Review

Thyroid side effects prophylaxis in front of nuclear power plant accidents

Prophylaxie des conséquences thyroïdiennes des accidents des centrales nucléaires

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Abstract

The better knowledge of the mechanisms of nuclear incidents and lessons learned from accidents in the recent past to improve the effectiveness of measures taken following a nuclear accident exposure to fallout of radioactive iodine isotopes. Thus, immediate, passive measures, such as containment, and stopping consumption of contaminated products are paramount. The earliest possible administration of stable iodine as potassium iodide (KI) reduces significantly (up to 90% if taken at the same time of the accident) thyroid radioactive contamination. These tablets should be given in priority to children and pregnant women. The side effects are minor. KI is not recommended for persons aged over 60 years, or for adults suffering from cardiovascular disorders.

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Keywords: Thyroid; Cancer; Iodine; Nuclear power plant accident

Résumé

La meilleure connaissance des mécanismes des incidents nucléaires et les leçons tirées des accidents survenus dans le passé récent améliorent l’efficacité des mesures prises suite à un accident nucléaire exposant à des retombées d’isotopes radioactifs de l’iode. Ainsi, des mesures immédiates, passives telles que le confinement, tout comme l’arrêt de la consommation de produits contaminés sont primordiales. L’administration la plus précoce possible d’iode stable sous la forme d’iodure de potassium (KI) permet de réduire de façon significative (jusqu’à 90 % en cas de prise au moment même de l’accident) la contamination thyroïdienne radioactive. Cette mesure s’adresse en priorité aux enfants et aux femmes enceintes. Elle s’accompagne de très peu d’effets secondaires, surtout si l’on respecte les rares contre-indications. Elle pourrait être inutile chez l’adulte, voire déconseillée après soixante ans et chez l’adulte aux antécédents de pathologie cardiovasculaire.

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Mots clés : Thyroïde ; Cancer ; Iode ; Accident nucléaire

1. Introduction

Several serious accidents involving nuclear power stations have occurred in recent decades, most of which remain etched in people’s minds years later (Table 1) [1–6]. First one, a level 5 accident on the 7-point International Nuclear Event Scale (INES) took place in the TMI-2 unit of the Three Mile Island nuclear power plant, USA, on March 28th 1979, less than 3 months after it had started normal service. Partial fusion of
Table 1
The seven levels of the International Nuclear Event Scale (INES).

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Simple functional anomalies at a nuclear installation, with no radioactive consequences</td>
</tr>
<tr>
<td>Level 2</td>
<td>Technical incidents significantly affecting the safety provisions or causing a breach of annual radiation standards for a worker</td>
</tr>
<tr>
<td>Level 3</td>
<td>Incidents seriously affecting the safety of the facility and/or leading to radioactive releases into the environment above the authorized limits and/or serious radiation exposure for one or more workers</td>
</tr>
<tr>
<td>Level 4</td>
<td>Accidents meeting one or more of the following criteria: releases not involving significant risks off-site, damage to the nuclear heart, radiation or contamination of one or more workers that can lead to death</td>
</tr>
<tr>
<td>Level 5</td>
<td>Accidents creating risk for the environment leading to implementation of the emergency plan and external protection provisions of the site due to risk of significant radioactive release. Severe damage causing release of large quantities of radiation within the installation</td>
</tr>
<tr>
<td>Level 6</td>
<td>Serious accidents involving very large radioactive releases to the outside (a significant portion of the radioactivity contained in a reactor heart)</td>
</tr>
<tr>
<td>Level 7</td>
<td>Major accidents leading to the release into the environment of a large part of the radioactive elements in the heart of a reactor. Discharges leading to serious damage to the environment and people’s health within a wide radius of the plant</td>
</tr>
</tbody>
</table>

The reactor core caused a large quantity of radioactive material to be released. Estimates suggest that 43,000 curies (1.59 PBq) of Krypton 85, a radioactive gas, entered the environment, along with up to 20 curies (740 GBq) of iodine 131. The second event was the Chernobyl disaster on April 26th 1986, when a dozen human errors and multiple design faults in the power station led to overheating of the fuel in reactor no. 4 following a poorly conducted experiment and a drop in power. Within a few hours, the temperature at the bottom of the reactor reached 2500 °C, and it exploded. Uranium, which melts at 1130 °C, turned into a sticky magma that destroyed the concrete and mixed with other components of the reactor. One second later, the hydrogen caught on fire and caused a second explosion, which lifted the reactor shield weighing 14,000 tonnes, exposing the reactor core to the air. It released dozens of tonnes of burning, high pressure, radioactive vapour into the atmosphere. The third accident was the result of the tsunami that hit the pacific coast of Tōhoku in Japan on March 11th 2011. According to estimates published by the Japanese Nuclear Safety Agency, the event released the equivalent of 10% of the radioactive material recorded following Chernobyl; i.e., between 1.3 and 1.5 × 10^{27} Bq of iodine 131 (compared to 1.8 × 10^{18} for Chernobyl), and between 6.1 and 12 × 10^{15} Bq of caesium 137 (compared to 8.5 × 10^{15}) making it the worst nuclear accident since Chernobyl. However, levels in the thyroid glands of Japanese children were substantially lower than those observed after the Chernobyl disaster (<50 mGy). As a result, few of the iodine doses released to more than a million people were actually used [7]. The 360,000 people aged 18 or less who were living in the Fukushima area at the time of the accident have been monitored since October 2011 using ultrasound of the thyroid gland.

On July 1 2013, a total of 427 nuclear reactors an average of 28 years old were functioning in 31 different countries, roughly one hundred of them in the US and 58 in France. Of the total output of 364 gigawatts hours, 63 gigawatts hours were generated in France. In 2012, roughly 10% of all global energy production was nuclear in origin [8]. At the time of writing in 2014, 58 nuclear reactors are operational in France, spreading over 19 sites. Nuclear energy accounts for 3/4 of French electricity production. France owns 44% of all European nuclear reactors and produces 14% of the world’s nuclear electricity, making it the world’s second largest producer of nuclear power [9]. These installations carry various nuclear risks, such as those linked to aging and corrosion, natural events, mechanical failure and technical issues and terrorist attacks [10].

Protection against the health risks associated with a nuclear event falls to the government, under the direction of the prime minister, to manage major crises (ministerial note n° 5567/SG, January 2nd 2012) [11]. In the case of a serious incident in a nuclear power plant, the prime minister gives operational authority to the interior minister, who then runs the interministerial crisis cell (CIC). The initial organisation is based on the activation of two networks: the representatives of local authorities (prefects for zones and regions), and nuclear bodies (safety, operators, IRSN) so as to guarantee a first level of response before activating the CIC. The zone prefect, once alerted, coordinates the necessary logistics for the local authority prefect via the zone operation centre (COZ). The population is warned by sirens that emit three long blasts of roughly 1 minute with a 3-second pause between each. Populations are asked to listen to the media, especially the radio, to receive real time information from the prefect and from outside [11].

2. Risk for the thyroid
2.1. Physiology of the absorption of iodine

Iodine plays a central role in thyroid physiology, as a constituent of the thyroid hormones and the thyroid metabolism regulator [12]. Iodine is first absorbed by the intestine in the form of iodides. The uptake of iodide by the thyrocytes is done through an active transport by the symporter NaI (NIS), ATP-dependent. Iodine is then oxidized by thyroperoxidase. It then binds to tyrosyl residues of thyroglobulin, giving rise to the precursor of thyroid hormones: monoiodothyronine (MIT) and diiodothyronine (DIT). Deiodinases devices allow the recycling of the iodine flowing to its reuptake by the gland.

In 1948, Wolff and Chaikoff showed that the uptake of iodide in the thyroid is decreased when the plasma levels of iodide are high, and that this adjustment can be done quickly in the presence of high permanent plasma concentrations of iodide [13]. The iodide administration decreases the expression of NIS mRNA and protein, decreasing uptake iodides in the thyroid. The concomitant decrease in the expression of TPO in this context could lead to iatrogen hypothyroidism [14].
2.2. Characteristics and biological effects of thyroid irradiation

In the case of a nuclear explosion, or a serious nuclear incident, most of the radioactive material is gas, aerosols and small particles of fuel. $^{131}$I and $^{137}$Cs are the main radionuclides involved when general populations are exposed, as was the case during the Chernobyl and Fukushima incidents [15]. It is a fission product from nuclear reactors, and it represents about 3% of the uranium fission products. Similar to $^{131}$I, $^{132}$I has a half-life of 2.3 hours. However, iodine 132 is the product of the breakdown of another radioisotope, $^{132}$Te (tellurium 132), which has a period of 3.26 days. Thus, during the first week following an incident like Chernobyl, the air is mainly contaminated with $^{131}$I and $^{132}$Te/$^{132}$I. The UNSCEAR 2000 report [16] estimates that cumulative iodine fallout following Chernobyl was around 4000 PBq. Tables 2 and 3 summarize the main radioactive fallouts from the Chernobyl and Fukushima disasters [16,17].

So, people exposed to iodine isotopes can be contaminated in three ways. The two main ones are inhalation (this occurs very early) and ingestion (specifically of fruits and green vegetables and fresh milk from animals left to graze in contaminated areas). These will be the main areas of concern for any protection/prevention measures. The third route, transcutaneous contamination through discarded husks, is much rarer (absorption through healthy skin is negligible when compared to the other means of contamination). Children are particularly at risk. When exposed to the same level, the dose to the thyroid gland is roughly 8–9 times that in adults. However, because of higher milk consumption, the estimated dose to the thyroid gland can be as much as 20 times higher [18].

Once it is absorbed or inhaled, radioactive iodine follows the same path as stable iodine and accumulates in the thyroid gland. It is the main emission source responsible for the dose to the thyroid gland. Ninety percent of the dose is delivered within a radius of 815 μm, which means the irradiation of roughly four thyroid vesicles. Thyroid radiation determines radiobiological effects subject to a threshold and dose proportional [19]. This particular irradiation takes place at a very low dose debent in tissue, and leads to uneven destruction, fast or delayed, of thyrocytes. Exposure to 1 Gy generates 1000 single-strand breaks and 40 double-strand breaks in DNA, which is lethal for the cell, as it cannot repair the damage. If the dose is weaker, DNA repair mechanisms can come into play with variable results ranging from restitution ad integrum to uneven repair.

2.3. Thyroid consequences in the Chernobyl disaster

More than 6 millions contaminated people (defined as living in an area where $^{137}$Cs activity >37 kBq/m²) were not evacuated after Chernobyl [18]. Secondary $^{131}$I fallout mainly affected northern Ukraine, south of Belarus and the Bryansk and Kaluga regions of Russia. Around 2 millions children were exposed to the fallout of radioactive iodine isotopes. Because of the delay in (or absence of) protective measures, around 7000 cases of thyroid cancers were reported in people under the age of 18 in 1986 living in heavily contaminated areas [20]. Iodine deficiency, which affected part of the exposed population, was
an aggravating factor for the risk of thyroid cancer. The epidemic of thyroid cancer in children that followed the event established an undeniable link between the nuclear event and neoplasia [21]. The spontaneous incidence of thyroid cancer in children is very low (1 case/million children). After Chernobyl, this figure was multiplied by 10 to 80 depending on area [22]. Furthermore, these cases of cancer have common epidemiological, clinical, histopathological and genetic characteristics. The outbreak occurred very fast, with reported cases as early as 1990 and a spike in the number of cases shortly thereafter. The cancers are papillary in 98% of cases, seem more aggressive, are N1 in 60% of cases at the time of diagnosis and M1 in 8% of observations [23]. However, life expectancy does not seem affected as these cancers often progress similarly to paediatric thyroid cancer and have a mortality of less than 1% [23]. In 2006, the WHO reported only 15 deaths out of a group of 4837 cases of infant thyroid cancer related to the nuclear accident, giving a mortality of 0.3%. The main reasons for a poor prognosis are more intense exposure to radiation, younger age and a larger tumour at the time of diagnosis. The genetic signature of radiation-induced thyroid cancer is RET/PTC rearrangement. The two most common forms of rearrangement are RET/PTC1 and RET/PTC3 during which RET is fused to gene CCDC6 or to gene NCOA4 (ELE1). RET/PTC1 rearrangements appear to be readily induced by radiation γ, RET/PTC3 rearrangements are caused by iodine 131 exposure as in Chernobyl [24]. Recent work has attempted to link RET/PTC rearrangements to thyroid cancer in children, rather than purely to radiation [20]. In France, the dose to the thyroid in children following the accident never went over a few mSv in the east of the country, which is comparable to the 2.4 mSv radiation that occurs naturally. There has been no reported increase in thyroid cancer among French children.

3. Iodine prophylaxis

3.1. Passive measures

In the case of exposure to radioactive iodine, the first response is to remove the population from the danger areas. If it is estimated that exposure will be higher than an effective dose of 10 mSv for the entire body, then the first measure would be to seek shelter. This means taking measures in the home or other building to reduce the risk of respiratory contamination. It is important not only to close all doors and windows but also to seal any cracks. If shelter is not available, wearing a mask can also be effective. A second important measure is to stop consuming fresh products, which are more likely to have been contaminated as rainfall can carry radioactive particles into the soil. As for children, adults need to avoid fresh dairy products produced in the contaminated area. Peak radioactivity levels of 40,000 Bq/Kg of milk were observed on May 8th 1986 around Chernobyl [25]. These measures must be followed by the evacuation of the population if there is still danger and/or if expected exposure is above an effective dose of 50 mSv for the whole body.

3.2. Scientific basis of prophylaxis by potassium iodide

Rapid and on going administration of stable iodine, in the form of potassium iodide (KI), will limit risk to the thyroid due to exposure to radioactive isotopes of iodine. This form of treatment is effective for multiple reasons. First through dilution, the higher the dose of KI, the lower the exposure to radioactive isotopes of iodine. This will restrict the transfer to the thyroid as it limits the sodium/iodine symporter (NIS). Moreover, a high intake of iodine inhibits its own use, the “organification” (into organic iodine), which is the Wolff-Chaikoff effect. Finally, by causing the creation of an organic iodine substance, the administered iodine blocks the iodine 131 link and prevents the recycling of organic radioactive iodine. KI acts fast, and results can be observed 30 minutes after ingestion [26]. This prophylactic approach is as effective as it is fast acting. KI can reduce irradiation of the thyroid by 95% if it is taken a few hours prior to, or during, the contamination, but its effectiveness drops to 50% if taken 6 hours later [20,27].

The effects of KI are temporary, the negative effects of radioactive iodine resume within 48 hours. Administration of stable iodine therefore needs to continue as long as there is a persisting risk of more than a few days. Intake may need to be daily. The risk of side effects increases with the length of the treatment.

3.3. Conditions and organisation of prophylaxis by potassium iodide

In France, the effectiveness of pre-emptively taking stable iodine to counteract radioactive iodine in the environment has led public authorities to distribute KI pills to at risk populations, there are two mechanisms set up for this.

A preventive distribution programme has been organised for inhabitants within a 10 km radius of structures liable to emit radioactive iodine. It takes place regularly depending on the use by dates of the iodine pills, and campaigns were organised in 1997, 2000, 2005 and 2009. The frequency of renewal of these pills has been lowered from 3 to 5 and then 7 years. The distribution campaigns are implemented by the interior minister and local health authorities under the supervision of the authority on nuclear safety (ASN). The latest of these distribution campaigns had three phases: a letter from public authorities invited citizens to go to their pharmacist to receive their free pills and some information documents. Those who had still not done this after 6 months (40% of people) were sent pills to their home. In total, 530,000 boxes of 10 KI pills each were given out. Pharmacists must always have extra stocks of the pills available to make sure all citizens and groups are covered. All the information for citizens is relayed by bodies participating in the campaign: the prefectures, the local bodies of the ASN, pharmacists, EDF nuclear power plants, local information commissions, town halls, healthcare workers and associations. Companies, public bodies, shopping centres, schools... within 10 km of the power plant are also invited to have a stock of pills. In the case of the pills being lost, or of moving within the 10 km zone, it is possible to obtain a box from a pharmacist by presenting a proof
of residency. The pharmacist will have fill out a form and give one box per five people.

Distribution can also be carried out in an emergency, following the ORSEC local iodine plan (civil society response organisation). The order to administer KI is given by the prefect. The threshold that triggers such intervention is a risk of exposure to a dose of more than 50 mSv in children. The state has a stock of 120 million pills containing 65 mg of stable iodine and has stores in each region designed to protect populations living more than 10 km away from a nuclear power plant site. The organisation for prevention and response to health emergencies (EPRUS) can distribute KI pills to local prefects following the conditions set out by the interministerial note dated July 11th 2011. The population is informed of distribution centres.

### 3.4. Recommended doses

The 65-mg iodine pills are made by the central military pharmacy and specify the date on which they were made but not the use by date. In the light of data on the stability of the molecule, the period during which the 65 mg pills can be consumed was increased to 5 then 7 years.

The protection of pregnant women and people under the age of 18 must be a priority. Prophylactic treatment is probably unnecessary after 40 years (unless the contamination is severe enough to risk of inducing hypothyroidism) and even potentially dangerous after 60 years and for persons at risk (history of thyroid dysfunction or heart disease). The dose contained in the pill was initially 130 mg but changed to 65 mg to harmonize with neighbouring countries. Pills can be swallowed or dissolved in a drink (water, milk, fruit juice...). They are, however, quite difficult to dissolve and an effervescent form would be welcome [28].

The recommended dosages are:

- two pills (130 mg) for adults, including pregnant women, and children over the age of 12;
- one pill (65 mg) for children aged 3 to 12;
- half a pill (32.5 mg) for children aged 1 month to 3 years;
- a quarter of a pill (16.25 mg) for babies up to 1 month.

People who have had a total thyroidectomy do not need to take KI. Taking KI is still recommended if you have had a partial thyroidectomy.

### 3.5. Side effects

KI pills are generally well tolerated [29]. Only one team has shared its “in the field” experience [30]. Carried out in Poland following the Chernobyl incident, this work took place during the prophylactic administration of KI to 10.5 million children and 7 million adults from April 28 1986. Nearly 35,000 people were monitored, 1/3 of them children. Side effects were classified as thyroid and extra-thyroid.

Nauman and Wolff [30] were unable to establish any thyroid side effects linked to iodine prophylaxis in children, or adults with no thyroid related medical history, not even in adults with a history of goitre or dysthyroidism. There was also no induction or exacerbation of thyrotoxicosis. Four adults (0.08%), (but no children) reported thyroid pain that was reversible. However, acute obstruction of the thyroid was reported in 0.37% of newborns, which led to a temporary increase in TSH levels and a decrease in T4. There was no permanent damage but the authors recommend caution when working with that age group, especially in the case of prolonged prophylaxis. Experimental work on chimpanzees has led to the suggestion of an alternative dosage of 1.5 mg/kg of KI in pregnancy and for newborns, especially with prolonged treatment [31,32].

Around 0.2% of people monitored reported a medically significant extra-thyroid side effect. Some symptoms may be linked to the stress of the situation or observance issues with KI [30]. Two adults allergic to iodine developed shortness of breath following the intake of potassium iodide. The reported extra-thyroid effects are presented in Table 4.

### 3.6. Interactions with KI, contraindications and alternatives

Iodine deficiency is linked to better thyroid absorption of iodine (radioactive or stable) that is inhibited by iodine overload — similar to taking thyroid hormones or amiodarone. Anti-thyroid agents, such as carbimazole, methimazole, propylthiouracil and perchlorate stop iodine absorption, as do tyrosine-kinase inhibitors used as a target treatment against neoplasia. However, lithium stimulates this effect [33]. Contraindications are rare; KI pills are not advised in the case of an iodine allergy, dysthyroidism (particularly active hyperthyroid), herpetiform dermatitis or hypocomplementaemia vascularity [34]. An alternative to KI could be potassium perchlorate at a dosage of 1 g [35].

### 4. Conclusion

The experience accumulated following the Chernobyl accident allowed us to learn the lessons of past mistakes and to be more effective when facing the tidal wave in Fukushima. The organised evacuation of people, confinement, and exclusion of local fresh product, was all effective. The major risk is the thyroid cancer that occurred particularly for children. It can be widely reduced by the administration of a potassium iodide prophylaxis. With few side effects, it can be administered in the form

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Table 4

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of children</th>
<th>% of adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>95.4</td>
<td>95.5</td>
</tr>
<tr>
<td>Headache</td>
<td>0.18</td>
<td>0.69</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>0.36</td>
<td>0.63</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.19</td>
<td>0.12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.38</td>
<td>0.85</td>
</tr>
<tr>
<td>Dyspea</td>
<td>0.11</td>
<td>0.63</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>1.07</td>
<td>1.24</td>
</tr>
<tr>
<td>Others</td>
<td>0.35</td>
<td>0.20</td>
</tr>
</tbody>
</table>

of 65 mg tables with a dosage to suit the age and priority to those most at risk (children and pregnant women).

Disclosure of interest

The authors declare that they have no competing interest.

References


