



# Iodine thyroid blocking

Guidelines for use in planning for and responding to radiological and nuclear emergencies



World Health  
Organization



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# Acronyms

CBRN	Chemical Biological Radiological Nuclear
DOI	declaration of interest
EPR	emergency preparedness and response
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GSR	general safety requirements
IAEA	International Atomic Energy Agency
IHR	International Health Regulations
I-131	iodine-131
ITB	iodine thyroid blocking
KIO <sub>3</sub>	potassium iodate
KI	potassium iodide
mSv	millisievert
PICO	population, intervention, comparator, outcome
PHE	Public Health, Environmental and Social Determinants of Health
REMPAN	Radiation Emergency Medical Preparedness and Assistance Network
WHO	World Health Organization



# Executive summary

These guidelines are an update of the 1999 World Health Organization (WHO) guidance on the use of iodine thyroid blocking (ITB) with a special focus on public health considerations of ITB implementation.

## Background

During a nuclear accident, radioactive iodine may be released in a plume, or cloud, contaminating the environment, thus resulting in external exposure. Inhalation of contaminated air and ingestion of contaminated food and drinking water may lead to internal radiation exposure and uptake of radioactive iodine mainly by the thyroid. The thyroid gland uses iodine to produce thyroid hormones and does not differentiate between radioactive and stable iodine. Hence after a nuclear accident, if radioactive iodine is inhaled or ingested, the thyroid gland absorbs it in the same way as stable iodine. If stable iodine is administered prior to, or at the onset of the exposure to radioactive iodine, the uptake of the latter will be blocked by saturation of the thyroid gland with stable iodine, thus effectively reducing internal exposure of the thyroid. Overall, oral administration of stable iodine (together with control of food and drinking water) is considered an appropriate strategy for reducing the risk of adverse health outcomes in people exposed to an accidental release of radioactive iodine and is included in many countries preparedness plans.

## Purpose and objectives

The technical guidance provided in these guidelines aims to support public health preparedness for radiation emergencies in Member States, as required by the International Health Regulations (IHR). It is confined to planning and implementation of ITB before and during a radiation emergency. These guidelines do not address the radiation protection basis set for ITB planning and implementation, but rather complements the relevant international safety standards and technical guides published by the International Atomic Energy Agency (IAEA) and co-sponsored by WHO and other international organizations.

The main objectives of these guidelines are to:

- assess the evidence base and provide guidance on the implementation of ITB in case of radiological or nuclear emergencies, including advice on timing and repeated administration during continuing release of radioactive iodine;
- identify most vulnerable groups and specify the applicability and modalities of ITB implementation for those groups, considering the side effects and associated risks of ITB use; and
- identify research gaps in relation to ITB evidence base.

## Target audience

The primary audience for these guidelines is health authorities and public health professionals responsible for, or otherwise involved in, planning and responding to radiation emergencies. It is also relevant for all other specialists involved in planning and responding to radiation emergencies.

## How were these guidelines developed?

The methodology presented in the WHO *Handbook for guideline development* was used to ensure transparency, and systematic use of evidence in developing these guidelines. A panel of independent experts – the Guideline Development Group (GDG) – was set up and followed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence and evidence-based decision-making. The process of developing the recommendation is described in detail in Chapter 2.

### Recommendation

During a radiological or nuclear emergency, provision of iodine thyroid blocking (ITB) to people who are at risk of being exposed to radioiodine should be implemented as an urgent protective action, within the frame of a justified and optimized protection strategy.

*Quality of evidence:* very low

*Strength of the recommendation:* conditional

## Public health considerations of ITB implementation

Key considerations for implementation of this recommendation are provided in the guidelines, including on ITB planning, logistics, form and dosage, and adverse effects of stable iodine.

The optimal period of administration of stable iodine is less than 24 hours prior to, and up to two hours after, the expected onset of exposure. It would still be reasonable to administer ITB up to eight hours after the estimated onset of exposure. However, starting with ITB later than 24 hours following exposure may yield more harm than benefit since it would prolong the biological half-life of radioactive iodine that has accumulated in the thyroid.

A single administration of an ITB agent is usually sufficient. However, repeated administration of stable iodine may be necessary in the case of prolonged (beyond 24 hours) or repeated exposure, unavoidable ingestion of contaminated food and drinking water, and where evacuation is not feasible. Neonates, pregnant and breastfeeding women and people older than 60 years, should not receive repeated ITB due to the risk of adverse effects. The following considerations should be kept in mind when administering ITB:

- Children, adolescents, pregnant and breastfeeding women, are most likely to benefit from ITB, whereas individuals over 40 years of age are less likely to benefit from it.

- Should the supply of stable iodine be limited, priority should be given to the children and younger adults.
- Individuals at risk of exposure to high doses of radioactive iodine (e.g. emergency workers involved in rescue or clean-up operations) are likely to benefit from ITB irrespective of their age and should be given priority.
- People living in iodine deficient areas are more likely to be affected by exposure to radioactive iodine. In such places, national or regional programmes targeting iodine deficiency should be considered.

Further research is required in the following areas to strengthen the evidence base for ITB:

- Radioiodine biokinetics in thyroid patients diagnosed or treated with radioisotopes of iodine.
- Dosage, optimal timing and regimens for multiple administrations of stable iodine in case of repeated or protracted releases of radioactive iodine and the adverse health effects of stable iodine administration. Studies in primates could be helpful for these purposes.
- Feasibility, acceptability and overall effect of use of ITB on psychosocial outcomes of radiation emergencies is needed.
- Detailed analysis of best practices for stable iodine pre-distribution and stockpiling is required in order to ensure a uniform way of dealing with a serious radiological or nuclear emergency situation, regardless of national borders, hence allowing for coherent and coordinated protective actions.



# 1. Introduction

## 1.1. Rationale

During a nuclear accident, radioactive iodine may be released in a plume, or cloud, contaminating the environment (i.e. air, water, soil, surfaces, plants, etc.) and settling on skin and clothing, resulting in external radiation exposure. Inhalation of contaminated air and ingestion of contaminated food and drinking water may lead to internal radiation exposure and uptake of radioactive iodine mainly by the thyroid. While absorption through the skin is a possible route it is negligible in comparison with inhalation or ingestion.

The thyroid gland uses iodine to produce metabolically active hormones and does not differentiate between radioactive and stable iodine. Hence, if radioactive iodine is inhaled or ingested, it will be absorbed by the thyroid gland. Studies of atomic bomb survivors indicate that thyroid tumours may develop following external exposure to ionizing radiation (1,2). The Chernobyl nuclear reactor accident in 1986 caused a large release of iodine-131 (I-131) and short-lived radioactive iodine into the environment. Higher rates of thyroid cancer were observed in individuals living in contaminated areas of Belarus, Ukraine and the western part of the Russian Federation. This increase in thyroid cancer incidence was linked to the internal exposure to radioactive iodine (3-6).

Children and adolescents are at higher risk of developing radiation-induced thyroid cancer compared to adults, due to a range of physiological and behavioural factors. These include a higher uptake rate of radioiodine during the development of the thyroid gland in childhood and adolescence, and a higher tissue dose due to the small size of the thyroid gland in children (3,5,7,8). Furthermore, younger children have different food intake than adults. For example, after the Chernobyl accident, milk was one of the main sources of exposure to radioiodine and its access was not immediately restricted. Since children tend to consume more milk than adults, this led to children being disproportionately affected.

Prenatal exposure to I-131 may also increase the risk of thyroid cancer (9). Potential transfer of I-131 from mothers to infants during breastfeeding has also been investigated as a risk factor (10,11). The younger the individual is at the time of exposure, the higher the risk of developing thyroid cancer (6,12). It has also been reported that iodine deficiency was associated with an increased risk of radiation-induced thyroid cancer in populations affected by the Chernobyl accident (13).

Oral administration of stable iodine is considered an appropriate strategy for avoiding the risk of thyroid cancer in people exposed to an accidental release of radioactive iodine (14-16). If taken before, or at the onset of exposure to radioactive iodine, stable

iodine blocks the uptake of radioactive iodine by saturating the thyroid gland with stable iodine, thus effectively reducing internal exposure of the thyroid.

The use of iodine thyroid blocking (ITB) as an urgent protective action following the release of radioiodine was first described in 1960s and 1970s (17-20) and addressed in detail in the World Health Organization (WHO) *Guidelines for iodine prophylaxis following nuclear accidents* published in 1989 (21). These guidelines were revised a decade later in 1999 to build on knowledge related to the risk of childhood thyroid cancer in the aftermath of the 1986 Chernobyl accident (14).

The radiation protection basis for implementing ITB is established in the International Atomic Energy Agency's international safety standards co-sponsored by WHO, including (IAEA) *Safety Standards Series General Safety Requirements (GS Part 7)* (22) and the *General Safety Guide – (GSG 2)* (23) publications. These guidelines support the generic criterion for a projected equivalent thyroid dose of 50 mSv for the first seven days since the onset of exposure, and focuses on public health aspects of ITB implementation, which are not included in the scope of the existing international safety standards.

In the aftermath of the nuclear accident following the Great East-Japan Earthquake and Tsunami in March 2011, many countries revisited their preparedness plans and strategies. One of the specific issues raised by the Fukushima Daiichi nuclear power plant accident was the use of ITB as an urgent protective action. The 2015 IAEA report on Fukushima states that, “Administration of stable iodine for iodine thyroid blocking was not implemented uniformly, primarily due to the lack of detailed arrangements” (24), highlighting the need for additional guidance on ITB implementation. Under the International Health Regulations (IHR) (25), WHO has a mandate to assist Member States in strengthening national capacities for public health preparedness and response to any emergency, including radiological emergencies and nuclear accidents. This includes technical support and guidance for developing national policies and for implementation of international safety requirements, provision of technical tools, training, education, and exercises aiming at building relevant national capacities. Therefore, the development of the current guidelines falls directly under the mandate of the organization.

## 1.2. Objectives

These guidelines aim to support Member States public health preparedness for radiation emergencies, as required by the IHR (25), through provision of technical guidance. The main objectives are to:

- assess the evidence base and provide guidance on the implementation of ITB following radiological or nuclear emergencies, including advice on timing and repeated administration following continuing release of radioactive iodine due to a radiological or nuclear emergency;
- identify most vulnerable groups and specify the applicability and modalities of ITB implementation for those groups, considering the side effects and associated risks of ITB use; and
- identify research gaps in relation to ITB evidence base.

### 1.3. Scope

These guidelines provide recommendation on ITB when planning for and responding to radiological or nuclear emergencies involving a release of radioactive iodine in the environment. The ITB implementation is discussed as an urgent protective action to safeguard potentially affected populations. Emergency and rescue workers are excluded from the scope of this document since the existing occupational safety standards for this category of workers explicitly prescribes the use of stable iodine prior to deployment if there is a risk of exposure to radioactive iodine.

### 1.4. Target audience

These guidelines are primarily intended for national and local health authorities and public health professionals responsible for, or otherwise involved in, preparing for, and responding to radiation emergencies. These guidelines are also relevant for other groups and stakeholders such as:

- radiation emergency medicine specialists and relevant professional associations;
- radiation protection, occupational safety professionals;
- health workers and health care facility managers;
- any other specialists involved in emergency response planning and management, including radiation protection and radiation safety specialists; and
- academia and researchers.



## 2. Methods

### 2.1. Process of developing these guidelines

The methodology set out in the *WHO Handbook for guideline development* (26) was used in developing these guidelines.

In response to the need for updated guidance on ITB, WHO, advised by external experts and stakeholders, convened a guideline development process to review the evidence base for public health aspects of ITB implementation. Starting in May 2014 through January 2017, three groups were convened to analyse the evidence and review these guidelines (see Annex 1 for the full names and affiliations of the members of these groups):

1. the WHO Steering Group, consisting of WHO staff with expertise relevant to ITB and response to radiation emergencies, including nutrition, cancer research and risk communication;
2. the independent Guideline Development Group (GDG), consisting of 14 members, (11 men and three women), selected on the basis of their technical expertise from 11 countries in four WHO regions (Region of the Americas, Eastern Mediterranean Region, European Region and Western Pacific Region). This geographical and gender distribution reflects the demographics of expertise in radiation protection, safety and radiation emergency response management, as well as the geography of countries, risk profiles including radio-nuclear hazards (27);
3. the External Review Group, made up of radiation experts, public health professionals and people representing potentially affected groups was set up to review the final recommendations. They provided extensive comments about the feasibility and applicability of the guidance.

In May 2014, a face-to-face meeting of the GDG was held at the University Hospital Würzburg, Germany. During the meeting the panel discussed and agreed on the scope of the guidelines, formulated the questions to guide the systematic review using PICO format (population, intervention, comparator and outcome), identified and prioritized the outcomes, set the timeline and distributed the tasks among the panel members (28). The protocol of the systematic review was published prior to developing the recommendation (16), and the systematic review was finalized at the end of 2015 and published in 2016 (29).

In January 2016, WHO organized a second face-to-face meeting of the GDG at Cisanello Hospital in Pisa, Italy to review the results of the systematic review, the GRADE



(Grading of Recommendations, Assessment, Development and Evaluation) evidence profile tables and other background work. The GDG discussed cost, use of resources, feasibility, acceptability, equity and implementation considerations related to the recommendations and proposed areas in which further research is required.

Between September 2016 and January 2017, the External Review Group, the GDG and the Internal Steering Group reviewed and provided further input into these guidelines. During 2016–2017, the on-going work was presented in various international fora to collect feedback from a wider stakeholder community.

## 2.2. Management of conflicts of interest

All experts participating in the development of these guidelines were asked to complete a declaration of interest (DOI) form detailing any interest relevant to the subject before their participation. In addition, all members of the GDG were asked to provide short biographies that were posted on the WHO public website<sup>1</sup> to facilitate feedback about any perceived conflicts. No public concerns were raised.

At the beginning of all GDG meetings, an explanation of what is considered or defined as a conflict of interest was provided. This includes any interest (e.g. financial, political or academic) that could be reasonably perceived to affect an individual's objectivity and independence while working with the WHO.

In addition, experts invited to participate in a substantive way in the development of the guidelines (including completion of the systematic review, developing evidence profiles, facilitating formulation of the recommendations and writing the guidelines) also completed a DOI form, and submitted it to the Secretariat.

The WHO Secretariat reviewed and assessed the declared interests – with the help of the Steering Group – prior to each meeting, to determine whether any participant had competing interests that may preclude or limit participation in the process.

At each GDG meeting, DOI forms were summarized and presented to the entire group, so that they were aware of any potentially competing interests declared by participants. In addition, all GDG members were asked to update or amend their declaration at the start of each meeting or between meetings (see Annex 1 for a summary of declared interests). Few experts declared potentially perceived non-financial conflicts of interests and were assessed by the Secretariat. None of these experts were deemed to have competing interests precluding their participation in the decision-making with regard to the recommendation and its implementation considerations.

## 2.3. Formulating questions in PICO format

Evidence-based approach uses a process of framing a research question with the following elements: problem/patient/population (P), intervention/indicator (I), compari-

1. Development of WHO Guidelines on Public Health Response to Radiological and Nuclear Emergencies (2012–2016). [http://www.who.int/ionizing\\_radiation/a\\_e/radiological-nuclear-emergencies/en/](http://www.who.int/ionizing_radiation/a_e/radiological-nuclear-emergencies/en/), accessed 20 September 2017.

son (C), and outcome (O) – PICO questions. The GDG developed the following key PICO question with the input of the Systematic Review team:

In a population exposed to radioiodine release (P), does the administration of stable iodine for thyroid blocking (I) against no administration (C) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)?

Further, two sub-questions were formulated to elaborate the main PICO question:

- In a population exposed to a single radioiodine release (P), does the timing of the administration of stable iodine prior to, shortly after the onset of the exposure (I) or later than two hours from the onset of the exposure (C) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)?
- In specific subgroups of a population exposed to a continuous or repeated radioiodine release (P), does a repeated administration of stable iodine (I) against a single administration (C) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)?

## 2.4. Evidence search and retrieval

The PICO questions were used to perform a systematic review of the literature using standard review methodology, i.e. selection of eligible studies, data extraction, assessment of risk of bias, assessment of heterogeneity, and data synthesis (see **figure 1**). The search was conducted in MEDLINE (via PubMed) and EMBASE, using terms related to the health condition, intervention and occurrence/location. No date or language restrictions were applied. The detailed protocol of the evidence retrieval and systematic review has been published (16).

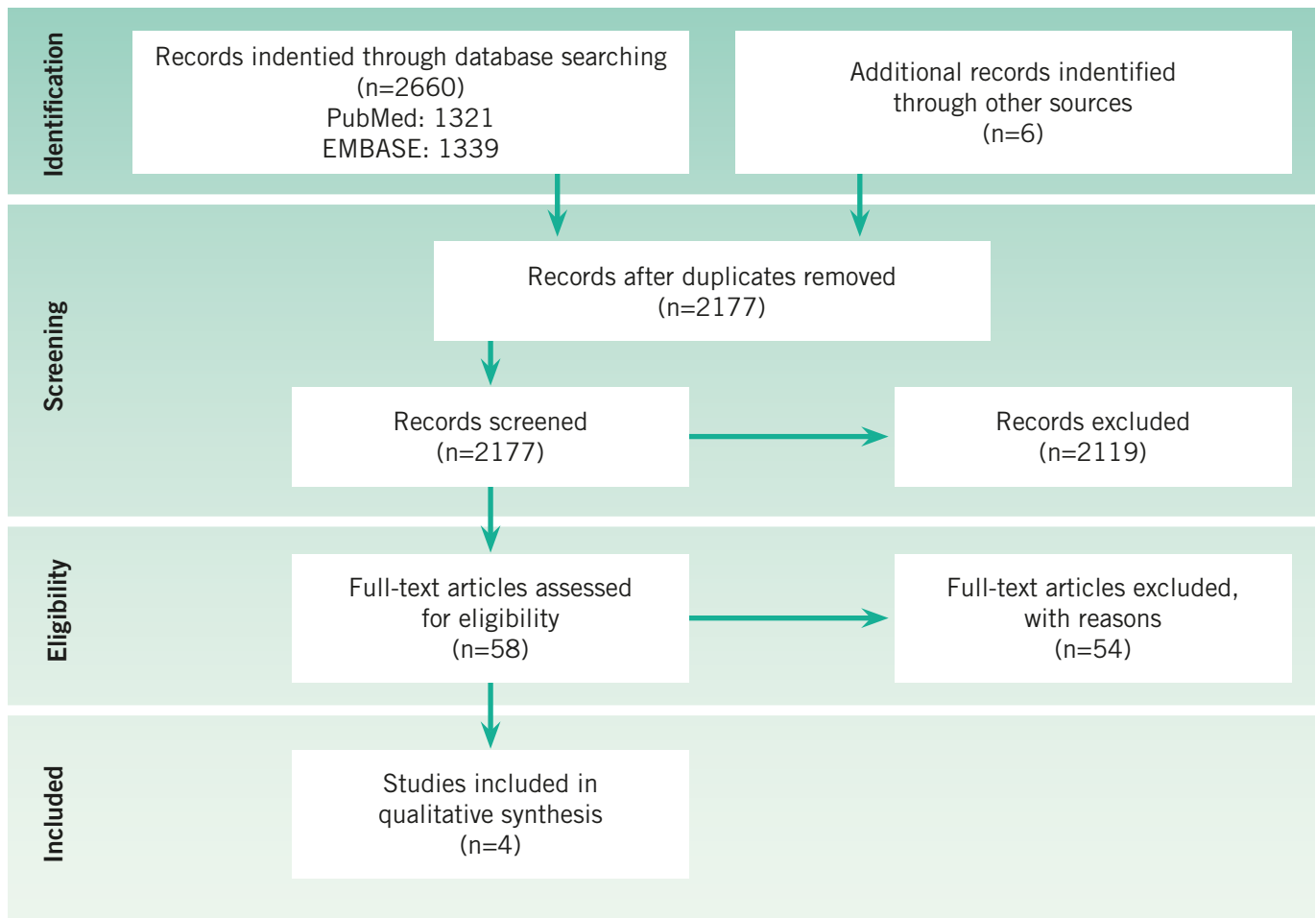
### Inclusion and exclusion criteria

Only human studies were included, as the specific outcomes of interest would be only relevant to human population. These comprised of studies comparing the effects of stable iodine administration versus no administration in relation to thyroid cancer, hypothyroidism and benign thyroid nodules in a population exposed to radioactive iodine release. Studies that did not meet the inclusion criteria were excluded. Indirect evidence from surrogate endpoints such as mechanistic models or studies in volunteers or animals may be applied to support recommendations in this area, if available (30). However, the studies on the type of outcomes that were selected by the GDG were not available.

### Systematic review outcomes

After application of the inclusion and exclusion criteria, the search yielded one cross-sectional study, one analytic cohort study and two case-control studies relating to the defined questions (see figure 1). The number of study participants ranged from 886 to 12 514. Two of the studies focused on children and two others on children and adults (29). A meta-analysis of individual studies was not considered feasible because of the great variability in the study design and populations identified.

Figure 1. Search strategy PRISMA flowchart



**Thyroid cancer.** The systematic review found evidence that use of stable iodine administration after a nuclear accident reduced the risk of thyroid cancer in children. However, most of the identified studies were not specifically designed to address the protective effect of stable iodine or the timing of the administration, and the effects of the methods of stable iodine administration and the dosage applied were not described. Therefore, the overall evidence was assessed as of either low or very low quality due to the limitations mentioned above (see next section of this document for the definition of quality of evidence).

**Hypothyroidism and benign thyroid nodules.** None of the studies investigated the effects of stable iodine administration on hypothyroidism and benign thyroid nodules.

## 2.5. Method used to assess the quality of evidence

The GRADE system was used to assess the quality of the evidence and evidence-based decision-making and to determine the strength of the recommendation (31). The quality of evidence refers to the degree of confidence in the estimate of effect (32). For questions of effectiveness of an intervention, evidence derived from analytical studies such as randomized controlled trials is rated as high quality evidence but may be then

downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias (33). Observational studies are initially rated as low level of quality of the evidence and can also be downgraded for reasons similar to those of randomized controlled trials, or on the contrary upgraded if the magnitude of the treatment effect is very large, if evidence, for example indicates a strong dose-response relationship. Quality of evidence can be categorized into: high, moderate, low and very low (see **Table 1** on the evidence quality grading scale). The higher the quality of evidence, the stronger the recommendation.

**Table 1.** GRADE definition of the quality of the evidence

Quality of the evidence	Definition
<b>High</b>	Very confident that the true effect lies close to that of the estimate of the effect
<b>Moderate</b>	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
<b>Low</b>	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
<b>Very low</b>	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

It should be noted, however, that applicability of the GRADE approach for assessing the quality of evidence to answer questions regarding environmental exposures is challenging, as the method does not fully apply to the evidence derived from the emergency situations, such as nuclear or radiological disasters due to a number of reasons, including:

- absence of randomized control studies;
- lack of statistical data that might be used to assess the effectiveness of various protective actions and health risks associated with their implementation.

The following factors affecting the grading of strength of recommendations were considered by the panel (see **Annex 2** for more detail on the use of these factors in the decision-making):

- **Priority of the problem.** The more prevalent and burdensome the condition, the stronger the recommendation.
- **Values and preferences.** The smaller the variability and uncertainty in values and preferences, the more likely the recommendation will be strong.
- **Balance of benefits and harms.** When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (harms or risks), considering any other alternative. The larger the difference between benefits and harm, the more likely the recommendation will be strong.
- **Resource use.** Most interventions have resource implications, including human resources, financial costs of the drug acquisition and storage, stockpile management

and maintenance, and staff training. Resource use, an important consideration for decision-makers, will differ between alternative interventions and management strategies. The lower the costs of an intervention, the more likely the recommendation will be strong.

- **Equity.** Policies that reduce inequities are ranked higher than the ones that do not, or those that increase inequities. It is important that decisions are fair and impartial such that no person or population is favoured over another. This also refers to equity in opportunity, access to resources, or the achieved distribution of societal resources. This is especially important when the most vulnerable population subgroups requiring special provisions are considered.
- **Acceptability.** The more acceptable an option is to the key stakeholders, the more likely it will be a priority and the recommendation will be strong.
- **Feasibility.** The more feasible an intervention, the greater its intervention, therefore the stronger the recommendation.

Understanding the limitations of GRADE's applicability for evidence derived from studies on environmental health hazards, especially those related to nuclear emergency situations, the GDG used the available evidence to address the harm, benefits, and feasibility of ITB administration during a radiation emergency to take a systematic approach when making recommendations and to make transparent judgments about the factors affecting the recommendations (see **Annex 2**). This provided the basis for an overarching recommendation accompanied by detailed remarks covering key considerations for implementation. The GDG also identified gaps in knowledge and defined the scope of further research.

All decisions were reached by consensus. These were further reviewed by the External Review Group, made up of professionals involved in radiation emergency and public health response planning and management, as well as representatives of potentially affected stakeholders (see **Annex 1**). The comments provided were used by GDG and the Secretariat to further refine and finalize the implementation considerations via online consultation.



# 3. Recommendation and public health recommendations

## Recommendation

During a radiological or nuclear emergency, provision of iodine thyroid blocking (ITB) to people who are at risk of being exposed to radioiodine should be implemented as an urgent protective action, within the frame of a justified and optimized protection strategy.

*Quality of evidence:* very low

*Strength of the recommendation:* conditional

The GDG considered that the quality evidence supporting the use of ITB in radiation emergencies was very low. Indeed, none of the four studies included in the systematic review directly addressed the effects of ITB administration in case of a nuclear accident on thyroid cancer, hypothyroidism and benign thyroid nodules. However, despite the lack of clinical or observational studies of the proposed intervention, the effectiveness of stable iodine in blocking thyroid uptake of radioactive iodine has been firmly established in mechanistic and observational studies.

In addition to the quality of evidence, the GDG considered such issues as feasibility and acceptability of the intervention, the priority of the problem, values and preferences of the various stakeholders (emergency response planners, policy makers, clinicians, and affected populations), balance of benefits and harms, equity and resource implications of the intervention. The GDG determined that the benefits of the intervention outweigh the disadvantages and costs. The use of ITB, if carefully planned and administered properly, has a low potential to cause harm. Stable iodine pills are available at an affordable price and most people would not object to take stable iodine, if instructed so, in case of a radiation emergency.

Based on these factors (acceptability, feasibility and affordability) coupled with the potentially beneficial effects of preventing thyroid cancer in children and younger adults, who would be otherwise at risk of exposure to radioactive iodine, the GDG decided to issue a conditional recommendation in favour of the use of ITB. A conditional recommendation is one for which the desirable effects of adherence outweigh the undesirable effects, although the trade-offs are uncertain, as the evidence base for the intervention is weak. With regard to policy-makers, a conditional recommendation implies that there is a need for additional research and a broader involvement of stakeholders to ensure the implementation of such urgent protective action, within the frame of the protection strategy.

### 3.1. Public health considerations of ITB implementation

The following key considerations for implementation of this recommendation are based on evidence of harm, benefits, feasibility and the experience and expertise of the GDG.

#### Planning and preparedness

ITB should not be considered a stand-alone protective action. A comprehensive public protection strategy covering all urgent and early protective actions, as well as other response actions, including evacuation and sheltering, restriction on consuming contaminated food, milk and drinking water, should be developed as per the IAEA's general safety requirements (22) and its supporting safety guide (23). These international safety standards and criteria for urgent protective actions and other response actions should be used as a basis for setting national criteria and developing a national protection strategy (22).

The comprehensive ITB implementation plan for preparedness and response should also include arrangements for training of health professionals and emergency workers on risk communication, to raise public awareness (e.g. provision of leaflets, organizing campaigns) to avoid unjustified use of ITB and giving false reassurance to the affected population.

When preparing for a radiological or nuclear emergency, countries sharing a border need to consider harmonizing national approaches for using ITB. A uniform approach to dealing with any serious radiological emergency situation, particularly in areas near the borders, will allow for coherent and coordinated protective actions to be implemented (34).

ITB is a protective action that is implemented only in the urgent phase (hours to one day after the onset of the emergency). Regarding the early phase (days to weeks) the effective way to limit the ingestion of radioiodine (as shown by the experience of Fukushima) and the most important method of limiting thyroid doses, especially to children, is to restrict the consumption of contaminated food, drinking water and fresh milk from grazing cows.

Provisions for ITB implementation need to be carefully reflected upon at the preparedness stage and should include considerations for: chemical form, packaging, dosage, timing of administration, stockpiling, distribution, and pre-distribution and identifying relevant locations (e.g. health care facilities, households, schools, workplaces, and kindergartens).

#### Chemical form, storage, and packaging

The agent most commonly used for protecting the thyroid from radioactive iodine is potassium iodide (KI). Although KI is the agent most commonly used, other chemical forms such as potassium iodate ( $KIO_3$ ) are equally valid, provided that the dosage is adapted to contain the same amount of iodine. There is no decisive difference in shelf life between KI and  $KIO_3$ . If storage conditions are adequate, tablets packed in a hermetic packaging and kept in a dry and cool place fully preserve their iodine content for five years. After five years, the iodine content may be checked and the shelf life extended, if needed. The shelf life is much more limited if stable iodine is in powder form or an aqueous solution. Further extension of shelf life is possible, if a formal protocol on testing such shelf life extensions has been established and validated (35).

Stable iodine can be given in either double scored tablet or liquid form. Tablets have the advantage of easy storage and distribution, including pre-distribution. Also, stable iodine is likely to cause less gastrointestinal irritation if administered in tablet form. Tablets can be crushed and mixed with fruit juice, jam, milk or similar substance. Tablets should be stored protected from air, heat, light and moisture. Age-dependent dosage and contraindications should be on the labelling.

## Dosage

Dosage information has remained unchanged since it was published in the 1999 WHO guidelines (see **table 2**).

**Table 2.** Recommended single dosage of stable iodine according to age group (6)

Age group	Mass of iodine, mg	Mass of KI, mg	Mass of KIO <sub>3</sub> , mg	Fraction of a tablet containing 100 mg of iodine	Fraction of a tablet containing 50 mg of iodine
Neonates (birth to 1 month)	12.5	16	21	1/8	1/4
Infants (1 month to 3 years)	25	32	42	1/4	1/2
Children (3 to 12 years)	50	65	85	1/2	1
Adults and adolescents (over 12 years)	100	130	170	1	2

## Adverse effects of stable iodine

Adverse reactions to stable iodine are rare and include iodine-induced transient hyper- or hypothyroidism, and allergic reactions (36,37). Reported severe clinically relevant reactions include: sialadenitis (an inflammation of the saliva gland – however, no cases of this were reported among users of KI in Poland after the Chernobyl accident), gastrointestinal disturbances and minor rashes. There are some rare but clinically relevant reactions, e.g. in patients with dermatitis herpetiformis or hypocomplementemic vasculitis. Risk groups for such reactions include those with pre-existing thyroid disorders and iodine hypersensitivity (38,39). In case of hypersensitivity to iodine, use of potassium perchlorate can be considered to suppress iodine uptake by the thyroid gland during the time of potential exposure (40). The use of additives, such as colourants, should be avoided as far as possible since they may cause adverse effects (e.g. allergies).

## Timing of administration

The optimal period of administration of stable iodine is less than 24 hours prior to, and up to two hours after, the expected onset of exposure (14) (36). It would still be reasonable to administer ITB up to eight hours after the estimated onset of exposure (41). Commencing ITB later than 24 hours following the exposure may do more harm than benefit (by prolonging the biological half-life of radioactive iodine that has already accumulated in the thyroid). A single administration of stable iodine is usually sufficient. However, in



the case of prolonged (beyond 24 hours) or repeated exposure, unavoidable ingestion of contaminated food and drinking water, and where evacuation is not feasible, repeated administration of stable iodine may be necessary (36). Neonates, pregnant and breastfeeding women and older adults (over 60 years), should not receive repeated ITB.

### Pre-distribution and distribution

As there is only limited time for implementation of ITB, prompt availability of the tablets to individuals has to be ensured if these are to be most effective. In the vicinity of nuclear reactors, pre-distribution of stable iodine to households should be considered, taking into account plans for evacuation and sheltering. Provisions for storing stable iodine in places that can be controlled by the responsible authorities should also be made. Clear instructions should be issued with the tablets, and public awareness of the procedures should be monitored on a regular basis.

In areas further away from the sites of release there is likely to be more time available for decision-making. If pre-distribution to households is not considered feasible, stocks of stable iodine should be stored strategically at, for example, schools, hospitals, pharmacies, fire stations, police stations and civil defence centres. Widespread storage may be warranted at considerable distances from the potential accident site. Storage should preferably be at places where proper stock control is standard practice. Planning should consider the use of redundant distribution areas to minimize delays in implementing ITB. Due consideration should also be given to whether the benefits of stable iodine distribution outweigh the disadvantages associated with any additional exposure of responsible emergency personnel.

Medical personnel likely to be consulted by the public should be provided with more detailed information. As a part of preparedness, people pre-distributing stable iodine should be trained and provided with information materials to ensure availability of professional advice to potentially affected individuals. For example, pharmacists dispensing stable iodine tablets should be able to answer questions, explain the purpose, benefits and appropriate use of stable iodine. It should be explained that stable iodine should not be considered by general public as a universal radiation antidote.

National authorities are advised that, because of the benefits of ITB and the generally minimal risks of side effects, voluntary purchase of iodine tablets by the general public should be allowed. However, within the framework of the overall radiation emergency plan, the responsibility for distribution of stable iodine and instructing the public on how to use it should be clearly assigned to the appropriate authorities.

National policies on stable iodine stockpiling, pre-distribution and distribution methods vary (42-46) and harmonization of policies across borders remains a challenge.

### Special consideration groups of the population

- The groups most likely to benefit from ITB are children, adolescents, pregnant and breastfeeding women (15,36), whereas individuals over 40 years of age are less likely to benefit from ITB.
- Should the supply of stable iodine be limited, priority should be given to the children and younger adults.

- Neonates and people older than 60 years are at higher risk of adverse health effects if they receive repeated doses of stable iodine (36,37).
- People living in iodine deficient areas are more likely to be affected by exposure to radioactive iodine (13,45). In such places, national or regional programmes targeting iodine deficiency should be considered (47).
- Individuals at risk of exposure to high doses of radioactive iodine (e.g. emergency workers involved in rescue or clean-up operations) are likely to benefit from ITB irrespective of their age and should be given priority.

Studies of the Chernobyl accident have found no association between thyroid tumours and radioactive iodine in adults. Therefore, individuals over 40 years of age are less likely to benefit from ITB. Should the supply of stable iodine be limited, priority should be given to children and younger adults (15). Note that even though some studies of atomic bomb survivors reported an indication of increased risk for thyroid cancer in people over 40 years of age, the exposure was external, and the risk estimates were not statistically significant (2).

### 3.2. Research priorities

The GDG experts identified the following research priorities in relation to the use of ITB during radiological and nuclear emergencies:

- Radioiodine biokinetics can be further studied in thyroid patients diagnosed or treated with radioisotopes of iodine. However desirable, randomized controlled studies on the effects of ITB in such patients are not ethical, hence studies are limited to observational.
- More data are needed on the dosage, optimal timing and regimens for multiple administrations of stable iodine in case of repeated or protracted releases of radioactive iodine and the adverse health effects of stable iodine administration. Studies in primates could be helpful for these purposes.
- Research on feasibility, acceptability and overall effect of use of ITB on psychosocial outcomes of radiation emergencies is needed.
- Detailed analysis of existing national practices for stable iodine pre-distribution and use is required in order to ensure a uniform way of dealing with any serious radiological emergency situation, regardless of national border line, hence allowing for coherent and coordinated protective actions.



# 4. Dissemination and implementation

## 4.1. Dissemination

These guidelines are available on the WHO website ([http://www.who.int/ionizing\\_radiation/a\\_e/en/](http://www.who.int/ionizing_radiation/a_e/en/)) and distributed by WHO regional and country offices, WHO Collaborating centres, as well as member institutions of the WHO's Radiation Emergency Medical Preparedness and Assistance Network (REMPAN). It is also shared with relevant international organizations, NGOs, professional associations, and other stakeholders.

Recommendations, implementation considerations and research priorities will be disseminated through presentations at professional societies and associations meetings and conferences.

Development of derivative products (e.g. check lists, protocols, frequently asked questions, infographics) will be considered along with the use of online interactive tools and open online training courses.

## 4.2. Implementation monitoring

A survey of national stable iodine policies was conducted in 2016 to monitor the implementation of the new recommendations on ITB. The findings of the survey form a baseline against which the implementation may be measured in the future.

## 4.3. Review-by date

These guidelines should be reviewed ten years from publication, unless a major incident or significant new evidence prompts the need for an earlier revision.



## 5. References

1. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiation Research*. 2007;168:1–64.
2. Furukawa K, Preston D, Funamoto S, Yonehara S, Ito M, Tokuoka S et al. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. *Int. J. Cancer*. 2013;132:1222–1226.
3. Kazakov V, Demidchik E, Astakhova L. Thyroid cancer after Chernobyl. *Nature*. 1992;359(6390):21.
4. Likhtarev I, Sobolev B, Kairo I, Tronko N, Bogdanova T, Oleinic V et al. Thyroid cancer in the Ukraine. *Nature*. 1995;375(6530):365.
5. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V et al. Risk of thyroid cancer after exposure to <sup>131</sup>I in childhood. *Journal of the National Cancer Institute*. 2005;97(10):724–732.
6. Health effects of the Chernobyl accident and special health care programmes. Geneva: World Health Organization; 2006.
7. Heidenreich WF, Kenigsberg J, Jacob P, Buglova E, Goulko G, Paretzke HG et al. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. *Radiation Research*. 1999; 151(5):617–25.
8. Klugbauer S, Lengfelder E, Demidchik EP, Rabes HM. High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene*. 1995;11(12):2459–2467.
9. Hatch M, Brenner A, Bogdanova T, Derevyanko A, Kuptsova N, Likhtarev I et al. A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to iodine-131 from Chernobyl fallout. *J Clin Endocrinol Metab*. 2009;94(3):899.
10. Schneider AB, Smith JM. Potassium iodide prophylaxis: what have we learned and questions raised by the accident at the Fukushima Daiichi Nuclear Power Plant. *Thyroid*. 2012;22(4):344–346.
11. Miller RW, Zanzonico PB. Radioiodine fallout and breast-feeding. *Radiat Res*. 2005;164(3):339–340.
12. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. *Br J Cancer*. 4 January 2011;104:181–187.
13. Shakhtarin VV, Tsyb AF, Stepanenko VF, Orlov MY, Kopecky KJ, Davis S. Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and ado-

- lescents in the Bryansk region of Russia following the Chernobyl power station accident. *Int J Epidemiol*. 2003;32(4):584–591.
14. Guidelines for iodine prophylaxis following nuclear accidents. Geneva: World Health Organization; 1999 update ([http://www.who.int/ionizing\\_radiation/pub\\_meet/iodine\\_Prophylaxis\\_guide.pdf](http://www.who.int/ionizing_radiation/pub_meet/iodine_Prophylaxis_guide.pdf), accessed 27 Nov 2017).
  15. Jang M, Kim HK, Choi CW, Kang CS. Age-dependent potassium iodide effect on the thyroid irradiation by <sup>131</sup>I and <sup>133</sup>I in the nuclear emergency. *Radiat Prot Dosimetry*. 2008;130(4):499–502.
  16. Dreger S, Pfinder M, Christianson L, Lhachimi SK, Zeeb H. The effects of iodine blocking following nuclear accidents on thyroid cancer, hypothyroidism, and benign thyroid nodules: a systematic review. *Syst Rev*. 2015 Sep 24;4:126 2015;4.
  17. Pochin EE, Barnaby CF. The effect of pharmacological doses of non-radioactive iodide on the course of radioiodine uptake by the thyroid. *Health Phys*. 1962;7:125–126.
  18. Ramsden D, Passant FH, Peabody CO, Speight RG. Radioiodine uptakes in the thyroid – Studies of the blocking and subsequent recovery of the gland following the administration of stable iodine. *Health Phys*. 1967;13:633–646.
  19. National Council on Radiation Protection and Measurements. Protection of the thyroid gland in the event of releases of radioiodine. Washington (DC): University of Michigan; 1977.
  20. Ilyin LA, Arkhangel'skaya GV, Konstantinov YO, Ikh'tarev IA. Radioactive iodine in the problem of radiation safety. English translation by United States Atomic Energy Commission 1974. Moscow: Atomizdat; 1972.
  21. Guidelines for iodine prophylaxis following nuclear accidents. Copenhagen: WHO Regional Office for Europe; 1989;38. Superseded by 1999 update.
  22. Preparedness and response for a nuclear or radiological emergency: general safety requirements part 7. Vienna: International Atomic Energy Agency; 2015. Jointly sponsored by the: Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, International Civil Aviation Organization, International Labour Organization, International Maritime Organization, INTERPOL, OECD Nuclear Energy Agency, Pan American Health Organization, Preparatory Commission for the Comprehensive Nuclear-Test-Ban-Treaty Organization, United Nations Environment Programme, United Nations Office for the Coordination of Humanitarian Affairs, World Health Organization, World Meteorological Organization.
  23. Criteria for use In preparedness and response for a nuclear or radiological emergency: general safety guide – GSG 2. Vienna: International Atomic Energy Agency; 2011;91. Jointly sponsored by the: Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, International Labour Organization, Pan American Health Organization, World Health Organization.
  24. The Fukushima Daiichi accident report by the Director General. Vienna: International Atomic Energy Agency; 2015. (<http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1710-ReportByTheDG-Web.pdf>, accessed 9 October 2017).

25. International health regulations (2005) – third edition. Geneva: World Health Organization; 2016;84.
26. WHO handbook for guideline development – second edition. Geneva: World Health Organization; 2014 ([http://www.who.int/publications/guidelines/handbook\\_2nd\\_ed.pdf](http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf), accessed 27 Nov. 2017).
27. Gillenwalters E, Martinez N. Review of gender and racial diversity in radiation protection. *Health Phys.* 2017;112(4):384-391.
28. Reiners C, Schneider R, Akashi M, Akl EA, Jourdain JR, Li C et al. The first meeting of the WHO guideline development group for the revision of the WHO 1999 guidelines for iodine thyroid blocking. *Rad Prot Dosimetry.* 2016;171(1):47-56.
29. Pfinder M, Dreger S, Christianson L, Lhachimi SK, Zeeb H. The effects of iodine thyroid blocking on thyroid cancer, hypothyroidism and benign thyroid nodules following nuclear accidents: a systematic review. *J Radiol Prot.* 2016;36(4):R112-R130.
30. Rooney AA, Cooper GS, Jahnke GD, Lam J, Morgan RL, Boyles AL et al, How credible are the study results? Evaluating and applying internal validity tools to literature-based assessments of environmental health hazards. *Environment Internat.* 2016;92–93;617–629.
31. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol.* April 2011;64(4):380–382.
32. Schünemann HJ, Brozek JL, Guyatt GH, Oxman AD, editors. GRADE handbook for grading quality of evidence and strength of recommendations – updated October 2013. GRADE Working Group. 2013.
33. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ.* 17 May 2008; 336(7653): 1106–1110.
34. HERCA-WENRA. Approach for a better cross-border coordination of protective actions during the early phase of a nuclear accident. Stockholm: Heads of the European Radiological Protection Component Authorities and Western European Nuclear Regulators' Association; 2014:50.
35. Guidance for Federal Agencies and State and Local Governments: potassium iodide tablets shelf life extension. FDA – Downloads – Drugs – Guidances. US Department of Health and Human Services. 2004 (<https://www.fda.gov/downloads/drugs/guidances/ucm080549.pdf>, accessed 27 Nov 2017).
36. Verger P, Aurengo A, Geoffroy B, Le Guen B. Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. *Thyroid.* 2004;11(4):353-60.
37. Agopiantz M, Elhanbali O, Demore B, Cuny T, Demarquet L, Ndiaye C et al. Paris Thyroid side effects prophylaxis in front of nuclear power plant accidents. *Ann Endocrinol.* February 2016;1–6.
38. Sicherer SH. Risk of severe allergic reactions from the use of potassium iodide for radiation emergencies. *J Allergy Clin Immunol.* 2004;114:1395–1397.

39. Spallek L, Krille L, Reiners C, Schneider R, Yamashita S, Zeeb H. Adverse effects of iodine thyroid blocking: a systematic review. *Radiat Prot Dosimetry*. July 2012;150:267–277.
40. Hänscheid H, Reiners C, Goulko G, Luster M, Schneider-Ludorff M, Buck AK et al. Facing the nuclear threat: Thyroid blocking revisited. *J Clin Endocrinol Metab*. 2011;96(11):3511–3516.
41. Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by <sup>131</sup>I from radioactive fallout. *Health Physics*. 6 June 2000;78:660–667.
42. 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. DG/Energy/ Nuclear Energy Unit D4. Radiation protection reports, No. 165. European Commission; 2010.
43. Le Guen B, Stricker L, Schlumberger M. Distributing KI pills to minimize thyroid radiation exposure in case of a nuclear accident in France. *Nat Clin Pract Endocrinol Metab*. 2007;3(9):611.
44. Leung AM, Bauer AJ, Benvenga S, Brenner AV, Hennessey JV, Hurley JR et al. American Thyroid Association scientific statement on the use of potassium iodide ingestion in a nuclear emergency. *Thyroid*. 7 July 2017;27:865–877.
45. International Council for the Control of Iodine Deficiency. Iodine and Japan Nuclear Accident. Japan Thyroid Association; 19 March 2011 ([http://www.japanthyroid.jp/en/hot\\_news.html#jta](http://www.japanthyroid.jp/en/hot_news.html#jta), accessed 27 Nov. 2017).
46. Turai I. Thyroid Blocking Policy in Hungary and Clarification of Terminology in the Light of Recommendations by International Organisations. *Rad Prot Dosimetry*. 2016;171(1):57-60.
47. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers – third edition. Geneva: World Health Organization; 2007;108.



# Annex 1. Composition of guideline advisory groups

## A. Guideline development group

Name	Affiliation	Expertise	Potential conflict of interest (CoI) declared <sup>1</sup>	WHO Region
<b>Akashi Makoto</b>	National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan	Public health, radiation emergency preparedness and response (EPR)	None	Western Pacific Region
<b>Akl Elie</b>	American University of Beirut, Lebanon	Guidelines development process methodology, GRADE methodology	None	Eastern Mediterranean Region
<b>Jourdain Jean-René</b>	Institute for Radiological Protection and Nuclear Safety, Fontenay-aux-Roses, France	Radiation biology, radiation EPR, toxicology	Principle investigator of a project supported by the French National Research Agency to conduct animal studies on efficacy, toxicity, and efficiency of stable iodine	European Region
<b>Li Chunsheng</b>	Health Canada, Ottawa, Canada	Radiation protection, radiation EPR	None	Region of the Americas
<b>Murith Christophe</b>	Swiss Federal Office of Public Health, Bern, Switzerland	Radiation protection, radiation EPR, public health	None	European Region
<b>Prosser Lesley</b>	Public Health England, Chilton, United Kingdom	Radiation protection, radiation EPR, public health	None	European Region
<b>Reiners Christoph</b>	University of Würzburg, Germany	Nuclear medicine, thyroid cancer	Conducted research and published on the subject. His travel to the meeting was paid by his employer – Würzburg University	European Region
<b>Schneider Rita</b>	University of Würzburg, Germany	Radiation emergency medicine, public health, radiation EPR	None	European Region

1. A conflict of interest is any interest declared by an expert (both of financial and non-financial nature) that may affect or reasonably be perceived to affect the expert's objectivity and independence in providing advice to WHO.



Name	Affiliation	Expertise	Potential conflict of interest (CoI) declared <sup>1</sup>	WHO Region
<b>Turai Istvan</b>	Semmelweis University and Eötvös Lóránd University, Budapest, Hungary	Radiation emergency medical response, ITB research and policy	Researched and published in the past on the subject of ITB	European Region
<b>Vitti Paulo</b>	University of Pisa, Italy	Endocrinology, thyroid disorders	None	European Region
<b>Van Bladel Lodewijk</b>	Federal Agency for Nuclear Control, Brussels, Belgium	Radiation protection, radiation EPR, public health	Public speaking on the subject and his travel expenses for the GDG meeting were paid by his employer	European Region
<b>Yamashita Shunichi</b>	Nagasaki University, Japan	Nuclear disaster medicine, radiation genetics, thyroid cancer	None	Western Pacific Region

## B. External Review Group

Name	Affiliation	Expertise	Potential conflict of interest (CoI) declared	WHO Region
<b>Bader Judy</b>	National Cancer Institute/National Institutes of Health, Bethesda, Maryland, United States of America	Medical response to radiation emergencies	None	Region of the Americas
<b>Bazyka Dmitry</b>	National Research Center for Radiation Medicine, Kiev, Ukraine	EPR, radiation protection, radiation emergency medicine, radiopathology	None	European Region
<b>Blumenstock James</b>	National Alliance for Radiation Readiness, Arlington, Virginia, United States of America	Represents affected stakeholder – a coalition of public health, healthcare, and emergency management organizations	Not applicable (N/A) for reviewers representing their organization	Region of the Americas
<b>De La Vega Ramon</b>	Incident and Emergency Center, International Atomic Energy Agency (IAEA), Austria	Radiation EPR, radiation protection	N/A	N/A
<b>Homma Toshimitsu</b>	Japan Atomic Energy Agency, Japan	Radiation protection and dosimetry	None	Western Pacific Region

Name	Affiliation	Expertise	Potential conflict of interest (CoI) declared	WHO Region
<b>Jammihal Ravindra</b>	Bhabha Atomic Research Centre, India	Emergency medicine, Chemical Biological Radiological Nuclear (CBRN) management	None	South-East Asia Region
<b>Krottmeier Martin</b>	International Federation of Red Cross and Red Crescent Societies, Switzerland	Disasters preparedness and response	N/A	N/A
<b>Kuhlen Johannes</b>	Radioecology, Environmental Radioactivity Surveillance, Emergency Preparedness and Response, Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety, Germany	Radiation EPR, radiation protection	N/A	European Region
<b>Mushaukwa Kabuku</b>	Radiation Protection Authority, Ministry of Health Zambia	Radiation EPR, radiation protection	None	African Region
<b>Nestorska-Madjunarova Svetlana</b>	Incident and Emergency Center, IAEA, Austria	Radiation EPR, radiation protection	N/A	N/A
<b>Perkins Daniel</b>	Department of Business, Energy and Nuclear Strategy, United Kingdom	Emergency response and resilience, radiation protection and stable iodine use	None	European Region
<b>Palliri Ravindran</b>	Directorate General of Health Services, Ministry of Health, India	Emergency medicine, CBRN management	N/A	South-East Asia Region
<b>Rbai Mohamed</b>	Department of Defence, Morocco	CBRN emergencies, radiation EPR	None	Eastern Mediterranean Region
<b>Schönhacker Stefan</b>	OeRK-W – Civil Defence, Vienna Austria	CBRN emergencies, radiation EPR	None	European Region
<b>Tanigawa Koichi</b>	Fukushima Medical University, Japan	Health impact of Fukushima nuclear accident, public health consequence management	None	Western Pacific Region

Name	Affiliation	Expertise	Potential conflict of interest (CoI) declared	WHO Region
<b>Tinker Rick</b>	Australian Radiation Protection and Nuclear Safety Agency, Australia	Radiation protection, public health	None	Western Pacific Region
<b>Whitcomb Robert</b>	Radiation Studies Branch Division of Environmental Hazards and Health Effects National Center for Environmental Health, Centers for Disease Control and Prevention, United States of America	Radiation EPR, health physics, public health	None	Region of the Americas
<b>Zeppa Paolo</b>	Italian National Institute for Environmental Protection and Research, Italy	Radiation EPR, radiation protection	None	European Region

## C. WHO Steering Group

Name	Affiliation	Expertise
<b>Allen Tomas</b>	Library Information Networks for Knowledge	Evidence retrieval, systematic reviews methodology
<b>Bouesseau Marie-Charlotte</b>	Health Information Systems, Service Delivery and Safety	Ethics of public health and clinical interventions
<b>Cross Caroline Marie</b>	Staff Health and Well-being Services	Medical response to health emergencies, staff health services
<b>Gamhewage Gaya</b>	WHO Health Emergencies Programme, Infectious Hazard Management, Experts Networks and Interventions	Emergency risk communication
<b>Ilbawi André</b>	Noncommunicable Diseases and Mental Health	Cancer control and prevention, oncology
<b>Kesminiene Ausrele</b>	WHO International Agency for Research on Cancer	Radiation epidemiology and radiation protection, cancer epidemiology
<b>Odugleh-Kolev Asiya</b>	Health Information Systems, Service Delivery and Safety	Social mobilization and community engagement in emergencies, risk communication
<b>Onyon, Lesley</b>	WHO Regional Office South-East Asia, Noncommunicable Diseases and Environmental Health	Environmental health, chemical safety

Name	Affiliation	Expertise
<b>Paunovic Elizabet</b>	WHO Regional office for Europe, Policy and Governance for Health and Well-being – Environmental Health Center	Environmental health, occupational health
<b>Peña-Rosas Juan Pablo</b>	Noncommunicable Diseases and Mental Health, Nutrition for Health and Development, Evidence and Programme Guidance	Iodine deficiency, epidemiologist, evidence and programme guidance
<b>Tempowski Joanna</b>	Climate and Other Determinants of Health, Public Health and Environment, Evidence and Policy on Environmental Health	Chemical safety and toxicology
<b>van Deventer Emilie</b>	Climate and Other Determinants of Health, Public Health and Environment, Interventions for Healthy Environments, Radiation Team	Radiation safety, guidelines development methodology



# Annex 2. Evidence-to-recommendation framework

Should stable iodine be administered versus not administered to people exposed to radioiodine release in the environment in the setting of radiological or nuclear emergency?

**Population:** people exposed to radioiodine release in the environment

**Intervention:** stable iodine administration

**Comparison:** no stable iodine administration

**Setting:** radiological or nuclear emergency

**Perspective:** public health

**Background:** Oral administration of stable iodine is considered an appropriate strategy for reducing the risk of adverse health outcomes in people exposed to an accidental release of radioactive iodine. (A1)  
The thyroid gland uses iodine to produce metabolically active hormones and does not differentiate between radioactive and stable iodine. (A2)  
Hence after a nuclear accident, if radioactive iodine is inhaled or ingested, it will be taken up selectively by the thyroid gland. If stable iodine is administered before or at the beginning of the exposure to radioactive iodine, the uptake of radioactive iodine is blocked by saturation of the thyroid gland with stable iodine, thus effectively reducing internal exposure of the thyroid.

**Subgroup considerations:** children and adolescents 0 to 18 years, pregnant or breast-feeding women, older adults

Criteria	Judgements	Research evidence	Additional considerations
<b>Problem</b>			
Is the problem a priority?	<input type="checkbox"/> No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ Paediatric thyroid cancer has a low background incidence rate, it is a rare disease</li> <li>■ Strong association was reported between exposure to radiiodine and increased risk of thyroid cancer for persons exposed between the age of 0 and 18 years. (A3–A5)</li> <li>■ Range of risk estimates is quite broad, with the indication of the increase starting from the exposure level of 50 millisievert (mSv) of thyroid dose among those between the age of 0 and 18 years at the time of exposure. (A6,A7)</li> <li>■ The thyroid iodine- 131 (I-131) absorbed dose is two-fold higher in regions with insufficient levels of dietary iodine. (A8)</li> <li>■ Despite a good response of thyroid cancer to clinical management (surgery followed by radioiodine therapy and hormone-replacement therapy) the reduced quality of life after a long time of follow-up. (A9)</li> </ul>	<p>Public perception of childhood thyroid cancer and nuclear accidents was formed due to Chernobyl experience and later on by Fukushima experience. The issue of Fukushima's childhood thyroid cancer is very high on the agenda currently. The key interventions to prevent this are restrictions on consuming food and drinking water and administration of stable iodine. However, this measure has never been properly implemented in the very few nuclear accidents that have occurred. Therefore, the direct evidence of stable iodine's efficient application in the setting of nuclear emergency does not exist. Hence the urgent need to address ITB issue and to produce an authoritative guidance.</p>

<b>Values</b>																					
Is there important uncertainty or variability about how much people value the main outcomes?	<input type="checkbox"/> Important uncertainty or variability <input checked="" type="checkbox"/> Possibly important uncertainty or variability <input type="checkbox"/> Probably no important uncertainty or variability <input type="checkbox"/> No important uncertainty or variability <input type="checkbox"/> No known undesirable outcomes	<p><b>The relative importance or values of the main outcomes of interest:</b></p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Variability</th> </tr> </thead> <tbody> <tr> <td>Thyroid cancer</td> <td>Critical for younger population</td> <td>–</td> </tr> <tr> <td>Hypothyroidism</td> <td>Not important for general population</td> <td>–</td> </tr> <tr> <td>Auto-immune thyroiditis</td> <td>Not important</td> <td>–</td> </tr> <tr> <td>Thyroidal adverse effects of stable iodine</td> <td>Important for neonates, breastfeeding mothers and older population</td> <td>May be more relevant in settings with iodine deficiency</td> </tr> <tr> <td>Non-thyroidal adverse effects of stable iodine</td> <td>Not important, very rare</td> <td>–</td> </tr> </tbody> </table>	Outcome	Relative importance	Variability	Thyroid cancer	Critical for younger population	–	Hypothyroidism	Not important for general population	–	Auto-immune thyroiditis	Not important	–	Thyroidal adverse effects of stable iodine	Important for neonates, breastfeeding mothers and older population	May be more relevant in settings with iodine deficiency	Non-thyroidal adverse effects of stable iodine	Not important, very rare	–	<ul style="list-style-type: none"> <li>■ The judgement was that there is possibly important variability for overall risk but maybe not for thyroid cancer specifically.</li> <li>■ Values may relate to whether the local population is benefiting from a nuclear energy source, which may make the population perception less negative and more accepting regarding potential risks.</li> </ul>
Outcome	Relative importance	Variability																			
Thyroid cancer	Critical for younger population	–																			
Hypothyroidism	Not important for general population	–																			
Auto-immune thyroiditis	Not important	–																			
Thyroidal adverse effects of stable iodine	Important for neonates, breastfeeding mothers and older population	May be more relevant in settings with iodine deficiency																			
Non-thyroidal adverse effects of stable iodine	Not important, very rare	–																			

Criteria	Judgements	Research evidence	Additional considerations
<b>Benefits &amp; harms</b>			
<b>What is the overall confidence in effect estimates (quality of evidence) ?</b>	<input checked="" type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High	<ul style="list-style-type: none"> <li>■ Chernobyl thyroid cancer incidence among persons &lt; 18 years with history of stable iodine intake around time of accident: 66/100,000 person-years; no intake 96/100,000. (A5)</li> </ul>	<ul style="list-style-type: none"> <li>■ Children and adolescents, pregnant and breast-feeding women are most likely to benefit from iodine thyroid blocking (ITB).</li> </ul>
<b>How substantial are the benefits?</b>	<input type="checkbox"/> Don't know <input type="checkbox"/> Not important <input type="checkbox"/> Somewhat important <input checked="" type="checkbox"/> Moderately important <input type="checkbox"/> Very important <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ Absolute effect of stable iodine intake based on data from Brenner et al. among 100,000 individuals aged between 0 and 18 years receiving potassium iodide (KI), 30 less people will develop thyroid cancer. Note that the benefit is likely to be greater if sufficient dose of KI is administered, resulting in almost complete blockage of radioactive iodine uptake. (A5)</li> <li>■ No high quality evidence. Polish data on transient functional changes (TSH increase) in 0.37% of neonates received KI or lughole solution 0.2% of extra-thyroid effects in adults (A10).</li> <li>■ Transient thyroid function effects in TEPCO workers. (A11)</li> <li>■ Data on the effect of timing of stable iodine administration is available in some reports. (A12)</li> </ul>	<ul style="list-style-type: none"> <li>■ Benefit will be higher in settings with nutritional iodine deficiency.</li> <li>■ Older adults are less likely to benefit from ITB</li> <li>■ Out of nine voting members of guideline development group (GDG), five voted very important, four – moderately important, keeping in mind that the issue is moderately important from societal and public health perspectives but could be very important from individual and clinical perspectives.</li> </ul>
<b>How substantial are the harms?</b>	<input type="checkbox"/> Don't know <input type="checkbox"/> Very important <input type="checkbox"/> Moderately important <input checked="" type="checkbox"/> Somewhat important <input type="checkbox"/> Not important <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ Older adults and persons with pre-existing thyroid diseases are more likely to be harmed by ITB. (A13,A14)</li> </ul>	
<b>Do the benefits outweigh the harms?</b>	<input type="checkbox"/> No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Varies		
<b>Resource use</b>			
<b>How large are the resource requirements?</b>	<input type="checkbox"/> Large costs <input checked="" type="checkbox"/> Moderate costs <input type="checkbox"/> Small <input type="checkbox"/> Moderate savings <input type="checkbox"/> Large savings <input type="checkbox"/> Varies/Uncertain	<ul style="list-style-type: none"> <li>■ There is limited evidence available on the estimated costs of ITB implementation in actual nuclear emergencies, as past experience is very limited. The issue was to some degree addressed in certain national reports. However, this does not allow for definitive conclusions. (A15,A16)</li> <li>■ Some earlier reports indicated that required resources for implementing ITB are low. (A17) However, this will depend on each country's specific situation and risk profile (e.g. number of nuclear power plants, population size and density, etc.).</li> </ul>	<ul style="list-style-type: none"> <li>■ Resources required include: stable iodine stockpile acquisition, management, disposal and renewal, storage, awareness-raising among the public and health care providers, communication campaigns, logistics of distribution/pre-distribution.</li> <li>■ Saved costs would be related to the burden caused by management of thyroid cancer.</li> </ul>

Criteria	Judgements	Research evidence	Additional considerations
<b>How large is the incremental cost relative to the net benefit?</b>	<input type="checkbox"/> Large costs <input checked="" type="checkbox"/> Moderate costs <input type="checkbox"/> Small <input type="checkbox"/> Moderate savings <input type="checkbox"/> Large savings <hr/> <input type="checkbox"/> Varies/ Uncertain	<ul style="list-style-type: none"> <li>■ Given the long-lasting health consequences of nuclear emergencies, health surveillance and treatment programmes are critical for management of health conditions, and emergency preparedness plans are needed to prevent or minimize the impact of future threats.</li> <li>■ An overview of probabilistic risk for core melt/severe reactor accident included data from the United States of America, Japan, France, Germany, etc. and demonstrated a low risk of such events. (A18,A19)</li> <li>■ A study from Germany, which followed a different approach to this issue by looking at the risk of exposure to radioactive fallout rather than the risk of nuclear accident to occur, resulted in higher estimates of a probability. (A20)</li> </ul>	<ul style="list-style-type: none"> <li>■ Here judgement applies to the stockpiling of stable iodine, rather than administering it, as latter requires ensuring that a stockpile is in place.</li> <li>■ Considering risk of a severe nuclear accident (5 in 100,000 reactor-years), the cost-effectiveness of ITB maybe low.</li> <li>■ From a health policy-maker's perspective, ITB cost-effectiveness may be higher, since the actual cost of stable iodine tablets is low, whereas the benefit of preventing thyroid cancer in children will be high.</li> </ul>

### Equity

<b>What would be the impact on health inequities?</b>	<input type="checkbox"/> Increased <input type="checkbox"/> Probably increased <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Probably reduced <input type="checkbox"/> Reduced <hr/> <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ No actual evidence was identified.</li> </ul>	<ul style="list-style-type: none"> <li>■ The issue relates to pre-distribution choice, which varies from country to country. Pre-distribution is not explicitly included in the scope of this guideline, however, having comprehensive national programmes on emergency preparedness and response (EPR) planning would lead to increased equity.</li> </ul>
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### Acceptability

<b>Is the option acceptable to key stakeholders?</b>	<input type="checkbox"/> No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <hr/> <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ No evidence was identified in peer reviewed literature.</li> <li>■ Public consultations and ITB campaigns have been reported, e.g. in Western Germany, there was a public discussion last year (2016) leading to official claims for pre-distribution of potassium iodine tablets even though the Belgian nuclear power plant is in the far vicinity.</li> </ul>	<ul style="list-style-type: none"> <li>■ The acceptability will vary depending on the stakeholder.</li> <li>■ Stakeholders are: policy makers, emergency response agencies, general public, health care professionals, nuclear operators, nuclear safety authorities, radiation protection authorities, researchers and academia, stable iodine tablet manufacturers, risk communicators, etc.</li> </ul>
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Criteria	Judgements	Research evidence	Additional considerations
<b>Feasibility</b>			
<b>Is the option feasible to implement?</b>	<input type="checkbox"/> No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <input type="checkbox"/> Varies	<ul style="list-style-type: none"> <li>■ Aside from the evidence from Poland on ITB implementation (A10), there is no documented use of stable iodine in case of an actual nuclear or radiological emergency in the peer reviewed literature.</li> <li>■ In Fukushima, ITB was not broadly implemented due to the post-disaster conditions, interrupted communication channels, and confusion with regard to practical implementation issues.</li> <li>■ TEPCO workers involved in clean up and restoration works at the Fukushima Daiichi nuclear power plant, were reported to be over using KI pills, taking up to 80 pills. (A11) Aside from transient changes in thyroid function no side effects of KI overdose were reported.</li> <li>■ National policies on the use of stable iodine in nuclear emergency situations have been put in place in many countries. (A21)</li> </ul>	<ul style="list-style-type: none"> <li>■ In general, ITB is feasible in most cases as stable iodine tablets usually are easy available. In addition, it has a low cost and a long shelf life. In many countries, national ITB policies and arrangements are already established as a part of the national EPR planning. However, harmonization of national policies on KI cross-border, issues of stockpiling, extending shelf life, distribution and pre-distribution, still represent a challenge in some cases.</li> </ul>

Type of recommendation				
We recommend against the ITB or for the alternative <input type="checkbox"/>	We suggest not to use the ITB or to use the alternative <input type="checkbox"/>	We suggest using either the ITB or the alternative <input type="checkbox"/>	We suggest using the ITB <input checked="" type="checkbox"/>	We recommend the use of ITB <input type="checkbox"/>

## Recommendation

The panel suggests that during a radiological or nuclear emergency, provision of ITB to people who are at risk of being exposed to a radioiodine should be implemented as an urgent protective action (conditional recommendation based on very low quality evidence).

### Key considerations:

- The panel is aware of the fact, that randomized clinical trials (RCT) on the efficiency (with respect to prevention of thyroid cancer) and side effects of ITB in the case of a nuclear emergency are not feasible. This leads to a low or very low quality of evidence according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.
- ITB should be implemented as a component of comprehensive public health approach in combination with other protection actions (evacuation and sheltering, restriction in consumption of contaminated food and drinking water). ITB should not be considered as a single alternative.

- Provisions for ITB implementation need to be carefully considered at the planning stage (see implementation considerations below).
- Optimal timing of administration starts 24 hours prior to and up to two hours after the expected onset of exposure. It would still be reasonable to administer ITB up to eight hours after the estimated onset of exposure.
- Starting ITB later than 24 hours following the exposure may cause more harm than benefit (by prolonging the biological half-life of radioactive iodine in the thyroid).
- Single stable iodine administration is typically sufficient. However, in the case of prolonged (beyond 24 hours) or repeated exposure, and unavoidable ingestion of contaminated food and water, and when evacuation is not feasible, consider repeated administration of stable iodine. Neonates and older adults (over 60 years) should not receive repeated stable iodine administration.

## Justification

- There is well-documented evidence from various sources (epidemiological, experimental, pathophysiological, clinical, etc.) pointing to more benefits than harm of ITB and serving as reliable surrogates for outcome studies related to prevention of thyroid cancer.
- In addition, there is a positive cost-benefit association, as the resources required for an acquisition of stable iodine tablets and maintaining the stockpile are in general moderate, whereas preventing thyroid cancer in children outweighs the resources factor.
- Despite the fact that the evidence quality was graded as low and very low, based on a very limited number of relevant publications (four papers), the GDG panel decided to use the phrase “should be implemented” due to the fact that this urgent protective action is included in the key intervention during response to a nuclear accident, as reflected in the international safety standards co-sponsored by the World Health Organization (WHO). In addition, the combination of a moderate cost of the intervention with high potential impact, supports the GDG decision to use more affirmative wording, such as “should be implemented”.

## Subgroup considerations

- Individuals most likely to benefit include children, adolescents, pregnant and breastfeeding women, and people living in iodine deficient areas.
- Individuals older than 40 years are less likely to benefit from ITB.
- Neonates and older adults are at higher risk of adverse health effects of stable iodine.
- Individuals exposed to higher dose (e.g. emergency workers) are likely to benefit from ITB irrespective of age.

## Implementation considerations

- Develop a comprehensive ITB implementation plan including considerations for: chemical form, packaging, stockpiling, distribution and pre-distribution and identifying relevant locations (e.g. health care facilities, households, schools, workplaces and

kindergartens). For example, the International Atomic Energy Agency (IAEA) safety standards/requirements for pre-distribution planning zones (General Safety Requirements Part 7, for Table II 1 and 2) (A22).

- KI administration plan should include risk communication, training of health professionals and emergency responders and awareness-raising with the public (e.g. provision of leaflets).
- In the context of pre-distribution of KI, consider making individual professional advice, e.g. a pharmacist dispensing KI would provide specific advice, available to the public.
- There is a strong need to harmonize national approaches to ITB cross-border.
- WHO publications on iodine deficiency management provide basis for national policies development for management of iodine deficiency.
- Adequate education and risk communication to accompany ITB to avoid unjustified and improper use of stable iodine as well as giving false reassurance of its use.

## Monitoring and evaluation considerations

- To enable WHO to monitor the implementation of the new recommendations on ITB, a survey of national stable iodine policies was conducted in August–November 2016. The findings of the survey formed a baseline against which the implementation will be measured in future. The survey report will be published this year (2017).

## Research priorities

- Radioiodine biokinetics can be further studied in thyroid patients diagnosed or treated with radioisotopes of iodine. However desirable, randomized controlled studies on the effects of ITB in such patients are not ethical for obvious reasons, hence studies must be observational.
- More data is needed on the dosage, optimal timing and regimens for multiple administrations of stable iodine in case of repeated or protracted releases of radioactive iodine and the adverse health effects of stable iodine administration. Studies in primates could be helpful for these purposes.
- Research on feasibility, acceptability and overall effect of use of ITB on psychosocial outcomes (i.e. the role of community resilience) of radiation emergencies is needed.
- Detailed analysis of existing national practices for stable iodine pre-distribution and use is required.

## References

- A1. Guidelines for Iodine Prophylaxis following Nuclear Accidents – Update 1999. Geneva: World Health Organization; 1999.
- A2. Verger P, Aurengo A, Geoffroy B, Le Guen B. Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. *Thyroid*. 2004;11.
- A3. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chernobyl accident. *Br J Cancer*. 4 January 2011;104(1):181–187.
- A4. Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst*. 5 July 2006;98(13):897–903.
- A5. Brenner AV, Tronko MD, Hatch M, Bogdanova TI, Oliynik VA, et al. I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. *Environ Health Perspect*. July 2011;119(7):933–939.
- A6. Health effects of the Chernobyl accident and special health care programmes. Geneva: World Health Organization; 2006.
- A7. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al. Risk of thyroid cancer after exposure to <sup>131</sup>I in childhood. *Journal of the National Cancer Institute*. 2005; 97(10):724–732.
- A8. Zanzonico PB, Becker DV: Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by <sup>131</sup>I from radioactive fallout. *Health Phys*. 78 (2000)660–667.
- A9. Hedman C, Djärv T, Strang, P, Lindgren, CI. The effect of thyroid-related symptoms on long-term quality of life in patients with differentiated thyroid carcinoma – a population- based study in Sweden (epub ahead of print). *Thyroid*. May 2017.
- A10. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Amer J. med*. 1993;94:524–532.
- A11. M. Akashi. 2016 – personal communication.
- A12. Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by <sup>131</sup>I from radioactive fallout. *Health physics*. 2000;78(6):660–667.
- A13. Jang M, Kim HK, Choi CW, Kang CS..Age-dependent potassium iodide effect on the thyroid irradiation by <sup>131</sup>I and <sup>133</sup>I in the nuclear emergency. *Radiat Prot Dosimetry*. 2008;130(4):499–502.
- A14. Spallek L, Krille L, Reiners C, Schneider R, Yamashita S, Zeeb H. Adverse effects of iodine thyroid blocking: a systematic review. *Radiat Prot Dosimetry*, 3, July 2012;150:267–277.
- A15. US NAS report on distribution and administration of potassium iodide in the event of a nuclear incident, National Academy Press; 2004.

- A16. ATA Scientific statement on the use of potassium iodide (KI) ingestion in a nuclear emergency. Thyroid. 2017.
- A17. Planning for off-site response to radiation accidents in nuclear facilities. Vienna: International Atomic Energy Agency; 1979.
- A18. B.A. Leurs, R.C.N. Wit. Environmentally harmful support measures in EU Member States – Report for Director General Environment of the European Commission.. European Commission; 2003.
- A19. François L'éveque. Estimating the costs of nuclear power: benchmarks and uncertainties. 2013. HAL Id: hal-00782190 <https://hal-mines-paristech.archives-ouvertes.fr/hal-00782190v2> (Accessed 27 Nov. 2017).
- A20. J. Lelieveld, D. Kunkel , M. G. Lawrence. Global risk of radioactive fallout after major nuclear reactor accidents. Atmos. Chem. Phys. 2012;12:4245–4258.
- A21. Medical effectiveness of iodine prophylaxis in a nuclear reactor emergency situation and overview of European practices Final Report of Contract REN/08/NUCL/SI2.520028. DG/Energy/ Nuclear Energy Unit D4. Radiation protection reports, No. 165. European Commission; 2010
- A22. Preparedness and response for a nuclear or radiological emergency: general safety requirements part 7. Vienna: International Atomic Energy Agency; 2015. Jointly sponsored by the: Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, International Civil Aviation Organization, International Labour Organization, International Maritime Organization, INTERPOL, OECD Nuclear Energy Agency, Pan American Health Organization, Preparatory Commission for the Comprehensive Nuclear-Test-Ban-Treaty Organization, United Nations Environment Programme, United Nations Office for the Coordination of Humanitarian Affairs, World Health Organization, World Meteorological Organization.



# Glossary

## Accident

Any unintended event, including operating errors, equipment failures and other mishaps, the potential consequences of which are not negligible from the point of view of protection or safety and that may lead to significant consequences to people, the environment or the facility.

## Affected population

A population that has suffered the direct effects of a disaster (deaths, injuries, material losses, evacuation) and was in the affected geographical area at the time of the accident. The affected population also includes those who suffer the indirect effects of a disaster (i.e. social, economic, psychological impacts, etc.).

## Dosage

Schedule for administration of a pharmaceutical compound (e.g. potassium iodide) in a prescribed amount.

## Emergency

A non-routine situation or event that necessitates prompt action, primarily to mitigate a hazard or adverse consequences for human life, health, property or the environment. This includes:

- nuclear and radiological emergencies and conventional emergencies such as fires, releases of hazardous chemicals, storms or earthquakes; and
- situations for which prompt action is warranted to mitigate the effects of a perceived hazard.

## Nuclear emergency

An emergency in which there is, or is perceived to be, a hazard due to the exposure to ionizing radiation resulting from a nuclear chain reaction or from the decay of the products of a chain reaction.

## Radiological emergency

An emergency in which there is an actual or potential exposure to ionizing radiation, either accidental or deliberate, not resulting from a nuclear chain reaction, nor the decay of the products of a chain reaction. Radiological accident examples may include a lost radioactive source, transport accident, or over-exposure in a medical, research or industrial facility as a result of inappropriate use of radioactive sources or exposure generating devices (e.g. linear accelerators in radiotherapy).

In this document, for the sake of brevity, the term radiological or nuclear emergency is replaced by radiation emergency, which encompasses both types, regardless of the origin and scenario.

**Emergency plan**

A description of the objectives, policy and concept of operations for the response to an emergency and of the structure, authorities and responsibilities for a systematic, coordinated and effective response. The emergency plan serves as the basis for the development of other plans, procedures and checklists.

**Emergency preparedness**

The capability to take actions that will effectively mitigate the consequences of an emergency for human life, health, property and the environment.

**Emergency response**

An action taken in response to a nuclear or radiological emergency to mitigate the consequences for human life, health, property and the environment. Emergency response actions comprise of protective actions and other response actions. Other response actions include, for example, medical examination, consultation and treatment; registration and longer term medical follow-up; providing psychological support; and public information and other actions for mitigating non-radiological consequences and for public reassurance.

**Formulation**

The composition, both in terms of chemical form and quantity, of a pharmaceutical product (e.g. the exact quantity of potassium iodide in milligrams in a tablet).

**Iodine deficiency**

Iodine deficiency is the lack of iodine in the diet. It is the world's most prevalent, yet easily preventable, cause of brain damage in children. Iodine deficiency disorders, which can start before birth, jeopardize children's mental health and often their very survival. Serious iodine deficiency during pregnancy can result in stillbirth, spontaneous abortion, and congenital abnormalities such as cretinism, a grave, irreversible form of mental retardation that affects people living in iodine-deficient areas of Africa and Asia. However, of far greater significance is iodine deficiency disorders' less visible, yet pervasive, mental impairment that reduces intellectual capacity at home, in school and at work.

**Iodine thyroid blocking**

An urgent protective action involving administration of stable iodine in case of a radiological emergency or nuclear accident under the following conditions: (a) if exposure due to radioactive iodine is involved, (b) before or shortly after a release of radioactive iodine, and (c) within only a short period before or after the intake of radioactive iodine.

**Hyperthyroidism**

A clinical condition resulting from the excessive functional activity of the thyroid gland and a consequent effect of the excess thyroid hormone on tissues. Also known as thyrotoxicosis, the term is often used for the condition caused by the excessive production of the thyroid hormone.

**Hypothyroidism**

A syndrome that results from abnormally low secretion of thyroid hormones from the thyroid gland, leading to a decrease in basal metabolic rate. In its most severe form, there is accumulation of mucopolysaccharides in the skin and oedema, known as myxedema. Hypothyroidism in fetuses and new-borns may lead to mental retardation.

### Pre-distribution

Distribution and supervised storage of a specific product or an item at households or at local public centres in the target planning zones. This can include households, police stations, hospitals, pharmacies, schools, kindergartens, fire stations and other locations, from where distribution to individuals can be made at short notice. Pre-distribution as an action is accompanied by a formal protocol for storing, retrieving, distributing and replenishing the stock and training of the responsible personnel.

### Protective action

An action for the purposes of avoiding or reducing radiation doses that might otherwise be received in an emergency exposure situation or an existing exposure situation.

#### Urgent protective action

A protective action in the event of a nuclear or radiological emergency, which must be taken promptly (usually within hours to a day) in order to be effective, and the effectiveness of which will be markedly reduced if it is delayed.

- Urgent protective actions include iodine thyroid blocking, evacuation, short term sheltering, actions to reduce inadvertent ingestion, decontamination of individuals and prevention of ingestion of food, milk or drinking water possibly with contamination.
- A precautionary urgent protective action is an urgent protective action taken before or shortly after a release of radioactive material, or an exposure, on the basis of the prevailing conditions to avoid or to minimize severe deterministic effects.

#### Early protective action

A protective action in the event of a nuclear or radiological emergency that can be implemented within days to weeks and still be effective.

- The most common early protective actions are relocation and longer term restriction of the consumption of food potentially affected by contamination.

### Radioiodine

Any of nine short-lived man-made artificial radioisotopes of iodine. Iodine-131 and iodine-125 are the most significant ones. Radioiodine is used as radioactive tracers in research and clinical diagnosis in nuclear medicine for diagnostic tests as well as in radiotherapy for hyperactive thyroid gland (hyperthyroidism).

### Stable iodine

Stable iodine or non-radioactive iodine, is an essential nutrient that humans need and get through intake of food. Iodine is essential for the thyroid gland to function properly and produce thyroid hormones.

### Thyroid

The thyroid gland, or simply thyroid, is an endocrine gland located at the front of the neck. The thyroid secretes thyroid hormones, which primarily influence the metabolic rate and protein synthesis. The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are created from iodine and tyrosine. The thyroid also produces the hormone calcitonin, which plays a role in calcium homeostasis. These hormones guide some of the body's



essential functions, such as growth, physical development, control of heart rate, blood pressure, body temperature, and blood pressure.

### **Thyroid cancer**

A relatively uncommon type of cancer, that forms in the thyroid. Cancer starts when cells in the thyroid begin to grow out of control invading surrounding tissue, blood or lymph vessels with the potential to form metastases. Four main types of thyroid cancer are papillary, follicular, medullary, and anaplastic thyroid cancer.

### **Thyroid nodule**

Thyroid nodules are solid or fluid-filled lumps that form within the thyroid. The great majority of thyroid nodules do not cause symptoms and are never diagnosed. Unless larger than a certain size, thyroid nodules are not considered a serious condition requiring medical intervention. Thyroid cancer accounts for a very small percentage of thyroid nodules.

### **Vulnerable population groups**

Population groups for whom special arrangements are necessary in order for effective protective actions to be taken in the event of a nuclear or radiological emergency:

- a) people who are specifically sensitive to radiation exposure (e.g. children, pregnant or lactating women);
- b) people who may have difficulties to get direct access to ITB (e.g. hospitalized patients, school children, out-of-town visitors and tourists, among others);
- c) people with limited mobility and institutionalized persons (e.g. persons with disabilities, residents of retirement houses, hospices, among others).







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