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IMPACT OF ENDOCRINE DISRUPTORS ON MAN: THE LIKELY CAUSES AND EFFECTS

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ABSTRACT
It is now common knowledge that synthetic chemicals in the environment can find access into the body of humans and wildlife, thereby mimicking the action of endogenous hormones that regulate maintenance of normal growth, metabolism and reproduction. The chemicals able to do this are known as Endocrine Disrupting Chemicals (EDCs) which come from various sources ranging from household items to synthetic products and pharmaceuticals to plant derived estrogens. Although data linking cause and effect of the EDCs is extremely rare in humans owing to the fact that ethical issues would not allow for the use of humans as experimental models, yet a growing body of literature suggests a strong link between either pre- or postnatal exposure to environmental chemicals and observed adverse health outcomes. This review intends to bring together previous efforts to ascertain the impact of EDCs on human health, the missing research link and the possible precautionary strategies. This is important considering the magnitude of the adverse risks that exposure to endocrine disruptors might cause. Also, scientific uncertainty shall not delay precautionary action in reducing exposure to these chemicals as data available indicates trans-generational effects at population level due to chronic exposure to these chemicals.
Keywords: endocrine disruptors, human health, chemicals, environment

INTRODUCTION

The body of both plants and animals require coordination for proper functioning; this is achieved in animals through integrated efforts of the nervous, immune and endocrine (hormonal) systems. The endocrine system comprises of chemical messengers produced from endocrine or ductless glands at one part of the body which are transported to the site of action or target organ via the blood stream, thereby controlling various basic functions such as reproduction, growth, maintenance, homeostasis and metabolism. These chemical messengers are known as hormones and are present in almost all multi - cellular animals.

Scientific observations and research in wildlife and humans have demonstrated the ability of certain environmental agents (chemicals) of human or anthropogenic origin to interfere with the hormonal system through mimicking, blocking or stimulating the action of endogenous hormones leading to undesired responses or disruption in the normal hormonal action, production or metabolism represented in adverse effects on the reproductive, health and developmental end points in a wide range of organisms. Such chemical agents are known as endocrine disruptors or endocrine disrupting chemicals. They are a heterogonous group arising from domestic, industrial, agricultural and pharmaceutical processes which consists of steroids, pesticides, polyaromatic hydrocarbons (PAHs), alkylphenolic surfactants and organic oxygen compounds (Lester and Birkett, 2003). The widespread application, persistence and bioaccumulation tendency of many in nature ensures vulnerability of the living to exposure via various routes like oral ingestion, ventilation, dermal contact and prenatal exposures. As such, the scope of the problem is beyond the organism or population level but on the ecosystem as a whole.

Research attention was focused on the pharmaceutical uses of synthetic estrogens since the ability of certain chemicals (substituted phenols) to mimic endogenous estrogen was noticed as far back as 1938 (Kavlock, 1999). This background paves access to explaining the observations on imposex in female dog whelks in the late 1960s (Crews *et al*., 2000), intersex in fish living downstream of sewage works in the early 1980s (Sweeting, 1981) and a decline in the population of alligators associated with inter alia (Crews *et al*., 2000). In all cases, environmental chemicals were implicated in the observations. The increasing trend of increase in the incidence of possible environmentally induced changes on reproductive system of aquatic animals, led to many research efforts attempting to identify specific chemical culprits, their possible mode of action and the possibility of human effects. Important markers on reproductive success considered in human studies include sperm count and quality, genital malformation, preterm labour or birth and timing of sexual maturity (Colborn *et al*., 1996). Others include abnormal menstrual cycle and other biological endpoints like development, nervous system and the incidence of cancers. In addition to pharmaceutical estrogens, attention was also given to pesticides and flame retardants due to their ubiquitous and persistent nature that qualify for direct and indirect human exposure from the environment and the womb. This suggests that all possible hormone mimics are chemical suspects as human bodies upon development depends on hormone production to vital organs.

Effects are much severe on the foetus and the developing young since timing of exposure is critical to severity of effects. Thus, any disruption on the normal hormone action or metabolism can result in devastating, permanent and irreversible effect.

DEVELOPMENTAL EFFECTS

Colborn *et al.* (1996) hinted the role of thyroid hormones in normal brain development and the contribution of other hormonal signalling systems like the sex steroids to sexual differentiation of the brain centres. It was also shown that if the different phases of development in the foetus are impacted by hormonal mimics, undesirable effects can result on the developing young which may be immediate and acute or chronic and trans-generational. The pathway of exposure can be through the mother's blood consequent of environmental uptake and effects that result from long term chronic exposure normally to low doses of a chemical or mixture.

Prenatal Exposures

Documented effects from prenatal exposures include disorders like autism, Attention Deficit Hyperactivity Disorder (ADHD) and decreased intelligence and behaviour from areas around lake Michigan (Jacobson *et al.*, 1990) and the great lakes region (Darvill *et al.*, 2000) where polychlorinated biphenyls (PCBs) and dioxins have been implicated. These findings imply the possibility of chemical accumulation in the food chain and their retarding effect on children learning and behaviour. In another development, effects on the immune system were reported by Turyk *et al.* (2009) as incidence in diabetes which was associated with DDE, a metabolite of the pesticide DDT. The incidence of developmental and immune system effects in different age groups (Koopman-Esseboom *et al.*, 1994; Schantz *et al.*, 2003; Stewart *et al.*, 2003) have been associated with synthetic organic pollutants and revealed consistent findings.

Accumulation Tendency

Synthetic pollutants like PCBs and dioxins are closely related in persistence and accumulation tendency, often with similar effects (Schantz *et al.*, 2003). The ability of dioxins to regulate the dopamine system was hinted by Akahoshi *et al.* (2009) as leading to the disruption of thyroid function, a phenomenon that can be caused by flame retardants like polybrominated diphenyl ethers (PBDEs) which can lead to several disabilities (Giordano *et al.*, 2008). Such disabilities include serum concentrations in infants, toddlers and adults varying in different studies (Costa and Giordano, 2007; Toms *et al.*, 2009). These observations according to Colborn *et al.* (1996) were attributed to factors like exposure source, ability to eliminate chemicals and cessation of breast feeding. With the advent of increased chemical production to meet the needs in agriculture, new group of chemicals are produced and this adds up to the various human endpoints being affected. A correlation between prenatal exposure to environmental tobacco smoke, pesticides and polycyclic aromatic hydrocarbons (PAHs) with birth defects like decreased head circumference, birth weight and cognitive development in teenagers was reported (Perera *et al.*, 2005). Similarly, association between exposure to agricultural pesticides in United States' children and neurologic development like diminished memory, physical stamina and a high risk of astrocytoma was reported (Shim *et al.*, 2009).

Myths versus Reality of Endocrine Disruptors

Although it is easy to accept that hormonal mimics can have adverse developmental effects on human systems, however understanding the molecular pathway through which these actions are achieved is difficult due to missing research links and other ethical considerations in using humans as experimental models. Indications of the dopamine system effect has however been shown by Akahoshi *et al.* (2009) and conclusions from a review (Laessig *et al.*, 1999), points out that developmental neurotoxicity may be one of the more sensitive consequences of exposure to EDCs from the relative sensitivity if the developing central nervous system is to bring a change in hormone secretion, metabolism and transport to the brain. The effect of the above has been shown on Intelligence Quotient (IQ) as demonstrated by Weiss (1990), with its societal impact from small losses in a population.

Impact on Population Level

Although studies on population impacts of EDCs were found to produce inconsistent findings at some points; they are however unanimous in attaching strong linkage between observed effects and chemical exposure. The degree of xenoestrogenic activity may vary between populations as reported by Eva *et al.* (2006) in European and Inuit populations. This variation was attached to the difference in chemical mixtures, genetic and lifestyle factors. In the same vein, Krüger *et al.* (2008) stressed the possibility of using non-steroidal xenohormone trans-activities as a biomarker for exposure to Persistent Organic Pollutants (POP). These reports imply that population level impact of EDCs are evident and that uptake and subsequent effects through bioaccumulation are of major concern (Kimberly *et al.*, 2005). Body concentration of pollutants like PBDE, PCBs, HCB and BFRs were associated with consumption of fish or eel among urban anglers (Domingo *et al.*, 2008). The observation went on to add that dietary sources such as fish and shellfish, oils, fats and bakery products contain high concentration of PBDEs. This proves the role of bioaccumulation as another risky exposure source to humans that could be difficult to deal with. Some contrasting findings have however been reported in the great lakes region (Anderson *et al.*, 2008) and supported by Knobeloch *et al.* (2009), which was attributed to the fact that chemical concentration may decline over time depending on its persistence in the environment.

The tendency of contaminants to remain in the body of organisms after long term exposure to dioxin was shown by Garabrant *et al.* (2009), where historic exposures were found to be more important than recent ones and factors like age determines it's serum level. Variations between individuals and populations on the severity and nature of effects associated with EDCs may come from other factors like study location

from other factors like study location, sample size and duration. The severity of effects to which an exposed individual or population is subjected, is a function of many combining factors, some from the chemical, the human subject and others from the environment (Colborn *et al*., 1996). Though most effects are chronic leading to disease and other forms of impairment, some population studies have demonstrated the possibility of mortality (Angela *et al*., 2009), elevated cancer risks (Consonni *et al*., 2008) and suicidal ideation (Jianmin *et al.,* 2009). This narrows down to the need for reducing exposures as a mitigation strategy since complete phasing out of suspecting chemicals will be more difficult.

Attention Deficit Hyperactivity Disorder (ADHD)

In assessing developmental effects in particular on the rising incidence of ADHD, the European Commission (Alberti *et al*., 1999) concludes that ADHD is a significant health problem and two independent researches from Britain and United States (Megson, 2000) and London and Etzel (2000) respectively, believed that ADHD is on the increase and is manifested in an individual's inability to pay attention and control impulsive behaviour. In the effort to substantiate the argument of nervous system disruption by chemicals, Wakefield (2002) attributes the incidence in these symptoms to neurotoxic chemicals. Consequently, it becomes necessary to minimise exposures and therefore the incidence of neurotoxic effects. A research by Stewart *et al.* (2003) showed how levels of PCBs in children, correlate to behavioural response inhibition. In a similar study (Hornig, 2004), where patients diagnosed with ADHD were examined, they were found to have smaller head circumference and brain volumes compared to normal children and this can possibly affect the IQ of the children with the ADHD. Another developmental effect is autism which is believed to have both genetic and environmental linkages.

Autism

Autism is exhibited in the lack of ability to form relationship and behave normally in young children of less than three years old. The ability of chemicals to possibly play a role in disrupting retinoids during the time of neural tube closure in the womb was posited by Madsen *et al*. (2003) or rather a difference in metabolism could be the cause (Charman, 2002). Nonetheless, the important thing is what triggers the disorder and it is clear that an environmental factor is responsible (Stern and Smith, 2003) in addition to chemicals as the most likely candidates. According to Walkowiak *et al*. (2001), the incidence of autism is on the increase as declared by the National Autistic Society of England and Wales stressing the need for attention. This further stressed the need to understand chemical contribution as plausible and the possible significant role played by prenatal exposures in leaving children that were supposed to be healthy and normal to suffer from offences committed by their parents. Since the sum of individual effects translates population and societal consequences, then unless something drastic is done to arrest this trend, the sustainability of human generations is at risk.

REPRODUCTIVE EFFECTS

Reproductive successes of human and wildlife populations have been reported to be seriously impacted by exposures to environmental chemicals (Colborn *et al*. 1996) and the affected endpoints include decreased sperm counts and quality, undescended testis (Cryptochidism), malformed penises (hypospadias) and testicular cancer in males. In females, cancers of the breast, cervix and endometrium have been recorded (Carlsen *et al*., 1992). Other effects include altered menstrual flow or bleed length and delay in time to pregnancy (Schettler *et al.,* 1999). In both sexes effects like altered sexual behaviour, timing of sexual maturity and a decline in sex ratio have been documented (Hollander, 1997). These problems are by no means attributed to the rising level of estrogen from natural and synthetic sources that find their way into the living systems thus, mimicking endogenous hormones and resulting in devastating consequences on the reproductive system. In some instances, especially when exposures are severe, feminization of male animals result from exposure to estrogenic or androgenic chemicals (Gross-Sorokin *et al*., 2006).The mode of action of these chemicals is either as agonist or antagonist to hormone action.

Sperm Count and Quality

Decline in sperm count and quality is a marker of population fertility and hence of reproductive success. Conflicting findings linking this assertion with exposure to environmental chemicals exist after a review by Carlsen *et al*. (1992) forming the background for further research. The review contains a meta-analysis of a worldwide survey that decline in sperm count and quality is not only real but worldwide and reflects a true biological phenomenon. This argument against the global trend was supported by the Danish Environmental Protection Agency (Toppari *et al*., 1995), where semen quality in Finnish men was found unchanged from 1958 to 1992. Although argued, Carlsen's work was able to establish an important fact, that is the reality of a decline in sperm count at least in parts of Europe studied and this indeed points to reproductive health problem. In the following years, this work was supported in a survey on French and Scottish men (Auger *et al*., 1996), from the United States (Fisch, 1996; Swan *et al*., 2003) linking agricultural use of pesticides to reduced sperm quality. Low sperm count was also linked to persistent organic pollutants (Gunnar *et al*., 2005). Similar observation on sperm quality in children was reported by Guo *et al*. (2000) by linking in utero exposure to PCBs and dibenzofurans. These data sets show progressive increase in the incidences of falling sperm count or quality and the linkage it has with exposure to environmental chemicals.

Testicular Deformations

Efforts towards linking exposure to observed effects using other end points were made severally, although with contrasting results. For example in 1995, Toppari *et al*. (1995) hinted the rising incidence of reproductive problems like testicular cancer,

cryptochidism and hypospadias while Vidaeff and Sever (2005) linked environmental estrogens to these form of problems in males. Although limited data is available to establish trends from this research, it was however supported by Olesen *et al.* (2007) and Julie *et al*. (2009) that the rising incidence of male reproductive problems could be linked to prenatal exposure to chemicals. An observation parallel to that of Carbone *et al*. (2007) reported no link between prenatal occupational exposure to EDCs and the incidence of cryptochidism and hypospadias in rural Sicily. Although Carbone *et al*. (2007) were conclusive in their findings, yet a substantial evidence (Rocheleau *et al*., 2009) points out the vulnerability of male humans to reproductive health problems which can be associated with prenatal occupational exposure to pesticides. This could be through dietary intake (Giordano *et al*., 2008) or maternal milk (Brucker-Davis *et al*., 2008). It is possible for environmental estrogens to have a combined effect in the placenta in addition to causing male reproductive impairment as stressed by Fernandez *et al.* (2007). Environmental factors rather than genetic as proposed by Carlsen *et al*. (1992), have so far been found to be associated with reproductive health problems in male humans and pesticides are chief sources of environmental estrogens. Thus, controlling pesticide production and usage will benefit the humans both in preventing and mitigating effects associated with exposure.

Effects on Population Changes

Variations in the degree of putative effects caused by exposure to environmental chemicals are found between different geographical regions (Swan *et al*., 2003). This may support the assumption that race, ethnic origin and lifestyle factors could be responsible for this observation. Similar observations in four regions of the United States were attributed to agricultural use of pesticides rather than geography. This may mean adversity of effects are determined by the chemical and its characteristics as shown by Travison *et al*. (2007) that normal aging and lifestyle factors do not play a role in falling testosterone levels in an individual or population. Since all age groups are at risk of chemical exposure and pesticide use from agriculture plays an important role, then a preventive strategy of new chemicals that are less toxic shall be formulated to replace the existing ones in order to save gene pools and the continuity of life.

Play behaviour in children is normally seen to reflect their sexes, but research into hormone mimics have shown that these norms can be altered as a result of exposure in the womb or from the environment to chemicals, thus making boys associated with more feminised play behaviour and vice versa. Observations from a Dutch study on children prenatally exposed to PCBs and dioxins shows higher levels of PCBs correlating with less masculinised play in boys while more feminised play behaviour is seen in both sexes after prenatal exposure to dioxins (Vreugdenhil *et al*., 2002).

Skewed Sex Ratios

Over the recent years, changes (shift) in the sex ratios are witnessed in Europe, US and Japan and environmental contaminants are being suspected. Geoffrey Lean of the World Wide Fund for Nature in 2009, reports skewed sex ratios to more female births on a Canadian Indian community, in Seveso, Italy and among Russian pesticide workers (Geoffrey, 2008). The report went on to say similar observations were made in Isreal, Taiwan, Brazil and the Arctic. This indicates how widespread chemical contaminants are and the variety of effects they can trigger. In 2007, Wise *et al*. (2007) were able to show an association between *in vitro* exposure to Diethlstilbestrol (DES) and secondary sex ratio resulting from chronic exposure. The list of health effects from exposure to EDCs is ever increasing with findings on menstrual function (Stephanie *et al*., 2005), increased breast cancer risk (Dai and Oyana, 2008) and preterm labour (Stephen *et al.,* 2007). It implies that almost all physiological functions regulated by hormones are under threat from a range of chemicals in the environment. The time to pregnancy is another factor in addressing reproductive success of a population and chemical exposure could as well affect this. Although Wise *et al*. (2007) did not attach DES to a delay in time to pregnancy, this does not however mean other chemicals with different exposure mode to DES cannot cause delay in time to pregnancy. The ability of estrogenic chemicals to disrupt sexual development in children and populations was documented since 1960s by Beas *et al*. (1969) and Halperin and Sizonenko (1983) on dermal application of ointments containing estrogens, although symptoms were seen to disappear on suspension of application. The bottom line as shown by Herman-Giddens *et al*. (1997), Blanck *et al.* (2000) and Colon *et al*. (2000) is that environmental chemicals are associated with early menstruation, pubic hair appearance and development of breast tissue. This can affect menopause and therefore reproductive success. Consequently, with the number of cosmetics in the market today, humans could be performing a dangerous experiment.

Those criticising the environmental endocrine disruption hypothesis and its application on human subjects argue on the fact that there was no real life exposure using human subjects to consolidate claims made by researchers. Also, most results are based on either epidemiological data from long time exposure or an extrapolation of results from wildlife like mice. Perhaps, the most novel finding what health effect in utero exposure to synthetic chemicals can have on the stillborn and upon development, comes from the DES experiment. Banned in 1971, the drug was administered in the 1950s - 1960s in order to prevent miscarriage. The ban followed an observation of vaginal cancer in teenage girls born to mothers that used the drug. Other defects include abnormal pregnancies and immune depression. This proves an important point in chronic toxicity and the possibility of trans-generational effects as posited in the 'Wingspread' consensus statement that "though effects cannot be seen in adults, the children can suffer a substantial damage". Thus, minimising exposure at pregnancy shall be given priority.

Cancers

Incidence of cancers and tumours are reported to be on the increase worldwide and has been contemplated whether environmental estrogens have any role to play. This was confirmed in a review by Davis and Bradlow (1995). Since the concentration of the hormone estradiol in the body is a risk factor, it implies that any exogenous estradiol mimic can significantly increase the chances of breast cancer and therefore prolonged exposure to synthetic estrogens is potentially risky. Another factor that may aid breast tissue carcinogenesis from estrogenic exposure is the lipophilic nature of synthetic estrogens and high fat dietary sources in use. In two separate studies linking breast cancer incidence to chemical exposure (Wolf *et al*., 1993; Krieger *et al*., 1994), contrasting results on serum levels of PCBs and DDE were found in different populations which could be explained by the sample population and selection criterion. But both results agree that the serum concentrations of PCBs and and DDE were enough for a public concern. Breast cancer can also result from exposure to estrogens found in underarm antiperspirants and deodorants as shown by Darbre (2006) and mortality from breast cancer is believed to be generally on the increase. The various observations on developmental, reproductive and other health effects of environmental chemicals on human populations, points out to the following facts;

- The principal sources of contamination are Agriculture, Industry, Pharmaceutical and household items. Exposure is common place and can not be averted owing to the ubiquitous and persistent nature of synthetic chemicals.
- That both intended (like DES) and unintended (like PCBs) uses of chemicals can have a devastating health effect especially to the developing young due to the relative sensitivity of their system which is under development.
- That both prenatal and environmental exposures, can lead to long term chronic effects on different biological end points in humans.
- Each chemical is as potent as another and that combined effects are possible in a mixture.
- There is the possibility of indirect exposure through bioaccumulation in the food chain in addition to trans-generational effects.
- Knowledge gap exists as there is little or no data available from other parts of the globe namely Africa, South & Central America and parts of Asia including the Middle East to arrive at a global conclusion.
- Human populations are facing a serious threat of survival and continuity from environmental chemicals.

CONCLUSIONS AND RECOMMENDATIONS

On the weight of evidence against synthetic chemicals on human health effects, it was suggested that precautionary principle be adopted as a global health policy by the World Health Organisation under the banner of the United Nations (UN). This will erase the assumption of waiting for complete data sets before embarking on mitigation action as applied in the United Kingdom for example, where this principle has been applied already to soap and detergent industries and the cleaning industry recommending them to phase out Alkylphenolepoxylates (APEs). All these are in addition to a coordinated research by the Interdepartmental Research Group on Endocrine Disrupters (IGED) into exposure and effects of EDCs on male reproductive health.

Both the pregnant mother and her developing foetus must be protected from exposure to these chemicals and this may mean special care and consideration on foods, cosmetics, drugs etc. during gestation. The developing young shall also be monitored of playing with foods, toys, napkins etc. that may contain endocrine disrupting chemicals as ingredients. Furthermore, respective stakeholders in the health and safety sectors shall take this issue as a matter of paramount concern for more researches and greater awareness campaign to the general populace. This shall be done hand in hand with strict monitoring of chemical companies to substitute more toxic chemicals with less toxic and persistent ones, or ban the most dangerous in the same way as PCBs & DDT were banned. Research in to the role played by ethnicity, lifestyle and geographical factors shall as well be given attention as it could go a long way in saving our ecosystem from gender benders and their threat to biodiversity and survival of human populations.

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