

REVIEW ARTICLE

Occupational and environmental agents as endocrine disruptors: Experimental and human evidence

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ABSTRACT. In the last few years great concern has arisen from the description of adverse endocrine effects of several occupational and environmental chemical agents on human and/or wildlife health. Such agents may exert their effects directly, specifically binding to hormone receptors, and/or indirectly, by altering the structure of endocrine glands and/or synthesis, release, transport, metabolism or action of endogenous hormones. Many studies have been focused on the outcomes of the expo-

sure to those chemicals mimicking estrogenic or androgenic actions. Nonetheless, the disruption of other hormonal pathways is not negligible. This paper reviews the experimental and human evidence of the effects of occupational and environmental chemical agents on hypothalamus-pituitary unit, pineal gland, parathyroid and calcium metabolism and adrenal glands.

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INTRODUCTION

The interest surrounding the interaction of environmental/occupational agents with the endocrine system is steadily increasing, thanks to the growing body of data indicating that humans, as well as domestic and wildlife species, may suffer from adverse health consequences deriving from exposure to endocrine disrupting chemicals. In point of fact, the hypothesis of such a relationship dates back to the last century, when endocrine glands were considered to exert anti-toxic actions (1-3). At the beginning of the twentieth century, Roger and Garnier (4) described the thyroid damage due to phosphorous poisoning. In 1929, Ferranini (5) remarked that "numerous industrial poisons inflict more or less deep injury on the functions and structure of the endocrine glands. Amongst the most dangerous poisons of the endocrine glands are lead, mercury, phosphorous, arsenic, benzene and the asphyxiating gas". Few years later, Vigliani (6) reported eight cases of hyperthyroidism associated with lead (Pb) poisoning, while Porritt (7) recorded the

Pb-induced histological changes in the thyroid gland. Those early studies reported the effects of very high exposure to industrial toxicants. Nowadays, it is apparent that exposure to even relatively low levels of environmental and occupational agents may alter the endocrine functions. The problem has become even more complex in recent times, when a large number of chemicals possessing hormonal activity have been produced and diffused into our environment. Typical example are those chemicals possessing an estrogenic action (8) that exert their effects directly, by specific hormonal activities, and/or indirectly, by altering the structure of endocrine glands and/or synthesis, release, transport, metabolism or action of endogenous hormones. The first – direct – mechanism is that shown, for instance, by Chlordecone (Kepone), a chlorinated hydrocarbon insecticide which binds and activates the estrogen receptor (9). Such property has been demonstrated after the occurrence of oligospermia in workers involved in the epidemic poisoning occurred in 1975 in a pesticide plant (10). Although polychlorinated biphenyls (PCBs) can bind to the estrogen receptor (11), they also are an example of the latter – indirect – mechanism of disruption, as in the case of some PCB mixtures that force the catabolism of 17- β -estradiol toward 4- and 2-hydroxylation, enhancing the production of molecules with residual estrogen activity (12).

In this review, xenobiotic effects are outlined in rela-

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tion to the function of the different endocrine glands with special concern with their effects on human subjects. Considering that the alterations of sexual and reproductive function, and the actions of xenobiotics exhibiting estrogenic or androgenic properties have been already extensively discussed (13-19), the present article will address the effects on hypothalamus-pituitary unit, pineal gland, parathyroid and calcium metabolism, and adrenal glands.

HYPOTHALAMUS AND PITUITARY

Hypothalamus-pituitary activity can vary in response to subtle variations of internal and external environment. As a consequence, many studies have attempted to evaluate the effects of environmental agents on hypothalamus-pituitary unit. The main features of human studies are detailed in Table 1.

Metals

Heavy metals are known to induce pituitary alterations. Pb effects on reproductive function have long been described (20). In the last decades, some investigators have suggested that gonadal Pb effects are secondary to the impairment of the hypothalamus-pi-

tuinary control (21). This view is supported by the observation in Pb-exposed adult rats of an altered release of LH (21). Recently, Gustafson *et al.* (22) showed a similar phenomenon also in humans. In workers moderately exposed to Pb (mean blood-Pb level 38 mg/dl) they described a decrease in plasma FSH which demonstrated the Pb effect on human hypothalamus-pituitary-gonadal axis. Pb also induces alterations of statural growth related, at least in part, to an impairment of growth hormone (GH) secretion, as shown by several animal studies (23). In Pb-poisoned children, who suffer from statural growth deficiency (24), a lowered GH response to a provocative stimulus (insulin tolerance test) has been reported (25).

Pb is also part of a large group of toxicants which may affect the hypothalamic inhibitory dopaminergic control of prolactin (PRL) secretion, resulting in an increase of PRL plasma concentrations (26). Although it has been suggested that Pb could interfere with pituitary dopaminergic receptors (as hypothesized after the report of a decreased sulphiride pituitary binding in Pb exposed rats), the main effect of Pb is the direct suppression of the hypothalamic dopaminergic tone (27). Among metals the same effect is exhibited by manganese (Mn), which is associated to high PRL levels in

Table 1 - Main features of human studies on the effects of chemical agents on pituitary function. All studies were cross-sectional in design.

Type of exposure (Ref.)	Markers of exposure/outcome	Outcome	Group size Exposed/ Non-exposed	Notes
Lead (26)	Zinc protoporphyrin (Zpp) and blood lead concentrations (PbB)/Prolactin serum levels	Hyperprolactinemia	76 exposed	Increase in prolactin levels in male workers with higher Zpp and PbB levels
Lead (22)	Blood lead levels/ Gonadotropin and free testosterone serum levels	Decrease in FSH	25/25	Male workers. No effect on testosterone serum levels
Lead (25)	Blood lead levels/ GH response to Insulin Tolerance Test	Decrease in GH response	12/12	Lead poisoned children (blood lead ≥ 40 $\mu\text{g/dl}$)
Lead (24)	Blood lead levels/ Stature measurements	Statural growth Deficiency	4319 children	Population based study. Linear negative correlation between blood lead and height
Manganese (28)	Manganese air levels/ Prolactin serum levels	Hyperprolactinemia	14/14	Male workers
Styrene (34)	Styrene air levels/ Prolactin serum levels	Hyperprolactinemia	46/30	Male workers
Tetrachloroethylene (36)	Tetrachloroethylene blood levels/ Prolactin serum levels	Hyperprolactinemia	60/30	Female workers
Toluene (37)	Toluene air and blood levels/ Gonadotropin serum levels	Hypogonadotropic hypogonadism	20/44	Male workers

exposed workers (28). Since dose-response relationship analysis indicates that the lowest dose able to elicit effects corresponds to Mn urinary excretion as low as 0.4 microgram/l, it has been suggested that, not only occupational, but also environmental exposure to Mn may actually cause hyperprolactinemia and, therefore, significantly contribute to abnormally high serum PRL in the general population (29).

TSH secretion might be altered by cadmium (Cd) exposure. Although there is no evidence of such an effect in humans, Cd was shown to cause secondary hypothyroidism in the catfish (*Clarias batrachus*); in that fish, experimental administration of Cd chloride caused a significant fall of TSH secretion, along with a typical thyroid histologic pattern of functional inactivity (30). The same authors also described a Cd effect on gonadotropins, whose circulating levels were reduced.

Solvents

Solvents are often indicated as disruptors of the pituitary function. Toluene and benzene were shown to increase corticosterone secretion in mice through hypothalamus-pituitary-adrenal axis activation (31). Suggestively, Shen *et al.* (32) observed, through immunohistochemical methods, the reduction of oxytocin, vasopressin and neuropeptide Y secreting neurons in toluene-injected rats.

The evidence of an association of pituitary tumors with solvent exposure is inconclusive. An inhalation toxicity study of the industrial solvent decahydronaphthalene (decalin) showed a slightly, not-dose-related, increased incidence of pituitary tumors in exposed mice and rats (33).

Occupational studies have demonstrated the effects of solvents on human pituitary. Bergamaschi *et al.* (34) investigated the effect of styrene exposure on PRL plasma levels and found that 30% of styrene-exposed male workers in glassfiber reinforced plastic plants had PRL values exceeding upper reference limits, vs 7% in the control group (Fig. 1). PRL hypersecretion was due to decreased dopaminergic inhibition, as confirmed by the reduction of dopamine β -hydroxylase (DBH) activity, taken as a measure of dopaminergic tone (35). A similar effect was detected in female dry-cleaners exposed to tetrachloroethylene (36).

Toluene exposure was associated to a slight reduction in gonadotropin and testosterone blood levels in exposed rotogravure printers (37).

Chlorinated aromatic hydrocarbons

Chlorinated aromatic hydrocarbons, such as PCBs, dioxins and furans, bioconcentrate in the food chain and can persist for decades in the environment. Many of them have become ubiquitous. Their half-life in humans is measured in years.

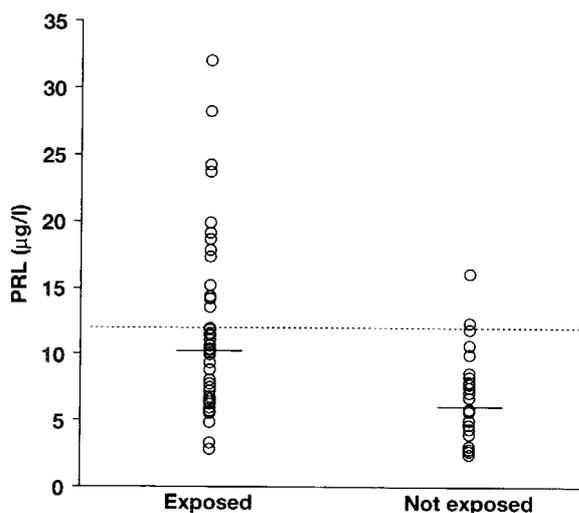


Fig. 1 - Concentrations of serum prolactin in styrene-exposed workers and controls. The dashed line represents the upper reference limit. Solid bars show medians for exposed and unexposed subjects. Modified from Bergamaschi *et al.* (34), with permission.

These organochlorine compounds have been proposed as disruptors of multiple pituitary tropins. Bestervelt *et al.* (38) investigated the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) on the hypothalamic-pituitary-adrenal axis, comparing the bioactivity of ACTH obtained from rat anterior pituitary cells treated with dioxin to that of normal ACTH. They demonstrated a weakened ability of the ACTH produced by dioxin-cultured cells to stimulate corticosterone secretion from adrenal cell cultures; this result implies a decreased hormone bioactivity which might be accountable for the impaired adrenal function induced by dioxin in rats (39). A similar action could be ascribed to PCBs according to the reduction of cortisol stress response to the capture exhibited by fishes living in environments polluted by PCBs, polycyclic aromatic hydrocarbons and mercury (40).

PCBs may also modify the pituitary gonadotropin release, as indicated by the lowered gonadotropin response to provocative tests in Aroclor 1254[®] administered male Atlantic croaker (41).

Jekat *et al.* (42) proposed the pesticide pentachlorophenol (PCP) as a disruptor of the hypothalamic-pituitary-thyroid axis because of the secondary hypothyroidism they observed in PCP treated rats.

Those stimulating observations have not been followed by similar studies in humans.

Modifiers of pituitary circadian rhythms

Environmental and occupational agents may not merely influence overall secretion of pituitary hor-

mones, but they can also impair the pulsatile patterns of hormone release. Stepanova (43) reported that chronic exposure of female rats to low concentrations of various xenobiotic (toluene, benzene, dioxane, styrene and lead) caused the disappearance of the circadian rhythm of the hypothalamus-pituitary-gonadal axis. Although it is reasonable to assume that such an effect may occur also in humans, there are no data currently available.

PINEAL

The pineal gland converts environmental light stimuli into an endocrine response which is constituted by melatonin secretion. The pineal is an important chronimmunomodulator and melatonin is presumed to prevent immunologic and neoplastic diseases (44). Hence, any agent which modifies melatonin release might entail serious health consequences.

On that ground, it has been speculated that the powerful dioxin neoplastic promoting action (45) might be mediated via the melatonin plasma level reduction ascertained in animal studies (46). By the same token,

experimental dimethyl-benzanthracene (DMBA) induced tumorigenesis was shown to be associated to a decrease in plasma melatonin in rats (47).

THYROID

Hormonal alterations and goiter

Many chemical agents may disrupt thyroid function (Table 2), acting on one of the steps of thyroid hormone synthesis or metabolism, frequently leading to the development of goiter.

Both structure-activity relationship (SAR) studies (48) and *in vitro* competitive binding/inhibiting experiments (49) showed that some organohalogen chemical compounds, whose chemical structure resembles that of triiodothyronine (T₃) and thyroxine (T₄) (Fig. 2), bind with varying degree of affinity to thyroid hormone receptors and thyroid hormone binding proteins.

Early processes of hormonal synthesis are the most affected by xenobiotics; those processes are the iodide (I⁻) trap, by which iodide is transported across the membrane into thyroid cells, and the thyroidal

Table 2 - Main features of human studies on the effects of chemical agents on thyroid function.

Type of exposure (Ref.)	Markers of exposure/outcome	Outcome	Study type	Group size Exposed/ Non-exposed	Notes
Cobalt (53)	Urinary Co content/ Serum thyroid hormones	Increased FT ₄ /FT ₃ I ratio	Occupational Cross-sectional	25/48	Female workers
Cyanides (50)	Serum thiocyanate levels/ Thyroid hormones	Decreased T ₄ and T ₃ , increased TSH	Occupational Cross-sectional	35/35	Male workers
Mercury (54)	Urinary and blood Hg levels/ Serum thyroid hormones	Increased FT ₄ /FT ₃ ratio	Occupational Cross-sectional	41/41	Male workers
PCBs (57)	History of "Yusho" disease/ Thyroid hormone blood levels	High TT ₄ and TT ₃	Cross sectional	123/43	Free T ₄ and TSH were normal
PCBs (58)	Occupational or residential history of exposure to PCB/ Thyroid laboratory and ultrasonography screening	Increased thyroid volume/ Increased frequency of TPO Ab in female workers and of TSHR Ab in exposed workers.	Cross sectional	238/572 adolescents 454/965 workers	
PCBs (59)	Occupational history of exposure/Thyroid hormone, Ab-Tg, Ab-Mc blood levels	Autoimmune thyroiditis	Occupational Cross-sectional	35/89	At variance with Stross et al. (60)
TCDD (63)	Residence rosters/death certificates	Thyroid cancer	Population based Mortality study	6748/232747	
TCDD (64)	Occupational history of exposure/Death certificates	Thyroid cancer	Occupational Mortality study	13482/3951	
Thiourea (52)	Occupational history of exposure/Thyroid hormones	Primary hypothyroidism	Occupational Prospective	227 exposed	Three index cases of hypothyroidism. No comparison with a not exposed control group

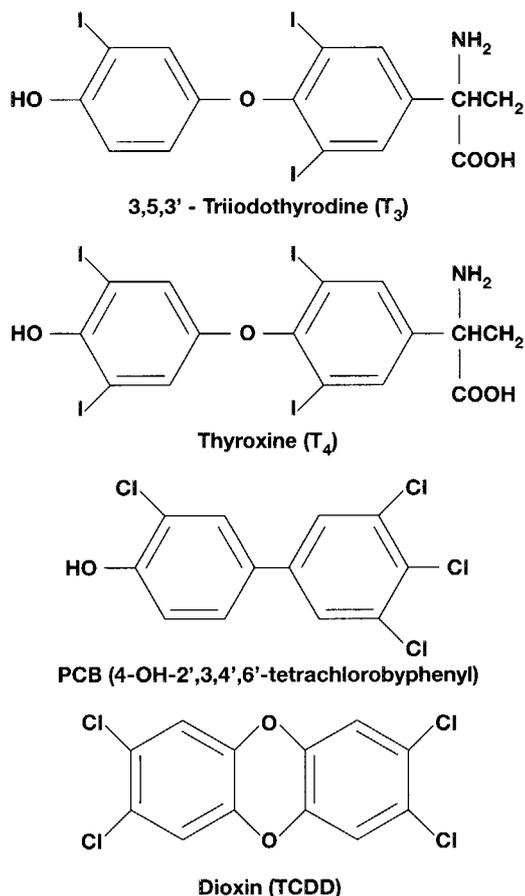


Fig. 2 - Chemical structure of thyroid hormones, polychlorinated biphenyls (PCBs) and dioxin.

peroxidase (TPO) activity that mediates I⁻ oxidation and its incorporation in the thyroglobulin. I⁻ transport is due to the intrinsic membrane protein Na⁺/I⁻ Symporter (NIS) which is saturable with large amounts of iodide and inhibited by negative ions such as perchlorate, thiocyanate, nitrate and pertechnetate. Exposure to such ions may induce a reduction of thyroid hormone release as shown by Banerjee *et al.* (50) in workers handling cyanide compounds (which are metabolized to thiocyanate) in an electroplating process of a cable industry. TPO is the target of thiocarbamide drugs – methimazole, propylthiouracil, carbimazole – routinely used in hyperthyroid patients to block thyroid hormone synthesis. Exposure to agents having a chemical structure similar to those drugs (Fig. 3) as, for example, the herbicide aminotriazole (51) and thiourea (52) can induce hypothyroidism in exposed workers. Thyroid hormone action can also be interfered by agents blocking the deiodination of T₄ to T₃: in rats

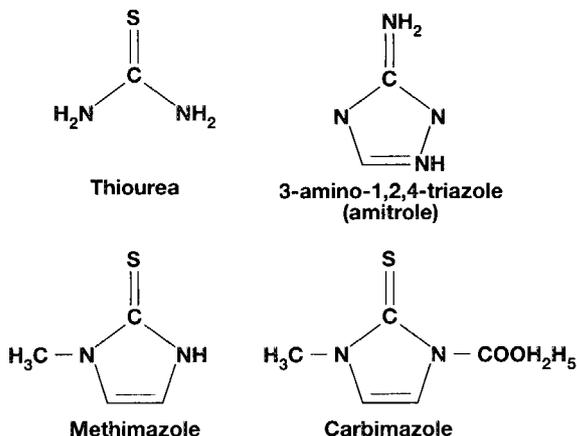


Fig. 3 - Common structural properties of thiocarbamide drugs (methimazole and carbimazole), thiourea, and 3-amino-1,2,4-triazole (Amitrole).

fed with erythrosine (FD&C Red No. 3) - a color additive used in foods, cosmetics, and pharmaceuticals - compensatory increased secretion of TSH, follicular cell hypertrophy and hyperplasia, and high incidence of follicular cells adenomas were found in presence of hormonal changes consistent with 5'-monodeiodinase inhibition (lowered T₃, heightened T₄/T₃ ratio and reverse T₃) (51). In occupational studies, a similar hormonal pattern, without any clinical or laboratory evidence of thyroid disease, was found in pottery painters exposed to cobalt blue dyes (53), and in mercury-exposed chloralkali workers (54).

Hepatic microsomal enzyme inducers have been shown to alter thyroid hormone levels in rodents, in which glucuronidation of T₄, followed by secretion into bile, is the major pathway of thyroid hormone biotransformation. Xenobiotics inducing liver microsomal enzymes and disrupting thyroid function in rats include chlorinated hydrocarbons (alchlor, chlordane, DDT, PCBs, dioxin), and polybrominated biphenyls (PBBs), in addition to a large number of drugs (phenobarbital, benzodiazepines, calcium channel blockers, steroids) (51, 55). In humans, in a retrospective cohort study, TCDD serum levels were positively associated with previous diagnosis of thyroid disease (56). In contrast, PCBs do not seem to reduce thyroid hormone serum concentration in human subjects. Thyroid function evaluation in Taiwanese adults, after the exposure to toxic levels of PCBs and polychlorodibenzofurans (PCDFs) in the Yusho rice-oil poisoning accident, revealed increased levels of total T₃ and T₄ (finding consistent with the estrogenic properties shown by some mixtures of PCBs), without modifications of serum TSH concentrations (57). Nonetheless, a large study in workers exposed to

PCBs in a production factory, and in adolescents from the surrounding polluted area showed an increase in mean thyroid volume measured by ultrasonography in comparison to an age- and sex-matched reference group living in a similar iodide sufficient environment (58). The health significance of these conflicting data has yet to be assessed and further research is required to elucidate the conceivable hazardous actions of organochlorine compounds on human thyroid.

Autoimmune thyroiditis

Although, in the recent past, a better knowledge of the immunologic mechanisms underlying autoimmune thyroiditis (AIT) was achieved, the causes that initiate and promote the pathogenic process are still largely obscure. Apart from I⁻ deficiency, few studies addressed the relationship between chemical agents and AIT.

Bahn *et al.* (59) suggested PBBs as AIT inducers, based on the high frequency of sub-clinical hypothyroidism and thyroid antimicrosomal antibody found in a cohort of workers employed in a chemical manufacturing firm producing PBBs and polybrominated biphenyl oxides (PBBO). The hypothesis was not confirmed by a later study by Stross (60) in a similarly exposed group. Recently, however, an increased prevalence of anti-peroxidase and anti-TSH receptor antibodies was found in an area heavily polluted by PCBs (58).

Thyroid carcinoma

A wide number of occupational and environmental agents have been proposed as thyroid carcinogens, but a direct oncogenic effect upon thyroid cells has never been ascertained.

Any chemical which causes a reduction of thyroid hormone levels and a compensatory hypersecretion of TSH, may result, when tested in sensitive species, as rats and mice, in an increased incidence of thyroid tumors (51). These agents, which usually show little or any mutagenicity, indirectly force the thyroid gland, through TSH hypersecretion, toward the development of hypertrophy, hyperplasia, adenomas and, less frequently, carcinomas. Recently, the U.S. Environmental Protection Agency (EPA) published a list of 24 pesticides (out of 240 screened) which produce thyroid follicular cell tumors in rats (61). In humans, it has been suggested that thyroid hyperstimulation by TSH could induce cancer only when acting in conjunction with other metabolic or immunologic abnormalities (62), as it could have occurred in dioxin exposed subjects, whose thyroid cancer risk was suggestively found to be increased by Pesatori *et al.* (63) in the Seveso contaminated population, and by Saracci *et al.* (64) in a pesticide sprayer cohort.

PARATHYROID AND CALCIUM METABOLISM

Parathyroid function and calcium (Ca²⁺) metabolism may be impaired by metal exposure (Table 3). The best-known example of Ca²⁺ control impairment induced by an environmental agent is the epidemic of osteomalacia and kidney damage (*itai-itai* disease) noted in Japan in the late 1940s, due to Cd contamination of water and rice by mine discharges (65). Later animal studies assessed that Cd interferes with vitamin D hydroxylation, reduces Ca²⁺ incorporation into the bone, Ca²⁺ absorption from the intestine, and Ca²⁺ renal re-absorption (66). Recently, a prospective population study carried out in an industrialized area in Belgium polluted by low levels of Cd, showed a consistent correlation of urinary Cd excretion to bone fractures risk and to decreased bone mineral density in women (67). Mean urinary Cd excretion in these subjects was 30-fold lower than in those with *itai-itai* disease.

Pb, also, interacts with Ca²⁺ homeostasis, as reported by Rosen *et al.* (68). In Pb intoxicated children, they found a strong negative correlation between 1,25 dihydroxyvitamin D and Pb levels (Fig. 4). In the same study, a slightly increased concentration of Ca²⁺ and an increased serum PTH were observed.

Aluminum (Al) is another metal which exhibit bone toxicity, slowing both osteoclast and osteoblast activities and leading to osteomalacia and adynamic bone disease (69). Human and animal studies have shown that Al reduces PTH circulating levels (69).

ADRENAL CORTEX

Although data concerning the interaction between occupational and environmental factors and adrenal cortex are limited, its sensitivity to such agents is sufficiently documented. *In vitro*, heavy metals (mercury, cadmium, cobalt) were noted to affect viability and ACTH-stimulated corticosterone secretion of rat adrenal cells obtained from *zona glomerulosa*, *fasciculata* and *reticularis* (70). In mice, Lin *et al.* (71) showed

Table 3 - Effect of metals on parathyroid function and calcium metabolism.

Aluminum	Osteomalacia Adynamic bone disease Primary hypoparathyroidism
Cadmium	Decrease in Vit. D3 and Ca ²⁺ gastro-enteric absorption Decrease in renal Ca ²⁺ re-absorption Osteomalacia
Lead	Direct bone toxicity Vit. D3 deficiency Secondary hyperparathyroidism

ADRENAL MEDULLA

Adrenal medulla, as part of the sympathetic nervous system, has been often studied in the attempt to identify reliable markers of neurotoxicity. Consequently, dopamine- β -hydroxylase (DBH), considered as a marker of nervous and adrenal catecholamine secretion, was determined in workers with relatively low exposure to many chemical agents (Table 4). The use of this method led to the recognition of the disrupting effects on the adrenergic system exerted by styrene (34), toluene (73) and carbon disulfide (CS₂) (74).

CONCLUSIONS

Many occupational and environmental agents are known to alter one or more endocrine functions of the human body. Experimental data (animal and *in vitro* studies) suggest similar capabilities for several additional agents. The study of the complex interactions between the environment and the endocrine system entails a series of methodological and substantive issues including the subtle nature of the endocrine functions themselves and the inherent large variability of many hormonal parameters, the low level of current exposures, the numerous confounders possibly affecting the association under scrutiny, and the size of the investigated population.

An example of how many variables contribute in determining the value of the measured functions comes from the proposed use of prolactin as a marker of dopaminergic damage (75), whose measurement could lead to misleading results or interpretations for the confounding effect of work-related stress factors (76).

The small number of subjects usually investigated, either is justified by the rarity of the diseases/defects being studied and/or the limited number of exposed workers per production unit. Efforts are needed to perform larger collaborative studies in the future.

It should also be realized that the cross-sectional design (almost exclusively used in the reviewed human studies) sometimes leaves open the determination of the precise temporal relation between exposure and endocrine alteration. Many exposures lead in a short time to (often subclinical) hormonal changes which are reversible after cessation of exposure (43, 75). However, the persistence of such a condition for a long time may give rise to a stable disease. This is the way, for instance, by which chemicals unbalancing thyroid hormone secretion or metabolism may lead to the development of goiter (51). At the opposite end, short exposures could

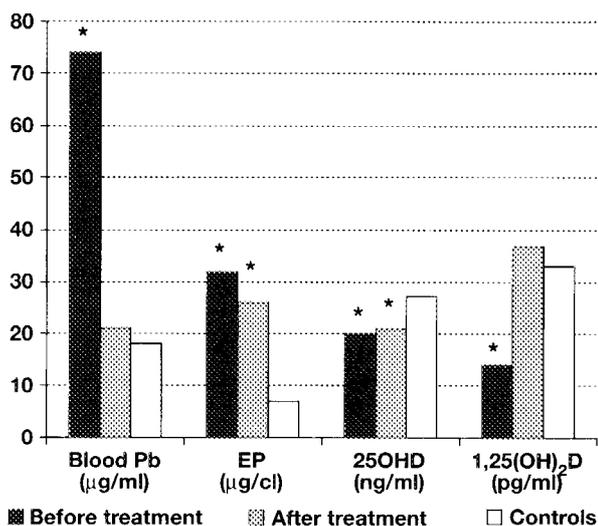


Fig. 4 - Mean blood lead (Pb), blood erythrocyte proto-porphyrin (EP), serum 25-hydroxyvitamin D (25OHD), and serum 1,25-dihydroxyvitamin D (1,25-(OH)₂D) levels in Pb-poisoned children before and after therapy with Pb-chelating agents, and in normal children. * $p < 0.001$ as compared with control children. After Rosen J.F. et al. (68).

that dioxin lessens the glucocorticoid receptor responsiveness in hepatic tissue. In humans, finally, Chia *et al.* (72) reported a significant increase of DHEA-S serum concentrations in a group of male workers chronically exposed to trichloroethylene (Fig. 5).

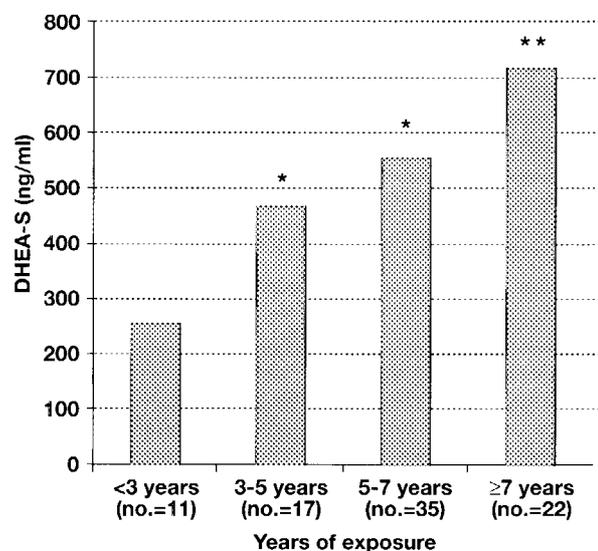


Fig. 5 - Mean DHEA-S serum concentration in male workers with exposure to trichloroethylene, by exposure duration. * < 0.01 , ** < 0.001 . After Chia S.E. et al. (72).

Table 4 - Main features of human studies on the effects of chemical agents on adrenal function in humans. All studies were cross-sectional in design.

Type of exposure	Markers of exposure/outcome	Outcome	Group size Exposed/ Non-exposed	Notes	Ref.
Carbon disulfide	Carbon disulfide air levels/ Serum DBH, urinary adrenaline excretion	Decrease of catecholamine secretion	90/50	Female workers	74
Lead	Blood lead levels/Plasma catecholamines levels	Increase of plasma catecholamines	27/27		77
Styrene	Air styrene levels, urine styrene metabolites content/Serum dopamine-β-hydroxylase	Decrease of catecholamine secretion	46/30	Male workers	30
Trichloroethylene	Urine trichloroacetic acid levels/ Serum DHEA-S	Increase of serum DHEA-S	85 Exposed	Male workers	72
Toluene	Urinary hippuric acid basal levels/ Serum dopamine-β-hydroxylase	Decrease of catecholamine secretion	10/10	Male workers	73

result in chronic illnesses, as it may occur in the case of the risk factors considered to be involved in the etiology of autoimmune thyroiditis (59).

It is, then, mandatory to conduct in the future follow-up and case-control studies in order to better understand the timing and the directionality of several hypothesized exposure-effect relationships.

Despite its complexity, a thorough knowledge of the interactions between occupational and environmental agents and endocrine system is essential to a deeper knowledge of the pathogenic mechanism of disparate health conditions, and to improve our means for primary and secondary prevention of work and environment related diseases.

Monitoring of reversible endocrine parameter alterations might also be effective in the assessment of known occupational and environmental hazards, thanks to the remarkable sensitivity of the endocrine system to external and internal stimuli; the possible low specificity is the limiting feature of such biomarkers, and careful consideration is required in confounding control.

Vital to a better definition of the hazard posed by several agents and to the identification of effective means for preventing their adverse effects is the clarification of the significance and prognostic relevance of the recognized endocrine alterations. A difficult and resource-consuming task which could be greatly facilitated by large, cooperative longitudinal studies of exposed populations.

Assessing the environmental and individual exposure to exogenous factors is a major problem common to many fields of health investigation. Remarkable

advancements have been made in recent years, and substantial efforts and resources are being devoted to this issue jointly by toxicologists, epidemiologists, and endocrinologists.

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