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SYSTEMATIC REVIEW

Plasticizers and Hormonal Imbalance: A Comprehensive Review of Rodent Endocrine Disruption Studies

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ABSTRACT

This study focuses on the potential impact of plasticizers on hormones in the body, as they are a common component of numerous plastic items. The research looks at the detrimental effects of traditional phthalate plasticizers including DEHP, DBP and BBP as well as newer non-phthalate alternatives on the reproductive system, brain, thyroid and adrenal glands by reviewing several studies that have been conducted on rodents. The results indicate that these chemicals can induce significant endocrine disruption, particularly in the early development and pregnancy. Male offspring of those exposed to plasticisers had reproductive abnormalities including decreased anogenital distance and disrupted hormone production, and females had lower fertility, irregular reproductive cycles, and changes in ovarian structure. The study also documents behavioural changes, brain development issues and thyroid and adrenal hormone dysfunction. It was discovered that these impacts can last long-term and impact future generations. The study also notes how plasticizers disrupt the binding of hormones to their receptors, processes that involve enzymes that are crucial to the production of hormones, and the regulation of genes. While the study primarily focused on rodents, it offers compelling evidence showing that plasticizers could be a significant health concern for humans, and further research and safety measures are warranted.

Keywords: Phthalates, Microplastics, Endocrine disruption, Environmental exposure, Reproductive toxicity, Hormonal imbalance

INTRODUCTION

Plasticisers are the chemicals used to give plastic a softness, flexibility and durability. Phthalates like DEHP and DBP, and bisphenol A (BPA) are among the more prevalent plasticisers used. These chemicals can be found in consumer products such as food packaging, medical equipment, cosmetics, toys, and household goods[1]. Man and animal are exposed to plastics on a daily basis via the environment, such as the air, water, food, and direct contact with plastic products[2]. The situation is more critical because of the growing contamination by micro-plastics and nano-plastics in the environment. These microscopic plastic pieces can transport toxic substances and can be more readily transported through living organisms and ecosystems, making them likelier to be ingested by humans. Many

plasticisers are known to disrupt the body's natural hormone system, which is known as an endocrine disrupting chemical. They can mimic or interfere with hormones and can also impact the production, transport and breakdown of hormones within the body. Therefore, contact with these chemicals has been associated with growth and reproduction, brain development, thyroid and adrenal gland activity problems in mammals[3]. Because they have biological systems similar to human beings, rats and mice are often used in research to gain insight into these health effects. But metabolism and genetics vary from individual to individual, and thus the results have to be applied with caution to people[4]. The rise in awareness of microplastics and nanoplastics in recent years has been amplified as these are able to carry and retain endocrine disrupting chemicals, which may pose greater risks to health in the long term, and over time, enter the food chain. To explore the complex interactions of plasticisers, MPs/NPs and mammalian endocrine system, this review provides a summary of the current state of the art[5].

LITERATURE SEARCH METHODOLOGY

A comprehensive literature search was performed to identify experimental studies evaluating the endocrine-disrupting effects of plasticizers in rodent models. The review followed established principles for transparent literature identification and study selection commonly recommended for environmental health reviews and systematic evidence synthesis, although it was conducted as a narrative review rather than a formal systematic review.

Electronic databases including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched to retrieve relevant peer-reviewed publications. The literature search included articles published from January 2010 to June 2025, with particular emphasis on studies published during the last decade to ensure inclusion of recent evidence on endocrine-disrupting chemicals (EDCs).

Reference lists of relevant review articles and eligible studies were manually screened to identify additional publications that were not retrieved during the electronic database search.

Studies were considered eligible if they:

- were published in peer-reviewed journals in English;
- employed rat or mouse models;
- investigated exposure to conventional or emerging plasticizers, including phthalates, bisphenols, or alternative plasticizers;
- reported endocrine-related outcomes involving reproductive, thyroid, adrenal, neurodevelopmental, metabolic, or molecular endocrine pathways; and
- provided original experimental findings.

Studies were excluded if they:

- involved only human epidemiological data or non-rodent species;
- were conference abstracts, editorials, commentaries, dissertations, or duplicate publications;
- lacked endocrine-related outcomes; or
- provided insufficient experimental information for data interpretation.

Information extracted from the eligible studies included the type of plasticizer, experimental animal model, exposure route, dose and duration, endocrine target organs, molecular mechanisms, hormonal alterations, histopathological observations, and major toxicological findings. Particular emphasis was placed on studies describing receptor-mediated mechanisms, oxidative stress, epigenetic regulation, and disruption of endocrine signaling pathways to provide an integrated overview of the current understanding of plasticizer-induced endocrine toxicity in rodents. Recent publications were preferentially incorporated to ensure that the review reflects current advances in endocrine-disrupting chemical research.

SOURCES AND ENVIRONMENTAL EXPOSURES OF PLASTICIZERS

1. Primary Sources of Plasticizers

- **Indoor Environments & Building Materials:** Vinyl flooring continues to be the most important indoor source (representing around 52% of samples), followed by wallpaper, synthetic leather, and electric wire sheathing[6].
- **Food Packaging & Consumer Goods**: Bottled water and food containers continue to leak phthalate esters (PAEs) and bisphenol-A (BPA), particularly when stored at high temperatures[7].
- **Medical Devices:** DEHP remains a critical component in PVC-based medical tubing and bags, though non-phthalate alternatives like DINCH and DEHT are rapidly gaining market share[8].

2. Environmental Exposure Pathways

1. Semi-volatile organic compounds (SVOCs) known as plasticisers migrate inevitably because they do not form a chemical link with their host polymers.

- **Ingestion:** The primary route, occurring through the consumption of contaminated food (leached from packaging) and drinking water[9].
- **Inhalation:** Plasticisers attach themselves to settled dust and airborne particles. According to recent research from 2025, children are especially at risk in "sleeping

microenvironments" because of the emissions from bedding and mattresses[10].

- **Dermal Absorption:** Direct contact with plasticized products (toys, synthetic clothing, and medical devices) allows for transdermal uptake[11].
- **Environmental Transport:** Additives are released into the soil and aquatic food webs due to the mechanical fragmentation and weathering of plastic debris in landfills and oceans[12].

Table 1: Major Plasticizers and Their Primary Endocrine Targets

Plasticizer	Chemical Class	Primary Molecular Target(s)	Major Endocrine Effect	Principal Outcome
Bisphenol A (BPA)	Bisphenol	ERα, ERβ	Estrogenic activity	Reproductive dysfunction
Di-(2-ethylhexyl) phthalate (DEHP)	Phthalate	AR, PPARα/γ	Anti-androgenic activity	Reduced testosterone and impaired fertility
Dibutyl phthalate (DBP)	Phthalate	AR	Steroidogenesis inhibition	Testicular toxicity
Benzyl butyl phthalate (BBP)	Phthalate	ER, AR	Hormonal imbalance	Ovarian dysfunction
Diisononyl phthalate (DINP)	Phthalate	PPARγ	Metabolic dysregulation	Obesity and insulin resistance
Diisodecyl phthalate (DIDP)	Phthalate	PPARα	Lipid metabolism alteration	Metabolic disturbances
Bisphenol S (BPS)	Bisphenol	ER, TR	Thyroid disruption	Neurodevelopmental effects
Bisphenol F (BPF)	Bisphenol	ER	Endocrine disruption	Reproductive toxicity
Diisononyl cyclohexane-1,2-dicarboxylate (DINCH)	Alternative plasticizer	PPARγ	Metabolic alteration	Potential endocrine effects
Di-(2-ethylhexyl) adipate (DEHA)	Alternative plasticizer	TR	Thyroid hormone imbalance	Thyroid dysfunction

HISTORY OF PLASTICIZERS AND ENDOCRINE DISRUPTION

During the second half of the 20th century, advances in endocrinology and environmental toxicology have resulted in plasticisers being identified as EDCs. In the early 1980s, it was discovered that phthalates such as DEHP are present in environmental samples and linked to reproductive anomalies in rodents[13]. Initial research with male rats indicated that 6 DEHP exposure resulted in reduced sperm production and testicular weight which prompted concerns regarding its impact on hormones[14]. A major discovery in the 1990s was the discovery of Bisphenol A (BPA), a xenoestrogen, which has the ability to bind to the oestrogen receptor. Research revealed that BPA could alter the reproductive development in female rodents, resulting in alteration of the ovarian structure and disruption of the oestrous cycle[15]. Early 2000s studies have demonstrated that MPs and NPs can be able to load with plasticisers and carry them into living organisms, leading to higher levels of plasticisers in these organisms and, potentially, greater toxicity. This also showed the long-term presence of these pollutants in the environment[2]. In the 2010s, because of rising concerns about their possible to interfere with normal thyroid function[16], scientific attention gradually turned towards non-phthalate plasticisers, including acetyl tributyl citrate (ATBC) and di(2-ethylhexyl) adipate (DEHA). Recent research has further suggested that exposure to endocrine-disrupting chemicals (EDCs) in one generation may affect the hormonal balance and reproductive health of future generations through epigenetic mechanisms, including DNA methylation and histone modification[17].

This historical progression highlights the increasing complexity of plasticiser research and its impact on mammalian health, thereby underscoring the need for continuous investigation into newly developed plasticisers and their long-term effects.

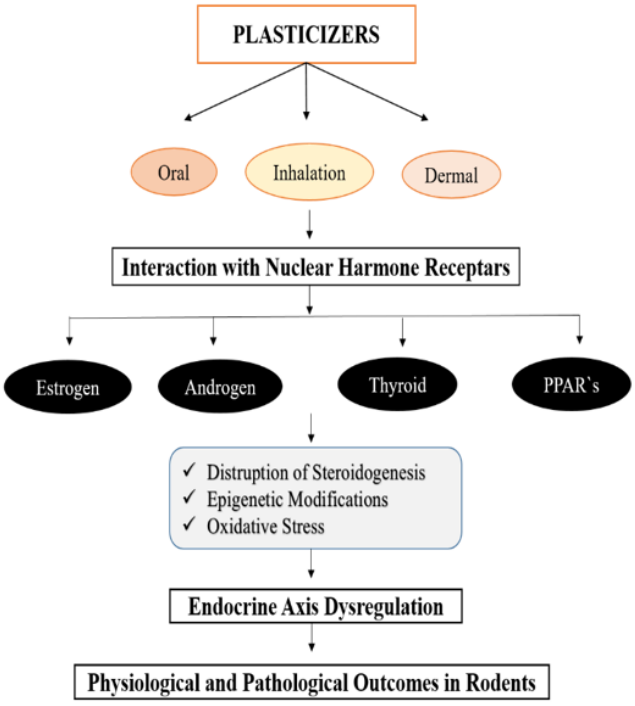
EXPERIMENTAL APPROACHES IN RODENT MODELS

Because of their genetic and physiological resemblance to humans, rodent models are essential to EDC research. The reviewed studies commonly employ the following experimental approaches:

In Vivo Exposure Studies:

In experimental studies, rodents such as rats and mice are commonly exposed to plasticisers through oral gavage, incorporation into feed, or drinking water to mimic possible human exposure pathways. DEHP is typically administered in doses ranging from 10 to 1000 mg/kg/day to investigate dose-related effects on reproductive tissues and organs. Long-term studies, including those lasting around 90 days, are carried out to evaluate chronic toxicity, while perinatal studies focus on sensitive stages of development during early life[13].

- **Behavioral Assays:** Behavioral studies assessing the effects of phthalates and BPA commonly examine changes in anxiety-related behavior, movement activity, and cognitive performance using experimental models such as the elevated plus maze, open field test, and Morris water maze[18].
- **Histological and Molecular Analysis:** Changes in molecular expression such as thyroid hormone receptor (THR) and oestrogen receptor alpha (ERα) levels are evaluated in tissue samples taken from the thyroid, adrenal and reproductive organs as well as histopathological abnormalities such as testicular atrophy and adrenal hyperplasia[16, 19].
- **Transgenerational Studies:** [17] reported that multigenerational exposure studies are used to evaluate epigenetic alterations in the offspring of exposed rodents, including modifications such as DNA methylation and histone acetylation.
- **In Vitro Assays:** The use of Leydig and Sertoli cells is used to investigate the interaction between plasticisers and hormone receptors which provide mechanistic evidence that corroborates in vivo observations[16].



Molecular Mechanisms of Plasticizer-Induced Endocrine Disruption

Instead of using a single toxicological mechanism, plasticizers disturb endocrine homeostasis through a number of interrelated molecular mechanisms. These substances can disrupt hormone synthesis, receptor activation, intracellular signaling, oxidative balance, and gene control after entering the body through eating, inhalation, or skin contact. Their capacity to mimic endogenous hormones, antagonize hormone receptors, change the activity of steroidogenic enzymes, and cause long-term epigenetic changes determines their endocrine-disrupting effect. These molecular changes are consistently linked to neurodevelopmental impairment, metabolic disorders, thyroid abnormalities, reproductive failure, and transgenerational consequences, according to experimental research conducted in rodents. When taken as a whole, these results suggest that several molecular events interact to cause endocrine disruption rather than discrete biochemical alterations[1, 16].

1. Interaction with Hormone Receptors

Nuclear hormone receptor interaction is one of the main ways plasticizers cause endocrine damage. A number of plasticizers have structural properties that allow them to bind either directly or indirectly to thyroid hormone receptors (TRα and TRβ), androgen receptors (AR), estrogen receptors (ERα and ERβ), and peroxisome proliferator-activated receptors (PPARs). Because of its estrogen-like activity, bisphenol A (BPA) is one of the best-characterized endocrine-disrupting chemicals.

These interactions alter normal hormone-dependent gene transcription and disrupt physiological endocrine communication. BPA modifies ovarian function, mammary gland physiology, and reproductive development by binding to estrogen receptors and triggering transcriptional responses that mimic endogenous estrogen. Studies on rodents have shown that exposure to BPA during development alters the expression of estrogen-responsive genes and raises the risk of reproductive problems in maturity[1].

On the other hand, phthalates that mostly show anti-androgenic activity include dibutyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP). These substances disrupt the development of male reproductive organs, decrease sperm production, and lower fertility by suppressing testosterone biosynthesis and reducing androgen receptor signaling. It has been demonstrated that exposure during fetal development disrupts androgen-dependent developmental processes, interfering with appropriate sexual differentiation[1].

Thyroid hormone signaling can potentially be disrupted by plasticizers. According to recent research, phthalates and a

number of non-phthalate plasticizers change the action of thyroid hormone receptors, change the expression of genes associated to the thyroid, and disrupt the levels of thyroid hormone in the blood. These changes may affect proper endocrine development, metabolic control, and neural maturation, especially after exposure during pregnancy and early life[16].

2. Disruption of Steroidogenesis

The coordinated production of steroid hormones by the gonads and adrenal glands is essential for normal endocrine function. Exposure to plasticizers has been shown to disrupt this process by changing the expression and activity of steroidogenesis-related enzymes. Following exposure to phthalates and BPA, experimental studies have shown decreased expression of steroidogenic acute regulatory protein (StAR), cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), and aromatase (CYP19A1). Because these enzymes are crucial for the production of progesterone, estradiol, testosterone, and other steroid hormones, their inhibition has a direct impact on endocrine homeostasis[1].

In rat models, decreased fertility, aberrant ovarian follicular development, altered estrous cyclicity, and poor spermatogenesis are all caused by reduced steroid hormone production. Additionally, endocrine disorders that persist into adulthood may result from disruption of steroidogenic pathways during crucial developmental windows, highlighting the significance of developmental sensitivity to endocrine-disrupting substances[1].

3. Activation of Peroxisome Proliferator-Activated Receptors (PPARs)

Ligand-activated transcription factors called peroxisome proliferator-activated receptors (PPARα and PPARγ) control inflammation, adipocyte differentiation, lipid metabolism, glucose consumption, and cellular energy homeostasis. As agonists of these receptors, a number of phthalates and related plasticizers have been found to alter the expression of genes involved in metabolic control. Increased adipogenesis, altered lipid metabolism, insulin resistance, and disruptions in glucose homeostasis have all been linked to persistent activation of PPAR signaling. According to experimental data, these metabolic changes may be linked to type 2 diabetes, obesity, and metabolic syndrome after prolonged exposure to substances that disrupt hormones. PPAR activation interacts with inflammatory and endocrine signaling networks in addition to controlling metabolic pathways, underscoring the intricate molecular impacts of plasticizers beyond reproductive harm[1].

4. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is considered one of the major mechanisms contributing to plasticizer-induced endocrine toxicity. Exposure to BPA and phthalates promotes excessive production of reactive oxygen species (ROS), resulting in oxidative damage to lipids, proteins, and nucleic acids. Increased oxidative stress simultaneously reduces endogenous antioxidant defenses, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx), thereby increasing the susceptibility of endocrine tissues to cellular injury[1].

Persistent oxidative stress also impairs mitochondrial integrity and ATP production, leading to mitochondrial dysfunction and activation of apoptotic pathways. Structural and functional damage has been reported in the testes, ovaries, thyroid gland, adrenal cortex, and pancreatic tissue following chronic exposure to plasticizers. Mitochondrial dysfunction further amplifies inflammatory responses and endocrine imbalance, creating a cycle of cellular injury that contributes to progressive endocrine dysfunction[16].

Recent studies further indicate that oxidative stress and mitochondrial dysfunction interact with epigenetic regulatory mechanisms, thereby influencing gene expression and increasing the likelihood of persistent endocrine abnormalities following developmental exposure. These interconnected molecular events emphasize that oxidative injury represents not only a consequence of plasticizer exposure but also a driving force behind long-term endocrine disruption[20].

5. Epigenetic Regulation

Accumulating evidence indicates that plasticizers not only alter endocrine signaling during exposure but also induce persistent changes in gene regulation through epigenetic mechanisms. Unlike genetic mutations, epigenetic modifications alter gene expression without changing the underlying DNA sequence. These modifications primarily include DNA methylation, histone acetylation, histone methylation, chromatin remodeling, and non-coding RNA regulation. Such changes are particularly important during embryonic and early postnatal development, when endocrine organs are highly sensitive to environmental stimuli. BPA and several phthalates have been shown to modify the epigenetic landscape of reproductive tissues, resulting in long-term alterations in hormone synthesis, gonadal development, and reproductive capacity[20].

Experimental studies in rodents have demonstrated that prenatal exposure to DEHP and BPA alters DNA methylation patterns in germ cells and reproductive tissues, leading to abnormal expression of genes involved in steroidogenesis, folliculogenesis, spermatogenesis, and embryonic development. These epigenetic alterations may persist throughout life and, in some instances, can be transmitted to subsequent generations, thereby contributing to transgenerational endocrine dysfunction. Altered

expression of microRNAs and histone modifications has also been implicated in the regulation of oxidative stress, inflammatory responses, and hormone receptor signaling following plasticizer exposure[17].

6. Disruption of Neuroendocrine Axes

Normal endocrine homeostasis depends on coordinated communication between the hypothalamus, pituitary gland, and peripheral endocrine organs. Plasticizers interfere with this regulatory network by altering the function of the hypothalamic–pituitary–gonadal (HPG), hypothalamic–pituitary–thyroid (HPT), and hypothalamic–pituitary–adrenal (HPA) axes.

Disruption of the HPG axis has been extensively reported in rodent studies. Plasticizer exposure suppresses gonadotropin-releasing hormone (GnRH) secretion and alters circulating concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), ultimately reducing testosterone and estradiol production. These hormonal disturbances impair spermatogenesis, ovarian follicular maturation, sexual differentiation, and reproductive performance[1, 29].

The HPT axis is another important molecular target. Several phthalates and alternative plasticizers modify thyroid hormone synthesis and interfere with thyroid hormone receptor signaling, resulting in altered circulating triiodothyronine (T3) and thyroxine (T4) concentrations. Because thyroid hormones regulate neuronal differentiation, metabolism, and growth, disruption of this axis during early development may lead to irreversible neurodevelopmental abnormalities and metabolic dysfunction[16, 27].

Plasticizers also influence the HPA axis, which regulates stress responses and glucocorticoid secretion. Experimental evidence indicates altered hypothalamic corticotropin-releasing hormone (CRH) signaling, changes in adrenocorticotropic hormone (ACTH) release, and abnormal corticosterone or cortisol concentrations following chronic exposure. Dysregulation of the HPA axis contributes to metabolic disturbances, immune dysfunction, behavioral abnormalities, and increased susceptibility to chronic disease[28, 29].

7. Inflammatory Signaling Pathways

Inflammation represents an important component of plasticizer-induced endocrine toxicity. Increasing evidence suggests that endocrine-disrupting chemicals activate inflammatory signaling cascades that amplify oxidative damage and impair endocrine function. Experimental studies have reported elevated concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1) in endocrine tissues following exposure to BPA and phthalates. These cytokines promote recruitment of inflammatory cells, tissue remodeling, and cellular injury, thereby contributing to endocrine dysfunction[1, 29].

Activation of the nuclear factor-kappa B (NF-κB) pathway is considered a central event linking oxidative stress and inflammation. Enhanced NF-κB signaling stimulates the transcription of numerous pro-inflammatory genes, perpetuating chronic inflammatory responses within reproductive organs, thyroid tissue, and the central nervous system. Persistent inflammation further aggravates mitochondrial dysfunction and endocrine imbalance, creating a self-sustaining cycle of tissue injury and hormonal dysregulation. These findings suggest that inflammatory signaling plays a critical role in the progression of plasticizer-induced endocrine disorders[29].

8. Integrated Molecular Mechanisms of Endocrine Disruption

Current evidence demonstrates that endocrine disruption induced by plasticizers results from the interaction of multiple molecular pathways rather than from a single toxicological mechanism. Plasticizers initially interact with nuclear hormone receptors, including estrogen receptors, androgen receptors, thyroid hormone receptors, and PPARs, thereby altering hormone-responsive gene expression. Simultaneously, disruption of steroidogenic enzyme activity reduces the synthesis of essential steroid hormones. These molecular events are accompanied by excessive production of reactive oxygen species, mitochondrial dysfunction, activation of inflammatory signaling pathways, and epigenetic modifications that collectively impair endocrine homeostasis[1, 16].

Table 2. Major Molecular Mechanisms of Plasticizer-Induced Endocrine Disruption

Molecular Mechanism	Principal Target(s)	Biological Consequences
Hormone receptor modulation	ER, AR, TR	Altered endocrine signaling
Steroidogenesis inhibition	StAR, CYP11A1, CYP17A1, CYP19A1	Reduced synthesis of steroid hormones
Oxidative stress	ROS, SOD, CAT, GSH	Cellular damage and apoptosis
Inflammatory signaling	NF-κB, TNF-α, IL-6, IL-1β	Chronic inflammation and tissue injury
Epigenetic regulation	DNA methylation, Histone modification, miRNA	Persistent changes in gene expression
PPAR activation	PPARα, PPARγ	Altered lipid and glucose metabolism
Endocrine axis disruption	HPG, HPT, HPA axes	Hormonal imbalance and endocrine dysfunction

The convergence of these mechanisms ultimately disrupts the HPG, HPT, and HPA axes, leading to reproductive abnormalities, thyroid dysfunction, altered stress responses, neurodevelopmental impairment, and metabolic disturbances. Developmental exposure appears to be particularly important because endocrine organs are highly susceptible during prenatal and early postnatal life. Furthermore, recent evidence indicates that epigenetic alterations induced by plasticizers may persist across generations, suggesting that endocrine-disrupting effects extend beyond directly exposed individuals. Continued investigation of these interconnected molecular mechanisms will improve toxicological risk assessment, support regulatory decision-making, and facilitate the identification of safer alternatives to conventional plasticizers[28].

ENDOCRINE EFFECTS BY SYSTEM

Table 3: Endocrine Systems Affected by Plasticizers in Rodent Models

Endocrine System	Major Hormones Affected	Representative Effects
Reproductive system	Testosterone, Estrogen, Progesterone	Reduced fertility, impaired spermatogenesis, ovarian dysfunction
Thyroid system	T3, T4, TSH	Thyroid hormone imbalance and altered metabolism
Adrenal system	Corticosterone, ACTH	Impaired stress response and adrenal dysfunction
Nervous system	Thyroid hormones, Estrogen	Neurodevelopmental and behavioral alterations
Metabolic system	Insulin, Leptin	Insulin resistance, obesity and metabolic disturbances

Reproductive System

Plasticisers can have profound effects on the reproductive system, and there is a considerable amount of research on the effects of phthalates and BPA. Testosterone production is decreased following exposure to DEHP, leading to decreased testicular weight, diameter of seminiferous tubules, and number of sperm in males of rodents[13]. BPA changes ERα expression, decreases ovarian follicle numbers, and interferes with the oestrous cycle in female rodents [15]. By making it easier for plasticiser to reach gonadal tissues, MPs and NPs worsen these effects [5]. According to transgenerational research, DEHP exposure during pregnancy causes epigenetic changes that lower male offspring fertility[17].

Nervous System and Behaviour

BPA and phthalates affect the nervous system, especially by interfering with the HPA axis. Female rodents exposed to DBP exhibit more anxiety-like behaviours[18]. Cognitive abnormalities result from BPA exposure's disruption of neurogenesis in the developing brain[20]. By passing through the blood-brain barrier, MPs and NPs intensify these effects[5].

Thyroid and Adrenal Function

Rats T3 and T4 levels are lowered when DEHA binds to thyroid hormone receptors[16]. Exposure to BPA increases the production of cortisol and causes adrenal hyperplasia[19]. In endocrine glands, MPs and NPs boost bioavailability[2].

Applications of Rodent Research

Restrictions on phthalates and BPA in consumer goods have resulted from the use of rodent research to guide risk evaluations for human health[1]. Neurotoxicity evaluations are guided by behavioural data[18], and research toward safer plasticisers is driven by thyroid/adrenal effects[16]. However, translation to humans is complicated by genetic and metabolic variations[4].

ADVANTAGES AND DISADVANTAGES OF RODENT MODELS

Advantages

- **Natural and Safe: Natural and Safe:** Rodent models are regarded as safe and reliable for researching endocrine-disrupting chemicals (EDCs)[4].
- **Physiological Similarity:** Physiological Similarity: Rodents and humans have conserved endocrine pathways, which makes them appropriate for mechanistic studies[4].
- **Controlled Experiments:** These experimental models allow precise regulation of exposure conditions, such as the administered dose, duration of exposure, and route of administration[13].
- **Transgenerational Studies:** Their brief reproductive cycles enable effective multigenerational research to assess heritable epigenetic impacts[17].

Disadvantages

- **Metabolic Differences:** Rodents often metabolize endocrine-disrupting chemicals (EDCs) at a faster rate than humans, which can lead to either an overestimation or underestimation of their toxic effects[4].
- **Limited Genetic Diversity:** The limited genetic variability present in inbred rodent strains reduces the ability to generalize findings to the genetically diverse human population[4].
- **Behavioural Complexity:** Behavioral studies conducted in rodents may not fully represent the complexity and

variability of human brain responses[18].

- **High-Dose Studies:** Several studies employ high levels of endocrine-disrupting chemicals (EDCs) that are much higher than those found in the environment and, as a result, the conclusions of these studies are less applicable to the real world[13].

FUTURE PERSPECTIVES

- **Extended and Multigenerational Research**

Future studies should address the long-term and multigenerational effects of plasticisers in rodents to gain greater understanding of the long-term effects on endocrine function. Exposures to plasticisers, especially phthalates, indicate reproductive and metabolic abnormalities which can be passed down generations via epigenetic pathways. Study of these inter-generational effects will yield a better understanding of the potential long-term adverse health impacts of endocrine disrupting plasticisers (EDPs)[21].

- **Application of Omics and Molecular Techniques**

Advanced molecular tools like transcriptomics, proteomics and epigenomics are predicted to improve knowledge of the molecular mechanisms by which plasticisers can disrupt endocrine pathways. Molecular-level studies have been shown to have the ability to reveal changes in gene expression profiles and DNA methylation patterns that occur upon exposure to phthalates, emphasizing the need for molecular-level studies to identify biomarkers of endocrine disruption[22].

- **Assessment of Mixture Toxicity**

Organisms are typically not exposed to individual plasticisers in the wild, but rather to complex mixtures of plastics and other EDCs. In order to effectively recreate environmental exposure scenarios and comprehend synergistic or antagonistic effects across chemicals, future rodent research should look into combination toxicity[23].

- **Evaluation of Alternative Plasticizers**

Industries are proposing substitute substances as regulatory bodies limit the use of conventional plasticisers like bisphenol A and certain phthalates. However, nothing is known about these alternatives' endocrine safety. To determine whether these substitutes also have endocrine-disrupting qualities, more toxicological research with rodent models is required[24].

- **Sex-Specific and Developmental Stage Sensitivity**

Future research should focus on sensitive developmental windows, such as the prenatal and early postnatal stages, and sex-specific reactions. There is evidence that endocrine-disrupting substances can disrupt hormone signalling and neuroendocrine development at crucial developmental stages[25].

- **Epigenetic Mechanisms and Gene Regulation**

According to recent studies, plasticisers may cause epigenetic changes such DNA methylation, histone modification, and microRNA regulation, which might change endocrine signalling pathways and perhaps be passed down through the generations. Determining molecular targets for intervention and enhancing risk assessment will require an understanding of these pathways[26].

Table 4: Current Knowledge Gaps and Future Research Priorities

Research Gap	Future Research Direction
Limited long-term toxicity studies	Conduct chronic and life-stage exposure studies
Insufficient evidence on alternative plasticizers	Evaluate endocrine safety of replacement plasticizers
Limited understanding of epigenetic inheritance	Perform multigenerational and transgenerational studies
Incomplete molecular mechanisms	Integrate transcriptomics, proteomics and metabolomics approaches
Limited studies on mixed chemical exposure	Assess combined effects of multiple plasticizers
Poor translation from animal models to humans	Strengthen human-relevant models and risk assessment strategies

CONCLUSION

It is well known that plasticizers, such as phthalates, bisphenols, and newly developed alternative plasticizers, are endocrine-disrupting substances that can disrupt hormonal homeostasis via a variety of molecular and physiological pathways. Exposure to these substances disrupts steroidogenesis, modifies hormone receptor signaling, causes oxidative stress and inflammation, modifies epigenetic regulation, and dysregulates the hypothalamic-pituitary-thyroid, hypothalamic-pituitary-adrenal, and hypothalamic-pituitary-gonadal axes, according to evidence from rodent studies. Particularly after developmental and chronic exposure, these changes lead to metabolic problems, thyroid dysfunction, neurodevelopmental abnormalities, adrenal difficulties, and reproductive impairment. Despite the fact that rodent models offer important mechanistic insights into endocrine toxicity, extending results to humans requires careful consideration due to variations in exposure patterns, metabolism, and species-specific responses. In order to further characterize the endocrine safety of alternative plasticizers, future research should focus on intergenerational evaluations, improved molecular techniques, chronic low-dose and mixture exposure studies, and rigorous evaluation. Enhancing toxicological evidence

thru combined experimental and translational research will enhance risk assessment for human health and facilitate the creation of safer materials and evidence-based regulations. In general, further research is necessary to reduce the endocrine dangers associated with plasticizers and to advance long-term methods of safeguarding the environment and public health.

Dislosure

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