obtained from a donor who does not consume milk, while the 3 samples (2, 19, 22), that were below the optimum iodine daily intake were from donors who consume milk less frequently. In addition, one donor (4) does not consume salt at all, and their daily intake was estimated to be near the optimal daily intake. The remaining individuals follow regular diets and consumed dairy and used salt on a daily basis. Therefore, their iodine daily intakes were optimal. However, two samples exceeded the iodine recommended daily allowance RDA. These two samples were belonged to an Asian couple, who may consume food items rich in iodine. It well documented that the Asian population has a high iodine consumption which can reach 6600 µg/day, and their mean urinary iodine concentration have been reported to range from 640 µg/L to 3800 µg/L (Kwon, Chung, and Jin 2021).

Table 4.13 Estimation of iodine daily intake (µg/day) for 25 urine samples.

Sample	Using salt	Drinking milk	^{127}I in Urine (µg/L)	Calculated ^{127}I daily intake (µg/day)	^{129}I in Urine (10^6 atoms/L)	Calculated ^{129}I daily intake (µg/day)	^{129}I/^{127}I ratio X 10^{-10}
1	Monthly	Daily	225.6	400.4	238.3	9.06E-08	2.23
2	Daily	Weekly	79.7	141.4	61.8	2.35E-08	1.64
3	Daily	Daily	3543.9	6289.4	884.0	3.36E-07	0.56
4	None	Daily	85.0	150.9	109.5	4.16E-08	2.72
5	Daily	Daily	94.4	167.5	3.3	1.25E-09	0.07
6	Daily	Daily	1197.0	2124.3	798.6	3.04E-07	1.41
7	Weekly	Weekly	207.2	367.7	217.3	8.26E-08	2.21
8	Daily	Daily	339.7	602.9	318.4	1.21E-07	1.98
9	Weekly	Daily	94.8	168.2	16.1	6.12E-09	0.36
10	Daily	Daily	255.4	453.3	40.2	1.53E-08	0.33
11	Daily	None	24.1	42.8	15.3	5.82E-09	1.33
12	Daily	Daily	143.1	254.0	87.7	3.33E-08	1.29
13	Daily	Daily	139.6	247.8	180.2	6.85E-08	2.72
14	Weekly	Daily	482.5	856.3	84.5	3.21E-08	0.37
15	Daily	Weekly	394.8	700.7	340.6	1.29E-07	1.82
16	Monthly	Daily	185.9	329.9	264.6	1.01E-07	3.00
17	Daily	Weekly	338.8	601.3	108.7	4.13E-08	0.68
18	Daily	Daily	122.6	217.6	52.2	1.98E-08	0.90
19	Daily	Monthly	81.0	143.8	12.4	4.71E-09	0.32
20	Weekly	Daily	160.4	284.7	50.8	1.93E-08	0.67
21	Daily	Daily	131.0	232.5	32.1	1.22E-08	0.52
22	Daily	Weekly	83.3	147.8	156.6	5.95E-08	3.97
23	Daily	Daily	102.3	181.6	14.2	5.40E-09	0.29
24	Weekly	Daily	441.8	784.1	231.0	8.78E-08	1.10
25	Monthly	Daily	222.7	395.2	157.5	5.99E-08	1.49

Iodine status was assessed in the Canadian Health Measures Survey 2007-2009, and the results were presented based on gender and ages. Using these data, the daily iodine intake for these population groups was then estimated using AMBER (Table 4.14). Results show a sufficient daily iodine intake for all ages (19-79) and genders with median of 349.4 µg/day for males, and 290.8 µg/day for females. Interestingly, the daily iodine intake for females in all age groups is lower than in males. This difference in intake between men and women can be explained in terms of physiological need, and food consumption rates. Females have a lower iodine requirement due to their lower thyroid production which is associated with a lower body size (Johner et al. 2013). Because men have a larger body size than women, they consume more food as well; leading to differences in minerals and vitamins quantities consumed with men consuming more. Moreover, the preference for specific type of food influences the amount of specific nutrient consumed. For instance, preferring warmer food, such as soup and steak which may have more iodine from adding salt, is more common among males, while the preference for snack comfort food is more prevalent among females (Wansink, Cheney, and Chan 2003). Furthermore, as milk is a major contributor of iodine, several studies have observed that men tend to consume more milk than woman (van der Reijden, Zimmermann, and Galetti 2017). Despite this difference, the iodine daily intake in adult Canadians is sufficient. Additional studies are required to cover other type of population such as children and pregnant women.

Table 4.14 Estimation of iodine daily intake (µg/day) for Canadian based on urinary iodine that was measured by Health Canada 2007-2009.

Age group	Urinary iodine concentration µmole/L	Urinary iodine concentration µg/L	Estimated daily intake (µg/day)
19-30 M	1.62	205.74	365.20
19-30 F	1.28	162.56	288.55
31-50 M	1.46	185.42	329.13
31-50 F	1.20	152.4	270.52
51-70 M	1.58	200.66	356.18
51-70 F	1.36	172.72	306.58
71-79 M	1.82	231.14	410.28
71-79 F	1.59	201.93	358.43
19-79 M	1.55	196.85	349.42
19-79 F	1.29	163.83	290.80

M: male, F: female

4.3.4.2 Estimation of ^{129}I iodine daily intake

The daily iodine-129 intakes were estimated for 25 people living in Ottawa, Ontario, using the single dataset that measured ^{129}I in urine by using AMS in Canada (Alotaibi et al. 2021). The results (Table 4.13) ranged from $1.3\text{x}10^{-9}$ to $3.4\ \text{x}10^{-7}$ µg/day, with a median of $4.1\ \text{X}10^{-8}$ µg/day. The highest intake of ^{129}I was observed in 5 individuals (3,6,8,15, and 16), three of which were children. The lowest intake of ^{129}I was observed in three individuals (5,11,19), one of which (11) does not consume milk at all, and rarely eats vegetables, while individual (19) consumes milk rarely. Although most of the 25 participants consumed vegetables and grains on daily basis, the estimates of ^{129}I intake are lower than what were estimated previously based on diet (4.3.3.2). The mean isotopic ratio for 25 individual was 1.3×10^{-10}, while the mean ratio for regular diet scenarios was 2.9 x 10^{-9}. One possible explanation for this difference may be related to the time of sampling. In (Alotaibi et al. 2021), urine samples were collected in the winter where most fruits and vegetables are imported from the USA or Central America. The import of vegetables and fruits is necessary to fulfill Canadian demand year-round, due to Canada's short growing season. Foods from the USA or Central America could have widely differing ^{129}I concentration depending on where in the USA they are from. As a result, we expect that the sources of ^{129}I to the Canadian population varies seasonally. More studies are required to confirm the seasonal difference in iodine 129 concentration among people. In addition to seasonal variation the source of the food also likely plays a significant role in ^{129}I intake. For example, ^{129}I concentrations in much of Europe are significantly higher than in North America. As a result, the consumption of food products from Europe could represent an important additional source of ^{129}I. In summary, the high variability of food sources, both spatially and seasonally, introduces significant variability into the daily intake of ^{129}I for Canadians.

4.4 Conclusion

The findings and strengths of this study can be summarized in several points. The AMBER model was validated using a number of studies to determine if modelled results for UIC compare well to measured data when using daily dietary iodine intake as a source. AMBER performed admirably and yielded results that were very similar to the measured data showing it can be used to estimate UIC's in people and most effectively when urine volume is known. Using an iodine biokinetic model and implementing it in AMBER allowed an assessment of iodine status in different sub-populations without the need for urine collection. Generally, it is a large and expensive undertaking to collect and analyze urine samples for a population. In addition, a detailed assessment of iodine intake requires significant effort on the part of participants to accurately track their diet. Using AMBER has overcome these challenges and allowed a rapid and responsive analysis of UIC which can easily be modified to account for individual participant differences or population scales. Second, data mining and collection of data from multiple Canadian sources allowed for the input of best-estimates of daily iodine intakes, especially in terms of table salt and dairy consumption rates which are key contributors to dietary iodine. Third, we estimated the daily intake for Canadian population based on different dietary choices, and used these estimations to model UIC and assess which foods are important sources of dietary iodine with emphasis on iodized salt. Our findings, suggest that dairy products are the major source of ^{127}I in most diets, except for vegan diets, which are dominated by grain products as an iodine source. In contrast, grains, vegetables and fruits are the major source of ^{129}I, however, this result may be an artifact of the assumptions made regarding ^{129}I concentration in food items as specific data is sparse.

Our study has several limitations that should be considered when interpreting the results. First, measured concentrations of ^{129}I in Canadian food were available only for water, salt, and milk.

Therefore, the mean value of milk was used for all dairy products, and also for meat, chicken and eggs. Moreover, the iodine-129 concentration in vegetables and fruits was adopted from a ^{129}I concentration reported for Ontarian cedar leaves (Falls et al. 2005). These indirect estimations increase the uncertainty of the results. Second, this study might be underestimating the consumption rates of some food in more restrictive diets such as the consumption of milk alternatives. For example, vegans do not consume cow's milk; however, they may consume plant-based milk such as oat milk, cashew milk, or soya milk. These alternatives have iodine that should be included in vegan diet (Ma, He, and Braverman 2016). Compared to cow's milk, alternative milk has a lower iodine concentration (Dineva, Rayman, and Bath 2021) and the content varies based on the plant. A Norwegian study found that higher iodine content in alternative milk was found in oat-based milk (Dahl et al. 2021). This study confirms our estimation that 70% of iodine in vegan diet is from grains products. There are no such studies measured iodine in plant-based milk in Canadian market, so a study to measure iodine content in plant-based milk and its daily intake is desirable in order to more fully estimate iodine sources to vegans or others on low dairy diets. Detailed studies on food consumption patterns and rates are needed for each diet type individually to more accurately predict specific iodine status for these diets.

In summary, this work shows that with the right estimation of daily iodine intake and urine volume, a biokinetic model of iodine, built in the AMBER, can predict urinary iodine concentration with a high degree of accuracy. Using the iodine biokinetic model of Leggat, 2017, the urinary iodine concentration was measured in 78 Canadian infants using their measured breastmilk daily intakes. Their median urinary iodine concentration was 304.7 µg/L and the median urinary iodine was 115.2 µg/day. These results were compared to urinary iodine concentrations measured for the same population by Health Canada, demonstrating a non significant difference. Both the measured data and AMBER conclude that there is sufficient iodine intake in infants in the study population.

The AMBER model was also applied to model the iodine status of a variety of diets. The daily iodine intake for seven diets: vegan, ovo-vegetarian, lacto-vegetarian, lacto-ovo-vegetarian, regular, keto, and low carb was estimated and the UIC values modelled for each diet. The assessment shows that the primary contribution of dietary iodine is from diary productions (38%) and iodized salt is a secondary contributor (23%) in a regular diet. However, iodized salt is an extremely important source of dietary iodine for vegan (58%) and vegetarian diets (50%). Moreover, the assessment confirms that dairy products are the main source of iodine in Canadian population. Therefore, the Elementary School Milk Program (ESMP) that was implemented by dairy farmer of Ontario (DFO) since 1986, plays an important role in the reduction of iodine deficiency in children. In term of ^{129}I results, the ^{129}I/^{127}I ratio ranged from 1.1 x10^{-9} to 1.2 x10^{-8} with a median of 2.8 x10^{-9}. This study shows that the main contribution of iodine 129 is from grains products, vegetables, and fruits, although further work must be done to confirm this result.

A reverse model was developed to estimate daily intakes of ^{129}I and ^{127}I for two datasets of Canadian urine samples. The results for ^{127}I daily intake estimation agree well with diet estimations, where it indicates the important of dairy product as a major source of iodine in Canadian population. This work also showed that there may be a seasonality to ^{129}I intakes due to both the source of the food item and the regional concentration of ^{129}I. In summary, AMBER has shown to be useful for both the estimation of urinary iodine concentration and the estimation of daily iodine intake and to yield robust results comparable to reported literature values.

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5 Chapter 5: Conclusion and discussion

5.1 Radioactive ^{129}I

5.1.1 Research highlights

The primary objective of this thesis, outlined in Section 1.7, was to expand the applications of ^{129}I in biomedical and nutritional fields. ^{129}I was measured using accelerator mass spectrometry and ^{127}I through ICP-MS. The research in this thesis has contributed to the body of knowledge concerning ^{129}I and ^{127}I in humans through three related research projects.

The first developed a new method for the extraction of ^{129}I from urine samples using autoclave as a digestion instrument with ^{125}I as a quantitative tracer to measure the ^{129}I concentration and ^{129}I/^{127}I in urine from 25 Ottawa residents. This newly developed extraction technique has determined the optimal conditions needed to extract ^{129}I from urine efficiently. This includes, using hydrogen peroxide as a solvent instead of an acid or base, using autoclave instead of expensive lab microwave, and minimizing the amount of acid used to avoid any iodine loss. This method helped us to observe the significant correlation between ^{127}I and ^{129}I concentration in human urine (Section 2.4.2) which to our knowledge is the first time this has been observed. This correlation suggests that ^{129}I could be a potential tracer of dietary ^{127}I. Moreover, the ^{129}I/^{127}I ratios in Ottawa urine were generally similar to the ^{129}I/^{127}I ratios from environmental samples collected around Ottawa.

The second project refined a method for the extraction of ^{129}I from breastmilk using combustion extraction with ^{125}I as a quantitative tracer and the determination of radiological dose to infants from ^{129}I in breastmilk. By applying the combustion technique, the concentrations of ^{129}I were measured in Canadian women breastmilk samples (Section 3.3.2), and estimation of their infant daily intake was assessed. The iodine 129 daily intake was converted to (Bq/year) in order to estimate thyroid dose in infants (Table 3.5). A correlation was also observed between ^{127}I and ^{129}I concentrations in breastmilk.

The third project investigated the main sources of ^{127}I and ^{129}I in the Canadian diet based on daily food consumption and modelling the urinary iodine concentration for adults and infants through the novel application of a well-established compartment model. By using an iodine biokinetic model implemented in the AMBER software, the daily iodine intake for seven diets was estimated using published consumption rates and iodine concentrations. The model was validated using published data and mother-infant pairs in which the daily iodine intake was known and the UIC previously measured. The urinary iodine concentrations were also modelled for several dietary options (Section 4.3.3). The estimations of ^{129}I and ^{127}I daily intakes based on urine concentration was also addressed to compare them with the dietary assessments (section 4.3.4).

5.1.2 Concentration of ^{129}I and ^{129}I/^{127}I in Canadians

Although ^{129}I is produced naturally by the nuclear interaction of cosmic rays with xenon in the upper atmosphere and by the spontaneous fission of uranium-238 in minerals, the concentration of ^{129}I in the environment has increased sharply since 1945 due to anthropogenic nuclear activities. The primary sources of ^{129}I today are from liquid and atmospheric discharges of nuclear fuel reprocessing, such as La Hague in France, which has released 3119 kg of ^{129}I into hydrosphere and 68 kg into the atmosphere, and Sellafield in UK which released 1371 kg in liquid discharge and 182 kg of ^{129}I atmospheric discharge (Herod et al. 2013). It is estimated that 3.52 x10^{25} atoms of ^{129}I are volatilized from oceans every year (Herod et al. 2013; Snyder, Aldahan, and Possnert 2010). These anthropogenic contribution to the global ^{129}I inventory has far outweighed what is produced naturally, raising the isotopic ^{129}I/^{127}I ratio by several orders of magnitude. Depending on proximity to a point source of ^{129}I, the I^{129}/I^{127} ratio in environmental samples ranges from 10^{-12} up to 10^{-4} (Zhang and Hou 2013). It well known that iodine can travel great distances because its atmospheric residence time is approximately two weeks (Herod et al. 2013). Therefore, in Canada today, the primary source of ^{129}I is wet deposition from long-range atmospheric transport of ^{129}I from European fuel reprocessing and recycled ^{129}I from weapons testing and ocean volatilization (Wetherbee et al. 2012). The isotopic ^{129}I/^{127}I ratio was measured in different Canadian environmental samples; for instance, the ^{129}I concentration was measured in several Canadian rivers and watersheds giving an isotopic ^{129}I/^{127}I ratio ranged from 10^{-8} up to 10^{-11} (Herod 2015). Similarly, isotopic ^{129}I/^{127}I ratio was measured in groundwater, snow, soil, and grass in Canadian cites such Sturgeon Falls, Ontario, where the ratio was also ranged from 10^{-8} up to 10^{-11} (Renaud et al. 2005).

This thesis shows that there is a strong influence from place of residence on the concentration of ^{129}I and the ^{129}I/^{127}I ratio in people. The concentration of ^{129}I in people in Canada is similar its level in the local environment. For example, the ^{129}I/^{127}I ratio in urine (Chapter 2) ranged from 7.38 x 10^{-12} to 3.97 x 10^{-10} with a mean of 1.3 x 10^{-10}, while in breastmilk (Chapter 3) ^{129}I/^{127}I ratio ranged from 1.27x10^{-10} to 9.9x10^{-10} with a median of 2.13x10^{-10}. In addition, the dietary assessment of ^{129}I (Chapter 4) yielded a modelled ratio ranging from 10^{-8} to 10^{-10}. These isotopic ratios are close to published values for Canadian environmental samples, where the ratios range from 10^{-8} to 10^{-11}.

5.1.3 Sources of ^{129}I in humans

To date, no studies have measured ^{129}I in human urine or breastmilk by accelerator mass spectrometry. The data from this thesis shows that humans are exposed to ^{129}I from birth through breastmilk. Other food items contribute ^{129}I later in life. The significant correlation between ^{127}I and ^{129}I in human urine (Chapter 2) and breastmilk (Chapter 3) shows that the source of both isotopes in human body is similar and most likely is from food. Chapter 4 tested the relative importance of different foods in terms of their contribution to the daily intake of ^{127}I and ^{129}I and using a biokinetic model determined the ^{129}I/^{127}I in the human body. This modelling found that the source of iodine-127 in Canadian diet is primarily from dairy products and a secondary contribution from salt, while the source of iodine-129 is mainly from grain products, vegetables, and fruits, although this finding is subject to a number of assumptions about the concentration of ^{129}I in food items as data is scarce. Based on this we can qualitatively predict the source of iodine-127 using isotopic ratio ^{129}I/^{127}I. For example, in cases where the isotopic ratio was between 10^{-8} and 10^{-9}, therefore, the main sources of iodine in this person may be from grain products, vegetables, and fruits and in cases where the isotopic ratio was between 10^{-10} and 10^{-11} and the main sources of iodine in this person may be from dairy products and some contribution from salt.

5.2 Iodized salt and other strategies to combat iodine deficiency in Canada

Universal salt iodization is the main strategy adopted by WHO organization to eliminate iodine deficiency. Although iodized salt was successfully used to reduce IDD, WHO recommended a reduction by 30% of salt daily intake consumption by 2025. Several studies had evaluated the effect of salt reduction on iodine status and finding that 30% reduction will not compromise iodine status (He et al. 2016; K. E. Charlton et al. 2013). This indicate that people obtain their daily iodine requirement from sources other than iodized salt. This is the case for Canada where table salt consumption is less than 1 g/day (Garriguet 2007). Based on the dietary assessment made in Chapter 4, we observed that dairy products are the primary source of iodine in most diet variations, and the contribution of iodized salt when added to a diet is less than 30% except for vegans. These observations encourage us to change our view of the best methods to combat IDD. Using salt was and still is one of the most successful ways to achieve the daily requirements of iodine. Nevertheless, the change in lifestyle and diets, with the increase in awareness of the health impact of excessive intake of salt may diminish the contribution of iodized salt. Diversifying strategies to control iodine deficiency may be a necessary solution to secure continued daily sufficiency. These strategies should be classified based on sub-population as follow:

1- for pregnant and lactating women, or people with strict diet, using iodine oil or multivitamin and mineral MVM supplement is recommended to meet their daily requirements.

2- for children, establishing a similar program to the Elementary School Milk Program (ESMP) in other provinces and territories, and motivating students to drink milk and eat dairy products such as cheese in daily bases will improve their iodine status.

All these strategies should be maintained with media campaigns to remind the population of the importance of iodine on a daily basis.

5.3 Implication and future works

Measuring ^{129}I in humans should enable researchers to use this isotope in biomedical fields. As a start, it used here in this thesis as a nutritional tracer where it helps to detect the sources of stable iodine in human body based on isotopic ratio. Another and most important application of this extraction method is to evaluate ^{129}I exposure directly in the human body for those who live nearby nuclear fuel reprocessing plants. Moreover, assessing ^{129}I in human can help in investigations of ^{131}I uptake in the event of a nuclear emergency using ^{129}I in urine as a proxy.

Throughout this thesis, several gaps that require investigation were discovered. A list of recommendations is presented as follow:

- Measuring ^{127}I and ^{129}I concentrations in different Canadian foods items. This should include vegetarian foods alternatives such as vegetarian meat, vegetarian eggs, and vegetarian milk, in geographically diverse population centres in Canada.

- Measuring ^{127}I concentration in sensitive Canadian populations such as pre-school children, pregnant women, and elderly in order to ensure iodine sufficiency in these sub-populations given the varying intakes of different foods.

- Assessing the seasonal difference in iodine 127 and iodine 129 concentrations among people to determine if there is a seasonality component to urinary iodine status given the widely globalized food source consumed by the Canadian population.

6 Appendix A: Supplementary material for Chapter 2

6.1 Consent form

Consent Form

Title of the study: *Using Tracer for the sources of elements in Human Diet*

Researcher:

:

Supervisor:

:

Invitation to Participate: I am invited to participate in the above-mentioned research study conducted by Fahad.

Purpose of the Study: A significant percentage of essential elements enter the human body through food consumption. The purpose of the study is to detect which types of foods have the most contribution of halogens such as iodine, chloride and others in human diet by using human urine.

Participation: My participation will consist of donating my urine sample and answering one questionnaire about my diet as long as I do not have any sever or mild medical condition.

Risks: My participation in this study will not have any risk.

Benefits: My participation in this study will benefit the researcher to complete his PhD thesis and might influence a change in the way how medical community think of elements sources in human body. There is no direct benefit to me for participating in this research.

Confidentiality and anonymity: I have received assurance from the researcher that the information I will share will remain strictly confidential. My Anonymity is guaranteed because the urine sample I provide and questionnaire I complete will not be linked to my name. No code list will be kept. Once my questionnaire and urine sample are provided to the researcher, it will be identified by a number that will not be linked to me in any way.

Conservation of data: The original questionnaire data collected will be kept in a locked filing cabinet in the office of the researcher and a second copy with his supervisor at the University of Ottawa for a period of five years at which time they will be shredded, while the urine sample will be used in the lab until its finished or thrown out.

Compensation: I have been informed that there is no compensation in participation with this study.

Voluntary Participation: I am under no obligation to participate in this study and if I choose to participate, I can refuse to answer any questions or donate urine, without suffering any negative consequences. My decision on whether or not to participate will in no way affect my employment, schooling, or relationship with the University of Ottawa or the study's researchers.

Acceptance: I, …………………agree to participate in the above research study conducted by …………Department of Chemistry, Faculty of Sciences, University of Ottawa which research is under the supervision of Professor Jack Cornett.

If I have any questions about the study, I may contact the researcher or his supervisor. If I have any questions regarding the ethical conduct of this study, I may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5

There are two copies of the consent form, one of which is mine to keep.

Participant's signature: Researcher's signature: Date:

6.2 Questionnaire form

Sampling Form

Research subject: Using I 129 as Tracer for the sources of Iodine in Human Diet

Researcher:

University of Ottawa/ARC, 245-25 Templeton Street, Ottawa, ON, K1N 6N5

Sample Type: ☐ Urine

SECTION 1: Donor Information				
Sample's Lab code: U2017-03-		**UOH number:**		
Age	**3-18**	**19-40**	**41-65**	**>66**
	☐	☐	☐	☐

SECTION 2: Donor Diet				
	Daily	Weekly	Monthly	None
Using Salt	☐	☐	☐	☐
Drinking Milk	☐	☐	☐	☐
Eating Sea Food	☐	☐	☐	☐

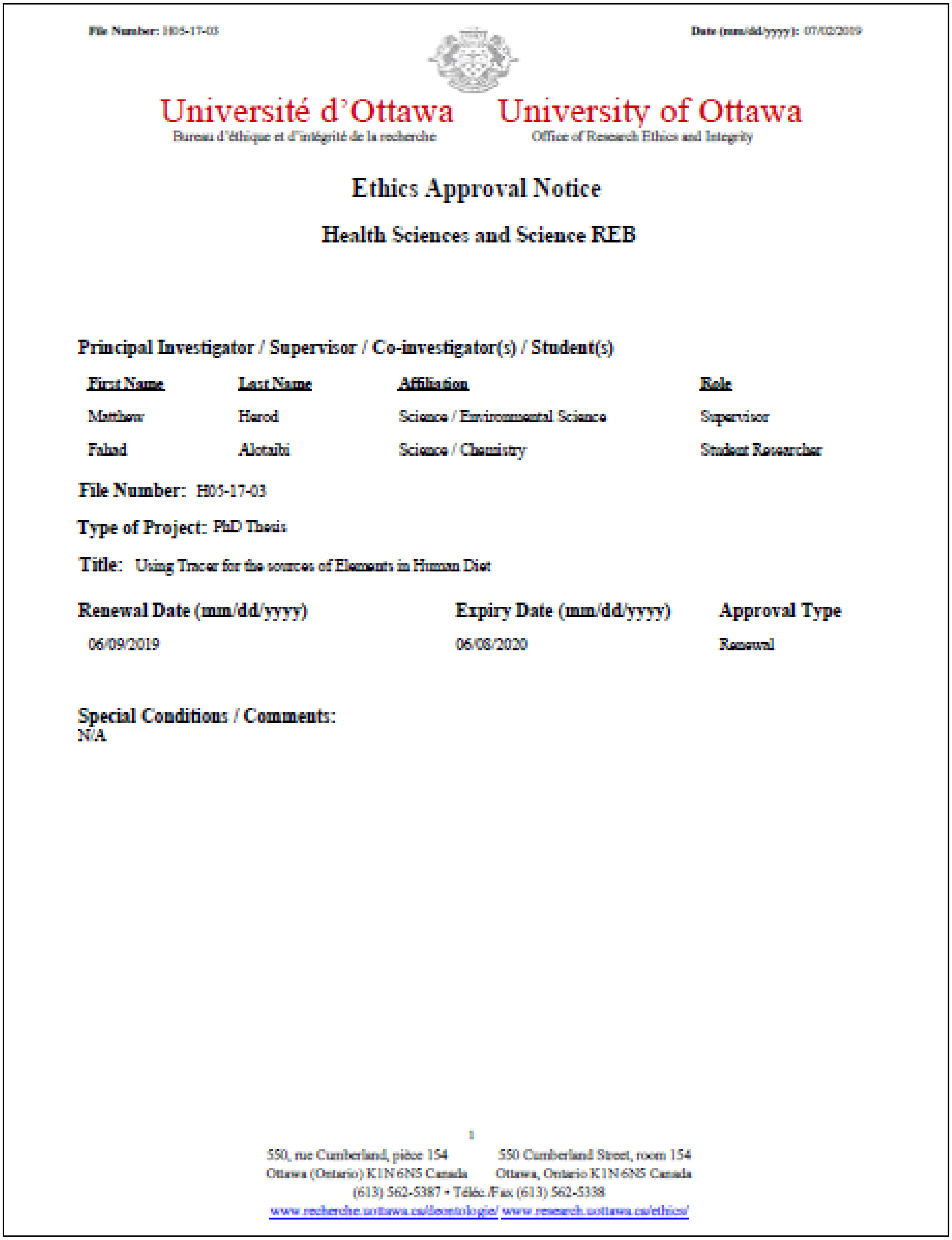
Eating Bread	☐	☐	☐	☐
Eating Vegetables	☐	☐	☐	☐
Eating Processed meat	☐	☐	☐	☐

This Form is for Internal Laboratory use only

6.3 Questionnaire Answers

Sample	Age	Using Salt	Milk	Sea Food	Bread	Vegetables
1	41-65	Monthly	Daily	Monthly	None	Daily
2	19-40	Daily	Weekly	Monthly	Daily	Daily
3	3 18	Daily	Daily	Monthly	Daily	Weekly
4	19-40	None	Daily	Monthly	Daily	Daily
5	19-40	Daily	Daily	Monthly	Daily	Daily
6	19-40	Daily	Daily	Monthly	Daily	Daily
7	41-65	Weekly	Weekly	Monthly	Daily	Daily
8	3 18	Daily	Daily	Monthly	Daily	Daily
9	41-65	Weekly	Daily	Weekly	Weekly	Daily
10	41-65	Daily	Daily	Weekly	Daily	Daily
11	19-40	Daily	None	Monthly	Daily	Monthly
12	19-40	Daily	Daily	Monthly	Daily	Daily
13	19-40	Daily	Daily	Weekly	Daily	Daily
14	19-40	Weekly	Daily	Weekly	Daily	Daily
15	19-40	Daily	Weekly	Monthly	Daily	Daily
16	3 18	Monthly	Daily	Weekly	Daily	Daily
17	19-40	Daily	Weekly	Weekly	Daily	Daily
18	19-40	Daily	Daily	Weekly	Weekly	Daily
19	41-65	Daily	Monthly	Weekly	Daily	Daily
20	41-65	Weekly	Daily	Monthly	Daily	Weekly
21	>66	Daily	Daily	Weekly	Daily	Daily
22	41-65	Daily	Weekly	Weekly	Daily	Daily
23	19-40	Daily	Daily	Weekly	Weekly	Weekly
24	19-40	Weekly	Daily	Monthly	Daily	Weekly
25	41-65	Monthly	Daily	Weekly	Daily	Daily

6.4 Ethics certificate details



File Number: H05-17-03 **Date (mm/dd/yyyy):** 07/02/2019

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Matthew	Herod	Science / Environmental Science	Supervisor
Fahad	Alotaibi	Science / Chemistry	Student Researcher

File Number: H05-17-03

Type of Project: PhD Thesis

Title: Using Tracer for the sources of Elements in Human Diet

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
06/09/2019	06/08/2020	Renewal

Special Conditions / Comments:
N/A

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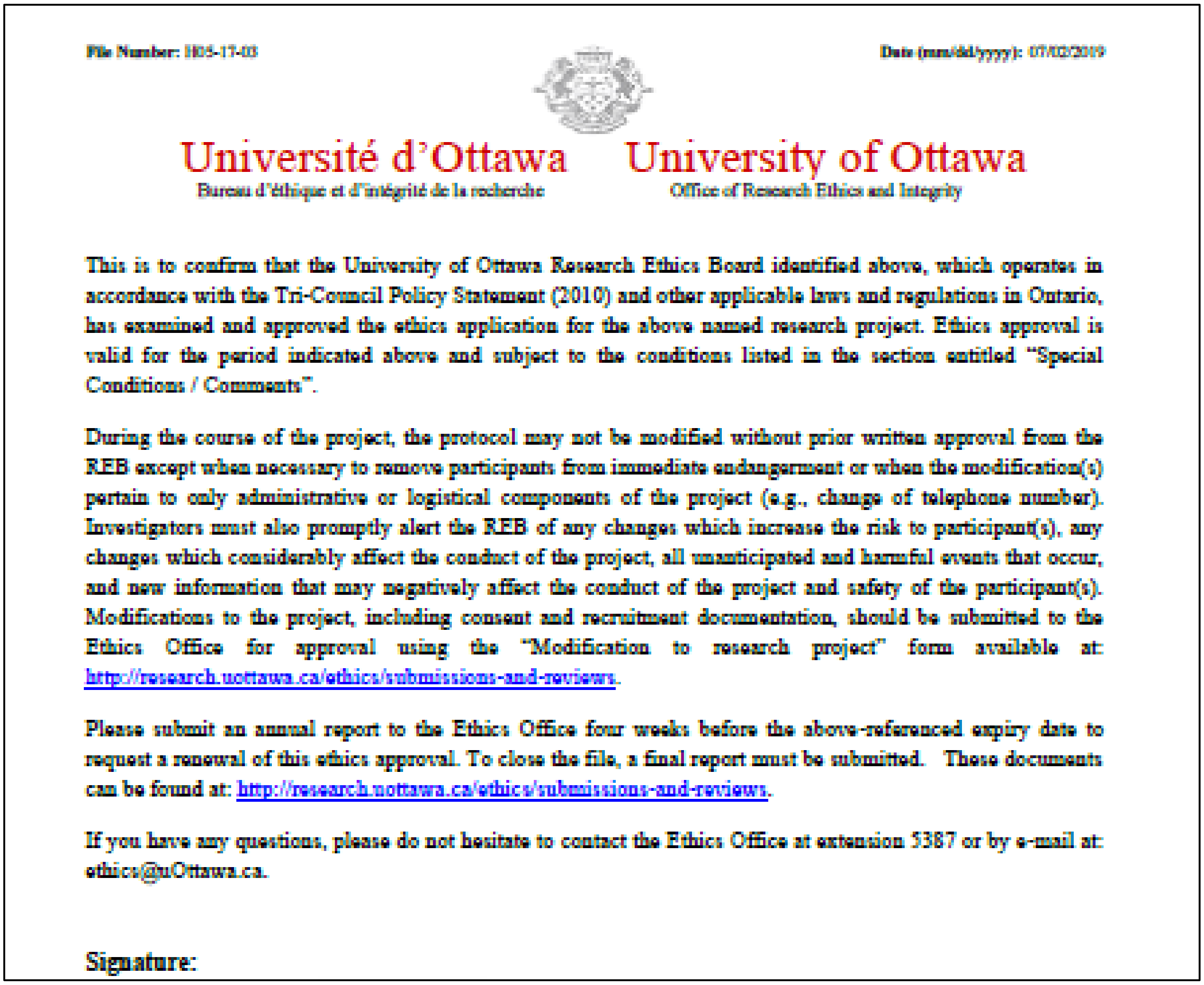

File Number: H05-17-03

Date (mm/dd/yyyy): 07/02/2019

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://research.uottawa.ca/ethics/submissions-and-reviews.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: http://research.uottawa.ca/ethics/submissions-and-reviews.

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5387 or by e-mail at: ethics@uOttawa.ca.

Signature:

7 Appendix B: Additional data to Chapter 4; an assessment of iodine-129 in humans' thyroid

7.1 Introduction

Analysis of ^{129}I in the thyroid is important because thyroid absorbs the iodine from environmental sources and bar it from moving or being transported to other organs. Many studies analyze iodine-129 in thyroids as part of environmental investigations and they have been undertaking with environmental samples (Hou et al. 2000). For instance, measuring ^{129}I in thyroid helps researchers to reconstruct the thyroids dose from ^{131}I in the areas where ^{131}I has decayed away and could not be measured (Michel et al. 2005)(Hou et al. 2003). In addition, measuring ^{129}I in animal thyroids helps to determine the source of contamination in the environment (Chao and Tseng 1996). Some studies used ^{129}I in thyroids as indicator for contamination of nuclear waste in the environment (Chemistry and Carolina 2000).

Studies of ^{129}I in thyroid can be classified based on their locations such as USA, Europe, Taiwan, Japan, UK, Australia, Argentina, and China (R.Seki and T.Hatano 1994; Szidat et al. 2000; Negri et al. 2012; Fréchou et al. 2002; Singh, Searing, and Wreen 1988; Schmidt et al. 1998; Chao and Tseng 1996; Robens, Hauschild, and Aumann 1989; Michel et al. 2005; Bowlt and Howe 1995; Hou et al. 2000; Chemistry and Carolina 2000), or based on their techniques (NAA, AMS, Gamma spectrometry), or based on their types of samples (human thyroid, animal thyroid). Table (7.1) collect these studies and classify them based on their type of sample and techniques used.

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Based on Table (7.1), there are 10 studies performed on human thyroid compared to 19 studies were performed on animal thyroid. Also, the last human thyroid analysis was done in 2000 while the last animal thyroid analysis was done in 2012. In addition, the table shows that all human thyroid analyses were performed by NAA not AMS. Absence of ^{129}I analysis in human and animal thyroids in Canada is concluded. Therefore; analysis of ^{129}I in human thyroid in Canada should be performed to fill the gap about ^{129}I in Canada and establishing data for future investigations.

Table 7.1 The concentration of ^{129}I in human and animal thyroids

Sample	Location	Instrument	Result	Reference
Human Thyroid	USA, before 1945	NAA	25x10^{-10}	Keisch et.al 1965
Human Thyroid	USA, before 1936	NAA	0.4x10^{-10}	Edwards et.al 1968
Human Thyroid	USA, before 1936	NAA	＜0.4x10^{-10}	Brauer et.al 1973
Human Thyroid	USA, 1970 -1974	NAA	4x10^{-7}	Ballad et.al 1978
Human Thyroid	USA, 1940s	NAA	1.8x10^{-9}	N.P Singh et.al 1988
Human Thyroid	Japan,1983	NAA	4.1x10^{-10} -1.3x10^{-9}	Seki & Hatano 1994
Human Thyroid	Chile, 1985-1986	NAA	1-2x10^{-9}	Handl et.al 1996
Human Thyroid	Germany,1979-1990	NAA	1-7.5x10^{-8}	Handl et.al 1996
Human Thyroid	USA, 1943	AMS	0.07x10^{-10}	A. Schmidt et.al 1998
Human Thyroid	Tianjin, China	NAA	1.1x10^{-9}	X. Hou et.al 2000
Human Thyroid	USA, before 1945	NAA	25x10^{-10}	Keisch et.al 1965
Animal Thyroid	USA, before 1945	NAA	8 x10^{-10}	Keisch et.al 1965
Animal Thyroid	USA, 1950s	NAA	1x10^{-6}	Keisch et.al 1965
Animal Thyroid	NY, USA 1971	NAA	1.6x10^{-4}	Magno et.al 1972
Animal Thyroid	USA, 1972-1976	NAA	7.1x10^{-7}	Markham et.al 1983
Animal Thyroid	Germany,1979-1981	NAA	4x10^{-10} - 9x10^{-8}	Aumann et.al 1985
Animal Thyroid	Germany, 1983	NAA	0.9-1.5x10^{-5}	Robens et.al 1988
Animal Thyroid	Japan, 1994	NAA	8.3 x10^{-10}	Seki & Hatano 1994
Animal Thyroid	Japan, 1994	NAA	35-380 x10^{-10}	Seki & Hatano 1994
Animal Thyroid	UK. 1995	ɣ-Counter	7.9 mBq/g	C.Bowlt & Howe 1995
Animal Thyroid	Taiwan,1995-1996	NAA	0.23–23x10^{-10}	Chao and Tseng 1996
Animal Thyroid	Taiwan,1995-1996	NAA	2.5–66x10^{-10}	Chao and Tseng 1996
Animal Thyroid	Taiwan, 1995-1996	NAA	3.1–82x10^{-10}	Chao and Tseng 1996
Animal Thyroid	Australia,1957&1989	NAA	5-6x10^{-10}	Handl et.al 1996
Animal Thyroid	Chile, 1985-1986	NAA	10–42x10^{-10}	Handl et.al 1996
Animal Thyroid	Europe, 1978 -1981	NAA	47-820x10^{-10}	Handl et.al 1996
Animal Thyroid	Germany, 1989-1990	NAA	130–600x10^{-10}	Handl et.al 1996
Animal Thyroid	USA,2000	x-ray spectrometry +NAA	10^{-2} Bq/g	VanMiddlesworth et.al 2000
Animal Thyroid	France,1980-1999	NAA	0.1-250 x10^{-6}	C.Frechou et.al 2002
Animal Thyroid	Argentina, 2012	AMS+GC	10^{-12} up to 4x 10^{-10}	A.E Negri et.al 2012

7.2 Method

Due to Covid-19 pandemic, thyroid and urine samples were not collected and ethical approval was not processed. However, through AMBER software, the estimation of ^{129}I and ^{127}I in human thyroid was obtained through daily intakes established in previous chapters. For infant, the daily intake for ^{129}I is calculated from chapter 3 and summarized in table (7.2).

7.2: Iodine 129 daily intake in infants

Sample	^{129}I concentration in Breastmilk µg/L	^{127}I concentration in Breastmilk µg/L	BM daily intake g/day	^{129}I Daily intake µg/day	^{127}I Daily intake µg/day	^{129}I /^{127}I ratio
82	3.47E-08	172.2	0.55	1.91E-08	95.1	2.01E-10
83	4.22E-08	327.3	0.85	3.59E-08	278.9	1.29E-10
91	4.45E-08	230.3	1.01	4.48E-08	231.7	1.93E-10
93	3.31E-08	100.8	0.64	2.11E-08	64.3	3.29E-10
94	1.31E-07	472.7	0.85	1.12E-07	402.7	2.77E-10
95	1.05E-07	302.7	0.58	6.09E-08	176.2	3.46E-10
101	5.85E-08	358.3	0.86	5.03E-08	308.1	1.63E-10
103	6.36E-08	328.2	0.51	3.24E-08	167.4	1.94E-10
104	3.82E-08	97.7	0.76	2.90E-08	74.3	3.91E-10
106	1.42E-07	140.5	0.82	1.17E-07	115.8	1.01E-09
111	2.70E-08	115.2	0.73	1.97E-08	84.1	2.34E-10
112	4.33E-08	220.2	0.80	3.44E-08	175.3	1.96E-10
118	4.57E-08	198.2	0.73	3.34E-08	144.7	2.31E-10
119	4.56E-08	251.9	0.86	3.90E-08	215.4	1.81E-10
average	6.10E-08	2.37E+02	7.53E-01	4.64E-08	1.81E+02	2.91E-10

7.3 Result and discussion

Based on type of diet (Table 7.3), the iodine content ranged from 5861 µg to 14,367 µg while for ^{129}I it ranged from 1.35x10^{-5} µg to 3.07 x10^{-5} µg. The average iodine content in 23 individuals was 17,784 µg, while the ^{129}I content was 2.4x10^{-6} µg. For infant, the iodine content in the thyroid was 738 µg, while ^{129}I was 2.68 x10^{-7}µg. The ^{129}I /^{127}I ratio in diet ranged from 1.09 x10^{-9} up to 4.8 x10^{-9}. The ^{129}I /^{127}I ratio in 23 individual was 1.3 x10^{-10} while in infant was 3.63 x10^{-10}.

Table 7.3: Iodine content in human thyroid based on diet and ages.

Sample	^{127}I Daily intake (µg/day)	^{127}I content in thyroid (g)	^{129}I Daily intake (µg/day)	^{129}I content in thyroid (g)	^{129}I /^{127}I ratio
Regular diet	276.5	0.014367	5.9 E-7	3.07E-11	2.13E-09
Vegan diet	112.8	0.005861	5.4 E-7	2.81E-11	4.79E-09
Lacto-ovo-Vegetarian	234.7	0.012195	5.5 E-7	2.86E-11	2.34E-09
Lacto-Vegetarian	217.5	0.011301	5.5 E-7	2.86E-11	2.53E-09
Ovo-Vegetarian	130	0.006755	5.4 E-7	2.81E-11	4.15E-09
Ketogenic diet	238.6	0.012397	2.6 E-7	1.35E-11	1.09E-09
Low carbohydrate diet	242.9	0.012621	4.0 E-7	2.08E-11	1.65E-09
Average (23) individual (chapter 2)	342.27	0.017784	4.62 E-8	2.40E-12	1.35E-10
Average Canadian infant (chapter 3)	127.9	0.000738	4.64 E-8	2.68E-13	3.63E-10

Based our estimation, the amount of ^{127}I in adult thyroid ranged from 5-17 mg, which is similar to literature value. In its normal condition, the thyroid gland contain 70-80% of total iodine in the body which is approximately between 12 -16 mg of iodine (Sun 2014). In (Burman 2016), the amount of iodine in the thyroid was reported between 5 -10 mg. There is no conflict between these values as it has been shown here that the content of stable iodine stored in thyroid is influenced by diet.

The ^{129}I /^{127}I ratios in these samples range from 10^{-9} to 10^{-10}, and are similar to those reported in several human thyroid samples collected before the 1950s in the United States (table 7.1). This similarity suggests that the sources of ^{129}I in Canada are limited and the Canadian ^{129}I /^{127}I ratio is likely less affected by nuclear activities.

7.4 Reference

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