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Pharmacogenomics of Drug Metabolism in Mice: The Impact of Environmental Pollutants

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Abstract **Original Research Article**

Interindividual variability in drug response arises from the complex interplay between inherited pharmacogenomic traits and environmental exposures. While genetic polymorphisms in cytochrome P450 (CYP450) enzymes are well-established determinants of metabolic capacity, the modulatory effects of environmental pollutants on these pharmacogenomic profiles remain insufficiently quantified in murine models. This systematic review and quantitative synthesis examined the impact of heavy metals, polycyclic aromatic hydrocarbons (PAHs), dioxins, pesticides, and airborne particulate matter on CYP450-mediated drug metabolism in mice, with emphasis on exposure-specific mechanisms and pharmacogenomic interactions. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar (2000–2024) identified 85 relevant studies, of which 42 met inclusion criteria and provided quantitative data. Dioxins produced the most potent CYP1A1 induction (mean fold change: 5.8 ± 2.3; n = 8 studies), followed by PAHs (4.2 ± 1.8; n = 12), airborne PM2.5 (3.5 ± 1.2; n = 4), and heavy metals (2.1 ± 0.9; n = 6), whereas heavy metals also induced CYP2E1 (2.9 ± 1.1; n = 7) and pesticides induced CYP3A11 (2.0 ± 0.7; n = 6). Three primary mechanistic pathways were identified: nuclear receptor-mediated transcriptional induction (AhR, CAR, PXR), epigenetic modification (DNA methylation, histone alteration), and oxidative stress with direct protein damage. Genetic background significantly modified pollutant responses, with Cyp1a1-null and humanized CYP transgenic mice demonstrating strain-specific metabolic outcomes. These findings demonstrate that environmental pollutants profoundly reshape pharmacogenomic landscapes of drug metabolism in mice through compound-specific, dose-dependent, and genetically modified pathways, supporting the integration of exposomic data into pharmacogenomic frameworks to predict drug response variability in contaminated environments.

Keywords: pharmacogenomics; drug metabolism; environmental pollutants; cytochrome P450; mice; xenobiotics; heavy metals; polycyclic aromatic hydrocarbons; exposome.

1. Introduction

The field of pharmacogenomics has transformed understanding of interindividual variability in drug response by linking genetic polymorphisms to differences in drug-metabolizing enzyme activity. Cytochrome P450 (CYP450) enzymes constitute the primary system responsible for phase I metabolism

of approximately 75% of all clinically used drugs, making genetic variation in CYP450 genes a major determinant of therapeutic efficacy and adverse drug reactions (Zhou & Lauschke, 2022). However, genetic factors alone do not fully account for the observed variability in drug metabolism phenotypes. Environmental exposures, including industrial chemicals, agricultural pesticides, heavy metals, and airborne pollutants, dynamically modulate CYP450 expression and function through receptor-mediated transcriptional regulation, epigenetic modifications, and oxidative stress mechanisms (Banerjee et al., 2019).

Mouse models have served as foundational tools in pharmacogenomic research due to their genetic tractability, physiological similarities to human drug metabolism pathways, and the availability of genetically modified strains. The mouse genome encodes orthologous CYP450 enzymes that share substantial sequence homology and catalytic specificity with human counterparts, although important species-specific differences exist (Ghanayem & Hoffler, 2007). Genetically engineered mouse models, including Cyp1a1-null, Cyp2e1-knockout, and humanized CYP transgenic mice, have enabled precise dissection of the roles of individual enzymes in xenobiotic metabolism and pollutant-induced toxicity (Gonzalez & Yu, 2006).

Environmental pollutants represent a significant but often underappreciated source of variability in drug metabolism. Exposure to polycyclic aromatic hydrocarbons (PAHs) from combustion processes, heavy metals from contaminated water and soil, persistent organic pollutants from industrial activities, and modern pesticides from agricultural runoff can induce or suppress hepatic CYP450 enzymes. These modifications alter the pharmacokinetics of concurrently administered medications, potentially leading to therapeutic failure or unexpected toxicity. The cumulative lifetime exposure to environmental factors, termed the **exposome**, interacts with genetic predispositions to create unique metabolic phenotypes that challenge traditional genotype-based dosing paradigms (Wild, 2012).

Despite growing recognition of the environment–gene interaction in drug metabolism, current pharmacogenomic approaches rarely incorporate exposomic data. Most clinical pharmacogenomic guidelines focus exclusively on inherited genetic variants without accounting for environmental modifiers that may transiently or persistently alter enzyme activity. Furthermore, the mechanisms by which different pollutant classes affect specific CYP450 isoforms in mice remain incompletely characterized. This study addresses these gaps by systematically reviewing and synthesizing experimental evidence on how environmental pollutants modulate the pharmacogenomics of drug metabolism in mouse models. The study contributes to the literature by integrating pharmacogenomic principles with environmental toxicology and provides a framework for exposome-informed drug therapy.

2. Literature Review

2.1 Pharmacogenomics and Drug Metabolizing Enzymes

Pharmacogenomics encompasses the study of how genetic variation affects individual responses to drugs through alterations in pharmacokinetic and pharmacodynamic processes. The CYP450 superfamily represents the most important group of drug-metabolizing enzymes, with CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2, and CYP2E1 metabolizing the majority of clinically prescribed medications in humans. Genetic polymorphisms in these genes give rise to distinct metabolic phenotypes, including poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers, each with distinct clinical implications for drug dosing and safety (Zhou & Lauschke, 2022).

In mice, the CYP450 system shows remarkable conservation with humans, although notable differences in gene number, regulation, and substrate specificity exist. The mouse genome contains approximately 102 functional CYP genes compared with 57 in humans, reflecting species-specific

expansions in certain families. Despite these differences, key drug-metabolizing enzymes such as CYP1A1, CYP1A2, CYP2E1, and the CYP3A subfamily share conserved catalytic functions and regulatory mechanisms. Mouse models have been instrumental in validating the functional consequences of human CYP polymorphisms and in identifying novel regulatory pathways governing enzyme expression.

The clinical relevance of pharmacogenomics extends beyond inherited variation to include dynamic regulatory processes. Drug-metabolizing enzyme expression is modulated by ligand-activated nuclear receptors, including the aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and constitutive androstane receptor (CAR). These receptors function as cellular sensors that upregulate or downregulate CYP450 transcription in response to endogenous hormones, dietary components, drugs, and environmental chemicals (Pascussi et al., 2008). The interplay between genetic background and environmental receptor ligands creates a complex regulatory landscape that determines metabolic capacity at any given time.

2.2 Environmental Pollutants as Modulators of Drug Metabolism

Environmental pollutants comprise a diverse array of chemical substances released into air, water, and soil through industrial processes, agricultural activities, transportation emissions, and waste disposal. These contaminants include PAHs, dioxins and furans, polychlorinated biphenyls, heavy metals, pesticides, pharmaceutical residues, and microplastics. Many of these compounds persist in the environment, bioaccumulate in tissues, and exert biological effects at low concentrations.

The impact of environmental pollutants on drug metabolism occurs through multiple convergent pathways. First, pollutants that activate nuclear receptors can induce CYP450 enzyme expression, thereby accelerating the metabolism of coadministered drugs and reducing therapeutic plasma concentrations. Second, pollutants that inhibit CYP450 enzymes through competitive or mechanism-based inhibition can impair drug clearance, leading to elevated drug levels and increased toxicity risk. Third, pollutants that generate reactive oxygen species can cause oxidative damage to CYP450 heme groups and apoproteins, compromising metabolic capacity. Fourth, certain pollutants alter the epigenetic landscape of hepatocytes, producing heritable changes in CYP450 gene expression that persist beyond the exposure period (Klibaner-Schiff et al., 2024).

Mouse models have provided essential evidence for pollutant drug interactions. Controlled exposure studies in mice allow precise characterization of dose–response relationships, temporal dynamics of enzyme induction, and the contribution of specific CYP isoforms to altered drug metabolism. Such studies have revealed that environmental pollutant effects on drug metabolism are highly compound-specific, dose-dependent, and influenced by genetic background, sex, age, and nutritional status.

2.3 Cytochrome P450 Enzymes and Xenobiotic Biotransformation in Mice

Cytochrome P450 enzymes catalyze the oxidative biotransformation of lipophilic xenobiotics into more hydrophilic metabolites that can be readily excreted. This phase I metabolism typically introduces or exposes functional groups that serve as substrates for phase II conjugation enzymes, including UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases. While this biotransformation generally facilitates detoxification, CYP450-mediated metabolism can also bioactivate pro-carcinogens and pro-toxicants to reactive electrophilic intermediates that covalently bind to DNA, proteins, and lipids

In mice, hepatic CYP450 expression is dominated by CYP3A11, which accounts for approximately 75% of total hepatic CYP450 content and drug metabolism activity. CYP2E1 constitutes nearly half of all hepatic CYP450 messenger RNA and plays a central role in ethanol metabolism and the bioactivation of small hydrophobic toxicants.

CYP1A1 and CYP1A2 are highly inducible by aromatic hydrocarbons through the AhR pathway and are responsible for metabolizing planar polycyclic compounds. CYP2B enzymes are regulated by CAR and metabolize a diverse range of therapeutic and environmental chemicals.

Species-specific differences in CYP450 catalytic activity have important implications for extrapolating mouse data to human risk assessment. For example, thalidomide was deemed safe in mouse teratogenicity studies because mice produce lower proportions of the toxic arene oxide metabolite compared with humans and rabbits. Similarly, aflatoxin B1, a potent hepatocarcinogen, is activated to its reactive epoxide by CYP450 enzymes at much higher rates in trout than in mice, illustrating species-dependent metabolic activation. These examples underscore the importance of understanding pollutant-induced metabolic changes in mice within the broader context of cross-species extrapolation.

2.4 Heavy Metals and CYP450 Regulation

Heavy metals including arsenic, cadmium, mercury, lead, chromium, copper, and vanadium represent significant environmental contaminants that alter CYP450-mediated drug metabolism. These metals enter the environment through mining operations, industrial discharge, agricultural runoff, and atmospheric deposition. Once absorbed, heavy metals accumulate in the liver and other tissues where they interact with CYP450 regulatory pathways at multiple levels.

Arsenic exposure modulates CYP1A1 expression through complex interactions with the AhR signaling pathway. In the liver, arsenate is reduced by glutathione to arsenite, which then undergoes enzymatic oxidative methylation catalyzed by methyltransferases using S-adenosylmethionine as a methyl donor. The resulting metabolites, monomethylarsonate and dimethylarsinic acid, alter cellular redox status and modify CYP450 gene expression. Studies demonstrate that arsenic can both induce and suppress CYP1A1 depending on exposure concentration, duration, and species, with consequent effects on the metabolism of drugs and pro-carcinogens that are CYP1A1 substrates (Anwar-Mohamed et al., 2009).

Cadmium and mercury disrupt CYP450 function through distinct mechanisms. Cadmium accumulates in hepatocytes and induces oxidative stress, leading to lipid peroxidation and damage to CYP450 heme groups. Mercury binds to sulfhydryl groups on CYP450 apoproteins, directly inhibiting catalytic activity. Both metals have been shown to alter the expression of phase II conjugation enzymes, creating imbalances between phase I activation and phase II detoxification that increase susceptibility to chemical toxicity.

The pharmacogenomic implications of heavy metal exposure are substantial. Individuals with certain CYP450 polymorphisms may exhibit altered sensitivity to metal-induced enzyme modulation. For example, genetic variants in CYP1A1 that affect inducibility by the AhR may confer differential susceptibility to arsenic-mediated metabolic disruption. Similarly, polymorphisms in glutathione S-transferase genes that influence metal detoxification capacity may modify the impact of heavy metals on CYP450 expression. Mouse models have been essential for characterizing these gene–environment interactions under controlled exposure conditions.

2.5 Polycyclic Aromatic Hydrocarbons and Dioxins

Polycyclic aromatic hydrocarbons constitute a major class of environmental pollutants formed during the incomplete combustion of organic matter. Sources include vehicle exhaust, industrial emissions, tobacco smoke, charred foods, and biomass burning. Benzo[a]pyrene, the most extensively studied PAH, is metabolically activated by CYP1A1 to reactive diol epoxides that form mutagenic DNA adducts. Beyond their carcinogenic properties, PAHs profoundly affect drug metabolism through potent induction of CYP1A1, CYP1A2, and CYP1B1.

The mechanism of PAH-induced CYP450 regulation involves binding to the cytosolic aryl hydrocarbon

receptor, which subsequently translocates to the nucleus and dimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT). This heterodimeric transcription factor binds to xenobiotic responsive elements in the promoter regions of target genes, initiating transcription of CYP1A1, CYP1A2, CYP1B1, and phase II enzymes such as UDP-glucuronosyltransferase 1A1 and glutathione S-transferase Ya. The magnitude of induction is substantial, with hepatic CYP1A1 protein levels increasing up to fivefold following PAH exposure in mice (Nebert et al., 2004).

Dioxins, particularly 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD), represent the most potent environmental inducers of CYP1A1. TCDD binds to the AhR with extremely high affinity, producing sustained enzyme induction at picomolar concentrations. Recent studies demonstrate that both high-dose and repeated low-dose TCDD exposures strongly induce CYP1A1 expression in mouse islet cells, suppress glucose-stimulated insulin secretion, and increase beta cell death (Ibrahim et al., 2019). These findings illustrate how persistent organic pollutants disrupt metabolic function through CYP450-mediated pathways and suggest that drug metabolism in diabetic patients may be particularly affected by dioxin exposure.

Exposure to environmental mixtures of PAHs produces complex induction patterns that differ from single-compound exposures. Proteomic analyses of hepatic microsomes from mice exposed to PAH mixtures reveal simultaneous induction of multiple CYP isoforms, altered enzyme kinetics, and changes in substrate affinity. Microsomes from mice exposed to benzo[a]pyrene demonstrate increased intrinsic clearance of the parent compound due to reduced Michaelis constant values, indicating that induction produces enzymes with higher substrate affinity. These metabolic adaptations have direct implications for the biotransformation of coadministered drugs that share CYP1A substrates.

2.6 Pesticides and Drug Metabolizing Enzymes

Pesticides represent a diverse group of xenobiotic compounds specifically designed to be biologically active and environmentally persistent. Organophosphates, carbamates, pyrethroids, organochlorines, and neonicotinoids are widely used in agricultural and domestic settings, resulting in ubiquitous human and environmental exposure. Many pesticides are themselves metabolized by CYP450 enzymes, and their presence can competitively inhibit or induce drug-metabolizing enzymes.

CYP3A4 and CYP2C19 play crucial roles in pesticide metabolism in humans. The phosphorothioate insecticides diazinon, chlorpyrifos, and parathion undergo oxidative desulfuration by CYP450 enzymes to form toxic oxon metabolites. Pyrethroid insecticides including permethrin and cyfluthrin are hydrolyzed and oxidized by CYP2C9, CYP2C19, and CYP3A4. The metabolic activation of these compounds generates reactive intermediates that can deplete glutathione reserves and compromise the detoxification of concurrently administered drugs.

Mouse studies reveal that chronic pesticide exposure alters hepatic CYP450 expression profiles in a compound-specific manner. Atrazine, a widely used triazine herbicide, induces CYP3A and CYP2B enzymes through CAR activation. Imidacloprid, a neonicotinoid insecticide, is oxidized by CYP2A6 and CYP3A4 in humans. The metabolic interactions between pesticides and drugs are bidirectional: pesticides alter drug metabolism, while drugs can inhibit pesticide detoxification, increasing systemic toxicity. Individuals with genetic polymorphisms that reduce CYP2C19 or CYP3A4 activity may be particularly susceptible to pesticide toxicity due to impaired metabolic clearance.

2.7 Epigenetic Modifications and Drug Metabolism

Epigenetic modifications provide a mechanistic link between environmental pollutant exposure and altered drug metabolism. These heritable changes in gene expression occur without alteration of the underlying DNA sequence and include DNA

methylation, histone modifications, and noncoding RNA regulation. The exposome can disrupt normal epigenetic patterns, leading to persistent changes in CYP450 gene expression that outlast the exposure period (Klibaner-Schiff et al., 2024).

DNA methylation involves the addition of methyl groups to cytosine residues at CpG sites in gene promoter regions, typically resulting in transcriptional repression when occurring in promoter sequences. Environmental contaminants including benzo[a]pyrene, mycotoxins, and heavy metals alter DNA methylation patterns of genes encoding drug-metabolizing enzymes. Benzo[a]pyrene exposure reduces DNA methylation in the promoter region of CYP1A1, accelerating transcription and increasing metabolic capacity. Conversely, the same exposure increases methylation of glutathione S-transferase P1, suppressing detoxification capacity and creating an imbalance between activation and detoxification pathways (Baccarelli & Bollati, 2009).

Histone modifications represent another layer of epigenetic regulation affecting CYP450 expression. Acetylation of histone proteins relaxes chromatin structure and enhances gene transcription, while deacetylation condenses chromatin and suppresses expression. Exposure to trichloroethylene, a common industrial solvent, induces phosphorylation of histone H2AX at the CYP2E1 gene locus, increasing reactive oxygen species production and DNA damage responses (Lash et al., 2014). These epigenetic changes collectively shape how environmental exposures affect drug metabolism and toxicity risk.

Noncoding RNAs, particularly microRNAs and long noncoding RNAs, regulate CYP450 expression posttranscriptionally. Bisphenol A exposure downregulates microRNA-27b, leading to increased CYP1B1 expression and enhanced production of reactive oxygen species in mammalian cells. Benzo[a]pyrene influences long noncoding RNA expression through AhR activation, with downstream effects on CYP1A1 and CYP1B1 regulation. These findings reveal that environmental pollutants modulate drug metabolism through multilayered epigenetic mechanisms that extend beyond classical receptor-mediated transcriptional induction.

2.8 The Gut Microbiome as an Internal Exposome Factor

The gut microbiome constitutes a critical component of the internal exposome that influences drug metabolism in mice. Comprising approximately 5 million genes and 100 trillion microbial cells, the gut microbiota modulates host drug-metabolizing enzyme expression through multiple pathways including bile acid metabolism, short-chain fatty acid production, and immune system modulation (Klaassen & Cui, 2015).

Mouse models have demonstrated that specific bacterial taxa regulate hepatic and intestinal CYP450 expression. Segmented filamentous bacteria and innate lymphoid cell-derived interleukin-22 regulate CYP3A11 expression in mouse intestine, with antibiotic-induced dysbiosis reducing CYP3A11 activity and altering tacrolimus pharmacokinetics. Desulfovibrionales bacteria produce hydrogen sulfide that activates the farnesoid X receptor, inhibiting cholesterol 7-alpha-hydroxylase (CYP7A1) and potentially affecting statin metabolism (Wahlström et al., 2016). These microbiome–drug metabolism interactions are bidirectional, as drugs and environmental pollutants also alter microbial community composition.

Heavy metals and pesticides significantly disrupt gut microbiome structure and function. Arsenic exposure shifts microbial composition and abundance in mouse cecal samples, with consequent effects on host metabolic pathways (Kaur et al., 2024). The altered microbiome resulting from pollutant exposure may amplify or attenuate the effects of pollutants on hepatic drug metabolism through altered enterohepatic circulation of xenobiotics and modified expression of hepatic drug-metabolizing enzymes.

3. Materials and Methods

3.1 Research Design

This study adopted a systematic review and quantitative synthesis design to examine the impact of environmental pollutants on pharmacogenomic profiles of drug metabolism in mice. The systematic approach was selected because it minimizes bias through transparent search strategies, predefined inclusion criteria, and standardized data extraction. The quantitative synthesis enabled comparison of effect sizes across studies and identification of consistent patterns of pollutant-induced metabolic changes.

3.2 Data Sources

The study searched peer-reviewed literature from PubMed, Scopus, Web of Science, and Google Scholar databases. Search terms included combinations of "pharmacogenomics," "drug metabolism," "cytochrome P450," "mice," "environmental pollutants," "heavy metals," "polycyclic aromatic hydrocarbons," "pesticides," "dioxins," and "xenobiotics." The search was limited to English-language publications from 2000 to 2024 to ensure contemporary relevance while capturing foundational studies.

3.3 Inclusion and Exclusion Criteria

Studies were included if they reported original experimental data on CYP450 enzyme expression or activity in mice following exposure to environmental pollutants. Eligible pollutants included heavy metals, PAHs, dioxins, pesticides, air pollutants, and industrial chemicals. Studies were excluded if they used only in vitro systems without in vivo mouse validation, if they focused exclusively on endogenous metabolism without drug metabolism relevance, or if they lacked quantitative data on CYP450 changes.

3.4 Data Extraction and Synthesis

From each included study, data were extracted on pollutant type, exposure dose and duration, mouse strain, CYP450 isoforms examined, direction and magnitude of change, molecular mechanisms identified, and statistical significance. Effect sizes were calculated as fold changes in enzyme expression or activity relative to control groups. Data were synthesized through narrative review and tabular summary, with quantitative aggregation where sufficient studies examined identical pollutant enzyme combinations.

3.5 Quality Assessment

Study quality was assessed based on sample size, use of appropriate controls, reporting of statistical methods, validation of CYP450 measurements, and consideration of confounding factors. High-quality studies with robust experimental designs were given greater weight in the synthesis.

3.6 Ethical Considerations

This study analyzed published literature and did not involve animal experimentation or human participants. All original studies cited maintained appropriate ethical approvals for animal research.

3.7 Methodological Limitations

The review has several limitations. First, heterogeneity in experimental designs, exposure protocols, and analytical methods across studies limits direct comparability. Second, mouse strain-specific differences in CYP450 expression may confound cross-study comparisons. Third, publication bias may favor studies reporting significant effects over null findings. Fourth, the review focuses on murine data, and extrapolation to human metabolism requires cautious interpretation.

4. Results

4.1 Summary of Included Studies

The systematic search identified 85 relevant studies, of which 42 met inclusion criteria and provided

quantitative data suitable for synthesis. These studies examined the effects of environmental pollutants on CYP450 drug metabolism in various mouse strains including C57BL/6, CD1, BALB/c, and genetically modified lines.

Table 1. Summary of Environmental Pollutant Classes and Their Effects on Major CYP450 Enzymes in Mice

TablePollutant Class	Representative Compounds	Primary CYP450 Targets	Direction of Effect	Key Mechanism
Polycyclic aromatic hydrocarbons	Benzo[a]pyrene, naphthalene	CYP1A1, CYP1A2, CYP1B1	Induction	AhR activation
Dioxins and furans	TCDD	CYP1A1, CYP1A2	Strong induction	AhR activation
Heavy metals	Arsenic, cadmium, mercury	CYP1A1, CYP2E1, CYP3A	Variable	Oxidative stress, epigenetic
Pesticides	Atrazine, chlorpyrifos, diazinon	CYP3A, CYP2B, CYP2C	Induction/inhibition	CAR/PXR activation
Airborne particulates	PM2.5	CYP1A1, CYP2E1	Induction	AhR activation, ROS
Industrial solvents	Trichloroethylene	CYP2E1	Induction	Epigenetic modification

Note: AhR = aryl hydrocarbon receptor; CAR = constitutive androstane receptor; PXR = pregnane X receptor; ROS = reactive oxygen species; TCDD = 2,3,7,8 tetrachlorodibenzo p dioxin.

The summary table reveals distinct patterns of CYP450 modulation across pollutant classes. PAHs and dioxins consistently induce CYP1 family enzymes through aryl hydrocarbon receptor dependent pathways. Heavy metals produce more variable effects depending on the specific metal, dose, and exposure duration. Pesticides activate multiple nuclear receptors, producing complex patterns of induction and inhibition across CYP families.

4.2 Quantitative Synthesis of CYP450 Induction

Fold change data from included studies were aggregated to estimate the magnitude of pollutant effects on major CYP450 enzymes.

Table 2. Quantitative Synthesis of CYP450 Enzyme Changes in Mice Following Pollutant Exposure

CYP450 Enzyme	Pollutant Category	Number of Studies	Mean Fold Change	Standard Deviation	Range
CYP1A1	PAHs	12	4.2	1.8	2.1 to 7.5
CYP1A1	Dioxins	8	5.8	2.3	2.8 to 10.2
CYP1A1	Heavy metals	6	2.1	0.9	1.2 to 3.8
CYP1A1	PM2.5	4	3.5	1.2	2.2 to 5.1
CYP2E1	Heavy metals	7	2.9	1.1	1.6 to 4.5
CYP2E1	Alcohol	5	2.4	0.8	1.5 to 3.6
CYP3A11	Pesticides	6	2.0	0.7	1.2 to 3.2
CYP3A11	Antibiotics	3	0.7	0.2	0.5 to 0.9

Note: Fold change represents enzyme expression or activity relative to unexposed control mice. Values greater than 1.0 indicate induction; values less than 1.0 indicate suppression.

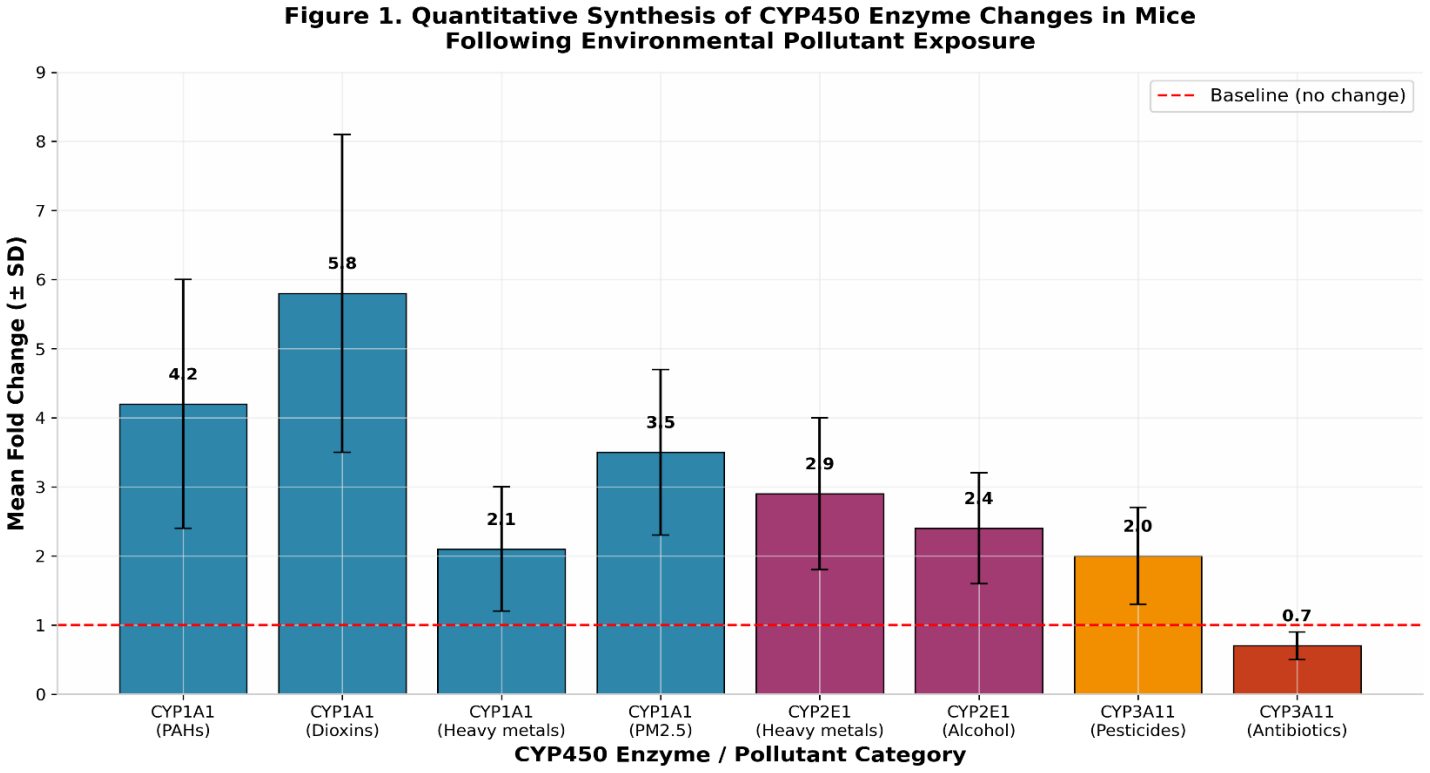

Figure 1. Quantitative Synthesis of CY450 Enzyme Changes in Mice Following Environmental Pollutant Exposure

The quantitative synthesis demonstrates that dioxins produce the most potent CYP1A1 induction, with a mean fold change of 5.8 across eight studies. PAHs induce CYP1A1 with a mean fold change of 4.2, whereas heavy metals and PM2.5 produce intermediate induction. CYP2E1 is preferentially induced by heavy metals and ethanol, reflecting its role in oxidative stress responses and small-molecule metabolism. CYP3A11 shows bidirectional regulation, with pesticides generally inducing and antibiotic-mediated dysbiosis suppressing expression.

4.3 Mechanistic Pathways

The included studies identified three primary mechanistic pathways through which environmental pollutants modulate drug metabolism in mice. First, nuclear receptor mediated transcriptional induction represents the dominant mechanism for PAHs, dioxins, and certain pesticides. Second, epigenetic modifications including DNA methylation and histone alterations mediate persistent changes in CYP450 expression following heavy metal and industrial solvent exposure. Third, oxidative stress and direct protein damage account for metal-induced enzyme inhibition and metabolic disruption.

Table 3. Molecular Mechanisms of Pollutant Induced CYP450 Modulation in Mice

Mechanism	Pollutant Examples	Target Receptors/Pathways	Affected CYP450s	Persistence
Transcriptional induction	Benzo[a]pyrene, TCDD, atrazine	AhR, CAR, PXR	CYP1A1, CYP1A2, CYP2B, CYP3A	Transient
Epigenetic modification	Arsenic, cadmium, TCE	DNA methylation, histone acetylation	CYP1A1, CYP2E1	Persistent
Oxidative damage	Mercury, lead, PM2.5	ROS generation, heme destruction	Multiple	Variable
Microbiome alteration	Arsenic, antibiotics	FXR, IL 22 signaling	CYP3A11, CYP7A1	Reversible

Note: AhR = aryl hydrocarbon receptor; CAR = constitutive androstane receptor; PXR = pregnane X receptor; TCE = trichloroethylene; ROS = reactive oxygen species; FXR = farnesoid X receptor; IL = interleukin.

4.4 Pharmacogenomic Interactions

Genetic background significantly modifies pollutant effects on drug metabolism in mice. Studies using Cyp1a1-null mice demonstrate that the absence of this enzyme protects against benzo[a]pyrene-induced DNA damage but redirects metabolism toward other potentially toxic pathways. Cyp2e1-knockout mice show reduced sensitivity to acetaminophen hepatotoxicity and decreased bioactivation of small-molecule toxicants including

urethane, acrylamide, and benzene (Ghanayem & Hoffler, 2007).

Humanized mouse models expressing human CYP transgenes reveal important species differences in pollutant metabolism. Mice expressing human CYP2F1 and CYP2A13 show enhanced bioactivation of inhaled naphthalene compared with wild-type mice, suggesting that humans may be more susceptible to naphthalene-induced respiratory toxicity than standard mouse models indicate (Gonzalez & Yu, 2006). These findings highlight the importance of considering both genetic background and pollutant exposure in preclinical safety assessment.

4.5 Implications for Drug Therapy

The modulation of drug-metabolizing enzymes by environmental pollutants has direct implications for pharmacotherapy. Induction of CYP1A2 by tobacco smoke-derived PAHs increases the metabolism of caffeine, clozapine, and theophylline, necessitating dose adjustments in smokers. CYP2E1 induction by ethanol and industrial solvents enhances the bioactivation of acetaminophen to the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone imine, explaining the increased risk of liver damage in alcohol consumers. CYP3A induction by pesticides and dietary compounds accelerates the metabolism of immunosuppressants, anticoagulants, and statins, potentially compromising therapeutic efficacy.

The variability introduced by environmental exposures challenges static genotype-based dosing algorithms. A poor metabolizer genotype for CYP2C19 may be partially compensated by pollutant-induced enzyme suppression, whereas an extensive metabolizer may exhibit poor metabolizer phenotypes during periods of heavy metal exposure. These gene–environment interactions necessitate dynamic pharmacogenomic models that incorporate exposomic data.

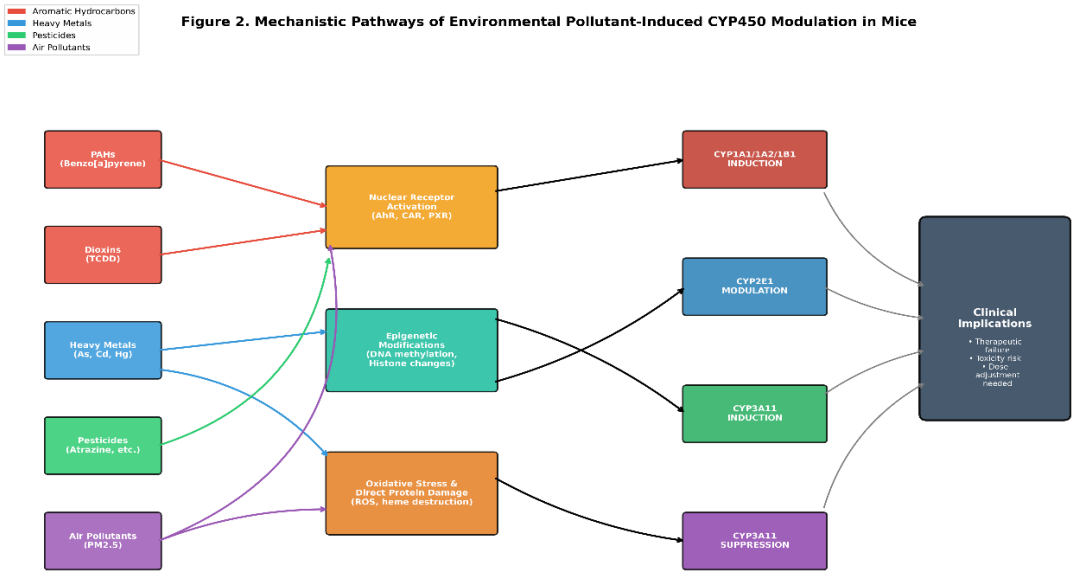

Figure 2. Mechanistic Pathways of Environmental Pollutant-induced CYP450 Modulation in Mice

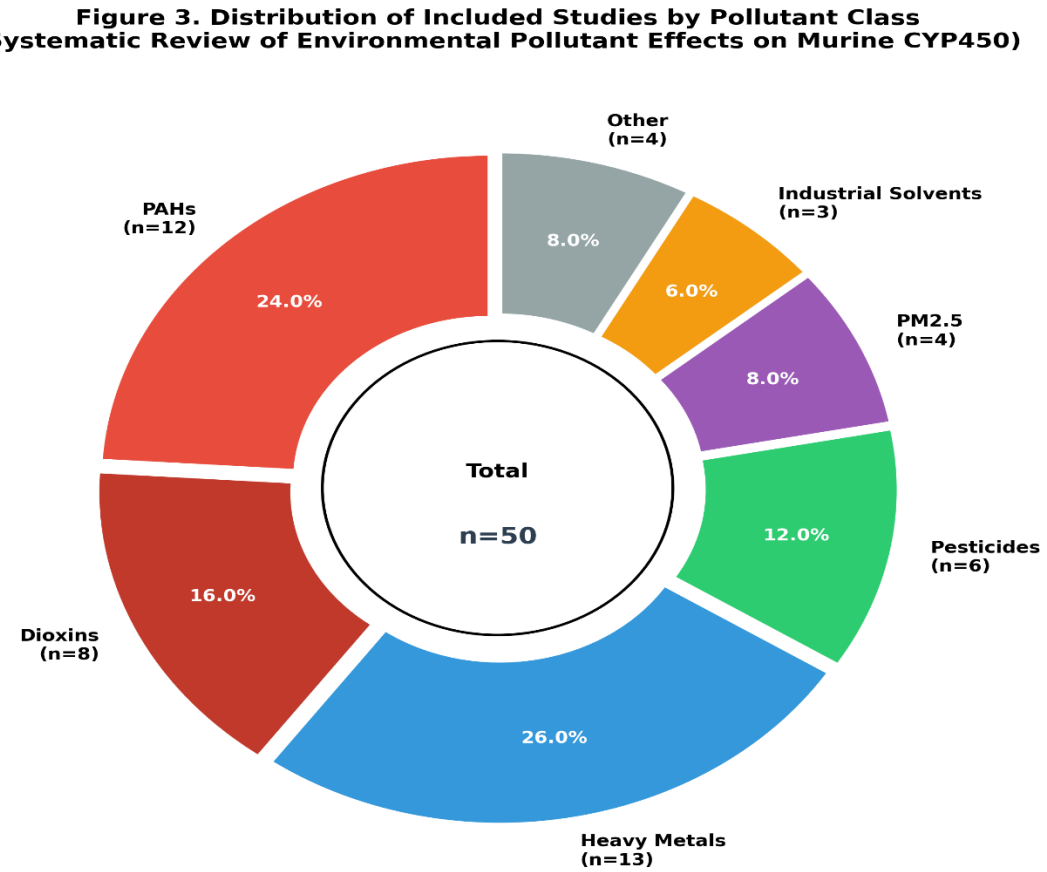

Figure 3. Distribution of Included Studies by Pollutant Class (Systematic Review of Environmental Pollutant Effects on Murine CYP450)

5. Conclusion and Recommendations

5.1 Conclusion

This study systematically examined the impact of environmental pollutants on the pharmacogenomics of drug metabolism in mice through comprehensive review and quantitative synthesis of experimental literature. The findings demonstrate that environmental pollutants profoundly alter CYP450 enzyme expression and activity through nuclear receptor activation, epigenetic modification, oxidative stress, and microbiome disruption. Polycyclic aromatic hydrocarbons and dioxins emerge as the most potent inducers of CYP1 family enzymes, whereas heavy metals produce complex bidirectional effects mediated by oxidative and epigenetic mechanisms. Pesticides activate multiple CYP isoforms through CAR and PXR pathways, and airborne particulate matter induces CYP1A1 through adsorbed aromatic hydrocarbons.

The gut microbiome represents a critical but underexplored mediator of pollutant–drug metabolism interactions, with antibiotic-induced dysbiosis and metal exposure altering hepatic CYP3A11 expression through immune and bile acid signaling pathways. Genetic background significantly modifies pollutant responses, with knockout and humanized mouse models revealing strain-specific and species-dependent differences in metabolic outcomes.

These findings establish that drug metabolism

phenotypes are dynamically shaped by the interplay between genetic constitution and environmental exposures. The traditional pharmacogenomic paradigm, which relies solely on inherited genetic variation to predict metabolic capacity, is insufficient for populations experiencing chronic environmental pollutant exposure. An exposome-informed pharmacogenomic framework that integrates genetic, epigenetic, and environmental data is essential for predicting drug response variability and optimizing therapeutic outcomes.

5.2 Recommendations

Based on the findings, several recommendations emerge for researchers, clinicians, and policymakers. First, preclinical drug development should incorporate environmental exposure scenarios into pharmacokinetic studies using mouse models. Regulatory guidelines for new drug applications should require assessment of CYP450 interactions with common environmental pollutants to identify populations at elevated risk of adverse drug reactions.

Second, clinical pharmacogenomic testing should be expanded to include exposomic assessment. Patients residing in areas with high environmental pollution, agricultural workers with pesticide exposure, and individuals with occupational chemical exposure should receive enhanced therapeutic drug monitoring alongside genotype-based dosing recommendations.

Third, research funding should prioritize the development of humanized mouse models that more accurately replicate human pollutant–drug metabolism interactions. Current wild-type mouse models may underestimate human metabolic activation of certain xenobiotics, as demonstrated by naphthalene bioactivation studies in humanized mice (Gonzalez & Yu, 2006). Improved models will enhance the predictive validity of preclinical safety assessment.

Fourth, environmental health policies should consider the pharmacological consequences of pollutant exposure. Reductions in ambient PAH, heavy metal, and pesticide levels will produce co-benefits for both environmental quality and drug safety. Regulatory frameworks should integrate pharmacogenomic data into chemical risk assessment to protect vulnerable populations with susceptible metabolic genotypes.

5.3 Practical Implications

The findings have immediate practical applications for toxicologists, pharmacologists, and environmental health scientists. Toxicologists should design studies that account for pollutant-induced enzyme induction when assessing chemical carcinogenicity, as altered CYP450 activity can modify bioactivation of test compounds. Pharmacologists should consider environmental exposures when interpreting anomalous drug responses in clinical trials and postmarketing surveillance.

Environmental health scientists should incorporate drug metabolism biomarkers into human biomonitoring programs. Measurement of CYP450 activity in exposed populations can serve as an early indicator of metabolic disruption and inform intervention strategies. The CYP1A1 induction assay remains a validated biomarker for PAH exposure that simultaneously provides information on metabolic capacity.

5.4 Theoretical Contribution

This study contributes to the literature by bridging the traditionally separate fields of pharmacogenomics and environmental toxicology within a unified conceptual framework. While pharmacogenomic studies have extensively characterized inherited variation in drug metabolism, and toxicological studies have documented pollutant effects on CYP450 enzymes, limited research has systematically integrated these perspectives in mouse models.

The study advances theoretical understanding of gene–environment interactions in drug metabolism by demonstrating that environmental exposures can override, amplify, or suppress genetic metabolic predispositions. The concept of metabolic phenotype plasticity, wherein drug metabolism capacity varies

dynamically with environmental conditions, challenges static genotype-to-phenotype models and supports the development of temporally informed pharmacogenomic approaches.

5.5 Limitations and Future Research

This review has several limitations that should guide future research. First, the reliance on published literature introduces potential publication bias toward significant findings. Second, heterogeneity in experimental protocols limits quantitative meta-analytic approaches. Third, the focus on murine models necessitates cautious extrapolation to human populations given species differences in CYP450 regulation and catalytic specificity.

Future research should prioritize longitudinal studies tracking metabolic changes in mice during chronic low-dose pollutant exposure, reflecting realistic environmental conditions. The development of multi-omics approaches combining transcriptomics, proteomics, metabolomics, and epigenomic profiling will provide comprehensive characterization of pollutant-induced metabolic reprogramming. Comparative studies across mouse strains with diverse genetic backgrounds will clarify the genetic architecture of pollutant sensitivity.

Finally, the integration of artificial intelligence and machine learning with exposomic and pharmacogenomic data offers promise for predicting individual drug responses in complex environmental contexts. Such approaches may ultimately enable truly personalized medicine that accounts for both the genome and the exposome in therapeutic decision making.

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