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Endocrine Disruptors and Carcinogenesis

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Abstract

Environmental chemicals that at certain doses interfere with the endocrine system are called endocrine disruptors; the disruption of homeostasis induced is including birth defects, feminizing effects and cancerous tumors. The critical window of development for most organisms is the *in utero* period where substantial damage to a developing fetus takes place after exposure to these chemicals; further, the risk of cancer development increases after environmental or occupational exposure later in life. In this review, epidemiological data are quoted regarding the increased cancer risk after the exposure to endocrine disruptors, while a current quantitation method of the chemical carcinogenesis evolving is also provided.

Keywords: Endocrine disruptors; Carcinogenesis

Introduction

According to European Commission: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations". Endocrine disruptors fall into six categories of chemicals including pesticides (DDT and methoxychlor), fungicides (vinclozolin), herbicides (atrazine), industrial chemicals (PCBs, dioxins), plastics (phthalates, bisphenol A, alkylphenols) and plant hormones (phytoestrogens) [1]. The most important assigned effect for the endocrine disruptors is genomic instability, defined as an increased tendency of the genome to acquire mutations [2]. It occurs when various processes involved in maintaining the genome are dysfunctional or when exposure to carcinogenic chemicals occurs [3].

The sovereign consideration for environmental influences on disease etiology is the developmental stage of exposure. Exposures during a critical time of development can alter genome activity associated with the differentiation program of cells or organ systems. This altered program and genes expression can then promote a disturbed homeostasis and disease at the later stage of development [4]. Transgenerational actions of endocrine disruptors are described by Skinner as follows: ''In the event an environmental toxicant such as an endocrine disruptor modifies the epigenome of a somatic cell, this may promote disease in the individual exposed, but not be transmitted to the next generation. In the event a toxicant modifies the epigenome of the germ line permanently, then the disease promoted can become transgenerationaly transmitted to subsequent progeny'' [5].

Transgenerational inheritance and endocrine disruptors

Exposure to environmental chemicals can induce the epigenetic transgenerational inheritance of the disease. The question that emerges is if these ''epimutations'' –adult-onset disease and associated differential DNA methylation regions– come up in the presence (secondary) or in the absence of genetic change (primary) regarding the exposure of endocrine disruptors [6]. Mc Carrey exposed pregnant female rats carrying the lacI mutation-reporter transgene to vinclozolin and assessed the frequency of mutations in kidney tissue and sperm recovered from F1 and F3 generation progeny. The results confirm that vinclozolin induces primary epimutations rather than secondary [6]. It is suggested that the environmental induction of the epigenetic transgenerational inheritance of sperm epimutations promotes genome instability, such that genetic mutations are acquired in later generations [7] **(Table 1).**

Further, gestating F0 generation female rats were transiently exposed to methoxychlor during fetal day 8 to day 14 and then adult-onset disease was evaluated in adult F1 and F3 generation progeny. Increases were observed in the incidence of kidney disease, ovary disease, and obesity in the methoxychlor lineage animals. Kidney disease was characterized by either the presence of an increased number of proteinaceous fluid filled cysts or reduction in size of glomeruli or abnormality of Bowman's capsule thickness [8]. The ovarian disease was presented as a primordial follicle pool decrease or polycystic ovary disease. In females and males, the

incidence of disease increased in both the F1 and the F3 generations and the incidence of multiple disease increased in the F3 generation [8].

Table 1 Transgenerational effects of endocrine disruptors.

Exposure effect of endocrine disruptors		
Generations	**Somatic cells**	**Germ cells**
	F0 (may be endpoints for disease incidence)	F0 (germline transmission of abnormal epigenome)
		F1 offspring (transmission of altered epigenome)
		F2 offspring (phenotype harboring 'epimutations' established at F1 generation)

Regarding the ability of dioxin to promote trangenerational inheritance, gestating F0 generation females were exposed to dioxin during fetal day 8 to day 14 and adult-onset disease was evaluated. The incidences of total disease and multiple disease increased in F1 and F3 generations. Prostate disease, ovarian primordial follicle loss and polycystic ovary disease were increased in F1 generation dioxin lineage; prostate disease was characterized by atrophic prostatic duct epithelium. Only the F1 generation dioxin lineage rats showed an increase in prostate histopathology [9]. Kidney disease in males, pubertal abnormalities in females, ovarian primordial follicle loss and polycystic ovary disease were increased in F3 generation dioxin lineage animals [9]. Concurrently, the actions of environmental toxicants and relevant mixtures in promoting the epigenetic transgenerational inheritance of ovarian disease was investigated with the use of a fungicide, a pesticide mixture, a plastic mixture, dioxin and a hydrocarbon mixture. After transient exposure of an F0 gestating female rat during embryonic gonadal sex determination, the F1 and F3 generation progeny adult onset ovarian disease was assessed. Transgenerational inheritance of phenotypes observed included an increase in cysts resembling human polycystic ovarian disease and a decrease in the ovarian primordial follicle pool size resembling primary ovarian insufficiency [10].

Similarly, benzo[a]pyrene, in F3 medaka (*Oryzias latipes*) larvae, at an environmentally relevant concentration (1µg/L) has previously been shown to affect bone development in a transgenerational manner. It was demonstrated that the impaired bone formation at an early life stage is not recoverable and can result in a persistent transgenerational impairment of bone metabolism in F3 adult fish [11]. Considering that the underlying mechanisms of bone formation are conserved between medaka and mammals, the results may also shed light on the potential transgenerational effect of benzo[a]pyrene on skeletal disorders in mammals/humans [11]. Histological and transcriptomic changes in male zebrafish testes following early life exposure to low level dioxin included the altered expression of genes associated with testis development, steroidogenesis, spermatogenesis, hormone metabolism, and xenobiotic response [12]. However, the majority of environmental chemicals acts on somatic tissues and influence the physiology of the individual exposed; in some cases, these environmental factors promote transgenerational inheritance, where the germ cell is affected [5].

Quantifying the endocrine disruptors—driven carcinogenicity

Dioxin, benzene, kepone have all been classified as carcinogenic [13]. Back in the 1930s, industrial smoke and tobacco smoke were identified as sources of carcinogens, including benzo[a]pyrene, nitrosamines and reactive aldehydes —found in plastics industry. Vinyl chloride is a human carcinogen posing elevated risks of rare angiosarcoma, brain and lung tumors, and malignant haematopoietic lymphatic tumors [14]. Heterocyclic amines represent an important class of carcinogens in foods. They are mutagens and carcinogens at numerous organ sites in experimental animals, produced when meats are overheated for long periods; like most other chemical carcinogens, they are not carcinogenic per se but need to be metabolized by a family of cytochrome P450 enzymes to initiate a carcinogenic response [15].

In the last decade, it has been reported that an abundant class of small non-coding single-stranded RNAs, known as microRNAs (miRNAs), function as negative regulators of gene expression and may have important roles in the development of cancer. The expression of miRNAs is deregulated in almost all human malignancies. Characterization of these aberrantly expressed miRNAs indicates that they might also function as oncogenes and tumor-suppressors, thus they have been collectively named as “oncomirs” [16]. The onco-miR-21 is an estrogen-regulated miRNA and as such, plays an important role in breast cancer [17]. BPA and DDT, two well-known endocrine disruptors, alter the expression profiles of miRNA in MCF-7 breast cancer cells [18]. Phthalates and phenols are two classes of suspected endocrine disruptors that are used in a variety of everyday consumer products, including plastics, epoxy resins, and cosmetics; prenatal phenol and phthalate exposure is associated with altered miRNA expression in placenta [19]. The detectable miRNAs in tissue, blood, and other body fluids with high stability provide an abundant source for miRNA-based biomarkers in human cancers [20]. Of

utmost importance was the recent study of Vrijens and colleagues [21]; they reviewed on the potential of using miRNAs as biomarkers for environmental exposure including cigarette smoke, air pollution, nanoparticles, and diverse chemicals; miRNAs that had expression alterations associated with smoking observed in multiple studies are miR-21, miR-34b, miR-125b, miR-146a, miR-223, and miR-340; and those miRNAs that were observed in multiple air pollution studies are miR-9, miR-10b, miR-21, miR-128, miR-143, miR-155, miR-222, miR-223, and miR-338. They concluded that miRNA changes may be sensitive indicators of the effects of acute and chronic environmental exposure [21].

This candidate miRNA approach as potential signature of environmental exposure was demonstrated in utero, since exposure to airborne pollution at this critical window of development, affects miRNAs expression as well as its downstream target tumor suppressor phosphatase and tensin homolog (PTEN) [22]. Earlier, Cao had demonstrated the miRNA-dependent regulation of PTEN after arsenic trioxide treatment in bladder cancer cell line T24 [23]. Recently added was the link between miRNAs as novel biomarkers of deployment status and exposure to polychlorinated dibenzo-p-dioxins and dibenzofurans [24]. Experimental data in rodents demonstrated that prenatal DES exposure can cause alteration in miRNA expression profile in mothers and fetuses reflecting oncogenic and immunological changes [25]. On the other hand, Hsu et al. demonstrated that the expression of 82 miRNAs, barely 9.1% of the 898 miRNAs evaluated, were altered in breast epithelial cells when exposed to diethylstilbestrol (DES) [26].

Data linking exposure to endocrine disruptors with cancer

According to the World Health Organization, around 20% of all cancers would be due to environmental factors. Among these factors, several chemicals are indeed well recognized carcinogens [27]. Exposure to endocrine disruptors during critical stages of development impedes normal hormonal signaling and results in altered gene expression. Iatrogenic gestational exposure to DES induced alterations of the genital tract and predisposed individuals to develop clear cell carcinoma of the vagina. An increased risk of cervical intraepithelial neoplasia among DES daughters was observed [28].

Gestational exposure of rodents to a related compound, the xenoestrogen bisphenol A (BPA) increases the propensity to develop mammary cancer during adulthood, long after cessation of exposure, enhancing the hypothesis of estrogens being in the wrong place at the wrong time [29]. Low-dose exposure to BPA can affect mammary gland development in male and female rats, although higher doses show a different pattern of effects. The observed intraductal hyperplasia in female rats could be associated with an increased risk for developing hyperplastic lesions, which are parallels to early signs of breast neoplasia in women [30]. Long-term exposure to BPA or benzo[a]pyrene alters the fate of human mammary epithelial stem cells by pre-activating bone morhogenetic proteins signaling [31]. Treatment with BPA and methoxychlor results in the growth of human breast cancer cells and alteration of the expression of cell cycle-related genes, cyclin D1 and p21, via an estrogen receptor-dependent signaling pathway [32].

Enhancer of Zeste Homolog 2 (EZH2) is a histone methyltransferase that has been linked to breast cancer risk and epigenetic regulation of tumorigenesis. Mice exposed in utero to DES or BPA showed increased EZH2 expression in the mammary gland [33]. Especially, among diverse endocrine disruptors, xenoestrogens such as BPA, dioxins, and di(2-ethylhexyl) phthalate, have been shown to activate estrogen receptors (ERs) and modulate cellular functions induced by ERs. Furthermore, they appear to be closely related with carcinogenicity in estrogen-dependent cancers, including breast, ovary, and prostate cancers [34].

Researchers aimed to assess associations of dietary PCB exposure with breast, endometrial and ovarian cancer risk in middle-aged and elderly women, finding out that dietary exposure to PCBs plays no critical role in the development of these cancer entities [35]; further, previously observed associations between cumulative PCB exposure and prostate cancer mortality were not confirmed in the study of Ruder et al. [36]. Nevertheless, during 4.5 years of follow-up, Donat-Vargas et al., ascertained 67 incident cases of melanoma. After multivariable adjustments, exposure to dietary PCBs was associated with four-fold increased risk of malignant melanoma [37]. Regarding the effects of decabrominated diphenyl ether (PBDE-209) in regulation of growth and apoptosis of breast, ovarian, and cervical cancer cells, it has been shown to alter cell cycle distribution by inducing the S phase or G2/M phase. Furthermore, PBDE-209 partially suppressed tamoxifen-induced cell apoptosis in the breast cancer cell lines [38]. Organotin compounds, such as tributyltin, induce G2/M cell cycle arrest in human embryonic carcinoma cells [39], while cell growth of BG-1 ovarian cancer cells was promoted by 4-tert-octylphenol and 4-nonylphenol via downregulation of TGF-β receptor 2 and upregulation of c-myc [40].

Of note is that analyses revealed a dose-response relationship between lung cancer occurrence and increasing arsenic concentrations in drinking water as well as cumulative arsenic exposure among the residents with low methylation capacity. The relationship between arsenic exposure and lung cancer among high methylaters was not statistically significant [41]. Chang et al. recruited 205 patients with urothelial carcinoma and 406 control participants for a 2 year-case-control study; patients with urothelial carcinoma showed higher urinary levels of arsenic, cadmium, chromium, nickel and lead than the controls [42].

Evidence for genotoxicity in humans has involved detection of chromosomal aberrations, sister chromatid exchanges in lymphocytes and micronucleus formation in lymphocytes, buccal mucosal cells, and exfoliated urothelial cells in the urine. Cohen supported that though difficulties have been identified in the interpretation of such results, including inadequate assessment of exposure to arsenic, measurement

of micronuclei, and potential confounding factors such as tobacco exposure, folate deficiency, inorganic arsenic is a non-genotoxic carcinogen [43].

Exposure to benzene, which is used as a solvent, is linked to acute myelogenous leukemia. The question raised is whether children represent a subpopulation in which a higher risk of leukemia is associated with very low levels exposure to environmental benzene [44,45].

Occupational exposure to environmental chemicals and carcinogenesis

Human exposure to asbestos is through inhalation i.e., from disruption of materials containing asbestos and ingestion i.e., contaminated food/water. Asbestos is linked to increased risk of lung cancer, and development of mesothelioma; translocation of inhaled asbestos fibers from the lung to other tissues, such as the pleura and the peritoneum, occurs frequently, and that chrysotile may be more actively translocated from the lung playing an important role in the induction of either malignant mesothelioma and/or hyaline plaques [46]. Greater or equal lung asbestos burden was found in shipyard and construction workers with mesothelioma [47]. Associations between asbestos exposure and mortality from lung, peritoneal and pleural cancers, mesothelioma and asbestosis were confirmed by Harding, while evidence of associations with stroke and stomach cancer mortality was observed as well among British asbestos workers undergoing regular medical examinations during 1971-2005 [48] **(Table 2)**.

Table 2 Examples of occupational exposure to endocrine disruptors.

Endocrine disruptor	Associated Cancer	Occupational exposure
Trichloroethylene	Prostate	Dry Cleaning Solvent
	Kidney	Coffee Decaffeination
	Liver	Chemical Industries: Dyes
		Polyvinyl Chloride
		Perfumes
Vinyl Chloride	Liver	Plastics and Vinyl Products
		Refrigerant in Furniture Automobile Wall
		Coverings
Lead	Lung	Mining
	Brain (Gliomas)	Ships or Bridges
Cadmium	Prostate	Batteries
		Metal Paintings
Arsenic	Lung	Smelting Product
	Skin	Herbicide
		Fungicide
		Drinking water
Acrylonitrile	Lung	Precursor in the Industry of Acrylamide
		Emissions
		Fumigant
		Auto exhaust
Benzene	Leukemia (AML and CML)	Paint
		Rubber
	Hodgkin's Lymphoma	Dry Cleaning
		Use as solvent
Dioxins (TCDD)	Non-Hodgkin's Lymphoma	Combustion Sources
		Chemical Manufacturing Sources Metal

	Endometriosis	Smelting
		Herbicide

Crystalline silica is considered as one of the most common and serious occupational hazards to workers' health. The results of Poinen-Rughooputh meta-analysis supported the carcinogenic role of silica on the lungs, which was more pronounced at higher levels of exposure, in the presence of silicosis and in the mining industry [49]. Surprisingly, it was indicated that geometric and arithmetic mean of exposure was higher than threshold limit value for silica dust in all demolition sites [50], while estimating the lifetime lung cancer mortality showed a higher risk of mortality from lung cancer in building demolition workers. Steenland, earlier, conducted a pooled exposure-response analysis of 10 silica-exposed cohorts to investigate lung cancer; the results supported the decision by the International Agency for Research on Cancer to classify inhaled silica in occupational settings as a carcinogen, and suggest that the exposure limits in many countries were inadequate [51].

Occupational exposure to solvents like perchloroethylene or trichloroethylene may increase the risk of head and neck cancer in women [52]. Further, a consistent association between occupational exposure to diesel motor exhaust and increased risk of lung cancer was found [53]. Against, occupational polycyclic aromatic hydrocarbons exposure does not appear to substantially contribute to the burden of lung cancer in Central and Eastern Europe [54]. Bricklayers may be exposed to several lung carcinogens, including crystalline silica and asbestos. Consonni et al. examined lung cancer risk among bricklayers within SYNERGY, a large international pooled analysis of case-control studies on lung cancer and the joint effects of occupational carcinogens and found that the relative risk was higher for squamous and small cell carcinomas, than for adenocarcinoma [55].

Occupations where elevated risk of high grade prostate cancer was found included gasoline station attendants and textile processing occupations. Occupations with reduced risk included farmers and aircraft maintenance workers [56]. For occupational exposures to hydrazine, trichloroethylene (TCE), polycyclic aromatic hydrocarbons, benzene and mineral oil, associations between chemical exposures and prostate cancer incidence were assessed; high levels of TCE exposure were associated with prostate cancer among workers in aerospace and radiation workers [57]. Scott conducted a meta-analysis focusing on studies with high potential for TCE exposure to provide quantitative evaluations of the evidence for associations between exposure and kidney, liver, and non-Hodgkin's lymphoma cancers; the findings provide strong support for a causal association between TCE exposure and kidney cancer. The support is strong for non-Hodgkin's lymphoma, where issues of study heterogeneity, and weaker exposure-response results contribute uncertainty, being more limited for liver cancer [58].

Risk of prostate cancer linearly increased with exposure to metalworking fluids in late puberty. Autoworkers exposed to metalworking fluids at a young age also had an increased risk associated with this exposure incurred later in life [59]. The information available on the individual constituents for bio-based metalworking fluids indicates that they had biocides and preservatives, corrosion inhibitors, extreme pressure, and anti-wear components, which are also common additives in petroleum-based metalworking fluids. Precautionary approaches should be taken when promoting bio-based metalworking fluids as "green products" until individual components are evaluated for their health and safety impacts [60].

Cadmium is a heavy metal that has been suggested to be a carcinogen by evidence. It is the interference with proteins involved in the cellular response to DNA damage, the deregulation of cell growth as well as resistance to apoptosis that appear to be involved in cadmium-induced carcinogenicity [61]. However, compared with non-occupational exposure, high occupational cadmium exposure may be associated with the increased risk of prostate cancer [62].

Lotti supported that appraisals of the literature reached contradictory conclusions about hepatocellular carcinoma, cirrhosis and occupational exposures to vinyl chloride. Pathology reports seem to indicate a possible development of hepatocellular carcinoma but not of cirrhosis after high exposures to vinyl chloride [63]. Further, Guardiola demonstrated that occupational exposure to polyvinyl chloride generated a distinct plasma metabolome with markedly altered lipid and amino acid metabolites [64]. Recently, in a vinyl chloride-exposed worker without cirrhosis and any known risk factor for chronic liver disease, angiosarcoma showed a KRAS G12D point mutation, which is considered to be characteristic of vinyl chloride-induced angiosarcoma [65].

In Australia, lead remains an important exposure in many different occupational circumstances; this information can be used to support decisions on priorities for intervention and control of occupational exposure to lead and estimates of burden of cancer [66]. Increased risk of mortality was observed for the a priori outcomes of lung cancer, cardiovascular disease (including cerebrovascular disease) and chronic kidney disease regarding lead smelter workers [67]; results pointed out a significantly increased risk in Terni foundry workers, determining an interesting brain cancer cluster [68]. Mc Elvenny, on examining the mortality of a cohort of workers in Great Britain with blood lead measurements, found an excess of lung cancer although the risk was not clearly associated with increasing blood lead levels [69]. Workers exposed to beryllium including general industry, shipyards and construction are at increased risk of developing chronic beryllium disease and lung cancer, too [70].

Occupational and environmental factors (i.e., dioxin) may contribute to immune deficiency and altered immunity, which are among the best characterized risk factors of non-Hodgkin's lymphomas [71]. Collins et al. demonstrated the mortality experience of workers exposed to dioxins during trichlorophenol and pentachlorophenol production; in pentachlorophenol workers, there were eight deaths from non-Hodgkin's lymphoma [72]. This working team previously examined 1,615 workers exposed to dioxins in trichlorophenol production in Michigan, to determine if there were increased mortality rates from exposure; observed deaths for leukemia and non-Hodgkin's lymphoma were slightly greater than expected [73]. Findings possibly provide new insights in the etiology of non-Hodgkin's lymphoma and the mechanisms through which 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) can increase lymphoma risk; in particular plasma levels of interleukin 1 receptor antagonist tended to decrease with increasing TCDD levels, suggesting immunosuppression, with decreasing cytokine levels on increasing exposures [74]. Changes in lymphocyte subsets in workers exposed to TCDD were observed; interestingly, most lymphocyte subsets, in particular the B cell compartment, showed a decrease with increasing levels of TCDD exposure [75].

Issues arising

The question raised is whether the known carcinogens asbestos and silica could possibly be sorted as endocrine disruptors, since arsenic, cadmium, lead and mercury have already been classified as those according to the National Institute of Environmental Health Sciences in US. '' History presents plenty of examples of innovation trajectories that later proved to be problematic — for instance involving asbestos, benzene, thalidomide, dioxins, lead in petrol, tobacco, many pesticides, mercury, chlorine and endocrine-disrupting compounds.'', Professor Andrew Stirling wrote in the newspaper 'The guardian' that was published in November of 2014, commenting on 'Fracking could carry unforeseen risks as thalidomide and asbestos did'. What is observed is that most of the subsets of chemical carcinogens being mentioned above are already part of the group of compounds named endocrine disruptors.

Conclusion

The identification of environmental agents that result in the development of human cancer is a difficult process. On searching for the list of known carcinogens, many chemicals called endocrine disruptors cast to the list. Perhaps, the output from the field of biochemistry and endocrinology sciences in the science of oncology is timely as ever on the overlap of the definition of a substance, being a *carcinogen and/or an endocrine disruptor*, and the mechanism of its action.

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