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Exploring the Role of SULT1E1- A Metabolic Gatekeeper or Risk Factor for Diseases

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ABSTRACT
Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), pose a significant threat to human health by interfering with hormonal homeostasis. This review posits that the cytosolic sulfotransferase enzyme SULT1E1—a critical gatekeeper for inactivating both endogenous estrogens and exogenous xenoestrogens via sulfation—serves as a central mechanistic node linking environmental EDC exposure to the pathogenesis of reproductive and metabolic disorders. We synthesize evidence demonstrating that BPA, a ubiquitous EDC, disrupts endocrine function not only by mimicking estrogen but also by directly inhibiting SULT1E1 activity. This inhibition leads to a state of functional hyperestrogenemia, which provides a plausible explanatory model for the comorbid development of conditions such as polycystic ovary syndrome (PCOS), infertility, and hormone-sensitive cancers (e.g., breast and endometrial cancer). Furthermore, SULT1E1 dysfunction extends to systemic metabolism, contributing to insulin resistance and thyroid hormone disruption. The review critically evaluates the diagnostic and therapeutic potential of targeting the SULT1E1 pathway, including strategies to restore its protective sulfation function. We conclude that the impairment of SULT1E1 by EDCs like BPA represents a unifying biological mechanism connecting pervasive environmental chemical exposure to the rising burden of chronic non-communicable diseases, underscoring an urgent need for both enhanced regulatory policies and targeted biomedical interventions.

I. Introduction

Endocrine-disrupting chemicals (EDCs) are a pervasive class of environmental pollutants that interfere with hormonal systems, leading to a range of adverse health outcomes. These chemicals, which include industrial chemicals, pesticides, and personal care products, are found in everyday items such as plastics and cosmetics, and exposure occurs through inhalation, dermal contact, and ingestion (Srivastava & Balyan, 2025; Chakraborty et al., 2024; Stroustrup & Swan, 2024). EDCs can mimic, block, or alter hormone actions by interacting with hormone receptors and affecting signaling pathways at both genomic and non-genomic levels (Stroustrup & Swan, 2024; Priyadarshini et al., 2023). This interference can result in metabolic disorders like obesity and diabetes, reproductive impairments such as infertility, and an increased risk of hormone-sensitive cancers (Srivastava & Balyan, 2025; Yilmaz et al., 2020; Kumar et al., 2020). The molecular mechanisms through which EDCs exert their effects involve complex interactions with nuclear receptors and aryl hydrocarbon receptors, which are

crucial for metabolic functions (Ansari et al., 2023). These interactions can disrupt glucose and fat metabolism, contributing to metabolic disorders (Swedenborg et al., 2009). Furthermore, EDCs can cause epigenetic changes, such as DNA methylation and alterations in microRNA expression, which may have long-term health implications (Ansari et al., 2023). The persistence and bioaccumulation of EDCs in the environment, coupled with their ability to act at low doses, complicate their detection and regulation (Srivastava & Balyan, 2025; Yilmaz et al., 2020). Given the widespread presence of EDCs and their potential to cause significant health issues, there is an urgent need for comprehensive research to elucidate their molecular pathways and for the development of effective regulatory frameworks to mitigate their impact on human health (Srivastava & Balyan, 2025; Kumar et al., 2020; Metcalfe et al., 2022).

The human body's detoxification system is a complex, multi-phase process designed to metabolize and eliminate xenobiotics, which are foreign compounds that can include drugs, environmental contaminants, and industrial chemicals. This system is divided into three phases: Phase I involves functionalization reactions, primarily catalyzed by cytochrome P450 enzymes, which introduce reactive groups to xenobiotics, increasing their solubility and preparing them for further processing (Chen, 2024; Stanley, 2024). Phase II, the conjugation phase, involves enzymes such as sulfotransferases, which play a crucial role in detoxifying these activated compounds by attaching polar moieties, thereby enhancing their water solubility and facilitating their excretion (Chen, 2024; Silva & Carvalho, 2018). Among these enzymes, estrogen sulfotransferase (SULT1E1) is particularly significant due to its high affinity for estrogens, such as estradiol, and its role in maintaining estrogen homeostasis by sulfonating and inactivating these potent hormones (Silva & Carvalho, 2018). SULT1E1 also contributes to the detoxification of estrogen-mimicking endocrine-disrupting chemicals (EDCs) like bisphenol A (BPA), which can mimic estrogen and disrupt hormonal balance (Quesnot et al., 2014). However, the protective function of SULT1E1 can be compromised when it becomes a target of disruption itself, as BPA and other xenobiotics can modulate the activity of metabolizing enzymes, either inducing or inhibiting them, which may alter their own toxicity or that of other chemicals (Quesnot et al., 2014). This modulation can occur at doses of BPA that are relevant to human exposure, highlighting the potential for significant impacts on the detoxification process and overall metabolic homeostasis (Quesnot et al., 2014). The interplay between these phases and the potential for enzyme modulation underscores the complexity and vulnerability of the detoxification system, emphasizing the need for further

research into the mechanisms of enzyme regulation and the impacts of xenobiotic exposure (Kadlubar & Kadlubar, 2010; Stanley, 2017).

Bisphenol A (BPA) is a pervasive endocrine-disrupting chemical (EDC) that mimics estrogen due to its structural similarity to estradiol, allowing it to bind to estrogen receptors and disrupt hormonal signaling pathways. This disruption is particularly concerning in the context of Phase II metabolism, where BPA competes with endogenous estrogens for sulfation by the enzyme SULT1E1, potentially leading to an accumulation of active, unsulfated estrogens and prolonged estrogenic signaling. Such interference with a key metabolic gatekeeper provides a plausible mechanistic link between environmental BPA exposure and the pathogenesis of estrogen-driven disorders, including hormone-related cancers like breast cancer (Ariba & Banerjee, 2024; Pupo & Maggiolini, 2013). BPA's weak binding affinity to estrogen receptors, despite its structural mimicry, can still trigger multiple cell death pathways and disrupt various cellular processes, contributing to a range of health issues such as reproductive abnormalities, metabolic syndrome, and immune dysfunction (Yukta et al., 2025; Lazúrová & Lazúrová, 2013). The chemical's widespread use in polycarbonate plastics and epoxy resins results in ubiquitous human exposure through various routes, including diet, inhalation, and dermal contact, with significant detection in human biological samples like urine and blood (Pupo & Maggiolini, 2013; Abraham & Chakraborty, 2020). Epidemiological studies have linked BPA exposure to metabolic disorders, including obesity and type 2 diabetes, by altering insulin homeostasis and liver enzyme activity, further implicating BPA in metabolic syndrome (Saal & Myers, 2008; Amiri-Dashatan et al., 2024). Additionally, BPA's impact on female reproductive health, such as menstrual irregularities and polycystic ovary syndrome (PCOS), underscores its role in disrupting endocrine function during critical life stages (Kawa et al., 2021). Given these multifaceted health risks, there is a pressing need for revised safety standards and interdisciplinary strategies to mitigate BPA exposure and its adverse effects (Ariba & Banerjee, 2024; Pupo & Maggiolini, 2013).

Despite regulatory efforts in various countries, including India's ban on BPA in baby bottles, human exposure remains widespread due to its persistent use in food can linings, receipts, and dental materials. This continued exposure, coupled with emerging evidence, positions SULT1E1 not merely as a metabolic enzyme but as a central node in environmental health. Its function—or dysfunction—may determine individual susceptibility to a cluster of modern diseases. Therefore, this review aims to synthesize current knowledge to argue that SULT1E1

sits at a critical crossroads: its impairment by EDCs like BPA serves as a unifying mechanistic link between environmental exposure and the comorbid development of reproductive and metabolic diseases. We will critically evaluate its role in polycystic ovary syndrome (PCOS), infertility, and hormone-sensitive cancers, explore its emerging diagnostic and therapeutic potential, and contextualize these findings within the specific public health challenges of high-exposure regions.

II. Sulfotransferases (SULTs) and the Central Role of SULT1E1

The detoxification of xenobiotics through Phase II conjugation reactions, particularly those mediated by sulfotransferases (SULTs), is a critical process for enhancing the solubility and excretion of various compounds, including drugs, hormones, and environmental chemicals. SULTs catalyze the transfer of a sulfonate group from 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to hydroxyl or amine groups on substrates, a process often referred to as sulfonation, although it is sometimes incorrectly termed sulfation (Wang & James, 2006; Hempel et al., 2005). The human SULT family is diverse, with several isoforms such as SULT1A1, SULT1A3, and SULT1C4, each exhibiting distinct substrate specificities and tissue distributions (Hempel et al., 2005; Guidry et al., 2016; Dombrovski et al., 2006). SULT1C4, for instance, is notably expressed in fetal tissues and plays a role in detoxifying environmental estrogens like bisphenol A, which can have detrimental effects on fetal development (Guidry et al., 2016). The inhibition of SULTs by xenobiotics, including drugs and environmental chemicals, can disrupt normal metabolic processes, potentially leading to adverse health effects such as interference with thyroid hormone transport and estradiol sulfonation (Wang & James, 2006). Despite the overlapping substrate selectivity among SULT isoforms, specific inhibitors or enhancers can differentially affect their activity, highlighting the complexity of SULT-mediated detoxification pathways (James & Ambadapadi, 2013). Furthermore, the structural and functional diversity of SULTs, as evidenced by the crystal structures of SULT1B1 and SULT1C1, underscores their varied roles in modulating the activity of endogenous and exogenous compounds (Dombrovski et al., 2006). Understanding the regulation and expression of SULTs, as well as their interactions with xenobiotics, is crucial for elucidating their role in drug metabolism and the detoxification of harmful substances (Suiko et al., 2017; Duffel, 2023). This knowledge is essential for developing strategies to mitigate the toxic effects of xenobiotics and protect human health and the environment (Mahanayak, 2024).

The human sulfotransferase (SULT) family is a diverse group of enzymes that play a crucial role in the metabolism of both endogenous and exogenous compounds through sulfonation, a process that typically increases the water solubility of molecules, facilitating their excretion. Among the various SULT isoforms, SULT1E1 is particularly significant for its role in the sulfation of physiological estrogens such as estradiol, estrone, and estriol. This isoform exhibits a uniquely high affinity for these hormones, operating efficiently at low nanomolar concentrations, which distinguishes it from other SULTs that only contribute to estrogen sulfation at supraphysiological levels (James & Ambadapadi, 2013; Lindsay et al., 2008). SULT1E1's specificity and high affinity make it the principal regulator of free, bioactive estrogen levels in estrogen-responsive tissues, including the breast, endometrium, ovary, and liver (Falany et al., 2006; Riches et al., 2009). The tissue-specific expression of SULT1E1, along with its kinetic properties, underscores its critical role in maintaining hormonal balance and regulating estrogen activity in these tissues (Riches et al., 2009; Gamage et al., 2006). Furthermore, the structural and functional characteristics of SULT1E1, as part of the SULT1 family, highlight its substrate-binding specificity for simple phenols and steroid hormones, which is essential for its function in estrogen metabolism (Dombrovski et al., 2006). The regulation of SULT1E1 and its interaction with other SULT isoforms, such as SULT1A1 and SULT2A1, which also participate in the sulfation of various compounds, further illustrates the complex network of sulfotransferase activity that modulates hormone levels and detoxifies xenobiotics (James & Ambadapadi, 2013; Wang et al., 2016). Understanding the dynamics and regulation of SULT1E1 is crucial for insights into its role in endocrine function and potential implications in diseases related to estrogen metabolism (Duffel, 2024; Gamage et al., 2006).A refined understanding of this enzymatic landscape is best presented in a consolidated table, which clarifies the distinct roles of each major isoform (**Table 1**). This table synthesizes information on gene locus, primary substrates, biological functions, and key regulatory tissues, providing a clear reference for the functional diversity within the SULT family.

Table 1: The Human Cytosolic Sulfotransferase (SULT) Family: Isoforms, Localization, and Primary Functions

SULT Isoform	Gene Locus	Major Tissue Expression	Primary Substrate Classes	Key Biological Function	References
SULT1A1	16p11.2	Liver, intestine, platelets, lung	Simple phenols, therapeutic drugs (e.g., acetaminophen, minoxidil),	High-capacity detoxification of xenobiotic phenols; bioactivation of some procarcinogens.	(Coughtrie, 2016)

			estrogens (at high µM conc.)		
SULT1A2	16p11.2	Liver (low expression)	Phenolic compounds	Minor role; potential genetic variant contributing to interindividual detoxification capacity.	(Nowell & Falany, 2006)
SULT1A3	16p12.1	Intestine, brain, platelets	Catecholamines (dopamine, norepinephrine), catechol estrogens	Inactivation of neurotransmitters in the gut; modulation of catecholamine activity.	(Bairam et al., 2018)
SULT1B1	4q13.3	Liver, intestine, colon	Thyroid hormones (T3, T4), phenols	Regulation of bioactive thyroid hormone levels; xenobiotic phenol metabolism.	(Kurogi et al., 2021)
SULT1C2/3/4	2q12.3	Fetal liver, kidney, stomach	Phenols, xenobiotics	Fetal and developmental detoxification; limited expression in adults.	(Runge-Morris & Kocarek, 2013)
SULT1E1	4q13.3	Liver, endometrium, breast, ovary, placenta, lung	**Estrogens (E2, E1, E3) at nM conc.,** BPA, other phenolic EDCs	**High-affinity inactivation of estrogens;** maintenance of estrogen homeostasis; defense against xenoestrogens.	(Adjei et al., 2003; Yi et al., 2021)
SULT2A1	19q13.3	Liver, adrenal cortex, intestine	DHEA, pregnenolone, bile acids, steroids	Regulation of steroid hormone synthesis (androgen/estrogen precursor pool); bile acid metabolism.	(Thomae et al., 2002)
SULT2B1a/b	19q13.3	Skin, prostate, brain, placenta	Cholesterol, oxysterols, pregnenolone	Cholesterol sulfation in skin barrier; neurosteroid metabolism; localized steroid regulation.	(Cheung et al., 2017)
SULT4A1	22q13.2	Brain (neurons)	Unknown (endogenous brain substrate)	Neurodevelopment, neuronal protection; potential role in neurological disorders.	(Culotta et al., 2020)
SULT6B1	2q12.3	Testis	Unknown (testis-specific)	Potential role in spermatogenesis, testicular steroid metabolism, and male fertility.	(Sun et al., 2020)

Note: Conc. = concentration; DHEA = Dehydroepiandrosterone; EDCs = Endocrine-disrupting chemicals.

SULT1E1, a key enzyme in the sulfation of estrogens, plays a crucial role in both endocrine homeostasis and the detoxification of environmental estrogens, such as bisphenol A (BPA). This enzyme facilitates the inactivation and renal clearance of xenoestrogens by increasing their water solubility, thereby reducing their estrogenic potential and mitigating their impact on estrogen receptor signaling (Suiko et al., 2005; Kapoor et al., 2007). The expression and activity of SULT1E1 are intricately regulated by nuclear receptors, including the pregnane X receptor (PXR), constitutive androstane receptor (CAR), and peroxisome proliferator-activated receptors (PPARs), which allow the enzyme to adapt to metabolic and xenobiotic challenges (Barbosa et al., 2019). However, the function of SULT1E1 can be compromised by various factors, such as genetic polymorphisms, oxidative stress, and direct inhibition by endocrine-disrupting compounds (EDCs). For instance, hydroxylated metabolites of polyhalogenated aromatic hydrocarbons (PHAHs) and polychlorinated biphenyls (PCBs) have been shown to inhibit SULT1E1, potentially increasing the bioavailability of estrogens and disrupting hormonal balance (Kester et al., 2002; Parker et al., 2016). This inhibition can occur at nanomolar concentrations, indicating a potent effect even at low exposure levels (Parker et al., 2016). Furthermore, the overlapping substrate selectivity among sulfotransferases means that inhibitors or enhancers of one isoform can affect others, complicating the enzyme's regulatory dynamics (James & Ambadapadi, 2013). The sulfation of estrogenic drugs like ethinyl estradiol by SULT1E1 also highlights its role in drug metabolism, with SULT1E1 being a low Km isoform, indicating high affinity and efficiency in catalyzing these reactions (Schrag et al., 2004). Disruptions in SULT1E1 activity, therefore, not only affect the detoxification of environmental estrogens but also have broader implications for drug metabolism and endocrine function, underscoring the enzyme's critical role as a defensive gatekeeper against chemical insults (Reinen & Vermeulen, 2014).

III. Bisphenol A (BPA): Ubiquitous Exposure and Molecular Mechanisms of SULT1E1 Disruption

Bisphenol A (BPA) is a pervasive industrial chemical used extensively in the production of polycarbonate plastics and epoxy resins, which are integral to a wide array of consumer products such as food storage containers, water bottles, and the linings of food and beverage cans (Bernardo et al., 2015; Aguilar et al., 2007.). Despite its industrial utility, BPA is a known endocrine disruptor, capable of mimicking estrogen and interfering with hormonal functions, which raises significant health concerns (Haripriya & Sendhilvadivu, 2021; Rasheed, 2014).

Biomonitoring studies have consistently detected BPA in human biological samples, including urine, blood, and even fetal tissues, indicating widespread and continuous exposure across various demographics (Betts, 2010; Mørck, 2011). The primary route of human exposure is dietary, as BPA can leach into food and beverages from packaging materials, posing a risk of prolonged low-dose exposure (Almeida et al., 2018; Donderis & Saldaña, 2025). Although regulatory agencies have established tentative daily intake limits, such as the European Food Safety Authority's Tolerable Daily Intake (TDI) of 0.05 mg/kg body weight, biomonitoring data often reveal exposure levels that challenge these regulatory assumptions (Aguilar et al., 2007). For instance, studies have shown that BPA concentrations in human blood serum can exceed levels predicted by toxicokinetic models, suggesting that current regulatory frameworks may underestimate actual exposure and associated risks (Betts, 2010). Furthermore, children and adolescents are particularly vulnerable, with studies indicating higher BPA levels in these groups compared to adults (Hartmann et al., 2016; Betts, 2010). The potential health impacts of BPA exposure are diverse, ranging from reproductive and developmental issues to metabolic disorders and cancer, necessitating ongoing research and possibly stricter regulatory measures to mitigate exposure and protect public health (Rasheed, 2014; Donderis & Saldaña, 2025).

BPA have endocrine-disrupting properties, primarily due to its ability to mimic estrogen and bind to estrogen receptors (ERα and ERβ) with lower affinity than estradiol (Calivarathan & Maniradhan, 2022; Sonavane, 2022; Bulzomi et al., 2011). Despite this lower affinity, BPA can activate estrogen-responsive genes and influence cellular processes such as proliferation, differentiation, and apoptosis, which are critical in various health disorders, including reproductive abnormalities and metabolic syndromes (Calivarathan & Maniradhan, 2022; Bulzomi et al., 2011). BPA's endocrine-disrupting effects are not limited to classical estrogen receptor pathways; it also engages non-classical pathways, such as membrane ER interactions that trigger rapid estrogenic signaling and activate cellular kinase systems (Sonavane, 2022). This multifaceted interaction with estrogen receptors allows BPA to exert significant biological effects even at low concentrations, sometimes with potency comparable to natural estrogens (Barrett, 2014; Ben-Jonathan & Steinmetz, 1998). Furthermore, BPA's interference with estrogen metabolism at the enzymatic level is notable, as it is primarily detoxified in the liver through Phase II glucuronidation and sulfation, involving enzymes such as SULT1A1 and SULT1E1 (Calivarathan & Maniradhan, 2022). This metabolic interference can lead to altered hormone concentrations and disrupted cellular homeostasis, contributing to various health issues, including obesity, insulin resistance, and reproductive disorders (Calivarathan &

Maniradhan, 2022; Yukta et al., 2025; Manzoor et al., 2022). The widespread presence of BPA in consumer products and its ability to leach into the environment underscore the importance of understanding its toxicological impacts and the need for safer alternatives (Yukta et al., 2025; İyİgÜndoĞdu et al., 2019). Given the complexity of BPA's mechanisms of action, further research is essential to elucidate its full range of effects and to develop strategies to mitigate its impact on human health (Manzoor et al., 2022; Yoon et al., 2014).

Bisphenol A (BPA) interacts with sulfotransferase 1E1 (SULT1E1) in a manner that significantly impacts estrogen metabolism, acting both as a substrate and an inhibitor, which can lead to endocrine disruption. BPA competes with endogenous estradiol for the active site of SULT1E1, potentially inhibiting the enzyme's activity and reducing the sulfation capacity for both BPA and natural estrogens. This dual role of BPA is supported by studies showing that BPA can inhibit the normal metabolism of estradiol, as evidenced by the blockage of oestrone sulfate formation in embryonic development models, suggesting that BPA exposure can lead to inappropriate estrogen signaling and retention of active estrogens (Clairardin et al., 2013). Additionally, BPA's inhibitory effects on SULT1E1 are similar to those observed with other environmental pollutants, such as hydroxylated polychlorinated biphenyls (OH-PCBs), which also inhibit SULT1E1 and SULT2A1, leading to increased bioavailability of estrogens and potential endocrine disruption (Parker et al., 2016; Kester et al., 2002). The inhibition of SULT1E1 by BPA and similar compounds can result in a state of functional hyperestrogenemia, as the reduced sulfation capacity prolongs the half-life of active estrogens, exacerbating their effects even in the presence of normal ovarian estrogen production (Duffel, 2024). This mechanism is further supported by molecular docking studies that demonstrate BPA's ability to bind to estrogen receptors, mimicking estrogenic activity and potentially hindering natural hormone binding (Diptendu et al., 2024). The inhibition of SULT1E1 by BPA and its metabolites, therefore, provides a plausible explanation for the endocrine pathologies associated with chronic, low-level BPA exposure, highlighting the enzyme's critical role in maintaining estrogen homeostasis and the potential for BPA to disrupt this balance (Cole et al., 2010).

IV. The Emerging Role of SULT1E1 in PCOS Pathophysiology and Infertility

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder affecting women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic

ovarian morphology. The etiology of PCOS is complex, involving genetic, metabolic, and environmental factors, with recent attention on the role of endocrine disruptors like bisphenol A (BPA) in its pathogenesis. BPA is an environmental chemical that can interfere with hormonal functions, and its association with PCOS has been supported by both mechanistic and epidemiological evidence. Women with PCOS have been found to have higher serum BPA levels compared to controls, which correlates with hormonal and metabolic disturbances such as insulin resistance and hyperandrogenism (Hu et al., 2018; Amin et al., 2023). The dysfunction of the enzyme SULT1E1, which is involved in estrogen metabolism, has been hypothesized as a mechanism by which BPA contributes to PCOS pathogenesis. This enzyme dysfunction may exacerbate the hyperandrogenic state characteristic of PCOS (Reger-Tan & Führer-Sakel, 2015). Furthermore, studies have shown that BPA exposure is linked to various gynecological complications, including infertility and abnormal uterine bleeding, as well as metabolic issues like diabetes and hypertension in women with PCOS (Amin et al., 2023). The multifactorial nature of PCOS, involving genetic predispositions and environmental exposures, underscores the need for comprehensive management strategies that address both lifestyle and environmental factors (Bashir et al., 2025; Hajam et al., 2024). Despite the growing body of evidence, further research is needed to fully elucidate the role of BPA and other environmental factors in PCOS, which could lead to more targeted and effective interventions for affected women (Hu et al., 2018; Hajam et al., 2024).

The pathophysiological cascade initiated by Bisphenol A (BPA) exposure, particularly its impact on SULT1E1 activity in the liver and ovary, is a significant concern in understanding its role in reproductive disorders such as polycystic ovary syndrome (PCOS). BPA, a well-known endocrine disruptor, mimics estrogen and disrupts hormonal signaling pathways, leading to elevated levels of free estradiol and estrone due to impaired estrogen sulfation. This hormonal imbalance disrupts the hypothalamic-pituitary-ovarian (HPO) axis, altering the pulsatile secretion of gonadotropin-releasing hormone (GnRH) and favoring a sustained increase in luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) (Reetuparna et al., 2021; Samova & Doctor, 2025). Elevated LH levels overstimulate ovarian theca cells, resulting in excessive androgen synthesis, a condition known as hyperandrogenism, which is a hallmark of PCOS (Akin et al., 2015; Pivonello et al., 2020). Concurrently, the altered estrogen-to-androgen ratio and direct effects on folliculogenesis contribute to follicular arrest, anovulation, and the formation of multiple small cysts, characteristic of PCOS (Ptak et al., 2017; Pandey et al., 2024). BPA's interference with ovarian granulosa cell steroidogenesis

further exacerbates these conditions by disrupting the synthesis of steroid hormones, including progesterone and estradiol, and affecting the expression of genes related to steroid hormone synthesis (Téteau et al., 2023; Shi et al., 2021). Additionally, BPA exposure has been linked to oxidative stress and inflammation within the ovary, which can impair oocyte quality and contribute to the pathogenesis of PCOS (Pandey et al., 2024; Kania et al., 2024). The pervasive presence of BPA in consumer products and its potential for long-term reproductive health effects underscore the need for strategies to minimize exposure and further research into its mechanisms of action (Samova & Doctor, 2025; Kania et al., 2024). Overall, the evidence suggests that BPA plays a significant role in disrupting the HPO axis and ovarian function, contributing to the development of PCOS-like symptoms (Reetuparna et al., 2021; Palioura et al., 2014).

SULT1E1 dysfunction in polycystic ovary syndrome (PCOS) contributes to a complex interplay of hormonal imbalances that exacerbate reproductive dysfunctions, including infertility. PCOS is characterized by hyperandrogenism, anovulation, and metabolic disturbances such as insulin resistance, which collectively impair fertility (Jahan & Wing, 2020; Deuro et al., 2022). The hyperandrogenic environment in PCOS not only disrupts ovulation but also affects endometrial receptivity, a critical factor for successful embryo implantation (Jiang & Li, 2021; Yusuf et al., 2023). Elevated androgen levels alter the expression of key molecular markers of endometrial receptivity, such as αvβ3 integrin and glycodelin, leading to a less favorable environment for embryo implantation (Giudice & Lessey, 2008). Additionally, insulin resistance, a common feature in PCOS, further impairs endometrial function by inhibiting normal decidualization processes (Giudice & Lessey, 2008). This hormonal milieu also affects cervical mucus quality, hindering sperm transport and further complicating conception (Deuro et al., 2022). The interplay between hyperandrogenism, insulin resistance, and chronic inflammation creates a vicious cycle that perpetuates reproductive dysfunctions in PCOS (Deuro et al., 2022; Kicińska et al., 2023). Environmental factors and xenobiotic compounds may exacerbate these metabolic and hormonal imbalances, suggesting a potential link between environmental exposures and the pathophysiology of PCOS (Bhalerao & Aranha, 2021). While lifestyle modifications and pharmacological interventions, such as insulin-sensitizing agents, can improve ovulation and endometrial receptivity, the complex nature of PCOS-related infertility necessitates a multifaceted treatment approach (Kumari, 2025; Kicińska et al., 2023). Understanding the molecular

mechanisms underlying these dysfunctions, including the role of SULT1E1, could provide new therapeutic targets to improve fertility outcomes in women with PCOS (Kicińska et al., 2023).

V. SULT1E1 in Hormone-Sensitive Cancers: Breast and Endometrial Cancer

In estrogen-responsive tissues, the balance between estrogen activation and inactivation is crucial for regulating cellular proliferation, and its dysregulation can lead to carcinogenesis. SULT1E1, an estrogen sulfotransferase, plays a significant tumor-suppressive role by maintaining low intracellular concentrations of bioactive estradiol through sulfation, which inactivates estrogens by converting them into sulfated forms that cannot bind to estrogen receptors (Falany et al., 2002; Suzuki et al., 2003). In normal breast and endometrial tissues, SULT1E1 expression is robust, effectively keeping estrogen-driven proliferation in check (Xu et al., 2012; Falany et al., 2002). However, in many hormone-dependent cancers, there is a shift towards estrogenic activation, often characterized by reduced SULT1E1 expression, which correlates with increased tumor growth and poor prognosis (Paré et al., 2009). Studies have shown that overexpression of SULT1E1 in breast cancer cells inhibits proliferation, induces apoptosis, and suppresses tumor growth by activating PPARγ and downregulating oncogenic factors such as c-myc and cyclin D1 (Xu et al., 2018). Furthermore, SULT1E1 expression is inversely correlated with tumor size and lymph node status, suggesting its potential as a prognostic marker (Suzuki et al., 2003). The enzyme's expression is also regulated by oxidative stress and redox-dependent pathways, which may offer therapeutic targets for modulating its activity in cancer treatment (Nazmeen et al., 2020). Despite its tumor-suppressive role, the expression of SULT1E1 varies significantly across different tumors, indicating a complex regulatory mechanism that might involve interactions with other metabolic pathways and factors such as steroid sulfatase (STS), which counteracts SULT1E1 by converting inactive estrogen sulfates back to active forms (Wang et al., 2023; Paré et al., 2009). Therefore, understanding the regulation and function of SULT1E1 in estrogen metabolism is critical for developing strategies to manage hormone-dependent cancers effectively.

In breast cancer, the downregulation of estrogen sulfotransferase (SULT1E1) and the upregulation of steroid sulfatase (STS) create a biochemical environment conducive to the proliferation of estrogen receptor (ER)-positive cancer cells. SULT1E1 is responsible for the sulfation and inactivation of estrogens, converting them into their inactive sulfate forms, thereby reducing their ability to stimulate cancer cell growth (Secky et al., 2013; Wang et al., 2023). Conversely, STS hydrolyzes these inactive sulfates back into active estrogens, thus

promoting tumor progression (Suzuki et al., 2003; Paré et al., 2009). The imbalance between these two enzymes, particularly a low SULT1E1:STS ratio, is increasingly recognized as a poor prognostic indicator in breast cancer (Secky et al., 2013). Studies have shown that SULT1E1 expression is significantly lower in breast cancer tissues compared to adjacent normal tissues, correlating with a worse prognosis and higher recurrence rates (Falany et al., 2002). In contrast, STS is often overexpressed in breast cancer, further exacerbating the availability of active estrogens and contributing to tumor growth (Paré et al., 2009; Sasano et al., 2009). The expression of SULT1E1 is also influenced by various factors, including the proliferation state of cells, which can modulate its expression and, consequently, the growth and therapeutic response of tumors (Fu, 2011; Fu et al., 2010). Therapeutic strategies targeting these pathways, such as the use of STS inhibitors, are being explored to reduce active estrogen levels and potentially improve clinical outcomes in patients with hormone-dependent breast cancers (Secky et al., 2013; Sasano et al., 2009). The regulation of estrogen metabolism through SULT1E1 and STS is crucial in the pathophysiology of breast cancer, and their expression levels serve as important molecular markers for prognosis and potential therapeutic targets (Suzuki et al., 2003; Xu et al., 2012).

The role of progesterone and its receptor (PR) in endometrial cancer is multifaceted, involving genetic, hormonal, and environmental factors. Progesterone acts as a natural inhibitor of endometrial carcinogenesis by opposing estrogen-driven proliferation and inducing differentiation through its receptor, PR (Kim & Chapman-Davis, 2010; Yang et al., 2011). However, in endometrial hyperplasia and carcinoma, the loss of progesterone opposition is often observed, which can be attributed to diminished expression of SULT1E1, an enzyme that counterbalances estrogen's effects by sulfating and inactivating it (Rebbeck et al., 2006). Genetic polymorphisms in the SULT1E1 gene, such as the G → A variant in its promoter, have been associated with increased endometrial cancer risk, highlighting the importance of its genetic integrity (Rebbeck et al., 2006). Additionally, polymorphisms in the progesterone receptor gene, such as rs11224561 and +331G/A, have been linked to increased endometrial cancer risk, suggesting that genetic variations can influence the effectiveness of progesterone in opposing estrogen's effects (O'Mara et al., 2011; Vivo et al., 2002). Environmental factors, such as exposure to bisphenol A (BPA), may further inhibit SULT1E1, exacerbating the risk of unopposed estrogenic stimulation and subsequent carcinogenesis (Rebbeck et al., 2006). The convergence of these genetic, epigenetic, and environmental factors underscores the complexity of endometrial cancer pathogenesis and the critical role of SULT1E1 and

progesterone receptor pathways in its development and progression. Understanding these interactions provides a basis for potential therapeutic strategies, such as combining progestins with epigenetic modulators to enhance PR expression and improve treatment outcomes in endometrial cancer (Yang et al., 2014).

VI. SULT1E1 and Systemic Metabolic Disorders

SULT1E1 dysfunction, which affects estrogen metabolism, has significant implications for systemic metabolism, influencing conditions such as thyroid dysfunction, insulin resistance, and diabetes through complex hormonal interactions. Estrogen plays a crucial role in modulating glucose and lipid metabolism, impacting insulin secretion, sensitivity, and adipose tissue function. It facilitates insulin secretion and controls glucose availability, while also modulating energy partitioning to favor lipid use over carbohydrates when available, thus maintaining energy homeostasis (Alemany, 2021; Kim et al., 2014). Estrogen's influence extends to adipose tissue, where it regulates development and improves systemic glucose homeostasis, potentially mitigating obesity-related metabolic disorders (Kim et al., 2014). Furthermore, estrogen and thyroid hormone pathways exhibit significant cross-talk. Estrogen can affect the expression and activity of deiodinase enzymes, which are responsible for converting thyroxine (T4) to the active triiodothyronine (T3), thereby influencing thyroid hormone homeostasis (McGregor, 2015). This interaction is crucial as thyroid hormones themselves play a role in glucose homeostasis by affecting pancreatic β-cell development and glucose metabolism across various organs (Eom et al., 2022). The interplay between estrogen and thyroid hormones underscores the complexity of hormonal regulation in metabolic processes, where estrogen's modulation of deiodinase activity can impact thyroid function and, consequently, glucose metabolism. Additionally, estrogen's protective role against insulin resistance, a component of metabolic syndrome, highlights its importance in maintaining metabolic health, with deficiencies in estrogen signaling linked to increased risks of metabolic disorders (Faulds et al., 2012; Paoli et al., 2021). This intricate hormonal interplay suggests that disruptions in estrogen metabolism, such as those caused by SULT1E1 dysfunction, can have widespread effects on systemic metabolism, contributing to the development of metabolic diseases (Mauvais-Jarvis, 2012).

The inhibition of SULT1E1, leading to hyperestrogenemia, can indeed have significant metabolic consequences, including the suppression of type 2 deiodinase (DIO2) activity, which

is crucial for the conversion of thyroxine (T4) to the active thyroid hormone triiodothyronine (T3). This suppression can result in a hypothyroid-like state characterized by reduced T3 production, weight gain, fatigue, and a decreased basal metabolic rate, as DIO2 is a major source of plasma T3 in euthyroid humans and plays a critical role in maintaining thyroid hormone homeostasis (Maia et al., 2005; Castagna et al., 2017). Elevated estrogen levels can also disrupt insulin signaling pathways. In pancreatic β-cells, chronic estrogenic overstimulation initially enhances insulin secretion but can eventually lead to β-cell exhaustion and apoptosis, contributing to insulin resistance and metabolic dysfunction (Mauvais-Jarvis et al., 2013). In peripheral tissues such as muscle and fat, altered estrogen signaling can impair the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which is essential for the translocation of glucose transporter 4 (GLUT4) and subsequent glucose uptake, further exacerbating insulin resistance (Mauvais-Jarvis et al., 2013). This disruption in glucose homeostasis is compounded by the role of thyroid hormones in energy expenditure and metabolic efficiency, where a decrease in T3 due to impaired DIO2 activity can lead to decreased energy expenditure and a hypothyroid-like metabolic state (Yehuda-Shnaidman et al., 2012; Araujo & Carvalho, 2011). Additionally, the interplay between estrogen and thyroid hormone metabolism is complex, as estrogen deficiency itself can promote metabolic dysfunction, predisposing individuals to obesity and type 2 diabetes, highlighting the intricate balance required for maintaining metabolic health (Mauvais-Jarvis et al., 2013). The inhibition of SULT1E1 and the resulting hyperestrogenemia can have profound effects on both thyroid hormone metabolism and insulin signaling, leading to significant metabolic disturbances.

The relationship between metabolic disruptions and reproductive disorders such as polycystic ovary syndrome (PCOS) is increasingly understood through the lens of environmental factors, particularly the role of endocrine-disrupting chemicals (EDCs) like Bisphenol A (BPA). BPA is implicated in the pathogenesis of PCOS due to its ability to mimic estrogen and bind to estrogen receptors, thereby disrupting hormonal balance and metabolic processes. This disruption is evident in the clinical clustering of PCOS with insulin resistance, metabolic syndrome, and an elevated risk of type 2 diabetes, suggesting a common upstream cause linked to environmental insults (Palioura & Diamanti-Kandarakis, 2015; Palioura et al., 2014; Hussain, 2024). The BPA-SULT1E1 axis provides a plausible explanatory model, where BPA exposure leads to hormonal imbalances that affect ovarian function and concurrently seed metabolic dysfunction. This is supported by evidence showing elevated BPA levels in women with PCOS, which correlate with hyperandrogenemia and metabolic abnormalities such as

insulin resistance and obesity (Palioura & Diamanti-Kandarakis, 2015; Mukhopadhyay et al., 2022). Animal studies further corroborate these findings, demonstrating that BPA exposure can impair folliculogenesis and insulin signaling, contributing to the PCOS phenotype (Hussain, 2024; Calivarathan & Maniradhan, 2022). The systemic impact of BPA is also reflected in its interaction with adipose tissue, promoting adipogenesis and lipid accumulation, which exacerbates metabolic disorders (Calivarathan & Maniradhan, 2022). Moreover, the multifactorial nature of PCOS, involving genetic predispositions and environmental factors, underscores the complexity of its pathophysiology, where BPA acts as an environmental modifier that can exacerbate symptoms in genetically susceptible individuals (Palioura et al., 2014; *Rutkowska* et al., 2016). This highlights the need for further research into the precise mechanisms by which BPA and other EDCs influence both reproductive and metabolic pathways, potentially guiding targeted prevention and intervention strategies (Yin et al., 2025; Lubrano et al., 2015).

VII. Diagnostic and Therapeutic Perspectives

SULT1E1, a key enzyme in estrogen metabolism, plays a significant role in the pathogenesis of various diseases, making it a promising candidate for both diagnostic and therapeutic applications. As a biomarker, SULT1E1 expression levels can provide insights into the estrogen inactivation capacity, which is crucial for stratifying risk in estrogen-dependent diseases such as polycystic ovary syndrome (PCOS) and hormone-sensitive cancers. For instance, in lung adenocarcinoma (LUAD), reduced SULT1E1 expression correlates with disease progression and poor prognosis, suggesting its potential as a diagnostic marker for LUAD (Wang et al., 2025). Similarly, in breast cancer, SULT1E1 inhibits tumor growth and invasion by activating PPARγ, highlighting its tumor suppressor role and therapeutic potential (Xu et al., 2018). However, challenges such as tissue-specific expression patterns and the lack of standardized assays complicate its clinical application. The expression of SULT1E1 varies significantly across different tumors, indicating a dual role in both inhibiting and promoting tumor growth, which necessitates a nuanced understanding of its function in various contexts (Wang et al., 2023). Moreover, genetic polymorphisms in SULT1E1 can affect its enzymatic activity, potentially influencing the pathophysiology of estrogen-dependent diseases and the metabolism of exogenous estrogens (Adjei et al., 2003). The inhibition of SULT1E1 by certain drugs, such as ziritaxestat, further complicates its role in drug interactions, particularly in the metabolism of estrogens like 17α-ethinyl estradiol (Rodrigues et al., 2023). Additionally, the

sulfatase pathway, involving SULT1E1, is crucial in the local production of active estrogens in tissues, impacting the progression of hormone-associated tumors (Secky et al., 2013). Despite these complexities, the potential of SULT1E1 as a biomarker and therapeutic target remains significant, provided that future research addresses these challenges and establishes clinically relevant thresholds for its expression and activity.

Therapeutic strategies targeting the restoration of sulfation's protective function in hormone-dependent cancers have shown promise, particularly through the inhibition of steroid sulfatase (STS). STS is crucial in converting inactive sulfated estrogens into active forms, which are implicated in the progression of estrogen-dependent cancers such as breast and endometrial cancers (Anbar et al., 2021; Secky et al., 2013). Irosustat, a first-generation STS inhibitor, has demonstrated efficacy in clinical trials for these cancers, offering a novel approach to endocrine therapy by preventing the reactivation of estrogens (Palmieri et al., 2011; Sadozai, 2013). The development of STS inhibitors has been extensive, with Irosustat being the most advanced, having completed phase I/II trials and showing potential in treating not only breast cancer but also prostate and endometrial cancers (Foster, 2021; Purohit & Foster, 2012). The mechanism of STS inhibitors involves blocking the sulfatase pathway, thereby reducing active estrogen levels and potentially overcoming resistance to traditional endocrine therapies (Secky et al., 2013; Iwamori, 2005). Additionally, dual-targeting compounds, such as dual aromatase-sulfatase inhibitors (DASI), are being explored to enhance therapeutic efficacy and address resistance mechanisms (Sadozai, 2013; Morozkina & Shavva, 2019). Another promising strategy involves the upregulation or activation of SULT1E1, the enzyme responsible for converting active estrogens back to their inactive sulfated forms. Natural compounds like resveratrol and quercetin, which activate transcription factors such as Nrf2 and PPARγ, are being investigated for their potential to enhance SULT1E1 expression, although their broad effects necessitate careful evaluation (Secky et al., 2013). These approaches collectively represent a significant advancement in the treatment of hormone-dependent cancers, offering new avenues for therapy that could complement existing treatments and improve patient outcomes.

VIII. Conclusion and Future Directions

This review has synthesized evidence positioning estrogen sulfotransferase (SULT1E1) as far more than a mere metabolic enzyme; it is a critical gatekeeper at the interface between environment and endocrinology. Its function in sulfating and inactivating both endogenous

estrogens and exogenous xenoestrogens like BPA is essential for maintaining hormonal homeostasis. Compromise of this function—through genetic variation, epigenetic silencing, or direct inhibition by EDCs—emerges as a plausible unifying mechanism contributing to the pathogenesis of a spectrum of diseases, including PCOS, infertility, hormone-sensitive cancers, and metabolic disorders.

The story of SULT1E1 underscores a fundamental principle of modern environmental health: widespread chemical exposures can hijack ancient metabolic pathways to drive contemporary chronic diseases. This is particularly relevant for regions like India, experiencing rapid industrialization and plastic use, where BPA exposure may be high and regulatory enforcement faces challenges. Future research must move from association to causation and translation. Key priorities include: conducting large-scale longitudinal studies to correlate SULT1E1 activity metrics with disease incidence; developing sensitive, non-invasive methods to assess SULT1E1 function *in vivo*; and exploring safe pharmacologic or nutraceutical means to modulate its activity.

Ultimately, safeguarding SULT1E1 function requires a dual approach: advancing personalized medical strategies for those already affected and implementing stronger, science-based public health policies to reduce population-wide exposure to disruptive chemicals like BPA. By protecting this metabolic gatekeeper, we may take a significant step toward preventing the complex, interlinked disorders that define much of today's global non-communicable disease burden.

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