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● NO 165 — MEDICAL EFFECTIVENESS OF IODINE PROPHYLAXIS IN A NUCLEAR REACTOR EMERGENCY SITUATION AND OVERVIEW OF EUROPEAN PRACTICES

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RADIATION PROTECTION NO 165

Medical effectiveness of iodine prophylaxis in a nuclear reactor emergency situation and overview of European practices

Final Report of Contract TREN/08/NUCL/SI2.520028

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This report was prepared by RISKAUDIT IRSN/GRS International in collaboration with Institut de radioprotection et de sûreté nucléaire (IRSN), France for the European Commission and represents these organisations' views on the subject matter. These views have not been adopted or in any way approved by the Commission and should not be relied upon as a statement of the Commission's views.
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FOREWORD

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Community legislation requires the EU Member States to prepare for nuclear and radiological emergencies and to intervene in order to protect the population from excessive radiation doses caused by accidental releases of radioactive substances. Intake of stable iodine is a well-established protective countermeasure in the event of a nuclear reactor accident where radioactive iodine is released to the environment. Most European countries have included that in their emergency plans; its effectiveness in protecting the human thyroid from harmful radioactive iodine is medically well proven, and possible adverse health effects are not significant.

In Europe an accidental release of radioactive iodine may cross national borders very quickly and therefore it is vital that the authorities in each country have a harmonised basis for protecting the population on their territory. In 2002-05 the Euratom Article 31 Experts had a working group discussing practical ways of achieving this harmonisation and the possible problem areas. The group concluded that despite iodine prophylaxis being a generally accepted countermeasure there were significant differences in its practical application.

For a long time the European Commission has worked on harmonising the radiation protection regulations in Europe, including the provisions for emergency countermeasures. This study done by RISKAUDIT IRSN/GRS International in collaboration with Institut de Radioprotection et de Sûreté Nucléaire (IRSN), aims at updating the medical knowledge on stable iodine prophylaxis and surveying the current application in Europe. The report presents a consensual European approach, which hopefully will form a basis for further harmonisation efforts not only within the EU but also in a wider international context.

The Group of Experts working under Euratom Treaty Article 31 has reviewed this document and has fully endorsed its publication in the Radiation Protection series.

Augustin Janssens
Head of Radiation Protection Unit

CONTENTS

1. INTRODUCTION

In the event of accidents in nuclear facilities, particularly nuclear power plants, release of radioactive iodine may occur and affect the health of the population exposed to the cloud and then to the deposition. When inhaled or ingested, radioiodine tends to concentrate in the thyroid gland giving rise to high concentrations in this organ. High concentrations of radioiodine in the thyroid gland increase the risk of thyroid cancer development in the exposed people.

When taken in due time at the appropriate dosage, potassium iodide tablets prevent the accumulation of radioactive iodine in the thyroid gland by saturating it with non-radioactive iodine. This protection action is recommended by several international organizations and has been adopted by several countries worldwide.

The ICRP, IAEA and WHO have taken positions on intervention action level and target population in order to reinforce the prevention measures by targeting the more sensitive groups. These recommendations are based primarily on the results from thyroid cancer studies in exposed children.

The recommendations adopted for the iodine prophylaxis, in particular those regarding the administration timing, the iodine quantity to be given, and the possible side effects occurring as a result of this measure, were made based on the scientific information available for the medical community concerning the effects of stable iodine on the health status of people receiving the treatment. Since then, many teams around the world have continued their research (basic research and clinical research), especially those dealing with the iodine transfer mechanisms through the cell within the thyroid gland, and those regarding the side effects observed after the administration of stable iodine, in response to the information provided by the physicians who noted the adverse health effects observed in people receiving stable iodine.

The results from these studies have gained new data about the iodine metabolism in the body, thanks to a better understanding of the events observed in the tissues, both at the cellular and molecular level. Thus, these studies have clarified the differences in the iodine behaviour in some special groups of the population, such as people suffering from an iodine deficiency. Also, in the context of harmonization process of iodine prophylaxis practices in Europe, it was essential to ensure that the proposed recommendations will take into account the latest scientific and medical knowledge relating to the metabolism of the iodine in human beings, particularly among special population groups, such as infants, children, pregnant women, lactating women, or people with iodine sensitivity.

Many countries have adopted the recommendations provided by international organizations regarding iodine prophylaxis. Nevertheless, although the final objective is the same, these countries have not introduced identical practices to implement this preventive and protective measure, regarding the medicine itself (formulation, dosage, package insert), decision-making (absorbed dose by thyroid as an operational basis for a quick decision (intervention level), targeted population, dose assessment tools…), and preventive actions (geographic coverage, preventive distribution mode, articulation with other countermeasures, population information, etc.).

Therefore population living close to country borders could feel not protected in a same way because of a lack of harmonization between national strategies and possible contradiction among countermeasures adopted during an emergency. In particular, experience shows that during the early stage (approximately 24 hours since the alert), protective actions have to be taken promptly and thus with an inevitably limited preliminary international coordination. It is

then of the utmost importance to harmonize the preventive and protection actions in advance.

Neighbouring countries that could have concerns with the risk of an exposure to radioactive iodine following an accident in a nuclear power plant with trans-boundary release have already engaged in some efforts for harmonization.

The Directorate-General for Energy and Transport (DG TREN) of the European Commission (EC) has launched a study aiming at having (i) an update of the latest medical knowledge regarding the safety and efficiency of stable iodine intake in case of a nuclear emergency and (ii) a comprehensive picture of the practices in all European Countries, with the aim of further informing the European national authorities and exploring ways towards a European harmonization.

RISKAUDIT together with IRSN, the French Institute for Radiological Protection and Nuclear Safety, were asked to achieve this study.

The present document is the final report of the EC contract No. TREN/08/NUCL/SI2.520028.

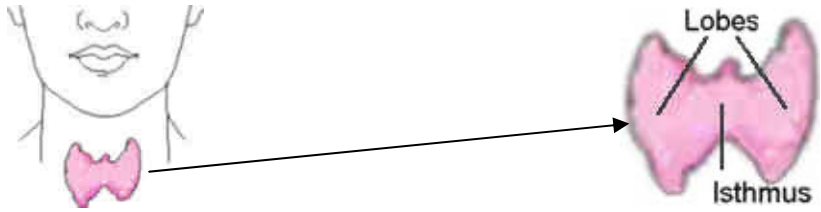
2. MEDICAL EFFECTIVENESS OF IODINE PROPHYLAXIS

2.1. Thyroid gland

2.1.1. Anatomy of the thyroid gland

The thyroid is a brownish-red and highly vascular gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic. The thyroid is situated just below the "Adams apple" or larynx. During development (inside the womb) the thyroid gland originates in the back of the tongue, but it normally migrates to the front of the neck before birth. Sometimes it fails to migrate properly and is located high in the neck or even in the back of the tongue (lingual thyroid). This is very rare. At other times it may migrate too far and ends up in the chest (this is also rare).

Figure 1. Anatomy of the thyroid gland



(From http://www.endocrineweb.com/thyfunction.html)

The gland varies from an H to a U shape and is formed by two elongated lateral lobes with superior and inferior poles connected by a median isthmus (with an average height of 12-15 mm) overlying the second to fourth tracheal rings. The isthmus is encountered during routine tracheotomy and must be retracted (superiorly or inferiorly) or divided. Occasionally, the isthmus is absent, and the gland exists as 2 distinct lobes. Each lobe is 50-60 mm long, with the superior poles diverging laterally at the level of the oblique lines on the *laminae* of the thyroid cartilage. The lower poles diverge laterally at the level of the fifth tracheal cartilage. Thyroid weight varies but averages 25-30 g in adults (slightly heavier in women). The gland enlarges during menstruation and pregnancy.

2.1.2. Role of the thyroid gland

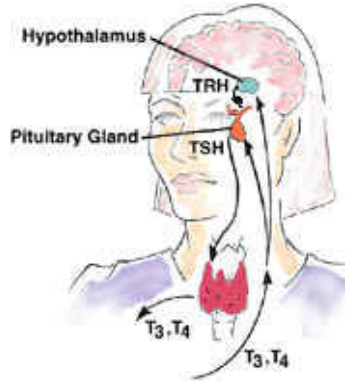
The thyroid gland produces thyroid hormones. These are peptides containing iodine. The two most important hormones are tetraiodothyronine (thyroxine or T4) and triiodothyronine (T3). These hormones are essential for life and have many effects on body metabolism, growth, and development. Their purpose is to regulate the rate of metabolism in every cell of the body:

- T4 is the one most abundant in the body representing approximately 80% of thyroid hormones but is also a precursor to T3.
- T3 represents approximately 20% of thyroid hormones found in the body. When the body has enough T3 available, any excess T4 remaining in reserve will be rendered inactive by the conversion of it into “Reverse T3” (RT3). This process is ongoing due to the fact that the thyroid gland continues to absorb iodine from the diet. This process, which also occurs in the liver and kidneys, is a safeguard against over-stimulation of body metabolism from an excess of T3 hormone.

The thyroid gland (shown in Figure 2) is also influenced by hormones produced by two other organs:

- The pituitary gland, a small gland of the size of a peanut located at the base of the brain, which produces thyroid-stimulating hormone (TSH).
- The hypothalamus, a small part of the brain above the pituitary, which produces thyrotropin-releasing hormone (TRH).

Figure 2. Axis "Hypothalamus-pituitary gland - thyroid gland"



(From http://www.endocrineweb.com/thyfunction.html)

When low levels of thyroid hormones (T3 and T4) in the blood are detected by the hypothalamus and the pituitary gland, TRH is released, stimulating the pituitary gland to release TSH. Increased levels of TSH, in turn, stimulate the thyroid to produce more thyroid hormone, thereby returning the level of thyroid hormone in the blood back to normal.

Thyroid hormones are essential and play a key role in a number of systems [Leclère, 2001]:

- The central nervous system maturation during the first months of life and its functioning in adult;
- The differentiation and maturation of bone during the fetal period and for bone resorption in adult;
- The basal metabolism (thermogenesis), as well as the metabolisms of carbohydrate (thyroid hormones are hyperglycemic), lipid (especially cholesterol), protein (they increase protein synthesis but have also an effect on catabolism), and hydromineral metabolism (they increase the glomerular filtration and renal blood flow);
- The cardiac rhythm;
- Controlling the contraction of muscle and metabolism of creatine;
- Promoting the gastrointestinal transit;
- The regulation of the development of blood cells (hematopoiesis) and iron metabolism.

2.1.3. Physiopathology of the thyroid gland

The state of normal thyroid function is called euthyroidism. The main causes of thyroid disease are:

- Too much thyroid hormone production or hyperthyroidism.

- Too little thyroid hormone production or hypothyroidism.

Abnormalities of the thyroid gland are common and affect one in twenty (5%) of the population living in developed countries in average. All thyroid disorders are much more common in women than in men. Because of the widespread use of iodized salt, lack of iodine is no longer a cause of thyroid disease in most of developed countries as it was some 50 years ago.

Autoimmune disorders of the thyroid gland are common. These autoimmune disorders are caused by abnormal proteins, (called antibodies), and the white blood cells which act together to stimulate or damage the thyroid gland. Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism) are diseases of this type. Graves' disease affects about 1% of the population, whereas Hashimoto's thyroiditis is even more common:

- Graves' disease (thyrotoxicosis) is due to a unique antibody called "thyroid stimulating antibody" which stimulates the thyroid cells to grow larger and to produce excessive amounts of thyroid hormones. In this disease, the goiter is due not to TSH but to this unique antibody.
- In Hashimoto's thyroiditis, the goiter is caused by an accumulation of white blood cells and fluid (inflammation) in the thyroid gland. This leads to destruction of the thyroid cells and, eventually, thyroid failure (hypothyroidism). As the gland is destroyed, thyroid hormone production decreases; as a result, TSH increases, making the goiter even larger.

Other less common causes of thyroid disease include nodule, thyroid cancer, subacute thyroiditis and primary hypothyroidism. Nodules, mostly benign are very common.

2.2. Exposure of the thyroid gland to radioactive iodine

Because of the extensive use of radioactive iodine in medical practice, groups of people representing a wide range of age have been exposed to radioiodines, both for diagnostic procedures and for radiotherapy used to treat diseases such as hyperthyroidism and thyroid cancer.

Although accidental external irradiation is a well-known cause of human thyroid cancer since years, the risk from accidental exposure of the thyroid gland to internal radiation was not well defined before the Chernobyl accident. Thus, the thyroid radiation exposures due to the releases of radioiodines into the environment were virtually all internal, and it has been concluded that the contribution of external radiation was negligible for most individuals, despite some degree of uncertainty in the doses received.

2.2.1. Medical use of radioactive iodine

Radioactive iodines play an important role in the diagnosis and treatment of various thyroid disorders. The five iodine isotopes used for those purposes are ^{123}I, primarily a gamma-emitter with a short physical half-life of 13 hours; ^{131}I, a beta- and gamma-emitter with a longer physical half-life of 8 days; ^{124}I, a positron emitter with a half-life of 4.2 days, and ^{125}I preferred for laboratory use because of its long half-life of 60 days; ^{125}I is also used as a sealed source that could be implemented inside tumours (e.g. in the prostate gland) to irradiate and destroy as much as possible the cancerous cells.

For diagnostic use, despite moderately energetic gamma emission, ^{131}I is suitable for external measurement of the quantity and localization. ^{123}I is now the preferred choice for diagnostic studies of the thyroid, since greater cellular damage or cell death is produced by

the higher energy beta emissions of ^{131}I than by the gamma emissions of either isotope. Thus, the short half-life of ^{123}I and mainly its gamma emission reduce potential radiation effects on the thyroid. Nowadays, ^{124}I is coming into use for PET scanning.

The ability of the thyroid to concentrate iodine permits the use of radioiodine to quantify the iodine concentration activity of the thyroid because the isotope equilibrates with blood iodine and reflects the uptake of stable (non-radioactive) iodine into the thyroid. Thyroid radioiodine uptake is elevated in patients with hyperthyroidism, is usually low in hypothyroid patients, and varies inversely with iodine intake. Thus, the radioiodine uptake will be higher than normal in subjects with low iodine intake and lower in subjects with high iodine intake. The former probably occurred in Chernobyl because of dietary iodine deficiency, and the latter would occur in Japan, where iodine intake is high. The ability of the thyroid to concentrate radioiodine also permits visualization of the thyroid with appropriate imaging instruments (e.g., gamma camera or PET SCAN) to determine its location, configuration, and the functional status of thyroid nodules if they are present.

Radioiodine concentrated by the thyroid in large amounts can cause cell death primarily because of ^{131}I's beta radiation. Large doses of ^{131}I are, therefore, given to treat patients with hyperthyroidism; those who have large nodular goiters that are causing local compressive symptoms on the trachea and esophagus, and those who cannot tolerate thyroid surgery; and to ablate functioning residual normal or malignant thyroid tissue after definitive surgery for thyroid cancer. The very large doses used to treat thyroid cancer occasionally lead to radiation-induced salivary gland inflammation and loss of taste because iodine is also concentrated by the salivary glands.

Despite several extensive retrospective studies, no convincing evidence has come forth to implicate ^{131}I as a cause of thyroid cancer in treated patients. Finally, medical use of radioiodine has not been observed to cause thyroid cancer but almost all of the treated patients were young adults or older, an age group much less likely to develop thyroid cancer after radiation exposure. However, very few of the patients studied were young children, the group most sensitive to thyroid radiation: in the few studies of children given therapeutic ^{131}I for hyperthyroidism, no malignant nodules were found after the treatment but the statistical power to demonstrate oncogenesis in these small groups of patients was limited [Robbins, 2000].

2.2.2. Exposure of populations to radioiodine from a radiation incident

Radioactive iodines (radioiodines, such as ^{131}I) are produced during the operation of nuclear power plants (NPPs) and during the detonation of nuclear weapons. Radioiodine is one of the contaminants that could be released into the environment in the event of a radiation incident that involves a disruption of the integrity of the fuel assembly and containment structures of a nuclear power plant (NPP), because of an accident or terrorist activity. Because iodine concentrates in the thyroid gland and because the thyroid cannot distinguish between radioactive iodine and non-radioactive iodine, exposure to radioiodine by inhalation of contaminated air or ingestion of contaminated milk or other food can lead to radiation injury to the thyroid, including increased risk of thyroid cancer and other thyroid diseases. The risk of thyroid cancer resulting from exposure to radioiodine is strongly age-related; foetuses, infants, and children are at highest risk. Fetuses are at risk through their pregnant mother's exposure and breast-feeding infants are at risk through breast-feeding milk from their exposed mothers, or through inhalation or ingestion from another source.

The Chernobyl reactor accident of April 1986 provides the best-documented example of a massive radionuclide release in which large numbers of people across a broad geographical area were exposed acutely to radioiodines released into the atmosphere. The Chernobyl

data are the most comprehensive and reliable data available describing the relationship between thyroid radiation dose and risk for thyroid cancer following an environmental release of ^{131}I.

2.2.3. Harmful effects of radioactive Iodine

A large amount of ^{131}I delivered to the thyroid almost always leads to hypothyroidism because of permanent radiation-induced destruction of thyroid cells. Therefore, with a smaller population of vulnerable thyroid cells remaining, these large radiation doses from ^{131}I are much less likely to cause thyroid cancer. In contrast, a surprising number of children exposed to a relatively low radiation dose (say less than 300 mGy) from ^{131}I and possibly other shorter-lived isotopes of iodine after the 1986 Chernobyl accident developed thyroid cancer within a few years.

Thus, following the accident at the Chernobyl nuclear power plant in 1986 a significant rise in thyroid cancer cases in the exposed children has been observed in Belarus, the south-western part of the Russian Federation (oblast of Bryansk) and the northern part of the Ukraine. About 1,800 thyroid cancer cases have occurred up to 1998 in those who were children or adolescents at the time of the accident [UNSCEAR, 2000]. In these regions, for the first 4 years of the striking increase in the incidence of thyroid cancer among children and adolescents, observed cases of thyroid cancer among children aged 0 through 4 years at the time of the accident exceeded expected number of cases by 30- to 60-fold. During the ensuing years, in the most heavily affected areas, incidence is as much as 100-fold compared to the pre-Chernobyl rates [Robbins, 2000].

Thus, following the Chernobyl accident there were thousands of children who accumulated a dose to the thyroid of several Gy. Nevertheless, the majority of cases occurred in the children who apparently received less than 300 mGy to the thyroid [Astakhova, 1998]. There has been an excess thyroid cancer incidence even in areas where the mean dose to the thyroid in children was estimated below 100 mGy [Jacob, 1998].

As noted above, large amounts of ^{131}I can result in thyroid-cell death. In contrast, low-dose exposure damages but does not kill thyroid cells and can induce nuclear damage and mutations, which can result in thyroid cancer. Thus, there are several potential reasons for the differences between the medical use of radioactive iodine and exposure to radiation fallout in causing thyroid cancer:

- Radioiodine released to the atmosphere may likely include a number of shorter-lived isotopes of iodine in addition to ^{131}I, which are also potentially carcinogenic;
- Because their thyroid-cells divide more frequently than in adults, children are at far greater risk of nuclear mutations and thyroid cancer when exposed to low-level radiation to the thyroid;
- The presumed low dietary iodine intake in the Chernobyl area probably resulted in an increased uptake of radioactive iodines.

Finally, despite the fact that uncertainty in the individual estimates of the thyroid dose is difficult to quantify, the experience from the Chernobyl accident shows that there is a real risk to develop thyroid cancer in young children after an exposure to radioiodine. This experience confirms that thyroid sensitivity in young children is high, while the thyroid sensitivity in adults to both external and internal radiation seems to be minimal, or even absent in the elderly. These observations argue also that neonates, infants, children, and adolescents are the critical groups of concern to be protected in priority in case of accidental exposure to radioactive iodine, because these groups are at high risk to develop thyroid cancer in the aftermath of the exposure.

2.3. Stable iodine prophylaxis

The term “prophylaxis” is defined as a measure or a set of measures designed to preserve health (as of an individual or of a society) and prevent the spread of a disease. Even if the main issue addressed within the present report concerns the stable iodine prophylaxis arrangements in the event of an accidental release of radioiodines, the authors have considered of the utmost importance to not restrict this section to the topic mentioned previously, but to extend it to the lessons learnt from the actions implemented in the frame of the worldwide eradication of iodine deficiency, anticipating that such a public health experience could bring relevant information, especially regarding the side effects of stable iodine.

2.3.1. Objectives

The stable iodine prophylaxis aims at achieving two different objectives:

- The first one, which is not the less important in terms of public health concern, is to fight against the iodine deficiency, which is common in developing countries where supplementation, mainly through salt iodization, may be considered, in contrast with industrialized countries where iodine deficiency is rare;
- The second one, which is the issue addressed within the present report, is to limit the binding of radioactive iodine in the thyroid and to reduce the extent to which it is irradiated in situ when radioactive iodine is accidentally released into the atmosphere or incorporated in the foodstuffs that human beings eat, such as milk, vegetables, mushrooms, etc.

2.3.2. Daily iodine requirements

As already stated above, iodine plays an important role in the function of the thyroid gland. It has been recognized for more than 50 years that iodine is an essential component of the thyroid hormones T4 and T3. Iodine is the chief component of thyroid hormones, and is essential for their production.

The thyroid gland is healthy when there is just enough iodine in the body, about 10-15 milligrams (approximately 70-90% of the total body iodine content is in the thyroid gland), so that just the right amount of thyroid hormones is produced [US-HHS, 2004].

A daily amount of about 150 micrograms of iodine is appropriate for normal adult thyroid function, with additional allowances of 25 and 50 micrograms per day during pregnancy and lactation, respectively [US-HHS, 2004]. Depending on the iodine concentration in foodstuffs, the presence of iodine supplementation arrangements, the use of medicines containing iodine (e.g., amiodarone, an antiarrhythmic agent, which provides 75 mg of iodide per pill), the age, the gender or the physiological status, the daily iodine requirements may differ from one country to another.

In France, the national average dietary iodine intake is comprised between 80 and 100 micrograms [Aurengo, 2002], with regional values ranging from 55 to 174 micrograms [Le Guen, 2002]. Table I shows typical average daily iodine requirements as a function of age, gender and physiological status [Aurengo, 2002], [Le Guen, 2002].

Table I. Average daily iodine requirements

Group of population	Daily iodine requirements (micrograms)
Infants	25-45
Children	50-100
Adult females*	100-120
Adult pregnant or lactating females	125-200
Adult males*	150

**Some authors don't make differences between adult females (pregnant and lactating female excluded) and males, indicating average daily iodine requirement of 100-115 micrograms for both, whatever the gender [Aurengo, 2002]. Because others argue that thyroid uptakes in females appear to be 10-30% higher than in males [US-HHS, 2004], it is not surprising to find scientific data indicating higher iodine requirement in males [Le Guen, 2002]. However, it should be noted that the orders of magnitude are roughly the same.*

Iodine is obtained from the water that people drink and the food they eat. In areas of the world where there is an iodine deficiency, iodine must be added to the salt or bread. The thyroid responds to dietary iodine deficiency by enlarging and more actively transporting iodine from the blood, thereby concentrating sufficient iodine to maintain normal function. Severe iodine deficiency (less than 50 micrograms iodine intake daily) is the major cause of mental retardation and endemic goiter and cretinism (due to hypothyroidism that could occur at birth) worldwide. The Swiss Alps, the Great Lakes area of Canada and the U.S., and Tasmania are such areas. In Europe, Canada and the U.S., most of the salt is iodized, thus the iodine intake is more than adequate.

Major efforts have been made over the last decades to eradicate iodine deficiency, and remarkable success has been achieved. National salt iodization programs have been initiated for example in Iran in 1989 [Soveid, 2007], Sri Lanka in 1993 [Mazziotti, 2003], China in 1996 [Teng, 2006] and Poland in 1997. However, much work remains and careful continued monitoring of populations is necessary to confirm that proper iodine intake continues, since some countries have decided to stop salt iodization program for economic reasons only.

As an example, in Poland iodine prophylaxis using the household salt had been implemented from 1930s till 1980 (with an interruption during World War II), and was dropped for economic reasons. Because the result of a nationwide study performed in about 20,000 schoolchildren showed that Poland was an area of mild or moderate iodine deficiency, an obligatory iodine prophylaxis was established in 1997 through iodization of household salt with 30±10 micrograms KI/kg [Lewinski, 2003].

Table II gives some examples of daily iodine intake in different countries [Aurengo, 2002].

Table II. Average values of daily iodine intake in different countries

Country	Daily iodine intake (micrograms/day)
Bulgaria	50-80
France	80-100
USA	300-400
Japan	1,200

In contrast, when iodine ingestion is excessive in healthy subjects, it may slightly decrease the secretion of T4 and T3 from the thyroid with a small compensatory rise in the serum TSH to maintain the serum T4 and T3 concentrations well within the normal range. Thus, many studies have reported that pharmacologic quantities of iodine given to healthy volunteers (without underlying thyroid disease) will induce small decreases in serum T4 and a compensatory small rise in serum TSH; both remain well within the normal range. Those findings indicate that healthy subjects can ingest excessive quantities of iodine for a long period of time, i.e. escape from the acute Wolff-Chaikoff effect (i.e. the decreased formation and release of thyroid hormone in the presence of an excess of iodine in the bloodstream), and maintain the euthyroid (i.e. thyroid gland functioning normally) state.

2.3.3. Toxicokinetics

Absorption: Most of the iodine that enters the body comes from the ingested food and a smaller amount comes from the drinking water. Iodine will enter the body also if it is in the breathed air or when it is injected into the blood for special medical tests or treatments. Some forms of iodine can enter the body when placed on the skin. When ingested, iodine from foodstuffs is absorbed in the digestive tract (stomach and small intestine) in its reduced chemical form, namely iodide (I^-) [Le Guen, 2002].

The gastrointestinal absorption of iodine is generally considered to be approximately 100% after an ingested dose of water soluble iodide salts, such as potassium iodide (KI) [US-HHS, 2004]. Intestinal absorption begins as soon as the iodine arrives in the stomach. Considering an absorption delay of roughly 10-15 minutes for foodstuffs in the stomach, ***absorption is complete in almost all subjects within a maximum of 1 hour*** [Aurengo, 2002] ***or 2 hours after ingestion*** [Verger, 2001].

Gastrointestinal absorption of iodine appears to be similar in children, adolescents, and adults. Absorption in infants, however, may be lower than in children and adults. Evidence for this comes from studies comparing measurements of thyroid uptake of radioiodine in newborns who received tracer doses of radioiodine orally *versus* by injection. For example, the average peak thyroid uptake (30 hours after the dose) was approximately 50% of the dose in newborn infants who received iodine orally, compared to an average of 70% (25 hours after the dose) in infants who received iodine by intramuscular injection. The ratio of the thyroid uptakes after the oral and injected iodine doses suggests a fractional oral absorption of approximately 70%. However, the rapid changes in iodine status and bio kinetics in the early weeks of postnatal life make interpretations of comparisons between injection data for a few groups of infants with ingestion data for other groups highly uncertain [US-HHS, 2004].

Distribution: Once in the bloodstream, iodide rapidly diffuses into the extracellular area (serum); serum concentrations of iodide normally range from 5 to 15 micrograms/L. This would suggest a total extracellular iodide content (i.e. the iodide that is not accumulated in the thyroid, salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat glands) of the human body of approximately 50-100 micrograms, assuming an extracellular fluid volume of approximately 20 L [Le Guen, 2002]; these data are roughly consistent with information provided by the U.S. Agency for Toxic Substances and Disease Registry in its document describing the toxicological profile for iodine, which mentions a total extracellular iodide content of the human body of approximately 85-170 micrograms/L under normal circumstances (i.e. in euthyroid subjects with normal thyroid function), assuming an extracellular fluid volume of approximately 17 L [US-HHS, 2004].

Then, the extracellular iodide pool is taken up by the thyroid gland and utilized in the production of thyroid hormones, which are stored in the gland: iodide concentration in the thyroid is usually 20-50 times that of the serum. ***The thyroid uptake begins rapidly and***

reaches a plateau at 10% to 40% of the total iodine ingested in 24 to 48 hours [Verger, 2001].

Iodide uptake into the thyroid gland is adaptive and highly sensitive to the iodine intake:

- ***At very low intakes, representing iodine deficiency (e.g., 20 micrograms/day), uptake of iodide into the thyroid is increased*** [US-HHS, 2004]***.*** This adaptive mechanism could explain why the population suffering from an iodine deficiency is at a higher risk to develop a thyroid cancer when exposed to radioiodine, since the thyroid dose increases proportionally.
- ***In case of sudden or chronic excess of iodine, uptake of iodide into the thyroid is decreased.*** The U.S. National Cancer Institute has analyzed data on 24-hour thyroid uptakes of radioiodine reported over the period from 1950 to 1980 and concluded that thyroid uptakes in adults have decreased in the United States over time from approximately 20-40% of the dose in the 1950-1960 period to approximately 15-20% currently. This decrease appears to be related to a concurrent increase in the average dietary intake of iodine in the population from approximately 200 micrograms/day to approximately 800 micrograms/day [NCI, 1997].
- However, ***the mechanisms that permit the thyroid to adapt to a sudden or chronic excess of iodine are immature in newborns and sometimes deficient in adults*** [Aurengo, 2002]. Consequently, ***thyroid uptakes in newborns are 3-4 times greater during the first 10 days of postnatal life than in adults,*** and decline to adult levels after approximately age 10-14 days [US-HHS, 2004].
- ***Thyroid uptake seems to be higher in adolescents than adults*** and decreases progressively with age [Verger, 2001].
- In pregnant women, because ***iodide crosses the placenta barrier***, a fraction of the ingested iodine begin to be taken by the foetus and placenta around 10 to 12 weeks, but remains low until 22 weeks. After the 22 weeks of pregnancy, the iodide concentration increases rapidly until term. Consequently, if the mother is exposed to radioiodine ***during the second half of the pregnancy, the concentration of radioiodine will be higher in the foetal thyroid than the maternal thyroid*** [Verger, 2001]***.*** This means that administration of stable iodine during the second half of the pregnancy aims at protecting firstly the foetus.

Elimination: The orally absorbed iodine is excreted primarily in the urine and faeces. ***Urinary excretion normally accounts for >97%***, while fecal excretion accounts for approximately 1-2% of absorbed iodine [US-HHS, 2004].

Renal excretion is rapid in the first hours, reaching a plateau at the end of 24 to 48 hours. The whole-body elimination half-time of absorbed iodine has been estimated to be approximately 31 days in healthy adult males; however, there appears to be considerable inter-individual variability in the half-time [US-HHS, 2004].

In contrast with iodide uptake into the thyroid gland, iodine elimination is not adaptive and not sensitive to the iodine intake:

- The renal iodine clearance is not saturable;
- ***Urinary excretion is increased in pregnant women*** [Verger, 2001].
- The iodide is also excreted in exhaled air, tears, and sweat, especially under conditions of strenuous physical activity;
- The iodide is secreted in saliva in humans: the salivary secretion of iodide may be an important pathway for recycling of iodine; however, the quantitative contribution of the saliva pathway to excretion of iodine has not been reported so far, and is probably minimal [US-HHS, 2004].

- Most important, ***iodide is excreted in human breast milk also.*** Most of the iodide is excreted in the milk in the 48 hours after ingestion. The fraction of the absorbed iodide excreted in breast milk varies with functional status of the thyroid gland and with the iodine intake. Thus, ***the excretion in breast milk is much larger (about 10-fold) in patient suffering from hypothyroidism*** compared to patient who was hyperthyroid when iodide was absorbed [Hedrick, 1986], [Morita, 1998], [Robinson, 1994].

2.3.4. Mechanisms of action

Whatever the chemical form used, the active chemical entity is the ion iodide I-. Ion iodide acts on the thyroid and prevents binding of radioiodine by five mechanisms [Schlumberger, 1986]:

- As substrate, it will dilute the radioiodine circulating inside the body available for thyroid uptake;
- By saturating the active transport mechanism of iodine mediated by the sodium iodide symporter (NIS) located on the thyroid-cell surface;
- By inhibiting the organification of iodide, also called Wolff-Chaikoff (W-C) phenomenon, a mechanism that could lead to a decrease of synthesis of thyroid hormones and a possible hypothyroidism; this effect is usually of short duration, but the foetus and the newborn can be affected;
- By generating an organic iodine compound that inhibits the binding of ^{131}I;
- By inhibiting the secretion of iodine organification by the thyroid.

Isotopic dilution and saturation are the principal mechanisms of the protective action of KI: they compete with radioactive iodine *via* an active iodine transport system in the thyroid [Verger, 2001].

Thus, under normal circumstances, excess iodine decreases NIS (sodium iodine symporter) on the thyroid-cell surface, thereby inhibiting the further entrance of iodine into the thyroid. Excess iodide administration at the appropriate time decreases the thyroid radioactive iodine uptake by decreasing NIS and by increasing the amount of non-radioactive iodine available for binding to thyroid cells.

However, while the active transport mechanism of iodine is being saturated, penetration of radioiodine is still possible, thanks to its passive diffusion [Saenger, 1977].

Knowing what stable iodine cannot do is also important. Thus, it cannot prevent radioactive iodine from entering the body, recognizing that it protects only the thyroid from radioactive iodine, not other parts of the body. As a result, stable iodine cannot reverse the health effects caused by radioactive iodine once damage to the thyroid has occurred, as well as stable iodine cannot protect the body from radioactive elements other than radioactive iodine [US-HHS, 2006].

2.3.5. Dosage

According to the WHO *Guidelines for Stable Iodine Prophylaxis Following Nuclear Accidents*, the uptake of radioiodine by the thyroid is effectively blocked by administration of 100 mg of stable iodine, corresponding to 130 mg of KI or 170 mg of potassium iodate, KIO_3, in adults and adolescents. For children, the administered dosage of KI must be reduced. The recommendations have been implemented in most of the countries worldwide, except in the

United States where some slight differences are observed concerning the dosage for adolescents over 12 years and the threshold for predicted exposure of those up to 18 years of age and pregnant or lactating women that should trigger stable iodine prophylaxis. Table XX in chapter "*Arrangements outside Europe*" describes the differences between WHO and FDA recommendations.

Table III summarizes single dosage of stable iodine for different age groups recommended by the WHO in 1999 [WHO, 1999].

Table III. Single dosage of stable iodine for different age groups recommended by the WHO in 1999

Age Group	Mass of Iodine (mg)	Mass of KI (mg)	Mass of KIO_3 (mg)	Fraction of 100 mg tablet
Adults and adolescents (over 12 years old)	100	130	170	1
Children (3-12 years old)	50	65	85	½
Infants (1 month to 3 years old)	25	32	42	¼
Neonates (birth to 1 month old)	12.5	16	21	⅛

2.3.6. Efficacy

Stable iodine may not give a person 100% protection against radioactive iodine. Thus, how well stable iodine blocks radioactive iodine depends on the given amount of KI, the time of KI ingestion and various other factors.

2.3.6.1. Efficacy as a function of the amount of KI

Several studies summarized by Verger 2001 [Verger, 2001] showed that thyroid uptake blockade varied as a function of the amount of KI administered. ***A percentage of dose averted exceeding 90% was obtained among adults for a dosage on the order of 20 mg when KI was administered simultaneously with radioactive iodine exposure.*** Nonetheless, the minimum dosage leading to such blockade depends on individual characteristics: it is higher among subjects with an elevated uptake than among others.

For iodide dosages of 100 and 200 mg administered simultaneously with the tracer the dose averted to the thyroid, 24 hours after ingestion of the tracer, exceeded 95% for most subjects. The increase of dosage of KI above 100 to 200 mg did not appear to improve the averted thyroid dose.

Repeated measures of thyroid uptake were carried out in nine subjects who had received a mixture of ^{132}I and ^{131}I after iodide doses ranging from 37 to 247 mg administered at different times (from 5.5 hours before to 4 days after the tracer). The authors found a percentage of averted thyroid dose of 86% when a 37 mg iodide dose was administered 24 hours before the tracer.

Modelling the data obtained in this study also showed that ***the uptake blockade was effective within a half hour after a KI dosage of 100 mg. This delay did not change with a higher dosage, but increased to 2.5 hours for a dosage below 25 mg.***

2.3.6.2. Efficacy as a function of the time of KI ingestion

A simulation that was based on a pharmacokinetic model estimated the percentage of thyroid dose adverted as a function of the time of KI administration in relation to time of exposure. For subjects with normal iodine intake the percentage of averted thyroid was estimated at 40% when KI was administered 8 hours after exposure. Another study yielded very similar results and showed that ***the optimum moment to give KI is 1 hour before exposure to radioactive iodine.***

2.3.6.3. Duration of the protection

Some authors examined protection by KI 48 and 72 hours after its administration, by administering another dose of radioactive iodine. ***A potassium iodide dosage of 25 mg did not block uptake after 48 hours; dosages of 50 mg and 100 mg did block 66% and 78%, respectively, of the thyroid dose. At 72 hours, a KI dosage of 100 mg blocked only about 25% of the thyroid dose.***

The duration of the protection was studied for an 8-day period in a sample of 5 women and 5 men free of any thyroid or renal disorder and hospitalized for gastric ulcers of myocardial infarct. These patients had not received any medication containing iodine. ***They received 200 mg of iodine (260 mg of KI)*** and their thyroid uptake was measured daily after an oral dose of ^{132}I. ***The averted thyroid dose was greater than 75% during the first 2 days of KI administration; it fell below 50% on the third day and to 15% on the fourth. Thyroid uptake returned to its baseline value after 8 days for most subjects.***

Finally, other authors showed than ***an averted thyroid dose of more than 90% can be maintained, after an initial administration of 100 mg of iodine (130 mg of KI), by the repeated dosage for several successive days at 15 mg of iodine (about 20 mg of KI).***

2.3.6.4. Efficacy as a function of other factors

The efficacy of the thyroid uptake blockade by cutaneous application of tincture of iodine has been shown in animals and humans. In a study of 24 men between 24 and 51 years old, thyroid uptake after an oral dose of KI (130 mg) was compared to that measured among subjects who had had tincture of iodine applied to their forearms (4 mL at 2%, or 80 mg) or abdomen (8 mL at 2%, or 160 mg). The mean percentage of averted dose was, respectively, 96.9%, 35.8%, and 81.7%.

Animal studies provide the only data available about the efficacy of the thyroid uptake blockade in foetuses after administration of KI to their mothers. ***An experimental study with chimpanzees evaluated the efficacy of the thyroid blockade by KI in foetuses at between 19 and 21 weeks gestation.*** The iodide was administered orally 1 hour before the tracer. ***The iodide dosages ranged from 0.5 mg/kg to 5.0 mg/kg (25-250 mg of iodide for a 50-kg subject).*** For comparison's sake, the recommended dosage for pregnant women is 100 mg of iodide.

Five animals received these dosages. Basal thyroid uptake was also measured in 13 control animals. ***Without KI, the thyroid uptake of the tracer in the chimpanzee foetus was similar to that of the human foetus.*** All three iodide dosages resulted in percentages of averted thyroid dose greater than 90% when tracer was injected 1 hour after KI administration. However, ***20 hours after KI administration, the percentage of averted dose was above 90% for only the two highest dosages, while for the lowest, it was 40%.***

Dietary iodine intake levels may modify the efficacy of the thyroid uptake blockade.

Authors have estimated ***the protective effect of KI when administered after intake of radioactive iodine. It was significantly lower in iodine-deficient compared with subjects whose iodine intake was normal.***

2.3.7. Adverse effects

Because the potassium iodide administration experiences with the objective of protecting people against the radiation-induced effects of exposure to radioiodine released following a nuclear accident are very rare, there is very little well documented scientific data on side effects observed in these populations.

In contrast, because there are numerous national programs of iodine supplementation in salt or bread, aiming at avoiding the occurrence of severe effects due to iodine deficiency, the side effects possibly resulting from such an administration have been widely studied.

The adverse effects of iodine come from also observations after treatments with drugs containing iodine.

The possible adverse effects of KI are iodine-induced hyperthyroidism, iodine-induced hypothyroidism, and non-thyroidal adverse effects. The severity of these effects depends on age, situation, and usual iodine intake. The possible adverse effects of KI have been very well described in a review published in 2001 [Verger, 2001].

2.3.7.1. Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism has been observed after treatments with drugs containing iodine that were prescribed for long period of time and after iodine prophylaxis programs in regions with iodine deficiency. Iodine-induced hyperthyroidism represents 6% of all diagnosed cases of thyrotoxicosis, with amiodarone, a drug given in patients suffering from cardiac rhythm disorders, being the most frequent cause. Amiodarone iodine-induced hyperthyroidism is also caused by mechanisms other than excess iodine, including direct toxicity to the thyrocyte. Its incidence has been reported to vary between 2% and 12% and to be higher in regions with iodine deficiency. Besides amiodarone, many other treatments and iodinated radiology contrast agents can cause adult iodine-induced hyperthyroidism.

Iodine-induced hyperthyroidism may appear in an apparently normal thyroid in the case of sudden acute or chronic iodine overload, especially in persons with low dietary iodine intake. It occurs most frequently, however, in multinodular thyroid glands, with or without goiters, or in cases of Graves' disease or toxic multinodular goiters that had remained latent because of an iodine deficiency.

The cardiac consequences of iodine-induced hyperthyroidism may be severe, particularly in the elderly or patients with patent or latent cardiac or coronary insufficiency. For example, atrial fibrillation occurs in 15% to 20% of patients with hyperthyroidism and in less than 1% of euthyroid adults.

Underlying thyroid disorders and other clinical situations that would predispose to iodine-induced hyperthyroidism are listed in Table IV.

Table IV. Risk groups for iodine-induced hyperthyroidism

Underlying thyroid disease
Iodine supplementation for endemic iodine-deficiency goiter
Iodine administration to patients with euthyroid Graves disease, especially those in remission after antithyroid drug therapy
Nontoxic nodular goiter
Autonomous nodules
Nontoxic diffuse goiter
No underlying thyroid disease
Iodine administration to patients with no recognized underlying thyroid disease, especially in areas of mild to moderate iodine deficiency

2.3.7.2. Iodine-induced hypothyroidism

Iodine-induced hypothyroidism occurs when the uptake does not escape from the Wolff-Chaikoff effect. Among adults, this occurs most often when there are pre-existing thyroid abnormalities: autoimmune thyroiditis, postpartum thyroiditis, radioiodine treatment for thyrotoxicosis, subacute thyroiditis.

Iodine-induced hypothyroidism is very frequent in newborns, especially in preterm babies, among whom an acute mild iodine overload (only 2 to 6 times the normal iodine intake) can result in hypothyroidism. The sensitivity of newborns to this effect is explained by their low thyroid iodine levels and by the immaturity of their iodine uptake regulation system. Iodine-induced hypothyroidism can occur after an iodine overload in the mother either before delivery or during breastfeeding. Cases of severe neonatal hypothyroidism and sometimes of goiters have been observed after the cutaneous application of iodine antiseptics at delivery.

Undiagnosed iodine-induced hypothyroidism during the neonatal period, even if transient, may impair the baby's long-term neurological and mental development. Conversely, once diagnosed, hypothyroidism is easily treated by hormonal therapy.

The possibility of foetal hypothyroidism after maternal iodine overload cannot be excluded. Its detection is difficult: a goiter might be seen during ultrasonography. Treatment of the mother is necessary to correct the disorder.

Table V. Risk groups for iodine-induced hypothyroidism

No underlying thyroid disease	
	Foetus and neonate, mostly preterm
	Secondary to transplacental passage of iodine or exposure of neonate to topical or parenteral iodine-rich substances
	Infant
	Occasionally reported in infants drinking iodine-rich water
	Adult
	In Japanese subjects with high iodine intake where Hashimoto's thyroiditis has been excluded
	Elderly
	Reported in elderly subjects with and without possible defective organification and autoimmune thyroiditis

No underlying thyroid disease
Chronic non-thyroidal illness
Cystic fibrosis
Chronic lung disease (including Hashimoto's thyroiditis)
Chronic dialysis treatment
Thalassemia major
Anorexia nervosa
Underlying thyroid disease
Hashimoto's thyroiditis
Euthyroid patients previously treated for Graves disease with ^{131}I, thyroidectomy, or antithyroid drugs
Subclinical hypothyroidism, especially in the elderly
After transient postpartum thyroiditis
After subacute painful thyroiditis
After hemithyroidectomy for benign nodules
Euthyroid patients with a previous episode of amiodarone-induced destructive thyrotoxicosis
Euthyroid patients with a previous episode of interferon-alpha-induced thyroid disorders
Patients receiving lithium therapy

2.3.7.3. Non-thyroidal adverse effects

Few non-thyroidal side effects were observed after KI administration to a large population, including children, in Poland after the Chernobyl accident [Nauman, 1993]. Indeed, it would be difficult to attribute some reported effects, such as skin rashes and gastrointestinal symptoms, to a single administration of KI inasmuch as such mild events are common, especially in infants and children.

Most of the potential non-thyroidal side effects reported although often unverified, are listed below. It should be understood that most of these are very rare.

- Gastrointestinal side effects: nausea, vomiting, diarrhea, and stomach pain;
- Allergy-related effects: angio-oedema (generalized swelling, in particular of the face and body), shortness of breath, arthralgia (joint pains), eosinophilia (abnormal white blood cells), lymphadenopathy (enlarged lymph nodes), urticaria (itching);
- Skin rashes.

Allergic and anaphylactic responses to iodine have been described by several authors. They may include gastrointestinal disorder (nausea, vomiting, diarrhea, and stomach pain), fever, swelling of the face and body, shortness of breath, and various skin rashes (called "iododermas"). Such consequences are exceptional, and the role of iodine in these symptoms has not been clearly demonstrated.

Extremely rare disorders reported to be aggravated by excess iodine ingestion include dermatitis herpetiform Duhring, ioderma tuberosum, hypocomplementemia vasculitis, and myotonia congenital.

2.3.7.4. The polish experience [Nauman, 1993], [Zarzycki, 1994]

The 29th of April 1986, 3 days after the Chernobyl explosion, the Polish Minister of Health asked the centralized pharmacy to provide the 11 provinces where the expected thyroid dose for children under 16 years would exceed 50 mSv, with KI solution. The recommended dosage was as follows:

- 15 mg for newborns;
- 50 mg for children 5 years or under;
- 70 mg for all other children under 16 years;
- Iodine prophylaxis was recommended for pregnant and lactating women, but was not mandatory;
- Iodine prophylaxis was not recommended for other adults;
- Multiple doses were not recommended.

A total of 17.5 million doses of KI were given: 10.5 million doses to children and 7 million doses to adults. Finally, 95.3% of children under 16 years received iodine prophylaxis and 23.2% of adults took KI, although not recommended by the Health Authorities.

With the iodine prophylaxis, additional protective measures were implemented, such as (i) banning countrywide the feeding of cows on pastures or with fresh fodder, (ii) banning the consumption by children and pregnant or lactating women of fresh milk with radioactivity above 1,000 Bq/L, (iii) providing all children under the age of 4 with powdered milk and (iv) advising children and pregnant or lactating women to eat a minimum of fresh leafy vegetables.

After the acute protective phase was terminated, the Health Authorities have conducted a retrospective study among a group of 34,491 persons, comprising 12,641 children and 20,578 adults. In addition, screening studies for congenital hypothyroidism in central Poland were performed on 120,000 to 140,000 newborns for the years 1985, 1986, and 1987.

The main outcomes of studies conducted by the Polish health authorities are as follows:

- More than 95% of 12,040 children and 5,061 adults who received stable iodine and answered a dedicated questionnaire didn't exhibit any extrathyroidal side effects; in those who showed adverse effects, the most frequently observed effects were vomiting (286 children and 43 adults), skin rashes (129 children and 63 adults), stomach ache (43 children and 32 adults), and headache (22 children and 35 adults);
- Two adults, despite chronic obstructive lung disease and known sensitivity to iodides, promptly developed acute respiratory distress after taking KI;
- No severe complications in pregnant women who took the recommended dose of KI were observed;
- No permanent thyroid dysfunction evaluated with the thyroid-stimulating hormone concentration in the serum was found among 12,084 children who received KI;
- No statistical differences between the protected children (12,084 patients) and unprotected children (557 patients) groups were noted;
- Only 12 of 3,214 newborns who received KI prophylaxis on the second day of life showed a transient thyroid inhibition; this thyroid inhibition was not observed anymore at the 16th day of life.

Finally, the incidence of medically significant, but not serious, the percentage of reactions to a single dose of KI among this very large population was estimated to

0.2%. However, it should be regretted that the studies performed in such a large population do not provide any information concerning the age of adults who received KI. It would be highly valuable to know whether adults above 40 years in age exhibited side effects, such as hyperthyroidism.

2.4. Conclusions about the medical effectiveness of iodine prophylaxis

From the data presented in this section, it is apparent that exposure of susceptible populations to radioiodine from a radiation incident poses an increased risk of thyroid cancer and other thyroid conditions. KI is a chemical compound that contains iodine and can be used to protect the thyroid gland from possible radiation injury by reducing the amount of radioiodine concentrated by the thyroid after inhalation of radioiodine. KI is also effective for protection against the harmful thyroid effects of radioiodine ingested in contaminated milk and other foods.

KI is highly effective in blocking uptake of radioiodine if taken shortly before or shortly after exposure, and side effects after short-term use have been minimal. Foetuses, infants, children, and pregnant women (to protect the foetus because iodine readily crosses the placenta), and nursing mothers (to protect breast-feeding infants because iodine is concentrated in breast milk) are most in need of protection from radioiodine exposure and most likely to benefit from KI, because foetuses, infants, and children are at highest risk of cancer. Pregnant and lactating women should take KI to protect their unborn or breast-fed children. Among older adults, despite there is little risk of thyroid cancer and non negligible risk of complications from KI, *it seems that there is still benefit in providing KI for adults over 40 years old.* To be most effective, KI must be taken within a few hours before or after exposure to inhaled or ingested radioiodine.

3. EUROPEAN NATIONAL PRACTICES

In order to have a good survey of current national practices of using the iodine prophylaxis in the EU Member States, Candidate Countries, Norway and Switzerland, IRSN drew up a questionnaire (see Appendix) with the aim to compare current arrangements, identify good practices and look at encountered difficulties.

Items pointed out in the questionnaire were as follows:

- Formulation and dosage,
- Effectiveness duration,
- Intake timing, possibility of second intake,
- Emergency reference level,
- Targeted population,
- Decision-making process,
- Link with other countermeasures,
- Iodine storage and distribution,
- Geographical coverage,
- Pre-distribution area,
- Encountered difficulties,
- Communication arrangements (before and during an emergency),
- Harmonization efforts with neighbouring countries.

It was sent to 27 EU Member States, 3 EU Candidate Countries, Norway and Switzerland. As a total, IRSN obtained 26 answers. The countries that have answered are listed in Table VI.

Table VI. List of countries having answered the IRSN questionnaire

Belgium	Malta
Czech Republic	Norway
Croatia	Netherlands
Denmark	Poland
Estonia	Republic of Macedonia
Finland	Romania
France	Slovakia
Germany	Slovenia
Hungary	Spain
Ireland	Sweden
Italy	Switzerland
Lithuania	United Kingdom
Luxembourg	Turkey

A review of answers received for each topic is presented below.

3.1. Countries without any iodine prophylaxis arrangements currently implemented

Few countries have no iodine prophylaxis arrangements to face a nuclear emergency. It is the case of **Malta** since it does not have nuclear power plants in its territory or in the vicinity. **Estonia** as well did not introduce iodine prophylaxis arrangements as the nearest nuclear power plant (Leningrad NPP) is located at a distance of about 80 km from the Estonian border.

Croatia government adopted last year a state plan and program of ionizing radiation protection measures and emergency interventions. Before that, there was no plan of emergency preparedness at all. Several documents are under preparation concerning emergency actions, but no detailed information is available on iodine prophylaxis.

So far the **Republic of Macedonia** has not adopted the iodine prophylaxis, as it has neither nuclear installation on its territory nor any nuclear material. But the Radiation Safety Directorate is preparing new regulations covering specific radiation protection and safety requirements, among which it establishes the intervention levels for undertaking protective actions in a case of radiation emergency in accordance with the IAEA Safety Standards Series GS-R-2. These draft regulations were expected to be adopted by the end of 2009 and therefore an intervention level of 100 mGy of avertable committed absorbed dose to the thyroid due to radioiodine will be established. Establishing the operational intervention levels and a practice to implement the iodine prophylaxis will be the next step of planning radiation emergency preparedness and response.

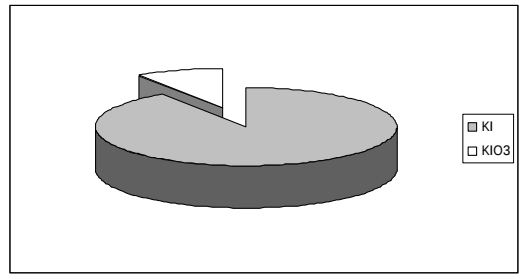
Ireland has decided to discontinue future distribution of iodine tablets. During 2002, iodine tablets, intended to be taken in the event of a major nuclear accident that might result in the release of radioactive iodine, were issued to each household. The Minister for Health and Children has decided in 2008, on the basis of expert risk management advice, not to re-issue the tablets. It was recognized that the risks, which may have existed, have now been substantially reduced with the closure of two of the oldest and most vulnerable nuclear reactors in the UK, namely the Calder Hall and Chapleross reactors in the Sellafield site. The closest nuclear power station to Ireland is the Wylfa Nuclear Power Plant in North Wales, which is located at 114 km from the Irish coastline. The potential impact on Ireland of an accident or incident at Wylfa was examined. It was concluded that, even in the worst-case scenario, the use of iodine tablets would not be justified in Ireland.

3.2. Formulation and dosage

3.2.1. Formulation

The most widely used formulation is potassium iodide (KI). From 21 countries having answered to the questionnaire and having iodine prophylaxis arrangements already implemented, 18 have adopted this form against 2 using potassium iodate (KIO_3) – United Kingdom and the Netherlands.

Figure 3. Proportion of European countries having adopted potassium Iodide form



There are no medical grounds for preferring the iodate form over the iodide form, despite observation reported that iodate seems to be more irritant for the gastrointestinal tract. In addition, it should be noted that the FDA does not approve KIO_3 for use in the United States so far. Therefore, although it is not of the utmost importance, the interest of harmonizing formulation in European countries could be an issue to address to facilitate communication towards the public.

3.2.2. Tablet mass

The mass of one tablet may differ from one country to another, mainly from 65 mg to 130 mg. Table VII shows the equivalent mass of iodine per tablet in the different countries: a tablet contains in general 65 mg of potassium iodide (corresponding to 50 mg iodine), except in Finland, the Netherlands, Spain and Turkey which have adopted 130 mg tablets. France recently moved to 65 mg tablets, with an aim of harmonization with neighbouring countries [Common Report, 2007]. Poland has 25 mg tablets.

Table VII. Equivalent mass of iodine per tablet

	Equivalent mass of iodine per tablet (mg)		Equivalent mass of iodine per tablet (mg)
Belgium	50	Netherlands	100
Bulgaria	50	Norway	50
Czech Republic	50	Poland	25
Denmark	55	Romania	50
Finland	100	Slovakia	50
France	50	Slovenia	50
Germany	50	Spain	100
Hungary	50	Sweden	50
Italy	50	Switzerland	50
Lithuania	50	Turkey	100
Luxembourg	50	United Kingdom	50

It can be noted that 32.7 or 65 mg tablets are easier to administrate to neonates (½ or ¼ a tablet), babies and young children (1 or ½ tablet) than 100 mg tablets. This argument may be considered when deciding on mass of tablets for a new distribution campaign or stock renewal.

3.2.3. Dosage

Table VIII shows the age-related dosages in equivalent mass of iodine recommended in each country. It can be seen that dosages are quite consistent in the different countries. Some

countries have defined an age limit above which they do not prescribe iodine prophylaxis. The age limit is about 40 to 45 years. It is the case of Denmark, Germany, Hungary, Lithuania, the Netherlands, Norway, Romania and Slovenia. In Czech Republic, iodine prophylaxis is not prescribed for persons over 45 years in case of contra-indications as iodine allergy, disturbance in thyroid function or thyroiditis.

Table VIII. Age-related dosages in equivalent mass of iodine

	12,5 mg (I)	25 mg (I)	50 mg (I)	100 mg (I)	0
Belgium	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Bulgaria	< 2 m.	2 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Czech Republic	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Denmark	< 1 m.	1 m. - 3 y.	3 y. - 12 y. (55)	> 12 y.	> 40 y.
Finland	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
France	-	< 3 y.	3 y. - 12 y.	> 12 y.	-
Germany	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	> 45 y.
Hungary	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	> 45 y.
Italy	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Lithuania	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Luxembourg	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Netherlands	-	-	< 3 y.	> 3 y.	> 45 y.
Norway	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	
Poland	< 3 m.	3 m. - 2 y.	2 y. - 6 y.	> 6 y.	
Romania	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	> 45 y.
Slovakia	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Slovenia	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	> 40 y.
Sweden	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	> 40 y.
Switzerland	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
Turkey	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-
United Kingdom	< 1 m.	1 m. - 3 y.	3 y. - 12 y.	> 12 y.	-

It can be noted that if KI tablets are not available, Lithuania suggests using 5% iodine tincture. For infants under 2 years old, the dose is 1-2 drops of iodine tincture 3 times per day not longer than 7 days. Drops of tincture can be mixed with 100 ml of milk or other liquid food. To children over 2 years and adults the dose is 3-5 drops of 5% iodine tincture 3 times per day not longer than 7 days. This could be considered as a good practice.

Concerning the adults over 45 years, it can be noted that Belgium has launched an information campaign aimed at physicians and pharmacists around the nuclear sites. Physicians and pharmacists were asked to perform preventive screening to detect the contraindications of iodine intake among their patients/customers. This could be retained as well as a good practice.

3.2.4. Status of stable iodine tablet

In most countries, potassium iodide or iodate is considered as a pharmaceutical product except in Lithuania, Poland and Romania. In Romania only iodine tablets used for prophylaxis of iodine deficiency, e.g. having a content of 1 mg of potassium iodide are considered as a pharmaceutical product.

In Poland stable iodine tablets are produced according to the requirements concerning pharmaceutical products, but they do not need to be registered as such.

The status of "pharmaceutical" attributed to this product may limit its accepted validity, although the tablets stored under good conditions hardly deteriorate and remain active for a very long time. The validity varies between 36 and 180 months. It must be noted that the validity of the product in Sweden is 15 years.

Table IX indicates the different validity times considered in each country.

Table IX. Validity time of iodine tablets

	Validity (months)
Belgium	120
Bulgaria	unknown
Czech Republic	60
Denmark	60
Finland	60
France	84
Germany	120 (for tablets sold in pharmacy)
Hungary	60
Italy	60
Lithuania	60
Luxembourg	(manufacture date only)
Netherlands	3 years ?
Norway	60
Poland	48
Romania	60
Slovakia	60
Slovenia	60
Spain	120
Sweden	60 (for predistribution only)
Switzerland	120
Turkey	60
United-Kingdom	30

In Germany there is an expiry date only on tablets sold in pharmacies (for legal reasons), but not on the stored and pre-distributed ones provided by the authorities. In Sweden a validity limit is indicated only for pre-distributed tablets. There is no special limit for tablets in national storage.

***Good practice:* A way to avoid problems with an "expiry" date could be to mention the production date on the box instead as it is done in Luxembourg. Validity could then be extended more easily. For national or regional storage, it could be suggested, when possible, to indicate the production date.**

In France the expiration date is still an issue of controversy: despite the expiration date of the 130-mg KI pill formulation has been extended to 7 years (84 months) by the "French FDA" (AFSSAPS), the expiration date foreseen for the new 65-mg KI pill formulation currently under production by the French Army Pharmacy (PCA) is 30 months [PCA, 2009]. Thus, because the production process is new, the PCA was asked by the AFSSAPS to perform additional tests before extending the expiration date of the new KI formulation to 5 or 7 years, although that it is unofficially recognized that pills keep their efficiency for at least 10 years. Indeed, after 10 years there may be a slight oxidation of the iodide that turns out to a brown color, but which does not affect significantly the product efficiency. Nevertheless the pills may crumble, which makes them more difficult to uptake, for children in particular. However, a significant change will be introduced when the 65-mg KI pill formulation will become available, since the

AFSSAPS has agreed that the packaging will indicate the production date only and will not mention the expiration date anymore.

3.3. Time for intakes, Iodine blockade effectiveness

3.3.1. Time for the first intake and iodine blockade effectiveness

Table X supplies answers received concerning the optimal time for intake regarding the beginning of the release (i.e. for population shortly exposed to the radioactive release) and the effectiveness duration considered by each country.

Table X. Considerations on time for intake and effectiveness duration

	Time for intake	Effectiveness duration
Belgium	As soon as possible before the beginning of the exposure	24h for puff releases (inhalation scenarios) - more for long lasting releases depending on the time profile
Czech Republic	Optimal time is 2 hours before exposure	As soon as possible, not late than 10 hours, then it could be ineffective
Denmark	As soon as possible	24h
Finland	When it is predicted that there might be a release	1-2 days
France	Just before release or, if not possible, as soon as possible after the start of radioiodine release	24h
Germany	Just before the release or as soon as possible after the start of radioiodine release	24h
Hungary	Administration before the plume arrives to the settlements	Maximum 5h
Italy	Before the arrival of the radioactive cloud and in any case not later than 6 hours from the beginning of the exposition	6h
Lithuania	2-3 hours before release if unavoidable and immediately after release	2-3 hours
Luxembourg	Before or during the arrival of a nuclear cloud and **in coordination with other affected neighboring regions.**	24 hours
The Netherlands	6 hours before till 6-8 hours after a release	6-8 hours
Norway	Preferentially before the release arrival or at the beginning of the release	6 h but not advised after 24h
Poland	Before starting inhalation of radioactive iodine (several hours before)	12-18 hours after release, iodine administration would no more be effective - Approximately 6 hours
Romania	6 hours before the arrival of the radioactive cloud	2-3 days

	Time for intake	Effectiveness duration
Slovakia	Before release, beginning of release	24 up to 48 hours
Slovenia	Before releases - at least 6 hours	One to two days
Spain	Before release	2h
Sweden	Before release, at the alarm level "general emergency"	Up to 2 days
Switzerland	Just before release	24h
Turkey	10 hours before the iodine intake is considered for maximum protection	24h
United Kingdom	Promptly following a release (ideally within 3-4 hours)	24h

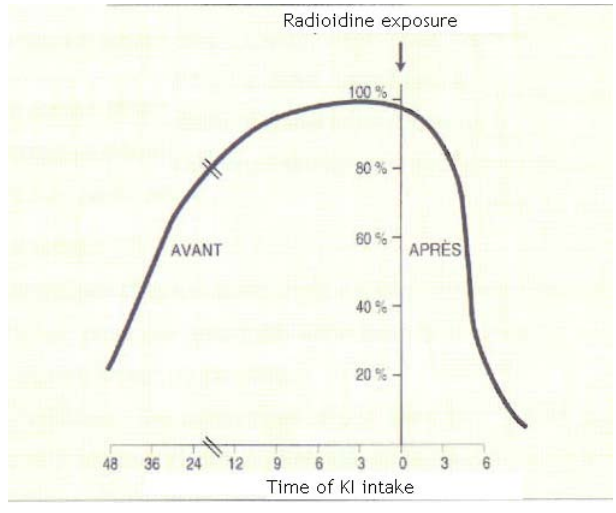
Table X points out quite variable practices regarding the recommended time for intake. In general, the intake is advised before the release or as soon as possible after it begins, but in some countries intake is recommended several hours before the beginning of the release, up to 12 hours at an optimum considered by the Netherlands.

These differences may induce problems in case of an accident with stable iodine decisions and announcements taken in neighbouring countries at different times.

Quite important differences appear also on the effectiveness duration. If most countries consider that iodine is effective during 24 hours after intake, some countries are considering a shorter time from 2 to 10 hours.

Figure 4 [Hémidy, 2004] shows the effectiveness of iodine against the time of the release. Effectiveness of iodine prophylaxis highly depends on the possibility to administrate the tablets in the period preceding the exposure to radioiodine or as soon as possible after the releases into the atmosphere. The moment of the ingestion of stable iodine is fundamental to ensure a good protection of the thyroid.

Figure 4. KI effectiveness as a function of intake time regarding exposure



Consequently, detailed emergency plans should provide for the stable iodine tablets to be administered promptly, as the health benefit reduces with increased delay in administration.

3.3.2. Second intake

In some accidents, exposure to radioactive iodine may be prolonged or may occur later than initially predicted and thus makes repeated KI doses necessary.

Several countries intend to recommend a second intake in case of a radioactive release. Table XI shows the different approaches encountered in Europe.

Table XI. Second intake

	Second intake	Time between intakes	Comments	Countries specificities
Belgium	No		Exceptions are e.g. for protracted release with impossibility to evacuate or contamination of food with no possibility to timely provide non contaminated substitutes	Mild chronic iodine deficiency. No prophylaxis is organised for the present time but this might be applied in a next future.
Bulgaria	Yes	24h	Except for newborns up to 2 months - total dose should not exceed 1g on 10 days	
Czech Republic	Yes	24h	Third intake possible, half of the original dosage	
Denmark	Yes	24h	For exposure of iodine on more than 24h, continuation with the same dosage per day, except for newborns (max 1 time) and for pregnant and breastfeeding women (max 2 times)	During the last 10 years, a program for adding stable iodine to salt has been in place - lowering the iodine deficiency in the population
Finland	No		Very unlikely and very restrictively, to children only, and only in case of prolonged release (more than 1-2 days)	
France	No	24h	Except if it is impossible to evacuate the people	
Germany	Yes	24h		
Hungary	Yes	24h	Same dosage, one time if necessary	
Italy	Yes, except neonates		For exposure of iodine on more than 24h - for pregnant and breastfeeding women, limitation of the administration to a second dose on the second day	
Lithuania	Yes			
Luxembourg	Yes, except neonates, pregnant and breastfeeding women	within 2 days	In case of release duration of several days, one or several consecutive intakes may be envisaged. It will be decided by the authorities.	
Nether-lands	No			

	Second intake	Time between intakes	Comments	Countries specificities
Norway	No		Second intake can nevertheless be envisaged for neonates and pregnant women	
Poland	Yes	2-3 days	Second intake carried out if release is still observed 2-3 days after the first intake and if there is still a risk of receiving by any person a minimum dose of 100 mGy to the thyroid.	Salt (NaCl) is used as ingredient in food processing, accessible in free market in food shops, include some amount of Iodine Chlorine (KCl)
Romania	Yes (except neonates and infants)	12h	Half dosage, in case of a continuous release, no longer than 10 days or maximum total dose one gram.	
Slovakia	Yes	24h up to 48h after the first intake		
Slovenia	No	24h	Only if nuclear medicine proposes to	
Spain	Yes			
Sweden	Yes		Depending to the accident	
Switzer-land	Yes	24h		
Turkey	Yes		Total dose (Iodine Eqv.) must not exceed 1g	
United Kingdom	No			

It can be seen that a second intake is envisaged in most countries, mainly in case of long-lasting releases, with a similar or lower dosage than for the first intake. In the United Kingdom and Belgium, stable iodine prophylaxis may be used also as a temporary measure to provide protection for young children against the ingestion exposure pathway, until food restrictions can be imposed.

A second intake is generally envisaged 24 hours after the first one. The second intake is sometimes only envisaged for the most radiosensitive population, i.e. newborns, young children, pregnant and breast feeding women. In Romania stable iodine may be administrated several times on a maximum of ten days. In [Verger, 2001], it is indicated that for adults, smaller dosages after the initial one would maintain a very efficient protection of the thyroid and minimize the risks of adverse effects. More research is needed to verify whether this strategy, which is not recommended for infants and children [WHO, 1999] could also be applied to this most radiosensitive population. The existence of a threshold above which risks of adverse effects may become more important should be studied. Therefore, the necessity of defining a maximum dosage in iodine equivalent (1 g), as set up in Turkey and Bulgaria should be examined. Thus, it could be anticipated a benefit from such a decision in terms of communication with the public, recognizing that defining a maximum dosage may assist in avoiding panic reactions within the population, reactions which could lead to severe intoxication due to the ingestion of a number of tablets or boxes of tablets.

3.4. Decision-making process concerning iodine prophylaxis

3.4.1. Emergency reference levels

Table XII gives emergency reference levels (ERLs) regarding equivalent dose to the thyroid used in Europe. Countries have been also questioned on their intention to review these levels in the near future.

Table XII. Emergency reference levels in Europe

	Emergency reference level for iodine intake	Type of dose considered (equivalent to the thyroid)	Intention to review the intervention level for iodine intake
Belgium	Children, pregnant and breastfeeding women : **10 mSv** / Adults : **50 mSv**	Projected dose	No
Croatia	**10 mSv** in the future (maybe a different choice will be made)	not known	
Czech Republic	**100 mSv**	Averted committed equivalent dose	No
Denmark	**50 mGy**	Averted dose	No
Finland	**10 mSv** thyroid dose for children, **100 mGy** for adults	Projected dose	Ongoing project to be finished by the end of year 2009 where all intervention levels are reconsidered for early and intermediate phases of an emergency. Iodine prophylaxis is also included.
France	**50 mSv** based on common works performed with Belgium, Germany, Luxembourg and Switzerland to harmonize practices concerning iodine prophylaxis	Projected dose on the duration of the release or 24/48 hours	No, recently reviewed
Germany	**50 mSv** for children/adolescents under 18 years and pregnant women; **250 mSv** for adults (based on WHO last recommendations)	Projected dose	No
Hungary	**100 mGy**	Averted dose	Yes, in one year
Italy	**10 mSv** for neonates, children, adolescents up to 18 years and pregnant and breastfeeding women, **100 mSv** for the adults	Averted dose	No
Lithuania	**10 mGy** for neonates, children, adolescents up to 18 years and pregnant and lactating women, **100 mGy** for adults under 40 years ; **5 Gy** for adults above 40 years.	Projected dose	No
Luxem-bourg	Flexible approach: harmonized countermeasures with border countries - The value of **50 mSv** should be adopted in the very near future (based on common work performed with neighboring countries).	Projected dose	No, just reviewed
Nether-lands	Under review	Averted dose	No

	Emergency reference level for iodine intake	Type of dose considered (equivalent to the thyroid)	Intention to review the intervention level for iodine intake
Norway	**10 mSv** at the thyroid for children and adolescents	Projected dose	Yes. Depends on when the new international recommendations will be available (WHO, IAEA BSS, EU etc…)
Poland	**100 mGy**	Projected dose	No, but introduction of OILs is foreseen according to the IAEA Safety Standards DS44
Romania	Between **30 and 300 mSv** on 24h	Projected dose	Yes, according to new international BSS recommendations and to EU recommendations
Slovakia	Fixed by national legislation concerning radiation protection	Averted dose	Yes, within 3 to 5 years
Slovenia	**100 mGy** (based on IAEA BSS N°115, schedule V, paragraph 9)	Averted dose	No
Spain	**100 mGy**	Projected dose on 2 days	Participation to the EPAL group
Sweden	No numeric intervention level value : there is no time to first measure the content of iodine in the air and then decide on iodine tablets. It will be too late. Since the side effects of stable iodine are very low it has been decided to recommend intake of predistributed tablets if there is even a small risk of thyroïd dose in the order of **1-10 mGy** or above for children, which is a general emergency situation within 15 km.	Projected dose	No
Switzer-land	**30-300 mSv**	Projected dose on two days or the duration of the cloud passage / ingestion pathway not considered	It is planned to adopt an intervention level of 50 mSv in 2010 based on the proposal of the working group on harmonization of iodine prophylaxis. However Switzerland will not adopt age-specific intervention levels because tablets are available for everybody and side effects are judged as a minor problem.
Turkey	**100 mSv**	Averted dose	May be revised depending on the future changes of international guidance

	Emergency reference level for iodine intake	Type of dose considered (equivalent to the thyroid)	Intention to review the intervention level for iodine intake
United Kingdom	**30 - 300 mGy** to the thyroid	Averted dose	Yes. HPA has prepared a document on the subject which was sent out for consultation. HPA is waiting for the publication of the WHO guidance on iodine before publishing its own report since it refers to the WHO guidance.

Generally, it can be seen from Table XII that emergency reference levels vary between 10 and 100 mSv in equivalent thyroid dose for most countries, but it should be noted that ERLs are expressed either in projected or averted dose.

Several countries have different intervention levels for the different categories of population. Iodine intake is not recommended for the elderly population (> 40 or 45 years) in few countries. It is generally considered that side effects are a minor problem.

In some countries these emergency reference levels are used mainly for emergency planning purposes. Then, in case of accident, the decision to order iodine intake may be based on a lower level, depending on the context (limited geographical area, optimization of the protection, decisions taken in neighbouring countries…). In Sweden for instance, the area for iodine pre-distribution is defined by considering a possible averted dose of 100 mGy (i.e. 15 km around NPP) in case of an accident. Then, in case of an emergency, the decision on iodine prophylaxis is in the order of 1 mGy for use of pre-distributed tablets. In France as well, ERL's are used for designing emergency planning zones. The decision in case of an accident will take into account different elements of context that could lead to a recommendation of iodine intake for lower levels.

3.4.2. Decision-making process

Table XIII. Decision-making supporting elements for iodine intake

	Key decision-making elements	Considered pathways	Target population for calculation	Effectiveness of CM considered in the calculation
Belgium	Projected dose calculation on the release duration	Inhalation	Children, pregnant and breastfeeding women, adults	No
Czech Republic	Averted dose assessed by atmosphere dispersion models under actual meteorological conditions	Inhalation	Not known	No
Denmark	Averted dose - age independent - days / no ingestion	Inhalation	Different ages	No

	Key decision-making elements	Considered pathways	Target population for calculation	Effectiveness of CM considered in the calculation
Finland	Safety assessment of the situation (prediction of the development of the event, foreseeable releases of radioioidine into the environment), meteorological conditions and projected dose assessment.	Inhalation mainly / ingestion only if it is not possible to cope with restricted consumption	Especially children but adults too	
France	Safety assessment of the situation (prediction of the development of the event, foreseeable releases of radioioidine into the environment), meteorological conditions and projected dose assessment as a function of time.	Inhalation	1-year old child (most radiosensitive population for a release from a NPP)	No
Germany	Projected equivalent thyroid dose assessment (using RODOS for some *Länder*)	Inhalation	Children and adult	No
Hungary	Thyroid dose assessments based on radioiodine concentration in the air calculated by RODOS model. (RODOS built-in method) - averted dose	Inhalation	Not known	No
Italy	Averted thyroid equivalent dose calculation	Inhalation	Not known	
Lithuania	Projected dose calculation on the release duration	Inhalation and ingestion	Not known	Yes
Luxem-bourg	Projected doses assessment	Inhalation	Most sensitive group (children)	No
Nether-lands	Adverted dose on 24 hours	Inhalation	One year old child who is sheltering in place	Yes
Norway	Argos projected dose prognosis - time when information about release is available, time needed to distribute + time of arrival of the plume. Calculation on most cases on 12 hours.	Inhalation	Children, pregnant and breastfeeding women	Yes
Poland	Prognosis calculation performed with ARGOS and/or RODOS computer codes and measurements results	Inhalation	Most sensitive group	Yes
Romania	Prognosis of iodine release, due to the nuclear power plant/projected equivalent thyroid dose due to the cloud passage (projected dose)	Inhalation in the early phase and ingestion in the late phase		Yes
Slovakia	Methodological procedure for assessing the dose - use of the RODOS computer code - averted dose	ERL defined for inhalation - ingestion pathway considered in the evaluation	Critical group of population	Yes
Slovenia	Inhalation projected and averted dose calculation	Inhalation and ingestion in regulation		
Spain	Results of release models (projected dose on 2 days) and measurements	Inhalation		No

	Key decision-making elements	Considered pathways	Target population for calculation	Effectiveness of CM considered in the calculation
Sweden	General emergency level	Inhalation		No
Switzer-land	Dispersion modeling and dose calculation based on the source term estimation (projected dose)	Inhalation	Most sensitive group (children)	Yes
Turkey	Projected dose calculation	Inhalation		Yes
United Kingdom	Following advice from the site operator - simple gaussian plume model to calculate time integrated air concerntrations on basis of monitoring data (either air concentrations or dose rates). Calculation of the committed dose to the thyroid from inhalation to children over the integration period. It is assumed that I-131 and 100% dose saving from the application of the countermeasure. Values calculated are compared with ERLs and derive distances at which the countermeasure should apply is defined.	Inhalation	7 days but it is not a fixed recommended value. It is a generic time used by HPA ; different sites may have different times for their emergency plans.	Yes

The decision-making process is mainly based on a dose assessment performed with calculation means. Assessment is performed for the most sensitive population, i.e. children. Assessment can be performed for different ages. Effectiveness of countermeasures may be considered in the calculation. Table XIII shows that even with a similar intervention level, differences in dose assessment, due in particular to different source term and atmospheric dispersion models, may lead to different decisions.

Inhalation pathway is generally considered, except when food restrictions could not be applied in the very short term.

Some countries have defined operational intervention levels to set up iodine prophylaxis when measurement results exceed some predetermined values.

3.4.3. Operational intervention levels

Seven countries have defined operational intervention levels in order to be able to take promptly the decision for ordering iodine intake when the release is on-going. They are generally expressed as dose rate but could be also expressed as volume activity per hour (Slovenia).

Table XIV. Operational intervention levels in Europe

	Operational intervention levels
Croatia	1 mSv/h
Finland	10μSv/h for children and 100μSv/h for adults if there is a reason to believe that radioiodine is present.
Lithuania	Ambient dose rate in the plume ≥ 0,1 mSv/h Ambient dose rate from deposition ≥ 1μSv/h
Netherlands	Yes
Slovakia	Yes

	Operational intervention levels
Slovenia	220 (kBq/m^3).h for Krško NPP (it is the product of iodine -131 concentration and duration of inhalation). Determined from avertable equivalent dose of 100 mSv to the thyroid (5 mSv for effective dose), which is equivalent to intake of 220 kBq of I-131, if we use dose conversion factor 23 nSv/Bq.
Turkey	0,1 mSv/h for ambient dose rate in the plume

The optimal time for iodine intake is before the start of releases. Therefore, operational intervention levels may be useful, but just as “back up” parameters for cases where alert was not correctly done or when dose prediction seriously underestimates actual releases.

3.4.4. Combination with other countermeasures

Table XV. Countermeasures combined with iodine prophylaxis

	Combination with other countermeasures
Belgium	Sheltering and food bans
Czech Republic	Sheltering
Denmark	Sheltering and appropriate food ban
Finland	OIL for adults is the same as for general sheltering indoors. If only the OIL for children is reached, it is combined with a recommendation for children not to spend unnecessary time playing outdoors.
France	Sheltering and food ban (food ban introduced separetely)
Germany	Sheltering and food ban
Hungary	No
Italy	No
Lithuania	Can be combined with other countermeasures planned in case of emergency
Luxembourg	Sheltering and food ban
Netherlands	Sheltering and food ban
Norway	Not systematically but in most cases, sheltering and food bans will be recommended also
Poland	Sheltering and food ban but it is not automatic
Romania	No KI if successful evacuation
Slovakia	Depending on the dose rate
Slovenia	Sheltering
Spain	Sheltering and food and water ban
Sweden	Sheltering out to 15 km and prompt preventive evacuation out to 3 km. Food bans.
Switzerland	Sheltering and food ban
Turkey	Sheltering and food ban
United Kingdom	Iodine prophylaxis is generally combined with sheltering, since the two together offer greater degree of protection. Food bans are introduced separately but there is a link; if food bans cannot be implemented, averted doses for iodine blockade should include ingestion.

Because of the very specific protection offered by iodine prophylaxis, it is used in several countries in conjunction with other countermeasures to contribute to a broad spectrum of protection against all pathways and sources of exposure. Hence, current advice is that if iodine prophylaxis is appropriate, sheltering is also advised. Food bans are generally announced as well as complementary actions. Possible coupling with evacuation was not really mentioned in the answers to the questionnaire but it is envisaged in different countries, for example in the United Kingdom and France. Iodine prophylaxis may be recommended when population is evacuated during radioactive release.

3.5. Emergency planning areas

3.5.1. Pre-distribution

Currently, stable iodine is pre-distributed around NPPs in 14 countries. All countries having nuclear power plants in their territories are pre-distributing stable iodine. The area for pre-distribution varies from 5 km radius around the NPP to 50 km for the Ignalina NPP in Lithuania. In most cases, stable iodine is delivered to the whole population. Pre-distribution may be of the responsibility of NPP operators or of local authorities.

Table XVI shows the situation in the 14 countries pre-distributing iodine.

Table XVI. Iodine pre-distribution practices

	Area for predistribution	Target population within predistribution area	Method of distribution
Belgium	**20 km**	All	Withdrawal in pharmacies
Czech Republic	Dukovany NPP: **13 km** - Temelin NPP: **20 km** (EPZ)	All	NPPs are responsible - organisation with the help of local authorities
Finland	**5 km** (households and summer houses) - kindergartens and schools keep tablets in the whole country.	All	By mail
France	**10 km** around NPP; 2,5 km around facility producing radioactive iodine for medical use	All	Withdrawal in pharmacies and if not done, send by mail
Germany	Up to **5 km**, pre-distribution to all households is recommended, from 5 to 10 km either a pre-distribution or stores at several points in the municipality (e.g. town hall, schools, hospitals, businesses) and for distances from 10 to 25 km storing in the municipality is recommended. The implementation of distribution is in the responsibility of the State authorities.	All	The implementation of distribution is in the responsibility of the State authorities.
Lithuania	**50 km**	All	By municipalities

	Area for predistribution	Target population within predistribution area	Method of distribution
Luxembourg	In the whole territory	Parents for those children under 5 years of age	Parents receive individual packet containing KI upon the birth of their children + distribution to parents whose children are under 5 years
Netherlands	**Between 10 and 20 km** (predistribution planned for the beginning of 2010)	Target people only: under 46 years	Coordination by pharmacies after mail-information. Local authorities are responsible for execution.
Romania	**Between 10 and 30 km**		Free predistribution to each family
Slovakia	**25 km** around Bohunice NPP and **20 km** around Mochovce NPP	All	Taken at determined point
Sweden	**15 km**	All	By mail
Switzerland	**20 km** (households, schools and working places)	All	By mail
United Kingdom	Around NPP - area defined by the operator	Remote communities / schools / potential rest centres	Initially by Health Protection Agency Nurse, then by mail - tablets are free

Areas around NPPs provided with pre-distributed iodine vary from one country to another and, sometimes, depend on the NPP. Iodine is generally pre-distributed to all the population, except in the Netherlands where people over 45 years do not receive iodine tablets.

Method of distribution is also specific to the country, and sometimes to the region when local authorities are responsible for the distribution or even to the NPP when the operator is performing the distribution.

3.5.2. Stockpiling

Table XVII. Iodine stockpiles

	Local stockpiles	Regional stock-piles	National Stock Piles	Geographical coverage	Time needed for distribution
Belgium	Yes (pharmacies)	Yes (civil protection units)	Yes	Whole country	From few hours up to 1 day
Bulgaria					
Czech Republic	Yes (NPP and small stockpile prepared in the Central Hospital Pharmacy in the vicinity of the NPP)	No	No	Coverage of about 10% of all needed KI for both Emergency Planning Zones around Temelin and Dukovany NPP	

	Local stockpiles	Regional stock-piles	National Stock Piles	Geographical coverage	Time needed for distribution
Denmark	No (emergency workers have stocks)	No	No		
Finland	Decentralized stockpiles : buildings, work places, pharmacies, health care centres, public shelters… (within 20 km around NPPs, people are well aware of the importance of iodine tablets and virtually every households keeps tablets, and employers keep tablets for their personnel.				
France	Yes (pharmacies, schools…)			Whole country	Depends on the moment of the accident
Germany	No	No	Yes - 8 central stocks in Germany	Whole country, for children/adolescents (up to the age of 18 years) and pregnant women	Depends on the state
Hungary	At NPP and settlements, based at organisations on 24h duty	Yes	Yes	30 km radius for local stockpiles	Max. 2 hours for distribution within the planning zone (30 km)
Italy	Yes (North-western and North-eastern regions)	No	No	Area likely to be exposed to a equivalent thyroid dose exceeding 10 mSv (neonates and children)	Six hours from the beginning of exposure
Lithuania	No	No	Yes		
Luxembourg	Every school + iodine made available in the emergency planning zone	Civil protection centers			
Nether-lands		Yes	Yes	Whole country	Approx. 4 hours to move from national to regional stockpiles
Norway	Yes		Yes	Northern Norway and around research reactors	2 to 6 hours
Poland	No	No	Yes	Whole country	24 hours

	Local stockpiles	Regional stock-piles	National Stock Piles	Geographical coverage	Time needed for distribution
Romania	Yes (sanitary units from the territory)	No	No	Only for Cernavoda and Kozlodui NPPs	Immediate
Slovakia	County offices and pharmacies	No	No	-	
Slovenia	Yes (pharmacies and commune warehouses) - withdrawal in pharmacies + by local civil protection teams (fire brigades)		Yes	10 km around Krško NPP for local stockpiles - whole country	Few hours
Spain	Yes			10 km radius	About 3 hours
Sweden	Yes - at the plant	Yes, within 100 km from the plant	Yes, within 150 km from the plant		Very short for local stockpiles, about 12 hours for regional ones and maximum 24 hours for national ones.
Switzer-land	Yes (up to 20 km): purchase from pharmacies, only for those who would not find their tablets when needed in an emergency situation	Yes	Yes	whole country	Within 12 hours
Turkey	Will be set up in the future, in the eastern part of Turkey near to the Armenian NPP Medsamor.	No	No		Within 2 to 4 hours when local stockpiles exist
United Kingdom	Yes	No	Yes		

It can be seen from Table XVII that practices in terms of stockpiling are quite specific to each country. Some countries have decided to cover the whole territory as others have limited the coverage to the area around NPPs (up to 30 km). The time needed for distribution varies also. Several countries have encountered difficulties concerning this time. The Netherlands envisages pre-distribution and the constitution of local stockpiles to solve these problems. In the past, Finland also encountered distribution problems. The adopted solution was to decentralize national stockpiles and to entrust distribution responsibilities to the local level ("*Tablets should be available where people spend their time.*"). In Poland the same solution has been implemented: national stockpiles are disseminated to all 16 provinces. The distribution system was implemented by province crisis management services in cooperation with local authorities, one distribution point being designed for not more 5,000 inhabitants, in well-known places (e.g. schools, public health entities, local authority entities, hospitals, churches). The distribution points are provided with stable iodine tablets by services managed by the regional governor.

Sweden as well mentioned practical problems with the distribution from the national stockpiles: it is not certain that the iodine could be distributed within 12 hours. A working group will be created to solve this problem.

Deficiencies have been identified in national distribution policy in Slovenia but no details were given except that these deficiencies have not yet been solved.

Romania indicates that a great part of the tablets pre-distributed directly to the population is lost, some of them having been used as ordinary medicine. Storage at the local sanitary units seems to be a better solution.

On the other hand, new inhabitants in target zones are not reached by periodical pre-distribution campaigns. It is the case in particular for tourist and exhibition areas.

In France, time needed to distribute iodine from national and regional stockpiles is too long. Difficulties are as well encountered in stockpile management, which does not guarantee conditions for good preserving of the pills.

In Czech Republic, stable iodine tablets are not available for the public outside emergency planning zones (even in pharmacies). The procedure of distribution is difficult because the NPP must distribute medicaments and has to fulfil special conditions. In Denmark as well, iodine could be obtained only if prescribed.

Croatia plans to have local, regional and national stockpiles in the future.

As a conclusion, it can be said that both solutions (pre-distribution and stockpiling) present inconveniencies. Concerning pre-distribution, the main problem is that tablets are lost and that new inhabitants are not reached by periodical distribution. Therefore, even if iodine shelf live is almost 10 to 15 years, organization of periodical distribution campaigns is needed (for instance every 5 years).

For tourist areas, many non-permanent residents may be in the area during the accident, depending on the period of the year. Interest to have stockpiles in camping areas or tourist sites located close to a NPP should be examined.

Stockpiling in schools and pharmacies, even when iodine is pre-distributed, seems to be a good practice. This is done in most countries. Stockpiles raise the problem of storing the pills in good conditions and of distributing them during the accident in a short time.

In Hungary, the distribution system is quite effective, as a maximum of 2 hours is needed for distributing iodine within the 30 km zone. This is made possible by delegating the distribution to organizations on 24h duty. But these organizations may be involved in other tasks of emergency management; their capability may not be sufficient in all countries. It can be noted as a good practice to be examined by countries having difficulties with distribution time in case of accident. In Poland as well, time for distribution is quite short. ***Dissemination of national stockpiles in regions or provinces, which are in charge to organize the distribution in case of an accident, should be considered as a good practice.***

It could be also recommended to provide schools and hospitals, at least those located in the vicinity of a NPP, with stockpiles. Then, if the accident occurs during school hours, it can be decided to distribute as preventive measure iodine pills before returning home. In severe cases, an intake at the school may be necessary but this is not permitted in several countries due to the status of iodine pills as pharmaceutical product.

Good practice: Pre-distributing iodine around NPP is a good solution to reduce the time of intake when the release occurs shortly after the alert. Complementary measures should nevertheless be envisaged for tourism or exhibition areas. Local stockpiles should be set up in schools, hospitals, offices, etc.

Concerning stockpiles, the delegation of the distribution to organizations on 24-h duty may limit the time needed for distribution in case of an accident. Moreover,

dissemination of national stockpiles in regional or local levels, which are, then in charge to organize the distribution in case of accident is also a good practice.

3.6. Public awareness and communication issues

Table XVIII. Communication arrangements

Country	Communication arrangements
Belgium	General public: General information – national campaign (to be repeated every fifth year) More specific information within the 20 km zone with press conferences, information sessions in municipalities (TV spots and folders) Specific info: Medical doctors, pharmacists Governors of concerned provinces, mayors, emergency services School, rest houses for seniors, … Specific information sessions, specific brochures, specific web page
Czech Republic	General public: Information leaflets, "user-friendly" brochures, lectures – no national campaign, local campaign organized by the NPP every 5 years with supporting brochures and information done by village mayors Specific info: Actions organized in the Epps during KI distribution and also the opportunities of the school visits at NPP information centers are used for informing medical doctors and school teachers
Denmark	No national campaign
Finland	General public: Leaflets issued by different organizations (licensees, municipalities) + instructions in all telephone directories on use of stable iodine in case of accident National information campaign irregular, about at 5-year interval 3-year interval for local campaigns – leaflets distributed by NPP to all households within emergency planning zone (municipalities about 20 km). Specific info: General information may be sent to health care centers, schools and kindergartens, e.g. before major exercises
France	General public: Local media, Leaflets sent by post Specific info: Pharmacists, physicians and other professionals of the health sector (by the Ministry of Health) Fire brigades (general information) Local communities ("CLI") and mayor Press conferences
Germany	General public: Leaflets sent by post in the zone of 10 km around the installation (updated every 5 years).
Hungary	General public: Local campaign once per year, no specific information towards medical doctors, school teachers
Italy	Recently updated version of national plan under approval will be followed by operative agreements with the local authorities for public information, distribution of tablets during emergency
Lithuania	General public: National information campaign performed annually Specific info: Medical doctors, school teachers: theoretical and practical training, brochures, web pages
Luxembourg	General public: Brochure distributed in all households (no great interest of the public until an accident happens)

Country	Communication arrangements
The Netherlands	General public: No national campaign but population around NPP sites is informed by local authorities. New inhabitants in relevant areas (emergency zones) are informed by the local authorities. Specific info: Pharmacists as pharmacies are or will be involved in stocking/local distribution
Norway	No national nor local information campaign
Poland	General public: No national campaign Specific info: Arranged package of lectures and workshops for emergency medical service department
Romania	General public: Information sheets distributed to each family – national campaign during emergency exercises – local campaigns (frequency varies from one to 4 years) Specific info: Information to medical doctors: training courses on medical response in case of nuclear emergencies
Slovakia	General public: Handbooks, folders, guidance, training, education of public in EPZ Specific info: Regular visits of scholars, together with school teachers in NPPs info centres
Slovenia	Objective is to have national campaign of information – frequency is not yet defined Local campaign with a frequency of 6 to 8 years (3 in the future). Delivery of brochures, maps, posters and radiobroadcasts
Spain	General public: Local information campaign every 2 years Specific info: Periodic training and general information brochures distributed to medical doctors and school teachers
Sweden	National information campaign every 5 years No specific information to medical doctors or school teachers
Switzerland	General public: Information sheet with general information distributed together with the tablets in 2004 (national campaign of information during pre-distribution). Information by media during distribution. Specific info: Pharmacists, medical doctors heads of schools, enterprises All information is published at www.kaliumiodid.ch
Turkey	General public: Public information leaflets every 2 years around site + national campaign information / brochures and public information seminars are organized in routine basis Specific info: In case of emergency: national and local TV/radio broadcasting stations will make special announcements + warning system to give information to the public
United Kingdom	General public: Public information leaflets distributed every two years around sites. Web site carries download of leaflet. Specific info: Occasional briefings of schoolteachers are held.

***Good practices*: Organization of emergency exercises, especially the ones involving population, and of distribution campaign give a good opportunity to inform the population about the possible causes and effects of an accident that may occur in a NPP, about the various alarm signals and siren types, the prescribed protective actions and the appropriate behaviour to be adopted in case of an alarm followed by the implementation of the national rescue plan. It is also recommended to supply specific information to physicians, pharmacists and schoolteachers.**

3.7. European harmonization

The last question of the questionnaire was the following: If a harmonized European approach is proposed, would you be ready to reconsider existing national practices?

Almost all countries answered positively. Some countries like France, Luxembourg and Switzerland have just converged to different arrangements related to iodine prophylaxis; it will be difficult for them to submit a new proposal to their government in the short term but nevertheless, they have answered positively to the question.

In Finland, as the country is virtually covered by stable iodine, implementation in any affected region would be cheap, easy and effective. It would therefore be difficult to change the intervention level of children upwards as a result of international pressure. Intervention level for adults may be reconsidered.

The Netherlands agrees on the principle but mentioned that it could be difficult, because they are modifying intervention levels to harmonize as much as possible with Belgium and Germany. Still there are some differences among other things (e.g. calculation models, dose rates, tablets etc) and differences in food situations (e.g. iodine in salt/bread…). Moreover, they are currently in the process of pre-distributing around Borssele NPP and in its bordering areas. But of course, they estimate that a harmonized European approach including harmonized decision-making would make communication a lot easier.

In Sweden, the nuclear and radiation protection authority estimates that a European approach needs to consider the two different situations, preplanning and response. In particular, Sweden will not accept one single intervention level. The emergency reference level considered for planning purposes is about 100 mGy against 1 to 10 mGy for the use of iodine that is predistributed in an emergency situation.

4. ARRANGEMENTS OUTSIDE EUROPE

As a complement to the overview of European national practices, IRSN studied relevant practices in the USA, Russia and Japan in order to provide comparison with European arrangements. A comparison with international organizations' recommendations (ICRP, IAEA, WHO) and the UNSCEAR [UNSCEAR, 2000] is as well provided.

4.1. International organizations' recommendations

Different recommendations or evaluations exist at the international level. Mainly the ICRP, IAEA, UNSCEAR and WHO make them. That is, in a chronological order:

- ICRP: **500 mSv** thyroid equivalent dose (which corresponds to a level almost always justified which can be lowered but not by more than a factor of 10, that is **50 mSv**) – [ICRP, 1991];
- IAEA: **100 mGy** absorbed dose by thyroid, which is a generic optimized value (according to the particular situations, higher or lower intervention level may be retained) – [IAEA, 1996];
- WHO: in 1989, the WHO Regional Office for Europe issued "*Guidelines for iodine prophylaxis following nuclear accidents*" at the request of two Member States. Workshops were held to discuss the various issues of iodine prophylaxis. In 1991, there were indications of a significant increase in thyroid cancers in the population of children in the areas surrounding the Chernobyl NPP. The World Health Organization (WHO) convened a technical group to advise it on the need to revise its guidelines on iodine prophylaxis.

  WHO published the result of this re-evaluation in 1999. These guidelines evaluated the apparent heightened sensitivity of children and adolescents to radioactive iodine uptake. As a result of the increase in children's thyroid cancers in the areas surrounding the Chernobyl reactor, the WHO recommended KI prophylaxis at lower intervention levels, as low as **10 mGy** for the population at risk (young children, pregnant or nursing women). The WHO states, "*The sensitivity of the child's thyroid to the carcinogenic effects of radiation represents a significant public health risk in the event of exposure to radioactive iodine. With effective planning and the use of stable iodine prophylaxis, in association with other preventive measures, this risk is to large degree avoidable*" - [WHO, 1999].
- UNSCEAR: the UNSCEAR 2000 report is consistent with and fully supportive of the WHO report; it says that several studies on the late health effects of the Chernobyl accident were carried out in Europe and have been critically reviewed and summarized. No increase in thyroid cancer among children was observed. In addition, this report underlines that the papers available for review by the committee to date regarding the evaluation of health effects of the Chernobyl accident have in many instances suffered from methodological weaknesses that make them difficult to interpret – [UNSCEAR, 2000];
- IAEA/WHO: as a result of the publication of the WHO guidance, the IAEA met to review the guidance in Safety Series 109 and 115. In 2001, the IAEA recommended that the requirements be amended to reflect the following [IAEA, 2001]:

  "*The administration of stable iodine to the public is an early effective measure for the protection of the thyroid to prevent deterministic and to minimize stochastic effects at any age. However, it is primarily intended for the protection of children, including unborn.*

  The current GIL (generic intervention level) of 100 mGy provides an operational basis for rapid decision and an efficient application in case of a nuclear emergency.

However, as there are strong indications of an age-dependency of the risk induced by radioactive iodine, to recognize the higher radioactive iodine sensitivity of children and the unborn, the administration of stable iodine may be recommended at significantly lower levels of avertable dose.

This framework is intended to be used as a starting point for planning and to be optimized to take into account specific practical, operational, social and economic considerations and it must also consider the introduction of other protective actions such as sheltering and food control as measures to reduce the uptake of radioactive iodine."

- WHO: confirm uncertainties, which exist on the estimates of received doses and on the relation between received doses and thyroid cancer for low dose levels [WHO, 2006].

Intervention levels adopted in European countries have been based mainly on the publications of these international organizations.

The WHO is expected to publish new recommendations in 2010. Some countries, like the United Kingdom for instance, are waiting for this publication to change existing arrangements, in particular their emergency reference level.

4.2. Iodine prophylaxis arrangements in Japan, Russia and United States

The objective in studying existing arrangements Japan, Russia and United States was to identify if there were main differences with European practices and good practices. In fact, there is no major difference. An overview of practices in Japan and United States is given below.

4.2.1. Japan

Japanese representative has kindly accepted to answer the questionnaire. Given information is provided below:

- Iodine tablet active compound: KI;
- Equivalent mass of iodine per tablet: 50 mg;
- Iodine tablets are considered as a pharmaceutical product;
- Validity is 36 months;
- Dosage is as follows:
  - Neonates (< 1 month): 12.5 mg
  - Children aged 1 month – 3 years: 25 mg
  - Children aged 3-12 years: 38 mg
  - Children aged 12-18 years: 76 mg
  - Adults (< 40): 76 mg
  - Elderly: 0 mg
- It is not intended to recommend a KI second intake; evacuation is preferred.

It should be pointed out that there is a paediatric formulation for children less than 7 years in age (KI solution in syrup).

There is no pre-distribution of iodine tablets around nuclear sites. In case of emergency, the area where iodine should be administered is assessed according to dose estimation. There are some stockpiles at the local level, the local headquarters being in charge of decision-making.

The intervention level for iodine prophylaxis during the early phase of a nuclear and radiological emergency is **100 mSv as equivalent projected dose to thyroid**. During the emergency, dose calculation is performed for the child and iodine intake is recommended to all the population. Effectiveness of protective actions is not considered in the assessment. Stable iodine intake recommendation is not automatically combined with other countermeasures. In general, evacuation is also considered but not automatically combined.

Regarding communication arrangements, there are some local campaigns once a year, which belong to the local government. A brochure is delivered as the advertisement of the campaign. There is no specific information delivered to medical doctors or schoolteachers.

Iodine prophylaxis arrangements set up in Japan are totally consistent with practices in Europe.

4.2.2. Russia

Iodine arrangements are now under revision in Russia, with an aim of harmonizing practices in the different states. Some proposals have been elaborated but the decision has not yet been taken. Therefore, it is not possible to present Russian practices in terms of iodine prophylaxis in this report. A special attention should be paid to these new arrangements when communicated since several European countries are neighbouring Russia.

4.2.3. United States

In United States as well, there is an on-going project to review existing arrangements with the aim to harmonize the practices amongst American states. In 2001, the US NRC modified its emergency planning regulations to include consideration of KI as a protective measure for the general public that would supplement evacuation and sheltering. It is clearly pointed out that use of KI is intended to supplement, not replace, other protective measures, such as evacuation or sheltering, which the NRC continues to view as the most effective measures in the event of a radiological emergency. The NRC has chosen to leave the decision on prophylactic use of KI to states and local emergency response planners, who may find that KI should be a supplementary protective measure, rather than to mandate its use. Consequently, some states have decided not to include KI arrangements in their response plan.

In 2002 the US Congress passed legislation meant to increase the availability of KI to cover a 32-km (20-mile) radius around nuclear reactors; in 2004 the US National Academy of Sciences endorsed the distribution of KI. A 32 km KI distribution program has not yet been instituted, and in 2007 responsibility for it was reassigned to the President's scientific advisory office. Well-known scientists declaring no competing interests consider that this delay of over 5 years may reflect "*concern that an expanded KI distribution program would increase public resistance to increasing nuclear power generation capacity*" [Robbins, 2008].

Information given below is based on the guidance published by the Food and Drug Administration (FDA) in 2001 [US-HHS, 2001] and the fact sheet on potassium iodide edited by the Centers for Disease Control and Prevention (CDC) [US-HHS, 2006]. The adoption and implementation for these recommendations are at the discretion of the states and local

governments responsible for developing regional emergency response plans related to radiation emergencies.

Intervention level as predicted dose to the thyroid is **5,000 mGy for adults over 40 years, 100 mGy for adults over 18 through 40 years** and **50 mGy for pregnant and breastfeeding women, children, infants (including breast-fed infants) and neonates**.

Regarding the adults older than 40 years, the CDC clearly states that they should not take KI unless public health or emergency management officials say that contamination with a very large dose of radioactive iodine is expected (predicted thyroid exposure >5,000 mGy), recognizing that adults older than 40 years have the lowest chance of developing thyroid cancer or thyroid injury after contamination with radioactive iodine, although they also have a greater chance of having allergic reactions to KI [US-HHS, 2006]. This recommendation aims at preventing hypothyroidism in this part of the population [US-HHS, 2001].

The FDA has approved two different forms of KI-tablets and a liquid that people can take orally. Tablets come in two strengths, 130 mg and 65 mg. Each millilitre (mL) of the oral liquid solution contains 65 mg of KI. Table XIX describes the treatment recommendations. The CDC recommends not taking KI for people who are allergic to iodine and/or have certain skin disorders (such as dermatitis herpetiformis or uricaria vasculatis). People suffering from thyroid disease may be treated with KI under careful supervision of a medical doctor [US-HHS, 2006].

The protective effects of KI are considered to last approximately 24 hours. For optimal use, FDA recommends that KI be dosed daily, until a risk of significant exposure to radioiodine by either inhalation or ingestion no longer exists. However, the CDC recommends avoiding repeat dosing with KI for pregnant and breastfeeding women and newborn infants. Those individuals may need to be evacuated until levels of radioactive iodine in the environment fall [US-HHS, 2006].

Table XIX. US-HHS Recommended doses of KI for different risk groups

	KI dose (mg)	Number of 130 mg tablets of KI	Number of 65 mg tablets of KI	Number of mL of solution of KI	Equivalent mass of iodine (mg)
Adults over 40 yrs	**For adults over 40 years, the information indicated below is to be considered only if the predicted thyroid exposure is >5,000 mGy**				
	130	1	2	2	**100**
Adults over 18 through 40 yrs	130	1	2	2	**100**
Pregnant or lactating women*	130	1	2	2	**100**
Adolescents over 12 through 18 yrs*	65	½	1	1	**50**
Children over 3 through 12 yrs	65	½	1	1	**50**
Infants 1 month through 3 yrs	32	¼	½	½	**25**

	KI dose (mg)	Number of 130 mg tablets of KI	Number of 65 mg tablets of KI	Number of mL of solution of KI	Equivalent mass of iodine (mg)
Newborns from birth through 1 month**	16	⅛	¼	¼	**12.5**

**Pregnant and breastfeeding women should take only one dose of KI. CDC recommends that women internally contaminated with (or are likely to be contaminated with) radioactive iodine stop breastfeeding and feed their child baby formula of other food if it is available. If breast milk is the only food available for an infant, nursing should continue.*

***Adolescents approaching adult size (>70 kg) should receive the full adult dose (130 mg of KI).*

****The dose is both for nursing and non-nursing newborn infants.*

Table XX shows the differences between the WHO recommendations and the FDA recommendations, since the FDA recommendations differ from the WHO 1999 guidelines in two ways [WHO, 1999], [US-HHS, 2001]:

- Dosage for adolescents over 12 years: WHO recommends a 130-mg dose of KI for adolescents over 12 years, while the FDA recommends a 65-mg dose as standard for all school-age children while allowing for the adult dose (130 mg of KI) in adolescents approaching adult size;
- Threshold for predicted exposure of those up to 18 years of age and of pregnant or lactating women that should trigger stable iodine prophylaxis: WHO recommends a reference level for consideration in planning stable iodine prophylaxis of 10 mGy avertable dose to the thyroid for neonates, infants, children, adolescents to 18 years and pregnant and lactating women; in contrast, FDA recommends a threshold thyroid radioactive exposure of 50 mGy (predicted thyroid exposure) for neonates, infants, children, adolescents to 18 years and pregnant and lactating women. Thus, FDA has concluded from the Chernobyl data that the most reliable evidence supports a marked increase in risk of thyroid cancer in children with exposures of 50 mGy or greater, recognizing that a few cases of thyroid cancer occurred in children exposed to estimated doses below 10 mGy.

Table XX. Comparison between WHO and FDA recommendations for iodine prophylaxis

	Reference level: Avertable dose to the thyroid (mGy)		Mass of KI (mg)		Mass of iodine (mg)	
	WHO	**FDA**	**WHO**	**FDA**	**WHO**	**FDA***
Adults over 40 yrs	5,000	5,000	130	130	100	100
Adults over 18 through 40 yrs	100	100	130	130	100	100
Pregnant or lactating women*	10	50	130	130	100	100
Adolescents over 12 through 18 yrs	10	50	130	65	100	50

	Reference level: Avertable dose to the thyroid (mGy)		Mass of KI (mg)		Mass of iodine (mg)	
	WHO	**FDA**	**WHO**	**FDA**	**WHO**	**FDA***
Children over 3 through 12 yrs	10	50	65	65	50	50
Infants 1 month through 3 yrs	10	50	32	32	25	25
Newborns from birth through 1 month**	10	50	16	16	12.5	12.5

**It should be noted that the U.S. Department of Health and Human Services do not make any reference to numbers expressing a mass of stable iodine. In its 2 documents cited in this section ([US-HHS, 2001] and [US-HHS], 2006]), the U.S. Department of Health and Human Services refers to quantities of potassium iodide (KI) only. To make possible the comparison of data from WHO and FDA, the figures mentioned in this column have been calculated.*

For optimal protection against inhaled radioiodine, KI should be administered before or immediately coincident with passage of the radioactive cloud, though KI may still have a substantial protective effect even if taken 3 to 4 hours after exposure.

Prevention of thyroid uptake of ingested radioiodine, once the plume has passed and radiation protection measures are in place, is best accomplished by food control measures and not by repeated administration of KI.

As time is a crucial parameter for an optimal prophylaxis with KI, timely administration to the public is a critical consideration in planning the emergency response to a radiation accident and requires a ready supply of KI. Therefore, countries choosing to incorporate KI into their emergency response plans may consider the option of pre-distribution of KI to those individuals who do not have a medical condition precluding its use.

Regarding communication aspects, a study conveyed in different states shows that, *"KI pill distribution requires a significant education and outreach component for it to be effective"* [FEMA, 2007]. The pre-distribution cannot be effective if it's not accompanied by a comprehensible communication campaign.

5. EUROPEAN HARMONIZATION APPROACH

On the basis of the elements presented above, an outline for a European approach on stable iodine intake in the event of a nuclear reactor accident is proposed in this chapter. The proposal is based on the survey of medical studies performed on KI and common practices identified in European countries and outside Europe.

5.1. Emergency preparedness / Emergency response

- The priority for emergency planning for stable iodine prophylaxis should be the protection of newborn babies (neonates), children and adolescents aged less than 18 years, and pregnant and nursing women, as they are more radiosensitive.
- Stable iodine prophylaxis should be planned for protection against inhaled radioiodine only. Protection against ingestion of radioiodine in food is better achieved using food restrictions. Therefore, equivalent thyroid dose assessment should consider only exposure due to inhalation. Nevertheless, iodine prophylaxis may be used as a temporary measure to provide protection for young children against the ingestion exposure pathway, until food restrictions can be imposed. Then, the sum of the expected doses from inhalation and ingestion should be considered when taking the decision of KI prophylaxis.
- IRSN estimates that it is not necessary to have a system of age-related ERLs, provided that the ERL is appropriate for children under 18 and that the relevant planning should emphasize the priority of administration to these age groups. It clearly facilitates the communication to the population and thus contributes to the effectiveness of the countermeasure implementation in case of emergency.
- The recommended value of ERLs, for planning purposes, is about **50 mSv** as thyroid equivalent dose, for the most sensitive population, on the duration of the release or 7 days.
- Flexibility should be observed in decision-making during an emergency. There is no specific recommendation of ERL for emergency management. The decision should be, as far as possible, based on a lower value than the ERL fixed for planning purposes, taking into account that iodine prophylaxis is a low risk countermeasure with the potential for large benefits.
- For optimal protection against inhaled radioiodine, KI should be administered before (6 hours maximum) or just after the exposure, though KI may still have a substantial protective effect even if taken 3 or 4 hours after exposure. Emergency plans should then provide for the stable iodine tables to be administered promptly.
- Because of the very specific protection offered by iodine prophylaxis, it should be used in conjunction with other countermeasures to contribute to a broad spectrum of protection against all pathways and sources of exposure. Hence, if iodine prophylaxis is appropriate, sheltering and food ban is also advised. Iodine intake may be envisaged as well during an evacuation, when it is performed after releases have started.
- Emergency plans should adopt tablet distribution strategies, potentially including pre-distribution, which will offer the greatest likelihood that those at the highest risk will be protected within this period. Distribution by organizations on 24h duty may be envisaged if these organizations are not involved in other tasks of emergency management.
- As time is a crucial parameter to be considered for an optimal prophylaxis with KI, timely administration to the public is a critical consideration in planning the emergency response to a radiation accident and requires an available supply of KI. The option of predistribution

of KI to the population located in the vicinity of a nuclear power plant (in a radius of 5 to 30 km) should be considered by authorities, as feedback experience in several countries has shown that door-to-door distribution during an emergency is too slow. As a complement, taking into account the high sensitivity of children regarding iodine, it is then recommended to have stable iodine stockpiles in all hospitals with maternity units, kindergartens and schools in an area of 100 km from nuclear power plants. Stocks of iodine crystals or 5% iodine tincture may be used for the preparation of accurate dosages of stable iodine for neonates in the first few days of life.

- Decision-making on iodine prophylaxis should be made preferentially on the basis of projected dose assessment, without taking into account countermeasures protective effects. The use of averted dose does not seem relevant as it is directly linked with the time of intake, which is unknown.

5.2. Formulation and dosage

- For harmonization purposes, it is suggested to use preferentially potassium iodide (KI), even if there are no serious medical (excepting the fact that KIO_3 seems to be a stronger intestinal irritant) or practical reasons for choosing between potassium iodide and potassium iodate (it should be noted that FDA does not approve KIO_3 for use in the United States so far). Thus, it is recommended to adopt the 65-mg KI tablets formulation (i.e. 50 mg iodine per pill) in Europe. This formulation will limit the risk of over dosage, because tablets are quarterly-divisible.
- The recommended age-related dosages of iodine, for a first intake, is as follows:
    - Neonates (< 1 month): 12.5 mg
    - Children aged 1 month – 3 years: 25 mg
    - Children aged 3-12 years: 50 mg
    - Children > 12 years and adults: 100 mg
    - Taking into account the low risk of adverse effects even for elderly population, it is not proposed to have a specific recommendation for adults older than 40 or 45 years. However, both physicians and pharmacists located in the emergency planning zones should be strongly encouraged to perform a preventive screening aiming at detecting possible contraindications of the iodine intake among their patients, especially in iodine deficient areas (metabolic disturbances affecting the thyroid are more frequent with increasing age).
- Pregnant women should be given KI for their own protection and for that of the fetus, as iodine readily crosses the placenta. However, because of the risk of blocking fetal thyroid function with excess stable iodine, repeat dosing with KI of pregnant women should be avoided. Lactating females should be administered KI for their own protection, as for other young adults, and potentially to reduce the radioiodine content of the breast milk, but not as a mean to deliver KI to infants, who should get their KI directly. As for direct administration of KI, stable iodine as a component of breast milk may also pose a risk of hypothyroidism in nursing neonates. Therefore, repeat dosing with KI should be avoided in the lactating mother, except during continuing severe contamination. If repeat dosing of the mother is necessary, the nursing neonate should be monitored.
- A second intake may be envisaged after 24 hours, and repeated on a few days' intervals in case of long-lasting releases or when radioactive iodine exposure may occur later than initially predicted. It could be envisaged also as an (emergency) interim measure, in the event that the planned prompt implementation of adequate food restrictions was not

possible. When successive iodine uptakes are judged necessary, it is advised to limit the dose of iodine to 1 g.

- The possibility to indicate a production date on iodine pills stored in stockpiles instead of an expiry date may limit significantly the costs of emergency preparedness regarding iodine. Concerning pre-distributed tablets, it is recommended to organize distribution campaigns periodically.

5.3. Information / Communication

- The provision of appropriate information and support for those receiving stable iodine prophylaxis should be considered as part of emergency planning. As recommended by [Common Report, 2007], as package inserts are not designed for the public but more or less for experts, it is suggested to develop general public information handouts or leaflets to supplement the package insert by general understandable information. The idea is to have an information handout with simple texts, diagrams or illustrations and an attractive presentation. This could be handed out together with the tablet box (possibly inside), so that it can be read just before the ingestion of the tablet. It may be harmonized for the different countries leaving the choice of the language(s) to the country. There should also be space for national or regional particularities.
- Harmonized answers for frequently asked questions might be prepared as well and shared by European countries.
- The provision of appropriate information and support for those not receiving stable iodine prophylaxis should be as well considered as a part of emergency planning.

5.4. Decision-making during an emergency situation

- Countries are highly encouraged to establish conventions with their neighbouring countries to define communication channels for alerting and exchanging information in case of emergency. In particular, it is necessary to identify entities having a similar role (decision-making, technical assessment, implementation…) and to define the content of the information to be exchanged. This aims to contribute to the coherence of the countermeasures set up in the different countries in the vicinity of a border in case of accident. Such conventions should be regularly tested (about one exercise per year).
- Adopting a similar emergency reference level in European countries does not guarantee the coherence of countermeasures implemented in case of an accident. The following proposal, adopted by Belgium, Luxembourg, France, Germany and Switzerland may be submitted to European countries and discussed in the frame of the above-mentioned conventions: it is proposed that the decision on iodine prophylaxis be taken on the basis of the predicted dose assessment made by the country where the accident takes place. This requires that neighbouring counties have a good understanding of the decision-making process beforehand and are aware of the main hypotheses used for the calculation. This proposal aims at having a rapid decision and avoiding differences due to calculation codes as far as possible.

APPENDIX: QUESTIONNAIRE ON IODINE PROPHYLAXIS NATIONAL PRACTICES IN EUROPE

1. Galenic form and posology

1.1. What is the iodine tablet active compound?

☐ KI

☐ KIO_3

☐ Other (please specify):

1.2. What is the equivalent mass of iodine (mg) per tablet (please fill in the box where applicable)?

KI:		mg
KIO3:		mg
Other (please specify:	):	mg

1.3. What is (are) the pack size(s)?

☐ Box of tablets of mg (equivalent mass of iodine per tablet)

☐ Bottle of tablets of mg (equivalent mass of iodine per tablet)

1.4. Do you use a paediatric formulation for children?

If yes, please specify:

1.5. Are iodine tablets considered a pharmaceutical product in your country?

1.6. What is the expiration date (please fill in the box where applicable)?

KI:		months
KIO3:		months
Other (please specify:	):	months

1.7. Is there an age limit above which you do not prescribe iodine prophylaxis?

1.8. What are the recommended age-related dosages (equivalent mass of iodine)?

Neonates (birth – under 1 month):	mg
Children aged 1 month – under 3 years:	mg
Children aged 3 – 12 years:	mg
Children aged 12 – 18 years:	mg

Adults:	mg
Pregnant women:	mg
Breastfeeding women:	mg
Elderly:	mg

1.9. Do you intend to recommend a second intake in case of radioactive iodine release?

☐ Yes ☐ No

Are there some specific conditions? (Minimum time between intakes, posology of the second intake, target population…).

Please specify:

1.10. Do you have country specificities regarding iodine prophylaxis (for instance, chronic iodine deficiency in the population)?

Please specify:

2. Set up – emergency planning

2.1. Could you please describe the national distribution policy?

2.2. Are iodine tablets pre-distributed around nuclear site?

☐ Yes ☐ No

What is the corresponding planning zone?

2.3. Are iodine tablets pre-distributed to everyone or only to target population(s)?

What is the target population(s) (if applicable)?

2.4. How is the pre-distribution organized?

☐ by mail ☐ by withdrawal in pharmacies ☐ door to door selling

☐ others (please specify):

2.5. How the perimeter has been defined (on the basis of accident dose assessment or others? What kind of dose? Time of exposure? Population considered? – please specify)?

2.6. Are there currently national/regional iodine stockpiles for nuclear event in your country?

- ☐ Yes
  - ☐ National stockpile
  - ☐ Regional stockpile
  - ☐ Local stockpile
- ☐ No
- ☐ There will be in the future

2.7. What is the geographic coverage? What is the average time needed for distribution?

2.8. Did you identify deficiencies in your national distribution policy (practical problems met with the distribution, difficulties met with stockpiling)? What are the solutions found or envisaged to encounter the difficulties?

3. Intervention level

3.1. What is the intervention level for iodine prophylaxis during the early phase of a nuclear and radiological emergency? Please describe briefly the key decision-making elements that led to this intervention level.

3.2. Is it defined for the inhalation pathway only or also for ingestion?

- ☐ Inhalation
- ☐ Ingestion

3.3. Is there an emergency operational level used to decide on iodine intake (EOLs)?

☐ Yes ☐ No

If yes, please give the value(s) and explain how it has been determined.

3.4. Is the intervention level regarding iodine prophylaxis valid for the early phase of the accident only or also for the intermediate phase?

- ☐ Early phase
- ☐ Intermediate phase

3.5. Do you intend to review intervention level regarding iodine in the next future?

☐ Yes ☐ No

If yes, when do you foresee to review it?

4. Decision-making process during an emergency

4.1. How the area for iodine intake is defined in case of emergency?

Are there some pre-determined perimeters depending on emergency level (general emergency, site emergency…)?

☐ Yes ☐ No

What are the basic considerations for decision-making on iodine?

4.2. If the decision is taken on the basis of dose assessment, what kind of dose is calculated?

☐ Projected dose

☐ Averted dose

☐ Residual dose?

What is the population considered?

What is the duration taken into account?

Do you consider the effectiveness of protective actions in the assessment?

☐ Yes ☐ No

Is the ingestion pathway considered in the assessment?

☐ Yes ☐ No

Please explain the assessment methodology for thyroid dose:

4.3. Is the stable iodine intake recommendation automatically combined with other countermeasures recommendations (sheltering, food ban, other medical countermeasures distributed in the same time, e.g. Prussian Blue or DTPA)?

☐ Yes ☐ No

Please explain:

5. Time for intake and effectiveness

5.1. What is the adequate time for iodine intake considered in the decision-making process in your country? (Before release, how many hours before, at the beginning of release…)

5.2. For how long time do you consider stable iodine intake effective after the beginning of the exposure?

5.3. What is the maximum time considered for recommending iodine intake after the end of releases?

5.4. Did you observe unexpected side effects in people who absorbed already stable iodine?

☐ Yes ☐ No

If yes, please describe the nature of the observed side effects and provide information about people who exhibited its (children, breast-feeding women, pregnant women, elderly, etc.)

6. Public awareness and communication issues

6.1. Please describe communication arrangements during preparedness and response phases regarding iodine prophylaxis.

6.2. Is there some national campaign of information on iodine prophylaxis?

☐ Yes ☐ No

What is the frequency?

6.3. What is the frequency of local campaign of public information around NPP sites? Who is responsible for? What are the supports (brochures, radio…)?

6.4. Do you arrange specific action towards medical doctors, schoolteachers to increase public awareness on this issue?

☐ Yes ☐ No

If yes, please describe briefly:

6.5. Do you provide package insert giving pedagogic instruction concerning iodine intake as a complement to the information mentioned in the pharmaceutical notice?

☐ Yes ☐ No

If yes, please describe briefly:

6.6. In case of accident, how the population is alerted and informed of the necessity to absorb iodine? What is the time foreseen between the decision and intake?

7. Role of the various stakeholders

7.1. Who is responsible for initiating iodine administration? Please indicate corresponding level (national, regional, local authorities, operator).

7.2. Who is in charge of dose assessment in your country?

7.3. Who is in charge of the distribution of iodine stockpiles?

7.4. Who is responsible for the organization of information campaign on iodine prophylaxis, at national level, at local level? How is this action funded?

8. Harmonization efforts between neighbouring countries

8.1. Did you conclude some particular arrangements with neighbouring countries aiming to take harmonized or at least coherent decision on iodine prophylaxis? Could you please explain or provide documentation on the subject?

8.2. If a harmonized European approach is proposed, would you be ready to reconsider existing national practices?

☐ Yes ☐ No

If no, please specify the reasons:

ABBREVIATIONS, ACKNOWLEDGMENTS & REFERENCES

Abbreviations

CDC	Centers for Disease Control and Prevention
DG TREN	Directorate-General for Energy and Transport
DTPA	Diethylene Triamine Pentacetic Acid
EC	European Commission
EPZ	Emergency Planning Zone
ERL	Emergency Reference Level
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
KI	Potassium Iodide
KIO_3	Potassium Iodate
NEA	Nuclear Energy Agency
NIS	Sodium Iodide Symporter
NPP	Nuclear Power Plant
NRPB	National Radiological Protection Board
OECD	Organization for Economic Cooperation and Development
OIL	Operational Intervention Level
PCA	Pharmacie Centrale des Armées
PET	Positron Emission Tomography
RT3	Reverse Triiodothyronine
T3	Triiodothyronine
T4	Tetraiodothyronine = Thyroxine
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Simulating Hormone
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
US-HHS	U.S. Department of Health and Human Services
W-C	Wolff-Chaikoff
WHO	World Health Organization

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