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REVIEW PAPER

Endocrine Disrupting Effects of Carbon Nanotubes: A Systematic Review on Next Generation Nanotechnology based Agrochemicals

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ABSTRACT

The etiological factors for increased risk of endocrine and reproductive disorders remain largely unclear but a huge number of data from *in vitro*, *in vivo,* and epidemiological studies, support the association of their incidence and prevalence with long term exposure to endocrine-disrupting chemicals /agrochemicals in the modern world. Engineered Nanomaterials (ENMs) could be considered as new alternatives to overcome the environmental challenges of endocrine-disrupting pesticides and fertilizers and to reduce human health risks of cancer and endocrine toxicity based on their unique physicochemical properties. Carbon nanotubes (CNTs) are the initiative members of the big family of ENMs used for developing "Nanotechnology-Based Agrochemical" but despite remarkable detoxifying effects mediated by CNTs, several controversies and key questions address the toxicity and endocrine-disrupting properties of these authoritative agents which may introduce to the global markets a new generation of as nano fertilizers, nano adsorbents, and nano pesticides soon. The actual issue stems from a limited number of studies invalid toxicology models on CNTs related endocrine disruption and absence of systematic reviews on CNTs exposure-mediated endocrine health hazards especially concerning epidemiological and human data. In this direction this systematic review focused on the following sub-topics: (1) an overview on CNTs applications as novel agrochemicals (2) environmental risks and benefits of CNTs 3) toxicokinetic and toxicodynamic of CNTs (4) contribution of CNTs in the pathogenesis of obesity, diabetes and cardiovascular effects 4) evidence on the involvement of CNTs in developmental and reproductive toxicities from *in vitro* and *in vivo* studies (5) conclusions and perspectives.

Keywords: *Endocrine Disrupting Chemicals, Carbon Nanotubes, Agrochemicals, Pesticides, Fertilizers, Adsorbents*

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INTRODUCTION

Endocrine-disrupting chemicals (EDCs) comprise a huge number of synthetic or natural chemicals with industrial, agricultural, pharmaceutical, cosmetic, and hygienic applications. They mimic the activities of natural hormones through lifetime dietary intakes, inhalational exposures, or other possible routes of administration [1] . Extensive increase in the incidence and prevalence of non-infectious environmental induced diseases e.g. breast cancer [2] prostate cancer [3], infertility [4] reproductive disorders [5], congenital abnormalities [6], neurodegenerative diseases [7]and immune dysfunctions [8] , could be the consequence of massive use of EDCs over the past 50 years [9] Fig. 1 describes some of the identifiedhuman health effects of EDCs in both genders.

Most of the agrochemicals (e.g. pesticides and fertilizers) have endocrine-disrupting properties based on their anti-androgenic and/or estrogenic effects [10] Nowadays massive use of pesticides

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and fertilizers in the chain of food production/ preservation and uncontrolled human exposure to these hazardous chemicals, have become a very big challenge for global health systems. The annual estimated cost of uncontrolled exposure to EDCs was determined as $340 billion (2·33% of GDP) in the United States and €163 billion in European Union (EU) (1·28%) due to health-care costs and lost productivity but this cost estimation is limited to the present generations, not to the intergenerational and trans-generational epigenetic inheritance [11]. The structural diversity of agrochemicals as well as their presence in most environmental sources at undetectable levels by conventional analytical methods, bioaccumulation, biopersitance, and unknown metabolic fate, make the environmental detection and risk assessment of endocrine disrupting agrochemicals more complicated.

Research into nanotechnology applications in the development of novel agrochemicals in the form of "nano fertilizers", "nano adsorbents" and "nano pesticides"to overcome current health challenges of routine agrochemicals (e.g. organophosphates, carbamates, organochlorines, synthetic pyrethroids) and improvement of crop protection, has become increasingly popular over the past decade. Unfortunately, a large number of risk assessment studies on engineered nanomaterials have characterized the endocrine-disrupting properties for CNTs because they mimic the natural body hormones and interact with hormone receptors in humans and wildlife [12]. Therefore several controversies and key questions address endocrine disrupting properties of CNTs which may soon introduce to future market of novel agrochemicals. This review aims to identify existing knowledge gaps regarding the endocrine-disrupting properties of CNTs and provide directions for future studies in parallel to regulatory activities for the development and promotion of safer nano agrochemicals.

METHODOLOGY

Study subjects

To specify our focus on the role of CNTs on human endocrine disruption through environmental exposures by food, water, and air contamination, all available original and review articles in PubMed were considered for this review

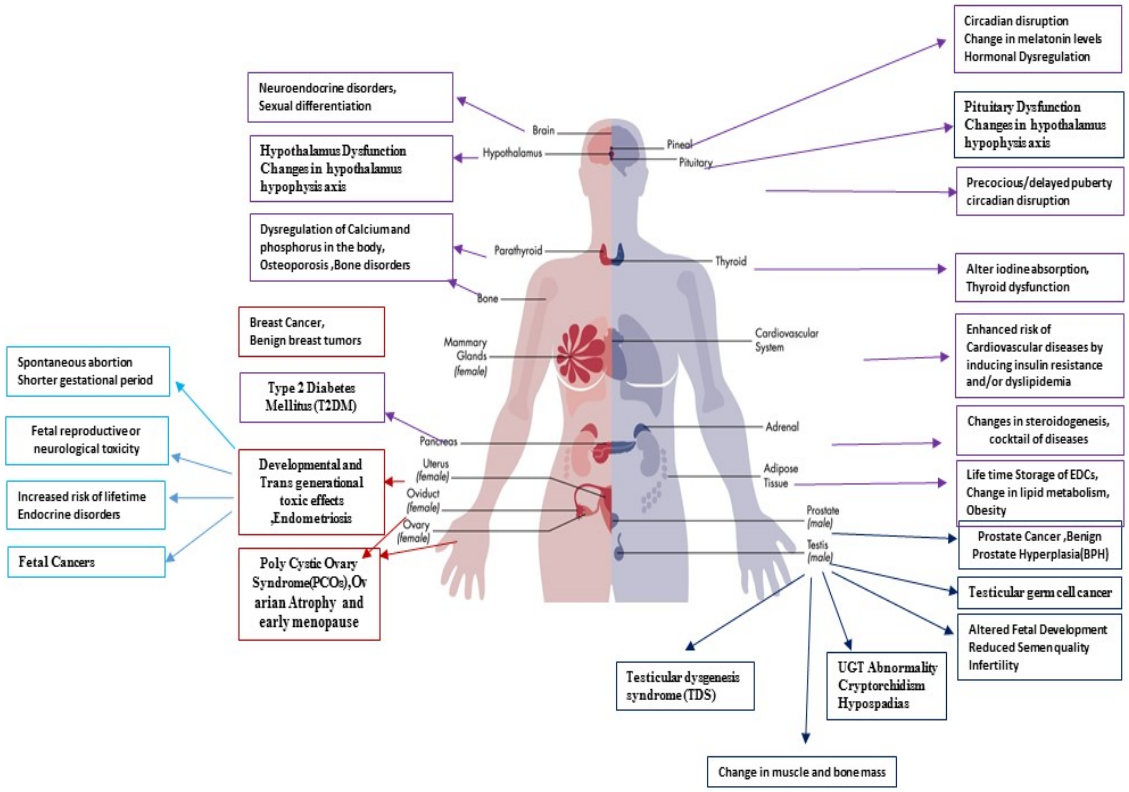

Fig. 1: Schematic and differential overview of some endocrine toxic responses of glands to Endocrine Disrupting Chemicals(EDCs)

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using the following keywords for inclusion and exclusion of selected studies.

Keywords

Carbon nanotube OR CNTs OR Single-Wall Carbon Nanotubes OR SWCNTs OR Multi-Walled Carbon Nanotubes OR Multi-Wall Carbon Nanotube OR MWNT OR MWCNT

And

Nanoagrochemicals OR Agriculture OR Pesticide OR Nanopesticide OR Fertilizer OR Nano fertilizer OR Endocrine Disruption OR Aryl Hydrocarbon Receptor OR AhR ORLipid metabolism OR Obesity OR Fat accumulation OR Diabetes OR Cardiotoxicity OR Cardiovascular effects OR cardiovascular diseases OR Sexual development OR, Female Reproductive Health OR Teratogenicity OR Teratogen OR Embryotoxicity OREstrogen OR Progesterone OR Testosterone OR Androgen OR FSH OR LH OR Cortisol OR Ovary OR Ovaries OR Uterine, OR vagina OR Hypothalamus–hypophysis axis OR Reproductive cycles OR Pregnancy OR birth OR Male Reproductive Health effects OR Semen quality OR Hypospadias OR Sperm OR Cryptorchidism OR Prostate

NOT

Nanocarrier, Drug Delivery, Medicine, Therapy, Protein Detection, cell and organ transplantation,imaging system, Nanodevice, bone tissue regeneration, cancer diagnosis, Vector, scaffold

RESULTS

Applications of Carbon Nanotubes asnano agrochemicals

CNTs are authoritative members of the big family of ENMs based on their special physicochemical properties, a wide range of agrochemical applications, and a rapid surge of industrial attractions in the last decade. CNTs are classified into the following two categories: SWNCTs – Single-Walled Carbon Nanotubes and MWCNTs – Multiple-Walled Carbon Nanotubes. Table 1 shows the capabilities of CNTs' efficient fertilizer (plant growth inducer) by increasing the water uptake of plants and enhancing root/shoot lengths and plant dry biomass [13], [14]. Table 1 shows also the potentials of CNTs as excellent chemicals for the detection and remediation of environmental pollutants e.g. heavy metals, persistent organic pollutants (POPs) especially organochlorine pesticides, dyes, the residue of pharmaceuticals and EDCs based on exhibiting strong adsorptive properties [15] and their antimicrobial and antifungal properties.

Environmental risks and benefits of CNTs applications

Due to the highly porous and hollow structure of CNTs, large specific surface area, excellent adsorptive capacities as well as their short equilibrium times and strong interaction between CNTs and pollutant molecules, these highly available nanomaterials, have been gradually applied for the removal of organic contaminants with endocrine-disrupting effects from wastewater through adsorption process as novel absorbent [16]. Soluble carbon nanotubes (CNTs) have shown promising roles as adsorptive materials against Endocrine-disrupting chemicals(EDCs)such as Bisphenol A (BPA) but the adsorptive capabilities of CNTs to EDCs may change the final toxic properties of the possible complexes in human and other living organisms and cause reproductive toxicity[17].

Besides the above remarkable effects of CNTs in agriculture and remediation, CNTs provide toxic effects on plants by inducing reactive oxygen species (ROS) leading to abnormal cell death. Unusual accumulation of CNTs in soils can cause hazardous effects on soil microbial population, diversity, and composition. They can modify the balance between plant-toxic metals in soil and accelerate the translocation of heavy metals and metalloids into the plant tissues. [18]. CNTs release into water and wastewater treatment systems when it is used as an adsorbent for water and soil treatment [19]. Studies on adsorptive properties of SWCNTs indicate that SWCNTs effectively adsorbed 17β-estradiol and natural hormones in animals and plants which cause hormonal deficiencies [20]. Increasing environmental levels of MWCNTs is dangerous due to their strong affinities to estrogenic compounds (17β-estradiol) in aquatic systems. Hormonal affinities of MWCNTs cause definite alterations in estrogenic responses to other EDCs by increasing their bioavailability[21].It seems that other harmful chemicals would be able to bind and activate soluble estrogen receptors (ERs) and make more critical situations for determining the potential health risks of CNTs alone in biological systems.

Table 1: Applications of CNTs as nanotechnology-based agrochemicals

Carbon Nanomaterial	Treatment	Effects	Ref.
	Novel nano-carbon fertilizer		
ZnO/MWCNT nanocomposite	Optimum concentration (15µg/mL) of ZnO/MWCNT nanocomposite in aqueous medium	Seedling growth of onion seeds with the maximum number of cells in telophase. Maximum synergistic effects with zinc at optimum concentration without any plant toxicity.	[50]
MWCNTs , Fe-CNTs, FeCo-CNTs)	Three different carbon nanotubes (MWCNTs, Fe-CNTs, and FeCo-CNTs) at concentrations of 0, 10, 50, and 300 mg/L.	All three types of CNTs caused significant inhibition of rice (Oryza sativa L.) growth by decreasing the concentrations of endogenous plant hormones and a significant decrease in carbon to nitrogen ratio (C: N ratio) in rice	[51]
MWNTs	MWCNTs applied at 50 mg/L, and treatment exposure ranged from 0 to 60 minutes with ultrasonic irradiation (US)	MWNTs physically disrupted the seed coat of soaking tomato (Solanum Lycopersicon) but the integrity of the semipermeable layer was not impaired. The germination percentage and seedling length and weight were enhanced in the presence of MWNTs.	[14]
	Detection and remediation of environmental pollutants		
Commercial MWCNT	MWCNT and biochar pyrolyzed from soybean stover at 300 °C (BC) and concentrations of 0.5, 1, and 2.5% (w w^{-1}) were used to remediate the contaminated soil with Pb, Cu, and Sb in an incubation experiment.	MWCNT was less efficient than BC in immobilizing mobile Pb and Cu in the soil. MWCNTs increased Sb bioavailability by 1.4-fold and 1.6-fold, respectively, in DTPA extraction, compared to the control.	[52]
MWCNT-COOH MWCNT-OH	the concentration range of 5-60 mg/L	The adsorption capacity of Cr (VI) to Cr (III) in soils reached 8.09 and 7.85 mg/g, respectively. MWCNT-COOH was 1.3-fold efficient than MWCNT-OH at a pH of 3.2.	[53]
MWCNTs	Adsorption experiments in aqueous concentrations Cd and Phenanthrene in overlying water from physical and chemical aspects tested.	MWCNTs reduced the phytotoxicity of the sediments contaminated by Cd and phenanthrene	[54]
Activated carbon (AC) MWCNTs	Sediment treated with semipermeable membrane devices (SPMDs) treated with AC and MWCNTs) 2 wt% of for 150 days	Additional MWCNTs to contaminated sediment did not significantly decrease aqueous equilibrium concentration and organochlorine pesticides (DDTs and HCH)	[55]
MWCNTs	0.7 g of MWCNTs, over very short stirring times (5 min).	Complete removal of unleaded gasoline was obtained using small amounts of unleaded gasoline hydrocarbon components from polluted waters.	[56]
SWCNTs, MWCNTs Carboxyl SWCNTs (SWCNT-COOHs)	Interactions between CNTs and biphenyl-degrading bacterium were investigated in concentrations of 1.0- 1.5 mg/L .	Significant increase in biodegradation efficacy and growth of aromatic-degrading bacterium.	[57]
	Nanopesticide(Fungicide)		
MWCNT-graft-poly(citric acid) (MWCNT-g-PCA) hybrid materials	Encapsulated pesticide (EP) in the polycitric acid shell provided by trapping Zineb and mancozeb (Pesticides) in aqueous solution by MWCNT-g-PCA hybrid materials	CNT-g-PCA-EP hybrid material showed higher fungicide properties and increased toxic effects on Alternaria alternata fungi in comparison with bulk pesticide	[58]

Toxicokinetic and toxicodynamic of CNTs as strong endocrine disruptors

3-1Biodistribution: Environmental induced toxic effects of CNTs are highly dependent on the route of exposure which usually happens through the ingestion of possible residues in food resources or inhalation of contaminated air during occupational activities. The toxicity of CNTs, biodistribution, bioaccumulation, and target organ toxicity are complex subjects and mostly related to the structure and physicochemical properties. The number of walls, chirality, diameter and length [22], purity, production method and CNT functionalization [23] fibrogenic properties, hydrophobicity, high surface area and biopersistence [24] is the most important CNTs characteristics that may cause organ toxicity and systemic adverse health in the endocrine system but among mentioned variables, the quality of functionalization is the most important factor which may change the future of CNTs in the body [23]. Covalently functionalized CNTs tend to be excreted through urine, whereas pristine and non-covalently functionalized CNTs tend to accumulate in spleen and liver of exposed organisms and these types of bioaccumulation in liver and spleen may cause short term or long term toxic responses and disease development [25].

Metabolism: After total body intake and making biological effective concentrations of CNTs, some members especially SWCNTs isoforms could act as competitive inhibitors of CYP3A4, CYP3A5, and CYP2D6 and these enzyme inhibitions may potentiate the endocrine-disrupting properties of other xenobiotics in co-exposure models. Computational and animal models showed the interaction of CNTs with CYP3A4, a critical and high abundance drug-metabolizing cytochrome P450 enzyme [26].

3-3Hormonal effects: Dose-dependent inhibition of CYP3A4 by CNTs mediates the conversion of testosterone (male steroid hormone) to its major metabolite, 6β-hydroxy testosterone and finally cause male hormonal dysregulation, interfere with the metabolism of other xenobiotics and provides a molecular mechanism for toxic responses [27]. Binding assays indicate the binding capacities of SWCNTs to Estrogen receptors (ER) as one of the most important receptors of human reproductive system .Interacting of SWCNTs to estrogen receptor alpha in a very low concentration range (26.43 - 259.01 pg/ml) could be considered as a very critical mechanism and the main molecular initiating event leading to endocrine and reproductive toxicity of SWCNTs[28] . Interactions of CNTs with gonadotropins is another key mechanism for endocrine-disrupting effects of CNTs.Strong affinities between blood glycoproteins and CNTs have been described by molecular and experimental studies. Molecular dynamics, structure, and free binding energy of human Follicle Stimulating Hormone (FSH) on the surface of SWCNT causes that human FSH in aqueous solution strongly adsorbs onto SWCNT and this strong interaction could change the hormonal activity of FSH, causes dysregulations in hypothalamus-hypophysis axis and endocrine and reproductive toxicity [29]. The same interaction could be predictable between other types of CNTs and circulating hormones in the body based on the mentioned physicochemical properties.

Effects on ovaries: The effects of MWCNTs on ovarian function and granulosa cell steroidogenesis showed the inhibitory role of MWCNTs with different lengths on progesterone secretion and the expression of steroidogenic acute regulatory protein based on cytotoxicity, oxidative stress and mitochondria damages mechanisms [30].

CONTRIBUTION ON CNTS IN THE PATHOGENESIS OF OBESITY, DIABETES, AND CARDIOVASCULAR EFFECTS

Lipid metabolism and obesogenic effects of CNTs

Because of the global increase in the prevalence of obesity [31] and its related syndromes e.g. nonalcoholic fatty liver disease (NAFLD) [32] and metabolic syndrome [33], the metabolic and obesogenic effects of all chemicals and nanomaterials should be concerned by health regulatory agencies before any official approval. For the first time, one study points towards the cardiovascular risks of MWCNTs through inhalational exposures and showed the role of a single intratracheal instillation of MWCNTs in a dose range of 0, 18, 54 or 162μg/mouse on lipid profile of female C57BL/6 mice. Treated animals showed a significant increase in plasma total cholesterol, low-density/very low-density lipoprotein (LDL, VLDL), APR proteins, SAA3 and haptoglobin, and histopathological studies showed abnormal changes in liver morphology following exposure to MWCNTs with different physicochemical properties. The results of this study link the importance of MWCNTs pulmonary exposure with abnormal body weight gain, changes in lipid metabolism, and increased

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risk of cardiovascular disease [34].

Another parallel study at the same year (2015) revealed the role of intratracheal exposure to two different MWCNTs on development of nonalcoholic steatohepatitis (NASH)-like phenotype, characterized by inflammation, hepatic steatosis, and fibrosis as well as NASH-like phenotype which was consistent with up-regulation of interleukin 6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1). Other abnormalities including overexpression of NF-κB, p65, impaired cholesterol homeostasis, and suppression of peroxisome proliferator-activated receptor-gamma (PPARγ) in the hepatocytes of exposed animals were also detected [35]. The next study confirmed the aggravating role of MWCNTs in nonalcoholic steatohepatitis in Sprague Dawley rats by inducing oxidative injury [36].

Diabetogenic effects of CNTs

The growing use of carbon nanotubes (CNTs) in agrochemicals, emphasizes the importance of studies on biocompatibility evaluation and specific toxic effects of CNTs in the pancreas. In silico studies and computational analysis have provided insights into the toxic response of CNTs which causes Type 2 Diabetes Mellitus (T2DM) because CNTs could be recognized as pathogens by the Toll-like receptors that may induce the expression of inflammatory secretory proteins [37]. A study in three months old BALB/c mice that exposed to CNTs via injectional rout showed the pancreatic uptake of CNTs but the pancreas remained histologically normal, with no tissue damage, inflammatory infiltrate or inorganic deposits despite inducing hepatic, renal, pulmonary and spleen tissue damages[38] .One other study on the effects of SWCNTs on islets and β-cells, demonstrated decreased viability of islets cells in a dose-dependent manner by overproduction of reactive oxygen species (ROS) and raise of oxidative stress biomarkers including activities of superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA);and glutathione (GSH) peroxidase (GSH-Px); and content of GSH and mitochondrial membrane potential (MMP) [39] Direct diabetogenic effects of SWCNTs and MWCNTs should be considered as important subjects for further preclinical evaluations in realistic models by different routes of administration.

Cardiovascular effects CNTs

There are several primary mechanisms to link CNTs' exposure to cardiovascular toxicity. The first is their inflammatory and oxidative properties, direct particle interactions based on their excellent systemic absorption, bioreactivity, and their capacities for neural and hormonal alterations [40] . Oral administration of SWCNTs could induce cardiovascular diseases in mice and rats after excellent GI absorption and distribution throughout most of the body organs including the liver, lungs, brain, and spleen by inducing oxidative stress and eliminating through kidney and bile duct [41]. SWCNTs induced oxidative stress has investigated rat aortic endothelial cells (RAECs) and showed cellular, DNA, and protein damages and oxidative damage following SWCNT exposure which may result in the progression of many serious diseases especially cardiovascular abnormalities [42].

The potential cardiotoxicity of MWCNT has not been elucidated yet but an initial study demonstrated the bioreactivity of MWCNT by increasing cell permeability in human microvascular endothelial cells (HMVEC). This toxic effect was mediated by reactive oxygen species (ROS) production, actin filament remodeling, and promoting cell migration in HMVEC. Studies supported the role of MWCNT on elevating the levels of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule 1 (ICAM-1) in HMVEC and elucidated the potential human toxicity of MWCNT at the cellular level [43]. Male C57BL/6J mice, exposed to single doses of three different forms of MWCNTat doses of 0.01 - 100 μg showed myocardial ischemia/reperfusion injuries based on the form of administered MWCNTs [44].Another study in 2014, confirmed previous findings regarding the cardiotoxic effects of MWCNTs following single intratracheal instillation of 1, 10 or 100 μg MWCNT in Sprague-Dawley rats inLangendorff isolated heart model. Increased endothelin-1 (ET-1) release and depression of coronary flow during early reperfusion were observed in exposed rats and the promoting role of MWCNTs on cardiac injury and depressed coronary flow by invoking vasoconstrictive mechanisms involving ET-1, thromboxane, Rho-kinase, and cyclooxygenase was discovered [45]. One more study also indicated that exposure to MWCNT increases the adherence of monocytes onto the endothelium, elevates the levels of oxidative stress-mediated transformation of monocytes to foam cells which are closely correlated with accelerated progression

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of atherosclerosis [46].

Later studies in 2015 showed the cardiovascular toxicity of long-term exposure to MWCNTs particularly in occupationally exposed workers with preexisting cardiovascular disorders. In this study, four different MWCNTs with different iron contents and length caused a persistent decrease in the heart rate of spontaneously hypertensive (SH) rats by inducing sustain inflammation of the lung and heart of animals as well as morphological lesions after 30 days repeated dose exposures by intratracheal instillation[47] Another study in mice model of atherosclerosis showed that pharyngeal aspiration of 40 μg MWCNT, once a week for 16 consecutive weeks to female apolipoprotein E-deficient (apo E-/-) mice, elevates the levels of total protein and lactate dehydrogenase (LDH), surfactant protein-D, and mucin without any markedly effect on plasma cholesterol levels [48] These in vivo and epidemiological evidence suggest the cardiotoxicity of both types of CNTs and increased risk of myocardial ischemia and atherosclerosis in repeated dose and long term exposures.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF CNTS

The underlying mechanisms of CNTs' hormonal activities reviewed in the last sections of this paper. As described in Table 2, MWCNTs are embryotoxic in rodent and aquatic models. Collected data show the dose/concentration-dependent developmental toxicity of MWCNTs and SWCNTs with different physicochemical properties in acute and repeated models by inducing early and late resorption of the fetus, decreased fetal weights, fetal malformations, fetal death in rodent and aquatic models.

CONCLUSION AND PERSPECTIVES

Despite restricted, conflicted, and inconclusive body of information concerning the real concentrations and behavior of CNTs in vitro and in vivo models and lack of epidemiological studies on CNTs, present evidence suggests the prominent role of CNTs in the pathogenesis of endocrine and reproductive disorders. The fact that CNTs can disrupt the endocrine and reproductive system, which may eventually lead to cardiovascular toxicity, obesity, changes in lipid metabolism, has gathered support from several in vitro and in vivo which described in the present review.This review showed the underlying mechanism following the interference of EDCs with the body's endocrine system which induces structural and functional abnormalities in gonads and increases the risk of adverse health effects. Differential adverse health effects of CNTs start usually after excellent systemic absorption through direct binding to circulating hormones or hormone receptors, alteration of hormonal activity and synthesis and changing the biological responses of other EDCs therefore beside available data about the CNTs interactions with various cells, tissues, endocrine organs, and organ systems and whole organs as a prerequisite for safety evaluations, special attention to their endocrine-disrupting properties for registered new CNTs based agrochemicals as new candidates for agricultural, medical and industrial applications. This review to show a new picture from CNTs which could be more complicated than described because the wide range of CNTs with different physicochemical properties and unrecognized conformational changes (e.g. agglomeration) with potential impact on bioavailability and endocrine toxicity may cause unpredicted toxicities in human exposure based on their background factors e.g. nutrition, drugs, occupation, and lifestyle factors moreover any Chemical change in CNTs (functionalization) or conformational alteration (agglomeration) can significantly influence their toxicity potential and their receptor interactions.

Apart from these knowledge gaps, some initial properties of CNTs, relevant for their interactions with plants during agricultural applications have been identified and explained in this review. Exposure of plants with CNTs is frequently associated also with internal translocation of CNTs and some systemic effects because they can be taken up by herbs and their absorbed fractions can induce systemic physiological responses. Low plant tissue levels of CNTs (<100 mg L^{-1}) could have beneficial e.g. improved seed germination, hormesis, or lack of toxicity but higher external concentrations usually cause inhibitory effects on plant growth and differentiation. Formation of reactive Oxygen Species (ROS) and oxidative stress are the main common toxic mechanisms of CNTs in plants and animals but despite indicated facts, CNTs have been proposed as the main engineered nanomaterials for developing next generation of nano agrochemicals by industries.

Since the discovery of the first generation of synthetic pesticides during World War II, numerous chemicals have been developed and

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Table 2: Female reproductive toxicity of Carbon nanotubes

Carbon Nanomaterial; Nanoparticle Dimension	Toxicity Model ; Concentrations; Exposure	Toxicology Endpoint	Results	Ref.
MWCNTs (Mitsui N1WCNT-7)	CD1(ICR) mice 8-13 week Acute; single doses of 2,3,4,5 mg/kg doses at day 9 of gestation, i.p and intratracheal	Day 18: Female mated, Female died, gestated female with >live fetus, Corpora lutea/litter, Implantation/litter, Early Resorption of fetuses, Late Resorption of fetuses, Live fetus/litter	Mated females remained alive but the number of fetuses decreased significantly in doses upper than 4mg/kg . Early and late resorption of a fetus happened in doses upper than 4mg/kg. Decreased fetal weights were seen in doses above 2 mg/kg, fetal malformations were seen in all dose groups of animals. Fetal death and malformations were gender independent.	[59]
Amino-functionalized PEG-SWCNT	CD1 pregnant mice doses (0.1-30 µg/mouse), I.V injection in single or multiple administrations	Morphological evaluations	No adverse effects both on embryos and dams up to the dose of 10 µg /mouse. Occasional teratogenic effects at the dose of 30 µg/mouse associated with placental damage in single bolus (1 out of 10 dams; 1 malformed embryo) or as multiple doses (2 out of 10 dams; 5 malformed embryos). Hepatic damage in the multiple exposures	[60].
SWCNT, 1–2 nm in diameter, 5–30 µm in length	CD-1 mice Acute, 5, 10 or 100 mg/kg at day 9 of gestation Oral gavage	Morphological evaluations	Skeletal abnormalities and external defects	[61]
MWCNTs-COOH	zebrafish embryos/larvae 5, 10, 20 mg/L at 4 h after fertilization and grown until 96 hpf	Morphologic, biochemical and molecular parameters.	Concentration-dependent increase in the mortality rate, delayed hatching, decrease in the heartbeat rate, yolk sac edema, pericardial edema, head, tail malformations, and vertebral deformities, changes in the expression of oxidative stress (mtf-1, hsp70, and nfkb) and innate immune system (il-1β, tlr-4, tlr-22, trf, and cebp) related genes, especially an increased in the expression of the hsp70 and il-1β.	[62]
MWCNTs	zebrafish (Danio rerio) 24 hours post-fertilization (hpf), 48 hpf and 72 hpf.		Teratogenic effects in concentrations upper than 40 µg/mL, phenotypic defects at 60 microg/mLand higher concentrations caused slimy mucus around the embryo. At high concentrations, apoptosis, delayed hatching and formation of abnormal spinal chords recorded.	[63]
Nf-MWCNTs f-MWCNTs	*Ruditapes philippinarum*	Alterations induced in clams' oxidative status, neurotoxicity, and metabolic capacity.	Both MWCNT materials induced higher metabolic capacity, lower glycogen, and protein and lipid concentrations in clams. Oxidative stress expressed in higher lipid peroxidation neurotoxicity and Cholinesterases inhibition in organisms exposed to both MWCNTs.	[64]
MWCNTs	Zebrafish embryos concentrations (1, 5, 10, 50, 100 mg/L) for 96 h. 2-h post-fertilization (hpf)	Spontaneous movement, heart rate, hatching rate, length of larvae, mortality, and malformations	MWCNTs decreased the length of the hatched larvae at 96 hpf. No obvious morphological malformation or mortality was observed after exposure to MWCNTs.	[65]
Functionalized MWCNTs(FITC-BSA-MWCNTs)	zebrafish embryos at 1-cell stage and 72 h post-fertilization through microinjection	Morphological, hematological in multi-generation levels	Accumulating circulating WBC at the trunk region, lysosome-like vesicles in the blastoderm cells of the treated embryos, negative effects on the reproduction potential of the second generation.	[66]
SWCNT functionalized with PEG at 600 Da	zebrafish embryos 0.01, 0.1 and 1 mg/L from 3 to 96 h post-fertilization (hpf).	Spontaneous movement, heart rate, hatching rate, length of larvae, mortality, and malformations	Mortality, delayed hatching, malformations, reduced body length, increased ROS production, and DNA damage.	[67]

applied as an insecticide, rodenticide, fungicide, herbicide, fumigants, and disinfectants. Despite overproduction and large scale application of conventional pesticides, a wide variety of them have become practically inefficient because they were unable to reach the specific pests or the targeted strains may become resistant against them [49]. In parallel with the production of old and new molecules, undetermined cases of acute pesticide poisoning (APP), and countless human and animal death via indirect or indirect poisoning through systemic absorption of pesticide residues in contaminated water, air, and food or by occupational routs have happened. Is it possible to have similar tragedies with CNTs as novel agrochemicals in the next decades?

Although the production and application of highly toxic pesticides banned in many countries, widespread use and lack of standardized case definition, risk assessment, risk management, and regulation globally, led to the pollution of ecosystems, a decline in populations of insect pollinators, and increased risk of pesticide-induced human diseases. However, a surprisingly restricted, conflicted, and inconclusive body of information exists concerning the real concentrations and behavior of these materials in biological systems especially in humans and their interactions with various cells, tissues, organs, organ systems, and whole organs as a prerequisite for safety evaluations. Now the critical question is about environmental and human safety regarding their future wide range of applications, their residues in environmental " Is humanity waiting for a similar or even worse scenario with CNTs as the new generation of agrochemicals for the next decades? " In an optimistic scenario, applications of MWCNTs and SWCNTs in the agriculture sector showing potential impacts on the endocrine system and their efficacy in improvement of plant growth as nano fertilizer, absorption of pollutants as nano adsorbents or pes control as nano pesticides are at a very nascent stage and more risk assessment studies are necessary for their future applications. Evaluation of endocrine disrupting properties of CNTs should be considered as an essential step in risk assessment and management of CNTs through *in vivo* and *in vitro* studies using valid biomarkers to emphasize their roles of endocrine systems and hormone-dependent although these models are not always valid or enough for human risk evaluations this is a critical, initial and mandatory step for regulating all new chemicals for health, agricultural or industrial applications especially CNTs which described in this review.

CONFLICT OF INTEREST

Author declares no conflict of interest.

ABBREVIATIONS

Apolipoprotein E-deficient mice	apoE-/-mice
Acute-phase proteins/ acute-phase reactant (APR)	APR proteins
Carbon Nanotubes	CNTs
Catalase	CAT
Cytochrome P450 enzyme	Cyp450/CYP
Endocrine-disrupting chemicals	EDCs
Endothelin-1	ET-1
Engineered Nanomaterials	ENMs
Follicle Stimulating Hormone	FSH
Glutathione	GSH
Human microvascular endothelial cells	HMVEC
Glutathione peroxidase	GSH-Px
Interleukin 6	IL-6
Intercellular adhesion molecule 1	ICAM-1
GDP	Gross Domestic Product
Single-Wall Carbon Nanotubes	SWCNTs
Monocyte chemoattractant protein-1	MCP-1
Multi-Walled Carbon Nanotubes	MWCNT
Nonalcoholic steatohepatitis	NASH
Nonalcoholic fatty liver disease	NAFLD
Reactive Oxygen Species	ROS
Serum amyloid A 3	SAA3
Type 2 Diabetes Mellitus	T2DM
Lactate dehydrogenase	LDH
Low-density lipoprotein	LDL
Luteinizing Hormone	LH
Malondialdehyde	MDA
Mitochondrial membrane potential	MMP
Plasminogen activator inhibitor	PAI-1
Peroxisome proliferator-activated receptor-gamma	PPARγ
Rat aortic endothelial cells	RAECs
Spontaneously hypertensive rats	SH rats
Superoxide dismutase	SOD
Nuclear factor-kappa B	NF-κB
Very low-density lipoprotein	VLDL

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