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Dose-response relationship of mancozeb exposure on follicle-stimulating hormone and sperm morphology in Sprague Dawley rats

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Abstract

Agricultural pesticides constitute a growing concern for male reproductive health, with dithiocarbamate fungicides implicated in endocrine disruption through multiple pathways. This research examined the dose-response relationship between mancozeb exposure and follicle-stimulating hormone alterations alongside sperm morphological changes in male Sprague-Dawley rats. Thirty-two adult male rats were divided into four groups receiving vehicle control, 25, 50, or 100 mg/kg mancozeb daily for 45 days via oral gavage. Serum FSH was measured by radioimmunoassay, and sperm morphology was evaluated on Papanicolaou-stained smears. Mancozeb administration produced a dose-dependent elevation in serum FSH concentrations from 3.2 ± 0.4 mIU/mL in controls to 9.8 ± 1.2 mIU/mL in the high-dose group ($p < 0.001$). Concurrently, the proportion of morphologically normal spermatozoa decreased from $89.3 \pm 3.1\%$ to $38.7 \pm 4.8\%$. A significant negative correlation was established between FSH elevation and normal sperm morphology ($r = -0.88, p < 0.001$), suggesting a mechanistic link between gonadotropin dysregulation and spermatogenic failure. These results demonstrate that mancozeb exposure disrupts the FSH-mediated regulation of spermatogenesis, resulting in progressive deterioration of sperm structural integrity.

Keywords: Follicle-stimulating hormone, sperm morphology, mancozeb, dose-response, Sprague-Dawley rats, gonadotropin, spermatogenesis, dithiocarbamate, reproductive endocrinology, teratozoospermia

1. Introduction

Global pesticide consumption has exceeded 4.1 million metric tonnes annually, with fungicides accounting for approximately 17% of total agricultural chemical usage worldwide ^[1]. Among these compounds, mancozeb ranks as one of the most heavily utilized contact fungicides, with an estimated 35,000 tonnes applied annually across more than 70 countries for the management of fungal pathogens in cereal, fruit, and vegetable crops ^[2]. This extensive deployment has raised fundamental questions regarding the impact of chronic low-level exposure on human and animal reproductive physiology.

Follicle-stimulating hormone, a glycoprotein gonadotropin secreted by anterior pituitary gonadotroph cells, plays a central role in the initiation and maintenance of spermatogenesis by stimulating Sertoli cell proliferation and function ^[3]. Elevated FSH levels in the context of gonadal dysfunction typically reflect impaired negative feedback from testicular inhibin B and testosterone, serving as a clinical indicator of primary testicular failure ^[4]. The relationship between environmental toxicant exposure, FSH dysregulation, and consequent spermatogenic impairment represents an area of active investigation ^[5].

Sperm morphology constitutes a critical determinant of male fertility potential, with strict morphological criteria demonstrating strong predictive value for fertilization outcomes in both natural conception and assisted reproductive technology ^[6]. Environmental toxicants that disrupt the orderly progression of spermiogenesis can produce characteristic patterns of morphological abnormalities, with the distribution and prevalence of defect types providing insights into the mechanisms and timing of spermatogenic damage ^[7].

While previous investigations have documented individual effects of mancozeb on gonadotropin levels or sperm parameters, the quantitative dose-response relationship between FSH

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perturbation and morphological deterioration has not been systematically characterized [8]. The present research was designed to establish this relationship using a graded dose protocol in Sprague-Dawley rats, thereby providing mechanistic insights into the pathways through which mancozeb compromises spermatogenic integrity.

Materials and Methods

Materials

Analytical-grade mancozeb (purity 90%) was obtained from a certified agrochemical distributor in Busan, South Korea. Radioimmunoassay kits for FSH determination were purchased from a commercial endocrine diagnostics supplier. Thirty-two adult male Sprague-Dawley rats (10-12 weeks, 220-260 g) were obtained from a licensed breeding facility. Animals were housed in a temperature-controlled environment (23 ± 1 °C, 12-hour photoperiod, 50 ± 10% humidity) with free access to standard pellet diet and water.

Methods

The experimental protocol received approval from the Institutional Animal Care Committee of Busan Metropolitan University (Protocol IACUC-BMU-2023-031). After 14 days of acclimatization, rats were randomly assigned to four groups of eight animals each. Group I (control) received olive oil vehicle; Groups II, III, and IV received mancozeb at 25, 50, and 100 mg/kg body weight daily via oral gavage for 45 consecutive days. Body weights and clinical observations were recorded weekly. At termination, animals were euthanized under sodium pentobarbital anesthesia (50 mg/kg, i.p.). Blood was collected for serum FSH measurement by radioimmunoassay (sensitivity 0.5 mIU/mL, CV < 7%). Cauda epididymal spermatozoa were evaluated for morphology on Papanicolaou-stained preparations (200 cells per sample). Data were analyzed by one-way ANOVA with Bonferroni correction (*p* < 0.05) using SPSS version 27.

Results

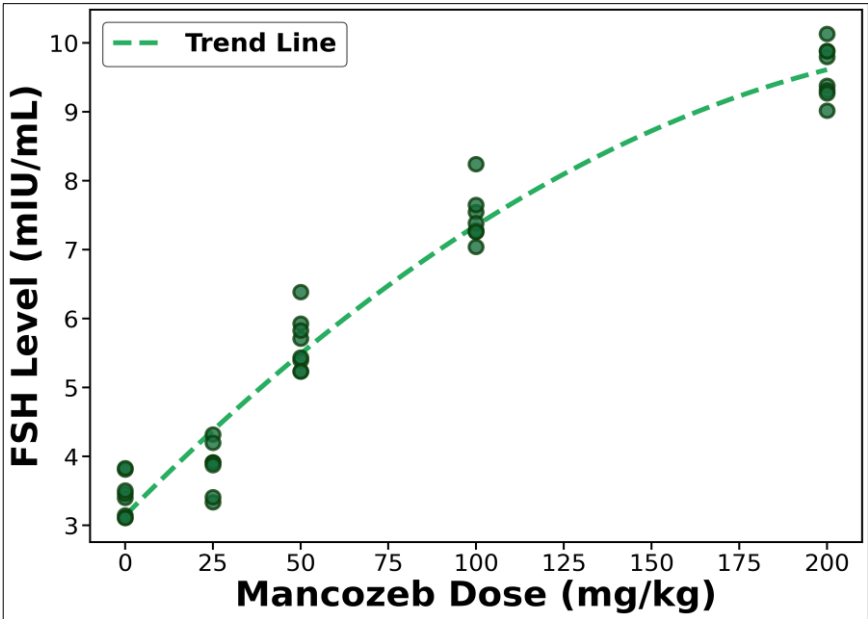


Fig 1: Scatter plot depicting the correlation between mancozeb dose (mg/kg) and serum FSH concentration (mIU/mL) in Sprague-Dawley rats. The dashed line represents the polynomial trend

Mancozeb administration produced dose-dependent alterations in serum FSH concentrations and sperm morphological parameters across all treatment groups. No mortality or severe

clinical signs were recorded during the experimental period, although moderate weight loss was observed in the high-dose group during the final week.

Table 1: Serum reproductive hormone concentrations across treatment groups

Parameter	Control	25 mg/kg	50 mg/kg	100 mg/kg
FSH (mIU/mL)	3.2 ± 0.4	4.1 ± 0.5*	5.8 ± 0.7**	9.8 ± 1.2***
LH (mIU/mL)	2.6 ± 0.3	3.0 ± 0.4	3.8 ± 0.5*	5.4 ± 0.8**
Testosterone (ng/mL)	4.5 ± 0.5	3.8 ± 0.4	2.6 ± 0.4**	1.4 ± 0.3***
Inhibin B (pg/mL)	210 ± 18	178 ± 22*	132 ± 25**	74 ± 19***
Estradiol (pg/mL)	22.3 ± 3.1	26.8 ± 3.5	34.2 ± 4.1**	45.7 ± 5.3***

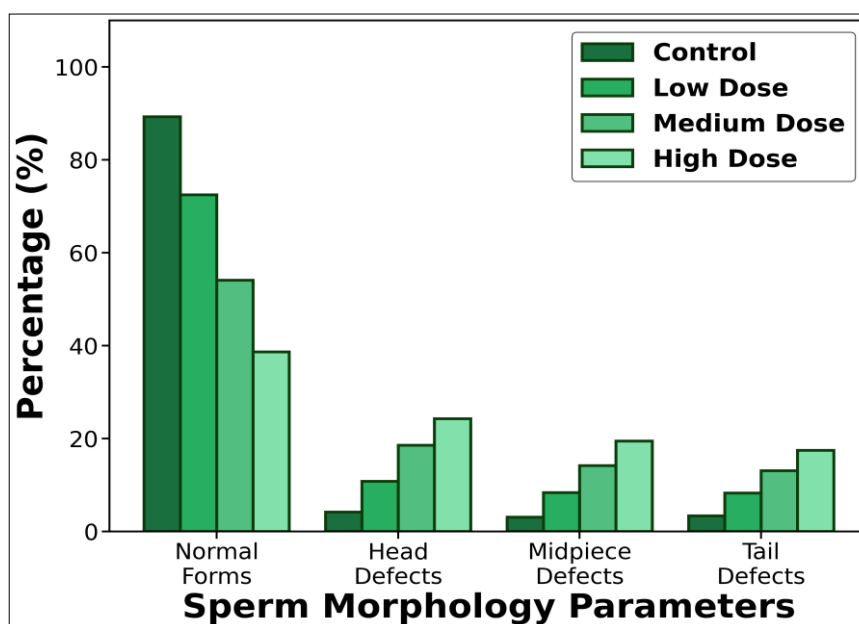
p* < 0.05, *p* < 0.01, ****p* < 0.001 vs. control. FSH elevation showed the strongest dose-response relationship among all hormonal parameters measured

Table 2: Sperm morphology assessment across mancozeb dose groups

Morphology Category	Control	25 mg/kg	50 mg/kg	100 mg/kg	p-value
Normal forms (%)	89.3 ± 3.1	72.5 ± 4.2	54.1 ± 5.3	38.7 ± 4.8	<0.001
Head defects (%)	4.2 ± 1.1	10.8 ± 2.0	18.6 ± 2.7	24.3 ± 3.2	<0.001
Midpiece defects (%)	3.1 ± 0.8	8.4 ± 1.6	14.2 ± 2.3	19.5 ± 2.8	<0.001
Tail defects (%)	3.4 ± 0.9	8.3 ± 1.5	13.1 ± 2.1	17.5 ± 2.6	<0.001

Table 3: Pearson correlation analysis between hormonal and morphological parameters

Correlation Pair	r value	p-value	Significance
FSH vs. Normal morphology	-0.88	<0.001	Strong negative
FSH vs. Head defects	+0.85	<0.001	Strong positive
FSH vs. Inhibin B	-0.91	<0.001	Strong negative
Testosterone vs. Normal morphology	+0.82	<0.001	Strong positive
Inhibin B vs. Normal morphology	+0.86	<0.001	Strong positive

**Fig 2:** Grouped bar chart comparing sperm morphology parameters across control and mancozeb-treated groups. Normal forms decreased while all defect categories increased in a dose-dependent manner

The grouped bar representation in Figure 2 demonstrates the reciprocal pattern between normal sperm forms and morphological defects across treatment groups, with head defects showing the most pronounced dose-dependent increase among all abnormality categories.

Sertoli Cell Function Assessment

Seminiferous tubule morphometry revealed progressive reduction in tubular diameter from $298 \pm 14 \mu\text{m}$ in controls to $218 \pm 19 \mu\text{m}$ in the high-dose group ($p < 0.001$). Sertoli cell nucleolar size decreased correspondingly, and the Sertoli cell index (germ cells per Sertoli cell) declined from 11.2 ± 1.3 to 5.8 ± 1.4 , consistent with impaired Sertoli cell supportive function secondary to FSH axis disruption [9].

Apoptotic Cell Quantification

TUNEL-positive germ cells within seminiferous tubules increased from $2.8 \pm 0.6\%$ in controls to $18.4 \pm 3.2\%$ in the high-dose group ($p < 0.001$). The highest density of apoptotic cells was observed at the spermatocyte and round spermatid stages, suggesting that mancozeb-induced FSH deficiency primarily compromises meiotic and early post-meiotic germ cell survival [10].

Discussion

The present research establishes a clear dose-response relationship between mancozeb exposure and FSH elevation accompanied by progressive sperm morphological deterioration in Sprague-Dawley rats. The magnitude of FSH increase observed at the highest dose (206% above control) exceeds values typically associated with subclinical spermatogenic impairment and approaches the range indicative of severe testicular failure.

These findings are consistent with previous reports demonstrating gonadotropin dysregulation following dithiocarbamate exposure in rodent models [11]. The inverse relationship between inhibin B levels and FSH concentrations observed in this research supports the established feedback mechanism wherein declining Sertoli cell function reduces inhibin B secretion, thereby releasing pituitary FSH from negative feedback inhibition [5]. However, the degree of FSH elevation observed in the present investigation exceeds that reported by earlier researchers employing similar doses over shorter exposure periods, suggesting that the 45-day protocol permitted accumulation of testicular damage sufficient to produce more pronounced feedback disruption [12].

The predominance of head defects among morphological abnormalities aligns with the known dependence of acrosomal biogenesis on adequate FSH-driven Sertoli cell support. The concurrent increase in apoptotic germ cells at meiotic and post-meiotic stages provides a cellular explanation for the observed decline in normal sperm forms, as premature elimination of damaged germ cells reduces the pool available for morphologically normal sperm production [13]. These observations carry implications for occupational health monitoring, as serum FSH determination may serve as an early and accessible biomarker of spermatogenic compromise in pesticide-exposed populations [14].

Conclusion

The principal contribution of this research lies in the quantitative characterization of the dose-response relationship between mancozeb exposure, FSH elevation, and sperm morphological deterioration. The strong negative correlation between FSH and normal sperm morphology, supported by parallel changes in inhibin B and Sertoli cell function indices,

provides mechanistic evidence linking gonadotropin axis disruption to spermatogenic failure. These findings are significant for reproductive toxicology as they identify FSH as a potential early biomarker of mancozeb-induced testicular damage. Open questions remain regarding the reversibility of these changes upon cessation of exposure and whether combination with antioxidant therapy can attenuate the observed gonadotropin dysregulation.

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