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GESTATIONAL AND EARLY-LIFE CO-EXPOSURE TO CADMIUM AND DEHP DISRUPTS HEPATIC BIOMARKERS AND ENDOCRINE REGULATION IN RATS

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Abstract: Environmental exposure to chemical mixture represents a growing concern for maternal and developmental health. Cadmium (Cd) and di-(2-ethylhexyl) phthalate (DEHP) are ubiquitous environmental contaminants with well-documented endocrine-disrupting and hepatotoxic properties. However, toxicological evaluations largely rely on single-compound exposure models, which inadequately reflect real-life scenarios. The present study investigated whether combined gestational exposure to Cd and DEHP exacerbates hepatic dysfunction and hormonal imbalance compared to individual exposures. Pregnant Wistar rats were orally exposed to Cd, DEHP, or their combination throughout gestation. Serum hepatic biomarkers (ALP, SGOT, SGPT, LDH) and endocrine parameters (TSH, T3, T4, Cortisol) were assessed. Combined exposure produced a marked elevation of liver enzymes, particularly LDH, indicating synergistic hepatocellular injury. Simultaneously, significant disruption of thyroid hormones and cortisol levels was observed, reflecting dysregulation of the hypothalamic–pituitary–thyroid and adrenal axes. These findings demonstrate that gestational co-exposure to Cd and DEHP induces aggravated hepatic and endocrine toxicity, emphasizing the need for mixture-based risk assessment approaches.

Keywords: Cadmium, DEHP, Endocrine disruption, Gestational exposure, Hepatotoxicity, TSH, T3, T4.

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INTRODUCTION

Environmental chemical exposure has become an inevitable component of modern life, with increasing evidence that humans are exposed not to single toxicants but to complex mixture of chemicals (Prakash and Verma, 2020). Among these, cadmium (Cd) and phthalates, such as di-(2-ethylhexyl) phthalate (DEHP), are of major toxicological concern due to their widespread environmental presence, persistence and bioaccumulative nature (Kortenkamp, 2007; Gore *et al.*, 2015).

Cadmium is a non-essential heavy metal introduced into the environment through industrial emissions, contaminated food and water, and tobacco smoke (Shaw *et al.,* 2025). Chronic Cd exposure has been linked to hepatic injury, endocrine disruption, metabolic disorders, and developmental toxicity (Kang *et al.*, 2013; Ali *et al.*, 2014). DEHP, a commonly used plasticizer, readily leaches from consumer products and medical devices, resulting in continuous human exposure. DEHP and its metabolites are recognized endocrine-disrupting chemicals capable of

interfering with thyroid, reproductive, and stress hormone signaling (Meeker and Ferguson, 2011; Ye *et al.,* 2017).

Pregnancy represents a critical period of vulnerability during which exposure to toxicants can disrupt maternal physiology and permanently alter fetal development. Thyroid hormones (T3, T4, and TSH) are essential for fetal neurodevelopment and metabolic programming, while cortisol plays a key role in stress adaptation and energy balance (Bernal, 2007; Verma, 2017; Derakhshan *et al.,* 2021). The liver, being the primary site for xenobiotic metabolism as well as thyroid hormone conversion, is particularly susceptible to injury caused by toxicants. This susceptibility is reflected in changes in serum enzymes such as ALP, SGOT, SGPT, and LDH (Yu *et al.,* 2021).

Although the individual toxicities of cadmium (Cd) and di - (2-ethylhexyl) phthalate (DEHP) are well documented, real-world exposure often occurs in combination rather than in isolation. Both experimental and epidemiological studies suggest that combined exposure to endocrine disruptors can result in additive or synergistic toxicity, leading to effects that cannot be predicted based on single-compound studies (Dong *et al.,* 2019; Papaioannou *et al.,* 2021). However, there is limited data on the combined effects of Cd and DEHP on hepatic and endocrine systems during gestation. Therefore, the present study was designed to evaluate whether combined exposure to cadmium and DEHP during pregnancy exacerbates alterations in hepatic biomarkers and hormonal imbalances in rats, compared to individual exposures. This study aims to provide mechanistic insights into mixture toxicity during gestation and to offer biologically relevant evidence that can improve environmental risk assessment strategies.

MATERIALS AND METHODS

Experimental Animals and Ethics

Adult female Wistar rats were kept under standard laboratory conditions, with a temperature of 22 ± 2 °C and a 12-hour light-dark cycle. They had free access to food and water. All experimental procedures were conducted in accordance with the guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and received approval from the Institutional Animal Ethics Committee (IAEC, NO: 402/GO/Re/01/CPCSEA/002).

Chemicals and Toxicity exposure

Cadmium chloride and DEHP were obtained from standard analytical-grade (Sigma-Aldrich Ltd). DEHP was dissolved in olive oil, which served as the vehicle control. The exposure doses used in this study were selected based on preliminary effective concentration (EC50) screening conducted in the parent thesis work, using oxidative stress biomarkers to ensure biological relevance without inducing overt systemic toxicity. DEHP was administered at 100 mg/kg body weight, a sub-lethal dose shown to elicit measurable oxidative responses at the lower end of the EC50 range. Cadmium was administered at one mg per kg body weight, corresponding to the EC50 window identified for oxidative stress markers. For combined exposure, DEHP and cadmium were administered concurrently at the same doses to evaluate integrated toxicological effects under biologically effective but non-lethal conditions.

Experimental Design

Pregnant rats were randomly assigned to five groups (n = 6): control, vehicle control (olive oil), cadmium (exposed, 1 mg/kg), DEHP (exposed, 100 mg/kg), and combined DEHP + cadmium. Treatments were administered orally by gavage to pregnant dams throughout the gestational period, and exposure was continued indirectly in the pups during lactation via maternal transfer. For maternal evaluation, pregnant dams were euthanized on gestational day (GD) 19, and blood samples were collected for hormonal analysis. Offspring were allowed to remain with their mothers until weaning and were subsequently euthanized on postnatal day (PND) 21 for the assessment of hormonal and biochemical parameters.

Biochemical and Hormonal Analysis

At the end of gestation, blood samples were collected, and serum was separated for analysis. The biochemical parameters in the serum were quantified using standardized enzymatic assay kits in a controlled laboratory environment. The activity of serum lactate dehydrogenase (LDH) was measured using modified enzymatic methods, following the recommendations of the Scandinavian Committee on Enzymes. The activity of alkaline phosphatase (ALP) was estimated according to standardized protocols provided by the German Society for Clinical Chemistry (DGKC), with absorbance readings taken at 405 nm. Additionally, serum levels of aspartate amino-transferase (AST/SGOT) and alanine amino-transferase (ALT/SGPT) were determined using UV-kinetic methods in accordance with the guidelines set by the International Federation of Clinical Chemistry (IFCC). Furthermore, the serum levels of thyroid hormones (FT3, FT4, and TSH), as well as estradiol and cortisol, were quantified using a fully automated chemiluminescent immunoassay (CLIA) system. This

high-sensitivity, bidirectionally interfaced analyzer ensured precise hormone quantification with minimal manual intervention and facilitated automated data integration.

Statistical Analysis

Statistical analysis was conducted using SPSS version 20.0. The data are presented as mean ± SEM. Since the parameters did not follow a normal distribution (Shapiro-Wilk test, $p < 0.05$), authors employed non-parametric Kruskal-Wallis tests, followed by Dunn's post-hoc test for multiple pairwise comparisons, to identify significant differences between treatment groups. A p-value <0.05 was considered statistically significant. Non-parametric Kruskal-Wallis tests followed by Dunn's post-hoc test for multiple pairwise comparisons were used to determine significant differences between treatment groups. Statistical significance was defined as $p < 0.05$.

RESULTS

Maternal endocrine alterations (GD-19)

Perinatal exposure to cadmium and DEHP led to significant endocrine disturbances in pregnant dams, particularly affecting their thyroid and reproductive hormones. The co-exposure resulted in a severe hypothyroid condition, characterized by a notable increase in TSH levels (+141.7%) and significant suppression of circulating thyroid hormones (FT3: −66.7%; FT4: −52.0%) (Fig. 1 A-C). These changes indicate a disruption in thyroid hormone synthesis and feedback regulation.

Offspring endocrine profile (PND-21)

The endocrine profile of the offspring showed a distinct and paradoxical thyroid response compared to that of the dams. Cadmium exposure alone significantly increased TSH levels (+117.6%), while combined exposure resulted in a marked reduction of TSH (−68.4%). Concurrently, FT3 levels were significantly decreased (−64.0%), but FT4 levels were paradoxically elevated (+30.2%), indicating dysregulated peripheral thyroid hormone metabolism and altered signaling within the hypothalamic-pituitary-thyroid axis (Fig. 1 A-C). Additionally, cortisol levels were notably increased in both DEHP-exposed and co-exposed offspring, reflecting activation of the stress axis. The increase was most pronounced in DEHP-exposed pups (+250%), followed closely by the co-exposure group (+216.7%) (Fig. 1 D), that suggest a sustained endocrine stress and systemic hormonal imbalance during early postnatal life.

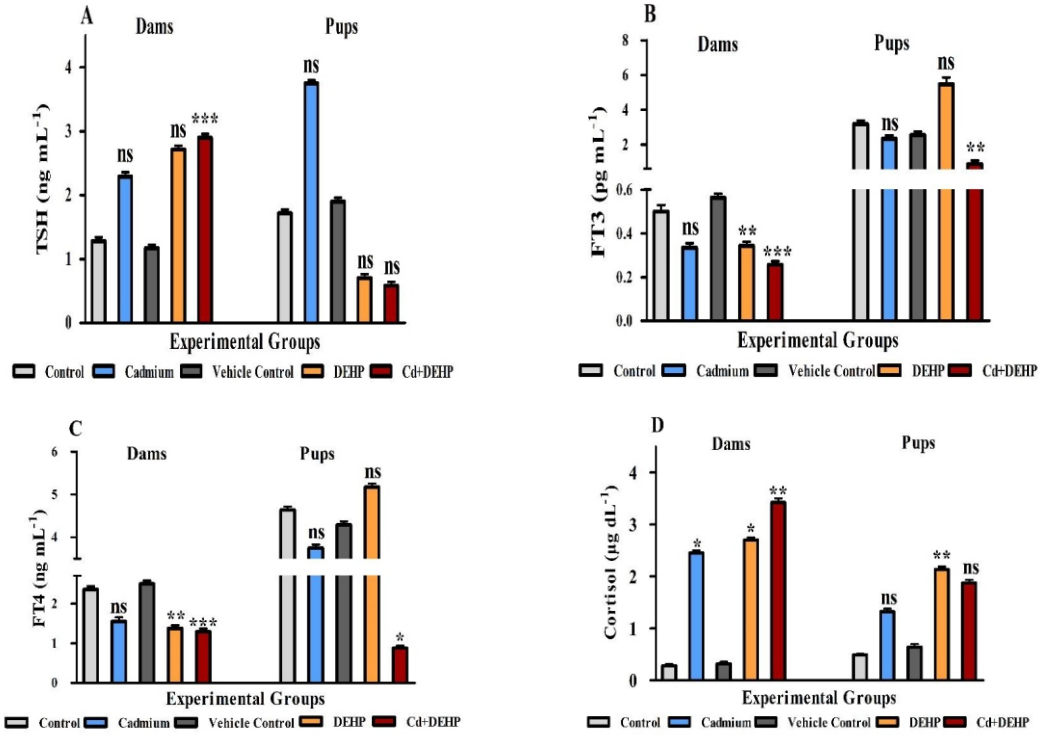

Fig. 1: Representative bar graphs illustrating alterations in serum hormone levels in gestational rats (GD-19) and their offspring (PND-22) following different experimental exposures. (A) TSH, (B) T3, (C) T4, and (D) Cortisol. The experimental groups include Control, Vehicle control (olive oil), Cd, DEHP, and combined DEHP+Cd exposure administered throughout the gestational period. Data are expressed as Mean±SEM (n=6 animals/group). Symbol '*' represents significantly different as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and 'ns' non-significant from their corresponding controls as determined by Dunn's post hoc test.

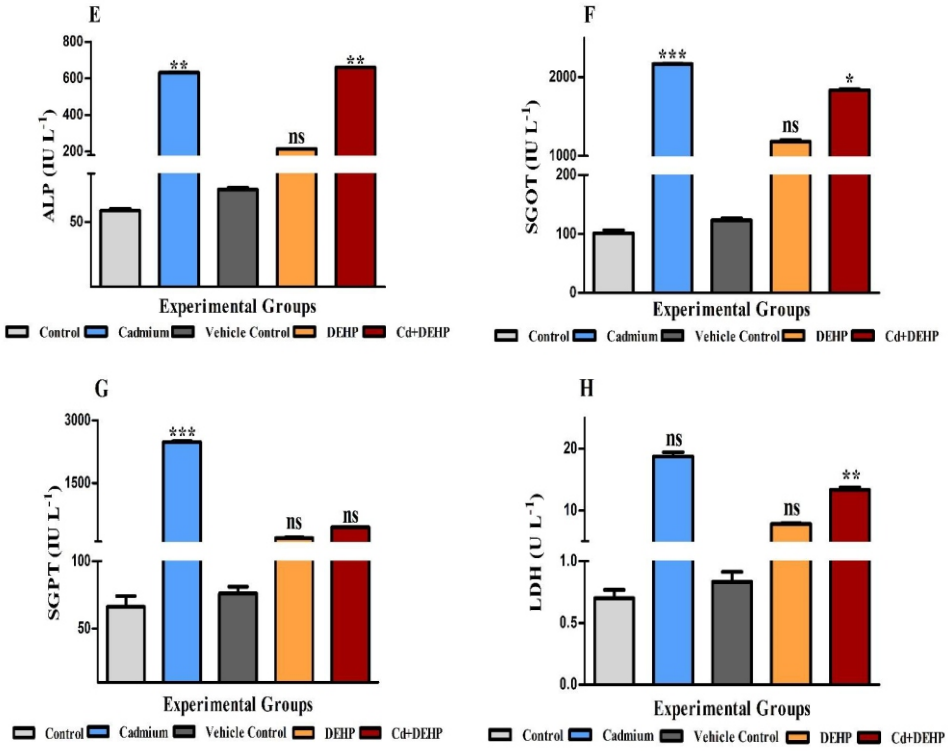

Fig. 2: Representative bar graphs illustrating alterations in liver enzyme activity levels in offspring (PND-22) following different experimental exposures. (E) ALP, (F) SGOT/AST, (G) SGPT/ALT and (H) LDH. The treatment groups include Control, Vehicle control (olive oil), Cd, DEHP, and combined DEHP+Cd exposure administered throughout the gestational period. Values are expressed as Mean±SEM (n=6 animals/group). Symbol '*' represents significantly different as * p < 0.05, ** p < 0.01, *** p < 0.001 and 'ns' non-significant from their corresponding controls as determined by Dunn's post hoc test.

Offspring serum hepatic biomarkers (PND-21)

A biochemical analysis of the serum revealed severe hepatocellular injury in offspring exposed to DEHP and cadmium, showing evidence of synergistic toxicity when these substances were combined (Fig. 1F-G). The levels of SGOT and SGPT were significantly elevated, indicating extensive damage to the liver cells. In the co-exposure group, SGOT levels increased by 1386%, while SGPT levels rose by 481% compared to the control group (Fig. 1 F-G).

Additionally, lactate dehydrogenase (LDH), which is a sensitive marker of cytotoxicity and membrane integrity, showed a remarkable and synergistic increase. In the combined exposure group, LDH activity surged by an astonishing 2312.7%, far surpassing the changes seen with individual toxicant exposure (Fig. 1-H). This significant rise points to extensive cellular damage and necrotic injury, highlighting the enhanced hepatotoxic potential of DEHP and cadmium when exposure occurs during development.

DISCUSSION

The present study shows that combined exposure to cadmium and DEHP during pregnancy worsens changes in liver biomarkers and disrupts hormonal balance in rats, with effects that are greater than those caused by individual exposures. The findings indicate that co-exposure during critical developmental period's leads to integrated systemic toxicity, resulting in coordinated disturbances in hormone regulation for mothers and their offspring, as well as impairment of liver function in the offspring. Notably, while the exposure concentrations used in this study were based on EC_{50} thresholds derived from oxidative stress endpoints in neural tissues, the downstream effects observed in the liver and endocrine systems indicate a broader toxicity continuum that extends beyond the initial oxidative injury site.

EC_{50}-guided toxicity continuum linking neural oxidative stress to hepatic and endocrine dysfunction

Toxicological responses typically begin at the molecular and cellular levels before advancing to noticeable organ dysfunction (Alshehr *et al.,* 2021; Zhang *et al.,* 2023). In this study, we used EC_{50} values derived from oxidative stress biomarkers in specific brain regions as a basis for selecting sub-lethal,

biologically effective exposure concentrations. These EC_{50} thresholds indicate early redox imbalances, which are a key mechanism associated with the toxicity of both DEHP and cadmium. Although we did not directly assess oxidative stress in this communication, the EC_{50}-guided dosing approach allowed us to capture downstream systemic effects, establishing a link between early neural oxidative disturbances and functional outcomes in hepatic and endocrine systems.

Maternal endocrine vulnerability during gestation (GD-19)

Maternal endocrine assessment revealed that the perinatal exposure to cadmium and DEHP significantly disrupted the balance of thyroid and reproductive hormones. Co-exposure resulted in a noticeable hypothyroid state, marked by a substantial decrease in circulating free thyroxine (FT4) and free triiodothyronine (FT3), along with a compensatory increase in thyroid-stimulating hormone (TSH). This hormonal pattern suggests impaired thyroid hormone synthesis or peripheral conversion, which aligns with previous studies indicating that both DEHP and cadmium interfere with the integrity of thyroid follicles, iodide uptake, and pituitary feedback regulation (Sabir *et al.,* 2019; Filippini *et al.,* 2021). Maternal hypothyroidism during pregnancy is particularly concerning, as it can compromise placental function and fetal neurodevelopment, putting offspring at risk for long-term metabolic and endocrine issues (Barber and Topping, 1995; OECD, 2008).

Offspring endocrine dysregulation and the thyroid 'Paradox' (PND-21)

Preponderance of studies on offspring endocrine profiling has shown a complex and distinct hormonal response compared to that of the dams, highlighting the vulnerability associated with different developmental stages (Bernal, 2007; Derakhshan *et al.,* 2021). In this study the exposure to cadmium alone increased the levels of TSH, while the combination of DEHP and cadmium exposure led to a paradoxical suppression of TSH. This was accompanied by a significant reduction in FT3 levels and a concurrent increase in FT4. This discrepancy between pituitary signaling and peripheral thyroid hormone levels suggests that the maturation of the hypothalamic-pituitary-thyroid (HPT) axis and peripheral hormone metabolism may be disrupted (*Kang et al.*, 2013; Fu *et al.,* 2023). Such atypical thyroid profiles have been observed in developmental toxicology studies and are often linked to liver dysfunction, which can affect deiodinase activity, hormone transport proteins, and clearance mechanisms. These findings emphasize that the endocrine disruption during early life may not resemble adult responses, but rather reflects adaptive or maladaptive programming effects (Silins and Högberg, 2011; Shanmugam *et al.,* 2023).

Additionally, cortisol levels in the offspring were significantly elevated, especially in those exposed to DEHP or both DEHP and cadmium. This indicates activation of the hypothalamic-pituitary-adrenal (HPA) axis. Hypercortisolism is a well-known biomarker of systemic stress and has been associated with oxidative injury, liver dysfunction, and neuroendocrine imbalances (Zhang *et al.,* 2023). Elevated cortisol levels during early postnatal life may further contribute to metabolic dysregulation and affect long-term stress responses.

Synergistic hepatotoxicity in offspring (PND-21)

Consistent with endocrine disturbances, offspring serum biochemistry revealed severe hepatocellular injury under combined exposure conditions. Significant elevations in SGOT, SGPT, ALP, and particularly LDH indicate compromised hepatocyte membrane integrity and extensive cellular damage. The disproportionately high rise in LDH in the co-exposure group suggests potent synergistic cytotoxicity rather than additive effects. Given the liver's central role in xenobiotic metabolism and hormone regulation, such hepatotoxicity likely contributes directly to the endocrine disruptions observed in both maternal and offspring profiles. Previous studies have shown that oxidative stress–mediated hepatic injury can impair thyroid hormone conversion and steroid metabolism, providing a mechanistic link between liver dysfunction and endocrine imbalance (Barber and Topping, 1995; Fu *et al.,* 2023).

Integrated toxicity continuum and amplified effects

Taken together, these findings support a toxicity continuum model, wherein EC_{50}-defined oxidative stress thresholds represent an upstream event that propagates systemic dysfunction across multiple organ systems. Neural oxidative stress serves as an early indicator of toxic burden, hepatic enzyme alterations reflect metabolic and detoxification failure. The endocrine disruption clearly signifies a compromised regulatory homeostasis. The amplified effects observed under combined DEHP and cadmium exposure clearly highlight the limitations of single-compound risk assessment approaches and focus the importance of evaluating environmentally relevant chemical mixtures.

In conclusion, the EC_{50}-guided exposure paradigm employed in this study effectively bridges early

oxidative stress mechanisms with downstream hepatic and endocrine dysfunction in both dams and offspring. The results demonstrate that sub-lethal, developmentally relevant co-exposures to DEHP and cadmium can induce profound systemic toxicity, particularly during sensitive gestational and postnatal windows. These findings underscore the need for mixture-based toxicological assessments and have important implications for environmental health risk evaluation and regulatory policy development.

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