IOP Publishing | Society for Radiological Protection Journal of Radiological Protection
J. Radiol. Prot. **36** (2016) R112–R130 doi:10.1088/0952-4746/36/4/R112

Review

The effects of iodine blocking on thyroid cancer, hypothyroidism and benign thyroid nodules following nuclear accidents: a systematic review

M Pfinder[1,2,3,4,6,7], S Dreger[1,7], L Christianson[1], S K Lhachimi[1,2,3] and H Zeeb[1,5]

[1] Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany
[2] Collaborative Research Group for Evidence-Based Public Health, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany
[3] Institute for Public Health and Nursing Research, Health Sciences, University of Bremen, Bremen, Germany
[4] Department of Health Promotion and Occupational Health Management, AOK Baden-Wuerttemberg, Stuttgart, Germany
[5] Health Sciences Bremen, University of Bremen, Bremen, Germany

E-mail: dr.manuela.pfinder@bw.aok.de, dreger@bips.uni-bremen.de, christianson@bips.uni-bremen.de, lhachimi@bips.uni-bremen.de and zeeb@bips.uni-bremen.de

Received 16 December 2015, revised 9 June 2016
Accepted for publication 8 July 2016
Published 21 September 2016

Abstract

A potential radiation protection method to reduce the risk of adverse health outcomes in the case of accidental radioactive iodine release is the administration of potassium iodide (KI). Although KI administration is recommended by WHO's Guidelines for Iodine Prophylaxis following Nuclear Accidents, a systematic review of the scientific evidence for the guidelines is lacking. Therefore, this study aims to systematically review the effects of KI administration in the case of accidental radioactive iodine release on thyroid cancer, hypothyroidism and benign thyroid nodules. We applied standard systematic review methodology for a search of the literature, selection of eligible studies, data extraction, assessment of risk of bias, assessment of heterogeneity, data synthesis, and the assessment of the quality of the evidence. We searched MEDLINE (via PubMed) and EMBASE. We found one cross-sectional study, one analytic cohort study and two case-control

[6] Author to whom any correspondence should be addressed.
[7] Co-first authorship: Manuela Pfinder and Steffen Dreger contributed equally to the work.

studies relating to our question. The number of participants ranged from 886–12 514. Two studies were conducted in children and two other studies in children and adults. It was not possible to conduct a meta-analysis. We identified low to very low-quality evidence that KI administration after a nuclear accident resulted in a reduction of the risk of thyroid cancer in children; however, the KI administration and dose was not well described in the studies. None of the studies investigated the effects of KI administration in the case of a nuclear accident on hypothyroidism and benign thyroid nodules. Low to very low-quality evidence suggests that KI intake following a nuclear accident may reduce the risk of thyroid cancer in children. No conclusions can be drawn about the effectiveness of KI intake with respect to the prevention of hypothyroidism and benign thyroid nodules.

Keywords: stable oral iodine, potassium iodide, Chernobyl, health outcomes, I-131, reactor accident

(Some figures may appear in colour only in the online journal)

1. Introduction

Several radioactive isotopes of iodine (e.g. I-129, I-131, I-133) are generated in large amounts as a by-product of uranium fission, which is primarily used in nuclear reactors for energy production. In the event of a nuclear reactor accident and when radioactive material is released to the atmosphere, radioactive isotopes of iodine may be incorporated into the human body through inhalation or ingestion of contaminated food and milk (Braverman *et al* 2014). I-131 with a half-life of 8 d is particularly relevant because of its potential to concentrate in the thyroid gland (Reiners and Schneider 2013). When inhaled, about 10%–30% of the radioactive iodine I-131 will primarily accumulate in the thyroid, while the remaining amount will be discharged from the body with the urine (Yoshida *et al* 2014). As part of I-131's decay process, beta-radiation is emitted and affects the thyroid and its surrounding tissue, and may lead to adverse health outcomes such as thyroid dysfunctions and thyroid cancer.

From the Life Span study, there is evidence for the development of benign and malignant thyroid nodules as a result of external exposure to ionizing radiation among the atomic bomb survivors (e.g. Preston *et al* 2007). Following the Chernobyl reactor accident, which involved a large release of I-131 into the environment, significantly increased numbers of thyroid cancer and thyroid dysfunction such as hypothyroidism were observed in individuals from highly contaminated regions in Ukraine and Belarus (Kazakov *et al* 1992, Likhtarev *et al* 1995, Heidenreich *et al* 1999). Regarding thyroid cancer, a study from Belarus suggests that incidence rates between 1970 and 2001 increased from 0.4 per 100 000 to 3.5 per 100 000 among males and from 0.8 per 100 000 to 16.2 per 100 000 among females, with higher relative increases in high compared to lower exposure areas of Belarus (Mahoney *et al* 2004).

In addition, children and adolescents have been found to be at higher risk for developing thyroid diseases compared to adults. This is due to their smaller thyroid gland, its development during childhood and adolescence which leads to a 5–10 fold increase of committed thyroid dose, higher uptake of radioiodine, and higher sensitivity to radioiodine release of the organs, tissues and cells (Klugbauer *et al* 1995, Shakhtarin *et al* 2003, Cardis *et al* 2005). Furthermore, it is suggested that radiation exposure during the prenatal phase is associated

with an increased risk of thyroid cancer (Hatch *et al* 2009), and I-131 transmission from mother to infant during breastfeeding has been investigated as an additional risk factor for infants to develop thyroid cancer in later stages in life (Miller and Zanzonico 2005, Schneider and Smith 2012). In contrast, radiation-induced thyroid cancer risk for adults is thought to be very low and may be close to zero (Thompson *et al* 1994). Hypothyroidism is considered a potential outcome associated with ionizing radiation exposure caused by immediate cell killing after high radiation doses or as the late effect of lower doses, for example through the induction of autoimmune disease (Ron and Brenner 2010).

The oral administration of potassium iodide (KI) is assumed to be the most effective and preventive radiation protection measure to reduce the risk of adverse health outcomes for the exposed population in the event of an accidental release of any isotopes of radioactive iodine (Le Guen *et al* 2007, Jang *et al* 2008b). KI is essentially thought to saturate the iodide transport mechanism of the thyroid by inhibiting the intrathyroid organification of iodide (acute Wolff–Chaikoff effect), by dilution and by promoting excretion and thus, reducing the amount of committed dose to the thyroid gland, its surrounding tissue, and the body (Sternthal *et al* 1980, Becker 1983, Adelstein 1991).

The suggested KI administration dose depends on the predicted exposure levels to the thyroid of the defined population groups (i.e. intervention/action levels) (WHO 1999, European Commission 2010). The suggested KI doses further vary to account for the respective risks of vulnerable population groups (newborn, children and adolescents, and pregnant and lactating women). The effective blocking of the thyroid is thought to be achieved with a dose of 130–170 mg of KI (Federal Drug Administration 2001, European Commission 2010). Fractions of these quantities are suggested to be used in specific population groups (1 in adults and adolescents in addition to pregnant and lactating women, if necessary; 1/2 in children; 1/4 in infants; 1/8 in newborns) (WHO 1999, Federal Drug Administration 2001). Although KI administration blocks the thyroid gland, it does not provide complete protection from accumulating radioactive iodine. A single dose of KI approximately blocks the thyroid for between 24 and 36 h but the blocking capacity decreases with increased time after administration (Federal Drug Administration 2001, European Commission 2010). In the event of the continuous release of I-131, repeated administration may be required to ensure prolonged protection of the general population as the speculated protective effect of one KI dose is thought to decrease with time (WHO 1999).

The Polish government initiated KI administration in the Polish general population, in particular in children and adolescents, in late April and early May 1986 as a consequence of the reactor accident in Chernobyl and the subsequent discharge of radioactive iodine to the environment. Assessing the efficacy of KI administration, Nauman and Wolff (1993) estimated a reduction in committed thyroid dose between 40% and 62% for those children who were administered KI one to four days after the start of exposure. With regard to the timing of the intervention, a simulation study demonstrated higher protective KI efficacy when its administration is carried out in early exposure stages (78.9% versus 39.1% with KI given within 2 h or at 8 h after uptake of radioactive iodine, respectively) (Jang *et al* 2008a). It is notable that in Poland, where immediate thyroid blocking measures using KI solution were implemented within the first 4 d after the start of the exposure, about 90% of the children under the age of 16 showed thyroid dose commitments below the predicted mean maximal burden (<50 mSv) in this risk group (Nauman and Wolff 1993).

A recent systematic review further examined the adverse side effects of KI administration to block the thyroid (Spallek *et al* 2012). The evidence gathered suggested that even the administration of comparatively high doses of KI did not result in serious adverse health outcomes

in the exposed population groups. Severe reactions of clinical significance were rare and in particular observed in individuals with pre-existing thyroid disorders and iodine sensitivity. There was little data available on age differences. The review results, however, suggested that newborns and the elderly may experience more adverse side effects after KI administration compared to other age groups (Spallek *et al* 2012). Overall, the evidence-base was relatively weak, because with the exception of the Polish study by Nauman and Wolff (1993) most studies on the effects of KI were primarily set in the clinical context and addressed exposure reduction as part of therapy procedures, with comparatively high organ doses.

KI administration is endorsed by the 1999 WHO's Guidelines for Iodine Prophylaxis following Nuclear Accidents (WHO 1999) and is also widely implemented in most national guidelines (Federal Drug Administration 2001, National Radiological Protection Board 2001, European Commission 2010). To date, the current guidelines are primarily based on expert opinion, but the scientific base has not been reviewed systematically.

As part of the update of the existing WHO guideline from 1999 (WHO 1999), present WHO regulations for guidelines development require a systematic review of the scientific evidence in order to inform the updating process (WHO 2014). Thus, the present project aims to provide an up-to-date review on the efficacy of KI administration to reduce adverse health outcomes such as thyroid dysfunctions and thyroid cancer for the general population in the event of an accidental release of radioactive iodine to the environment.

We aimed to assess the effects of KI administration on thyroid cancer, hypothyroidism, and benign thyroid nodules in a population exposed to radioiodine release. Specifically, we wanted to

- assess whether specific population groups (e.g. children and adolescents between 0 and 18 years of age, pregnant or lactating women) are differentially affected by KI administration
- identify appropriate timing
- assess whether repeated KI administration may be warranted in circumstances of repeated/continuous exposure to reduce the accumulation of I-131 in the thyroid gland in the exposed population compared to no intervention.

The study's objective was based on the following specific question, formulated in the PICO (population, intervention, comparison, outcome) style:

In a population exposed to radioiodine release (P), does the administration of KI for prophylaxis (I) versus no administration of KI (C) affect the risk of relevant outcomes, including thyroid cancer, hypothyroidism, and benign thyroid nodules (O)?

Two sub-PICOs on the issue of the timing of KI administration and on repeat administration in the case of continuous release of radionuclides were also formulated, but are not reported in depth here as no evidence was found.

2. Methods

2.1. Criteria for considering studies for this review

The review covered a broad spectrum of study types, including randomized and non-randomized studies (RCTs, Quasi-RCTs, controlled before-after studies, time-series analysis, cohort studies, case-control studies, surveys, e.g. pharmaco-epidemiological studies). Individuals who were exposed to external ionizing radiation or radioactive iodine in the environment (including the general population and workers) were considered. Stable oral iodine/KI administration, irrespective of the dosing or timing, were considered as interventions, and no oral

iodine/KI administration as an eligible comparison. Studies that report on thyroid cancer, hypothyroidism, benign thyroid nodules, and mortality from thyroid cancer as outcome measures were included in this review.

2.2. Search methods for identification of studies

MEDLINE (via PubMed) and Excerpta Medica database (EMBASE) were searched using detailed, database-specific searches using a broad set of relevant keywords and terms. The search strategy was applied with additional keywords for possible comparators and without the use of filters for study types to improve the results of the literature search with respect to the total number of relevant studies. The literature search was limited to evidence from studies in humans. Databases, as listed above, were searched on 16 June 2015. All reference lists of relevant records were searched by hand for additional relevant studies. For details on the MEDLINE and EMBASE search strategies, see appendices A and B, respectively.

A review advisory group of experts supported the planning for the literature search and provided feedback on the research questions, the search strategy and the selected databases as well as on the review results.

2.3. Data collection and analysis

A research librarian assisted with conducting the database search for relevant studies (LC). First, studies' titles and abstracts, if feasible, as identified by the search were reviewed by two authors in duplicate and independently (SD, MP). Second, both reviewers compared their list of relevant studies and in the case of any disagreement the opinion of a third author was decisive (HZ). Third, full texts of potentially relevant studies were retrieved or obtained. Fourth, the full texts were screened by two reviewers in duplicate and independently (SD, MP). They used standardized and piloted data extraction forms. Fifth, the reviewers compared their list with each other and in the case of any disagreement the opinion of a third author was decisive (HZ). In addition, a third author screened the list of relevant studies (HZ).

Based on these steps, studies were included for the review. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart to visualize the selection of the included studies (see figure 1). Moreover, we provide a table with statements on excluded studies (overview available on request).

Data extraction was performed by two authors in duplicate and independently (SD, MP). In case of any disagreement, the opinion of a third author was decisive (HZ). We used a modified data extraction and assessment template from the Cochrane Public Health Group (CPHG). Previous to the major data extraction process, the authors piloted the data extraction form to ensure a standardized extraction. We extracted general information (publication type, country of study, funding source of study, potential conflict of interest from funding), study characteristics (type of study, participants, type of intervention, duration of intervention, type of control, and type of outcome measures, and other relevant information).

2.4. Assessment of risk of bias in included studies

The risk of bias of every included study was evaluated by two authors in duplicate and independently (SD, MP). In the case of any disagreement, the opinion of a third author was decisive (SL).

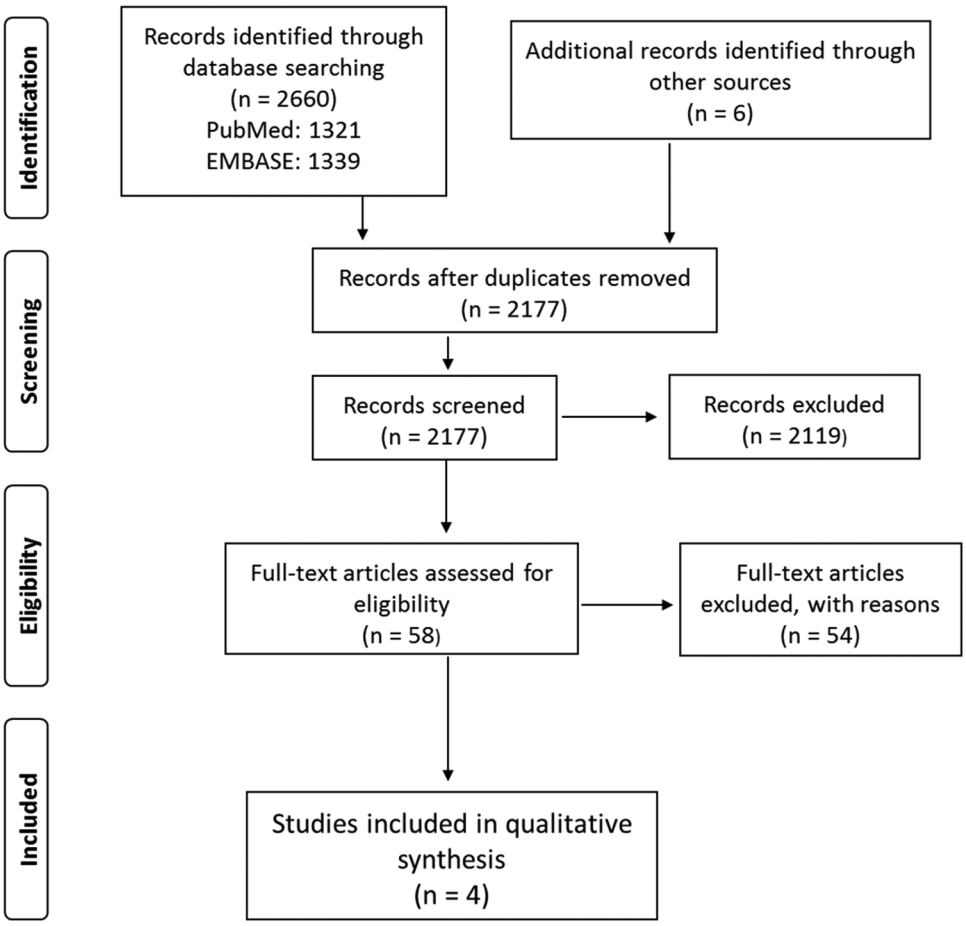

Figure 1. Study flow diagram.

We used the Quality Assessment Tool for Quantitative Studies, based on the Effective Public Health Practice Project (EPHPP) Guidelines. To judge the risk of bias according to the Quality Assessment Tool for Quantitative Studies, the following three categories were used: 'strong', 'moderate', and 'weak' (Jackson and Waters 2005).

We *a priori* considered unit of analysis issues, how to deal with missing data, assessment of heterogeneity, assessment of reporting bias, data synthesis, subgroup analysis, and sensitivity analysis. As we did not perform meta-analyses, there is no need to further deepen these methodological approaches in this context. However, details are outlined in the review protocol (Dreger *et al* 2015).

2.5. Assessment of the quality of evidence

We provided a 'GRADE evidence profile' table (The Cochrane Collaboration 2011) (appendix C). This table includes information on the outcomes, the study design, the relative and absolute effect, the number of patients/participants, the number of studies included, the quality assessment, and the overall quality of evidence.

3. Results

3.1. Description of studies

Figure 1 shows the amended PRISMA flow diagram of study selection. Out of 2260 initially identified records, we determined that 58 were potentially relevant for full text assessment. After screening the full texts, four studies fulfilled the inclusion criteria.

We excluded the remaining 54 for the following reasons: there were eight clinical experimental studies, four simulation studies, five dosimetry studies, eleven papers categorized as note, editorial, dossier or policy review, eight overview papers on KI administration and distribution, two papers with missing outcomes, two papers with missing interventions, and 14 papers on KI usage in Poland after Chernobyl (in the Polish language, screened by a native speaker) that did not meet the inclusion criteria, mostly because no data or selective results were reported. An overview of all excluded studies is available on request.

3.1.1. Study design. Of the four included studies, two studies are case-control studies (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010), one study is an analytic cohort (Brenner *et al* 2011), and one study is a cross-sectional study (Zarzycki *et al* 1994). All studies are related to the Chernobyl accident.

3.1.2. Participants. The number of participants ranged from 886–12 514. Participants were from Ukraine (Brenner *et al* 2011), Belarus and the Russian Federation (Cardis *et al* 2005), and Poland (Zarzycki *et al* 1994, Bandurska-Stankiewicz *et al* 2010). There was no overlap in the populations studied. Participants from the studies in Poland were from two different areas, namely Suwalki province (Zarzycki *et al* 1994) and Olsztyn province (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010).

The case-control studies had 1576 and 886 participants, respectively (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010). In the larger case-control study, the participants were younger than 15 years and in the smaller one, the participants were between 0 and 85+ years. In the analytic cohort study, 12 514 participants younger than 18 years were involved. The cross-sectional study had 1457 participants in the age range of 6–55 years (Zarzycki *et al* 1994).

3.1.3. Interventions. In all studies, some subjects received KI in the form of iodine prophylaxis (Zarzycki *et al* 1994), potassium iodine as antistrumin (Cardis *et al* 2005) or Lugol's solution (Brenner *et al* 2011). Although one study mentions that some participants repeated KI intake and some participants took KI during the five days following the nuclear accident, whereas others received KI later, differences in the health effects according to dosage and timing were not investigated (Zarzycki *et al* 1994). The reports on the studies by Cardis *et al* (2005) and Brenner *et al* (2011) do not allow a clear-cut differentiation as to whether KI was taken only after the accident, or possibly as a goiter prophylaxis even before the accident. No details on intake levels around the time of the accident were provided. I.e. a tablet of the reported agent (antistrumin = KI) usually contains 0.5–1 mg of KI, so that thyroid blocking could only be achieved with the intake of multiple tablets to reach the necessary amount of a 30–130 mg dose in adults. Iodine prophylaxis against endemic goiter, however, is usually performed with doses that are two to three magnitudes lower.

3.1.4. Outcomes. Thyroid cancer was generally defined as histologically confirmed cancer that was diagnosed after clinical and laboratory findings during screening examinations.

Table 1. Studies included in the review.

First authors (year)	Location	Study design	Population	Interventions	Outcomes
Zarzycki *et al* (1994)	Poland	Cross-sectional study	-1457 subjects -6–55 years of age	Iodine prophylaxis	-Anti-human thyroid membrane antibodies (ATMA) -Anti-thyreoglobulin antibodies (TGAb)
Cardis *et al* (2005)	Russia	Case-control study	-276 case patients with thyroid carcinoma -1300 control subjects - < 15 years of age at Chernobyl accident -Resided in Russia	Potassium iodide as antistrumin	Thyroid cancer
Brenner *et al* (2011)	Ukraine	Analytic cohort	-Individuals with direct thyroid radioactivity measurements - < 18 years of age on 26 April 1986 -Resided in Ukraine	Iodine prophylaxis	Thyroid cancer
Bandurska-Stankiewicz *et al* (2010)	Poland	Case-control study	-297 case patients with thyroid carcinoma -589 healthy control subjects -0–85+ years of age	Iodine prophylaxis (Lugol's solution)	Thyroid cancer

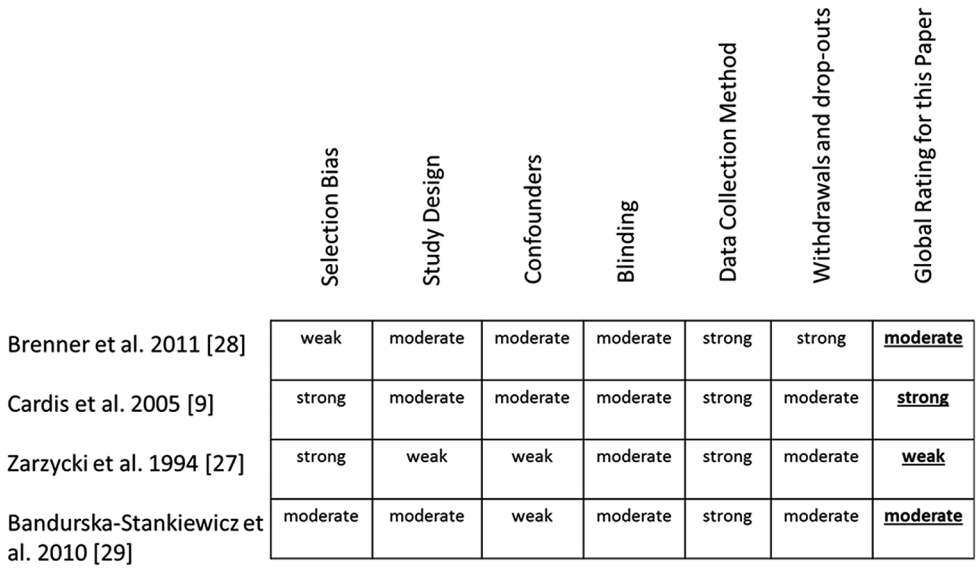

Figure 2. Methodological quality summary based on the EPHPP Guidelines.

None of the studies assessed hypothyroidism and benign thyroid nodules. The measured outcomes were antithyroid antibodies (TA) including anti-human thyroid membrane antibodies (ATMA) and anti-thyreoglobulin antibodies (TGAb) (Zarzycki *et al* 1994), and thyroid cancer (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010, Brenner *et al* 2011). TA were measured with the ELISA method using Plastomed reagent kits. Details of the characteristics of the included studies are shown in table 1.

3.2. Risk of bias in included studies

The methodological quality summary based on the EPHPP quality assessment tool is summarized in figure 2.

We *a priori* considered allocation concealment and blinding of participants and outcomes for RCT as outlined in the protocol. Withdrawals and losses to follow-up were described only by one study (Brenner *et al* 2011). None of the studies mentioned an intention-to-treat analysis. Selective reporting is not likely to have occurred as studies reported both significant and non-significant results.

Other potential sources of bias might be levels of KI administration and levels of exposure to radioactive iodine: As indicated, only the two studies with separate study populations from Poland focused on a post-accident KI intervention, while the other two studies reported on iodine prophylaxis without further detail, but with potentially much lower KI doses than required for thyroid blockage, as explained earlier. In all the studies, timing, exact dosage of KI administration (quantity and repetition) and levels of exposure to radioactive iodine were not clear. Therefore, the results might be biased by timing and dosage of KI administration and by levels of radioactive iodine exposure.

3.3. Effects of interventions

The effects of KI administration on ATMA, TGAb (Zarzycki *et al* 1994), and thyroid cancer (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010, Brenner *et al* 2011) are shown in appendix C.

3.3.1. Anti-human thyroid membrane antibodies and anti-thyreoglobulin antibodies. Zarzycki *et al* (1994) measured ATMA and TGAb. In the descriptive analysis they did not find significant differences between adult participants who took KI and the control group. Prevalence rates for ATMA were 13% in the KI group and 14% in the control group. Prevalence rates for TGAb were 10% in the KI group and 13% in the control group. Calculating the relative risk resulted in an OR of 0.92 (95% CI 0.56–1.50) for ATMA and OR 0.74 (95% CI 0.43–1.27) for TgAB. The size of the children subgroup was too small to compare the effects of KI on ATMA and TGAb. In general, the study population was too small to run multivariate analyses.

3.3.2. Thyroid cancer. Three of the four studies measured thyroid cancer (Cardis *et al* 2005, Bandurska-Stankiewicz *et al* 2010, Brenner *et al* 2011). Bandurska-Stankiewicz *et al* (2010) did not find significant differences in intake of KI in those who were diagnosed with cancer compared to the control group. Of the case patients with thyroid cancer, 31% had taken KI, while in the control group, 34% had taken KI. The respective OR was calculated as 0.87 (95% CI 0.65–1.18) for thyroid cancer after KI intake.

Brenner *et al* (2011) investigated the effect modification of the excess relative risk (ERR) of incident thyroid cancer per Gy of exposure according to KI intake. The effect modification was not significant ($p = 0.56$), with an ERR Gy^{-1} of 2.11 (95% CI 0.36–9.28) for no KI administration and an ERR $Gy^{-1}$of 1.03 (95% CI 0.08–9.84) for KI administration. Based on data given per person years, we calculated the unadjusted relative effect of thyroid cancer after KI intake, resulting in an OR of 0.68 (95% CI 0.36–1.28).

Cardis *et al* (2005) reported a statistically significant threefold reduction (OR_{adj} 0.31, 95% 0.1–0.9) in the odds of thyroid cancer at 1 Gy in the group who took KI (possibly at rather low doses) compared to the reference group. This low OR was independent of soil iodide content in the respective area of residence. Based on data provided from the study authors, a simple case-control analysis in RevMan 5.3 resulted in an OR of 0.38 (95% CI 0.20–0.70).

4. Discussion

4.1. Summary of main results

Expectedly, we did not find a randomized controlled trial relating to our study question. We included two case-control studies, an analytic cohort and one cross-sectional study. In total, the studies included did not assess all of the outcomes we considered important *a priori*. Thus, we cannot report on the effect of KI in the case of nuclear accident on two relevant outcomes, i.e. hypothyroidism and benign thyroid nodules. The studies identified as relevant did not allow extracting information on subgroups. We were not able to establish a dose–response relationship between KI intake and health outcomes as the studies did not assess different quantities and repeated intake of KI. Two studies reported non-significant results on the relationship between prophylactic KI and thyroid cancer. The confidence intervals were wide, but the studies showed a tendency of decreased risks of developing thyroid cancer if KI was administered. This tendency was supported by a significant result from one study in children on considerably reduced risks of thyroid cancer after KI intake, albeit at potentially lower doses than required for thyroid blockage. Low to very low-quality evidence suggests that KI intake following a nuclear accident may reduce the risk of thyroid cancer in children.

4.2. Overall completeness and applicability of evidence

The overall evidence base for the effect of KI administration after exposure to radioiodine release is rather incomplete, with the majority of studies investigating the association between KI intake and the risk of thyroid cancer. The review included studies from different countries and regions. It becomes apparent that comparability of results across studies is difficult due to diverse magnitudes of exposure in the different geographical regions, which were not always controlled. However, the limited evidence available suggests that the administration of KI might reduce the risk of adverse health outcomes after accidental release of radioiodine.

The studies included in the review focused on children, adults or both. Children may be the most vulnerable population due to the increased absorption of radioiodine. It is noteworthy that considerable effects of KI intake on the risk of developing thyroid cancer in children younger than 15 years were reported from one study included in the review (Cardis *et al* 2005), even if details of the KI administration and intake level remain uncertain.

The evidence base for outcomes was of very low to low quality. Key methodological limitations were control for confounding and the study design. Limitations in the study design and execution, as well as imprecision were major weaknesses for the outcomes (for details see appendix C).

4.3. Potential biases in the review process

We have performed an extensive literature research. However, there could be relevant gray literature and unpublished studies that we did not find during the search process, and therefore, did not consider in our review. We did, however, contact experts with specific overview of the publication landscape in Russian as well as in the Japanese language to help us identify potential data sources or regional data bases of relevance for our study question. However, no additional relevant information was obtained. Although we found studies from different geographical regions, our results might not apply to all countries and settings similarly, as levels of exposure might differ across geographical regions.

ATMA and TGAb are surrogates for the diagnosis of hypothyroidism. However, these antibodies are frequently detected in the general population not exposed to radioactive fallout. Therefore, results on ATMA and TGAb need to be interpreted with caution.

We are aware that experimental animal studies provide further valuable supporting evidence on the efficiency of thyroid blocking in preventing health-associated long-term consequences in the case of a nuclear accident. Our search strategy did not include animals as we focused on the effects in human populations for which the intervention is proposed; however, we highlight additional information from simulation studies, which might be considered equally informative.

Within and across studies, the timing and the quantity of KI intake was not specified, and therefore, the results might be biased in unknown ways.

4.4. Agreements and disagreements with other studies or reviews

This is the first systematic review on the effect of KI intake on thyroid cancer, hypothyroidism and benign thyroid nodules after a nuclear accident. Therefore, we cannot compare our results to other systematic reviews.

However, we found two simulation studies on the effect of KI on thyroid irradiation (Zanzonico and Becker 2000, Jang *et al* 2008b). These studies suggest that KI is highly

effective with regard to the prevention of radioiodine uptake when administered 48 h before and within two hours after exposure to radioiodine release. KI administration 48 h before exposure to radioiodine release results in an almost complete blocking of radioiodine uptake. However, the intake of KI 96 h before exposure to radioiodine release has no protective effect (Zanzonico and Becker 2000). These studies report a protective effect of KI intake after exposure to radioiodine release. The simulation studies report that the intake of KI within two hours after exposure to radioiodine release results in a blocking effectiveness of ca. 80% (Zanzonico and Becker 2000, Jang *et al* 2008b). The review authors consider this as important additional evidence.

Similarly, in the overall assessment of KI thyroid blocking (KITB), information on potential adverse effects should be included. We did not address this topic in the current systematic review, but an earlier review from our group found limited evidence for adverse effects. It was found that the intake of even comparatively high doses of KI did not result in serious adverse health outcomes in the exposed population groups. Severe reactions were rare and especially observed in individuals with pre-existing thyroid disorders and iodine sensitivity. Furthermore, the results suggested that adverse effects after KI administration may be more likely to occur in newborns and the elderly compared to other age groups (Spallek *et al* 2012).

4.5. Implications for practice

The results of this review suggest that KI administration following a nuclear accident may reduce the risk of thyroid cancer after exposure to radioactive iodine, particularly in children. However, this judgement is based on a small number of studies that provide low or very low-quality evidence. There is no evidence on the outcomes on hypothyroidism and benign thyroid nodules. The risk of the occurrence of immunological effects (ATMA and TgAB) could be reduced when subjects take KI in the case of a nuclear accident. Significant results on the decreased risks of thyroid cancer after KI intake following the release of radioiodine are based on data in children. The dosage and timing of KI administration in the study on persons who were aged <18 years at the time of the Chernobyl accident (Cardis *et al* 2005) were not well defined, and KI was potentially used at low doses. Therefore, the results need to be interpreted with caution.

4.6. Implications for research

Further studies of good quality are necessary to provide a better evidence base for the effects of KI on health outcomes in the case of nuclear accident. These studies should also investigate the effects in subgroups, e.g. pregnant women. In addition, the dosage and the timing of the intervention seem to be relevant for the effectiveness of KI on thyroid blockage. Therefore, future research must consider the timing and dosage when investigating the effects of KI on health outcomes after the release of radioiodine. Hypothyroidism and benign thyroid nodules should be additional outcomes of interest in future research on the effectiveness of KI administration after a nuclear accident. Conducting experimental studies with regard to these outcomes does not appear to be feasible due to ethical reasons.

Given that research on long-term intervention effects is possible only in the context of a—hopefully not-occurring—large-scale release of radionuclides, the verification of KITB effectiveness in experimental studies, such as randomized trials, is not conceivable, as the exposure generally constitutes an emergency situation. Nevertheless, in order to

obtain population-based evidence on the effectiveness, research planning is necessary. Considerations on how to include research components into emergency management plans for nuclear accidents might be a first step. Generally, an individualized radiation exposure assessment, coupled with specific information on KI intake, and a system for long-term follow-up of health effects would be needed to gain more reliable, cohort-based data on KITB effectiveness. Perhaps modern mobile communication technology could play an increasing role in planning and conducting such research in emergency situations, even though the vulnerability of ICT systems in disaster situations needs to be taken into account.

Acknowledgments

We wish to thank the review advisory board members Christoph Reiners, Rita Schneider (UK Würzburg, Germany), Elie Akl (American University of Beirut, Beirut, Lebanon), Zhanat Carr and Susan Norris (both WHO) for providing feedback on the research questions. Thank you also to Tomas Allen (WHO) who reviewed the search strategy and the selected databases, to Vladimir Saenko (Nagasaki University, Japan), who supported the literature search, and to Rafael Mikolajczyk for screening the studies in the Polish language. We also wish to thank Zohaib Khan for supporting the risk of bias assessment and the data extraction, and Elie Akl for carefully commenting on the final report.

This work was funded by the Federal Office for Radiation Protection (BfS), Germany under grant number 3614S60037.

Appendix A. MEDLINE/PubMed search

Block 1: Health conditions

Search name	Search query	Type of search	Results
1A(1)	"thyroid gland"[MeSH Terms] OR "hypothyroidism"[MeSH Terms] OR "thyroid diseases"[MeSH Terms] OR "thyroid neoplasms"[MeSH Terms] OR "neoplasms, radiation-induced"[MeSH Terms] OR "radiation dosage"[MeSH Terms] OR "radiation injuries"[MeSH Terms] OR "dose–response relationship, radiation"[MeSH Terms]	MeSH major & sub-terms	268.837
1B	((thyroid*[Title/Abstract]) AND dysfunction*[Title/Abstract] OR abnormality*[Title/Abstract] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumour[Title/Abstract] OR tumors[Title/Abstract] OR tumours[Title/Abstract] OR nodule*[Title/Abstract] OR carcinogen*[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignancy*[Title/Abstract] OR medullar*[Title/Abstract] OR metastases[Title/Abstract] OR metastasis*[Title/Abstract] OR enlarged[Title/Abstract] OR diseased*[Title/Abstract] OR hypothyroidism[Title/Abstract]))	Keyword TI/AB	85.439
1	1A(1) OR 1B		292.436

Block 2: Intervention(s)

Search name	Search query	Type of search	Results
2A(1)	"Potassium Iodide"[Mesh] OR "Iodine Radioisotopes"[Mesh]	MeSH major terms	50.555
2B	("ITB" OR "iodine thyroid blocking" OR "potassium iodide" OR "Iodine Radioisotope*" OR "KI" OR "sodium iodide" OR ((blockade* OR blocking OR administration) AND iodine) OR "stable iodine" OR ((prophylaxis OR prophylactic* OR "prophylactic agent*") AND (iodine* OR iodide*)))	keyword	83.987
2	2A(1) OR 2B		124.533

Block 3: Occurrence/location

Search name	Search query	Type of search	Results
3A	"Radioactive Hazard Release"[Mesh] OR "Radioactive Fallout"[Mesh] OR "Nuclear Warfare"[Mesh] OR "Nuclear Reactors"[Mesh] OR "Chernobyl Nuclear Accident"[Mesh] OR "Nuclear Power Plants"[Mesh] OR "Fukushima Nuclear Accident"[Mesh]	MESH major terms	15.430
3B(3)	((Nuclear* OR atomic OR reactor* OR radioactive* OR radiation OR radiological*) AND (accident* OR warfare OR contaminant* OR exposure* OR fallout OR meltdown OR disaster* OR catastrophe*)) OR ((Belarus OR Chernobyl OR Chornobyl OR Hiroshima OR Fukushima OR Gomel OR Homel OR Ukraine OR Minsk OR "3 mile" OR "three mile" OR Nagasaki OR Pripyat OR Poland OR Russia OR USSR OR "Soviet Union" OR Japan) AND (accident* OR warfare OR contaminant* OR exposure* OR fallout OR meltdown OR disaster* OR catastrophe*))	Keyword	175.763
3	3A OR 3B(3)		177.762

Limits: Publication types, human studies

Search name	Search query	Results
4A	"case reports"[Publication Type]	1.724.784
4B	("case reports"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])	1.908.867
4C	"animals"[Mesh]	17.833.169
4D	"humans"[Mesh]	13.824.418

Summary and results

Search name (saved in PubMed & EndNote)	Results
1 AND 2 AND 3	1.321
1 AND 2 AND 3 (AND) NOT 4A	1.240
1 AND 2 AND 3 (AND) NOT 4B	1.225

1 AND 2 AND 3 (AND) NOT 4A (AND) NOT 4C	47
1 AND 2 AND 3 (AND) NOT 4B (AND) NOT 4C	47
1 AND 2 AND 3 (AND) NOT 4A AND 4D	1.038
1 AND 2 AND 3 (AND) NOT 4B AND 4D	1.023

Appendix B. EMBASE search

Block 1: Health conditions

Search name	Search query	Type of search	Results
1A	("thyroid gland" or hypothyroidism or "thyroid disease" or "thyroid tumor" or "radiation induced neoplasm" or "radiation dose" or "radiation injury" or "radiation response").sh.	EMTREE headings & subheadings	200.489
1B	(thyroid* and (dysfuntion* or abnormality* or cancer* or tumor* or nodule* or carcinogen* or carcinoma* or malignancy* or medullar* or metastases or metastasis* or enlarged or diseased* or hypothyroidism)).ti,ab.	Keyword TI/AB	89.540
1	1A OR 1B		250.074

Block 2: Intervention(s)

Search name	Search query	Type of search	Results
2A	("potassium iodide" or "radioactive iodine").sh.	EMTREE headings & subheadings	13.298
2B	("ITB" or "iodine thyroid blocking" or "potassium iodide" or "Iodine Radioisotope*" or "KI" or "sodium iodide" or ((blockade* or blocking or administration) and iodine) or "stable iodine" or ((prophylaxis or prophylactic* or "prophylactic agent*") and (iodine* or iodide*))).mp.	mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword	71.537
2	2A OR 2B		79.961

Block 3: Occurrence/location

Search name	Search query	Type of search	Results
3A	("nuclear accident" or "radioactive waste" or "atomic warfare" or "Nuclear Reactor" or "Chernobyl accident" or "Nuclear Power Plant" or "Fukushima Nuclear Accident").sh.	EMTREE headings & subheadings	15.174

3B	(((Nuclear* or atomic or reactor* or radioactive* or radiation or radiological*) and (accident* or warfare or contaminant* or exposure* or fallout or meltdown or disaster* or catastrophe*)) or ((Belarus or Chernobyl or Chornobyl or Hiroshima or Fukushima or Gomel or Homel or Ukraine or Minsk or "3 mile" or "three mile" or Nagasaki or Pripyat or Poland or Russia or USSR or "Soviet Union" or Japan) and (accident* or warfare or contaminant* or exposure* or fallout or meltdown or disaster* or catastrophe*))).mp.	mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword	206.045
3	3A OR 3B		210.269

Limits

Search name	Search query	Results
4	elsevier.cr.	15.768.140

Summary and results

Search name	Results
1 AND 2 AND 3	1.339
1 AND 2 AND 3 AND 4	902

Translation of subject headings from MeSH to EMTREE terms
Block 1

MeSh term	EMTREE term
thyroid gland	thyroid gland
hypothyroidism	hypothyroidism
thyroid diseases	thyroid disease
Thyroid neoplasms	thyroid tumor
neoplasms, radiation-induced	radiation-induced neoplasm
radiation dosage	radiation dose
radiation injuries	radiation injury
dose–response relationship, radiation	radiation response

Block 2

MeSh term	EMTREE term
Potassium Iodide	potassium iodide
Iodine Radioisotopes	**radioactive iodine**

Block 3

MeSh term	EMTREE term
Radioactive Hazard Release	**Nuclear accident**
Radioactive Fallout	**Radioactive waste**
Nuclear Warfare	**atomic warfare**
Nuclear Reactors	Nuclear reactor
Chernobyl Nuclear Accident	**Chernobyl accident**
Nuclear Power Plants	Nuclear Power Plant
Fukushima Nuclear Accident	Fukushima Nuclear Accident

Appendix C. GRADE evidence profile

Is the administration of KI preferable to no treatment in people exposed to radioiodine release in the environment to reduce the risk of thyroid cancer, hypothyroidism and benign thyroid nodules?

		Quality assessment					Number of patients		Effect		
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	KI	No KI	Relative (95% CI)	Absolute (95% CI)	Quality
ATMA											
1	Cross-sectional study	Serious concern[a]	No serious concern	No serious concern	Very serious concern[b,c]	None	22/169 (13.0)	114/816 (14.0)	OR 0.92 (0.56–1.50)	10 fewer per 1000 (from 70 fewer to 50 more)	Very low
TGAb											
1	Cross-sectional study	Serious concern[a]	No serious concern	No serious concern	Very serious concern[b,c]	None	17/169 (10.1)	107/ 816 (13.1)	OR 0.74 (0.43–1.27)	30 fewer per 1000 (from 80 fewer to 20 more)	Very low
Thyroid cancer											
1	Analytic cohort	No serious concern	No serious concern	No serious concern	Serious concern[b]	None	12/ 18 154 (0.1)[f]	50/ 51 674 (0.1)[f]	OR 0.68 (0.36–1.28)[f]	——[f]	Low
2	Case-control study	Serious concern[a]	Serious concern[d]	No serious concern	Serious concern[b]	None	104/445 (23.4)[g]	313/1243 (25.2)[g]	OR 0.91 (0.70–1.17)[g]	10 fewer per 1000 (from 50 fewer to 10 more)[g]	Very low

[a] No control for confounding.
[b]Few events.
[c]Wide confidence intervals.
[d]Point estimates vary widely across studies and confidence intervals show no overlap.
[e]The absolute effect is based on the risk difference between the baseline of the control and the intervention group.
[f]Data are based on person years.
[g]Data are based on controls and cases.
CI: confidence interval; GRADE: grading of recommendations assessment, development and evaluation; OR: odds ratio.

References

Adelstein S 1991 Intervention Procedures for Radionuclides. In: *Anticarcinogenesis and Radiation Protection 2* O F Nygaard, A C Upton eds (New York: Plenum) pp 227–8

Bandurska-Stankiewicz E, Aksamit-Bialoszewska E, Stankiewicz A and Shafie D 2010 Did the Chernobyl atomic plant accident have an influence on the incidence of thyroid carcinoma in the province of Olsztyn? *Endokrynol. Pol.* **61** 437–42

Becker D V 1983 Physiological basis for the use of potassium iodide as a thyroid blocking agent logistic issues in its distribution *Bull. New York Acad. Med.* **59** 1003

Braverman E R, Blum K, Loeffke B, Baker R, Kreuk F, Yang S P and Hurley J R 2014 Managing terrorism or accidental nuclear errors, preparing for iodine-131 emergencies: a comprehensive review *Int. J. Environ. Res. Public Health* **11** 4158–200

Brenner A V *et al* 2011 I-131 dose response for incident thyroid cancers in Ukraine related to the Chornobyl accident *Environ. Health Perspect.* **119** 933–9

Cardis E *et al* 2005 Risk of thyroid cancer after exposure to 131I in childhood *J. Natl Cancer Inst.* **97** 724–32

Dreger S, Pfinder M, Christianson L, Lhachimi S K and Zeeb H 2015 The effects of iodine blocking following nuclear accidents on thyroid cancer, hypothyroidism, and benign thyroid nodules: design of a systematic review *Systematic Rev.* **4** 1–7

European Commission 2010 *Radiation Protection No. 165—Medical Effectiveness of Iodine Prophylaxis in a Nuclear Reactor Emergency Situation and Overview of European Practices* (Luxembourg: EC)

Federal Drug Administration 2001 *Guidance Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies* (FDA)

Hatch M *et al* 2009 A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to iodine-131 from Chernobyl fallout *J. Clin. End. Metab.* **94** 899–906

Heidenreich W F, Kenigsberg J, Jacob P, Buglova E, Goulko G, Paretzke H G, Demidchik E P and Golovneva A 1999 Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident *Radiat. Res.* **151** 617–25

Jackson N and Waters E 2005 Criteria for the systematic review of health promotion and public health interventions *Health Promotion Int.* **20** 367–74

Jang M, Kim H, Choi C and Kang C 2008a Age-dependent potassium iodide effect on the thyroid irradiation by 131I and 133I in the nuclear emergency *Radiat. Prot. Dosim.* **130** 499–502

Jang M, Kim H K, Choi C W and Kang C S 2008b Thyroid dose estimation with potassium iodide (KI) administration in a nuclear emergency *Radiat. Prot. Dosim.* **132** 303–7

Kazakov V, Demidchik E and Astakhova L 1992 Thyroid cancer after Chernobyl *Nature* **359** 21

Klugbauer S, Lengfelder E, Demidchik E P and Rabes H M 1995 High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident *Oncogene* **11** 2459–67

Le Guen B, Stricker L and Schlumberger M 2007 Distributing KI pills to minimize thyroid radiation exposure in case of a nuclear accident in France *Nat. Clin. Pract. End. Metab.* **3** 611

Likhtarev I, Sobolev B, Kairo I, Tronko N, Bogdanova T, Oleinic V, Epshtein E and Beral V 1995 Thyroid cancer in the Ukraine *Nature* **375** 365

Mahoney M C, Lawvere S, Falkner K L, Averkin Y I, Ostapenko V A, Michalek A M, Moysich K B and McCarthy P L 2004 Thyroid cancer incidence trends in Belarus: examining the impact of Chernobyl *Int. J. Epidemiol.* **33** 1025–33

Miller R W and Zanzonico P B 2005 Radioiodine fallout and breast-feeding *Radiat. Res.* **164** 339–40

National Radiological Protection Board 2001 *Stable Iodine Prophylaxis Recommendations of the 2nd UK Working Group on Stable Iodine Prophylaxis* (Didcot: NRPB)

Nauman J and Wolff J 1993 Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks *Am. J. Med.* **94** 524–32

Preston D L, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K and Kodama K 2007 Solid cancer incidence in atomic bomb survivors: 1958–1998 *Radiat. Res.* **168** 1–64

Reiners C and Schneider R 2013 Potassium iodide (KI) to block the thyroid from exposure to I-131: current questions and answers to be discussed *Radiat. Environ. Biophys.* **52** 189–93

Ron E and Brenner A 2010 Non-malignant thyroid diseases after a wide range of radiation exposures *Radiat. Res.* **174** 877–88

Schneider A B and Smith J M 2012 Potassium iodide prophylaxis: what have we learned and questions raised by the accident at the Fukushima Daiichi Nuclear Power Plant *Thyroid* **22** 344–6

Shakhtarin V V, Tsyb A F, Stepanenko V F, Orlov M Y, Kopecky K J and Davis S 2003 Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident *Int. J. Epidemiol.* **32** 584–91

Spallek L, Krille L, Reiners C, Schneider R, Yamashita S and Zeeb H 2012 Adverse effects of iodine thyroid blocking: a systematic review *Radiat. Prot. Dosim.* **150** 267–77

Sternthal E, Lipworth L, Stanley B, Abreau C, Fang S-L and Braverman L E 1980 Suppression of thyroid radioiodine uptake by various doses of stable iodide *New Engl. J. Med.* **303** 1083–8

The Cochrane Collaboration 2011 *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* J P Higgins and S Green eds (http://handbook.cochrane.org)

Thompson D E *et al* 1994 Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958–1987 *Radiat. Res.* **137** S17–67

WHO 1999 *Guidelines for Iodine Prophylaxis Following Nuclear Accidents: Update 1999* (Geneva: WHO)

WHO 2014 *WHO Handbook for Guideline Development* (Geneva: WHO)

Yoshida S, Ojino M, Ozaki T, Hatanaka T, Nomura K, Ishii M, Koriyama K and Akashi M 2014 Guidelines for iodine prophylaxis as a protective measure: information for physicians *Japan. Med. Assoc. J.* **57** 113–23

Zanzonico P B and Becker D V 2000 Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by 131I from radioactive fallout *Health Phys.* **78** 660–7

Zarzycki W, Zonenberg A, Telejko B and Kinalska I 1994 Iodine prophylaxis in the aftermath of the Chernobyl accident in the area of Sejny in north-eastern Poland *Hormone Metabolic Res. (Hormon- und Stoffwechselforschung = Hormones et Metabolisme)* **26** 293–6