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Source: Environmental Health Insights, 10(1)

Published By: SAGE Publishing

URL: https://doi.org/10.1177/EHI.S39825

The Increasing Prevalence in Intersex Variation from Toxicological Dysregulation in Fetal Reproductive Tissue Differentiation and Development by Endocrine-Disrupting Chemicals

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ABSTRACT: An increasing number of children are born with intersex variation (IV; ambiguous genitalia/hermaphrodite, pseudohermaphroditism, etc.). Evidence shows that endocrine-disrupting chemicals (EDCs) in the environment can cause reproductive variation through dysregulation of normal reproductive tissue differentiation, growth, and maturation if the fetus is exposed to EDCs during critical developmental times in utero. Animal studies support fish and reptile embryos exhibited IV and sex reversal when exposed to EDCs. Occupational studies verified higher prevalence of offspring with IV in chemically exposed workers (male and female). Chemicals associated with endocrine-disrupting ability in humans include organochlorine pesticides, polychlorinated biphenyls, bisphenol A, phthalates, dioxins, and furans. Intersex individuals may have concurrent physical disorders requiring lifelong medical intervention and experience gender dysphoria. An urgent need exists to determine which chemicals possess the greatest risk for IV and the mechanisms by which these chemicals are capable of interfering with normal physiological development in children.

KEYWORDS: intersex variation, endocrine disrupting chemicals, ambiguous genitalia, fetal development, pesticides, reproductive birth defect

CITATION: Rich et al. The Increasing Prevalence in Intersex Variation from Toxicological Dysregulation in Fetal Reproductive Tissue Differentiation and Development by Endocrine-Disrupting Chemicals. *Environmental Health Insights* 2016:10 163–171 doi: 10.4137/EHI.S39825.

TYPE: Review

RECEIVED: April 01, 2016. **RESUBMITTED:** June 16, 2016. **ACCEPTED FOR PUBLICATION:** June 20, 2016.

ACADEMIC EDITOR: Timothy Kelley, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 881 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Defining Intersex Variation

Intersex variation (IV) is a morphological and physiological anomaly where an individual is born with "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical".[1] In essence, the reproductive organs differ from those typically associated as being male or female.[2,3] Evidence supports the premise that at critical stages in fetal development exposure to exogenous chemicals known as endocrine-disrupting chemicals (EDCs) can disrupt reproductive organ differentiation and development in utero, leading to an IV condition.[4–10]

This study takes a closer look at the complex physiological mechanisms of fetal sex differentiation and development in utero and provides a better understanding of the vulnerability of the fetus to toxicological dysregulation by EDCs. With early surgical intervention of children presenting with IV no longer the preferred medical management practice, and with parents electing to delay surgery until development of secondary sex characteristics, the number of children with IV will increase.

Historically, the incidence and prevalence in IV have been difficult to quantify as few studies have been conducted classifying the numerous physical presentations of IV or quantifying specific IV conditions at birth. Some conditions of IV are reportable birth defects documented in the State Birth Defect Registries. Other variations from the physical *norm* are not defined as birth defects and therefore have not been documented as such. Current data indicate that an increasing trend in IV is being seen on a global basis. An early study by Lilford and Dear[11] suggested that one in 2,000 newborns had some form of external genital ambiguity, but the study was not well supported by medical or scientific data, as best can be determined. A more recent review by the World Health Organization (WHO, 2016) found that frequency in *sexual development variations* were highly variable and ranged from 1:600 (Klinefelter syndrome) to 1:5,000 (congenital adrenal hyperplasia [CAH]).[12] In 2004, an increasing trend was reported by Ahmed et al.[13], examining genital anomalies in single births (excluding multiple births) in Scotland. Prevalence in hypospadias and other genital anomalies increased over an 8-year period of time from 4.0 per 1,000 births (1988) to 5.9 per 1,000 births (1996). Gaspari et al.[14] also supported an increasing trend in the number of children born with IV. No study examined the incidence in IV as a comorbidity in deceased neonates or infants. Whether this increasing trend in IV is an artifact of recognition and documentation; expanded

inclusivity of morphological variations in genitalia; improved medical treatment in neonates, leading to a reduced mortality rate; or declining incidence in early surgical intervention is difficult to determine with few studies and data to rely upon.

Toxicological Dysregulation in Fetal Genital Differentiation

Toxicological dysregulation can interfere with fetal tissue differentiation and adversely affect normal development of male and female morphological characteristics while in utero. Differentiation in male or female external genitalia in the fetus begins during the seventh week of gestation. Prior to this time, internal genital ducts derived from the mesonephros are present, but the fetus is not recognizable as male or female externally. Masculinization is initiated by testicular androgens (derived from Greek term "andro" meaning male) in the fetus, defining the androgynous external genitalia into a recognizable form or *sex* between 8 and 12 weeks of gestation. Dihydrotestosterone, a metabolite of testosterone, activates genes causing the male reproductive tract and external genitalia to develop.[15] Abnormal hormone production, or action, can disrupt this process, resulting in incomplete masculinization.[16] In the absence of the hormonal influence of dihydrotestosterone, a fetus will essentially develop into a female. External genitalia differentiation is therefore strongly hormonally dependent.

During this critical time in sex differentiation, the fetus is the most susceptible to chemicals in the environment with the capacity to disrupt the sensitive endocrine system. Exposing the fetus to EDCs, during this critical stage, can affect tissue differentiation, growth, and physiologic maturation and may also affect later development of secondary sex characteristics.[17–19] Incomplete or partial differentiation of genitalia can result in development of both male and female reproductive organs, making it a challenge to clearly identify an infant as either male or female physically at the time of birth. Multiple genetic and nongenetic factors are capable of disrupting the dimorphic processes of sex determination, where developing gonads become a testis or ovary, and subsequent sex differentiation, where internal ducts and external genitalia form.[20] These unintended birth variations have been identified by different terms over time (ambiguous genitalia, hermaphrodite, pseudohermaphrodite, etc.) with the currently embraced terminology IV.

A fetus exposed to gender altering chemicals can be born with a spectrum of morphologic variations. Ambiguous genitalia (atypical genitalia) resulting in IV may present as cryptorchidism (absence of one or both testes), perineal hypospadias (urethra opening is not at head of the penis), epispadias (urethra opening on the dorsum of the penis), and clitoromegaly (abnormal enlargement of the clitoris).[21–23] IV may also be accompanied by other medical or chromosomal disorders including Turner syndrome, Klinefelter syndrome, and CAH. Exposure to EDCs has been associated with an increased incidence of CAH, which can be life threatening, depending on the severity. Approximately 95% of CAH cases are caused by a 21-hydroxylase deficiency (21-OHD), a mutation in the gene that codes for the enzyme 21-OH. A deficiency in 21-OH can result in an interference in cortisol and aldosterone synthesis efficiency, resulting in increased androgen production and early on-set puberty.[24–28] The severity of CAH is dependent upon the magnitude of enzyme disruption and resultant interference in the synthesis of these hormones. A milder form of CAH (nonclassic CAH) is not life threatening, with symptoms appearing in late childhood or early adulthood. Signs of infertility, short stature, and early puberty can be indicators of adrenal function disruption. Individuals with CAH produce more androgens, resulting in early and excessive development of male characteristics in both males and females. Excessive androgen production can interfere with normal development of secondary sex characteristics in females during puberty and appropriate gender identity association later in life.[29,30] Although not all CAH results in intersexuality, CAH is the most common cause of IV in females.[31] Studies support even low-dose EDC exposure has the ability to impact sensitive mechanisms in physiological and biochemical processes, rather than only high-dose exposure.[32–35] A study by Ostby et al.[36] examined low-level dicarboximide fungicide (vinclozolin) exposure with antiandrogenic effect to pregnant Long-Evans hooded rats. Male offspring developed numerous reproductive abnormalities including reduced anogenital distance and decreased ventral prostate size and weight. There was a significant increased incidence (+246%) of areolas in males at low-level exposure (3.125 mg kg^{-1}/day^{-1}) when compared to higher exposures (100 and 200 mg kg^{-1}/day^{-1}).[36] This finding supports the potential for a bimodal antiandrogenic effect in certain EDCs. EDCs may also lay the groundwork for future disease (testicular cancer),[37,38] and reproductive abnormalities (hypospadias, reduced anogenital distance, poor semen quality).[39,40]

Conditions of IV may present with a higher rate of heart defects. During the same time of genital development in the fetus, the heart continues differentiation and development. Early in the seventh week, the foramen secundum in the septum primum (precursor to interatrial septum of the embryological heart) closes and begins portioning into right and left heart chambers. The aortic and pulmonary trunks cleave during the eighth and ninth week in fetal development and the sinoatrial node (SA node or pacemaker of the heart) becomes identifiable as valve and septum morphogenesis continues.[41–46] The embryonic period (week 4–8) is a critical window of organogenesis where the embryo is at peak vulnerability to disruption in differentiation. Exposure to EDCs during this time can lead to major congenital anomalies including heart malformation, a potential indicator for CAH and IV.[47–50] Limb and craniofacial deformations are also associated with this critical window in fetal genital development.[51–53] Children with genital anomalies are at higher risk for early death due to

various congenital malformations, particularly those affecting the cardiovascular system.[54,55] Turner syndrome is one of the most common chromosomal abnormalities in humans and highly correlated with cardiovascular abnormalities.[56] A study by Davenport[57] found that 75% of fetuses with Turner syndrome had congenital heart disease. Congenital heart disease was also recorded in 25%–45% of females with Turner syndrome. Bicuspid aortic valve (16%) and coarctation of the aorta (11%) were identified as the most commonly expressed heart variation.[57] In addition to cardiovascular diseases, individuals with Turner syndrome can manifest a wide spectrum of comorbidities including stunted growth, hearing loss, learning disabilities, renal malformations, and infertility.[58–60] Genital anomalies have also been associated with facial dysmorphisms, musculoskeletal abnormalities, and renal and respiratory failure.[61] Psychological comorbidities associated with genital anomalies have also been documented. A study of Taiwanese women born with CAH showed a significant proportion of patients had been diagnosed with a psychiatric disorder.[62] Congenital malformations of the heart are often the primary factor in infant mortality and therefore are reported as the primary cause of death. Currently, reporting IV conditions as comorbidity (chromosomal disorders excluded) is not required in the U.S. and therefore lends to underreporting, further complexing the establishment of an accurate incidence or prevalence rate.

EDC and Effect on Brain Chemistry

The recent high-profile gender transition of the 1976 United States Olympic men's decathlon champion and heartthrob Bruce Jenner to the female Caitlyn Jenner has prompted considerable discussion and confusion as to what actually defines *gender*, or one's *gender identity*. EDCs can interfere with the complex biochemical pathways of the brain and development of secondary sex characteristics, affecting normal behavioral or gender development consistent with the sex of the child without dysregulation in tissue differentiation. This can affect brain chemistry and the way a person associates with his/her physiological sex or personifies his/her gender behaviorally.[63,64] This interference can result in a gender dysphoria (previously termed gender identify disorder), or people whose gender identity differs from their biological sex at time of birth, which may explain the desire for surgical gender reassignment in some individuals. The American Psychiatric Association clarifies that, "gender nonconformity is not in itself a mental disorder. The critical element of gender dysphoria is the presence of clinically significant distress associated with the condition.[65]

Possibly the truest aspect or expression of ones' sexuality may be best defined by the integration of an individual's reproductive system assignment, or *sex*, and the expression of their sex through sexual/social behavior or *gender identity*. The sex/gender interaction is therefore a complex dance between chromosomal factors, genetic factors, brain chemistry, and expression of those factors in behavioral display (sexual behavior, romantic, or intimate preference; Fig. 1).

EDCs and IV in Animal Studies

Decades of research on animals exposed to EDCs provide a solid basis for understanding EDCs potential to interfere in human reproductive organ development. Early research by Guillette et al.[66] examined abnormal gonadal development in juvenile alligator population of Lake Apopka, Florida. Results identified elevated estrogen/testosterone ratios in both male and female alligators exposed to estrogenic xenobiotic chemicals (dicofol, DDT, and DDT metabolites), from agricultural runoff and a pesticide manufacturing plant spill with embryos exhibiting sex reversal (male to female). Exposed male juvenile alligators had lower plasma testosterone concentrations when compared to unexposed juvenile alligators, while exposed female juvenile alligators had elevated polyovular follicles and polynuclear oocytes, which interfered in normal growth and development of the central and peripheral oocytes. The conclusion of the study determined that alteration in sexual development (abnormal size phalli, poorly organized seminiferous tubules) resulted in poor reproductive outcome.[66] Research by Colborn and Clement[67] reported poor growth, wasting, and lower rates of neonatal activity in animals exposed to elevated levels of estrogenic xenobiotics. Semenza et al.[68] supported the finding of high mortality in embryos and neonates in EDC exposed juvenile alligators with dramatic decline in overall alligator population over a seven-year period.

More recent research involving fish species exposed to EDCs support the historical studies in reptiles. Intersexuality in fish has long been associated with exposure to treated sewage effluent from industries such as paper mills, containing

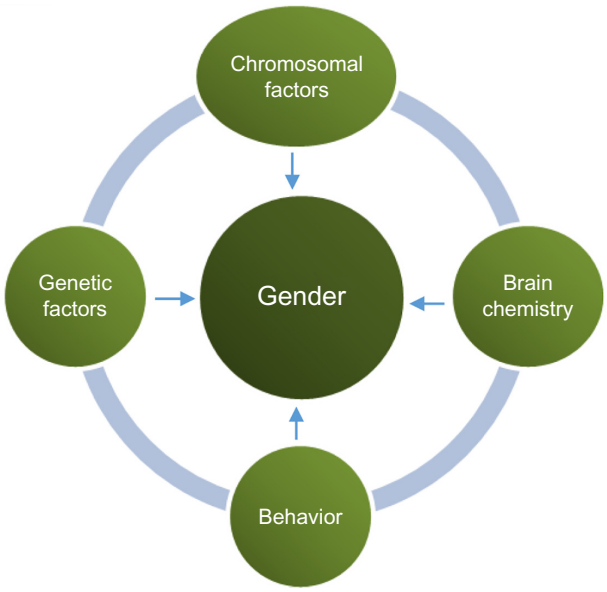

Figure 1. The expression of gender by an individual is the result of the interaction between chromosomal factors, brain chemistry, behavior, and genetic factors.

chemicals with estrogenic capabilities.[69] A study by Jobling et al.[70] found a high degree of intersexuality among populations of wild roach fish exposed to treated sewage effluent containing a mixture of EDCs. Fish also had lower milt volume and sperm density. Female mosquitofish (*Gambusia holbrooki*) exposed to effluent from a paper mill showed masculinized secondary sex characteristics and altered reproductive behavior further supporting EDCs impact on gender misalignment.[71]

A study by Aravindakshan et al.[72] of spottail shiner minnows in the St. Lawrence River showed evidence that immature and male spottail shiners exposed to xenoestrogens were linked to reduced male reproductive function (delayed spermatogenesis) and intersexuality. Ortiz-Zarragoitia et al.[73] showed an increase in male intersex in the mullet species associated with xenoestrogenic compound exposure during a critical time in juvenile sex differentiation. The exposure to EDCs from wastewater treatment plants were found to alter male reproductive tissues of some species causing them to present with feminization or intersex conditions.[74–78] Atrazine, a common pesticide classified as an EDC, has been shown to affect the reproductive systems of frogs inducing gonadal abnormalities (multiple gonads and hermaphroditic conditions), via endocrine-disrupting processes.[79] A study by Rey et al.[80] found that neonatal caiman exposed in ovum to Atrazine altered the histoarchitecture of the testis and organization of the seminiferous tubules.

Other environmental conditions may enhance the effect of chemical exposure. Temperature-dependent sex determination exists in many reptilian species. A simultaneous exposure to EDCs and change in temperature range and/or length of exposure can alter male or female sex determination, although timing in gonadal differentiation is species dependent and highly variable.[81,82] The synergistic potential of EDCs with temperature was examined in a study by Olmstead and LeBlanc.[83] Pyriproxyfen was found to be more biologically active and caused bilateral gynandromorphism (sexual dimorphism) in some crustaceans as temperatures increased.[83] Pyriproxyfen is an insecticide and juvenile hormone analog, which controls insect development cycles, preventing larvae from developing into adulthood and disabling them from reproducing.[84] Aquatic species are highly affected due to their unique position in the food chain and aquatic exposure. Disruption in endocrine balance has also been confirmed in top predator birds (osprey, falcons, and eagles) and mammals, which prey on aquatic species. Exposure to DDT has been directly associated with population declines in predator birds due to interference with the hormone responsible for eggshell production.[85–87]

Early 1960s' research in the Great Lakes Basin reported reproductive failure among ranched mink fed fish with high concentrations of organochlorine compounds. Fetal deaths and abnormalities were related to dioxin-like polychlorinated biphenyls (PCBs) and polychlorinated dibenzodioxins/polychlorinated dibenzofurans (PCDD/Fs).[88–90] A longitudinal study of Swedish otter populations spanning 30 years (1968–1999) showed an inverse relationship in PCB levels in the environment and successful pup outcome.[91] Research on gray and ringed seals (*Halichorerus grypus* and *Phoca hispida*) during the same time period in the Baltic Sea found a dramatic increase in spontaneous abortions and sterility, leading to a dramatic decline in the seal population. Seals were found to have high concentrations of DDT and PCBs absorbed through ingestion of contaminated fish. Malformations of the claws and presence of adrenal cortex hyperplasia was also identified in affected seals.[92–94] EDCs have been shown to cause genetic defects and hormonal effect in domestic animals even at low-level concentrations. A study by Gajezcka[95] examined the effects of low doses of zearalenone, a potent estrogenic mycotoxin metabolite, on estrogen receptors in the ovaries of prepubertal Beagle bitches. Intoxication of zearalenone during a critical developmental stage was found to lead to hyperestrogenism in prepubertal bitches.[95] A study evaluating EDC leaching from dog toys by Wooten and Smith[96] examined whether a subset of phthalates and bisphenol A (BPA) could leach out of dog toys and training devices (bumpers) into canine saliva. The synthetic EDCs commonly found in plastic revealed antiandrogenic activity of bumper leachates as well as estrogenic activity of both bumper and toy leachates, confirming the potential for endocrine disruption in pet dogs.[96]

Recent research examining the effect of EDCs on domestic dairy cattle found disruption of reproductive processes consistent with what has been exhibited in wild animal populations. In a study by Meijer et al.[97], drinking water contaminated with EDCs by sewage showed a decrease in overall milk production but an increase in the age at first calving. Sheep exposed to pastures fertilized with sewage sludge containing multiple EDC compounds showed reduced fetal testis development, testis weight, and altered hormone profiles.[98] Goats exposed to EDCs during gestation (PCB 125 and PCB 153) had similar results as domestic dairy cattle exhibiting reduced lactation and delayed onset of puberty. PCB 153 exposed animals showed significantly higher damaged DNA in sperm and altered plasma luteinizing hormone (LH) and testosterone levels.[99–102] Reduced bone strength was also seen in wildlife and domestic cattle and was thought to occur from increased mineral content from low-level pollutant mixture exposure.[103] Laboratory experiments on rodents validated the findings in the above studies. A study examining whether 4-tert-octylphenol (OP), an endocrine disruptor, interfered with the estrous cyclicity in neonatal rats provided strong evidence that it acted like estrogen in both neonatal and adult female rat.[104] A study by Markey et al[105] on the effects of BPA on mouse mammary glands revealed a disruption in the hypothalamic–pituitary–ovarian axis and/or misexpression of developmental genes in mice confirming the potential for endocrine disruption.

The primary purpose of domestic livestock is food production for human consumption. Many EDCs are lipophilic with

the ability to bioaccumulate and biomagnify and are therefore retained in highly fatty products like dairy and meat. Human exposure to EDCs from consumption of animal products is therefore both plausible and probable although the effect may vary widely, depending on consumption behavior, chemical concentration, and timing (critical life stages) of exposure.

EDCs Effect on Reproductive Development in Humans

Additional research has provided evidentiary support for the association between EDCs and adverse effects on reproductive development in both men and women. Female reproductive disorders, including declining conception rates and latent menopause, have been associated with environmental chemicals capable of mimicry or blocking natural hormones.[106,107] The effect EDCs may have on the female hypothalamic–pituitary–gonadal axis and regulation and initiation of the hormonal cascade that occurs during the transition from puberty to adulthood is complex at best and time dependent. The hypothalamus contains gonadotropin-releasing hormone-expressing neurons, which synthesizes gonadotrophin (GnRH) and releases the reproductive hormones from the pituitary gland, activating the gonads. Research by Bellingham et al.[108] confirmed EDCs ability to disrupt the sexually dimorphic estrogen-sensitive neuropeptides that stimulate the secretion of LH and follicle-stimulating hormone, affecting neurochemistry during early sexual development.[109]

A fetus or infant exposed to environmental triggers like EDCs during critical periods in development may not express biological disease or dysfunction until later in life. Effect of these chemicals are often first seen during early reproductive years when complications of fertility arise, and have also been identified as a potential factor in development of cancer later in life.[110] Research by Svechnikov et al.[111] supported the theory that the rapid increase in reproductive disorders and genital variations in humans over the past few decades are likely the cause of environmental or lifestyle factors rather than genetically caused mutations. EDCs, including organochlorine pesticides, polychlorinated biphenyls, BPA, phthalates, dioxins, and furans, have been found to possess strong estrogenic and antiandrogenic properties. Studies support that these same chemicals are associated with reproductive disorders in humans, as well as disorders in development and sexual differentiation in fish and alligator species.

Disruption of the endocrine system by EDCs in the environment has been confirmed through occupational studies of chemically exposed workers. In a study by Ratcliffe et al.[112], workers fumigating papaya fields in Hawaii with ethylene dibromide (exposure for ±5 years) showed a statistically significant decrease in the sperm count per ejaculate and decreased sperm viability and motility. An increase in the proportion of morphologically abnormal sperm, including those with tapered heads and abnormal tails, was also found in exposed workers.[112] A study by Gaspari et al.[113], examining the incidence in genital malformations in French newborn male infants, found a direct association between parental pesticide exposure and abnormal male external genital development, including an increase in cryptorchidism (1.25%), hypospadias (0.97%), micropenis (0.35%), and disorders of sex development (DSD) (0.14%). In one of the worst industrial chemical accidents in history, the town of Seveso, Italy, was exposed to high levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) from a manufacturing accidental release during chemical production. The initial study of exposed children at the time of the release was inconclusive for immediate health effects other than chloracne; however, an increased incidence in spontaneous abortions among exposed women was noted.[114] Particularly interesting is the change in sex ratio now being observed decades later in the children of the current generation, who were themselves children at the time of the Seveso accident. A study by Mocarelli et al.[115], found that men exposed to TCDD had a higher female:male sex ratio in offspring, which persisted years after parental exposure. On a global level, this has profound implications. With the half-life of dioxins in the atmosphere of 21 days, dioxins become a factor in local, regional, and global atmospheric impact. Due to its characteristic persistence and ability to bioaccumulate in the soil (half-life, 9–15 years), exposure of humans to dioxins can come from consumption of meat (beef, pork, poultry, and fish) and dairy (milk and cheese) products as well as environmental exposure.[116]

While many chemicals are known as EDCs, other chemicals may not be currently identified as EDCs, but may possess similar capacity for cellular disruption. Carbon disulfide (CS_2) has been found to impact the function of enzyme C21 hydroxylation (21-OH). Interference in 21-OH can cause decreased production in cortisol and aldosterone, and increased androgen production, resulting in early on-set puberty.[117] The mechanism of interference may be histologic changes to the adrenal corticoid cells affecting mitochondrial or endoplasmic reticulum activity, the primary organelles for steroid production. As each step in the synthesis of steroid hormones is catalyzed by a specific enzyme, even a slight change in enzymatic activity can result in different types or proportions of hormones produced. CS_2 also has the capability to inhibit CYP2B1 activity (active enzyme in the liver responsible for metabolism of xenobiotics), even at low levels. This increases the potential for hepatocellular damage from lipid peroxidation by reactive oxygen species resulting in elevated serum alanine transaminase (ALT) levels. A metabolite of CS_2, carbonyl sulfide (COS), produces carbon monoxide (CO) and hydrogen sulfide (H_2S) during biotransformation. H_2S can inhibit cellular respiration creating oxidative stress and microsomal membrane changes, contributing to hepatic damage.[118,119]

Carbon tetrachloride (CCl_4), a solvent and propellant, is more commonly known for its hepatotoxic and nephrotoxic capacity, but can also alter steroid hormone production pathways. Activation of CCL_4 causes cellular damage to the

adrenal cortex, affecting cortisol function. This results in impairment of adrenocorticoid activity by competing with steroid hormone receptor sites, reducing the number of receptor sites available for steroid hormone binding and interference in secretion.[120] In response to the growing body of evidence supporting the adverse effects of EDCs on reproductive health, a group of European countries and the World Health Organization (WHO) established Human Reproductive Health and General Environment Network (HURGENT) in 2013. The HURGENT is an international surveillance system that fosters collaboration and exchange of information in reproductive health and environmental risk factors among European countries. Establishing a network for scientific data exchange among nations will advance longitudinal research in transgenerational reproductive health and the influence of environmental risk factors on reproduction, providing the ability to assess long-term trends across Europe.[121]

Conclusion

With the increasing incidence of intersex birth variations, urgency exists to better understand how chemicals in the environment are affecting fetal development. Identifying specific chemicals that pose the greatest risk during this critical window in genital development and quantifying the level at which they are capable of asserting their influence is an ongoing challenge for scientists. Both genetic and nongenetic factors must be evaluated as both have been found to disrupt the dimorphic process of sex determination and subsequent sex differentiation.

Ambiguity or inability to classify individuals based on sex is not easily tolerated by our gender-centric society. Due to this emphasis on gender definition, a child identified as having an intersex condition historically underwent a course of surgeries and hormone treatments.[122] This early medical intervention compelled the intersex child into a more defined male or female form physiologically, but, ignored the impact and potential confusion in gender identify or gender expression later in life with the onset of puberty.[123] As reducing genital tissue is easier than building tissue, this often resulted in the medical surgical assignment of underdeveloped male genitalia to a female form only to have secondary sex characteristics expressed as male gender alignment later in life and a diagnosis of gender dysphoria. By medically assigning a defined sex to an intersex child through surgical procedures and hormone treatments, we have missed biologically significant factors affecting human sex, gender determination, and inherent variation in the human species.[124–128] We have also overlooked apparent changes EDCs are making to our environment and the severe ramifications to reproductive health in both animal and human species. The complex interaction that exists between the biological, psychological, social, and cultural factors influencing gender identity in intersex individuals necessitates medical decisions be made on a case-by-case basis.[129] When possible, children with IV and their families should be connected with multidisciplinary teams that include specialists in fields such as genetic counseling, child psychology, pediatric endocrinology, pediatric urology, gynecology, and public health to provide and coordinate the lifelong medical and social management IV children and their families need.[130] We must make an active choice to protect the fetus from environmental exposure to EDCs and their adverse effects while providing support for those living with IV conditions. As the population of IV children is increasing and will continue to increase as long as we produce and use chemicals with EDC potential, so will our struggle to understand, accept, protect, and integrate people with IV into our society. Similar to accommodating and accepting children with other special needs, it is crucial that IV children receive equal treatment, inclusivity, and protection.

Author Contributions

Conceived and designed the experiments: ALR, LMP. Analyzed the data: ALR, LMP, ST, HR, POD. Wrote the first draft of the manuscript: ALR, LMP. Contributed to the writing of the manuscript: ST, HR, POD. Agreed with manuscript results and conclusions: ALR, LMP, ST, HR, POD. Jointly developed the structure and arguments for the paper: ALR, LMP, ST, HR, POD. Made critical revisions and approved final version: ALR, LMP. All the authors reviewed and approved the final manuscript.

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