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Thyroid Disease Among Workers Exposed to Perfluorooctanoic Acid (PFOA)

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Abstract

Background: Perfluorooctanoic Acid (PFOA) is one of the Perfluoroalkyl acids family that can affect human health. It can act as an endocrine disruptors which interfered the hypothalamus–pituitary–thyroid (HPT) axis and targeted the biosynthesis and secretion of thyroid hormones, which can caused thyroid diseases. To determine the causal relationship between PFOA and thyroid diseases, it is necessary to look for some evidence regarding this relationship. The search for evidence is also complemented by a seven-step occupational disease assessment to establish occupational diseases.
Methods: The literature searching using the electronic database "PubMed", "Cochrane", and "Scopus" search engine. The keyword is "PFOA" "perfluoroalkyl substances" "perfluorooctanoic acid" "perfluorooctanoate" AND "thyroid disease" "thyroid function" "thyroid parameters" combined with MeSH and Title/Abstract terms. The inclusion criteria are research on humans, English language, free full article and the exclusion is duplicate articles.
Result: From the five literature obtained, there are differences in results. Four articles stated that there are association between PFOA and thyroid diseases but one articles stated PFOA concentrations measured in this study were not associated with thyroid hormones.
Conclusion: Althought most articles stated there are associations between PFOA and thyroid disease but it does not mean that PFOA can caused thyroid disease so it is still not clear the causal relationship between PFOA and thyroid disease especially in occupational setting.
Keywords: thyroid disease, perfluorooctanoic acid, workers, occupational exposure.

Introduction

The perfluoroalkyl substances (PFAS) are a family of synthetic, highly stable perfluorinated compounds with a wide range of uses in industrial and consumer products, from stain- and water-resistant coatings for carpets and fabrics to fast-food contact materials, fire-resistant foams, paints, and hydraulic fluids. Two of the PFAS most concern are the eight-carbon–chain perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA, also known as C8).[1]

The major exposure pathways for PFOA were proposed to be oral exposure resulting migration from paper packaging and wrapping into food, general food and water ingestion, inhalation from impregnated clothes, and dust ingestion. In Indonesia, PFOA are used in textile industries, non-stick cookware (Maxim teflon), fire extinguisher (Sevvo, Dexter), soccer shoes, outdoor paralel and canned fish.[2,3]

PFOA is both lipo and hydrophobic, and after absorption will bind to proteins in serum rather than accumulating in lipids. It has a half life in blood serum around 3,8-4 years dan human biomonitoring of the general population in various countries has shown that, PFOA may also be present in breast milk, liver, seminal fluid, and umbilical cord blood.[2]

PFOA can bind to nuclear receptors, such as peroxisome proliferator–activating receptor (PPARα) and act as a potential endocrine disruptor. As an endocrine disruptors, PFOA can interfere with the hypothalamus–pituitary–thyroid (HPT) axis and target the the biosynthesis and secretion of thyroid hormones, which caused thyroid disease. Studies revealed the thyroid disease that experienced by participant after exposed to FPOA can be hypothyroidism, hyperthyroidism or thyroid cancer.[2,4]

To determine the causal relationship between PFOA and thyroid diseases, it is necessary to look for some evidence regarding this relationship. The search for evidence is also complemented by a seven-step occupational disease assessment to establish occupational diseases.

Methods

A literature review was conducted on May 20, 2020 through a search of PubMed database using the keyword "PFOA" OR "perfluoroalkyl substances" OR "perfluorooctanoic acid" OR "perfluorooctanoate" AND "thyroid disease" OR "thyroid function" OR "thyroid parameters". Under this strategy, 41 articles were obtained.

Another search strategy was carried out on the same date using Cochrane database using the keyword "PFOA" OR "perfluoroalkyl substances" OR "perfluorooctanoic acid" OR "perfluorooctanoate" AND "thyroid disease" OR "thyroid function" OR "thyroid parameters". Under this strategy, 2 articles were obtained.

A database search of the Scopus was also conducted, using the "PFOA" OR "perfluoroalkyl substances" OR "perfluorooctanoic acid" OR "perfluorooctanoate" AND "thyroid disease" OR "thyroid function" OR "thyroid parameters", and under this strategy, 10 articles was obtained. Figure 1 below explain about the searching strategy flowchart.

After 5 articles were selected, it were critical appraised based on Criteria by Oxford Centre for Evidence-Based Medicine Levels of Evidence. The table 1 below explain about the critical appraisal of the 5 articles.

Result

The first article by Winquist A, Steenland K[5] (2014), studied the association between a wide PFOA exposure range and thyroid disease among community members and plant workers in a large longitudinal cohort study. In this article, 28,560 community cohort participants from C8 Health Project and 4,391 worker cohort participants who work at the chemical plant during 1948-2002 were recruited after completed a questionnaire about demographics, health-related behaviors, lifetime personal medical history and reported thyroid disease diagnosis. In retrospective analysis, using the cumulative exposure metric, the HRs for functional thyroid disease for quintiles 2-5 versus quintile 1 were 1.21,1.17,1.27, and 1.28 for the sexes combined (log-linear trend test: HR per log µg/ml-yr = 1.03, P = 0.09). The trend was more pronounced among women (HRs for quintiles 2-5 vs. quintile 1 = 1.24, 1.27, 1.36, and 1.37; HR per log µg/ml-yr = 1.04, P = 0.03) and was absent among men (FIRs for quintiles 2-5 vs. quintile 1 = 1.12,0.83,1.01, and 1.05; HR per log µg/ml-yr= 1.01, P=0.85). In prospective analysis, there was a suggestion of an

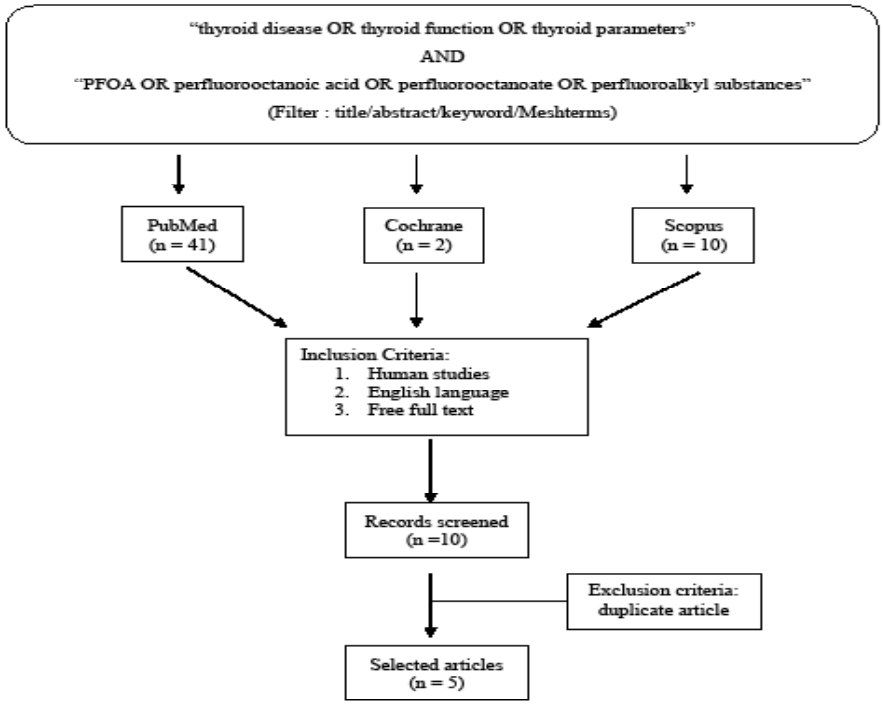

Figure 1. Searching Strategy Flowchart

Table 1. Critical Appraisal of the Selected Articles Based on Criteria by Oxford Centre for Evidence-Based Medicine Levels of Evidence

Articles									
	Study Design	Number of Participants	Outcome measure same ways in both group	Enough Follow up time	Diagnostic test for causation	Exposure preceded outcome	Dose response gradient	Consistent study to study	Level of Evidence
Winquist A, et al (2014)	CH	32.951	Yes	Yes	Yes	Yes	Yes	Yes	2a
Steenland K, et al (2015)	CH	3.713	Yes	Yes	Yes	Yes	Yes	Yes	2a
Knox SS, et al (2011)	CS	52.296	Yes	No	Yes	Yes	No	Yes	3b
Melzer D, et al (2010)	CS	3.974	Yes	No	Yes	Yes	Yes	Yes	3b
Olsen GW, et al (2007)	CS	506	Yes	No	Yes	Yes	No	Yes	4

Note: CH = Cohort; CS = Cross sectional

increasing hazards of functional thyroid disease with increasing cumulative exposure among men (HRs for quintiles 2-5 vs. quintile 1 = 1.35,1.37,1.44, and 1.85; HR per log μg/ml-year = 1.14, P=0.09).

The second article by Steenland K, Zhao L, Winquist A[6] (2015), studied about disease incident only among PFOA-exposed workers in Dupont Plant, West Virginia. About 3,713 participants cohort had retrospective exposure estimates and were included in this study. All participants were interviewed twice from 2008-2011 with the second interview seeking data about any new disease incidence since the first interview and the author using job exposure metrix (JEM) to estimated the restrospective yearly PFOA serum levels. There are a significant positive trend using the log of cumulative exposure for ulcerative colitis (n=28, p <0.05) and for rheumatoid arthritis (p=0.04, n=23). Prostate cancer (p 0,10; n=129), non-hepatitis (n=35, p=0,08) and male thyroid disease (n=82, p=0.06) showed a suggestive positive trends across quartile but there are some negative trends found in bladder cancer and asthma with medication.

The third article by Knox SS, Jackson T, Frisbee SJ, Javins B, Ducatman AM[7] (2011), studied about the extent to which PFOA and perfluorooctane sulfonate (PFOS) were associated with altered thyroid function in thyroid hormones in a large population based study. This is a cross sectional analysis of 52.296 adults with a year or more of exposure to PFOA from drinking water. Analysis were stratified by gender and age group (<20 – ≤50 years and >50 years) and the outcomes were tyroxine, T3 uptake and thyroid stimulating hormone (TSH). There was a significant positive association between serum PFOA and tyroxine in women in both age group (β = 0.05, p=<0.0001; and β = 0.08, p=<0.0001 for women ≤50 and >50, respectively) and in men >50 (β = 0.06, p=<0.001) after adjustment for covariates. In both age group of women and in men >50 years there was a small but significant inverse association between PFOA and T3 uptake. The association between PFOS and thyroid hormone resembles with PFOA.

The fourth article by Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS[1] (2010), studied about associations between serum PFOA and PFOS concentrations and thyroid disease prevalence in representative samples of the U.S. general population. 3,974 adult participants were asked about thyroid disease diagnosed by physician in the National Health and Nutrition Examination Survey (NHANES) for 1999–2000, 2003–2004, and 2005–2006. The serum PFOA and PFOS measured using high performance liquid chromatography. In fully adjusted logistic models, women with PFOA ≥ 5.7 ng/mL were more likely to report current treated thyroid disease (OR = 2.24; 95% CI, 1.38–3.65; p = 0.002) compared with PFOA ≤ 4.0 ng/mL and it had near significant similar trend in men (OR = 2.12; 95% CI, 0.93–4.82; p = 0.073). For PFOS, in men we found a similar association for those with PFOS ≥ 36.8 ng/mL versus ≤ 25.5 ng/mL (OR = 2.68; 95% CI, 1.03–6.98; p = 0.043) and in women this association was not significant.

The fifth article by Olsen GW, Zobel LR[8] (2007), studied the hypothesis that PFOA may be positively associated with increased blood lipid, hepatic and thyroid function across the three 3M fluorochemical production facilities. About 506 participants were included and their blood lipid, hepatic and thyroid function were measured. Most lipid, hepatic and thyroid function and PFOA had a p value <0.05 and can be concluded that there were no association between PFOA concentration with blood lipid, hepatic dan thyroid function.

Discussion

To determine the causal relationship between PFOA and thyroid disease, seven steps of occupational diagnosis can be applied.

The first step is to determine the clinical diagnosis. Thyroid disease can be established by anamnesis, physical examination, and supportive examination such as laboratory finding for thyroid function, neck ultrasound (USG) and fine needle aspiration.

The second step is to determine the exposure in the workplace. Workers can be exposed to PFOA through inhalation, skin, eyes and ingestion. In this case, we can ask the worker about PFOA exposure in the workplace and then we can measured PFOA concentration in the working environment. We also monitor PFOA concentration in human body, so biomonitoring is needed. Measurement of serum or whole-blood PFOA concentrations is the standard accepted biomarker of exposure in humans.[2]

The third step is to determine whether there is a relationship between exposure to disease. This relationship should be based on the previous five selested

articles and applying the Bradford Hill criteria used to determine whether there is sufficient evidence that PFOA can cause tyroid disease:

1. Strength of association
   All articles except article 5 revealed that there are association between serum PFOA with thyroid function or thyroid disease.
2. Consistency
   There are other studies that revealed that thyroid disease associated with PFOA exposure.
3. Specificity
   Not only PFOA can caused thyroid disease. Study by Walsh JP[9] in Australia said that iodine deficiency is the most common cause of thyroid disease. Thyroid diseases can also caused by an abnormal immune response to auto-antigens present in the thyroid gland. Study by Soon, et al[10] in Malaysia said that heavy metal like mercury, cadmium, lead, arsenic and nickel and chemical toxins such as pestisides, hair dyes and some household cleaners can also be link to thyroid diseases.
4. Temporality:
   In all journals, the participant exposed to PFOA first before participate in the studies. Four article except article 5 revealed that PFOA exposure can disrupt thyroid function or manifest to thyroid disease.
5. Dose response
   Article 1, 2 and 4 revealed that there are association between dose and duration of PFOA exposure that can disrupt thyroid function or manifest thyroid disease.
6. Plausibility
   Study by Coperchini, et al[4] said that the harmful effects of the endocrine disruptors (EDCs) were investigated by a growing number of studies on the male and female reproductive system, mammary gland, and the pancreatic. In addition, EDCs such as PFOA can interfere with the hypothalamus–pituitary–thyroid (HPT) axis. EDCs may directly affect the production of thyroid hormones by interfering with thyroglobulin synthesis, iodide uptake, and TPO activity or with feedback mechanisms.
7. Coherent
   Multiple different studie have evidence that support cause-effect interpretation, but there are some evidence that have different conclusion.
8. Experiment
   All articles did not conducts an experiment.
9. Analogy
   PFOA does not specifically cause thyroid disease only.

The fourth step was to determine the sufficiency of exposure in the workplace. In this step, we have to know the lengh of working in PFOA exposure area in workplace, duration time exposed to PFOA per day, measurement of PFOA level in the workplace and personal protective equipment used in workers. However, there are no data about TLV (treshold limit value) and PEL (permissible exposure limit) of PFOA in occupational setting as well as the biological exposure indice in human body by OSHA or ACGIH. There are are two thresholds which are MAK (Maximum Concentration Value) for PFOA inhalable fraction by ILO which is 0.005 mg/m^3 and treshold regulation for national drinking water and food standard by Environmental Protection Agency (EPA) which is 2x10^{-5} mg/kg/day or 0.07 µg/L (Lifetime Health Advisory).[11,12]

The fifth step was to determine the individual factors that play a role. There are several individual factors that can play a role such as gender, iodine deficiency and autoimmune disease. Those factors can make the workers more vulnerable to develop thyroid disease in PFOA exposure workplace.

The sixth step was to determine the factors outside workplace. Beside workplace, exposure to PFOA comes from household products, such as food containers, staining-resistant protection for clothing, furniture, and carpets, paints, food, drinking water, dust, and air. PFOA can be released in the environment at their production, at their assembly into commercial products, during the distribution and industrial or consumer use, or due to discharge of industrial and municipal wastewater.

The seventh step is to determine the occupational diagnosis. Eventhough the four articles stated that PFOA associated with thyroid disease or altered thyroid function, but it does not mean that PFOA can caused it. Beside, there are many cofounding factors that also can caused thyroid disease and it needed to be ruled out. So we can conclude that it is still not clear wether PFOA can caused thyroid disease or not especially in occupational setting.

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