International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY202650018

doi: 10.37766/inplasy2026.5.0018

Received: 4 May 2026

Published: 5 May 2026

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Polyethylene Microplastics and Mitochondrial-Redox Dysfunction in Preclinical Rodent Models: A Systematic Review and Meta-Analysis of Bioenergetic and Oxidative Stress Outcomes

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ADMINISTRATIVE INFORMATION

Support - This research received financial support from the funding agency “Program Management Unit for Competitiveness (PMUC)” (Grant No. C02F670127).

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650018

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 May 2026 and was last updated on 18 May 2026.

INTRODUCTION

Review question / Objective To systematically identify, critically appraise, and quantitatively synthesize all available controlled rodent studies reporting the effects of polyethylene microplastic (PE-MP) exposure on mitochondrial TCA cycle enzyme activities, ETC respiratory chain complex activities, and markers of cellular redox homeostasis across organ systems and to determine whether mitochondrial dysfunction and redox imbalance represent a convergent, reproducible, and dose-dependent mechanistic signature of PE-MP multi-organ toxicity in preclinical models.

Rationale Most available reviews of microplastic toxicology are narrative in style, often aggregating findings on a polymer-wide basis without isolating PE-MP-specific effects, and rarely employ quantitative meta-analytic methods to combine biochemical endpoints across studies. No systematic review has specifically critiqued preclinical rodent evidence for PE-MP-induced mitochondrial perturbation and redox imbalance as co-primary outcomes. This represents a substantial gap, particularly given the regulatory and public health implications of establishing whether a coherent, organ-transcendent mechanism of PE-MP toxicity exists in preclinical models.

Condition being studied Polyethylene microplastic (PE-MP) toxicity, specifically, mitochondrial bioenergetic failure and redox collapse in preclinical rodent models, spanning multiple organ systems (kidney, heart, lung, brain/prefrontal cortex, testis, ovary, liver, blood, and eye).

METHODS

Search strategy A comprehensive systematic search of four electronic databases was conducted:

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PubMed (accessed 13 March 2026) — using MeSH terms [Mesh] with title-and-abstract qualifiers [tiab]
Scopus (accessed 13 March 2026) — using TITLE-ABS-KEY field
ScienceDirect (accessed 13 March 2026)
AMED (accessed 13 March 2026)
The search was built on three concept blocks combined with AND:
PE-MP exposure: "microplastics" OR "polyethylene"
Oxidative stress/redox: "oxidative stress" OR "reactive oxygen species" OR "redox imbalance"
Mitochondrial dysfunction: "mitochondrial dysfunction" OR "mitochondrial damage" OR "mitochondria"
Rodent restriction: "rats" OR "mice" OR "rodent".

Participant or population Controlled in vivo studies using rodents (rats or mice of any strain, sex, or age) exposed to polyethylene microplastics.

Intervention Exposure specifically to polyethylene microplastics (PE-MPs) via any route of administration, oral gavage, dietary mixing, inhalation, or intraperitoneal injection at any dose and any duration.

Comparator Unexposed control groups receiving vehicle (e.g., normal saline, corn oil, CMC-Tween-80), sham exposure (clean air for inhalation studies), or no treatment.

Study designs to be included Full-text, peer-reviewed original research articles reporting controlled in vivo (preclinical) rodent studies. No restriction on publication year. Reporting guided by PRISMA 2020 and SYRCLE guidelines.

Eligibility criteria Inclusion Criteria:
Controlled in vivo studies using rodents (rats or mice of any strain)
Exposure specifically to PE-MPs (any route, dose, and duration)
Presence of an unexposed concurrent control group
Reporting at least one quantitative mitochondrial enzyme activity (CS, IDH, MDH, SDH, Complex I–IV) OR at least one redox marker (MDA, NO, GSH, CAT, SOD, GST, MPO, AA)
Full-text peer-reviewed publications; no year restriction

Exclusion Criteria:
Studies using non-PE microplastics exclusively (e.g., polystyrene, PVC, nylon)
Mixed polymer studies where PE-MP-specific data cannot be disaggregated
In vitro, ex vivo, or human studies
Studies without a concurrent control group
Studies reporting only qualitative/histological outcomes without biochemical data
Conference abstracts, review articles, editorials, letters, and book chapters
Studies where PE-MP exposure is combined with other toxicants, unless PE-MP-alone data are separately reported
Duplicate publications (most recent/complete version retained).

Information sources
PubMed (http://www.pubmed.gov)
Scopus (http://www.scopus.com)
ScienceDirect (https://www.sciencedirect.com/)
Allied and Complementary Medicine Database — AMED (https://about.ebsco.com/products/research-databases/allied-and-complementary-medicine-database-amed)

All accessed on 13 March 2026. Data presented in figures were extracted using WebPlotDigitizer. Study management and deduplication were performed using Rayyan systematic review software.

Main outcome(s) TCA Cycle Enzyme Activities:
Citrate synthase (CS), isocitrate dehydrogenase (IDH), malate dehydrogenase (MDH), and succinate dehydrogenase (SDH)
ETC Respiratory Chain Complex Activities: Complexes I, II, III, and IV
Pro-oxidant markers: Malondialdehyde (MDA) and Nitric Oxide (NO)
Antioxidant markers: Reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT).

Additional outcome(s) Glutathione-S-transferase (GST)
Myeloperoxidase (MPO)
Ascorbic acid (AA)
Organ-specific histopathological and functional outcomes (where co-reported).

Data management Data were extracted independently by two reviewers using a pre-piloted, standardized extraction form capturing: study characteristics (authors, year, country, funding, ethical approval, ARRIVE compliance); animal characteristics (species, strain, sex, age, body weight, sample size, housing); PE-MP exposure details (polymer type, particle size, shape, dose, route, duration, vehicle, suspension method); and outcome data (mean ± SD or SEM for all biochemical endpoints). For data presented exclusively in figures, numerical values were extracted using WebPlotDigitizer. Discrepancies

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were resolved by consensus. All analyses were performed in R (version 4.x) using the meta, metafor, dmetar, and ggplot2 packages, with RevMan 5.4 for additional validation.

Quality assessment / Risk of bias analysis Two complementary tools were used:
SYRCLE Risk of Bias Tool for Animal Studies — assessed 10 domains: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was rated low, high, or unclear risk.
CAMARADES 10-item Checklist — assessed: peer-reviewed publication status, temperature control, randomization, blinded induction of exposure, blinded outcome assessment, co-interventions, appropriateness of animal model, a priori sample size calculation, animal welfare compliance, and conflict of interest declaration.

Certainty of evidence was rated using the GRADE framework adapted for preclinical animal evidence (NTP/OHAT approach) across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias — yielding High, Moderate, Low, or Very Low ratings.

Strategy of data synthesis A random-effects meta-analysis using the DerSimonian-Laird approach with Restricted Maximum Likelihood (REML) estimation of between-study variance (τ^2) was applied. The primary effect measure was the standardized mean difference (SMD) computed as Hedges' g (adjusted for small sample sizes), with 95% confidence intervals. Heterogeneity was quantified using Cochran's Q test (significance level $p < 0.10$), I^2 statistic (thresholds: 75% considerable), and τ^2. Publication bias was assessed via visual funnel plot asymmetry, Egger's weighted regression test, and the trim-and-fill method to estimate the number of potentially missing studies and adjust the pooled effect size. Meta-regression was conducted to investigate continuous predictors of effect size (dose, duration, particle size).

Subgroup analysis Pre-specified subgroups for exploring sources of heterogeneity included:
Organ system: heart, lung, kidney, testis, brain/prefrontal cortex, liver, ovary, eye
Rodent species: rat vs. mouse
Sex: male vs. female
Dose level: low (≤15 mg/kg) vs. high (>15 mg/kg)
Duration of exposure: short (≤14 days) vs. subacute (15–28 days) vs. prolonged (>28 days)
Particle size: 50 µm.

Sensitivity analysis The following sensitivity analyses were pre-specified:
Restriction to low-risk of bias studies — studies scoring ≥7/10 on CAMARADES and rated overall low-risk on SYRCLE
Restriction by sample size — excluding studies with $n < 5$ per group
Leave-one-out analysis — each study omitted sequentially to assess its influence on the pooled estimate
Exclusion of studies from the same research group — to assess laboratory-specific bias
Organ-specific exclusion — e.g., excluding lung arms for SDH/Complex II to assess the impact of organ-specific adaptive upregulation on pooled effects (this was applied post-hoc for MDH and SDH).

Language restriction English language only. Non-English records identified during the database searches were noted but excluded. Full-text peer-reviewed publications in English were required for inclusion.

Country(ies) involved Thailand.

Other relevant information Not applicable.

Keywords polyethylene microplastics, mitochondrial dysfunction, oxidative stress, electron transport chain, TCA cycle, meta-analysis, redox imbalance, multi-organ toxicity.

Dissemination plans The manuscript has been prepared for submission to a peer-reviewed journal. The protocol was prospectively registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY®). Reporting adheres to PRISMA 2020 guidelines with a completed PRISMA 2020 checklist provided as supplementary material. The review is additionally guided by SYRCLE guidelines for preclinical systematic reviews.

Contributions of each author
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