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Review Article

Thyroid Dysfunction Secondary to Endocrine Disruptive Chemicals – A Systematic Review

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ABSTRACT

Objectives: To assess the epidemiological data and potential connection between different endocrine chemical disruptors and thyroid hormone abnormalities.

Study Design: The 2020 PRISMA standards were followed when conducting the systematic review. Ten research studies were found and examined after an in-depth review of the scientific literature.

Methodology: The systematic review was aimed to gather all pertinent information, including observational studies (prospective or retrospective cohorts) that address the relationship between exposure to endocrine disruptors and thyroid hormone imbalance.

Results: Ten studies were found, and they demonstrated that these substances, especially in adulthood, impact the level of thyroid hormone and the incidence of thyroid nodules.

Conclusions: Endocrine disruptive chemicals can compromise thyroid function by affecting hormone transporters, gene expression, and the hypothalamic-pituitary-thyroid axis.

Keywords: Endocrine Disruptors, systematic Review, thyroid Hormone, thyroid Diseases.

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INTRODUCTION

The state of the environment's contaminants is a growing global concern. The European Union defines environmental pollutants as undesirable compounds discharged into the environment due to human activity and jeopardising ecosystems and human health. Chemical, heavy metal, and pesticide pollution damage the ecosystem.[1] Toxins can cause permanent harm to health by entering the body through the skin, digestive tract, or respiratory system. Individuals employed in mining facilities, farms, and industrial facilities are especially susceptible to pollution. Over 61 million individuals are exposed to heavy metals in the fifty-nine nations under study.[2]

"Endocrine disruptors (EDs) are exogenous substances or chemical mixtures that interfere with any aspect of hormone action [3]." Endocrine disruptors can mimic the actions of the body's endogenous hormones, including thyroid hormones, androgenic substances, or oestrogens. It could modify natural hormones' in vivo metabolism, inhibiting the binding to the receptor. The virus can bind to the cell's receptor and inhibit the binding of the natural hormone.[4] An endocrine disruptor hinders the functioning of normal hormonal systems, and the effects can last well after the initial contact has ceased, sometimes even affecting future generations. EDCs can enter the human body through several routes, including ingesting food and drink, inhalation of gasses and particulates in the air, and absorption through the skin. Endocrine-disrupting chemicals (EDCs) can be passed through the pregnant woman to the developing foetus through the placenta and from the mother to the young kid through nursing.[4]

Phthalates, phenols, and flame-retardant substances are prominent chemicals that disrupt the endocrine system (FRs). They can be found in food containers, hygiene goods, plastics, and scents.[5]

There is a notable association between endocrine-disrupting chemicals (EDCs) and the thyroid gland. These substances exhibit diverse impacts on the thyroid hormones (TH). Thyroid problems are highly prevalent chronic illnesses.[6] Exposure to ED (Environmental Disruptors) can lead to obesity, illness, and cancer.

Thyroid-related cancers and autoimmune thyroid illnesses have shown an increase in prevalence in the past few decades.[7] Environmental factors, including heavy metals, may contribute to advancing malignant thyroid tumours. Cadmium (Cd) is widely dispersed in the environment, occurring naturally and being

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released from agricultural and industrial chemicals and other sources.[8]

Cadmium is a scarce drinking water supply in both urban and rural locations. Even at minimal amounts of chronic environmental exposure, Cadmium can have a wide range of negative consequences on the heart, liver, bones, kidneys, and testicles.[9]

Cadmium is a notable carcinogen in the thyroid gland. Cadmium does not effectively attach to DNA, but it can exert its effects by interfering with DNMT (DNA methyltransferase) activity, disrupting DNA repair pathways, and promoting the generation of reactive oxygen species (ROS).[10]

Because Cadmium can accumulate in living organisms and persist in the environment for extended periods, the associated health risks from exposure to Cadmium (Cd) are heightened. Scientific data suggests that even small doses of Cadmium can disrupt the normal functioning of the thyroid gland, both at the intended levels and when there is an excess of the metal. [11]

Researchers found multiple correlations between the amounts of thyroid hormones examined and the presence of metals in both blood and urine samples. The findings of these connections indicated a negative correlation between elevated metal concentrations and reduced hormone levels. [12]

EDCs and their impact on thyroid gland function have received significant attention recently. Thyroid hormones (THs), specifically the hormones thyroxine (T4) and triiodothyronine (T3), play a crucial role in regulating the growth and specialisation of multiple tissues and organs. They also maintain energy balance and support other essential metabolic processes. Thyroid hormones have a crucial function in the growth and formation of the central nervous system, which occurs throughout the perinatal period. Minor disruptions in the thyroid-hypothalamus axis can lead to significant cognitive impairment and neurological abnormalities.[13]

The primary goal of systematic analyses is to employ explicit, reliable, and consistently implemented criteria to minimise the reviewer's bias and misrepresentation of data. Systematic review procedures effectively establish a substantial correlation between exposure to EDCs and adverse health outcomes. These methodologies employ explicit and relevant criteria for selecting and evaluating studies, ensuring the reliability of the data.[14]

This systematic review seeks to provide an extensive review of observational studies investigating the association between endocrine-disrupting drugs and thyroid illness in adults.

Given that the research design involved a literature review, the authors did not consider ethical approval necessary and did not seek it.

METHODOLOGY

Inclusion Criteria: The review encompassed all observational studies, including cross-sectional, case-control, and cohort studies.

Included in the study were individuals of both genders who were above the age of 15.

All research that described endocrine disruptor substances were included, irrespective of their dosage or length of exposure.

This review only analysed papers published in English to ensure that the topic and vocabulary used were easily understandable and unambiguous.

Peer-reviewed articles were selected to safeguard the current research's validity.

Exclusion Criteria: Critiques, proposals, introductions, summaries, laboratory procedures, expositions, letters to the supervisor, and edited compositions were excluded from consideration.

Any information not related to disruptive endocrine substances and any data pertaining to children younger than 15 were excluded from the analysis.

Articles conveying personal thoughts or reflections, as well as those primarily providing information, such as those outlining clinical strategies, were not included.

Articles published in languages apart from English were also omitted.

Literature Search Protocol

The electronic databases Scopus, Web of Science, PubMed, Medline, EMBASE, and Science Direct were utilised to conduct the searches.

The authors reviewed specific journals, which encompassed the following:

i. Journal of Environmental International
ii. Journal of Hazardous Material

iii. Endocrine Reviews

iv. Journal of Molecular Endocrinology

v. Best Practice & Research Clinical Endocrinology & Metabolism

vi. International Journal of Environmental Research and Public Health

vii. International Journal of Hygiene and Environmental Health

Due to the diverse range of approaches employed in this evaluation, no rating or grading was conducted.

The searched keywords included thyroid, endocrine chemicals, disrupting chemicals, hormones, thyroid hormones, pollutants, environmental pollutants, endocrine-disruptive chemicals, thyroid disease, pesticides, metals, diet, food, thyroid hormone disruptors, adults, and health risks.

The data sought yielded the results of thyroid dysfunction illnesses, specifically hypothyroidism and hyperthyroidism.

Appraisal of Relevancy and Eligibility of Literature – Data Extraction Protocol

Due to the variable terminology used in the literature, including all relevant research other than the most essential ones, it took much work.[15] This issue remains prevalent in systematic reviews that primarily include qualitative studies.[16]

To tackle this issue, the authors employed a comprehensive search methodology encompassing a range of commonly used search terms in the published literature and met the criteria.

The referencing list, abstracts, and titles were examined to identify any possible duplication and assess their significance. Following the initial assessment, the data and conclusions that met the specified inclusion criteria, along with the names of the study's authors, were obtained.

To reduce this potential risk, qualifying articles were reassessed after a significant period. Upon a second evaluation, it became apparent that many research articles needed to meet the eligibility criteria.

Appraisal of Methodological Quality

The JBI-QARI, designed by the Joanna Briggs Institute, was used to standardise the quality evaluation.[17]

RESULTS

Of the 57 items obtained from the online literature search, 35 met the selection criteria. An additional ten publications were identified by examining the citations of the 35 selected papers. Forty-five published publications underwent a comprehensive assessment of precise criteria for inclusion and exclusion. Only ten papers satisfied the inclusion criterion after a thorough evaluation, as depicted in Figure-1.

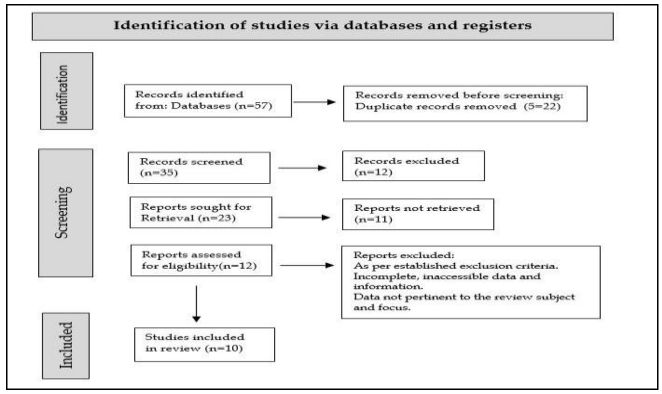

Figure-1: PRISMA 2020 Flow Diagram

A longitudinal investigation was undertaken to investigate the correlation between exposure to organochlorine pesticides and thyroid hormone levels in workers in the floriculture industry. The study was done on 136 male volunteers from Mexico and Morelos who had potentially been exposed to pesticides during both the high (rainy season) and low (dry season) pesticide exposure periods. The mean geometrical value of Dichlorodiphenyldichloroethylene (p.p'-DDE) remained relatively constant across time, with values of 6.17 ng/ml and 4.71 ng/ml. The average level of lipids did not distinguish clearly between the two consecutive periods of plant growth.[18]

During the wet season, almost 90% of workers had at least one Dialkyl phosphate (DAP) metabolite in their urine, compared to 69% in the dry season. The levels of dialkyl phosphate (DAP) were four times higher during the rainy season compared to the dry period (2.00 vs 0.48 mol/g creatinine; p= 0.001).[18]

A cross-sectional study utilised information from the National Health and Nutrition Examination Survey to obtain an appropriate, nationally representative sample. The dataset includes measurements of several metals (lead, Cadmium, and mercury) in the blood and measurements of other metals (caesium, molybdenum, barium, tungsten, antimony, uranium, and thallium) in the urine. Additionally, the dataset includes measurements of thyroid hormone levels, specifically Thyroid-Stimulating Hormone, and free and total T3. The connection between thyroid hormone concentrations and metals found in either urine or blood was modelled using multivariate linear regression. Merely 5% of the subjects exhibited elevated triiodothyronine, thyroxine, or thyroid-stimulating hormone above the normal range. Nevertheless, 9.2 per cent (with a standard error of 1.2%) exhibited low levels of T3, whilst 9.4 per cent (with a standard error of 1.1%) displayed low levels of T4. Metals were found in nearly all blood and urine specimens, with urinary molybdenum exhibiting the highest levels (median 42.5 g/L).[19]

When considering all blood metals, it was found that mercury was linked to decreased levels of Thyroxine and Triiodothyronine, while Cadmium was related to a decrease in Thyroid-Stimulating Hormone. There is a correlation between the presence of Cadmium in urine and increased levels of T3 and T4 hormones. Urinary levels of thallium and barium have been linked to decreased levels of Thyroxine and Triiodothyronine. Caesium was associated with decreased levels of TSH, while tungsten was associated with increased levels.[19]

DISCUSSION

Bisphenols exert a substantial influence on the probability of developing breast cancer. During the initial phases of pregnancy, exposure to BPA has the potential to negatively affect the thyroid's function, including deiodinase activity. However, despite prior studies suggesting a detrimental link, no substantial correlation has been discovered for thyroid-stimulating hormone.[20]

In Chinese research, individuals involved in plastic recycling exhibited higher levels of urinary phthalates, T3, and T3/T4 compared to the control group. These associations were not monotonic.[21]

No correlation was found between usage of drugs and thyroid function. There is scientific evidence indicating that some chemicals have the potential to influence the levels of thyroid hormones, and these effects may vary based on an individual's gender. In males, there was a significant inverse correlation with total T4, potentially indicating the influence of these substances on hormone synthesis. However, in females, it was linked to higher T3 levels.[22]

Although the substances in the serum were preserved for a lengthy period, a separate experiment did not find any connection between exposure to PCBs and the occurrence of endocrine and metabolic diseases.[23]

Studies reveal that females have a three times greater likelihood of having thyroid cancer compared to males. This study analysed a case study to investigate the connection between the levels of PBDE (polybrominated diphenyl ethers) in the blood and the likelihood of developing papillary thyroid cancer (PTC) affecting women who were exposed to one or more PBDE congeners. The study followed a case-control design. A total of 462 female volunteers, aged 21 to 84, were included in the research study. All individuals identified as Caucasians. A clear and significant relationship exists between PTC and BDE-209 levels found in home dust.[24]

Another study found insignificant evidence that getting exposed to PBDE increased the likelihood of developing thyroid cancer. The research found a correlation between BDE-209 and smaller, less aggressive thyroid nodules.[25]

Recent case-control research conducted on US military members has found a correlation between elevated levels of the BDE-28 congener and an increased risk of PTC. The correlation was observed in tumours larger than ten millimetres and was particularly prominent in females.[26]

Due to the possibility of chemical accumulation in fatty tissue, it has been discovered that individuals with higher levels of the substance or metabolic disorders are significantly prone to the detrimental effects of "Polybrominated diphenyl ethers (PBDE)" and, therefore, have significantly lower FT3. Extensive studies have substantiated that they disrupt the thyroid's activity and hormone transmission.[27]

A notable strength of the research effort is that it encompassed studies with diverse populations from different regions of the world. It is worth mentioning that most of the research included in the analysis was conducted recently, therefore offering the most up-to-date information (Figure-2).

The main constraint of the study is the absence of Randomised Controlled Trials, which resulted in their exclusion from the review. Randomised controlled trials (RCTs) are considered the most reliable methodology with minimal potential for bias. However, conducting studies to determine the causal relationship between endocrine-disrupting chemicals (EDCs) and their effects on people can present several difficulties and ethical constraints.

In the future, long-term research conducted through international collaboration should be conducted to determine causal associations. Extensive investigations can facilitate the global comparison of outcomes.

Figure-2: Salient Features of Literature Reviewed

Citation	Study Design	Findings
Tonelli FCP, 2020	Book Chapter	Heavy metals like arsenic, cadmium, and mercury accumulate due to industrial activities, posing health risks and environmental damage.
Sokal , 2021	Literature Review	The article discusses the impact of endocrine-disrupting chemicals (EDCs) on thyroid function. The article emphasizes the need for stricter food safety policies and the reduction of waste production to improve ecosystem quality and reduce thyroid disease risks.
Diamanti-Kandarakis, 2009	Scientific Statement	The study highlights the broad class of EDCs, such as pesticides, plastics, and industrial chemicals, and their potential to disrupt endocrine and reproductive systems
Monneret, 2017	Literature Review	EDCs and specifically, Diethylstilbestrol exposure led to significant adverse health effects, including clear cell carcinoma in females, increased risks of reproductive complications, infertility, obesity, testicular cancer, and urogenital abnormalities in males.
Darbre, 2018	Literature Review	The key findings indicate that EDCs in air can interfere with hormone function, potentially leading to adverse health effects. The review emphasizes the need for further research to understand the full impact of inhaling these chemicals on human endocrine health.
Kumar, 2020	Literature Review	The review highlights that EDCs, found in various industrial and agricultural pollutants, can disrupt hormonal balance, leading to reproductive health issues, metabolic disorders, and increased cancer risk.
Petrakis, 2017	Literature Review	The study highlights how EDCs interfere with cellular processes, induce inflammatory responses, and exhibit transcriptional and oncogenic activity. Key findings include the role of EDs in promoting adipogenesis, altering energy balance, and modifying gut microbiota. The review emphasizes the need for a strategic approach to address the global conditions related to energy management and the rising prevalence of obesity and related diseases.
ATSDR Toxicological Profile for Cadmium, 2017	A report by a US governmental agency	The report provides detailed information on the health effects, exposure risks, and toxicological data related to cadmium. The profile includes guidelines for safe exposure levels, methods for detecting cadmium in the environment, and recommendations for public health actions to mitigate risks associated with cadmium exposure.
Klaassen, 2009	Literature Review	Metallothionein plays a crucial role in retaining Cd in tissues and reducing biliary excretion. It protects against acute Cd-induced lethality and chronic toxicity to the liver, lung, and kidneys.
Liu, 2009	Literature Review	Acute Cd exposure leads to significant oxidative stress, generating superoxide anion, hydrogen peroxide, and hydroxyl radicals. In contrast, chronic Cd exposure induces adaptation mechanisms, such as increased glutathione levels, which reduce reactive oxygen species production
Jancic, 2014	Literature Review	Cadmium, a toxic metal with a long biological half-life, accumulates in the thyroid gland, causing oxidative stress and damage. It leads to various thyroid abnormalities, including colloid cystic goiter, follicular hyperplasia, and parafollicular cell hyperplasia.
Babić Leko, 2021	Literature Review	Lifestyle factors (such as smoking, BMI, and iodine intake) and environmental pollutants (like perchlorate) can impact thyroid hormone levels. Genetic factors also contribute significantly to variations in thyroid function. Future research is needed to better understand the effects of environmental factors, especially for vulnerable groups.
Jugan, 2010	Literature Review	The publication emphasizes the significance of understanding how endocrine disruptors affect thyroid function, which is crucial for maintaining overall health.

Vandenberg, 2016	Grounded Theory Framework Development	The proposed SYRINA framework aims to provide a transparent and consistent approach to evaluating the strength of evidence linking EDC exposures to adverse health or environmental outcomes.
Perrier, 2016	Bibliometric Study	The study analysed 1,148 studies to identify patterns in indexing, term usage, and definitions. It found that indexing terms in PubMed were not consistently applied, making it difficult to locate relevant studies. Additionally, definitions for these terms were often missing or inconsistent, complicating searches and usage. The study highlights the challenges in categorizing and retrieving literature in this field due to poor indexing and inconsistent terminology.
Cristofoli, 2016	Qualitative Comparative Analysis	The study focuses on four key factors: resource munificence, centralization of network structure, formalization of coordination mechanisms, and network management. By analysing 12 Swiss home care networks, the authors identify multiple paths to high network performance, highlighting that different combinations of these factors can lead to success.
Munn, 2014	Mixed Methods Study	The study developed a critical appraisal tool for systematic reviews addressing questions of prevalence. The tool was piloted among sixteen experienced healthcare researchers and found to be valid, acceptable, and easy to use.
Blanco-Munoz, 2016	Longitudinal Study	The study found that the geometric means of p,p′-DDE levels were higher during the rainy season. Positive associations were observed between serum levels of p,p′-DDE and total T3 and total T4, while TSH levels showed negative but non-significant changes. These results support the hypothesis that p,p′-DDE acts as a thyroid disruptor in humans.
Yorita Christensen, 2013	Observational Study.	The study found that dioxin-like polychlorinated biphenyls (PCBs), non-dioxin-like PCBs, and metals were significantly associated with elevated ALT levels. A significant interaction was detected between the class-level score for metals and the score for non-dioxin-like PCBs. When including all chemicals in one model, three chemicals (Mercury, PCB 180, 3,3′,4,4′,5-PNCB) accounted for 78% of the weight, with the remaining 22% associated with four chemicals (a dioxin and three PCBs). The weighted quartile sum estimator efficiently identified reproducible significant associations.
Derakhshan, 2019	Embedded Longitudinal Study	The study found that higher levels of bisphenol A were associated with lower TT4 concentrations and lower FT4/FT3 and TT4/TT3 ratios, particularly in early pregnancy. Higher BPF levels were linked to increased FT3. No significant associations were found between BPS or triclosan and thyroid hormone levels. These results suggest that BPA may affect thyroid function and deiodinase activities during early gestation.
Wang, 2018	Cross Sectional Study	The study found that workers exposed to phthalates had significantly higher levels of certain urinary phthalate metabolites and altered thyroid hormone levels compared to the control group. Specifically, the exposed workers had higher levels of urinary monobenzyl phthalate (MBzP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-n-octyl phthalate (MOP), as well as higher serum total triiodothyronine (T3) and the T3 to thyroxine (T4) ratio. The dose-response relationships between urinary phthalate metabolites and thyroid hormone parameters were found to be non-monotonic among the workers, indicating complex interactions that warrant further investigation.
Przybyla, 2008	Cross Sectional Study	The study found that higher exposure to a mixture of EDCs was associated with lower levels of thyroxine (T4) in males but not in females. In females, EDC levels were positively associated with triiodothyronine (T3) serum concentrations, though this was not statistically significant. The results suggest sex-specific differences in the exposure-response relationship between EDCs and thyroid hormone levels.

Zani, 2019	Cross Sectional Study	Serum levels of Polychlorinated biphenyls (PCBs) were positively associated with age and negatively with female gender, education, smoking habits, and BMI45. No significant associations were found between PCB serum levels and thyroid hormones, glycemia, or the prevalence of endocrine and metabolic diseases, including diabetes and hypertension.
Deziel, 2019	Case Control Study	The study found a decreased risk of papillary thyroid cancer (PTC) at the highest category of BDE-209 concentrations and an elevated risk at the highest category of BB-153 concentrations. In multi-pollutant models, an increase in BDE-100 concentrations was associated with increased PTC risk. However, hierarchical Bayesian logistic regression and principal components analysis did not yield statistically significant results. Overall, the results do not generally support a positive association between PBDE/PBB exposure and PTC risk.
Hoffman, 2017	Case Control Study	The study found that higher levels of certain flame-retardant chemicals (FRs), particularly decabromodiphenyl ether (BDE-209) and tris (2-chloroethyl) phosphate (TCEP), in household dust were associated with increased odds of papillary thyroid cancer (PTC). Participants with higher dust BDE-209 concentrations were 2.29 times more likely to have PTC. The associations varied based on tumour aggressiveness and mutation status, with TCEP linked to larger, more aggressive tumours and BDE-209 associated with smaller, less aggressive tumours. These results suggest that exposure to FRs in the home may be linked to PTC occurrence and severity, warranting further study.
Huang, 2020	Nested Case Control Study	The study found a significantly increased risk of classical papillary thyroid cancer (PTC) associated with higher levels of BDE-28, particularly for larger tumours (>10 mm) and more pronounced in women. No consistent associations were observed for other PBDE or PBB congeners.
Shiekh, 2020	Experimental Study	The study found that BDE-47 and BDE-99, along with their metabolites, have the potential to disrupt thyroid hormone transport by binding to TBG BDE-99 and its metabolites showed stronger binding to TBG compared to BDE-47, with 5-MeO-BDE-99 exhibiting binding affinity equal to thyroxine. This suggests that these compounds can interfere with thyroid function, posing a risk to human health.

CONCLUSION

Endocrine-disrupting chemicals can hinder thyroid function by influencing the hypothalamic-pituitary-thyroid axis, the expression of genes, and hormone transporters. Multiple studies have also indicated a correlation between being obese and metabolic syndrome, and this can also impact hormone levels and lead to the development of autoimmune thyroid disorders and subclinical hypothyroidism.

Conflict of Interest: The authors declare no conflict of interest. Additionally, No AI tools were used in any form or manner during the research process and in the composition of the manuscript.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SS & FM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AG & AA: Data acquisition, data analysis, approval of the final version to be published.

AB & SN Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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