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Title page:

Exposure to persistent organic pollutants and thyroid cancer risk: a study protocol of systematic review and meta-analysis

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Strengths and limitations of this study

- This will be the most comprehensive and up-to-date systematic review to synthesise the evidence on the health effects of exposure to any types of persistent organic pollutants on the incidence risk of thyroid cancer.
- We will use rigorous statistical methods to summarise all the currently eligible data from epidemiological studies, perform extensive sensitivity meta-analyses to evaluate the robustness of our findings.
- The main possible limitations of this study are a limited number of eligible studies and possibly significant heterogeneity between studies.
- Another potential limitation is that it may be difficult to evaluate publication bias if there are not sufficient studies included.

ABSTRACT:

Introduction: The thyroid cancer incidence has been increasing all over the world. However, the aetiology of thyroid cancer remains unclear. A growing body of evidence suggested exposure to persistent organic pollutants (POPs) may play a role in the initiation of thyroid cancer, but the results are generally inconsistent across studies. This review aims to synthesise the evidence for the health effects of POPs on the risk of thyroid cancer.

Methods and analysis: This protocol was reported in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statements. A comprehensive search, including electronic database search (e.g. PubMed, Embase, ProQuest, and CNKI), website search, and manual search, will be performed to identify all eligible studies. The Population, Exposure, Comparator and Outcome (PECO) framework was used to clarify the inclusion and exclusion criteria. The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of included studies. Maximally adjusted effect estimates from individual studies will be summarized with random-effect models in a conservative manner. I^2 statistics and Q-tests will be used to test the heterogeneity across studies. We will perform extensive sensitivity analyses, such as confounding RR, E-value, fixed-effect models, excluding the most relatively weighted study, including only the high-quality studies, and many predesigned subgroup analyses, etc. The findings will be reported in accordance to the PRISMA guidelines.

Ethics and dissemination: Ethical approval is not required in this systematic review of published literatures. The results will be published in a peer-reviewed journal and presented at relevant conferences.

PROSPERO registration number: CRD42020181343

1. INTRODUCTION

In the last decades, thyroid cancer was the most rapidly increasing cancer worldwide.[1 2] In 2020, there were 448,915 new cases in women worldwide, representing the fifth-most common cancer in women, compared with 137,287 new cases in men, representing the 16th-most common cancer in men.[1 3] In the United States, age-adjusted thyroid cancer incidence rate have increased approximately 4-fold from 4.8 cases/100,000 in 1975 to 17.4/100,000 in 2020 such that thyroid cancer incidence has been increased at an annual growth rate of about 3%.[3 4] This significant increase patter was not only unique to the United States but also to a lot of other countries. The growth rate in China was even higher than that in the United States.[5] In China, the estimated incidence of thyroid cancer reached 221,093 in 2020, accounting for about 38% of all annually diagnosed thyroid cancer cases.[3]

Although much of the increasing incidence of thyroid cancer is attributed to the improved detection and screening methods, this is unlikely to be the sole cause, since incidence rates are also obviously increasing among children, adolescents and young adults, or for more easily detectable cases with larger tumours.[6 7] Therefore, it is urgent to elucidate the aetiology of thyroid cancer. There are only a few well-established risk factors for thyroid cancer: gender, hereditary conditions, and ionizing radiation exposure (particularly when this exposure occurs during childhood).[1 2] However, the aetiology remains poorly understood. Recently, a growing body of evidence suggested exposure to persistent organic pollutants (POPs) may play a role in the initiation and development of thyroid cancer, but the results are not conclusive and generally inconsistent across studies.

POPs are a broad class of organic chemicals of global concern, that persist in the environment, bio-magnify and bio-accumulate through the food chain, can be transported all over the world.[8] There are three types of POPs most commonly encountered in the environment: 1) organochlorine pesticides (OCPs), such as dichlorodiphenyltrichloroethane (DDT) and its metabolites; 2) industrial chemicals, such as polychlorinated biphenyls (PCBs) and flame retardants (FRs) including polybrominated diphenyl ethers (PBDEs), brominated FRs (BFRs) and organophosphate FRs (PFRs); and 3) unintentional by-products of industrial processes such as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs).[9-11]

In our daily lives, POPs can be virtually detected in many products everywhere. Humans are exposed to POPs in various ways: mainly through diet, but also through the air and the skin absorption.[12 13] For the general population, the most common exposure route is dietary intake of contaminated fatty foods. Due to the bio-magnification and bio-accumulation through the food chain, the highest concentrations of POPs can be found in the human body, as the top of the food chain.[13]

A lot of evidence supports for their significant adverse effects on human health and the environment. Human exposure to these chemicals, even to low levels of POPs can result in many negative health effects including elevated cancer risk, endocrine disruption, immune function impairment, and reproductive disorders.[13 14] Recently, several epidemiological studies have shown that POP exposure has potential carcinogenesis properties in thyroid cancer.[15-19] However, the findings have been inconsistent. There is only one previous meta-analysis by Han et al. in 2019, which actually focused on the association of pesticides and thyroid cancer risk, but not for all types of POPs.[20]

Objectives

We therefore propose to conduct this systematic review and meta-analysis of epidemiological studies to comprehensively summarize the evidence for the effects of exposure to any types of POPs on the incidence risk of thyroid cancer in adult populations. The primary aims of this proposed study are to determine if there is an association between exposure to any types of POPs and the incidence risk of thyroid cancer; and to determine which subtypes of POPs exposure are associated with the thyroid cancer risk. The secondary aims will be to determine which individual POPs chemicals are associated with the thyroid cancer risk.

3. METHODS AND ANALYSIS

This study has been registered on PROSPERO (CRD42020181343).[21] The present protocol is in accordance to the PRISMA protocols guidelines (PRISMA-P).[22] This is an original research protocol. Any changes or modifications of the methods stated in this protocol will be updated via PROSPERO and reported in the final systematic review itself. We will report the study according to the PRISMA guidelines (PRISMA).[23]

3.1. Eligibility criteria

The Population, Exposure, Comparator and Outcome (PECO) framework was used to clarify the eligibility criteria.[24]

3.1.1. Types of populations

We included studies of adult populations (≥ 18 years old), while studies of children (< 18 years) were excluded. Studies that detected and provided exposure levels of individual POPs or any subtype of POPs in biological samples were included, while studies that used only occupations to estimate the occupational exposure to POPs were excluded.

3.1.2. Types of exposures

We will include studies of exposure to any types of POPs in accordance with the Stockholm Convention definition.[8] The exposure level to POPs could be detected directly with quantitative measurement in biological samples, including blood, urine, thyroid tissues, or adipose tissues.

3.1.3. Types of comparators

The included comparator will be participants with the lowest exposure level of POPs in individual studies. We will include all these comparisons of the higher exposure levels versus the lowest level of POPs exposure. When the highest exposure level was used as the comparator in original studies, we will use the reciprocal method (1/x) to convert the effect estimates of the lowest versus the highest level. We will exclude all other types of comparators.

3.1.4. Types of outcomes

We will include studies that define and classify thyroid cancers using the relevant diagnostic codes in ICD-10 or other versions of the ICD. If studies do not reported the ICD codes but they provide the information on the cancer site, we will also include these studies. All patients should be diagnosed with clinical-pathological confirmation. The following measurements of thyroid cancer cases should

be determined as eligible: 1) diagnosis by a physician; 2) medical records; 3) health insurance data; and 4) cancer registry data for diagnosis.

We will exclude all other measurements, including self-reported records without pathological diagnosis. Studies focusing on benign thyroid diseases (including thyroid enlargement and thyroid nodules, etc.) but not thyroid cancer will be excluded from this systematic review.

3.1.5. Types of studies

We will include a broad set of epidemiological studies that investigate the effect of exposure to POPs and thyroid cancer risk over any period. Eligible study designs will be cohort studies (both prospective and retrospective cohorts), case-cohort studies, case-control studies (including nested case-control studies, population- or hospital-based case-control studies). Due to rigorous ethical principles, there is no eligible randomized controlled trial or non-randomized intervention study in the preliminary search. We will exclude all other study designs (e.g. non-original studies, cross-sectional studies, case reports, case series, animal model researches, cell line researches, and other mechanism researches).

3.1.6. Types of effect measures

We will include the effect measures of exposure to any individual POPs or any combined subtype of POPs on the risk of developing thyroid cancer, compared with the lowest exposure level in each original research. All relative effect estimates, namely relative risk ratios (RR), odds ratios (OR), and hazard ratios (HR) are included.

If an original study reports effect estimates from two or more alternative models that have been unadjusted or adjusted for different confounders, then we will systematically prioritize the maximally adjusted estimates from models adjusted for more covariates over those from models adjusted for fewer. For example, if a study presents effect estimates from a crude unadjusted model (Model A), a model adjusted for gender (Model B), and a model adjusted for gender, age, and BMI (Model C), we will then prioritize the estimate from Model C.

3.2. Information sources and search

3.2.1. Electronic bibliographic databases

The following databases will be searched from the database inception to May 29, 2020: PubMed, Embase, ProQuest, and CNKI, with no language restrictions. We will use a combination of Medical Subject Headings (MeSH) terms and corresponding free-text terms to search relevant literatures and the full details of search strategy are presented in **online supplementary file 1**.

3.2.2. Other electronic database and website search

We will search two additional grey literature databases for potentially eligible studies:

- Grey Literature Report (http://greylit.org/).
- OpenGrey (http://www.opengrey.eu/).

We will also search the websites of two international organizations for eligible datasets:

- World Health Organization (www.who.int).
- International Agency for Research on Cancer (https://www.iarc.fr/).

3.2.4. Hand-searching and expert consultation

We (YXZ, YPL and SSM) will hand-search for potentially eligible studies in:

- Reference list of all original researches, relevant reviews, editorials, and letters.
- Reference list of relevant reviews, editorials, and letters.
- Study records that have cited the included studies (identified in Web of Science citation database).

3.3. Study selection

All literature records identified in the search will be imported into the Covidence software[25] and duplicates will be identified and deleted. Afterwards, two authors (YXZ and YPL) will independently screen titles and abstracts, and then read full-texts of potentially relevant literatures. Authors will record specific reasons for exclusion in the full-text screening. A third author (SSM) will resolve any discrepancies. The process of study selection will be reported as per PRISMA guidelines.

3.4. Data extraction and data items

Two authors (YXZ and YPL) will independently extract data, and a third author (SSM) will resolve conflicts. The extracted data items will include study characteristics (including authors, publication year, study country, participants age, gender, year of sample collection, and outcome), exposure (including types of POPs, detection methods, comparator), study design (including summary of study design, statistical analysis models used and effect estimates), risk of bias (including selection bias, reporting bias, confounding bias). We will use the predesigned standard sheet to extract data (see **online supplementary file 2**). This data extraction sheet will be trialled until the authors reach convergence and agreement. Data will be entered into and managed with the Microsoft Excel software. To request missing information, the corresponding author will be contacted by emails (maximum of three emails over four weeks).

3.5. Risk of bias in individual studies

Two authors (YXZ and YPL) will independently judge the quality and risk of bias for each study with the Newcastle-Ottawa Scale (NOS).[26] Any discrepancies will be resolved by discussion or consultation with a third author (XDL). All quality assessors will jointly trial the NOS criteria until they have synchronized their understanding and application of the NOS scale. The NOS scale consists of three domains of bias: selection (4 points), comparability (2 points), and outcome (3 points). According to the sum points of three domains, individual studies will be categorized as either high (≥6) or low (<6) quality. We will report the study-level risk of bias assessments by domains in a summary table (**online supplementary file 3**).

3.6. Synthesis of results

3.6.1. Quantitative synthesis

In the primary meta-analysis, we will use the maximally adjusted effect estimates and corresponding 95% confidence intervals (CI) to summarize the effect of POPs exposure on the risk of thyroid cancer. To be more rigorous and conservative, we will use random-effect models rather than fixed-effect models to summarize the effect sizes. In the primary meta-analysis, we will assess the overall effect of exposure to all types of POPs and each subtype of POPs on the thyroid cancer risk. We will also assess the effect of exposure to any individual POPs, if the number of eligible studies is no less than three.

When two or more studies from the same cohort or data source are eligible for inclusion in the meta-analysis, we will prioritize in this order: 1) the study with the highest quality score and the lowest risk of bias; 2) the study with the most informative measurements of exposure to POPs; 3) the study with large sample size; 4) the study with the longest follow-up; 5) the study with the maximal adjustment for relevant potential confounding factors.

When studies only report effect sizes for each individual POPs separately, we will initially combine these individual effects into a study-specific overall effect of total or subtype of POPs with fixed-effect models. When studies only report separately effect sizes on each individual types of thyroid cancer, we will also combine these effects into a study-specific overall effect for all types of thyroid cancer with fixed-effect models.

Comprehensive Meta Analysis version 2.2.046 (Biostat, Englewood, NJ, USA) will be used for all analyses. Statistical significance was defined as two-sided P-values less than 0.05 in the major meta-analysis. In all subgroup analyses, we will use the Bonferroni method to correct the level of statistical significance.

3.6.2. Heterogeneity inspection

We will calculate the I^2 statistic and perform the Cochrane Q-test to test the heterogeneity across studies and will report I^2 statistics and *P*-values in the systematic review. Based on the I^2 statistics, an I^2 value of ≤30% represents low heterogeneity, 30-50% moderate heterogeneity, 50-75% substantial heterogeneity, and >75% considerable heterogeneity. If there is substantial between-study heterogeneity, we will perform meta-regression and subgroup analyses to explore potential sources of the heterogeneity. Meta-regression analyses will be performed according to sample size, year of blood sample collection or study publication. Subgroup analyses are elaborated in the section of 3.6.4. Sensitivity analysis.

3.6.3. Publication bias

To assess potential publication bias, we will conduct the Begg's and Egger's tests and further rigorously adjusted for the summarized results by applying the Duval and Tweedie's trim and fill

method. We will also use funnel plots to ascertain presence of publication bias, if ten or more eligible studies (datasets or comparisons) are included in our systematic review.

3.6.4. Sensitivity analysis

We will perform a broad set of predesigned sensitivity analyses to evaluate the robustness of the findings, as follows:

- We will conduct a sensitivity analysis using fixed-effect models.
- The minimally adjusted effect estimates will be pooled and these results will be compared with the primary results from the maximally adjusted effects using the Confounding RR method, which is defined as the ratio of pooled results of the maximally adjusted versus minimally adjusted data.[27] Confounding RRs are used to evaluate whether the underlying confounders controlled in each individual studies could have influenced the results.
- To assess the potential impact of residual confounding bias, we will perform E-value analysis.[28] E-value shows the minimum strength of association that a hypothetical residual confounding factor would need to have with both the exposure to POPs and the incidence risk of thyroid cancer to fully explain the observed effect.
- A sensitivity analysis by removing the most relatively weighted study (or dataset) will be performed to assess its influence on the results and to explore potential sources of heterogeneity across studies.
- A sensitivity analysis including only the high-quality studies will be performed.
- We will also perform a sensitivity analysis by including only the prospective studies (including cohort studies, case-cohort studies, and nested case-control studies), because the prospective nature of these study designs is invaluable for confirming the temporal sequence of POPs exposure and thyroid cancer onset and therefore helps to examine causal associations.
- We will performed predefined subgroup meta-analyses by geographic regions (as per WHO Regions or World Bank Income Country Groups), sample size (≥median vs. <median), year of blood sample collection (before vs. after 2010), gender (female vs. male), and age of participants (<50 vs. ≥50 years), if eligible studies in each subgroup are no less than three. If else, these afore-mentioned subgroup analyses will be performed as sensitivity analyses by excluding the subgroup with less than three studies.

- We will also perform cumulative meta-analyses according to sample size of each individual studies from small to large, year of blood drawing or study publication in chronological order from front to latest.

We will also perform some post hoc subgroup analyses or other additional analyses, whenever feasible.

3.7. Quality of evidence assessment

All authors will together assess quality of evidence for the entire body of evidence by exposures (total POPs or subtypes of POPs). We will use the GRADE approach to grade the quality of evidence as "high", "moderate", "low", or "very low".[29] The GRADEproGDT software online version will be used to summarize the quality of evidence.

We will downgrade or upgrade the quality of evidence according to the following domains: 1) study design; 2) risk of bias; 3) inconsistency; 4) indirectness; 5) imprecision; 6) publication bias; and 7) confounding bias. Within each domain, we will categorize the concern for the quality of evidence as "none", "serious" and "very serious". In the meta-analysis, if the prospective epidemiological studies (including cohort, case-cohort, and nested case-control studies) accounted for more than 60% of all included studies, we will start at "high" for the quality of evidence; or else, we will start at "moderate". Afterwards, we will downgrade the quality of evidence for no concern by nil grades (0), for a serious concern by one grade (-1), or for a very serious concern by two grades (-2). We will upgrade the quality by one grade for each of the following reasons: large effect size (+1), a significant dose-response relationship (+1), or plausibility that residual confounders cannot explain the observed effect (+1).

For example, we start at "moderate" for a body of evidence consisting of 10 studies (including 5 cohorts and 5 case-control studies). If there is a serious concern for both risk of bias (-1) and inconsistency (-1), meanwhile the summarized effect size is large (+1); but there is no other concerns and no other upgrading reasons, then we will downgrade the quality by one grade from "moderate" to "low".

3.8. Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of our present study.

Ethics and Dissemination: Ethical approval is not required in this systematic review of published literatures. The results will be published in a peer-reviewed journal and presented at relevant conferences to promote knowledge transfer.

Availability of data and materials: Data collected through this systematic review will be managed by the present Research Group. The datasets used and/or analyses during the study will be presented within the manuscript or as supplementary materials. We promise that all the datasets analysed in this study will be publicly available for the general readers and researchers.

Author Contributions: **YXZ**, **YPL**, **ZYQ** and **SMM** conceived and designed this systematic review. All authors developed the selection criteria, risk bias assessment strategy, and data extraction criteria. **YXZ**, **YPL** and **SSM** developed the pilot search strategy. **YXZ** and **YPL** will be the two title, abstract, and full-text reviewers. **SSM** or **XDL** will be the third reviewer that will help resolve any discrepancy. **YXZ** and **YPL** wrote the initial draft of the protocol. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the systematic review to be published: All authors. **ZYQ** and **SMM** are the guarantor of the systematic review.

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Conflict of Interest: The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the writing and the publication of this work.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
2. American Cancer Society. Thyroid Cancer. Available at: https://www.cancer.org/cancer/thyroid-cancer.html. (Accessed November 22, 2020).
3. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/home. (Accessed November 22, 2020).
4. Lim H, Devesa SS, Sosa JA, et al. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* 2017;317(13):1338-48.
5. Frank W, Dillwyn W. Thyroid cancer. In: Stewart BW and Wild CP, eds. World Cancer Report 2014. Lyon, France, International Agency for Research on Cancer, WHO Press; 2014:738-750. .
6. Qian ZJ, Jin MC, Meister KD, et al. Pediatric Thyroid Cancer Incidence and Mortality Trends in the United States, 1973-2013. *JAMA Otolaryngol Head Neck Surg* 2019;145(7):617-23.
7. Bernier MO, Withrow DR, Berrington de Gonzalez A, et al. Trends in pediatric thyroid cancer incidence in the United States, 1998-2013. *Cancer* 2019;125(14):2497-505.
8. Stockholm Convention. The POPs. Available at: http://www.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx. (Accessed November 22, 2020).
9. European Commision Enviroment Chemicals. Persistant Organic Pollutants (POPs). Available at: https://ec.europa.eu/environment/chemicals/international_conventions/index_en.htm. (Accessed November 22, 2020).
10. Guo W, Pan B, Sakkiah S, et al. Persistent Organic Pollutants in Food: Contamination Sources, Health Effects and Detection Methods. *Int J Environ Res Public Health* 2019;16(22)
11. United States Environmental Protection Agency. International Cooperation. Persistent Organic Pollutants: A Global Issue, A Global Response. Available at: https://www.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response#pops. (Accessed December 02, 2020).
12. Abdallah MA, Pawar G, Harrad S. Evaluation of in vitro vs. in vivo methods for assessment of dermal absorption of organic flame retardants: a review. *Environ Int* 2015;74:13-22.
13. World Health Organization. Food safety: Persistent organic pollutants (POPs). Available at: https://www.who.int/news-room/q-a-detail/food-safety-persistent-organic-pollutants-(pops). (Accessed November 22, 2020).
14. Ashraf MA. Persistent organic pollutants (POPs): a global issue, a global challenge. *Environ Sci Pollut Res Int* 2017;24(5):4223-27.
15. Zhang Q, Hu M, Wu H, et al. Plasma polybrominated diphenyl ethers, urinary heavy metals and the risk of thyroid cancer: A case-control study in China. *Environ Pollut* 2020:116162.

16. Huang H, Sjodin A, Chen Y, et al. Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study. *Am J Epidemiol* 2020;189(2):120-32.
17. Han X, Meng L, Li Y, et al. Associations between Exposure to Persistent Organic Pollutants and Thyroid Function in a Case-Control Study of East China. *Environ Sci Technol* 2019;53(16):9866-75.
18. Marotta V, Russo G, Gambardella C, et al. Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules. *Chemosphere* 2019;218:885-94.
19. Deziel NC, Warren JL, Huang H, et al. Exposure to polychlorinated biphenyls and organochlorine pesticides and thyroid cancer in connecticut women. *Environ Res* 2021;192:110333.
20. Han MA, Kim JH, Song HS. Persistent organic pollutants, pesticides, and the risk of thyroid cancer: systematic review and meta-analysis. *Eur J Cancer Prev* 2019;28(4):344-49.
21. Liu Y, Zhang Y, Qu Z, et al. Associations between exposure to persistent organic pollutants and the risk of thyroid cancer: A systematic review and meta-analysis. PROSPERO 2020 CRD42020181343. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181343.
22. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
24. Morgan RL, Whaley P, Thayer KA, et al. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int* 2018;121(Pt 1):1027-31.
25. Covidence Community. Covidence, 2020. Available at: https://community.cochrane.org/help/tools-and-software/covidence. (Accessed Nov 25, 2020).
26. Wells GA, Shea B, O'Connell D, et al. The Newcastle -Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed December 16, 2020).
27. Greenland S, Pearce N. Statistical foundations for model-based adjustments. *Annu Rev Public Health* 2015;36:89-108.
28. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167(4):268-74.
29. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6.

ONLINE SUPPLEMENTARY FILES

Supplementary File 1. Detailed Electronic Search strategy.

- **PubMed:**

#1. "persistent organic pollutants"[MeSH Terms] OR "ddt"[MeSH Terms] OR "chlordan"[MeSH Terms] OR "aldrin"[MeSH Terms] OR "dieldrin"[MeSH Terms] OR "endrin"[MeSH Terms] OR "heptachlor"[MeSH Terms] OR "hexachlorobenzene"[MeSH Terms] OR "mirex"[MeSH Terms] OR "toxaphene"[MeSH Terms] OR "chlordecone"[MeSH Terms] OR "polychlorinated biphenyls"[MeSH Terms] OR "halogenated diphenyl ethers"[MeSH Terms] OR "dibenzofurans, polychlorinated"[MeSH Terms] OR "dioxins"[MeSH Terms] OR "dioxins and dioxin like compounds"[MeSH Terms] OR "polychlorinated dibenzodioxins"[MeSH Terms]

#2. "pentachlorobenzene"[Supplementary Concept] OR "decabromobiphenyl ether"[Supplementary Concept] OR "2 2 4 4 5 6 hexabromodiphenyl ether"[Supplementary Concept] OR "perfluorooctane sulfonic acid"[Supplementary Concept] OR "perfluorooctanoic acid"[Supplementary Concept]

#3. "persistent organic pollutants"[Title/Abstract] OR "persistent organic pollutant"[Title/Abstract] OR "POPs"[Title/Abstract] OR "organochlorine pesticides"[Title/Abstract] OR "OCPs"[Title/Abstract] OR "ddt"[Title/Abstract] OR "chlordan"[Title/Abstract] OR "aldrin"[Title/Abstract] OR "dieldrin"[Title/Abstract] OR "endrin"[Title/Abstract] OR "heptachlor"[Title/Abstract] OR "hexachlorobenzene"[Title/Abstract] OR "mirex"[Title/Abstract] OR "toxaphene"[Title/Abstract] OR "chlordecone"[Title/Abstract] OR "pentachlorobenzene"[Title/Abstract] OR "polychlorinated biphenyls"[Title/Abstract] OR "PCBs"[Title/Abstract] OR "polychlorinated naphthalenes"[Title/Abstract] OR "halogenated diphenyl ethers"[Title/Abstract] OR "polybrominated diphenyl ethers"[Title/Abstract] OR "PBDEs"[Title/Abstract] OR "c-decaBDE"[Title/Abstract] OR "dibenzofurans polychlorinated"[Title/Abstract] OR "dioxins"[Title/Abstract] OR "dioxins and dioxin like compounds"[Title/Abstract] OR "polychlorinated dibenzodioxins"[Title/Abstract] OR "decabromobiphenyl ether"[Title/Abstract] OR "2 2 4 4 5 6 hexabromodiphenyl ether"[Title/Abstract] OR "perfluorooctane sulfonic acid"[Title/Abstract] OR "perfluorooctanoic acid"[Title/Abstract] OR "PFOS"[Title/Abstract] OR "PFOA"[Title/Abstract]

#4. #1 OR #2 OR #3

#5. "thyroid neoplasms"[MeSH Terms]

#6. "thyroid neoplasm"[All Fields] OR "thyroid carcinomas"[All Fields] OR "thyroid carcinoma"[All Fields] OR "thyroid cancers"[All Fields] OR "thyroid cancer"[All Fields] OR "thyroid adenomas"[All Fields] OR "thyroid adenoma"[All Fields] OR "thyroid tumours"[All Fields] OR "thyroid tumour"[All Fields]

#7. #5 OR #6

#8. #4 AND #7

- **Embase:**

#1. 'persistent organic pollutants':ti,ab,kw OR 'persistent organic pollutant':ti,ab,kw OR POPs:ti,ab,kw OR 'organochlorine pesticides':ti,ab,kw OR OCPs:ti,ab,kw OR DDT:ti,ab,kw OR chlordan:ti,ab,kw OR aldrin:ti,ab,kw OR dieldrin:ti,ab,kw OR endrin:ti,ab,kw OR heptachlor:ti,ab,kw OR hexachlorobenzene:ti,ab,kw OR mirex:ti,ab,kw OR toxaphene:ti,ab,kw OR chlordecone:ti,ab,kw OR 'pentachlorobenzene':ti,ab,kw OR 'polychlorinated biphenyls':ti,ab,kw OR PCBs:ti,ab,kw OR 'polychlorinated naphthalenes':ti,ab,kw OR 'halogenated diphenyl ethers':ti,ab,kw OR 'polybrominated diphenyl ethers':ti,ab,kw OR PBDEs:ti,ab,kw OR c-decaBDE:ti,ab,kw OR 'dibenzofurans polychlorinated':ti,ab,kw OR dioxins:ti,ab,kw OR 'dioxins and dioxin like compounds':ti,ab,kw OR 'polychlorinated dibenzodioxins':ti,ab,kw OR 'decabromobiphenyl ether':ti,ab,kw OR '2 2 4 4 5 6 hexabromodiphenyl ether':ti,ab,kw OR 'perfluorooctane sulfonic acid':ti,ab,kw OR 'perfluorooctanoic acid':ti,ab,kw OR PFOS:ti,ab,kw OR PFOA:ti,ab,kw

#2. 'thyroid neoplasms':ti,ab,kw OR 'thyroid neoplasm':ti,ab,kw OR 'thyroid carcinomas':ti,ab,kw OR 'thyroid carcinoma':ti,ab,kw OR 'thyroid cancers':ti,ab,kw OR 'thyroid cancer':ti,ab,kw OR 'thyroid adenomas':ti,ab,kw OR 'thyroid adenoma':ti,ab,kw OR 'thyroid tumours':ti,ab,kw OR 'thyroid tumour':ti,ab,kw

#3. #1 AND #2

- **ProQuest:**

#1. mesh(persistent organic pollutants) OR mesh(DDT) OR mesh(chlordan) OR mesh(aldrin) OR mesh(dieldrin) OR mesh(endrin) OR mesh(heptachlor) OR mesh(hexachlorobenzene) OR mesh(mirex) OR mesh(toxaphene) OR mesh(chlordecone) OR mesh(polychlorinated biphenyls) OR mesh(halogenated diphenyl ethers) OR mesh(dibenzofurans, polychlorinated) OR mesh(dioxins) OR mesh(dioxins and dioxin like compounds) OR mesh(polychlorinated dibenzodioxins) OR mesh(pentachlorobenzene) OR mesh(decabromobiphenyl ether) OR mesh(2 2 4 4 5 6 hexabromodiphenyl ether) OR mesh(perfluorooctane sulfonic acid) OR mesh(perfluorooctanoic acid)

#2. ab(persistent organic pollutants) OR ab(persistent organic pollutant) OR ab(POPs) OR ab(organochlorine pesticides) OR ab(OCPs) OR ab(DDT) OR ab(chlordan) OR ab(aldrin) OR ab(dieldrin) OR ab(endrin) OR ab(heptachlor) OR ab(hexachlorobenzene) OR ab(mirex) OR ab(toxaphene) OR ab(chlordecone) OR ab(pentachlorobenzene) OR ab(polychlorinated biphenyls) OR ab(PCBs) OR ab(polychlorinated naphthalenes) OR ab(halogenated diphenyl ethers) OR ab(polybrominated diphenyl ethers) OR ab(PBDEs) OR ab(c-decaBDE) OR ab(dibenzofurans polychlorinated) OR ab(dioxins) OR ab(dioxins and dioxin like compounds) OR ab(polychlorinated dibenzodioxins) OR ab(decabromobiphenyl ether) OR ab(2 2 4 4 5 6 hexabromodiphenyl ether) OR ab(perfluorooctane sulfonic acid) OR ab(perfluorooctanoic acid) OR ab(PFOS) OR ab(PFOA)

#3. #1 OR #2

#4. mesh(thyroid neoplasms)

#5. ab(thyroid neoplasm) OR ab(thyroid carcinomas) OR ab(thyroid carcinoma) OR ab(thyroid cancers) OR ab(thyroid cancer) OR ab(thyroid adenomas) OR ab(thyroid adenoma) OR ab(thyroid tumours) OR ab(thyroid tumour)

#6. #4 OR #5

#7. #3 AND #6

- **CNKI:**

#1. SU=持久性有机污染物 OR SU=POPs OR SU=有机氯杀虫剂 OR SU=DDT OR SU=氯丹 OR SU=艾氏剂 OR SU=狄氏剂 OR SU=异狄氏剂 OR SU=七氯 OR SU=六氯苯 OR SU=灭蚁灵 OR SU=毒杀芬 OR SU=十氯酮 OR SU=五氯苯 OR SU=多氯联苯 OR SU=PCBs OR SU=多氯化萘 OR SU=卤代苯醚 OR SU=多溴联苯醚 OR SU=PBDEs OR SU=呋喃 OR SU=二恶英 OR SU=多氯二苯并二恶英 OR SU=十溴二苯醚 OR SU=六溴二苯醚 OR SU=全氟辛烷磺酸 OR SU=全氟辛酸 OR SU=persistent organic pollutants OR SU=organochlorine pesticides OR SU=polychlorinated biphenyls OR SU=halogenated diphenyl ethers OR SU=polybrominated diphenyl ethers

#2. KY=持久性有机污染物 OR KY=POPs OR KY=有机氯杀虫剂 OR KY=DDT OR KY=氯丹 OR KY=艾氏剂 OR KY=狄氏剂 OR KY=异狄氏剂 OR KY=七氯 OR KY=六氯苯 OR KY=灭蚁灵 OR KY=毒杀芬 OR KY=十氯酮 OR KY=五氯苯 OR KY=多氯联苯 OR KY=PCBs OR KY=多氯化萘 OR KY=卤代苯醚 OR KY=多溴联苯醚 OR KY=PBDEs OR KY=呋喃 OR KY=二恶英 OR KY=多氯二苯并二恶英 OR KY=十溴二苯醚 OR KY=六溴二苯醚 OR KY=全氟辛烷磺酸 OR KY=全氟辛酸 OR KY=persistent organic pollutants OR KY=organochlorine pesticides OR KY=polychlorinated biphenyls OR KY=halogenated diphenyl ethers OR KY=polybrominated diphenyl ethers

#3. #1 OR #2

#4. SU=甲状腺癌 OR SU=甲状腺肿瘤 OR SU=thyroid cancer OR SU=thyroid neoplasms

#5. KY=甲状腺癌 OR KY=甲状腺肿瘤 OR KY= thyroid cancer OR KY= thyroid neoplasms

#6. #4 OR #5

#7. #3 AND #6

Supplementary File 2. Main Characteristics extracted from individual studies included in this study.

Study	**Study characteristics**				**Population characteristics**				**Exposure characteristics**			**Outcomes characteristics**				**Quality score (NOS)**
First author, Publication year	Study design	Study implementation period (year),	Sample collection time (year),	Mean/median duration of follow-up (months), only for cohort	Country or region	Sample size	Age Median (range)/Mean age (SD), years	Gender Female /Male	Type of POPs	Detection method	Comparator	Outcomes	Analysis models	Effect estimates	Adjusted potential confounders	
Study 1																
Study 2																
Study 3																
Study 4																
Study 5																
Study 6																
…																

Supplementary File 3. Detailed quality scores of individual studies assessed with the Newcastle-Ottawa Quality Assessment Scale (NOS).

Study	Selection				Comparability		Exposure			Total Score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for the most important factor	Study controls for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Study 1	√	√	-	-	-	√	√	√	√	6
Study 2	√	√	√		√	√	√	√	√	8
Study 3	√	√	√	√	√	√	√	√	√	9
Study 4	√	√	√	√	-	-	√	√	√	7
Study 5	√	√	√	√	√	-	√	√	√	8
Study 6	√	-	√	√	-	-	√	-	-	4
…										

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Page(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7 and online supplementary file 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7 and online supplementary file 2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7-8 and online supplementary file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 11

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Exposure to persistent organic pollutants and thyroid cancer risk: a study protocol of systematic review and meta-analysis

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Date Submitted by the Author:	02-Jul-2021
Complete List of Authors:	Zhang, Yuxue; Harbin Medical University, Department of Preventive Medicine Liu, YuPeng; Wenzhou Medical University, Department of Epidemiology and Biostatistics Miao, SuSheng; Harbin Medical University, Department of Head and Neck Surgery Liu, Xiaodong; Wenzhou Medical University, Department of Occupational and Environmental Health Ma, ShuMei; Wenzhou Medical University, Department of Occupational and Environmental Health Qu, ZhangYi; Harbin Medical University, Department of Hygiene Microbiology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Oncology, Epidemiology, Occupational and environmental medicine, Public health
Keywords:	PUBLIC HEALTH, Thyroid disease < DIABETES & ENDOCRINOLOGY, Endocrine tumours < ONCOLOGY, Epidemiology < ONCOLOGY

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Title page:

Exposure to persistent organic pollutants and thyroid cancer risk: a study protocol of systematic review and meta-analysis

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Strengths and limitations of this study

- This will be the most comprehensive and up-to-date systematic review to synthesise the evidence on the health effects of exposure to any types of persistent organic pollutants on the incidence risk of thyroid cancer.
- We will use rigorous statistical methods to summarise all the currently eligible data from epidemiological studies, perform extensive sensitivity meta-analyses to evaluate the robustness of our findings.
- The main possible limitations of this study are a limited number of eligible studies and possibly significant heterogeneity between studies.
- Another potential limitation is that it may be difficult to evaluate publication bias if there are not sufficient studies included.

ABSTRACT:

Introduction: The thyroid cancer incidence has been increasing all over the world. However, the aetiology of thyroid cancer remains unclear. A growing body of evidence suggested exposure to persistent organic pollutants (POPs) may play a role in the initiation of thyroid cancer, but the results are generally inconsistent across studies. This review aims to synthesise the evidence for the health effects of POPs on the risk of thyroid cancer.

Methods and analysis: This protocol was reported in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statements. A comprehensive search, including electronic database search (e.g. PubMed, Embase, ProQuest, and CNKI), website search, and manual search, will be performed to identify all eligible studies. The Population, Exposure, Comparator and Outcome (PECO) framework was used to clarify the inclusion and exclusion criteria. The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of included studies. Maximally adjusted effect estimates from individual studies will be summarized with random-effect models in a conservative manner. I^2 statistics and Q-tests will be used to test the heterogeneity across studies. We will perform extensive sensitivity analyses, such as confounding risk ratio (confounding RR), E-value, fixed-effect models, excluding the most relatively weighted study, including only the high-quality studies, and many predesigned subgroup analyses, etc. The findings will be reported in accordance to the PRISMA guidelines.

Ethics and dissemination: Ethical approval is not required in this systematic review of published literatures. The results will be published in a peer-reviewed journal and presented at relevant conferences.

PROSPERO registration number: CRD42020181343

1. INTRODUCTION

In the last decades, thyroid cancer was the most rapidly increasing cancer worldwide.[1 2] In 2020, there were 448,915 new cases in women worldwide, representing the fifth-most common cancer in women, compared with 137,287 new cases in men, representing the 16th-most common cancer in men.[1 3] In the United States, age-adjusted thyroid cancer incidence rate have increased approximately 4-fold from 4.8 cases/100,000 in 1975 to 17.4/100,000 in 2020 such that thyroid cancer incidence has been increased at an annual growth rate of about 3%.[3 4] This significant increase pattern was not only unique to the United States but also to a lot of other countries. The growth rate in China was even higher than that in the United States.[5] In China, the estimated incident cases of thyroid cancer reached 221,093 in 2020, accounting for about 38% of all annually diagnosed thyroid cancer cases.[3]

Although much of the increasing incidence of thyroid cancer is attributed to the improved detection and screening methods, this is unlikely to be the sole cause, since incidence rates are also obviously increasing among children, adolescents and young adults, or for more easily detectable cases with larger tumours.[6 7] Therefore, it is urgent to elucidate the aetiology of thyroid cancer. There are only a few well-established risk factors for thyroid cancer: gender, hereditary conditions, and ionizing radiation exposure (particularly when this exposure occurs during childhood).[1 2] However, the aetiology remains poorly understood. Recently, a growing body of evidence suggested exposure to persistent organic pollutants (POPs) may play a role in the initiation and development of thyroid cancer, but the results are not conclusive and generally inconsistent across studies.

POPs are a broad class of organic chemicals of global concern, which persist in the environment, bio-magnify and bio-accumulate through the food chain, can be transported all over the world.[8] There are three types of POPs most commonly encountered in the environment: 1) organochlorine pesticides (OCPs), such as dichlorodiphenyltrichloroethane (DDT) and its metabolites; 2) industrial chemicals, such as polychlorinated biphenyls (PCBs) and flame retardants (FRs) including polybrominated diphenyl ethers (PBDEs), brominated FRs (BFRs) and organophosphate FRs (PFRs); and 3) unintentional by-products of industrial processes such as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs).[9-11]

In our daily lives, POPs can be virtually detected in many products everywhere. Humans are exposed to POPs in various ways: mainly through diet, but also through the air and the skin absorption.[12 13] For the general population, the most common exposure route is dietary intake of contaminated fatty foods. Due to the bioaccumulation and biomagnification through the food chain, the highest concentrations of POPs can be found in the human body, as the top of the food chain.[13]

A lot of evidence supports for their significant adverse effects on human health and the environment. Human exposure to these chemicals, even to low levels of POPs can result in many negative health effects including elevated cancer risk, endocrine disruption, immune function impairment, and reproductive disorders.[13 14] Recently, several epidemiological studies have shown that POP exposure has potential carcinogenesis properties in thyroid cancer.[15-18] However, the findings have been inconsistent. There is only one previous meta-analysis by Han et al. in 2019, which actually focused on the association of pesticides and thyroid cancer risk, but not for all types of POPs.[19]

2. OBJECTIVES

We therefore propose to conduct this systematic review and meta-analysis of epidemiological studies to comprehensively summarize the evidence for the effects of exposure to any types of POPs on the incidence risk of thyroid cancer in adult populations. The primary aims of this proposed study are to determine if there is an association between exposure to any types of POPs and the incidence risk of thyroid cancer; and to determine which subtypes of POPs exposure are associated with the thyroid cancer risk. The secondary aim will be to determine which individual POP chemicals are associated with the thyroid cancer risk.

3. METHODS AND ANALYSIS

This study has been registered in PROSPERO (CRD42020181343) on 2 may 2020.[20] We will complete the study by 30 December 2021. The present protocol is in accordance to the PRISMA protocols guidelines (PRISMA-P).[21] This is an original research protocol. Any changes or modifications of the methods stated in this protocol will be updated via PROSPERO and reported in the final systematic review itself. We will report the study according to the PRISMA guidelines (PRISMA).[22]

3.1. Eligibility criteria

The Population, Exposure, Comparator and Outcome (PECO) framework was used to clarify the eligibility criteria.[23]

3.1.1. Types of populations

We included studies of adult populations (≥ 18 years old), while studies of children (< 18 years) were excluded. Studies that detected and provided exposure levels of individual POPs or any subtype of POPs in biological samples were included, while studies that used only occupations to estimate the occupational exposure to POPs were excluded.

3.1.2. Types of exposures

We will include studies of exposure to any types of POPs in accordance with the Stockholm Convention definition.[8] The exposure level to POPs could be detected directly with quantitative measurement in biological samples, including blood, urine, thyroid tissues, or adipose tissues.

3.1.3. Types of comparators

The included comparator will be participants with the lowest exposure level of POPs in individual studies. We will include all these comparisons of the higher exposure levels versus the lowest level of POPs exposure. When the highest exposure level was used as the comparator in original studies, we will use the reciprocal method (1/x) to convert the effect estimates of the lowest versus the highest level. We will exclude all other types of comparators.

3.1.4. Types of outcomes

We will include studies that define and classify thyroid cancers using the relevant diagnostic codes in ICD-10 or other versions of the ICD. If studies do not reported the ICD codes but they provide the information on the cancer site, we will also include these studies. All patients should be diagnosed with clinical-pathological confirmation. The following measurements of thyroid cancer cases should

be determined as eligible: 1) diagnosis by a physician; 2) medical records; 3) health insurance data; and 4) cancer registry data for diagnosis.

We will exclude all other measurements, including self-reported records without pathological diagnosis. Studies focusing on benign thyroid diseases (including thyroid enlargement and thyroid nodules, etc.) but not thyroid cancer will be excluded from this systematic review.

3.1.5. Types of studies

We will include a broad set of epidemiological studies that investigate the effect of exposure to POPs and thyroid cancer risk over any period. Eligible study designs will be cohort studies (both prospective and retrospective cohorts), case-cohort studies, case-control studies (including nested case-control studies, population- or hospital-based case-control studies). Due to rigorous ethical principles, there is no eligible randomized controlled trial or non-randomized intervention study in the preliminary search. We will exclude all other study designs (e.g. non-original studies, cross-sectional studies, case reports, case series, animal model researches, cell line researches, and other mechanism researches).

3.1.6. Types of effect measures

We will include the effect measures of exposure to any individual POPs or any combined subtype of POPs on the risk of developing thyroid cancer, compared with the lowest exposure level in each original research. All relative effect estimates, namely relative risk ratios (RR), odds ratios (OR), and hazard ratios (HR) are included.

If an original study reports effect estimates from two or more alternative models that have been unadjusted or adjusted for different confounders, then we will systematically prioritize the maximally adjusted estimates from models adjusted for more covariates over those from models adjusted for fewer. For example, if a study presents effect estimates from a crude unadjusted model (Model A), a model adjusted for gender (Model B), and a model adjusted for gender, age, and BMI (Model C), we will then prioritize the estimate from Model C.

3.2. Information sources and search

3.2.1. Electronic bibliographic databases

The following databases will be searched from the database inception to May 29, 2020: PubMed, Embase, ProQuest, and CNKI, with no language restrictions. We will use a combination of Medical Subject Headings (MeSH) terms and corresponding free-text terms to search relevant literatures. The full details of search strategy are presented in **online supplementary file 1**.

3.2.2. Other electronic database and website search

We will search two additional grey literature databases for potentially eligible studies:

- Grey Literature Report (http://greylit.org/).
- OpenGrey (http://www.opengrey.eu/).

We will also search the websites of two international organizations for eligible datasets:

- World Health Organization (www.who.int).
- International Agency for Research on Cancer (https://www.iarc.fr/).

3.2.4. Hand-searching and expert consultation

We (YXZ, YPL and SSM) will hand-search for potentially eligible studies in:

- Reference list of all original researches, relevant reviews, editorials, and letters.
- Study records that have cited the included studies (identified in Web of Science citation database).

3.3. Study selection

All literature records identified in the search will be imported into the Covidence software[24] and duplicates will be identified and deleted. Afterwards, two authors (YXZ and YPL) will independently screen titles and abstracts, and then read full-texts of potentially relevant literatures. Authors will record specific reasons for exclusion in the full-text screening. A third author (SSM) will resolve any discrepancies. The process of study selection will be reported as per PRISMA guidelines.

3.4. Data extraction and data items

Two authors (YXZ and YPL) will independently extract data, and a third author (SSM) will resolve conflicts. The extracted data items will include study characteristics (including authors, publication year, study country, participants age, gender, year of sample collection, and outcome), exposure (including types of POPs, detection methods, comparator), study design (including summary of study design, statistical analysis models used and effect estimates), risk of bias (including selection bias, reporting bias, confounding bias). Extracted data will also include information on the subtype of thyroid cancer and pathophysiological characteristics of the subjects, if available. We will use the predesigned standard sheet to extract data (see **online supplementary file 2**). This data extraction sheet will be trialled until the authors reach convergence and agreement. Data will be entered into and managed with the Microsoft Excel software. To request missing information, the corresponding author will be contacted by emails (maximum of three emails over four weeks).

3.5. Risk of bias in individual studies

Two authors (YXZ and YPL) will independently judge the quality and risk of bias for each study with the Newcastle-Ottawa Scale (NOS).[25] Any discrepancies will be resolved by discussion or consultation with a third author (XDL). All quality assessors will jointly trial the NOS criteria until they have synchronized their understanding and application of the NOS scale. The NOS scale consists of three domains of bias: selection (4 points), comparability (2 points), and outcome (3 points). According to the sum points of three domains, individual studies will be categorized as either high (≥6) or low (<6) quality. We will report the study-level risk of bias assessments by domains in a summary table (**online supplementary file 3**).

3.6. Synthesis of results

3.6.1. Quantitative synthesis

In the primary meta-analysis, we will use the maximally adjusted effect estimates and corresponding 95% confidence intervals (CI) to summarize the effect of POPs exposure on the risk of thyroid cancer. To be more rigorous and conservative, we will use random-effect models rather than fixed-effect models to summarize the effect sizes. In the primary meta-analysis, we will assess the overall effect of

exposure to all types of POPs and each subtype of POPs on the thyroid cancer risk. We will also assess the effect of exposure to any individual POPs, if the number of eligible studies is no less than three.

When two or more studies from the same cohort or data source are eligible for inclusion in the meta-analysis, we will prioritize in this order: 1) the study with the highest quality score and the lowest risk of bias; 2) the study with the most informative measurements of exposure to POPs; 3) the study with large sample size; 4) the study with the longest follow-up; 5) the study with the maximum adjustment for relevant potential confounding factors.

When studies only report effect sizes for each individual POP separately, we will initially combine these individual effects into a study-specific overall effect of total or subtype of POPs with fixed-effect models. When studies only report separately effect sizes on each individual type of thyroid cancer, we will also combine these effects into a study-specific overall effect for all types of thyroid cancer with fixed-effect models.

Comprehensive Meta Analysis version 2.2.046 (Biostat, Englewood, NJ, USA) will be used for all analyses. Statistical significance was defined as two-sided P-values less than 0.05 in the major meta-analysis. In all subgroup analyses, we will use the Bonferroni method to correct the level of statistical significance.

3.6.2. Heterogeneity inspection

We will calculate the I^2 statistic and perform the Cochrane Q-test to test the heterogeneity across studies and will report I^2 statistics and *P*-values in the systematic review. Based on the I^2 statistics, an I^2 value of ≤30% represents low heterogeneity, 30-50% moderate heterogeneity, 50-75% substantial heterogeneity, and >75% considerable heterogeneity. If there is substantial between-study heterogeneity, we will perform meta-regression and subgroup analyses to explore potential sources of the heterogeneity. Meta-regression analyses will be performed according to sample size, year of blood sample collection or study publication. Subgroup analyses are elaborated in the section of 3.6.4. Sensitivity analysis.

3.6.3. Publication bias

To assess potential publication bias, we will conduct the Begg's and Egger's tests and further rigorously adjust for the summarized results by applying the Duval and Tweedie's trim and fill method. We will also use funnel plots to ascertain presence of publication bias, if ten or more eligible studies (datasets or comparisons) are included in our systematic review.

3.6.4. Sensitivity analysis

We will perform a broad set of predesigned sensitivity analyses to evaluate the robustness of the findings, as follows:

- We will conduct a sensitivity analysis using fixed-effect models.
- The minimally adjusted effect estimates will be pooled and these results will be compared with the primary results from the maximally adjusted effects using the Confounding RR method, which is defined as the ratio of pooled results of the maximally adjusted versus minimally adjusted data.[26] Confounding RRs are used to evaluate whether the underlying confounders controlled in each individual studies could have influenced the results.
- To assess the potential impact of residual confounding bias, we will perform E-value analysis.[27] E-value shows the minimum strength of association that a hypothetical residual confounding factor would need to have with both the exposure to POPs and the incidence risk of thyroid cancer to fully explain the observed effect.
- A sensitivity analysis by removing the most relatively weighted study (or dataset) will be performed to assess its influence on the results and to explore potential sources of heterogeneity across studies.
- A sensitivity analysis including only the high-quality studies will be performed.
- We will also perform a sensitivity analysis by including only the prospective studies (including cohort studies, case-cohort studies, and nested case-control studies), because the prospective nature of these study designs is invaluable for confirming the temporal sequence of POPs exposure and thyroid cancer onset and therefore helps to examine causal associations.
- We will performed predefined subgroup meta-analyses by geographic regions (as per WHO Regions or World Bank Income Country Groups), sample size (≥median vs. <median), year of blood sample collection (before vs. after 2010), gender (female vs. male), and age of participants (<50 vs. ≥50 years), if eligible studies in each subgroup are no less than three. If else, these afore-mentioned

subgroup analyses will be performed as sensitivity analyses by excluding the subgroup with less than three studies.

- We will also perform cumulative meta-analyses according to sample size of each individual study from small to large, year of blood drawing or study publication in chronological order from front to latest.

We will also perform some post hoc subgroup analyses or other additional analyses, whenever feasible.

3.7. Quality of evidence assessment

All authors will together assess quality of evidence for the entire body of evidence by exposures (total POPs or subtypes of POPs). We will use the GRADE approach to grade the quality of evidence as "high", "moderate", "low", or "very low".[28] The GRADEproGDT software online version will be used to summarize the quality of evidence.

We will downgrade or upgrade the quality of evidence according to the following domains: 1) study design; 2) risk of bias; 3) inconsistency; 4) indirectness; 5) imprecision; 6) publication bias; and 7) confounding bias. Within each domain, we will categorize the concern for the quality of evidence as "none", "serious" and "very serious". In the meta-analysis, if the prospective epidemiological studies (including cohort, case-cohort, and nested case-control studies) accounted for more than 60% of all included studies, we will start at "high" for the quality of evidence; or else, we will start at "moderate". Afterwards, we will downgrade the quality of evidence for no concern by nil grades (0), for a serious concern by one grade (-1), or for a very serious concern by two grades (-2). We will upgrade the quality by one grade for each of the following reasons: large effect size (+1), a significant dose-response relationship (+1), or plausibility that residual confounders cannot explain the observed effect (+1).

For example, we start at "moderate" for a body of evidence consisting of 10 studies (including 5 cohorts and 5 case-control studies). If there is a serious concern for both risk of bias (-1) and inconsistency (-1), meanwhile the summarized effect size is large (+1); but there is no other concerns

and no other upgrading reasons, then we will downgrade the quality by one grade from "moderate" to "low".

3.8. Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of our present study.

Ethics and Dissemination: Ethical approval is not required in this systematic review of published literatures. The results will be published in a peer-reviewed journal and presented at relevant conferences to promote knowledge transfer.

Availability of data and materials: Data collected through this systematic review will be managed by the present Research Group. The datasets used and/or analyses during the study will be presented within the manuscript or as supplementary materials. We promise that all the datasets analysed in this study will be publicly available for the general readers and researchers.

Author Contributions: **YXZ**, **YPL**, **ZYQ** and **SMM** conceived and designed this systematic review. All authors developed the selection criteria, risk bias assessment strategy, and data extraction criteria. **YXZ**, **YPL** and **SSM** developed the pilot search strategy. **YXZ** and **YPL** will be the two title, abstract, and full-text reviewers. **SSM** or **XDL** will be the third reviewer that will help resolve any discrepancy. **YXZ** and **YPL** wrote the initial draft of the protocol. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the systematic review to be published: All authors. **ZYQ** and **SMM** are the guarantor of the systematic review.

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Conflict of Interest: The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the writing and the publication of this work.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
2. American Cancer Society. Thyroid Cancer. Available at: https://www.cancer.org/cancer/thyroid-cancer.html. (Accessed November 22, 2020).
3. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/home. (Accessed November 22, 2020).
4. Lim H, Devesa SS, Sosa JA, et al. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* 2017;317(13):1338-48.
5. Frank W, Dillwyn W. Thyroid cancer. In: Stewart BW and Wild CP, eds. World Cancer Report 2014. Lyon, France, International Agency for Research on Cancer, WHO Press; 2014:738-750. .
6. Qian ZJ, Jin MC, Meister KD, et al. Pediatric Thyroid Cancer Incidence and Mortality Trends in the United States, 1973-2013. *JAMA Otolaryngol Head Neck Surg* 2019;145(7):617-23.
7. Bernier MO, Withrow DR, Berrington de Gonzalez A, et al. Trends in pediatric thyroid cancer incidence in the United States, 1998-2013. *Cancer* 2019;125(14):2497-505.
8. Stockholm Convention. The POPs. Available at: http://www.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx. (Accessed November 22, 2020).
9. European Commision Enviroment Chemicals. Persistant Organic Pollutants (POPs). Available at: https://ec.europa.eu/environment/chemicals/international_conventions/index_en.htm. (Accessed November 22, 2020).
10. Guo W, Pan B, Sakkiah S, et al. Persistent Organic Pollutants in Food: Contamination Sources, Health Effects and Detection Methods. *Int J Environ Res Public Health* 2019;16(22)
11. United States Environmental Protection Agency. International Cooperation. Persistent Organic Pollutants: A Global Issue, A Global Response. Available at: https://www.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response#pops. (Accessed December 02, 2020).
12. Abdallah MA, Pawar G, Harrad S. Evaluation of in vitro vs. in vivo methods for assessment of dermal absorption of organic flame retardants: a review. *Environ Int* 2015;74:13-22.
13. World Health Organization. Food safety: Persistent organic pollutants (POPs). Available at: https://www.who.int/news-room/q-a-detail/food-safety-persistent-organic-pollutants-(pops). (Accessed November 22, 2020).
14. Ashraf MA. Persistent organic pollutants (POPs): a global issue, a global challenge. *Environ Sci Pollut Res Int* 2017;24(5):4223-27.
15. Zhang Q, Hu M, Wu H, et al. Plasma polybrominated diphenyl ethers, urinary heavy metals and the risk of thyroid cancer: A case-control study in China. *Environ Pollut* 2020:116162.

16. Huang H, Sjodin A, Chen Y, et al. Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study. *Am J Epidemiol* 2020;189(2):120-32.
17. Han X, Meng L, Li Y, et al. Associations between Exposure to Persistent Organic Pollutants and Thyroid Function in a Case-Control Study of East China. *Environ Sci Technol* 2019;53(16):9866-75.
18. Deziel NC, Warren JL, Huang H, et al. Exposure to polychlorinated biphenyls and organochlorine pesticides and thyroid cancer in connecticut women. *Environ Res* 2021;192:110333.
19. Han MA, Kim JH, Song HS. Persistent organic pollutants, pesticides, and the risk of thyroid cancer: systematic review and meta-analysis. *Eur J Cancer Prev* 2019;28(4):344-49.
20. Liu Y, Zhang Y, Qu Z, et al. Associations between exposure to persistent organic pollutants and the risk of thyroid cancer: A systematic review and meta-analysis. PROSPERO 2020 CRD42020181343. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181343.
21. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
23. Morgan RL, Whaley P, Thayer KA, et al. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int* 2018;121(Pt 1):1027-31.
24. Covidence Community. Covidence, 2020. Available at: https://community.cochrane.org/help/tools-and-software/covidence. (Accessed Nov 25, 2020).
25. Wells GA, Shea B, O'Connell D, et al. The Newcastle -Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed December 16, 2020).
26. Greenland S, Pearce N. Statistical foundations for model-based adjustments. *Annu Rev Public Health* 2015;36:89-108.
27. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167(4):268-74.
28. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6.

SUPPLEMENTARY FILES

Exposure to persistent organic pollutants and thyroid cancer risk: a study protocol of systematic review and meta-analysis

YuXue Zhang, YuPeng Liu, SuSheng Miao, XiaoDong Liu, ShuMei Ma, ZhangYi Qu

Supplementary File 1. Detailed Electronic Search strategy.

- **PubMed:**

#1. "persistent organic pollutants"[MeSH Terms] OR "ddt"[MeSH Terms] OR "chlordan"[MeSH Terms] OR "aldrin"[MeSH Terms] OR "dieldrin"[MeSH Terms] OR "endrin"[MeSH Terms] OR "heptachlor"[MeSH Terms] OR "hexachlorobenzene"[MeSH Terms] OR "mirex"[MeSH Terms] OR "toxaphene"[MeSH Terms] OR "chlordecone"[MeSH Terms] OR "polychlorinated biphenyls"[MeSH Terms] OR "halogenated diphenyl ethers"[MeSH Terms] OR "dibenzofurans, polychlorinated"[MeSH Terms] OR "dioxins"[MeSH Terms] OR "dioxins and dioxin like compounds"[MeSH Terms] OR "polychlorinated dibenzodioxins"[MeSH Terms]

#2. "pentachlorobenzene"[Supplementary Concept] OR "decabromobiphenyl ether"[Supplementary Concept] OR "2 2 4 4 5 6 hexabromodiphenyl ether"[Supplementary Concept] OR "perfluorooctane sulfonic acid"[Supplementary Concept] OR "perfluorooctanoic acid"[Supplementary Concept]

#3. "persistent organic pollutants"[Title/Abstract] OR "persistent organic pollutant"[Title/Abstract] OR "POPs"[Title/Abstract] OR "organochlorine pesticides"[Title/Abstract] OR "OCPs"[Title/Abstract] OR "ddt"[Title/Abstract] OR "chlordan"[Title/Abstract] OR "aldrin"[Title/Abstract] OR "dieldrin"[Title/Abstract] OR "endrin"[Title/Abstract] OR "heptachlor"[Title/Abstract] OR "hexachlorobenzene"[Title/Abstract] OR "mirex"[Title/Abstract] OR "toxaphene"[Title/Abstract] OR "chlordecone"[Title/Abstract] OR "pentachlorobenzene"[Title/Abstract] OR "polychlorinated biphenyls"[Title/Abstract] OR "PCBs"[Title/Abstract] OR "polychlorinated naphthalenes"[Title/Abstract] OR "halogenated diphenyl ethers"[Title/Abstract] OR "polybrominated diphenyl ethers"[Title/Abstract] OR "PBDEs"[Title/Abstract] OR "c-decaBDE"[Title/Abstract] OR "dibenzofurans polychlorinated"[Title/Abstract] OR "dioxins"[Title/Abstract] OR "dioxins and dioxin like compounds"[Title/Abstract] OR "polychlorinated dibenzodioxins"[Title/Abstract] OR "decabromobiphenyl ether"[Title/Abstract] OR "2 2 4 4 5 6 hexabromodiphenyl ether"[Title/Abstract] OR "perfluorooctane sulfonic acid"[Title/Abstract] OR "perfluorooctanoic acid"[Title/Abstract] OR "PFOS"[Title/Abstract] OR "PFOA"[Title/Abstract]

#4. #1 OR #2 OR #3

#5. "thyroid neoplasms"[MeSH Terms]

#6. "thyroid neoplasm"[All Fields] OR "thyroid carcinomas"[All Fields] OR "thyroid carcinoma"[All Fields] OR "thyroid cancers"[All Fields] OR "thyroid cancer"[All Fields] OR "thyroid adenomas"[All Fields] OR "thyroid adenoma"[All Fields] OR "thyroid tumours"[All Fields] OR "thyroid tumour"[All Fields]

#7. #5 OR #6

#8. #4 AND #7

- **Embase:**

#1. 'persistent organic pollutants':ti,ab,kw OR 'persistent organic pollutant':ti,ab,kw OR POPs:ti,ab,kw OR 'organochlorine pesticides':ti,ab,kw OR OCPs:ti,ab,kw OR DDT:ti,ab,kw OR chlordan:ti,ab,kw OR aldrin:ti,ab,kw OR dieldrin:ti,ab,kw OR endrin:ti,ab,kw OR heptachlor:ti,ab,kw OR hexachlorobenzene:ti,ab,kw OR mirex:ti,ab,kw OR toxaphene:ti,ab,kw OR chlordecone:ti,ab,kw OR 'pentachlorobenzene':ti,ab,kw OR 'polychlorinated biphenyls':ti,ab,kw OR PCBs:ti,ab,kw OR 'polychlorinated naphthalenes':ti,ab,kw OR 'halogenated diphenyl ethers':ti,ab,kw OR 'polybrominated diphenyl ethers':ti,ab,kw OR PBDEs:ti,ab,kw OR c-decaBDE:ti,ab,kw OR 'dibenzofurans polychlorinated':ti,ab,kw OR dioxins:ti,ab,kw OR 'dioxins and dioxin like compounds':ti,ab,kw OR 'polychlorinated dibenzodioxins':ti,ab,kw OR 'decabromobiphenyl ether':ti,ab,kw OR '2 2 4 4 5 6 hexabromodiphenyl ether':ti,ab,kw OR 'perfluorooctane sulfonic acid':ti,ab,kw OR 'perfluorooctanoic acid':ti,ab,kw OR PFOS:ti,ab,kw OR PFOA:ti,ab,kw

#2. 'thyroid neoplasms':ti,ab,kw OR 'thyroid neoplasm':ti,ab,kw OR 'thyroid carcinomas':ti,ab,kw OR 'thyroid carcinoma':ti,ab,kw OR 'thyroid cancers':ti,ab,kw OR 'thyroid cancer':ti,ab,kw OR 'thyroid adenomas':ti,ab,kw OR 'thyroid adenoma':ti,ab,kw OR 'thyroid tumours':ti,ab,kw OR 'thyroid tumour':ti,ab,kw

#3. #1 AND #2

- **ProQuest:**

#1. mesh(persistent organic pollutants) OR mesh(DDT) OR mesh(chlordan) OR mesh(aldrin) OR mesh(dieldrin) OR mesh(endrin) OR mesh(heptachlor) OR mesh(hexachlorobenzene) OR mesh(mirex) OR mesh(toxaphene) OR mesh(chlordecone) OR mesh(polychlorinated biphenyls) OR mesh(halogenated diphenyl ethers) OR mesh(dibenzofurans, polychlorinated) OR mesh(dioxins) OR mesh(dioxins and dioxin like compounds) OR mesh(polychlorinated dibenzodioxins) OR mesh(pentachlorobenzene) OR mesh(decabromobiphenyl ether) OR mesh(2 2 4 4 5 6 hexabromodiphenyl ether) OR mesh(perfluorooctane sulfonic acid) OR mesh(perfluorooctanoic acid)

#2. ab(persistent organic pollutants) OR ab(persistent organic pollutant) OR ab(POPs) OR ab(organochlorine pesticides) OR ab(OCPs) OR ab(DDT) OR ab(chlordan) OR ab(aldrin) OR ab(dieldrin) OR ab(endrin) OR ab(heptachlor) OR ab(hexachlorobenzene) OR ab(mirex) OR ab(toxaphene) OR ab(chlordecone) OR ab(pentachlorobenzene) OR ab(polychlorinated biphenyls) OR ab(PCBs) OR ab(polychlorinated naphthalenes) OR ab(halogenated diphenyl ethers) OR ab(polybrominated diphenyl ethers) OR ab(PBDEs) OR ab(c-decaBDE) OR ab(dibenzofurans polychlorinated) OR ab(dioxins) OR ab(dioxins and dioxin like compounds) OR ab(polychlorinated dibenzodioxins) OR ab(decabromobiphenyl ether) OR ab(2 2 4 4 5 6 hexabromodiphenyl ether) OR ab(perfluorooctane sulfonic acid) OR ab(perfluorooctanoic acid) OR ab(PFOS) OR ab(PFOA)

#3. #1 OR #2

#4. mesh(thyroid neoplasms)

#5. ab(thyroid neoplasm) OR ab(thyroid carcinomas) OR ab(thyroid carcinoma) OR ab(thyroid cancers) OR ab(thyroid cancer) OR ab(thyroid adenomas) OR ab(thyroid adenoma) OR ab(thyroid tumours) OR ab(thyroid tumour)

#6. #4 OR #5

#7. #3 AND #6

- **CNKI:**

#1. SU=持久性有机污染物 OR SU=POPs OR SU=有机氯杀虫剂 OR SU=DDT OR SU=氯丹 OR SU=艾氏剂 OR SU=狄氏剂 OR SU=异狄氏剂 OR SU=七氯 OR SU=六氯苯 OR SU=灭蚁灵 OR SU=毒杀芬 OR SU=十氯酮 OR SU=五氯苯 OR SU=多氯联苯 OR SU=PCBs OR SU=多氯化萘 OR SU=卤代苯醚 OR SU=多溴联苯醚 OR SU=PBDEs OR SU=呋喃 OR SU=二恶英 OR SU=多氯二苯并二恶英 OR SU=十溴二苯醚 OR SU=六溴二苯醚 OR SU=全氟辛烷磺酸 OR SU=全氟辛酸 OR SU=persistent organic pollutants OR SU=organochlorine pesticides OR SU=polychlorinated biphenyls OR SU=halogenated diphenyl ethers OR SU=polybrominated diphenyl ethers

#2. KY=持久性有机污染物 OR KY=POPs OR KY=有机氯杀虫剂 OR KY=DDT OR KY=氯丹 OR KY=艾氏剂 OR KY=狄氏剂 OR KY=异狄氏剂 OR KY=七氯 OR KY=六氯苯 OR KY=灭蚁灵 OR KY=毒杀芬 OR KY=十氯酮 OR KY=五氯苯 OR KY=多氯联苯 OR KY=PCBs OR KY=多氯化萘 OR KY=卤代苯醚 OR KY=多溴联苯醚 OR KY=PBDEs OR KY=呋喃 OR KY=二恶英 OR KY=多氯二苯并二恶英 OR KY=十溴二苯醚 OR KY=六溴二苯醚 OR KY=全氟辛烷磺酸 OR KY=全氟辛酸 OR KY=persistent organic pollutants OR KY=organochlorine pesticides OR KY=polychlorinated biphenyls OR KY=halogenated diphenyl ethers OR KY=polybrominated diphenyl ethers

#3. #1 OR #2

#4. SU=甲状腺癌 OR SU=甲状腺肿瘤 OR SU=thyroid cancer OR SU=thyroid neoplasms

#5. KY=甲状腺癌 OR KY=甲状腺肿瘤 OR KY= thyroid cancer OR KY= thyroid neoplasms

#6. #4 OR #5

#7. #3 AND #6

Supplementary File 2. Main Characteristics extracted from individual studies included in this study.

Study	**Study characteristics**				**Population characteristics**				**Exposure characteristics**			**Outcomes characteristics**				**Quality score (NOS)**
First author, Publication year	Study design	Study implementation period (year),	Sample collection time (year),	Mean/median duration of follow-up (months), only for cohort	Country or region	Sample size	Age Median (range)/Mean age (SD), years	Gender Female /Male	Type of POPs	Detection method	Comparator	Outcomes	Analysis models	Effect estimates	Adjusted potential confounders	
Study 1																
Study 2																
Study 3																
Study 4																
Study 5																
Study 6																
…																

Supplementary File 3. Detailed quality scores of individual studies assessed with the Newcastle-Ottawa Quality Assessment Scale (NOS).

Study	Selection				Comparability		Exposure			Total Score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for the most important factor	Study controls for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Study 1	√	√	-	-	-	√	√	√	√	6
Study 2	√	√	√		√	√	√	√	√	8
Study 3	√	√	√	√	√	√	√	√	√	9
Study 4	√	√	√	√	-	-	√	√	√	7
Study 5	√	√	√	√	√	-	√	√	√	8
Study 6	√	-	√	√	-	-	√	-	-	4
…										

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Page(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7 and online supplementary file 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7 and online supplementary file 2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7-8 and online supplementary file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 11

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.