Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

Phenylmercuric Acetate as an Endocrine-Disrupting Compound: Mechanisms, Reproductive Toxicity and Evidence from Rodent Models

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Abstract

Phenylmercuric acetate (PMA) is a lipophilic organomercury compound that was widely used as a preservative, fungicide and antiseptic in pharmaceuticals, cosmetics, paints and agriculture. Although its use has been restricted in many jurisdictions, residual and occupational exposure persists. Mercury is a recognized endocrine toxicant, yet organomercurials such as PMA have received far less attention than methylmercury or inorganic mercury. This review summarizes what is known about the chemistry, toxicokinetic and endocrine-disrupting mechanisms of PMA, and integrates in vivo evidence from female Wistar rats across three experimental paradigms: an OECD TG 440 uterotrophic assay, an OECD TG 422 combined repeated-dose and reproductive/developmental screening study, and a 70-day juvenile exposure study. Oral PMA (2 to 8 mg/kg/day) increased uterine weight in ovariectomized rats, but in intact animals it suppressed LH, FSH and estradiol, prolonged diestrus, depleted healthy follicles, reduced pregnancy and delivery indices, increased implantation loss and delayed vaginal opening. These apparently opposite uterine responses suggest that PMA acts in a context-dependent manner, combining non-classical uterine irritation or weak estrogen-like activity with central and ovarian suppression of the hypothalamic-pituitary-ovarian axis. We discuss the likely mechanisms (sulfhydryl binding, oxidative stress, mitochondrial injury), critically appraise the data and the proposed no-observed-adverse-effect level (NOAEL), and outline research priorities, including receptor-level confirmation, thyroid and oxidative endpoints, and low-dose and developmental studies.

Keywords: Phenylmercuric acetate; organomercury; endocrine-disrupting chemicals; uterotrophic assay; estrous cycle; reproductive toxicity; juvenile rats.

1. Introduction

Endocrine-disrupting chemicals (EDCs) are exogenous substances that interfere with hormone synthesis, secretion, transport, receptor binding, action or elimination [1,2]. They act through nuclear receptors, steroidogenic enzymes, neuroendocrine feedback and epigenetic programming, and the developing reproductive system is particularly vulnerable [1,2]. Heavy metals form a distinct class of EDCs because they combine receptor-level interactions with enzyme inhibition and oxidative stress [3,6]. Mercury exists in elemental, inorganic and organic forms that differ markedly in absorption, distribution and toxicity [4,5]. Its endocrine effects have been described for the hypothalamus, pituitary, thyroid, adrenal and gonads in humans, laboratory animals and wildlife [3,13]. Most of this literature concerns inorganic mercury and methylmercury. Phenylmercuric acetate (PMA, CAS 62-38-4; C8H8HgO2), an aryl organomercurial, has been comparatively neglected in endocrine research despite its high lipophilicity, its history of use in consumer and pharmaceutical products, and its continued presence in some industrial and low-regulation settings [7,16]. The aims of this review are to (i) summarise the chemical, toxicokinetic and mechanistic background relevant to PMA as an EDC; (ii) consolidate experimental evidence in female rats from uterotrophic, repeated-dose/reproductive and juvenile-exposure studies; and (iii) critically evaluate the strength of the evidence and identify research gaps.

2. Chemistry, uses and exposure

PMA consists of a phenyl group covalently bound to mercury and complexed with an acetate moiety. This structure confers potent antimicrobial activity, which led to its use as a pharmaceutical and cosmetic preservative, a fungicide and seed disinfectant, and an antiseptic [7]. The carbon-mercury bond and the aromatic ring make PMA lipophilic, allowing passage across cell membranes and, as with other organomercurials, distribution to lipid-rich tissues including nervous and endocrine tissue [4,5]. Human exposure may occur through dermal contact with preserved products, inhalation or ingestion in occupational settings, and contaminated environmental media [5,7]. Many jurisdictions have restricted or phased out mercury-containing biocides and preservatives, and the Minamata Convention on Mercury [17] aims to reduce mercury-added products globally. Nevertheless, residual stocks, legacy contamination and use in less regulated contexts keep PMA toxicologically relevant, particularly for vulnerable groups such as pregnant women and children [7,16].

3. Toxicokinetic and biotransformation

Organomercurials are well absorbed after oral and dermal exposure and distribute widely, including across the blood-brain barrier and placenta [4,7]. Mercury has a very high affinity for thiol (sulfhydryl) groups, so it binds avidly to cysteine-containing proteins, glutathione and enzymes [4]. Aryl and alkyl mercurials undergo hepatic and renal biotransformation, including cleavage of the carbon-mercury bond to release inorganic divalent mercury, which accumulates preferentially in the kidney, while the intact organic fraction preferentially reaches the brain and other lipid-rich tissues [4,5]. The relative contribution of the parent compound and its inorganic metabolite to endocrine toxicity has not been resolved for PMA. This matters because both species are thiol-reactive and both can impair redox homeostasis.

4. Mechanisms of endocrine disruption

4.1 Hypothalamic-pituitary-gonadal (HPG) axis

Mercury has been reported to affect hypothalamic and pituitary function, gonadotropin secretion and steroid hormone synthesis [3,6]. Suppression of LH and FSH may arise from direct toxicity to GnRH neurons or pituitary gonadotrophs, or from altered feedback sensitivity, resulting in reduced ovarian steroidogenesis and impaired folliculogenesis [3]. In females, loss of gonadotropin support leads to persistent diestrus, follicular atresia and absent corpora lutea.

4.2 Direct gonadal and steroidogenic effects

Thiol-reactive metals can inhibit steroidogenic enzymes (for example 17β-hydroxysteroid dehydrogenase) and damage granulosa and theca cells, reducing estradiol and progesterone output [3,6]. In males, inorganic mercury produces testicular oxidative injury and altered testosterone and gonadotropin levels in rats [14], illustrating the gonadotoxic potential shared by mercury species.

4.3 Receptor-mediated activity

Some metals, including divalent mercury, have been described as "metalloestrogens" because they activate estrogen receptor alpha in cell-based assays [8,9]. Whether phenylmercury species share this property has not been established. Any estrogen-like uterine response to PMA in vivo therefore needs confirmation by receptor binding or transactivation assays and by co-treatment with an ER antagonist before it can be attributed to ER agonism.

4.4 Oxidative stress and mitochondrial injury

Mercury depletes glutathione, inhibits antioxidant enzymes (SOD, catalase, glutathione peroxidase), increases lipid peroxidation and impairs mitochondrial function, leading to apoptosis of germ, granulosa and luteal cells [4,5,14]. Oxidative damage is a plausible common pathway linking PMA exposure to follicular atresia, uterine degeneration and reduced implantation, although oxidative biomarkers have not yet been measured in the PMA studies discussed below.

4.5 Thyroid and adrenal axes

Mercury also perturbs the hypothalamic-pituitary-thyroid and adrenal axes [3,13]. Because thyroid hormone is essential for growth, neurodevelopment and pubertal timing, thyroid disruption may contribute to the growth retardation and delayed maturation seen after developmental exposure, but this remains untested for PMA.

5. Evidence from female rodent studies

The studies summarised here were conducted in female Wistar rats using oral gavage in corn oil, following OECD TG 440 and TG 422 where applicable [10,11,15,16].

5.1 Uterotrophic assay in ovariectomised rats

In an OECD TG 440 uterotrophic bioassay, ovariectomised adult rats (n = 6 per group) received corn oil, ethinyl estradiol (EE, 10 µg/kg/day, s.c.) or PMA (2 or 8 mg/kg/day, oral) for three consecutive days [10,15]. EE produced the expected strong response, validating the assay. PMA produced a dose-dependent increase in uterine wet weight, blotted weight and luminal fluid (Table 1), although smaller

than that of EE. High-dose PMA also significantly reduced food intake and produced a slight, non-significant fall in body weight [15,16].

Table 1. Uterine responses in ovariectomized rats after three days of dosing (mean ± SD, n = 6) [15,16].

Group	Wet weight (mg)	Blotted weight (mg)	Uterine fluid (mg)
Vehicle control	71.2 ± 6.0	61.2 ± 5.3	10.0 ± 1.2
EE 10 µg/kg	259.7 ± 20.7***	193.4 ± 11.4***	66.3 ± 11.0***
PMA 2 mg/kg	105.5 ± 8.7*	88.9 ± 7.5*	16.6 ± 2.1*
PMA 8 mg/kg	178.4 ± 15.3**	142.6 ± 12.7**	35.8 ± 4.6**

*p<0.05, **p<0.01, ***p<0.001 vs control.

Histology differed from the classical estrogenic pattern. EE produced epithelial hyperplasia, stromal edema and glandular cystic change, whereas PMA caused vacuolar epithelial degeneration and inflammatory infiltration at 2 mg/kg and, at 8 mg/kg, multifocal epithelial loss, extensive inflammatory infiltration and glandular degeneration [15,16]. The weight gain therefore reflects a mixture of proliferative, edematous and inflammatory components.

5.2 Combined repeated-dose and reproductive/developmental toxicity (OECD TG 422)

Male and female Wistar rats (12 per sex per group) received PMA at 0, 2, 4 or 8 mg/kg/day. Males were dosed for 28 days starting 14 days before mating. Females were dosed from 14 days before mating through lactation day 13, with satellite and recovery groups [11,16].

Systemic toxicity: There was no mortality. At 8 mg/kg/day, transient soft stools, transient reductions in food intake, reduced weight gain in males and reversible liver stress (higher ALT, lower total protein, higher absolute and relative liver weight in males) were observed, all resolving after recovery. Hematological changes were small and not significant [16].

Endocrine and cyclicity endpoints: PMA caused a dose-dependent fall in LH, FSH and estradiol in diestrus, significant already at 2 mg/kg/day (Table 2). At 8 mg/kg/day the cycle was shifted towards diestrus, with significant reductions in proestrus, estrus and a rise in the diestrus proportion ($p<0.01$). Estrous cycles at 2 and 4 mg/kg/day did not differ significantly from controls [16].

Table 2. Hormones and estrous cycle structure in adult female rats [16].

Group	LH (mIU/mL)	FSH (mIU/mL)	Estradiol (pg/mL)	Proestrus (% cycle)	Diestrus (% cycle)
Control	0.93 ± 0.012	0.90 ± 0.010	58.5 ± 0.60	13.86	41.67
PMA 2	0.88 ± 0.011*	0.80 ± 0.008*	50.4 ± 0.55*	13.08	43.09
PMA 4	0.71 ± 0.010**	0.72 ± 0.007**	38.6 ± 0.50**	12.95	43.29
PMA 8	0.59 ± 0.009***	0.65 ± 0.006***	29.8 ± 0.42***	8.98**	48.36**

Hormones: mean ± SEM; *p<0.05, **p<0.01, ***p<0.001 vs control.

Histopathology: At 4 mg/kg/day, uteri showed reduced endometrial thickness and glandular density, and ovaries showed fewer growing follicles, early granulosa disorganization and fewer corpora lutea. At 8 mg/kg/day, the endometrium was thin with collapsed glands, and ovaries showed marked follicular atresia, oocyte vacuolation, large cystic follicles and scarce corpora lutea [16].

Reproductive and developmental outcomes: Copulation and fertility indices were 100% in all groups, but pregnancy and delivery outcomes deteriorated at the high dose (Table 3). Implantation loss rose to 19.6%, gestation was prolonged by about one day, litter size and live-birth index fell, and early pup viability was reduced. No external malformations were observed, suggesting functional rather than teratogenic effects [16].

Table 3. Reproductive and developmental outcomes [16].

Endpoint	Control	PMA 2	PMA 4	PMA 8
Pregnancy index (%)	100	100	83.3	66.7
Implantation loss (%)	0.9 ± 1.8	2.5 ± 3.0	9.1 ± 18.7	19.6 ± 18.7*
Delivery index (%)	100	100	100	46.7
Gestation length (days)	22.3 ± 0.6	22.2 ± 0.4	22.0 ± 0.6	23.3 ± 0.5*
Pups born (mean)	13.6 ± 2.7	14.5 ± 2.2	12.4 ± 2.5	7.3 ± 5.9*
Live birth index (%)	90.1 ± 8.8	89.2 ± 11.8	89.3 ± 10.5	53.4 ± 41.1*
Viability index, day 4 (%)	98.2 ± 2.8	98.8 ± 2.8	88.8 ± 31.4	61.5 ± 51.0

***p<0.05 vs control.**

5.3 Juvenile female rats (70-day exposure)

Female Wistar rats (postnatal day 23 to 26, n = 10 per group) received PMA at 2, 4 or 8 mg/kg/day for 70 days from weaning through sexual maturation [16]. There was no mortality, although transient hypoactivity and piloerection occurred at 8 mg/kg/day during weeks 4 to 6. Findings at the high dose included reduced body weight gain from week 4, reduced rearing and increased hindlimb foot splay (suggesting mild neuromuscular and exploratory deficits), mild anemia, raised ALT, AST, creatinine and BUN, increased liver and kidney weights, and mild hepatocellular and renal tubular changes. Endocrine-relevant outcomes are summarised in Table 4. Vaginal opening was delayed by roughly three days, only 50% of animals showed regular cycles at days 50 to 70, and healthy ovarian follicles were depleted dose-dependently with a corresponding rise in atresia (about 28% fewer healthy follicles and 45% more atretic follicles at 8 mg/kg/day). PMA also altered uterine protein profiles in a cycle-phase-specific manner, with more pronounced changes in the luteal phase [16].

Table 4. Endocrine-relevant outcomes in juvenile female rats [16].

Endpoint	Control	PMA 2	PMA 4	PMA 8
Age at vaginal opening (days)	36.2 ± 1.1	n/r	n/r	39.3 ± 1.7*
Rats with regular cycles, days 50 to 70 (%)	90	n/r	n/r	50
Mean cycle length (days)	4.3 ± 0.5	n/r	n/r	5.9 ± 0.9*
Total healthy follicles (per ovary)	250.8 ± 8.5	240.1 ± 7.9	211.2 ± 7.4*	180.1 ± 6.8**

***p<0.05, **p<0.01 vs control; n/r, not reported for this dose. Follicle data are mean ± SE.**

6. Discussion

6.1 A context-dependent endocrine profile

The uterotrophic and repeated-dose data appear contradictory: PMA increased uterine weight in ovariectomized animals but caused uterine atrophy in intact, cycling animals. Several explanations are consistent with the data. First, in ovariectomized rats endogenous estradiol and gonadotropin feedback are absent, so any direct local effect of PMA on the uterus, whether weak ER activation or irritation, dominates the response. Second, in intact animals PMA lowers LH, FSH and estradiol (Table 2), and the resulting loss of trophic estrogen support would be expected to thin the endometrium and reduce glandular density, overriding any weak local stimulation. Third, the histology in ovariectomized rats (epithelial loss, inflammatory infiltration, glandular degeneration) points to an inflammatory contribution to uterine weight that is not diagnostic of ER agonism. This is a hypothesis rather than a conclusion. Receptor-binding or reporter assays, and uterotrophic co-treatment with an ER antagonist, are needed to separate ER-mediated growth from edema and inflammation, and OECD TG 440 itself recommends interpreting weight gains alongside histology [10,12].

6.2 Central versus ovarian sites of action

Reduced LH and FSH together with reduced estradiol, prolonged diestrus and loss of corpora lutea are consistent with suppression at the hypothalamic-pituitary level, with additional direct ovarian injury (granulosa disorganization, oocyte vacuolation, accelerated atresia). Distinguishing these requires GnRH challenge tests, gonadotropin and inhibin measurements, and in vitro granulosa and pituitary models. The mild, reversible hepatic effects at 8 mg/kg/day indicate that the reproductive effects occur at doses with only modest general toxicity, but food-intake reduction and body-weight effects mean that secondary, nutrition-related contributions cannot be excluded.

6.3 Life-stage sensitivity

The delay in vaginal opening, irregular cycles and follicle depletion after exposure from weaning indicate that the peripubertal period is sensitive, in line with the broader EDC concern about developmental windows [1,2]. The juvenile study also detected neuromotor changes, consistent with the neurotoxic potential of organomercurials [4,5]. However, dose-response information for pubertal

endpoints is limited to the highest dose in the data available, and delayed puberty co-occurring with lower weight gain may partly reflect growth retardation.

6.4 Interpreting the NOAEL

The source studies propose a NOAEL of about 4 mg/kg/day for reproductive endpoints [16]. This is supported for estrous cyclicity, copulation and fertility. It is less secure when all endpoints are considered, because LH, FSH and estradiol were already significantly reduced at 2 mg/kg/day, ovarian and uterine histology were altered at 4 mg/kg/day, healthy follicle numbers were significantly reduced at 4 mg/kg/day, and pregnancy index and implantation loss trended adversely at 4 mg/kg/day without reaching significance in a small sample. A conservative reading would treat 2 mg/kg/day as a LOAEL for hormonal endpoints. Replication with larger groups and benchmark-dose modelling would give a more defensible point of departure.

6.5 Limitations of the current evidence

- Group sizes are small (n = 6 to 12), and variance in litter outcomes is high, limiting power at 4 mg/kg/day.
- Hormones were measured at a single stage (diestrus) and limited to LH, FSH and estradiol; progesterone, testosterone, inhibin, thyroid hormones and corticosterone were not reported for PMA.
- Tissue mercury concentrations and PMA metabolites were not measured, so internal dose and the roles of parent compound versus inorganic mercury are unknown.
- Oxidative stress, apoptosis and steroidogenic enzyme expression were not measured in PMA-treated tissue, so these mechanisms remain inferred from the mercury literature.
- Doses (2 to 8 mg/kg/day) are well above likely human exposure levels, and low-dose and non-monotonic responses typical of EDCs have not been examined [1,2].
- Tests were single-sex and single-species, and extrapolation to humans requires caution.

6.6 Regulatory and public-health implications

The data support continued restriction of PMA and related organomercurial preservatives, and caution where legacy products remain in use. They also illustrate that adult-based thresholds may be insufficiently protective for juveniles and that reproductive endpoints should be integrated into the risk assessment of mercury compounds, consistent with regulatory frameworks that include endocrine endpoints in hazard identification [1,2,10,11].

7. Research priorities

1. **Mechanism:** ER alpha and beta binding and transactivation assays, ER antagonist co-treatment in uterotrophic studies, and steroidogenic enzyme and receptor expression.
2. **Biomarkers:** oxidative stress (MDA, GSH, SOD, CAT, GPx), apoptosis and inflammatory cytokines in ovary, uterus, hypothalamus and pituitary.
3. **Toxicokinetic:** tissue and blood mercury, speciation of parent PMA versus inorganic mercury, placental and lactational transfer.
4. **Broader endocrine coverage:** thyroid, adrenal and androgen endpoints, and male reproduction.

5. **Exposure realism:** low-dose, chronic and transgenerational studies, mixture studies with other preservatives such as parabens, and biomonitoring of occupational exposure.
6. **Mitigation:** evaluation of antioxidants and chelation strategies, which have been explored for other mercury compounds but not rigorously for PMA.

8. Conclusions

Phenylmercuric acetate is a reproductive and endocrine toxicant in female rats. Oral exposure increases uterine weight in ovariectomized animals through a response that includes inflammatory and degenerative change, while in intact and juvenile animals it suppresses gonadotropins and estradiol, disrupts estrous cyclicity, depletes ovarian follicles, delays puberty and, at 8 mg/kg/day, impairs implantation, parturition and neonatal survival. The profile is best described as context-dependent endocrine disruption with central and ovarian components rather than simple estrogen mimicry. The current evidence is limited by small groups, high doses and the absence of receptor-level, oxidative and toxicokinetic data, and the proposed NOAEL should be treated with caution. Targeted mechanistic and low-dose studies are needed to complete the hazard characterization of PMA and related organomercurials.

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