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Review Article

ENDOCRINE-DISRUPTING CHEMICALS AND REPRODUCTIVE TOXICITY: MOLECULAR MECHANISMS, ENVIRONMENTAL EXPOSURE, AND EMERGING EVIDENCE FROM ISOBUTYL PARABEN AND PHENYLMERCURIC ACETATE

Neelakanth S. Wali[1], Vishwajit B Darekar[2*]

[1]Department of Zoology, M.S.I. Degree College, Kalaburagi-585102, Karnataka, India.
[2*]Department of P.G. Studies and Research in Zoology, Sharnbasva University, Kalaburagi- 585103, Karnataka, India

Abstract

Endocrine-disrupting chemicals (EDCs) represent a diverse group of natural and synthetic substances capable of interfering with endocrine signaling and consequently affecting reproduction, development, metabolism, immunity and other physiological processes. Increasing evidence indicates that exposure to EDCs may occur through food, water, air, consumer products, occupational environments and contaminated ecosystems, with particular concern regarding exposure during sensitive developmental periods. This review summarizes the current understanding of the mechanisms, environmental exposure and reproductive consequences of EDCs, with particular emphasis on isobutyl paraben (IBP) and phenylmercuric acetate (PMA). EDCs can interfere with hormone synthesis, secretion, transport, metabolism and receptor-mediated signaling, thereby altering hypothalamic–pituitary–gonadal and other endocrine pathways. The review further examines the environmental occurrence, physicochemical characteristics, exposure routes and toxicological properties of IBP, a paraben preservative widely associated with personal-care and pharmaceutical products. Available evidence indicates that parabens may exert estrogenic and antiandrogenic activities and may interfere with steroid-metabolizing enzymes, reproductive development and gametogenesis. The review also evaluates PMA, an organomercury compound, with emphasis on oxidative stress, mitochondrial dysfunction, apoptosis, endocrine dysregulation, steroidogenesis and reproductive tissue injury. Experimental evidence indicates that mercury-related oxidative damage may contribute to impaired sperm quality, altered reproductive hormone profiles and histopathological changes in reproductive organs. The review highlights important knowledge gaps, including low-dose and chronic exposure, mixture effects, species-specific responses, developmental and transgenerational consequences, and limited human epidemiological evidence for some individual chemicals. Emerging approaches involving biomonitoring, omics technologies, computational toxicology, human-relevant in vitro models and artificial intelligence may improve the identification and characterization of EDCs. An integrated One Health approach combining human, animal and environmental perspectives is essential for improved risk assessment, exposure reduction and development of safer chemical alternatives.

Key Words: Endocrine-disrupting chemicals; reproductive toxicity; endocrine disruption; isobutyl paraben; phenylmercuric acetate; oxidative stress; steroidogenesis; reproductive health; environmental exposure; endocrine signaling.

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1. Introduction

Endocrine-Disrupting Compounds (EDCs)

Endocrine Disrupting Chemicals (EDCs) are a group of chemicals that can mock our own hormones secreted by various glands and also interfere with the endocrine system of people and wildlife. These EDCs can disturb the proper development and leads to a wide range of disorders: from birth defects, reproductive disorders and even may cause some cancers. More than 800 hundred chemicals are identified and suspected as EDCs by various researchers. They can be a part of food chain and also be found in thousands of other products WHO (2013). Some of the known endocrine-disrupting chemicals (EDCs) includes PCB, DDT, PBDE and some phthalates of cosmetics. Although there is no commonly accepted criteria avialable for the identification of EDCs are yet available.

Endocrine disrupting compounds (EDCs) are the broad class of naturally occurring or synthetic chemicals which interfere with the normal functioning of the endocrine system, affecting synthesis of hormones, release, transport, binding, action and also the elimination (Zoeller et. al, 2012). Because hormones regulate critical processes such as metabolism, reproduction, development and behaviour, EDCs can lead to some negative health effects outcomes in both human beings and wildlife—even at very low concentrations. According to few reports of the World Health Organization (WHO, 2013), about 800 chemicals are identified as suspected EDCs. They have been linked to a extensive range of diseases like infertility, cancer, metabolic disorders and neurodevelopmental abnormalities. In particular, developmental exposure to EDCs during most sensitive life stages—prenatal, neonatal and pubertal periods can lead to long-lasting and sometimes transgenerational effects.

Mechanism of action of EDCs

The endocrine system controls various physiological processes through feedback loops that involve the central nervous system (CNS), the pituitary gland and specific target organs. Endocrine-disrupting chemicals (EDCs) can disturb these processes by altering hormone synthesis, storage, transport or their interaction with receptors (Figure 1.10).

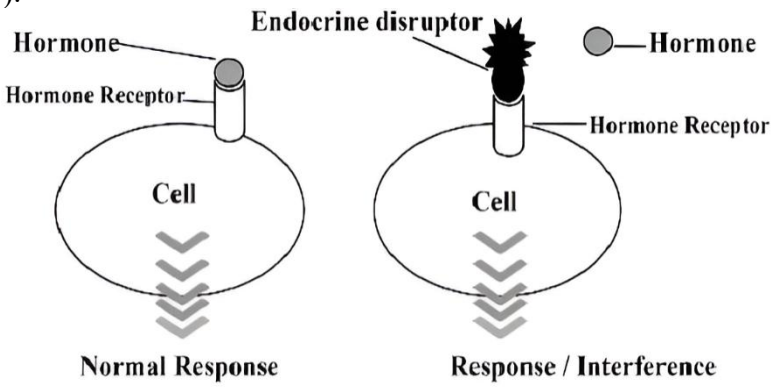

Figure 2.1: Mechanism of action of EDCs. (Hrouzkova, S. and Matisova, E., 2012).

Effect of EDCs on hormone synthesis

Several environmental chemicals have the capacity to interfere with the synthesis of key hormones. For example, the production of estrogen, an essential female reproductive hormone can be suppressed by exposure to aromatase inhibitors such as the fungicide fenarimol (Hirsch et. al, 1987; Vinggaard et. al, 2000). Additionally, gonadal steroids—and potentially environmental estrogens and androgens—can influence protein synthesis. Both estrogen and testosterone have been shown to directly affect the synthesis of pituitary hormones or indirectly through modifications in the glycosylation of luteinizing hormone (LH) and follicle-stimulating hormone

(FSH) (Wilson et. al, 1990). Consequently, any environmental compound that mimics or blocks the activity of these steroid hormones may disrupt normal glycosylation processes.

Effect of EDCs on Hormone Storage

Catecholamine hormones are normally stored in granular vesicles of chromaffin cells in the adrenal medulla as well as in presynaptic terminals of the central nervous system. This storage system is crucial for maintaining appropriate hormone levels so they can be released when needed. Steroid hormones, such as testosterone are synthesized by Leydig cells in the testes and are secreted upon activation of luteinizing hormone (LH) receptors. Therefore, chemicals that block LH receptors or inhibit the 3, 5-cyclic AMP (cAMP)-dependent signaling cascade involved in testosterone synthesis can significantly affect testosterone secretion. The release of many protein hormones relies on secondary messenger pathways, including cAMP, phosphatidylinositol-4, 5-bisphosphate, inositol-1, 4-triphosphate, tyrosine kinase and calcium signaling. Disruption of these pathways can alter circulating hormone concentrations. For example, numerous metal cations interfere with calcium flux, thereby impairing pituitary hormone release (Cooper et. al, 1987).

Effect of EDCs on hormone transport

In circulation, hormones are present either in a free state or bound to carrier proteins. Lipid-soluble hormones, such as estrogen and testosterone are mainly transported through the bloodstream by specific transport proteins produced in the liver including sex hormone-binding globulin (SHBG). The regulation of SHBG levels is critical, as changes in its concentration can directly influence the bioavailability of steroid hormones. Estrogen is known to elevate plasma SHBG levels, whereas androgens and glucocorticoids reduce them (Ingbar& Woeber, 1974).

Effect of EDCs on Hormone Receptor Recognition

Hormones bind to biological receptors to create their results to either intracellular receptors or receptors located on the cell membrane of target tissues. The specific interaction between a hormone and its receptor is a crucial step in mediating hormone action. Numerous environmental pollutants can cause problems this process by imitating natural ligands and functioning as agonists or by blocking receptor binding and thereby acting as antagonists. Compounds such as methoxychlor, kepone, DDT, polychlorinated biphenyls (PCBs) and alkylphenols (including nonylphenols and octylphenols) are well-documented disruptors of estrogen receptor (ER) signaling (Mueller & Kim, 1978; White et. al, 1994).

Bioaccumulation of EDCs

Endocrine-disrupting chemicals undergo bioaccumulation, leading to progressively higher concentrations within the food chain. Phytoplankton absorb these contaminants from water and small fish that feed on phytoplankton accumulate higher levels of EDCs. This accumulation continues at each trophic level, eventually causing physical abnormalities, impaired fertility and even mortality in top predators (Figure 1.11). EDCs are lipophilic, enabling them to persist and concentrate in fatty tissues of animals, including humans. Since humans occupy vulnerable to risk in their top position in the food chainelevated EDC levels. Furthermore, these chemicals degrade slowly and can remain in the body for years, leading to concentrations millions of times greater than those of natural hormones (Geyer et. al, 2000; Mato et. al, 2001; Pojanaet. al, 2007; Liu et. al, 2012; Salgueiro et. al, 2015).

Environmental Estrogen

Environmental estrogens, also referred to as xenoestrogens, are natural or synthetic compounds that imitate the biological activity of endogenous estrogens. Among the

various categories of endocrine disruptors, environmental estrogens have been the most extensively investigated (Figure 1.12). One of the most stable examples is diethylstilbestrol (DES), which was prescribed to pregnant women between the late 1940s and 1971 to prevent miscarriage. However, DES exposure was later associated with infertility and the development of vaginal adenocarcinomas in their daughters (Colborn et. al, 1993; Dietrich, 2010; Hoover et. al, 2011). Other instances include the recognition of higher vitellogenin levels in male rainbow trout exposed to wastewater from sewage treatment plants (Purdom et. al, 1994) and the feminization of male embryos in Western gulls linked to exposure to DDT and its metabolites in Southern California during the 1960s (Fry & Toone, 1981).

Sources of Environmental Estrogen

Human and wildlife exposure to environmental estrogenscomes from a variety of options, including contaminated food, air, water, soil and various household products (TABLE 2.1).

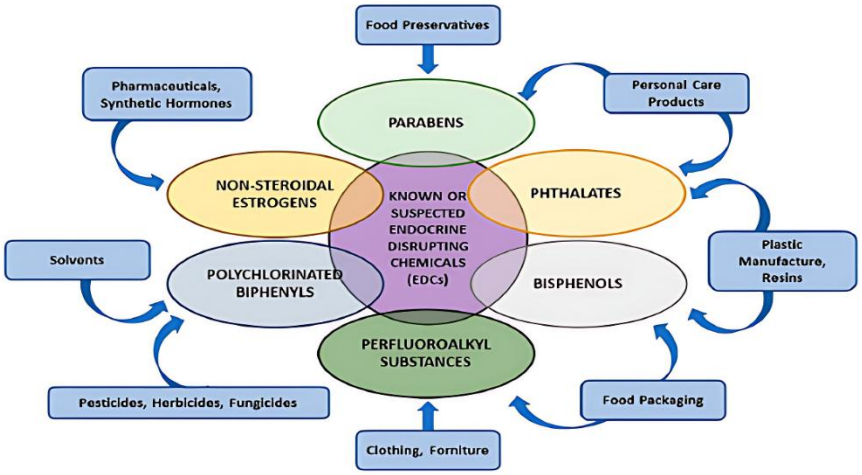

Figure 2.2: Most known Endocrine-Disrupting Chemicals (EDCs) Effects on Tumour

Classification and sources of Some Commonly Occurring EDCs

EDCs are chemically and structurally diverse and occur in multiple forms across different sectors:

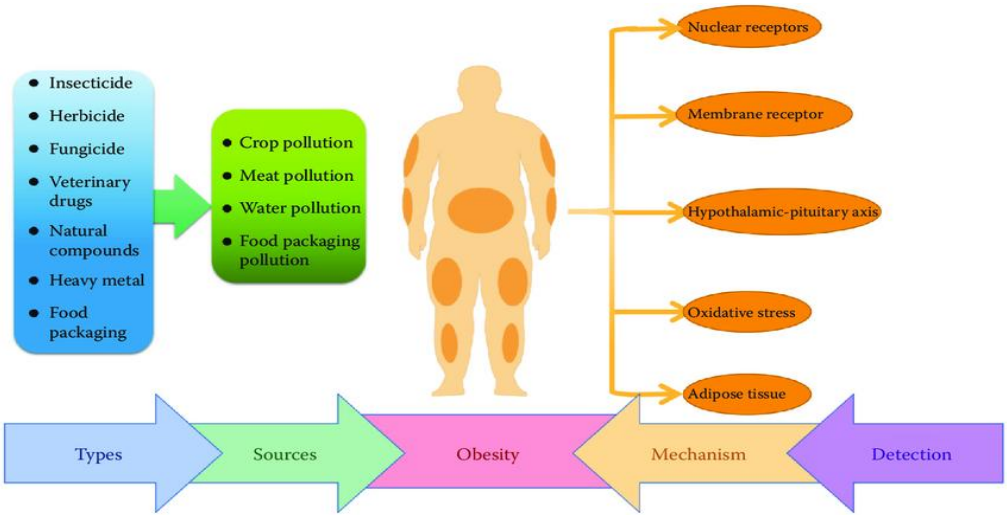

Figure 2.3: Endocrine disruptors in foods: Overlooked factors contributing to the prevalence of obesity

Table 2.1: Sources of Some Commonly Occurring EDCs

Chemical Class	Examples	Common Uses
Organochlorine pesticides	DDT, Endosulfan	Agriculture, vector control
Industrial chemicals	PCBs, Dioxins, PFAS	Electrical equipment, firefighting foam
Plasticizers	Phthalates, BPA	PVC products, food packaging, thermal paper
Pharmaceuticals	DES, Ethinylestradiol	Hormonal therapy, contraceptives
Personal care chemicals	Parabens, Benzophenones	Cosmetics, sunscreens
Heavy metals	Cadmium, Mercury, Lead	Batteries, paints, industrial emissions

Sonnenschein and Soto (1998), Vandenberg et. al, (2012) investigated the Environmental contamination occurs through wastewater discharge, agricultural runoff, landfill leachates and atmospheric deposition. EDCs have been spotted in air, water, food products, sediments and even in human breast milk, umbilical cord blood and adipose tissue (Figure 1.13).

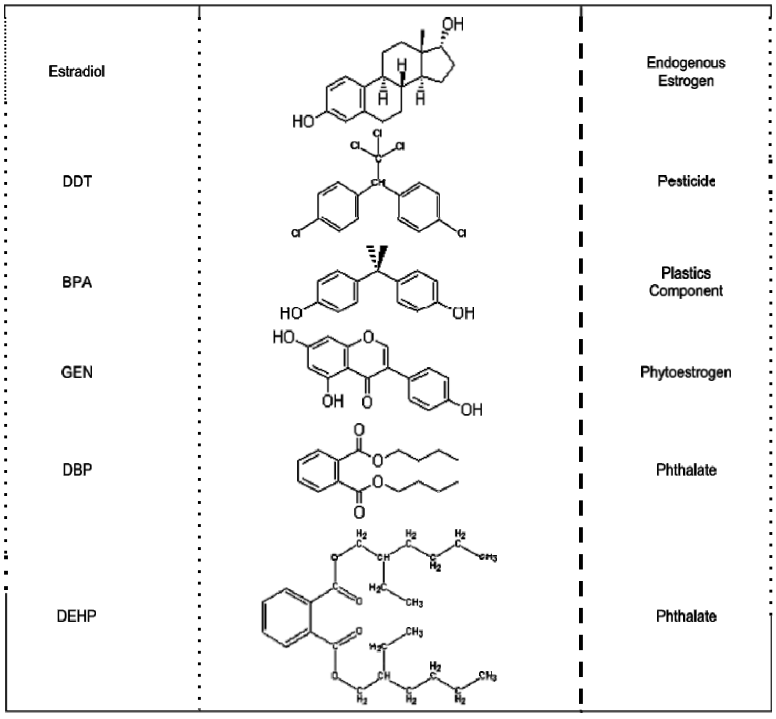

Figure 2.4: Chemical structures of selected environmental estrogens illustrating their structural resemblance to endogenous estrogen.

(Adapted from Patisaul & Adewale, 2009). Abbreviations: GEN – Genistein; DBP – Dibutyl phthalate; DEHP – Di(2-ethylhexyl) phthalate.

Reproductive and Developmental Toxicity

Endocrine Disrupting Chemicals had a strong connection to reproductive dysfunctions in both male and female:

Male reproductive effects

- **Decreased sperm quality:** Studies have shown that BPA, phthalates and pesticides

like DDE reduce sperm concentration and motility in both human being and also animals (Meeker et. al, 2008; Hauser et. al, 2007).

- **Hypospadias and cryptorchidism:** Prenatal exposure to estrogenic EDCs like DES has been related with malformations of the male reproductive tract.
- **Testicular dysgenesis syndrome (TDS):** A concept linking EDC exposure resulting in various disorders related to male reproductive system such as infertility, testicular cancer and hypospadias (Skakkebaek et. al, 2001).

Female reproductive effects

- Irregular estrous cycles: BPA and phthalates disrupt ovarian steroidogenesis, resulting in altered cycles and anovulation (Peretz et. al, 2014).
- Polycystic ovary-like symptoms: Developmental exposure to BPA and tributyltin leads to features resembling PCOS in rodents (Ziv-Gal and Flaws, 2016).
- Reduced fertility: Ovarian follicular development and uterine receptivity are affected in females exposed to organochlorine pesticides and heavy metals.

Transgenerational effects

Anway et. al, (2005) in their studies in rodents have demonstrated that EDCs like vinclozolin and methoxychlor can induce epigenetic changes in germ cells causing reproductive abnormalities in F2 and F3 generations.

Neuro developmental and Behavioral impacts

The developing brain is highly sensitive to hormonal cues. Disruption of thyroid or estrogen signaling during gestation can result in:

- Impaired learning, memory and attention (Braun et. al, 2011).
- Increased risk of autism spectrum disorders (ASDs): Elevated prenatal exposure to phthalates and PCBs is associated with neurodevelopmental delays (Lyall et. al, 2017).
- Altered sexual behavior and anxiety: Animal studies show masculinization of females and feminization of males after perinatal EDC exposure (Negri-Cesi, 2015).

Metabolic and Immune disorders

Metabolic disruption

Grun and Blumberg (2009) investigated that EDCs like organotins (e.g., tributyltin) and BPA have been identified as obesogens, promoting adipogenesis via activation of PPARγ and RXR receptors. Developmental exposure to obesogens can elevates the problems of childhood obesity and metabolic syndrome.

Thyroid function

Chemicals like perchlorate, PCBs and dioxins interfere with iodine uptake and thyroid hormone synthesis, leading to hypothyroidism and delayed brain development in children (Boas et. al, 2012).

Immune effects

In the study by EDCs Corsini et. al, (2014), impair immune function through altered cytokine production and antibody responses. For instance, phthalates suppress Th1-type immunity while dioxins promote autoimmune conditions in murine models.

Ecological consequences

EDCs are also a major threat to biodiversity:

- Causing feminization in male fish found in rivers which are contaminated with synthetic estrogens (Jobling et. al, 1998).
- Population collapses in alligators due to disrupted testosterone levels from pesticide exposure (Guillette et. al, 1994).
- Shell thinning and reduced hatchability in birds of prey due to DDT accumulation aquatic species are particularly vulnerable due to continuous exposure via effluents and

bioaccumulation.

Regulatory framework and challenges

Despite widespread evidence, regulating EDCs remains a challenge due to:

- Lack of standardized testing protocols.
- Diverse modes of action and low-dose effects.
- Difficulty in assessing mixture toxicity or cumulative exposure (Kortenkamp et. al, 2012).

The European Union has adopted a precautionary principle under REACH and the Biocidal Products Regulation, while the U.S. EPA's EDSP is being revised to incorporate in vitro and computational methods. Recently, the OECD has developed standardized test guidelines including the Hershberger assay, uterotrophic assay and extended one-generation reproductive toxicity studies.

Emerging research and future directions

- Microplastics and Nanoplastics: Act as carriers for EDCs, increasing exposure and potential bioavailability.
- Endocrine Disruption and Cancer: Associations are being explored between EDC exposure and some hormone-sensitized cancers like breast, ovarian, prostate and testicular cancer.
- One Health Perspective: Integration of human, animal and environmental health approaches is crucial to tackle EDC exposure holistically.
- Use of Omics and AI: High-throughput screening, transcriptomics and machine learning are aiding in the identification and prioritization of new EDCs.

Isobutyl Paraben

Isobutyl paraben (IBP) is a member of the paraben family chemicals which is the group of p-hydroxybenzoic acid esters widely utilized as antimicrobial preservatives. Chemically parabens are esters of para-hydroxybenzoic acid and IBP specifically belongs to the subgroup characterized by an isobutyl alkyl side chain differentiating it structurally and functionally from other parabens such as methylparaben or propylparaben (F. Alan Andersen, 2008). This ester configuration imparts specific physico chemical characteristics relevant to its preservative efficacy and toxicity profile. IBP is extensively used in cosmetic, personal care and various products of pharaniutical industry due to its wide range of antimicrobial properties. It serves as a preservative in formulations such as creams, lotions, shampoos and sunscreens, preventing microbial contamination and extending shelf life. The widespread use of IBP is corroborated by analyses indicating its presence in various cosmetic products in various types, including those thatskin-care items (F. Alan Andersen, 2008), (Nguyen, 2020).

Furthermore, regulatory assessments and formulation strategies continue to incorporate IBP either alone and also in association with other parabens to maintain efficient product preservation (Stevi, 2023). Given its pervasive use, there is growing scientific and public interest in characterizing IBP's toxicological profile. Exposure to this compound is essentially for consumers and workers involved in the production of personal care commodities. Concern is magnified by emerging evidence suggesting that parabens including IBP act as endocrine-disrupting chemicals (EDCs) can also intervene with hormone signaling pathways and reproductive functions (Bilal, 2020). Thus, studying IBP's toxicological potential, especially its general toxicity and effects on reproductive health, has become paramount.

Parabens as a Chemical Group and Their General Safety Profile

F. Alan Andersen (2008), reported the Parabens constitute one of the most common preservative groups employed worldwide, found in tens of thousands of consumer

products including cosmetics, pharmaceuticals and processed foods. Besides Parabens have antibiotic properties and valued for stability and low cost, contributing to their persistence in product formulations. The general consensus historically endorsed parabens as safe for use within regulated concentration limits, typically up to 0.4% for single parabens and 0.8% for mixtures containing IBP (F. Alan Andersen, 2008). These limits are established based on acute, sub-chronic and chronic toxicological studies in animals, which have demonstrated lower toxicity at permissible uses, with the majority of parabens showing minimal irritancy and sensitization potential in human (F. Alan Andersen, 2008). However, regulatory landscapes differ across jurisdictions concerning IBP usage.

The European Commission, for example, prohibits the use of IBP and some other longer alkyl-chain parabens in cosmetic products due to concerns about potential sensitization and endocrine-disrupting effects (Stevi, 2023). This contrasts with allowances for shorter-chain parabens such as methyl- and ethylparaben, which are often perceived as safer. These regulatory decisions reflect increasing caution in response to emerging scientific findings highlighting subtle biological effects at low-dose and chronic exposure levels. Public health concerns remain a driving force for rigorous toxicological reassessments, particularly for parabens like IBP that have been correlated with endocrine disruption and reproductive toxicity (Bilal, 2020). Research underscores the need to clarify the risks posed by cumulative exposure from multiple products, as well as potential vulnerable populations including infants and pregnant women. Such concerns motivate comprehensive evaluations of IBP's safety profile beyond traditional toxicological endpoints, examining mechanisms of action and long-term consequences at environmentally relevant dosages.

Chemical Properties and Environmental Fate of Isobutylparaben

Chemical structure and physicochemical properties

Isobutylparaben is structurally defined as the isobutyl ester of p-hydroxybenzoic acid. The paraben class shares a core para-hydroxybenzoate moiety, with variation in their ester side chains leading to distinct physical and biological properties (F. Alan Andersen, 2008). IBP's isobutyl side chain confers moderate lipophilicity relative to the shorter (methyl, ethyl) or longer alkyl-substituted (butyl, benzyl) parabens. This influences its affinity for biological membranes and consequent permeation capabilities. The physicochemical characteristics such as log P values impact both preservative action and bioaccumulation potential. Among parabens, those whose hydroxy stores are longer tend to show greater lipophilicity, enhanced penetration and a more prolonged presence in tissues (Manzetti, 2014). Such chemical attributes determine IBP's solubility, partitioning within biological and environmental compartments and metabolic fate. Understanding these properties is crucial to assess exposure risks and toxicokinetics in human.

Environmental Persistence and Degradation

IBP, like other parabens, enters wastewater systems predominantly through downstream disposal of personal care products. Wastewater treatment processes, including coagulation, flocculation and activated carbon adsorption have been shown to variably remove parabens (Eriksson, 2007). However, significant residual amounts of parabens including IBP can persist through conventional treatment, leading to environmental release. Parabens undergo biodegradation in aquatic environments, yet their chemical stability varies with the ester side chain structure. Factors such as microbial community composition, temperature and pH influence degradation rates. IBP exhibits moderate environmental persistence compared to shorter-chain parabens, leading to detecTABLE levels in surface waters and sediments (Manzetti, 2014). This environmental persistence facilitates exposure to aquatic organisms and potential bioaccumulation through food webs. Such environmental fate considerations are

critically important as they contribute to continuous human exposure via indirect routes such as intake of contaminated water or food materials, as well direct dermal contact.

Exposure Routes and Human Absorption

The prime path of exposure of human to the IBP is dermal, by the application of cosmetic or pharmaceutical products containing the compound. Studies indicate that IBP penetrates the stratum corneum and metabolizing enzymes such as carboxylesterases within the skin hydrolyze esters, reducing systemic accumulation. Nonetheless, unmetabolized IBP and its metabolites have been detected systemically, suggesting subcutaneous absorption beyond the skin barrier (F. Alan Andersen, 2008). Analytical investigations have quantified IBP in various human biological matrices, reflecting systemic exposure. These include plasma samples collected from women undergoing reconstructive breast surgery revealing measurable IBP concentrations (Parla, 2021).

Li, (2023) and Gonkowski (2024), study investigated the biomonitoring in keratinous matrices such as nails and hair demonstrates their utility to reflect longer-term cumulative exposure with IBP levels correlating to those found in urine and plasma. These findings emphasize pervasive exposure to IBP among the general community, highlighting the importance of a reliable pharmacological interpretation based on exposure assessment.

General Toxicity of Isobutylparaben

Acute and Subchronic Toxicity Data

Animal toxicological studies offer foundational insights into IBP's acute and subchronic toxicity. Data have largely demonstrated that parabens, including IBP, possess low acute toxicity across various administration routes such as oral, dermal and intravenous (F. Alan Andersen, 2008).

Alan Andersen (2008), evaluated the Median lethal doses (LD50) are typically high supporting the relative safety of parabens at consumer exposure levels. Subchronic feeding assays in rodents reveal minimal adverse effects at concentrations reflecting human exposure. However, increased effects on fore stomach cell proliferation and other endpoints have been observed with parabens possessing longer alkyl chains, including IBP, suggesting a relation between alkyl chain length and toxicity effectiveness. Some studies identify IBP as less potent compared to butyl or benzyl parabens in generating observable toxicity within the same dosing parameters.

Genotoxic and Cytogenetic Effects

Katavic (2023), despite general low toxicity, IBP has elicited certain genotoxic and cytogenetic responses in vitro. Chromosomal aberration tests reported elevations in acentric fragments and dicentric chromosomes in human lymphocytes exposed to IBP. These cytogenetic disruptions point towards a potential for DNA damage albeit at relatively high concentrations Comparisons across parabens show that shorter-chain methylparaben and ethylparaben may demonstrate similar or slightly less genotoxic potential than IBP (F. Alan Andersen, 2008). The mutagenic potential assessed through Ames testing and related genotoxicity assays generally characterizes parabens as nonmutagenic, though some evidence of chromosomal aberrations in hamster ovary cell lines has been reported for methyl- and ethylparaben specifically. IBP appears to have a marginal role in genotoxicity based on currently available data, necessitating further refined studies to establish its risk definitively.

Antimicrobial and Antioxidative Activities

The primary functional role of IBP as a preservative is linked to its antimicrobial activity. In vitro analyses demonstrate effective inhibition of bacterial and fungal growth at concentrations typically used in cosmetic formulations (Katavic, 2023). The minimum inhibitory concentrations (MICs) and minimum microbiocidal concentrations (MBCs) for IBP are within effective yet safe dosing ranges, confirming its utility in preventing microbial contamination. Additionally, IBP and other parabens exhibit antioxidative properties, as measured by assays such as DPPH free radical scavenging. In addition, this antioxidant exercise may help protect against oxidative stress. Certain biological contexts, although the interplay between these effects and potential cytotoxicity remains complex (Katavic, 2023). This dual role of IBP as antimicrobial and antioxidative agent informs its functional and safety evaluation.

Rigdon & Schadewald, 1972 and (Soret et. al, 1977), (Conner et. al,1983), in the experimental groups, neoplasms were observed in 57% of males and 57% of females, compared with 24% of males and 44% of females in the control groups. However, statistical analysis showed no significant differences in the overall tumor incidence either between treated and control mice or among the different dose levels of isobutylparaben. In male mice, the most common tumor types were lung adenomas and adenocarcinomas. Additionally, a relatively high frequency of hematopoietic neoplasms was observed in males at the 0.6% dose group and in treated females. Whereas other tumor sites in females showed only low incidences.Beyond neoplastic changes, amyloidosis occurred in 58% of treated males and 33% of treated females, compared with 25% of control males and 10% of control females. Although detailed information on amyloidosis incidence in historical controls is lacking, it is well documented that spontaneous amyloidosis is a common finding in mice, particularly in certain inbred strains and older animals.

Endocrine Disruption Potential of Isobutylparaben

Estrogenic and Antiandrogenic Activities

Boberg (2016), reported emerging evidence positions IBP as an endocrine-disrupting chemical shows demonstrated ability towards binding with estrogen receptors (ER) which are having lower affinity than endogenous 17β-estradiol but still capable of eliciting receptor-mediated responses. IBP exhibits weak competitive binding to androgen receptors indicating potential antiandrogenic effects but at considerably lower potency.

Lee (2010), in vitro studies utilizing rat uterine models and GH3 pituitary cells reveal that IBP exposure increases estrogen-responsive gene expression, including calbindin-D9k, an established biomarker for estrogenic activity. This induction is mediated partly through estrogen receptor alpha (ERα) and progesterone receptor (PR) pathways, as treatment with antagonists like fulvestrant and mifepristone reverses these effects. These findings support IBP's involvement in modulating hormone receptor signaling cascades.

Interaction with Steroid Metabolism Enzymes

Parabens including IBP have been investigated for their interference with steroid metabolism, particularly via inhibition of 17-hydroxysteroid dehydrogenases (17-HSD) enzymes which regulate estrogen activation and inactivation (Engeli, 2017). In vitro assays demonstrate that IBP and similar parabens inhibit 17-HSD1 activity in a size-dependent manner, potentially altering local estrogen concentrations and metabolism. This enzyme inhibition might lead to disrupted hormonal homeostasis and contributes mechanistically to observed endocrine-disrupting effects. The implications extend to androgen receptor signaling pathways, where weak antagonism by IBP could exacerbate dysregulation of steroid hormone actions, though the precise in vivo relevance of these effects remains to be conclusively demonstrated (F. Alan

Andersen, 2008).

Effects on Hormonal Biomarkers in Cell Models

Molecular biomarker studies show that exposure to IBP stimulates genes associated with estrogenic responses. In particular, calbindin-D9k (CaBP-9k) mRNA and protein levels are elevated in GH3 rat pituitary cells upon IBP treatment, corroborating its estrogen-like activity (Lee, 2010).

Co-exposure studies indicate synergistic activation of CaBP-9k in alliance with the other endocrine-disrupting chemicals, emphasizing risks posed by cumulative exposures (Vo, 2012). Furthermore, these effects occur in concentration-dependent manners and involve both ER and PR receptor signaling, signifying that IBP can modulate multiple endocrine pathways simultaneously (Vo, 2009). Such molecular insights provide mechanistic foundations for observed reproductive toxicities linked to IBP.

Reproductive Toxicity: Female Reproductive Effects

Effects on Oocyte Maturation and Quality

Meng (2020) by their recent research studies have highlighted the deleterious impacts of IBP on gametogenesis infemale, particularly oocyte maturation. Research employing porcine cumulus-oocyte complexes demonstrates that exposure to IBP at micromolar concentrations significantly reduces the extrusion of the first polar body, an indicator of successful meiotic progression. Higher IBP concentrations additionally impair the expansion of cumulus cells surrounding the oocyte, critical for follicular development.

Detailed cellular investigations reveal that IBP disrupts spindle microtubule organization, leads to chromosome misalignment and perturbs the distribution of actin filaments, crucial for cytoskeletal integrity. These structural aberrations suggest that IBP targets fundamental cytoskeletal components during oocyte maturation, potentially compromising fertilization competence (Meng, 2020). Simultaneously some oxidative stress markers such as reactive oxygen species (ROS) and apoptosis rates are elevated in exposed oocytes, indicating enhanced cellular damage (Meng, 2020).

Developmental and Morphological Changes in Female Reproductive Organs

In vivo studies in immature rodents showed that dietary subjection and exposure to IBP at various doses causes pronounced alterations in structure and function of reproductive tissues. Histopathological analyses reveal few interstitial cell abnormalities in ovaries, reduced corpora lutea, increase in cystic follicles and reduced thickness of follicular epithelium in a dose-dependent way(fashion) indicating disrupted folliculogenesis and ovulation potential (Lee, 2010).

Uterine morphological abnormalities, such as myometrial hyperplasia and dysplasia have been documented following IBP exposure accompanied by altered uterine weights and disrupted estrous cyclicity. These phenotypic changes are consistent with hormone-responsive organ disturbances and validate the estrogenic potential of IBP during critical developmental windows (Vo, 2009). Furthermore, hormonal assays confirm decreases in serum estradiol and thyroid hormone levels, suggesting interference with broader endocrine systems (Lee, 2010).

Epidemiological Insights Linking IBP and Female Reproductive Hormones

Human observational studies measuring urinary levels of parabens, including IBP provide evidence correlating exposure with alterations in reproductive hormone profiles among women. Cross-sectional analyses associate the higher paraben

concentrations with significant changes in follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin, implicating potential disruption of the hypothalamic-pituitary-gonadal axis (Malakootian, 2022). Although calculated hazard quotients and margins of exposure suggest low acute risks, the chronic low-dose effects and cumulative burdens raise concerns about long-term reproductive health outcomes.

Eddie-Amadi (2022), in his studies recognize the need for further longitudinal research to confirm causality and characterize mechanisms linking IBP exposure to female infertility, menstrual irregularities and other reproductive disorders.

Reproductive Toxicity: Male Reproductive Effects

Effects on Sperm Viability and Motility

The effect of IBP onthe male reproductive function had been investigated through both in vitro and in vivo models. Some studies report decreases in sperm viability, motility and counts following subjection (treating) of animal to IBP at relatively high doses, though findings are inconsistent.

Oishi S. (2001), in vitro assays reveals spermato toxic effects at concentrations ranging from 6 mg/mL down to lower dilutions, while in vivo rodent studies at 0.1% to 1.0% dosing sometimes show no significant spermatotoxicity, reflecting dose-dependent thresholds and interspecies variability. This variability underscores the complexity in interpreting male reproductive toxicity data and the influence of exposure route, duration and compound bioavailability.

Alterations in Male Reproductive Organ Weights and Function

Toxicity studies in rat models indicate that IBP exposure can cause decreases in epididymal and seminal vesicle weights at higher doses (approximately 1.0%), accompanied by histopathological abnormalities in testes and accessory sex organs. Such morphological changes imply impaired spermatogenesis and steroidogenic function (F. Alan Andersen, 2008). Moreover, butylparaben, chemically related to IBP has been shown to modulate testicular aromatase (CYP19a1) expression altering steroid hormone synthesis pathways. Although direct data for IBP on aromatase are limited, similarities suggest possible analogous disruptions in steroidogenesis (Boberg, 2016).

Molecular and Genetic Impacts on Male Reproductive Function

Strelchuk (2017), by molecular studies revealed that IBP exposure modulates gene expression profiles relevant to reproductive function. Investigations in hormone receptor-negative downregulation of breast cancer cells of aryl hydrocarbon receptor (AhR) mRNA alongside upregulation of cytochrome P450 enzymes (e.g., CYP1A1) and receptor activator of NF-kB ligand (RANKL), suggesting potential alteration of xenobiotic metabolism and cell-signaling are related to invasive phenotypes. These genetic perturbations may indirectly reflect mechanisms through which IBP disrupts androgen receptor signaling and reproductive tissue homeostasis. The cumulative evidence indicates that IBP compromises male reproductive capacity via combined functional, structural and genetic effects.

Cellular and Molecular Mechanisms Underlying Toxicity

Oxidative Stress Induction and Apoptosis

At the cellular level, IBP exposure promotes oxidative stress which is revealed by increaseed reactive oxygen species (ROS) levels. This observation is consistent across ovarian oocytes and lymphocyte cultures, implicating ROS-mediated pathways in

IBP-induced cytotoxicity (Meng, 2020). Correspondingly, apoptotic rates increase in oocytes exposed to IBP, linking oxidative damage to programmed cell death and impaired cellular viability.

Katavic (2023) reported that in vitro genotoxicity assays further reveal oxidative DNA damage phenomena, supporting the possibility that IBP causes mobile oxidative stress, which may underlie various toxic endpoints. These mechanisms are critical for understanding IBP's adverse reproductive effects, which often encompass declines in cell function and survival.

Epigenetic Modifications

Epigenetic changes from another axis of IBP-induced toxicity. Oocyte studies demonstrate significant alterations in histone methylation markers H3K9me3 and H3K27me3 following IBP treatment, indicating modifications in chromatin structure and gene regulatory landscapes (Meng, 2020). Such epigenetic perturbations during gametogenesis could have lasting impacts on gene expression patterns and developmental competence. These modifications highlight the insidious nature of IBP toxicity, where subcellular changes may contribute to reproductive impairments and possibly transgenerational effects.

Disruption of Signaling Pathways Related to Cell Proliferation and Metastasis

Strelchuk (2017) investigated that IBP also influences cellular signaling involved in proliferation and metastatic potential. Exposure of breast cancer cell lines to IBP downregulates AhR mRNA while inducing CYP1A1 and RANKL expression, pathways involved in xenobiotic metabolism, inflammation and bone remodeling. These gene expression shifts suggest that IBP not only interferes with hormonal signaling but may also promote pro-metastatic phenotypes, raising concerns about its potential carcinogenicity. Understanding these pathway disruptions is essential for risk assessment, given the global use of IBP in consumer commodities and its detection in human tissues.

Human Exposure Biomonitoring and Risk Assessment

Biomonitoring Matrices and Detection Methods

Advancements in analytical chemistry have enabled sensitive estimation of IBP in human biological matrix including plasma, urine, hair and nails. Techniques like the liquid chromatography when combined with bulk spectrome (LC-MS) offer precise measurement of both intact IBP and its metabolites (Parla, 2021); (Li, 2023). Biomonitoring studies in healthy populations and patients reveal widespread detection of IBP, with concentrations varying by factors such as geographical region, occupation and personal product usage (Gonkowski, 2024). Hair and nails provide prolonged exposure windows due to incorporation during growth, complementing plasma and urine measures that reflect more recent exposure (Li, 2023). These biomonitoring approaches are critical for exposure assessment and epidemiological linkage of IBP to health outcomes.

Exposure Levels from Cosmetics and Consumer Products

Nguyen (2020), by Quantitative analyses of cosmetic formulations reveal that IBP concentrations in commercial products range widely, measured from minimal traces up to milligrams per kilogram, depending on product type. Solid-phase extraction and ultra-high-performance liquid chromatography methods have been utilized to determine IBP in various cosmetics including creams, shampoos and gels at levels that coincide with regulatory limits.

By Gaberc (2023), daily use of multiple cosmetic products may lead to cumulative systemic exposure to IBP, with surveys indicating long-term consumer contact

exceeding decades in some cases This habitual exposure underscores the importance of evaluating cumulative risk and preservative efficacy balance.

Controversies, Knowledge Gaps and Health Implications

Inconsistencies in Toxicological Outcomes

The toxicological evaluation of IBP is marked by some inconsistencies and contradictory findings, particularly in reproductive toxicity. While some rodent studies demonstrate clear dose-dependent derangements in reproductive organ development and function, others report minimal or no effects at comparable doses (F. Alan Andersen, 2008).

The extrapolation of these findings to humans is further complicated by interspecies differences and variations in exposure routes. Epidemiological evidence linking IBP directly to cancer incidence or reproductive disorders remains limited and inconclusive. Some studies highlight associations with breast cancer risk modulation, but it's not known whether there is a causal link (Hager, 2022). These ambiguities call for cautious interpretation and further rigorous longitudinal research.

Challenges in Assessing Mixture Effects and Combined Exposures

In real-world settings, exposures to IBP occur concomitantly with other parabens and endocrine disruptors such as bisphenol A and alkylphenols. Studies reveal synergistic activities among these chemicals in modulating estrogen-responsive biomarkers, complicating risk assessments based on single chemicals (Vo, 2012).

Siddique (2016), claimed that the complexities of mixture toxicology, potential additive or antagonistic effects and variable metabolism present formidable challenges in defining clear safety margins. Moreover, differences in individual susceptibility, lifestyle factors and co-exposures necessitate integrated approaches combining biomonitoring, toxicogenomics and systems toxicology to unravel health risks comprehensively.

Phenylmercuric Acetate

Chemical Nature and Usage of PMA

Phenylmercuric acetate (PMA) is an organomercury compound characterized chemically by the presence of a phenyl group bound to a mercury atom, which is further complexed with an acetate moiety. This unique structure confers antimicrobial properties, making PMA historically valuable in industries such as preservation, agriculture and pharmaceuticals. Its ability to act as a biocide led to its extensive use in fungicides, disinfectants and as a preservative in various industrial and pharmaceutical formulations. However, the mercury content inherent to PMA gives rise to significant toxicological concerns. Mercury compounds are well-known environmental contaminants with the potential to accumulate in biological systems, notably affecting human health through diverse exposure pathways. Given the persistence of PMA in ecosystems and its biological activity, it is imperative to understand the compounds impact, particularly in sensitive biological processes such as reproduction (Moeller, 2012).

Overview of Mercury Toxicity with Emphasis on Organomercury Compounds

Mercury exists in multiple chemical forms, with inorganic mercury, elemental mercury and organic mercury compounds exhibiting varying degrees of bioaccumulation and toxicity. Organomercury compounds such as PMA hold particular significance due to their lipophilicity, facilitating tissue penetration and resulting in bioaccumulation, especially within the central nervous system and reproductive organs. Their prolonged existence in the environment and the capability to get biomagnified through food webs intensify health risks. Toxicological profiles

reveal that organomercurials disrupt cellular redox balance by promoting the extreme generation of reactive oxygen species. (ROS), establishing oxidative stress states within tissues (Sharma, 2014). Mercury compounds also trigger genotoxicity, neurotoxicity, nephrotoxicity and hepatotoxicity encroaching on multiple physiological systems. From a public health perspective, phenylmercuric compounds constitute a critical exposure risk necessitating comprehensive evaluation of their effects on reproductive function due to their capacity for endocrine disruption and direct reproductive tissue injury (Missimer, 2024).

Importance of Studying Reproductive Toxicity of PMA

Reproductive function is exquisitely sensitive to xenobiotic insults, particularly from heavy metals such as mercury. PMAs ability to induce oxidative stress, disrupt hormonal pathways and provoke direct cellular toxicity places it as a substance of concern within reproductive toxicology. Scientific interest in understanding PMAs reproductive ramifications stems both from regulatory imperatives to protect human health and ecological systems, as well as from advances in toxicological methodologies enabling detailed mechanistic insight. The reproductive system, encompassing spermatogenic and oogenic processes, steroidogenesis and associated hormonal feedback loops can be compromised by mercury exposure. This impairment might manifest as reduced fertility, altered sexual development and transgenerational consequences. Thorough exploration of PMAs impact on reproductive health is necessary to develop evidence-based guidelines and mitigation strategies to minimize exposure-related risks (Moeller, 2012).

Mechanisms of Phenylmercuric Acetate-Induced Toxicity

Oxidative Stress and Reactive Oxygen Species Generation

One among the primary toxicological mechanisms by which PMA exerts its deleterious effects pertains to the increased technology of reactive oxygen species, which contributes to oxidative stress. (ROS). Mercury-mediated redox imbalance leads to excessive ROS formation, including superoxide anions, hydrogen peroxide and hydroxyl radicals. These reactive species inflict oxidative damage on lipids, proteins and nucleic acids components critical for cellular integrity. In reproductive tissues, where cell proliferation and differentiation are tightly regulated, oxidative insult disrupts these processes.

In the investigated study by Sharma (2014), the imbalance arises due to mercury's capacity to inhibit antioxidant systems, either by direct interaction with enzymes such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx) or by depleting intracellular antioxidants like glutathione. Consequently, PMA-mediated oxidative damage compromises sperm membrane integrity, DNA stability and testicular cell viability contributing to reproductive dysfunction.

Cellular and Molecular Targets of PMA in Reproductive Cells

At the cellular level, PMA targets multiple organelles and molecular pathways. The mitochondria, pivotal regulators of energy metabolism and apoptosis are disrupted by PMA exposure, which prompts mitochondrial membrane depolarization, releasing of pro-apoptotic factors and activation of caspase cascades culminating in programmed cell death. Further, PMA interacts with genomic DNA and chromatin architecture, potentially modifying histone acetylation states that control gene expression pertinent to cell survival and differentiation (Rempel, 2015).

These genetic changes have an impact on the body. Expression of genes crucial for maintaining reproductive tissue homeostasis. Moreover, phenylmercuric acetate affects enzymatic systems integral to steroidogenesis and cellular signaling. For instance, perturbations in 17β-hydroxysteroid dehydrogenase activity and receptor-

mediated pathways disrupt the regulatory axes essential for reproductive function (Nakade, NaN).

Endocrine Disruption and Hormonal Dysregulation

PMAs influence extends to endocrine system perturbations, primarily affecting steroid hormone biosynthesis and signaling. The compound modifies the secretion and receptor binding of gonadotropins like luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as well as testosterone levels. Mercury exposure is reported to dampen these hormonal levels, possibly through direct testicular toxicity and hypothalamic-pituitary axis disruption (Nakade, NaN). The feedback loops regulating reproductive hormone synthesis become impaired, resulting in diminished steroidogenesis and altered reproductive organ function. These endocrine disruptions have downstream consequences on gametogenesis, sexual maturation and fertility. Hormonal dysregulation mediated by PMA also implicates possible interference with estrogen and progesterone pathways, further broadening the impact on reproductive health (Sharma, 2014).

In Vitro Studies of PMA on Reproductive Cells

Cytotoxicity Assays Using Human Hepatocytes and Reproductive Cell Lines

In vitro methods have provided profound insights into the cytotoxic potential of PMA on reproductive cells. Cryopreserved human hepatocytes, regarded as the gold standard for metabolic and toxicological investigations, have been utilized to evaluate phenylmercuric acetate toxicity. These models retain key enzymatic activities and serve to simulate human in vivo metabolism affecting PMA biotransformation (Moeller, 2012). Comparative studies reveal that reproductive cell lines, including spermatogonial and ovarian granulosa cells display varied susceptibility to PMA-induced cytotoxicity, often less sensitive than primary cells due to incomplete metabolic competence. Such assays, conducted in high-throughput formats have quantified dose-dependent decreases in cell viability, increased apoptosis and oxidative markers corroborating the toxic potential of PMA in reproductive cell populations.

Transcriptomic and Epigenomic Profiling Post PMA Exposure

Further depth into PMAs effects has been achieved through transcriptomic and epigenomic profiling. Exposure to PMA results in altered expression of genes governing apoptosis, oxidative stress responses and reproductive functions. For instance, transcriptome studies identify upregulation of pro-apoptotic genes and downregulation of antioxidative defense components. Moreover, histone modification patterns undergo perturbation, reflecting affected chromatin remodeling processes commonly associated with developmental toxicants (Rempel, 2015). Such molecular signatures serve as biomarkers for reproductive toxicity and facilitate classification of chemicals with similar modes of action. These approaches also underscore potential long-term effects on reproductive capacity through epigenetic inheritance, necessitating further exploration of PMA at the genomic regulation level.

Metabolic Activation and Biotransformation of PMA

The metabolism of PMA significantly influences its reproductive toxicity profile. Hepatic biotransformation alters PMA into reactive intermediates that may exert enhanced or reduced toxicity towards reproductive tissues. Variability in metabolic enzyme expression among individuals as demonstrated using multiple hepatocyte donors leads to differential susceptibility to PMA. Such biotransformation processes involve phase I and phase II enzymes, including cytochrome P450 isoforms, conjugation reactions and efflux transporters which modulate the systemic and tissue-specific availability of toxic mercury species (Moeller, 2012). Understanding these metabolic nuances these genetic changes have an impact on the body interspecies

extrapolation of in vitro findings to in vivo contexts.

In Vivo Animal Studies on Reproductive Effects of PMA

Effects on Male Reproductive Parameters

Experiments using rodent models have consistently demonstrated that PMA exposure adversely affects male reproductive parameters. Notably, sperm count, motility, morphology and viability are diminished in dose-dependent manners, reflecting impaired spermatogenesis. Histopathological examination reveals that damage to the seminiferous tubules, including degeneration of germinal epithelium, vacuolization and loss of spermatogenic cells. Hormonal analyses show decreased testosterone levels alongside altered levels of LH and FSH, confirming disruptions in endocrine regulation (Nakade, NaN). These findings are in line with useful principles fertility outcomes such as reduced mating success and litter sizes. The testicular tissues ultrastructural integrity is compromised, severely affecting the reproductive competence of exposed males.

Effects on Female Reproductive System

PMA also inflicts significant damage on the female reproductive system. Uterine examinations reveal inflammatory processes distinguished by thickening of the endometrium, tapering of the uterine lumen and degeneration of uterine glands. These histopathological features correlate with disruptions in the estrous cycle, often manifesting as irregularities or suppression of cyclicity. Ovarian impacts include altered follicular development and hormonal imbalances affecting estrogen and progesterone synthesis (Nakade, 2015. Such impairments have critical implications for ovulation, fertilization and gestation. The cumulative data from female models accentuate PMAs potential to compromise fertility and reproductive success via structural and endocrine perturbations.

Developmental and Transgenerational Impacts

The consequences of PMA exposure extend beyond immediate reproductive toxicity to include developmental and possible transgenerational effects. Studies indicate that prenatal and perinatal exposure to mercury compounds disrupts reproductive organ development, resulting in delayed puberty and endocrine imprinting alterations. For example, continuous exposure throughout developmental windows impairs vaginal opening and estrus cycling in females while suppressing testosterone production in males. These disruptions manifest as long-lasting impairments in reproductive physiology, raising concerns about PMAs ability to alter developmental trajectories and epigenetic programming of reproductive systems (Ronis, 1998). These findings underscore the necessity of vigilant exposure control during critical windows of reproductive organogenesis.

Oxidative Stress and Antioxidant Responses in PMA Reproductive Toxicity

Biomarkers of Oxidative Damage in Reproductive Organs

Even as a result of elevated levels of the malondialdehyde (MDA), which is a marker of lipid peroxidation and DNA fragmentation assays indicating oxidative DNA injury, reproductive toxicity brought on by PMA is closely related to oxidative damage. Elevated MDA reflects membrane lipid oxidation contributing to sperm dysfunction and testicular cell death. Concurrently, activities of antioxidant enzymes such as catalase, SOD and GPx are typically suppressed, indicating overwhelming oxidative stress that exhausts native defense systems. These biochemical indices serve as crucial biomarkers linking PMA exposure to cellular damage mechanisms in reproductive organs (Mustari, 2020).

Protective Effects of Natural and Synthetic Antioxidants Against PMA Toxicity

Emerging evidence highlights the ameliorative potential of various natural and

synthetic antioxidants against PMA-induced reproductive damage. Plant-derived extracts such as Nigella sativa seed oil and Cocos nucifera oil have demonstrated significant antioxidant properties, restoring sperm parameters, testicular histology and hormonal balances in mercury-intoxicated rodent models (Mustari, NaN), (Olaniyan, 2021). Moreover, supplementation with vitamins C and E has also been effective in counteracting ROS-mediated damage and improving reproductive outcomes by enhancing antioxidant enzyme activities (Ogbu, 2023). Resveratrol and other polyphenolic substances have shown promise. in upregulating antioxidant defense genes and enzyme activities, thereby mitigating oxidative insults (Mustari, NaN).

Therapeutic Interventions Targeting Oxidative Pathways

Therapeutic compounds targeting oxidative stress pathways have a growing fan base for them. Work efficacy in reversing PMA reproductive toxicity. Agents such as L-citrulline, naringenin, hesperidin and alpha-lipoic acid exhibit antioxidative, anti-inflammatory and hormone-modulatory effects in experimental models. L-citrulline supplementation ameliorates oxidative and hormonal disturbances induced by lead compounds restoring sperm quality and reproductive hormone profiles (Ogbu, 2023). Naringenin regime notably attenuates testicular inflammation and apoptosis via modulation of TGF/AKT/mTOR signaling, leading to improved spermatogenic function (Abu-Khudir, 2023). Hesperidin and alpha-lipoic acid contribute to reducing oxidative stress markers, restoring testicular histoarchitecture and normalizing reproductive hormones underscoring their potential as adjunct therapies against PMA reproductive toxicity (Abu-Khudir, 2023).

Histopathological and Ultrastructural Findings After PMA Exposure

Testicular and Epididymal Tissue Alterations

Histopathological examinations of testicular and epididymal tissues following PMA exposure reveal structural abnormalities including vacuolization in seminiferous epithelium, tubular atrophy and significant germ cell loss. Sertoli cell dysfunction and interstitial tissue alterations further exacerbate spermatogenic disruption. These histological abnormalities correspond with reduced sperm production and quality, manifesting as decreased counts, motility and increased morphological anomalies (Nakade, NaN).

Ovarian and Uterine Morphological Changes

The ovaries exhibit follicular atresia with impaired folliculogenesis, while the uterus displays epithelial degeneration and inflammation in response to PMA toxicity. Structural disturbances in endometrial glands and stromal tissues correspond to hormonal imbalances and reproductive inefficiency. Such morphological changes compromise the female reproductive environment, altering conditions essential for fertilization and implantation (Nakade, NaN).

Correlation Between Histopathology and Functional Reproductive Deficits

There is a consistent correlation between observed histopathological damage and functional reproductive deficits. Testicular and ovarian morphological injuries parallelly diminished sperm viability, reduced steroid hormone synthesis and impaired gametogenesis resulting in lowered fertility indices. These integrated pathological and functional findings provide a mechanistic understanding of PMA-induced reproductive dysfunction and justify the inclusion of morphological endpoints in risk assessment protocols (Ibraheem, 2022).

Comparative Toxicology of Phenylmercuric Acetate and Other Mercury Compounds

Comparison with Inorganic Mercury and Organic Mercury Toxicity Profiles

Phenylmercuric acetate, representative of organic mercury species, generally exhibits greater membrane permeability and cellular uptake compared to inorganic mercury

forms. Its toxicity profile includes robust induction of oxidative stress, apoptosis and endocrine disruption at lower exposure levels compared to inorganic mercury. However, inorganic mercury tends to accumulate in renal tissues preferentially. Whereas, PMA shows distinct distribution patterns affecting reproductive organs more notably (Sharma, 2014). Relative reproductive toxicity thus varies depending on mercury species with PMA ranking high in potency due to its biological availability and mechanistic pathways.

Species-Specific Variability in Response to PMA

Toxicological responses to PMA show marked species-specific differences. Rodent models, primarily rats and mice will reveal consistent reproductive toxicity signs, yet variations in metabolic processing influence exposure outcomes. Human-relevant in vitro systems using hepatocytes and reproductive cells reveal differential susceptibility largely attributed to metabolic enzyme heterogeneity (Moeller, 2012). These discrepancies highlight the necessity for cautious interspecies extrapolations and call for the integration of humanized in vitro models to enhance predictive accuracy.

Environmental Relevance and Human Exposure Considerations

Occupational and environmental exposures to PMA occur through dermal contact, inhalation and contaminated food or water. Given its use historically and persistence in certain industrial settings, chronic low-level human exposure remains a public health concern. Mercury's propensity for bioaccumulation and persistence further compounds risk. Therefore, understanding PMAs reproductive toxicity within environmental exposure contexts is critical, emphasizing the importance of biomonitoring, exposure mitigation and regulatory controls to safeguard reproductive health (Missimer, 2024), (Sharma, 2013).

Molecular and Cellular Pathways Impacted by PMA in Reproductive Toxicity

Apoptotic and Necrotic Pathways in Reproductive Tissues

PMA initiates apoptosis in reproductive cells through intrinsic mitochondrial pathways involving caspase activation and DNA fragmentation, as demonstrated by elevated caspase-3 activity and DNA damage assays like TUNEL. These pathways result in germ cell loss and impaired spermatogenic progression, contributing to reduced fertility. Necrosis from excessive oxidative stress may also play a supportive role. These programmed and unprogrammed cell death pathways are central to PMAs reproductive toxicity (Abu-Khudir, 2023).

Disruption of Steroidogenesis and Hormone Receptor Expression

PMA exposure decreases enzymatic activities including 17-hydroxysteroid dehydrogenase and inhibits expression of androgen receptors in testicular tissues. These disruptions culminate in diminished synthesis of testosterone and alterations in feedback control by LH and FSH. Consequently, endocrine signaling cascades governing spermatogenesis and sexual differentiation are adversely modulated, amplifying reproductive impairment (Wahab, 2019).

Inflammatory and Immune Responses in Reproductive Toxicity

Beyond direct cytotoxicity, PMA induces inflammatory responses in reproductive organs, observed as elevated pro-inflammatory cytokines for instance TNF-α, IL-1 and TGF-β. This immune activation worsens tissue damage, exacerbates oxidative stress and further impairs reproductive function. Mercury's immunomodulatory effects thus represent a compounding factor in reproductive toxicity the linking chemical exposure with systemic and local immuno-inflammatory processes (Mitra, 2022).

Current Gaps in Knowledge and Future Research Directions

Limitations in Existing Toxicological Data for PMA

While animal and in vitro studies provide substantial insight, human epidemiological data on PMA reproductive toxicity are scarce. Long-term exposure effects, low-dose chronic impacts and transgenerational consequences remain inadequately characterized. Moreover, the complex interactions between PMA metabolism, genetic susceptibilities and environmental co-exposures demand integrative studies employing multi-omics technologies to unravel comprehensive toxicity mechanisms (Moeller, 2012).

Emerging Models and Technologies for Reproductive Toxicity Testing

Advancements in stem cell-derived reproductive tissues and transcriptomics-based classifiers open avenues for mechanistic toxicity testing. These models facilitate high-throughput screening and mode-of-action grouping, improving predictive capacity for developmental and reproductive toxicants such as PMA. Incorporating human-relevant metabolic and epigenomic features promises enhanced translational relevance (Rempel, 2015).

2.5.2.Potential Strategies for Reducing PMA Reproductive Risks

Addressing PMAs reproductive risks requires combined regulatory and therapeutic strategies. Substituting PMA with safer antimicrobial agents, enforcing exposure limits and enhancing environmental decontamination comprise preventive measures. Concomitantly, antioxidant supplementation and targeted therapies offer remediation avenues for exposed populations, pending clinical validation (Mustari, NaN).

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