DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

MINIREVIEW

Special Section: Perspectives in Drug Metabolism and Disposition

Fifty years of aryl hydrocarbon receptor research as reflected in the pages of Drug Metabolism and Disposition

David S. Riddick

Department of Pharmacology and Toxicology, Medical Sciences Building,

University of Toronto, Toronto, Ontario, Canada

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Running title: Fifty years of AHR research in the pages of DMD

Corresponding author: David S. Riddick, Department of Pharmacology and Toxicology, Medical Sciences Building, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Tel: (416) 978-0813; Fax: (416) 978-6395;

E-mail: david.riddick@utoronto.ca

No. of text pages	34
No. of tables	0
No. of figures	2
No. of references	338
No. of words in Abstract	184
No. of words in Introduction	314
No. of words in Discussion	Not applicable

ABBREVIATIONS: AFB_1, aflatoxin B_1; AHH, aryl hydrocarbon hydroxylation; AHR, aryl hydrocarbon receptor; AHRR, AHR repressor; AIP, AHR-interacting protein; AKR, aldo-keto reductase; ALDH, aldehyde dehydrogenase; αNF, α-naphthoflavone; ARA9, AHR-associated protein 9; ARNT, AHR nuclear translocator; B[*a*]A, benzo[*a*]anthracene; B[*a*]P, benzo[*a*]pyrene; BCRP, breast cancer resistance protein; ßNF, ß-naphthoflavone; BSEP, bile salt export pump; CAR, constitutive androstane receptor; DEX, dexamethasone; DMD, Drug Metabolism and Disposition; DRE, dioxin-responsive element; EROD, 7-ethoxyresorufin O-deethylation; FICZ, 6-formylindolo[3,2-*b*]carbazole; FMO, flavin-containing monooxygenase; GH, growth hormone; GR, glucocorticoid receptor; GST, glutathione S-transferase; HAH, halogenated aromatic hydrocarbon; HNF, hepatocyte nuclear factor; hsp90, 90-kDa heat shock protein; HIF, hypoxia-inducible factor; I3C, indole-3-carbinol; MC, 3-methylcholanthrene; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NQO, NAD(P)H-quinone oxidoreductase; Nrf2, nuclear factor erythroid-derived 2-like 2; OATP, organic anion-transporting polypeptide; P450, cytochrome P450; PAH, polycyclic aromatic hydrocarbon; PB, phenobarbital; PCB, polychlorinated biphenyl; POR, NADPH-cytochrome P450 oxidoreductase; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; SULT, sulfotransferase; tBHQ, *t*-butylhydroquinone; TCB, 3,3',4,4'-tetrachlorobiphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, 2,3,7,8-tetrachlorodibenzofuran; TEF, toxic equivalency factor; TiPARP, TCDD-inducible poly(ADP-ribsose) polymerase; UGT, UDP-glucuronosyltransferase; XAP2, hepatitis B virus X-associated protein 2.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Abstract

The induction of multiple drug-metabolizing enzymes by halogenated and polycyclic aromatic hydrocarbon toxicants is mediated by the aryl hydrocarbons receptor (AHR). This fascinating receptor also has natural dietary and endogenous ligands, and much is now appreciated about the AHR's developmental and physiological roles, as well as its importance in cancer and other diseases. The past several years has witnessed increasing emphasis on understanding the multifaceted roles of the AHR in the immune system. Most would agree that the "discovery" of the AHR occurred in 1976, with the report of specific binding of a high affinity radioligand in mouse liver, just three years after the launch of the journal Drug Metabolism and Disposition (DMD) in 1973. Over the ensuing fifty years, the AHR and DMD have led parallel and often intersecting lives. The overall goal of this minireview is to provide a decade-by-decade overview of major historical landmark discoveries in the AHR field and to highlight the numerous contributions made by publications appearing in the pages of DMD. It is hoped that this historical tour might inspire current and future research in the AHR field.

Significance Statement

With the launch of Drug Metabolism and Disposition (DMD) in 1973 and the discovery of the aryl hydrocarbon receptor (AHR) in 1976, the journal and the receptor have led parallel and often intersecting lives over the past fifty years. Tracing the history of the AHR can reveal how knowledge in the field has evolved to the present and highlight the important contributions made by discoveries reported in DMD. This may inspire additional DMD papers reporting future AHR landmark discoveries.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Introduction

The aryl hydrocarbon receptor (AHR) is an intracellular protein that binds halogenated aromatic hydrocarbons (HAHs) such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and polycyclic aromatic hydrocarbons (PAHs) such as 3-methylcholanthrene (MC) and benzo[*a*]pyrene (B[*a*]P) (Okey, 2007). Most AHR ligands are toxic, carcinogenic environmental pollutants; however, there are also natural dietary and endogenous ligands (Nguyen and Bradfield, 2008). Many of the molecular details of AHR function have been derived from studies of the classic paradigm involving induction of the cytochrome P450 (P450) gene, *CYP1A1*, as illustrated in Fig. 1. In its unliganded state, the AHR resides in the cytoplasm in a complex with chaperones: a dimer of the 90-kDa heat shock protein (hsp90), p23, and a ~37-kDa immunophilin-related protein known as AHR-interacting protein (AIP). Ligand binding transforms the AHR into its activated nuclear form, a heterodimer of the AHR with the AHR nuclear translocator (ARNT). This heterodimer binds to specific *cis*-acting DNA enhancer sequences known as dioxin-responsive elements (DREs) in the 5'-flanking region of the *CYP1A1* gene, resulting in recruitment of transcriptional co-activators, altered histone acetylation, and chromatin remodeling. The result is increased transcription of the *CYP1A1* gene, enhanced synthesis of CYP1A1 mRNA and functional protein, with catalytic activity commonly assessed as aryl hydrocarbon hydroxylation (AHH) or 7-ethoxyresorufin O-deethylation (EROD). Acute ligand treatment often triggers AHR nuclear export, ubiquitination and proteasomal degradation.

The purpose of this minireview is to provide a decade-by-decade overview of major historical landmark discoveries in the AHR field and to illustrate the important contributions that have derived from work published in Drug Metabolism and Disposition (DMD). Interested readers are directed to the following sources for comprehensive tables and figures showing

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

timelines of AHR major milestone discoveries (Okey, 2007; Gasiewicz and Henry, 2012; Nebert, 2017), AHR ligands (Nguyen and Bradfield, 2008; Stevens et al., 2009; DeGroot et al., 2012), and AHR target genes (Boverhof et al., 2006; Boutros et al., 2008; Stevens et al., 2009).

The 1970s

Long before the 1970s, we must recognize as a key foundation of the AHR field the discovery of "MC-type" induction, in which prior exposure of rodents to MC could increase the synthesis of microsomal enzymes capable of biotransforming the inducing chemical and other substrates (Conney et al., 1956). Major landmarks in AHR research during the 1970s include characterization of differences at the *Ah* locus between the "responsive" C57BL/6 mouse strain and the "non-responsive" DBA/2 mouse strain (Gielen et al., 1972), identification of TCDD as a much more potent AHH inducer than PAHs such as MC (Poland and Glover, 1974), the use of [^{3}H]TCDD to demonstrate specific binding to the mouse hepatic AHR (Poland et al., 1976), and the discovery of AHR translocation from the cytoplasm to the nucleus (Okey et al., 1979).

The inaugural DMD issue was published in January 1973 and featured presentations from the 2nd Symposium on Microsomes and Drug Oxidations held at Stanford University in July 1972. A report from the Nebert group discussed genetic differences at the *Ah* locus between "responsive" and "non-responsive" mouse strains as assessed by AHH induction, and the text included the prescient speculation that "the inducer acts at some subcellular site (*question mark*), thereby causing synthesis of induction-specific RNA and protein – regulated in some manner, at least in certain mouse strains, by the dominant *Ah* allele" (Nebert et al., 1973). In a few short years, this "*question mark*" would be definitively identified as the AHR. The inaugural issue also contained a report of induction of AHH activity in human foreskins cultured in the presence of

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

B[*a*]P or benz[*a*]anthracene (B[*a*]A) (Alvares et al., 1973). The following year saw a report of EROD activity as a direct fluorimetric assay of microsomal P450s preferentially induced by MC (Burke and Mayer, 1974). A strong correlation was reported between the AHH activities in human lymphocyte cultures and plasma half-lives of antipyrine and phenylbutazone (Kellermann et al., 1975). Studying MC induction in several inbred mouse strains, AHH activity was found to be under similar regulatory control as phenacetin O-dealkylation (Poppers et al., 1975), which would eventually become a diagnostic marker activity for CYP1A2. Closing out the decade in DMD, a fascinating report showed that 2,3,7,8-tetrachlorodibenzofuran (TCDF) as a contaminant in a commercially available 99% pure polychlorinated biphenyl (PCB) isomer was the inducer of rat hepatic AHH activity (Goldstein et al., 1978).

The 1980s

Landmark discoveries during the 1980s include the demonstration that TCDD toxicity segregates with the *Ah* locus (Poland and Glover, 1980), early quantitative structure-activity relationships for AHR ligands (Bandiera et al., 1984), comparisons of the physicochemical properties of the cytosolic vs. nuclear AHR forms (Gasiewicz and Bauman, 1987), initial characterization of the highly TCDD-resistant Han/Wistar (Kuopio) rat strain (Pohjanvirta et al., 1987), identification of the human AHR by ligand binding (Manchester et al., 1987), and discovery of 6-formylindolo[3,2-*b*]carbazole (FICZ) as a candidate endogenous ligand (Rannug et al., 1987). The final years of the decade saw the definition of the DRE nucleotide sequence (Denison et al., 1988), identification of hsp90 as a component of the AHR cytosolic complex (Perdew, 1988), and demonstration of a low affinity AHR in the “non-responsive” DBA/2 mouse (Okey et al., 1989).

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

During the decade of the 1980s, DMD featured several interesting and important publications related to the AHR field. Three Bernard B. Brodie Award Lecture articles were particularly relevant to this topic. Donald Jerina reviewed the metabolism of aromatic hydrocarbons by P450s and epoxide hydrolases (Jerina, 1983). Among other topics, Gilbert Mannering's article contained the fascinating story of using phenobarbital (PB)- and MC-treated rats to derive some of the earliest evidence for distinct forms of P450s (Mannering, 1986). Daniel Nebert provided a wonderful historical overview of the first two decades of research on the *Ah* locus and the AHR (Nebert, 1988).

Some DMD papers further explored "MC-type" induction in rat and rabbit liver. Immunohistochemistry revealed induction of P450a (CYP2A1) by MC in mature female and immature male and female rats, but not mature male rats (Moody et al., 1983). In vivo treatment of rats with MC or a PCB mixture (Aroclor 1254) increases the metabolism of 8-hydroxymethylbenz[*a*]anthracene to the 8,9-dihydrodiol (Yang et al., 1984). In vivo treatment of rats with MC increases in vitro liver microsomal theobromine metabolism and in vivo theobromine elimination (Shively and Vesell, 1987) and hepatic microsomal conversion of the antiarrhythmic amiodarone to desethylamiodarone (Young and Mehendale, 1987). In vivo treatment of rats with ß-naphthoflavone (ßNF) increases in vitro liver microsomal 8-methoxypsoralen metabolism and in vivo total clearance of 8-methoxypsoralen (Mays et al., 1987). In vivo treatment of rats with nafimidone alcohol, the major metabolite of the anticonvulsant nafimidone, increases hepatic EROD activity, consistent with "MC-type" induction (Rush et al., 1987). N-Benzylimidazole displays both MC- and PB-type induction of phase I and II enzymes in rat liver (Papac and Franklin, 1988). MC protects rats from acute *trans*-4-acetylaminostilbene toxicity by increasing the rate of phase II conjugation pathways of

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

inactivation relative to oxidative activation (Pfeifer and Neumann, 1988). Hind-limb ischemia secondary to infrarenal aortic ligation (as a model of traumatic injury) results in induction of hepatic EROD activity and P-448 content, in contrast to a decrease in other P450 activities (Griffeth et al., 1984). In vivo treatment of rats with ßNF causes selective down-regulation of androgen-dependent testosterone hydroxylation activities (Shiverick, 1981). In vivo treatment of rabbits with ßNF increases the rate of B[a]P fluorescence elimination from individual hepatocytes based on microspectrofluorometry (Massey et al., 1986).

Several DMD papers exploited genetic differences at the *Ah* locus between "responsive" C57BL/6 mice and "non-responsive" DBA/2 mice. Examples included: induction of theophylline clearance by ßNF or MC (Betlach and Tozer, 1980); induction of 2,5-diol formation from biphenyl by ßNF (Halpaap-Wood et al., 1981); a comparison of the metabolism of two antitumor ellipticines (Roy et al., 1985); and a stronger AHH induction by MC in C57BL/6 mice, studied here as fast acetylators, than in slow acetylator A/J mice (Elves et al., 1985).

Some publications featured an extrahepatic focus. There are age-dependent differences in rat skin AHH inducibility by topically applied MC (Mukhtar and Bickers, 1983). Treatment of rabbits with TCDD induces the 7-hydroxylation of 2-acetylaminofluorene in most lung cell fractions separated by elutriation (Minchin et al., 1985). The PCB metabolite 4,4'-bis(methylsulfonyl)-2,2',5,5'-tetrachlorobiphenyl binds to protein residing in club and goblet-like cells in lung and the apical region of proximal tubular cells in kidney (Brandt et al., 1985), and these methylsulfonyl-PCBs bind with high affinity to secretory 13-kDa protein in rat lung club cells (Lund et al., 1988). Immunohistochemistry was used to define the regional and cellular selectivities shown in mouse lung for the major MC-inducible P450 forms (Forkert et al., 1989). Extrahepatic PAH metabolism and DNA binding featured in the following DMD papers.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Comparison of B[*a*]P covalent binding in perfused rat lung following systemic vs. intratracheal dosing reveals a partial protective effect of liver (Foth et al., 1984). Capsaicin, an active principle in hot peppers, inhibits B[*a*]P metabolism and DNA binding in mouse and human keratinocytes (Modly et al., 1986). In vivo treatment of pregnant rats with ßNF or MC induces B[*a*]P metabolism and DNA binding catalyzed by microsomes from the vascular labrynth zone tissues of rat placenta (Salhab et al., 1986). Topical application of MC to neonatal BALB/c mice causes maximal induction of PAH metabolism and DNA binding in the epidermal skin compartment (Das et al., 1986).

A few DMD papers had a glucuronidation focus. Several AHR activators (MC, B[*a*]P, TCDD) increase rat hepatic levels of UDP-glucuronic acid and this may influence glucuronidation (Watkins and Klaassen, 1983). Stereoselective glucuronidation of oxazepam can provide evidence for distinction between quite similar inducers such as MC and ßNF (Yost and Finley, 1985). B[*a*]A induces EROD activity and UDP-glucuronosyltransferase (UGT) activity toward 3-hydroxy B[*a*]P in rat hepatocytes (Forster et al., 1986). The disposition of HAHs was also a prominent topic. The disposition of [^{3}H]TCDD was compared in "responsive" vs. "non-responsive" mouse strains (Gasiewicz et al., 1983). The use of congenic mouse strains that differ at the *Ah* locus showed that the distribution and excretion of TCDD is mainly governed by the total genetic background rather than the allele at the *Ah* locus (Birnbaum, 1986). Studies of isolated hepatocytes from C57BL/6 and DBA/2 mice showed that uptake and metabolism of TCDD are not correlated with genetic differences at the *Ah* locus (Shen and Olson, 1987). Studies of isolated hepatocytes from rat and hamster, a species highly resistant to TCDD, showed that the effects of inducers (MC and TCDD) and inhibitors on metabolism of TCDD and B[*a*]P

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

reveal species differences in the substrate specificity of P-448 involved in TCDD metabolism (Wroblewski and Olson, 1988).

The remaining important DMD papers from the 1980s fall under the heading "of fish and men". In terms of fish, waterborne B[*a*]P exposure of freshwater *Poeciliopsis* species increases hepatic AHH and EROD activities (Goddard et al., 1987), and dietary MC or B[*a*]P causes preferential induction of intestinal AHH and EROD activities in spot, a marine teleost (van Veld et al., 1988). In terms of humans, an early study showed a weak, but significant, correlation between AHH activity in human liver biopsy samples and in vivo antipyrine half-life or clearance (Pelkonen et al., 1980). The 4-hydroxylation of 17ß-estradiol was induced in human placental microsomes from smokers, but the correlation with AHH activity shows an unusual threshold-type relationship (Juchau et al., 1982). Metabolism of 7,12-dimethylbenz[*a*]anthracene and DNA adduct formation were studied in human fetal kidney and intestinal cells in culture (Oravec et al., 1985). Theobromine plasma clearance was shown to be higher in smokers vs. non-smokers due to induction of multiple metabolic pathways, particularly 7-demethylation (Miners et al., 1985). Finally, studies in human liver microsomes characterized the biotransformation of caffeine, paraxanthine, theophylline, and theobromine by PAH-inducible P450s (Campbell et al., 1987).

The 1990s

This decade witnessed a noticeable acceleration of AHR research as new molecular tools and approaches became available. Many landmark discoveries can be highlighted. There was introduction of the toxic equivalency factor (TEF) approach to the risk assessment of dioxin-like chemicals acting through the AHR (Safe, 1990). The early 1990s saw the demonstration that the

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

transformed AHR is heteromeric (Elferink et al., 1990), and this was followed quickly by the purification of AHR protein (Bradfield et al., 1991), the raising of polyclonal antibodies to the AHR (Poland et al., 1991), and cloning of the AHR cDNAs from mouse (Burbach et al., 1992; Ema et al., 1992) and human (Dolwick et al., 1993). Discovery of ARNT revealed the identity of the AHR's nuclear heterodimerization partner (Reyes et al., 1992). Further molecular dissection revealed the arrangement of the AHR's functional domains (Fukunaga et al., 1995) and the generation of *Ahr*-null mice provided definitive evidence of the AHR's role in toxic responses to xenobiotics and developmental processes (Fernandez-Salguero et al., 1995; Schmidt et al., 1996; Mimura et al., 1997). Germ-line deletion of *Arnt* in mice was shown to result in embryonic lethality due to defective angiogenesis (Kozak et al., 1997; Maltepe et al., 1997). The remaining components of the AHR cytosolic complex were identified as a ~37-kDa immunophilin-related protein designated by various groups as AIP (Ma and Whitlock, 1997), AHR-associated protein 9 (ARA9) (Carver and Bradfield, 1997), or hepatitis B virus X-associated protein 2 (XAP2) (Meyer et al., 1998), along with p23 (Kazlauskas et al., 1999). To close the decade, acute ligand treatment was shown to result in ubiquitination and proteasomal degradation of AHR protein (Davarinos and Pollenz, 1999; Roberts and Whitelaw, 1999).

DMD featured Brodie Award Lecture articles by Wayne Levin and Fred Guengerich during the 1990s. The Levin review discussed the early observation that the spectral maximum of the ferrous carbonyl complex was at ~448 nm (instead of 450 nm) for microsomes from MC-treated rats, and the subsequent purification and raising of antibodies against the major constitutive, PB- and MC-inducible rat liver P450s (Levin, 1990). A pertinent aspect of the Guengerich review was the role of the major PAH-inducible human P450s (CYP1A1 and 1A2) in carcinogen activation (Guengerich, 1993). Alan Poland reported on an ASPET-sponsored

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

colloquium entitled “Receptor-acting xenobiotics and their risk assessment” held in October 1995; this meeting was stimulated by the release of the U.S. Environmental Protection Agency draft risk assessment of TCDD, the first for a xenobiotic exerting its toxic effects via a receptor (Poland, 1996). The Anthony Y.H. Lu Commemorative Issue of DMD appeared in December 1998 and contained a review from the Gonzalez group highlighting the toxic responses and developmental and physiological processes mediated by the receptor observed during the first few years after generation of *Ahr*-null mice (Gonzalez and Fernandez-Salguero, 1998). This same issue also contained a report on an ASPET symposium entitled “Physiological and pathophysiological regulation of cytochrome P450” held at Experimental Biology 1998; in this report, the Tukey group discussed the role of signal transduction in AHR-mediated transcriptional activation of the *CYP1A1* gene (Morgan et al., 1998).

Further work on mouse strain differences showed that PB induced CYP1A2 at the mRNA, protein, and enzyme activity levels in mouse strains that are either “responsive” or “non-responsive” to PAHs (Sakuma et al., 1999). Several DMD papers in the 1990s continued to characterize “MC-type” induction in rat liver. In MC-treated rats, formation clearance of 4-hydroxyantipyrine and metabolic clearance of theophylline are strongly correlated (Groen et al., 1992). Distinct mechanisms are involved in the induction of NAD(P)H-quinone oxidoreductase (NQO) in liver and kidney by arsenite vs. ßNF (Falkner et al., 1993). The potent AHR agonist, TCDD, was shown to decrease biliary excretion of total thiol-derived sulfur and reduced glutathione (Madhu et al., 1993). Studies of the modulation by glucocorticoids of induction responses to TCDD, B[*a*]A, and *t*-butylhydroquinone (tBHQ) revealed regulation of *Ah* battery genes via AHR-dependent and -independent processes in cultured rat hepatocytes (Xiao et al., 1995). The biphasic kinetics for the metabolism of the ß-adrenoceptor blocker, bunitrolol, in

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

microsomes from MC-treated rats are due to the involvement of both CYP1A1 and a CYP2D subfamily enzyme (Fujita et al., 1996). Caffeine, not polyphenols, is the component in tea responsible for induction of CYP1A2 protein and activity in rat liver (Chen et al., 1996). Among hydroxymethylglutaryl-coenzyme A reductase inhibitors tested, fluvastatin is unique in showing CYP1A1 inducing properties in primary cultured rat hepatocytes and in rat liver (Kocarek and Reddy, 1996). Among proton pump inhibitors, pantoprazole shows less CYP1A induction in rat liver compared to omeprazole or lansoprazole (Masubuchi et al., 1997). Using 7-ethoxycoumarin O-deethylation as a marker activity, rat liver slices underestimate the effects of the inducer ßNF compared to isolated hepatocytes and hepatic microsomes (Carlile et al., 1999). Finally, four DMD papers focused on indole-3-carbinol (I3C), an AHR activator found in cruciferous vegetables. Both ßNF and I3C inhibit aflatoxin B_1 (AFB_1) carcinogenesis, at least partly, by inducing P450s and enhancing net production of less toxic, hydroxylated AFB_1 metabolites (Stresser et al., 1994a). I3C, and ßNF to a lesser degree, protects against AFB_1 carcinogenesis by inducing glutathione S-transferases (GST) with high activity toward AFB_1 *exo*-epoxide, thereby decreasing DNA adducts (Stresser et al., 1994b). The disposition of I3C and its metabolites was characterized in male rats (Stresser et al., 1995) and I3C was shown to inhibit the activity and expression of flavin-containing monooxygenase (FMO)-1 in rat liver and intestine (Larsen-Su and Williams, 1996).

DMD papers from the 1990s with an extrahepatic focus included the report that the relative inducibility of CYP1A1 and EROD activity, but not NQO, in skin by dibenz[*a*,*c*]anthracene is regulated as a function of epidermal differentiation (Reiners et al., 1992). The induction of CYP1A1 mRNA by B[*a*]A and ßNF was also characterized in rat epidermis and cultured human epidermal keratinocytes (Khan et al., 1992). Expression of

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

CYP1A1 and 1A2 mRNA is enhanced in rat renal tissue after exposure to MC or pyridine (Kim et al., 1995). The inducibility of rat small intestinal CYP1A1 by ßNF diminishes from duodenum to ileum, and intestinal induction is more sensitive to oral vs. intraperitoneal ßNF (Zhang et al., 1996). Interestingly, the decrease in CYP1A1 inducibility from duodenum to ileum parallels the AHR protein levels (Zhang et al., 1997). The induction of rat CYP1A1 by intraperitoneal ßNF is much greater in airways and lung parenchyma compared to liver or trachea (Lee et al., 1998). Finally, dose-dependent induction of CYP1A by nicotine feeding was characterized in rat lung, kidney, and liver (Iba et al., 1999).

In terms of glucuronidation, treatment of rat hepatocytes with MC induces a high affinity phenol UGT, shifting benzene metabolism toward the production of less toxic metabolites (Schrenk and Bock, 1990). In human colon carcinoma Caco-2 cells, TCDD induces UGT1A6 and 1A9, whereas tBHQ induces UGT1A6, 1A9, and 2B7 (Munzel et al., 1999). DMD papers examining HAH disposition included the report that at two days following dosing, less than 0.1% of an immunosuppressive dose of [^{3}H]TCDD is distributed to mouse spleen (Neumann et al., 1992). Decreased AHR-mediated toxicity following oral administration of 3,3',4,4'-tetrachloroazobenzene vs. TCDD is largely due to extensive azo reduction and limited systemic absorption (Pillai et al., 1996). Similarly, for 3,3',4,4'-tetrachloroazoxybenzene, decreased toxicity is mainly due to reduced absorption and enhanced elimination of metabolites (Ziegler et al., 1996). The effects of age, sex, and pharmacologic agents on rat biliary elimination of TCDD were characterized (Jackson et al., 1998). With respects to PAHs, rat Kupffer cells were shown to act as a reservoir for B[a]P, reducing access to drug-metabolizing enzymes in the hepatic parenchymal cells (Zhong et al., 1994).

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Work with human cellular models showed: PAH inducibility of CYP1A enzyme activities in three long-term normal human hepatocyte lines cocultured with rat liver epithelial cells (Roberts et al., 1993), and strong induction of EROD activity by MC in primary human hepatocyte cultures (Donato et al., 1995). Studies with diverse species included monkey, chicken, and fish. Oral treatment of cynomolgus monkeys with ßNF induces hepatic CYP1A1/2 proteins and associated activities such as EROD and caffeine N3-demethylation (Bullock et al., 1995). In chick embryo hepatocytes, different TCDD-inducible CYP1-related P450s are responsible for arachidonic acid epoxygenation and AHH activity (Paroli et al., 1994), and the arachidonic acid epoxygenase (CYP1A5) is mainly responsible for uroporphyrinogen oxidation induced by AHR ligands in chicken liver and kidney (Sinclair et al., 1997). Induction of CYP1A1 in liver and extrahepatic tissues of the marine teleost scup by 3,3',4,4'-tetrachlorobiphenyl (TCB) and TCDF was studied by immunohistochemistry (Smolowitz et al., 1991), and AHR-regulated CYP1A enzymes were found to be involved in TCB metabolism in this fish species (White et al., 1997). CYP1A-dependent EROD and AHH activities are induced by dietary ßNF in the intestine, but not liver, of channel catfish (James et al., 1997).

The 2000s

Achievement of important milestones in AHR research continued apace during the first decade of the new millennium. The adoption of genome-wide approaches to the analysis of the transcriptome dramatically expanded the repertoire of genes up- and down-regulated by the activated AHR, and only a few of the early examples are cited here (Puga et al., 2000; Frueh et al., 2001; Thomas et al., 2001; Boverhof et al., 2006). The AHR repressor (AHRR) was discovered and characterized as a negative regulator of AHR signaling (Baba et al., 2001).

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Several novel and informative genetically-modified mouse models were generated and characterized: mice with a constitutively active AHR (McGuire et al., 2001), *AHR*-humanized mice (Moriguchi et al., 2003), and mice carrying a mutation in the AHR's nuclear localization signal (Bunger et al., 2003) or DNA-binding domain (Bunger et al., 2008). There was growing attention to the role of the AHR in the immune system, characterized by the seminal study showing control of T_{reg} and T_H17 differentiation by the AHR (Quintana et al., 2008).

The total annual page count for DMD and the number of papers related to the AHR appearing in the journal both reached peaks during the 2000s decade (Fig. 2). DMD featured several minireviews, symposium reports, and perspectives articles of relevance to the AHR field during the 2000s. A minireview reported on a symposium entitled "Molecular regulation of genes encoding xenobiotic-metabolizing enzymes: mechanisms involving endogenous factors" held in Boston, MA in 2000; this included a report from the Elferink group discussing the implications of AHR and retinoblastoma protein interactions for cell cycle control (Hines et al., 2001). The same meeting featured a symposium entitled "Glucuronidation and the UDP-glucuronosyltransferases in health and disease"; this symposium paper included reports from the Guillemette group on human UGT polymorphisms and smoking-related cancers, the Wells group on UGT deficiency as a determinant of B[*a*]P toxicity, and the Ritter group on PAH exposure as a cause of variation in UGT1A1 and 1A6 levels (Wells et al., 2004). A report on an ASPET symposium entitled "Transcriptional suppression of cytochrome P450 genes by endogenous and exogenous chemicals" held at Experimental Biology 2003 included our work on the transcriptional down-regulation of the male-specific growth hormone (GH) pulse-regulated rat hepatic *CYP2C11* by PAHs and HAHs via an incompletely understood mechanism that involves the AHR (Riddick et al., 2004). A review article published as a tribute to James R. Gillette

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

included consideration of the induction of small intestinal CYP1A1 and other drug-metabolizing enzymes by AHR activators (Kaminsky and Zhang, 2003). A minireview on metabolism-based drug-drug interactions featured discussions of how various aspects of AHR biology influence inter-individual variability in CYP1A inducibility (Tang et al., 2005). A perspectives article covered the important topic of CYP1A induction and human risk assessment (Ma and Lu, 2007). The year 2008 was memorable for ASPET and centennial perspectives articles focused on drug metabolism research included discussion of historical landmarks in the discovery of "MC-type" induction and the early characterization of the AHR system (Murphy, 2008a) and the continuing evolution of the AHR field into the realm of endogenous ligands (Murphy, 2008b). Perspectives from the Pharmaceutical Research and Manufacturers of America included surveys of current practices for in vitro assays of P450 inducers acting via the AHR and clinical drug-drug interaction studies involving CYP1A2 induction (Bjornsson et al., 2003; Chu et al., 2009).

Further characterization of "MC-type" induction in rat liver appeared in DMD research articles during this decade. I3C and a major acid condensation product, 3,3'-diindolylmethane, decrease rat hepatic FMO1 protein and enzyme activities while inducing P450 activities (Katchamart et al., 2000). Induction of CYP1A1 mRNA levels by ßNF in cultured rat hepatocytes was characterized using real-time RT-PCR and the RNA invasive cleavage assay (Burczynski et al., 2001). Taqman-based real-time RT-PCR was used to confirm CYP1A1 and 1A2 induction in rat liver by ßNF, and the technique was used to estimate the inductive potential of drug candidates undergoing rodent toxicity evaluation (Baldwin et al., 2006). The suspected human carcinogen, 3-nitrobenzanthrone, and its metabolite, 3-aminobenzanthrone, induce rat hepatic NQO1 and CYP1A, thereby promoting DNA adduct formation (Stiborova et al., 2006). Multiple DREs were implicated in the constitutive and MC-inducible expression of rat hepatic

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

aldehyde dehydrogenase ALDH3A1 (Reisdorph and Lindahl, 2007). The anticancer drug ellipticine modulates its own metabolic detoxification and DNA adduct formation by inducing rat hepatic CYP1A1 and 1A2 (Aimova et al., 2007).

Mouse animal and cellular models were a focus for AHR research in several DMD papers. Treatment of mice with ßNF causes strong induction of CYP1A1 protein in endothelial cells of blood-brain interfaces and a corresponding increase in irreversible binding of [^{3}H]7,12-dimethylbenz[*a*]anthracene (Granberg et al., 2003). MC induces human CYP1A2 mRNA and protein in chimeric mice with humanized liver (Katoh et al., 2005). TCDD triggers AHR-dependent induction of mouse hepatic FMO2 and FMO3 mRNAs (Celius et al., 2008). Mice with liver-specific deletion of ß-catenin show decreased AHR mRNA levels and diminished induction of AHR target genes by MC (Braeuning et al., 2009). Inoculation of human hepatocellular carcinoma cells into athymic nude mice has little impact on basal hepatic AHR mRNA levels and induction of AHR target genes by MC (Sugawara et al., 2009). Mercury and lead increase, whereas copper decreases, constitutive and TCDD-inducible expression of NQO1 and GST Ya mRNAs in mouse Hepa-1 cells via a transcriptional mechanism (Korashy and El-Kadi, 2006). Vanadium interferes with TCDD-induced transcriptional activation of *CYP1A1* in mouse Hepa-1 cells (Anwar-Mohamed and El-Kadi, 2008).

DMD papers with an extrahepatic focus included the report that mouse small intestinal CYP1A1 protein shows higher inducibility by ßNF proximally with decreasing induction distally, and induction is stronger in C57BL/6 vs. 129/Sv mice (Zhang et al., 2003). ßNF (van de Kerkhof et al., 2005) and several other AHR activators (van de Kerkhof et al., 2007) induce CYP1A-dependent 7-ethoxycoumarin O-deethylation in rat small intestinal and colon precision-cut slices. ßNF induces CYP1A1 and UGT1A6 mRNA levels in precision-cut slices from human

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

proximal jejunum and colon (van de Kerkhof et al., 2008). The C57BL/6 vs. DBA/2 mouse strain difference was used to demonstrate that CYP1A1 induction by ßNF in white adipose tissue is AHR-mediated (Yoshinari et al., 2006).

Regarding glucuronidation, MC induces UGT activity toward thyroxine in rat hepatocytes, but the response is not potentiated by dexamethasone (DEX) as is the case for UGT1A6 induction (Jemnitz et al., 2000). The dietary flavonoid, chrysin, a relatively weak AHR agonist, induces UGT1A1 in HepG2 cells (Walle et al., 2000). Comparisons of 22 flavonoids in HepG2 cells suggest that UGT1A1 induction by these compounds occurs via a novel non-AHR-mediated mechanism (Walle and Walle, 2002). Treatment of primary human hepatocytes with MC induces estradiol-3-glucuronidation in 4 of 5 donors (Soars et al., 2004). In contrast to the AHR-activating PCB mixture Aroclor 1254, treatment of rats with various catechols produces little effect on their own hepatic glucuronidation (Elovaara et al., 2004). Immunoactivation of rat peritoneal macrophages induces UGT1A7 mRNA and glucuronidation of 3-hydroxy-B[a]P (Tochigi et al., 2005). A comparison of Wistar vs. UGT1A-deficient Gunn rats showed that the decrease in serum thyroxine levels caused by the PCB mixture Kanechlor-500 is mostly due to thyroxine tissue accumulation rather than UGT induction (Kato et al., 2007). The AHR activator, 1,7-phenanthroline, induces CYP1A1 and UGT1A6 in rats fed a standard diet or a high-fat/high-sucrose diet; the diet also had no effect on hepatic AHR and ARNT protein levels, and AHR and ARNT showed no sex differences (Osabe et al., 2008). The proximity of a DRE to a glucocorticoid-responsive element in the 5'-flanking region of rat *UGT1A6* is involved in the diminished glucocorticoid induction following AHR activation (Falkner et al., 2008).

There was a large increase in the number of DMD papers dealing with the human AHR system during the 2000s. CYP1B1, an AHR target, is commonly expressed in human lung at the

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

mRNA and protein levels, and this is likely important for lung carcinogen metabolism (Spivack et al., 2001). The *CYP1B1*3/*3* genotype is associated with decreased mRNA expression in human leukocytes, CYP1B1 levels are higher in females vs. males, and tobacco smoke does not alter CYP1B1 levels (Helmig et al., 2009). AHR, ARNT, and CYP1A1 mRNA levels in lymphocytes from healthy subjects show strong correlations (Siest et al., 2008). The human AHR variants, K401R and N487D, display decreased transcriptional activity in response to MC, ßNF, and omeprazole, mainly through decreased protein expression due to accelerated proteasomal degradation (Koyano et al., 2005). In a study with precision-cut human liver slices, ßNF induced CYP1A2 protein levels, but CYP1A1 protein was not detected before or after treatment with model inducers (Edwards et al., 2003). DNA binding of B[*a*]P is associated with CYP1A1 and 1B1 induction in bioengineered human gingival epithelial tissue constructs (Walle et al., 2006). The sequential metabolism of 2,3,7-trichlorodibenzo-*p*-dioxin by CYP1A1 and UGTs was characterized in human liver microsomes (Kasai et al., 2004). The AHR-inducible human CYP2S1 showed negligible activity in the metabolism of nicotine and bioactivation of several cigarette smoke lung carcinogens (Wang et al., 2005).

DMD published several studies that characterized the presence and functionality of the AHR in human cellular models. This paragraph covers work done with cultured primary human hepatocytes. Quantitative real-time RT-PCR was used to characterize CYP1A1 induction by MC, omeprazole, and lansoprazole (Bowen et al., 2000). Strong induction of CYP1A2 by ßNF was confirmed using data summarized from 62 hepatocyte preparations (Madan et al., 2003). The antitumor olivacine derivative, S 16020, induces CYP1A2 protein, CYP1A-dependent enzyme activities, and its own metabolism (Pichard-Garcia et al., 2004). Reliable assessment of the induction of CYP1A2 enzyme activity, with phenacetin as probe, by omeprazole was shown

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

using a substrate cassette strategy (Mohutsky et al., 2005). Induction of CYP1A2 mRNA, protein, and EROD activity by omeprazole was demonstrated in cryopreserved hepatocytes (Roymans et al., 2005). Simultaneous measurement of 23 human P450s confirmed strong induction of CYP1A1, 1A2, and 1B1 mRNA by MC (Girault et al., 2005). TCDD induces mRNA levels for multidrug resistance 1 (MDR1) and breast cancer resistance protein (BCRP) while down-regulating canalicular bile salt export pump (BSEP) and several sinusoidal transporters (Jigorel et al., 2006). Induction of CYP1A1 and 1A2 mRNA by omeprazole was confirmed in long-term cultures (Meneses-Lorente et al., 2007).

Work with HepG2 cells included the report that hazardous environmental metals (arsenic, lead, mercury, cadmium) decrease PAH-induced CYP1A1 activities (Vakharia et al., 2001). Arsenite decreases CYP1A1-mediated PAH bioactivation by down-regulating the transcriptional induction of *CYP1A1* by a prototypical PAH (Bessette et al., 2005). High-throughput screening of dietary flavonoids as inducers or AHR antagonists was conducted in HepG2 cells stably transfected with luciferase reporters under the control of the human *CYP1A1* promoter and 5'-flank (Allen et al., 2001). Although HepG2 cells display low P450 expression compared to primary human hepatocytes, both cell systems show comparable CYP1A1 and 1A2 mRNA inducibility by B[a]P and MC (Wilkening et al., 2003). Research with HepaRG cells showed induction of CYP1A1 and 1A2 mRNA and phenacetin O-deethylation activity by omeprazole (Kanebratt and Andersson, 2008b). The functional resemblance of HepaRG cells to primary human hepatocyte cultures was confirmed by comparing the basal expression of AHR mRNA and target genes such as CYP1A2, and the response to MC as a prototypical inducer (Aninat et al., 2006; Kanebratt and Andersson, 2008a). The responsiveness of HepaRG cells to induction of CYP1A2 activity by MC is well preserved for long culture times at confluence (Josse et al.,

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

2008). Using the Fa2N4 immortalized human hepatocyte cell line, omeprazole was shown to induce CYP1A2 activity with tacrine as a component of a probe substrate cocktail (Youdim et al., 2007). Fa2N4 cells display similar AHR levels compared to human hepatocytes and show strong induction of CYP1A2 mRNA and activity by omeprazole (Hariparsad et al., 2008).

Other human cell lines were important models for AHR research appearing in DMD. The transcriptional regulation and molecular function of the AHRR was characterized in human cell lines (Haarmann-Stemmann et al., 2007). The fluorinated benzothiazole, 5F 203, induces CYP1A1, leading to increased metabolic activation and covalent binding to cellular macromolecules only in human cancer cell lines sensitive to the drug's cytotoxic effects (Brantley et al., 2004). Emodin, an active component of herbal laxatives, induces CYP1A1 and 1B1 mRNA, protein, and activities in the CL5 human lung adenocarcinoma cell line (Wang et al., 2001). Induction of CYP1A1 and 1B1 by B[a]P in T-47D human breast cancer cells is diminished by arsenite, possibly via a post-transcriptional mechanism involving decreased heme availability (Spink et al., 2002). TCDD-induced CYP1B1 mRNA and protein expression in MCF-7 human breast cancer cells is suppressed by 2,4,3',5'-tetramethoxystilbene without altering AHR or ARNT mRNA levels (Chun et al., 2005).

DMD papers featuring diverse species included eel, swine, dog, guinea pig, and fish. B[a]P, TCB, and ßNF induce CYP1A and EROD activity in the heart and swimbladder rete mirabile of the eel, with induction occurring in endothelium (Schlezinger and Stegeman, 2000). Immunoreactive homologs of CYP1A1 and 1A2 and enzyme activities were characterized following exposure of swine to a cocktail of inducers including ßNF (Myers et al., 2001). Strong induction of CYP1A-dependent EROD activity was observed following in vivo treatment of beagle dogs with ßNF and treatment of beagle dog hepatocyte cultures with ßNF or MC (Graham

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

et al., 2002). Compound I, an inhibitor of human kinase insert domain-containing receptor, induces its own metabolism and clearance in beagle dogs because it is both an inducer and substrate for CYP1A (Gibson et al., 2005). The 5'-flanking region of the guinea pig *CYP1A2* gene was cloned and characterized for functional DRE sequences (Black and Quattrochi, 2004). Treatment of channel catfish with MC as a CYP1 inducer enhances formation of estrogenic metabolites from methoxychlor (Stuchal et al., 2006).

Several DMD publications reported the identification of novel AHR ligands. Compounds showing AHR activation in various experimental systems included: metabolites of the tryptophan photoproduct FICZ (Bergander et al., 2003); the antioxidant tBHQ (Gharavi and El-Kadi, 2005; Schreiber et al., 2006); the antiandrogen flutamide (Coe et al., 2006); imidazole drugs from distinct therapeutic classes, e.g. the aromatase inhibitor vorozole (Diani-Moore et al., 2006); the antiangiogenic agent TSU-68 (Kitamura et al., 2008); the calcium/calmodulin-dependent protein kinase kinase inhibitor STO-609 (Monteiro et al., 2008); and the glycogen synthase kinase inhibitor SB216763 (Braeuning and Buchmann, 2009). The Jun N-terminal kinase inhibitor SP600125 was characterized as an AHR antagonist (Joiakim et al., 2003).

The Klaassen group used the branched DNA signal amplification technology and other approaches to systematically characterize gene expression profiles in several contexts. These DMD papers included reports of: rat hepatic P450 induction by MC and other prototypical inducers (Hartley and Klaassen, 2000); enhanced rat liver UGT activity toward thyroxine by MC and Aroclor 1254 via increased expression of UGT1A6 (Vansell and Klaassen, 2002); and induction of mRNAs encoding multidrug resistance-associated proteins MRP2, 3, 5, 6, and 7 (Maher et al., 2005) and organic anion-transporting polypeptides OATP2B1 and 3A1 (Cheng et al., 2005) in mouse liver by the AHR activators TCDD, PCB126, and ßNF. Conversely,

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

microsomal enzyme inducers, including multiple AHR ligands, were unable to increase rat MDR1 gene expression (Brady et al., 2002). Further studies documented: induction of UGT1A3, 1A6, and 1A7 by AHR activators in the liver but not duodenum of rats (Shelby and Klaassen, 2006); peak hepatic AHR and ARNT mRNA levels around the light/dark transition (Zhang et al., 2009); and induction of mouse hepatic UGT1A1, 1A6, 1A9, and 2B35 and intestinal UGT1A6 and 1A7 by AHR activators (Buckley and Klaassen, 2009). Mouse AHR shows ubiquitous tissue distribution with no sex differences, hepatic AHR levels are induced by ßNF, spironolactone, clofibrate, and butylated hydroxyanisole, but not TCDD or PCB126, and AHR activation transcriptionally induces constitutive androstane receptor (CAR) and enhances induction of CAR target genes (Petrick and Klaassen, 2007).

Our laboratory used luciferase reporter plasmids driven by the rat *CYP2C11* promoter and 5'-flank to study down-regulation of this gene by PAHs and HAHs in cell culture models (Bhathena et al., 2002) and in rat liver in vivo (Sawaya and Riddick, 2008). We also reported the regulation of constitutive mouse hepatic P450s and GH signaling components by MC (Lee et al., 2006) and enhanced AHR expression and function by glucocorticoids in mouse Hepa-1 cells (Bielefeld et al., 2008).

The 2010s

The new decade was ushered in by landmark discoveries emphasizing the critical physiological functions of the AHR in the immune system, including the characterization of kynurenine as a candidate endogenous ligand (Mezrich et al., 2010), the demonstration that AHR activation by kynurenine suppresses the antitumor immune response (Opitz et al., 2011), the key regulatory role of the AHR in the maintenance of intraepithelial lymphocytes in skin and

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

intestine (Li et al., 2011), and the ability of natural dietary AHR ligands to stimulate the postnatal expansion of intestinal lymphoid cells, thereby contributing to intestinal homeostasis and protection against infection (Kiss et al., 2011). StemRegenin 1, an AHR antagonist, was shown to promote expansion of human hematopoietic stem cells (Boitano et al., 2010) and TCDD-inducible poly(ADP-ribose)polymerase (TiPARP/PARP7) was characterized as a transcriptional repressor of AHR, forming a negative feedback loop (MacPherson et al., 2013). Induction of TiPARP and related polymerases by TCDD causes NAD^+ loss and decreased activity of sirtuins, revealing a novel unifying mechanism for dioxin toxicities such as thymus atrophy and hepatosteatosis (Diani-Moore et al., 2017). AHR activation by endogenous tryptophan catabolites was shown to promote disease tolerance by controlling excess inflammation without compromising immunity (Bessede et al., 2014) and there was the demonstration that type I interferons generated in the CNS and gut microbial metabolites of dietary tryptophan act via the AHR in astrocytes to suppress CNS inflammation (Rothhammer et al., 2016). Finally, excessive CYP1A1-mediated degradation of AHR ligands in intestinal epithelial cells compromises intestinal immune function (Schiering et al., 2017) and tapinarof, an approved treatment for plaque psoriasis, exerts its anti-inflammatory effects via AHR activation (Smith et al., 2017).

In the 2010s decade, DMD featured several minireviews, symposium reports, commentaries, and perspectives articles with AHR relevance. A report on an ASPET symposium entitled “Targeting drug-metabolizing enzymes for effective chemoprevention and chemotherapy” held at Experimental Biology 2009 included a report from the Williams group on the role of AHR-regulated CYP1B1 in chemoprevention of PAH transplacental carcinogenesis (Swanson et al., 2010). A symposium report from Experimental Biology 2012 entitled “NADPH-

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Cytochrome P450 oxidoreductase: roles in physiology, pharmacology, and toxicology" included a report from the Wolf group on the reductase conditional null mouse in which administration of an AHR agonist drives Cre-recombinase expression under control of a *CYP1A1* promoter, resulting in NADPH-cytochrome P450 oxidoreductase (POR) deletion either in liver or liver and gastrointestinal tract depending on the AHR activator and dose (Riddick et al., 2013). The Experimental Biology 2013 meeting generated a symposium report entitled "Potential role of epigenetic mechanisms in the regulation of drug metabolism and transport" featuring a report from the Hankinson group on the role of DNA methylation in differential AHR-mediated induction of CYP1A1 vs. CYP1B1 by TCDD (Ingelman-Sundberg et al., 2013). A symposium entitled "Physiological regulation of drug metabolism and transport" was held at Experimental Biology 2017, and the report from the Cui group included consideration of the regulation of hepatic and intestinal AHR target genes by tryptophan metabolites generated by intestinal microbiota (Morgan et al., 2018). A perspectives article considered pharmacokinetic herb-drug interactions involving induction of drug-metabolizing enzymes and transporters, using milk thistle and resveratrol as examples (Brantley et al., 2014). A minireview on miRNA pharmacoepigenetics included discussion of the modulation of AHR expression by miR-29 and miR-124, and ARNT by miR-24 (Yu et al., 2016). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 featured a commentary introducing the concept that tryptophan metabolites produced by gut microbiota act via the AHR to regulate host immune function and intestinal health (Swanson, 2015). This topic was developed further in minireviews showing that AHR-activating xenobiotics can also alter the intestinal microbiome composition (Klaassen and Cui, 2015) and discussing physiological functions of AHR ligands derived from indole and tryptophan metabolism, encompassing dietary exposure, microbiota-derived products,

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

host metabolism of indoles and tryptophan, and photo-oxidation of tryptophan (Hubbard et al., 2015). A “Special Section on New Models in Drug Metabolism and Transport” from November 2018 included minireviews addressing progress and challenges with using *CYP1A1/1A2*-humanized and *CYP1B1*-humanized mice in pharmacological and toxicological investigations (Bissig et al., 2018) and discussing transcriptional induction of the *UGT1A1* gene in *UGT1*-humanized mice (Chen and Tukey, 2018). Finally, a minireview included discussion of using CRISPR-Cas9 to: knock-in a luciferase reporter into the human *CYP1A1* locus in induced pluripotent stem cells; insert mutations or knock-out fish *AHR2* genes; and knock-out AHR in human and mouse cell models (Karlgren et al., 2018).

Additional aspects of “MC-type” induction in rat liver were covered in DMD papers published during the 2010s decade. ßNF causes strong induction of CYP1A1 and moderate induction of UGT1A6 and CYP2B1 mRNAs in “Liverbeads”, rat hepatocytes entrapped in an alginate matrix (Al Khansa et al., 2010). AHR mRNA is detected in rat olfactory mucosa along with strong induction of CYP1A1 by MC and Aroclor 1254 (Thiebaud et al., 2010). A mechanism-based mathematical model related ßNF plasma concentrations, hepatic CYP1A1 and 1A2 mRNA levels, and EROD activity in rats (Chen et al., 2010). In cultured rat hepatocytes, arsenite decreases induction of CYP1A1 and 1A2 by TCDD via a mechanism involving decreased AHR nuclear accumulation, increased binding of cytosolic AHR to chaperones, and induction of heme oxygenase-1 (Anwar-Mohamed et al., 2012). In vivo treatment of rats with oxycodone increases hepatic AHR mRNA levels, but oxycodone and its major metabolites (noroxycodone and oxymorphone) are not direct AHR activators (Hassan et al., 2013). Recombinant rat CYP1A1 and 1A2 are active in converting arachidonic acid to terminal/ subterminal hydroxyeicosatetraenoic acids, and these activities are induced by in vivo MC

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

treatment in heart, lung, kidney, and liver, and inhibited by α-naphthoflavone (αNF) in lung and liver microsomes (El-Sherbeni and El-Kadi, 2014). Finally, destruction of serotonergic projections from raphe nuclei to the hypothalamus altered serum levels of multiple hormones and elevated rat hepatic CYP1A1 and 1A2 mRNA, CYP1A protein, and caffeine metabolism (Rysz et al., 2015).

DMD continued to feature important studies conducted in mice and mouse-derived cell models. Comparison of "responsive" C57BL/6 vs. "non-responsive" DBA/2 mice showed the decrease in serum thyroxine levels caused by PCB126 is due to induction of hepatic UGT activity toward thyroxine and enhanced hepatic accumulation of thyroxine (Kato et al., 2010). The reductase conditional null mouse, described earlier in this report, was used to study the role of hepatic P450s in DNA adduct formation by 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine (Arlt et al., 2011). Using a cocktail of P450 probe drugs, including phenacetin for CYP1A2, in a single-mouse pharmacokinetic approach, the in vivo inhibitory effect of αNF and inductive effect of MC were confirmed (Jilek et al., 2017). In a mouse model humanized for multiple P450s, including CYP1A1 and 1A2, in vivo treatment with ßNF enhances CYP1A-mediated clearance of the epidermal growth factor receptor inhibitor osimertinib (Henderson et al., 2019). *CYP1A1/1A2*-humanized mice show constitutive and TCDD-inducible CYP1A2 expression in liver and TCDD-inducible CYP1A1 expression in liver, lung, and small intestine, and this model was used to develop a method to distinguish the contributions of human CYP1A1 vs. 1A2 to the metabolism of model compounds (Kapelyukh et al., 2019). Multiple DREs in the distal 5'-flank of mouse *CYP1A2*, approximately 13-kb upstream, were shown to be involved in transcriptional activation by TCDD and MC in studies using primary cultures of mouse hepatocytes (Kawasaki et al., 2010). Studies of AHR relevance conducted in diverse species

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

during the 2010s were limited to a single chick embryo paper: TCDD-inducible avian P450s (e.g. CYP1A5) convert arachidonic acid to epoxyeicosatrienoic acids, which can be converted by epoxide hydrolase to dihydroxyeicosatrienoic acids, and the hepatic ratio of the epoxy:dihydroxy metabolites is increased by co-treatment with TCDD and an inhibitor of soluble epoxide hydrolase (Diani-Moore et al., 2014).

The strong emphasis on studies relevant to the human AHR system continued in DMD publications during the 2010s. Human white adipose tissue shows basal expression of AHR mRNA with high constitutive levels of CYP1B1, and strong induction of CYP1A1 and 1B1 by TCDD and prochloraz (Ellero et al., 2010). A "Special Section on Epigenetic Regulation of Drug-Metabolizing Enzymes and Transporters" from October 2013 featured a study identifying correlations between levels of specific miRNAs for AHRR, CYP1A1, and 1A2 in human liver (Rieger et al., 2013). A "Special Section on Transporters in Drug Disposition and Pharmacokinetic Prediction" from May 2018 included a report of a significant correlation between AHR and BCRP mRNA levels in 137 term placentas from uncomplicated pregnancies (Bircsak et al., 2018).

Several studies using human liver-derived cellular models were published in DMD in this decade. In sandwich cultured human hepatocytes, omeprazole induces CYP1A2 mRNA and phenacetin O-deethylation, as well as CYP1A2 protein as assessed via absolute quantitation by tandem mass spectrometry (Schaefer et al., 2012). In cryopreserved human hepatocytes, omeprazole induces CYP1A2 mRNA and EROD activity in all lots tested (Yajima et al., 2014). The endocannabinoid oleamide demonstrates neither agonist nor antagonist properties in an AHR-driven luciferase reporter in HepG2 cells and fails to induce CYP1A2 mRNA in primary human hepatocytes (Dovrtelova et al., 2018). A "Special Section on Pharmacokinetic and Drug

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Metabolism Properties of Novel Therapeutic Modalities" from October 2019 featured a report that five N-acetylgalactosamine-conjugated siRNAs failed to elicit AHR-mediated induction of CYP1A2 mRNA in primary human hepatocytes (Ramsden et al., 2019). Differentiated HepaRG cells over a 4-week period show stable basal AHR mRNA levels and induction of CYP1A2 mRNA and activity by omeprazole (Antherieu et al., 2010). Using HepaRG cells as a model for nonalcoholic fatty liver disease and steatohepatitis, inflammatory conditions do not diminish AHR-mediated induction of CYP1A1 and 1A2 mRNAs by MC (Tanner et al., 2018). Lastly, treatment of HepaRG cells with TCDD decreased mRNA levels for multiple sulfotransferases, with the exception of SULT1C3 (Dubaisi et al., 2018). The functionality of AHR was confirmed in the HC-AFW1 human hepatocellular carcinoma cell line by induction of CYP1A mRNAs, CYP1A2 activity with phenacetin as probe, and an AHR-driven luciferase reporter by TCDD, ßNF, and tBHQ (Braeuning et al., 2015).

Several other human cell lines formed important models for AHR research appearing in DMD. In human mammary epithelial MCF10A cultures, *p*-anilinoaniline, an inhibitor of an E2 ubiquitin-conjugating enzyme implicated in AHR degradation, enhances TCDD-induced *CYP1A1* transcription and AHR occupancy of the *CYP1A1* promoter, with effects dependent on cell cycle phase (Elliott et al., 2012). In the same cell model, TCDD and inhibitors of epidermal growth factor receptor kinase induce CYP1A1 and 1A2 synergistically, and CYP1A1 mRNA and protein levels display notable discordance (Joiakim et al., 2016). Two studies employed a human lymphoblastoid cell line model to characterize so-called "distant SNP effects": first, a SNP located hundreds of base-pairs from a DRE creates variability in MC-stimulated AHR binding and CYP1A1 inducibility (Liu et al., 2018); second, additional SNPs at a distance from DRE sequences were identified that function as "pharmacogenomic-expression quantitative trait

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

loci" that are dependent on AHR activation by a ligand (Neavin et al., 2019). The AHR-regulated CYP2S1 is induced by retinoids and UV radiation in the human keratinocyte HaCaT cell line (McNeilly et al., 2012). The antibacterial triclocarban is activated by recombinant human CYP1A1 and by TCDD-treated spontaneously immortalized human epidermal keratinocytes to produce glutathione adducts (Schebb et al., 2014). In human monocyte/macrophage-derived U937 and THP-1 cells, activation of the vitamin D receptor enhances induction of CYP1A1 by B[*a*]P, B[*a*]P metabolism and DNA adduct formation (Matsunawa et al., 2012). LS180 colorectal adenocarcinoma cells display basal AHR mRNA expression and selective induction of SULT1C3, as opposed to SULT1C2, by TCDD (Rondini et al., 2014).

Novel AHR ligands continued to be a focus for reports appearing in DMD. AHR activation was demonstrated for several interesting compounds: uncharacterized omeprazole metabolites generated by cecal bacteria (Shiizaki et al., 2014); the immunomodulator leflunomide (Patel et al., 2015); and bioactive alkaloids from *Euodia rutaecarpa* (Zhang et al., 2018). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 included a characterization of several tryptophan microbiota metabolites (indole, indole-3-acetate, indole-3-aldehyde, and tryptamine) as selective AHR modulators with complex patterns of ligand- and target gene-selectivity (Cheng et al., 2015).

Several systematic transcriptomic studies of AHR relevance from the Klaassen group utilized branched DNA signal amplification technology, multiplex suspension arrays, real-time RT-PCR, and RNA-Seq. Mouse hepatic AHR mRNA levels remain relatively constant with aging, with higher levels in females vs. males throughout the lifespan (Fu et al., 2012); AHR levels are decreased by energy restriction only in aged mice (Zhang et al., 2010). PCB congeners with high AHR affinity decrease rat serum thyroxine levels mainly by inducing hepatic UGT

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

activity toward thyroxine and increasing biliary excretion of the glucuronide (Martin et al., 2012). *Ahr*-null mice were used to demonstrate: suppression of hepatic arylacetamide deacetylase and carboxylesterase-3a by TCDD requires AHR (Zhang et al., 2012); the absence of AHR alters the constitutive hepatic expression of multiple phase I and II drug-metabolizing enzymes and transporters, and the induction of several target genes by TCDD is AHR-dependent (Aleksunes and Klaassen, 2012). TCDD induces mouse hepatic aldo-keto reductase AKR1B7 and 1C18 mRNA levels, while suppressing AKR1C22 (Pratt-Hyatt et al., 2013). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 featured the demonstration that the liver of germ-free mice shows increased AHR and CYP1A2 mRNA levels compared to conventional mice (Selwyn et al., 2015). Male mice show basal expression of AHR mRNA in liver, duodenum, jejunum, ileum, and large intestine with little divergence among these tissues (Fu et al., 2016). A "Special Section on Pediatric Drug Disposition and Pharmacokinetics" from July 2016 contained a paper reporting that mouse hepatic AHR, CAR, and pregnane X receptor (PXR) mRNA levels can be modulated by their own activators and activators of the other receptors; as well, AHR targets genes show developmental age selectivity in their TCDD inducibility (Li et al., 2016). Finally, the intestine of germ-free mice shows decreased CYP1A1 mRNA levels vs. conventional mice, with no difference in CYP1A2 or AHR levels (Fu et al., 2017).

Our laboratory showed that decreased hepatic AHR protein and POR activity in adrenalectomized rats are important determinants of altered AHR-mediated responses to MC (Mullen Grey and Riddick, 2011). In vivo studies of DEX dose-response, glucocorticoid receptor (GR)- and PXR-selective agonists, GR antagonism, and *PXR*-knockout rats showed important roles for GR in induction of rat liver ARNT by DEX and PXR in induction of rat liver POR by

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

DEX (Hunter et al., 2017). Using mice with conditional hepatic POR deletion, we showed that MC alters GH signaling components and target genes via mechanisms that are both dependent and independent of hepatic microsomal P450 activities (Lee et al., 2013b), and MC suppresses hepatic CYP3A11 expression by a pre-translational mechanism independent of hepatic microsomal P450 activities (Lee et al., 2013a). Lastly, MC down-regulates CYP3A4 expression in the liver of female humanized PXR-CAR-CYP3A4/3A7 mice and a similar, but more subtle, response was seen in males since the basal hepatic CYP3A4 levels are much higher in females vs. males (Crosby and Riddick, 2019).

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

The 2020s

A highly significant landmark discovery in the AHR field was reported very recently. The cryo-EM structure of the indirubin-bound AHR-hsp90-XAP2 complex ushers in a new era in the structure-based analysis of the AHR ligand-binding pocket (Gruszczyk et al., 2022).

DMD has published several minireviews and a commentary with AHR relevance in the early part of the new 2020s decade. Minireviews considered the ability of TCDD to modulate the alternative splicing patterns of AHR target genes such as *CYP1A1* and the existence of constitutively active AHR splice variants (Annalora et al., 2020), as well as circadian fluctuations in AHR and ARNT levels and diurnal expression and inducibility of CYP1A1 (Lu et al., 2020). Minireviews also covered the involvement of AHR in the transcriptional induction of MDR1 and BCRP by histone deacetylase inhibitors (You et al., 2020) and the overexpression of the AHR target gene *CYP1B1* in prostate cancer driven by hypomethylation of its promoter/enhancer region and not by altered AHR and ARNT levels (Wang et al., 2020). A "Special Section on Natural Products: Experimental Approaches to Elucidate Disposition

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Mechanisms and Predict Pharmacokinetic Drug Interactions" from October 2020 featured a minireview addressing the important roles of intestinal AHR in the regulation of drug-metabolizing enzymes and its immunomodulatory activity in maintaining the intestinal barrier (Li, 2020). A "Special Section on Bile Acids, Drug Metabolism, and Toxicity" from April 2022 offered four highly pertinent minireviews. First, there was discussion of sex-dependent effects of AHR agonists in mice on serum and liver bile acids and intestinal mRNA levels for fibroblast growth factor-15 (Choudhuri and Klaassen, 2022). Second, AHR-dependent effects of TCDD and TCDF on multiple aspects of bile acid homeostasis in rats and mice were covered (Taylor et al., 2022). Third, there was consideration of the interactions between nuclear factor erythroid-derived 2-like 2 (Nrf2) and AHR in which each xenosensor induces expression of the other (Rockwell et al., 2022). Fourth, the lowering of systemic thyroid hormone levels by AHR agonists was discussed in relation to impacts on thyroxine glucuronidation and other aspects of thyroid hormone homeostasis (Vansell, 2022). Down-regulation of AHR expression and attenuated CYP1A induction by TCDD caused by adenosine-to-inosine RNA editing in the 3'-untranslated region of AHR creating a recognition site for miR-378 was covered in a minireview (Nakano and Nakajima, 2022). A "Special Section on Drug Metabolism in Liver Injury and Repair" from May 2022 included a minireview describing improved liver regeneration in *Ahr*-null mice after acute toxic injury (Zhao et al., 2022). A "Special Section on Drug Metabolism and Regulation" from July 2022 featured a commentary by Tsuneo Omura offering historical perspectives on receptor-mediated induction of P450s by PAHs and barbiturates, and potential roles not related to drug metabolism for AHR counterparts in invertebrates (Omura, 2022). Lastly, a "Special Section on New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters" from September 2022 contained a minireview highlighting the regulation

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

of multiple rodent and human organic anion transporters and OATPs by AHR activators (Zhou and Shu, 2022).

A few DMD research papers from the 2020s decade have reported studies conducted with rat and mouse models. A *CYP1A2*-knockout rat model generated via a CRISPR-Cas9 approach shows no change in hepatic AHR mRNA levels but a strong compensatory increase in CYP1A1 expression (Sun et al., 2021). The induction of intestinal CYP1A1 by cadmium in *UGT1*-humanized mice is lost in this mouse model lacking Nrf2 (Paszek and Tukey, 2020). Hepatic AHR mRNA levels and expression of AHR target genes are induced in a peroxisome proliferator-activated receptor-α (PPARα)-dependent fashion by the *Olea europaea* constituent oleuropein (Malliou et al., 2021). In humanized apolipoprotein E4 knock-in mice, cadmium down-regulates hepatic CYP1A2, an AHR target, only in males (Wang et al., 2022).

Studies published in DMD during the current decade continued to emphasize the importance of the human AHR system. Transcriptomic analysis of 226 human livers showed lower AHR and CYP1A2 mRNA levels in females vs. males, but no effect of age or race/ethnicity (Liu et al., 2021). Omeprazole induces CYP1A1, but not CYP1A2, mRNA in tissue stem cell-derived human ileal and colon organoids (Stresser et al., 2021). Stabilization of hypoxia-inducible factor-α (HIF-α) by treatment of primary human hepatocytes with prolyl hydroxylase domain 2 inhibitors causes CYP1A2 down-regulation, a response accompanied by decreased ARNT mRNA levels and no change in AHR mRNA levels (Takano et al., 2021). Overexpression of the hepatocyte nuclear factor-4α (HNF-4α) antisense RNA 1 in Huh7 cells causes decreased basal expression of AHR and CYP1A2 mRNA (Wang et al., 2021). The following four studies were conducted with HepaRG cells. Knockdown of the histone methyltransferase G9a increases AHR mRNA levels but has no effect on AHR expression in a

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

steatotic condition (Pande et al., 2020). AHR-dependent induction of CYP1A2 by omeprazole is enhanced by knockout of CAR or PXR, but not in the CAR/PXR double knockout (Preiss et al., 2021). CYP1A2 expression and activity are enhanced under the lower perivenous oxygen tension vs. the periportal state and further enhanced by Wnt/ß-catenin signaling, although these manipulations do not impact AHR mRNA levels (DiProspero et al., 2022). A "Special Section on Mechanistic and Translational Research on Transporters in Toxicology" from October 2022 contained a paper showing that perfluorinated carboxylic acids modulate expression of amino acid and xenobiotic transporters, with AHR predicted to be an important upstream factor involved in this regulation (Lim et al., 2022).

With respect to novel AHR ligands recently reported in DMD publications, a monohydroxylated metabolite of 3,3'-diindolylmethane detected in humans, 3-((1H-indole-3-yl)methyl)indolin-2-one, was found to be an AHR agonist in a DRE-driven luciferase assay in mouse Hepa-1 cells (Vermillion Maier et al., 2021). Finally, the investigational anti-inflammatory compound, JNJ-2482272, is a potent activator of rat and human AHR (Coe et al., 2022).

Conclusions

With the launch of DMD in 1973 and the discovery of the AHR in 1976, the journal and the receptor have led parallel and often intersecting lives over the past fifty years. Tracing the history of a particular scientific field can help us to appreciate the major landmark discoveries, the key players and contributors, and also deepen our understanding of how knowledge in the field has evolved to the present. It may be helpful to recall Winston Churchill's paraphrasing of the Spanish philosopher George Santayana: "Those that fail to learn from history are doomed to

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

repeat it." By reflecting on the strong history of AHR-related publications in DMD over the years, it is my hope that this minireview will inspire current and future AHR scientists to pursue provocative questions and to contribute their most important findings to the pages of DMD.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Acknowledgments

The author thanks Dr. Jason Matthews for helpful discussions and Dr. Anne K. Mullen Grey for assistance with figures.

Authorship Contributions

Participated in research design: Riddick.

Performed data analysis: Riddick.

Wrote or contributed to the writing of the manuscript: Riddick.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

References

Aimova D, Svobodova L, Kotrbova V, Mrazova B, Hodek P, Hudecek J, Vaclavikova R, Frei E, and Stiborova M (2007) The anticancer drug ellipticine is a potent inducer of rat cytochromes P450 1A1 and 1A2, thereby modulating its own metabolism. *Drug Metab Dispos* **35:**1926-1934.

Al Khansa I, Blanck O, Guillouzo A, and Bars R (2010) Liverbeads: a practical and relevant in vitro model for gene induction investigations. *Drug Metab Dispos* **38:**1598-1604.

Aleksunes LM and Klaassen CD (2012) Coordinated regulation of hepatic phase I and II drug-metabolizing genes and transporters using AhR-, CAR-, PXR-, PPARα-, and Nrf2-null mice. *Drug Metab Dispos* **40:**1366-1379.

Allen SW, Mueller L, Williams SN, Quattrochi LC, and Raucy J (2001) The use of a high-volume screening procedure to assess the effects of dietary flavonoids on human CYP1A1 expression. *Drug Metab Dispos* **29:**1074-1079.

Alvares AP, Leigh S, Kappas A, Levin W, and Conney AH (1973) Induction of aryl hydrocarbon hydroxylase in human skin. *Drug Metab Dispos* **1:**386-390.

Aninat C, Piton A, Glaise D, LeCharpentier T, Langouet S, Morel F, Guguen-Guillouzo C, and Guillouzo A (2006) Expression of cytochromes P450, conjugating enzymes and nuclear receptors in human hepatoma HepaRG cells. *Drug Metab Dispos* **34:**75-83.

Annalora AJ, Marcus CB, and Iversen PL (2020) Alternative splicing in the nuclear receptor superfamily expands gene function to refine endo-xenobiotic metabolism. *Drug Metab Dispos* **48:**272-287.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Antherieu S, Chesne C, Li R, Camus S, Lahoz A, Picazo L, Turpeinen M, Tolonen A, Uusitalo J, Guguen-Guillouzo C, and Guillouzo A (2010) Stable expression, activity, and inducibility of cytochromes P450 in differentiated HepaRG cells. *Drug Metab Dispos* **38:**516-525.

Anwar-Mohamed A and El-Kadi AO (2008) Down-regulation of the carcinogen-metabolizing enzyme cytochrome P450 1A1 by vanadium. *Drug Metab Dispos* **36:**1819-1827.

Anwar-Mohamed A, Klotz LO, and El-Kadi AO (2012) Inhibition of heme oxygenase-1 partially reverses the arsenite-mediated decrease of CYP1A1, CYP1A2, CYP3A23, and CYP3A2 catalytic activity in isolated rat hepatocytes. *Drug Metab Dispos* **40:**504-514.

Arlt VM, Singh R, Stiborova M, Gamboa da Costa G, Frei E, Evans JD, Farmer PB, Wolf CR, Henderson CJ, and Phillips DH (2011) Effect of hepatic cytochrome P450 (P450) oxidoreductase deficiency on 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine-DNA adduct formation in P450 reductase conditional null mice. *Drug Metab Dispos* **39:**2169-2173.

Baba T, Mimura J, Gradin K, Kuroiwa A, Watanabe T, Matsuda Y, Inazawa J, Sogawa K, and Fujii-Kuriyama Y (2001) Structure and expression of the Ah receptor repressor gene. *J Biol Chem* **276:**33101-33110.

Baldwin SJ, Bramhall JL, Ashby CA, Yue L, Murdock PR, Hood SR, Ayrton AD, and Clarke SE (2006) Cytochrome P450 gene induction in rats ex vivo assessed by quantitative real-time reverse transcriptase-polymerase chain reaction (Taqman). *Drug Metab Dispos* **34:**1063-1069.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Bandiera S, Sawyer T, Romkes M, Zmudzka B, Safe L, Mason G, Keys B, and Safe S (1984) Polychlorinated dibenzofurans (PCDFs): effects of structure on binding to the 2,3,7,8-TCDD cytosolic receptor protein, AHH induction and toxicity. *Toxicology* **32:**131-144.

Bergander L, Wahlstrom N, Alsberg T, Bergman J, Rannug A, and Rannug U (2003) Characterization of in vitro metabolites of the aryl hydrocarbon receptor ligand 6-formylindolo[3,2-*b*] carbazole by liquid chromatography-mass spectrometry and NMR. *Drug Metab Dispos* **31:**233-241.

Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Bicciato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazia MA, Piobbico D, Zelante T, Funakoshi H, Nakamura T, Gilot D, Denison MS, Guillemin GJ, DuHadaway JB, Prendergast GC, Metz R, Geffard M, Boon L, Pirro M, Iorio A, Veyret B, Romani L, Grohmann U, Fallarino F, and Puccetti P (2014) Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature* **511:**184-190.

Bessette EE, Fasco MJ, Pentecost BT, and Kaminsky LS (2005) Mechanisms of arsenite-mediated decreases in benzo[*k*]fluoranthene-induced human cytochrome P4501A1 levels in HepG2 cells. *Drug Metab Dispos* **33:**312-320.

Betlach CJ and Tozer TN (1980) Biodisposition of theophylline. II. Effect of aromatic hydrocarbon treatment in mice. *Drug Metab Dispos* **8:**271-273.

Bhathena A, Lee C, and Riddick DS (2002) Suppression of cytochrome P4502C11 by aromatic hydrocarbons: mechanistic insights from studies of the 5'-flanking region of the *CYP2C11* gene. *Drug Metab Dispos* **30:**1385-1392.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Bielefeld KA, Lee C, and Riddick DS (2008) Regulation of aryl hydrocarbon receptor expression and function by glucocorticoids in mouse hepatoma cells. *Drug Metab Dispos* **36:**543-551.

Bircsak KM, Moscovitz JE, Wen X, Archer F, Yuen PYS, Mohammed M, Memon N, Weinberger BI, Saba LM, Vetrano AM, and Aleksunes LM (2018) Interindividual regulation of the breast cancer resistance protein/ABCG2 transporter in term human placentas. *Drug Metab Dispos* **46:**619-627.

Birnbaum LS (1986) Distribution and excretion of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in congenic strains of mice which differ at the Ah locus. *Drug Metab Dispos* **14:**34-40.

Bissig KD, Han W, Barzi M, Kovalchuk N, Ding L, Fan X, Pankowicz FP, Zhang QY, and Ding X (2018) P450-humanized and human liver chimeric mouse models for studying xenobiotic metabolism and toxicity. *Drug Metab Dispos* **46:**1734-1744.

Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, Kao J, King SP, Miwa G, Ni L, Kumar G, McLeod J, Obach RS, Roberts S, Roe A, Shah A, Snikeris F, Sullivan JT, Tweedie D, Vega JM, Walsh J, and Wrighton SA (2003) The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. *Drug Metab Dispos* **31:**815-832.

Black VH and Quattrochi LC (2004) Molecular cloning of the guinea pig *CYP1A2* gene 5'-flanking region: identification of functional aromatic hydrocarbon response element and characterization of CYP1A2 expression in GPC16 cells. *Drug Metab Dispos* **32:**595-602.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Boitano AE, Wang J, Romeo R, Bouchez LC, Parker AE, Sutton SE, Walker JR, Flaveny CA, Perdew GH, Denison MS, Schultz PG, and Cooke MP (2010) Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells. *Science* **329:**1345-1348.

Boutros PC, Yan R, Moffat ID, Pohjanvirta R, and Okey AB (2008) Transcriptomic responses to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in liver: comparison of rat and mouse. *BMC Genomics* **9:**419.

Boverhof DR, Burgoon LD, Tashiro C, Sharratt B, Chittim B, Harkema JR, Mendrick DL, and Zacharewski TR (2006) Comparative toxicogenomic analysis of the hepatotoxic effects of TCDD in Sprague Dawley rats and C57BL/6 mice. *Toxicol Sci* **94:**398-416.

Bowen WP, Carey JE, Miah A, McMurray HF, Munday PW, James RS, Coleman RA, and Brown AM (2000) Measurement of cytochrome P450 gene induction in human hepatocytes using quantitative real-time reverse transcriptase-polymerase chain reaction. *Drug Metab Dispos* **28:**781-788.

Bradfield CA, Glover E, and Poland A (1991) Purification and N-terminal amino acid sequence of the Ah receptor from the C57BL/6J mouse. *Mol Pharmacol* **39:**13-19.

Brady JM, Cherrington NJ, Hartley DP, Buist SC, Li N, and Klaassen CD (2002) Tissue distribution and chemical induction of multiple drug resistance genes in rats. *Drug Metab Dispos* **30:**838-844.

Braeuning A and Buchmann A (2009) The glycogen synthase kinase inhibitor 3-(2,4-dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione (SB216763) is a partial agonist of the aryl hydrocarbon receptor. *Drug Metab Dispos* **37:**1576-1580.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Braeuning A, Sanna R, Huelsken J, and Schwarz M (2009) Inducibility of drug-metabolizing enzymes by xenobiotics in mice with liver-specific knockout of *Ctnnb1*. *Drug Metab Dispos* **37:**1138-1145.

Braeuning A, Thomas M, Hofmann U, Vetter S, Zeller E, Petzuch B, Johanning J, Schroth W, Weiss TS, Zanger UM, and Schwarz M (2015) Comparative analysis and functional characterization of HC-AFW1 hepatocarcinoma cells: cytochrome P450 expression and induction by nuclear receptor agonists. *Drug Metab Dispos* **43:**1781-1787.

Brandt I, Lund J, Bergman A, Klasson-Wehler E, Poellinger L, and Gustafsson JA (1985) Target cells for the polychlorinated biphenyl metabolite 4,4'-bis(methylsulfonyl)-2,2',5,5'-tetrachlorobiphenyl in lung and kidney. *Drug Metab Dispos* **13:**490-496.

Brantley E, Trapani V, Alley MC, Hose CD, Bradshaw TD, Stevens MFG, Sausville EA, and Stinson SF (2004) Fluorinated 2-(4-amino-3-methylphenyl) benzothiazoles induce CYP1A1 expression, become metabolized, and bind to macromolecules in sensitive human cancer cells. *Drug Metab Dispos* **32:**1392-1401.

Brantley SJ, Argikar AA, Lin YS, Nagar S, and Paine MF (2014) Herb-drug interactions: challenges and opportunities for improved predictions. *Drug Metab Dispos* **42:**301-317.

Buckley DB and Klaassen CD (2009) Induction of mouse UDP-glucuronosyltransferase mRNA expression in liver and intestine by activators of aryl-hydrocarbon receptor, constitutive androstane receptor, pregnane X receptor, peroxisome proliferator-activated receptor α, and nuclear factor erythroid 2-related factor 2. *Drug Metab Dispos* **37:**847-856.

Bullock P, Pearce R, Draper A, Podval J, Bracken W, Veltman J, Thomas P, and Parkinson A (1995) Induction of liver microsomal cytochrome P450 in cynomolgus monkeys. *Drug Metab Dispos* **23:**736-748.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Bunger MK, Glover E, Moran SM, Walisser JA, Lahvis GP, Hsu EL, and Bradfield CA (2008) Abnormal liver development and resistance to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity in mice carrying a mutation in the DNA-binding domain of the aryl hydrocarbon receptor. *Toxicol Sci* **106:**83-92.

Bunger MK, Moran SM, Glover E, Thomae TL, Lahvis GP, Lin BC, and Bradfield CA (2003) Resistance to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and abnormal liver development in mice carrying a mutation in the nuclear localization sequence of the aryl hydrocarbon receptor. *J Biol Chem* **278:**17767-17774.

Burbach KM, Poland A, and Bradfield CA (1992) Cloning of the Ah-receptor cDNA reveals a distinctive ligand-activated transcription factor. *Proc Natl Acad Sci USA* **89:**8185-8189.

Burczynski ME, McMillian M, Parker JB, Bryant S, Leone A, Grant ER, Thorne JM, Zhong Z, Zivin RA, and Johnson MD (2001) Cytochrome P450 induction in rat hepatocytes assessed by quantitative real-time reverse-transcription polymerase chain reaction and the RNA invasive cleavage assay. *Drug Metab Dispos* **29:**1243-1250.

Burke MD and Mayer RT (1974) Ethoxyresorufin: direct fluorometric assay of a microsomal O-dealkylation which is preferentially inducible by 3-methylcholanthrene. *Drug Metab Dispos* **2:**583-588.

Campbell ME, Grant DM, Inaba T, and Kalow W (1987) Biotransformation of caffeine, paraxanthine, theophylline, and theobromine by polycyclic aromatic hydrocarbon-inducible cytochrome(s) P-450 in human liver microsomes. *Drug Metab Dispos* **15:**237-249.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Carlile DJ, Hakooz N, and Houston JB (1999) Kinetics of drug metabolism in rat liver slices: IV. Comparison of ethoxycoumarin clearance by liver slices, isolated hepatocytes, and hepatic microsomes from rats pretreated with known modifiers of cytochrome P-450 activity. *Drug Metab Dispos* **27:**526-532.

Carver LA and Bradfield CA (1997) Ligand-dependent interaction of the aryl hydrocarbon receptor with a novel immunophilin homolog in vivo. *J Biol Chem* **272:**11452-11456.

Celius T, Roblin S, Harper PA, Matthews J, Boutros PC, Pohjanvirta R, and Okey AB (2008) Aryl hydrocarbon receptor-dependent induction of flavin-containing monooxygenase mRNAs in mouse liver. *Drug Metab Dispos* **36:**2499-2505.

Chen EP, Chen L, Ji Y, Tai G, Wen YH, and Ellens H (2010) A mechanism-based mathematical model of aryl hydrocarbon receptor-mediated CYP1A induction in rats using ß-naphthoflavone as a tool compound. *Drug Metab Dispos* **38:**2278-2285.

Chen LS, Bondoc FY, Lee MJ, Hussin AH, Thomas PE, and Yang CS (1996) Caffeine induces cytochrome P4501A2: induction of CYP1A2 by tea in rats. *Drug Metab Dispos* **24:**529-533.

Chen S and Tukey RH (2018) Humanized UGT1 mice, regulation of UGT1A1, and the role of the intestinal tract in neonatal hyperbilirubinemia and breast milk-induced jaundice. *Drug Metab Dispos* **46:**1745-1755.

Cheng XG, Maher J, Dieter MZ, and Klaassen CD (2005) Regulation of mouse organic anion-transporting polypeptides (Oatps) in liver by prototypical microsomal enzyme inducers that activate distinct transcription factor pathways. *Drug Metab Dispos* **33:**1276-1282.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Cheng Y, Jin UH, Allred CD, Jayaraman A, Chapkin RS, and Safe S (2015) Aryl hydrocarbon receptor activity of tryptophan metabolites in young adult mouse colonocytes. *Drug Metab Dispos* **43:**1536-1543.

Choudhuri S and Klaassen CD (2022) Molecular regulation of bile acid homeostasis. *Drug Metab Dispos* **50:**425-455.

Chu V, Einolf HJ, Evers R, Kumar G, Moore D, Ripp S, Silva J, Sinha V, Sinz M, and Skerjanec A (2009) In vitro and in vivo induction of cytochrome P450. A survey of the current practices and recommendations: a Pharmaceutical Research and Manufacturers of America perspective. *Drug Metab Dispos* **37:**1339-1354.

Chun YJ, Lee SK, and Kim MY (2005) Modulation of human cytochrome P4501B1 expression by 2,4,3',5'-tetramethoxystilbene. *Drug Metab Dispos* **33:**1771-1776.

Coe KJ, Feinstein M, Higgins JW, Leung P, Scott BP, Skaptason J, Tam Y, Volak LP, Kinong J, Bittner A, McAllister H, Lim NM, Hack M, and Koudriakova T (2022) Characterization of JNJ-2482272 [4-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-yl) pyrimidine-2-amine] as a strong aryl hydrocarbon receptor activator in rat and human. *Drug Metab Dispos* **50:**1064-1076.

Coe KJ, Nelson SD, Ulrich RG, He YD, Dai XD, Cheng O, Caguyong M, Roberts CJ, and Slatter JG (2006) Profiling the hepatic effects of flutamide in rats: a microarray comparison with classical aryl hydrocarbon receptor ligands and atypical CYP1A inducers. *Drug Metab Dispos* **34:**1266-1275.

Conney AH, Miller EC, and Miller JA (1956) The metabolism of methylated aminoazo dyes. V. Evidence for induction of enzyme synthesis in the rat by 3-methylcholanthrene. *Cancer Res* **16:**450-459.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Crosby M and Riddick DS (2019) Suppression of hepatic CYP3A4 expression and activity by 3-methylcholanthrene in humanized PXR-CAR-CYP3A4/3A7 mice. *Drug Metab Dispos* **47:**279-282.

Das M, Bickers DR, and Mukhtar H (1986) Epidermis: the major site of cutaneous benzo[*a*]pyrene and benzo[*a*]pyrene 7,8-diol metabolism in neonatal BALB/c mice. *Drug Metab Dispos* **14:**637-642.

Davarinos NA and Pollenz RS (1999) Aryl hydrocarbon receptor imported into the nucleus following ligand binding is rapidly degraded via the cytosplasmic proteasome following nuclear export. *J Biol Chem* **274:**28708-28715.

DeGroot D, He G, Fraccalvieri D, Bonati L, Pandini A, and Denison MS (2012) AHR ligands: promiscuity in binding and diversity in response, in *The AH Receptor in Biology and Toxicology* (Pohjanvirta R, ed) pp 63-79, John Wiley & Sons, Inc., Hoboken NJ.

Denison MS, Fisher JM, and Whitlock JP, Jr. (1988) The DNA recognition site for the dioxin-Ah receptor complex: nucleotide sequence and functional analysis. *J Biol Chem* **263:**17221-17224.

Diani-Moore S, Ma Y, Gross SS, and Rifkind AB (2014) Increases in levels of epoxyeicosatrienoic and dihydroxyeicosatrienoic acids (EETs and DHETs) in liver and heart in vivo by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and in hepatic EET:DHET ratios by cotreatment with TCDD and the soluble epoxide hydrolase inhibitor AUDA. *Drug Metab Dispos* **42:**294-300.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Diani-Moore S, Papachristou F, Labitzke E, and Rifkind AB (2006) Induction of CYP1A and CYP2-mediated arachidonic acid epoxygenation and suppression of 20-hydroxy-eicosatetraenoic acid by imidazole derivatives including the aromatase inhibitor vorozole. *Drug Metab Dispos* **34:**1376-1385.

Diani-Moore S, Shoots J, Singh R, Zuk JB, and Rifkind AB (2017) NAD^+ loss, a new player in AhR biology: prevention of thymus atrophy and hepatosteatosis by NAD^+ repletion. *Sci Rep* **7:**2268.

DiProspero TJ, Brown LG, Fachko TD, and Lockett MR (2022) HepaRG cells adopt zonal-like drug-metabolizing phenotypes under physiologically relevant oxygen tensions and Wnt/ß-catenin signaling. *Drug Metab Dispos* **50:**1098-1105.

Dolwick KM, Schmidt JV, Carver LA, Swanson HI, and Bradfield CA (1993) Cloning and expression of a human Ah receptor cDNA. *Mol Pharmacol* **44:**911-917.

Donato MT, Castell JV, and Gomez-Lechon MJ (1995) Effect of model inducers on cytochrome P450 activities of human hepatocytes in primary culture. *Drug Metab Dispos* **23:**553-558.

Dovrtelova G, Zendulka O, Noskova K, Jurica J, Pes O, Dusek J, Carazo A, Zapletalova I, Hlavacova N, and Pavek P (2018) Effect of endocannabinoid oleamide on rat and human liver cytochrome P450 enzymes in in vitro and in vivo models. *Drug Metab Dispos* **46:**913-923.

Dubaisi S, Barrett KG, Fang H, Guzman-Lepe J, Soto-Gutierrez A, Kocarek TA, and Runge-Morris M (2018) Regulation of cytosolic sulfotransferases in models of human hepatocyte development. *Drug Metab Dispos* **46:**1146-1156.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Edwards RJ, Price RJ, Watts PS, Renwick AB, Tredger JM, Boobis AR, and Lake BG (2003) Induction of cytochrome P450 enzymes in cultured precision-cut human liver slices. *Drug Metab Dispos* **31:**282-288.

El-Sherbeni AA and El-Kadi AO (2014) Characterization of arachidonic acid metabolism by rat cytochrome P450 enzymes: the involvement of CYP1As. *Drug Metab Dispos* **42:**1498-1507.

Elferink CJ, Gasiewicz TA, and Whitlock JP, Jr. (1990) Protein-DNA interactions at a dioxin-responsive enhancer: evidence that the transformed AH receptor is heteromeric. *J Biol Chem* **265:**20708-20712.

Ellero S, Chakhtoura G, Barreau C, Langouet S, Benelli C, Penicaud L, Beaune P, and de Waziers I (2010) Xenobiotic-metabolizing cytochromes P450 in human white adipose tissue: expression and induction. *Drug Metab Dispos* **38:**679-686.

Elliott A, Joiakim A, Mathieu PA, Duniec-Dmuchowski Z, Kocarek TA, and Reiners JJ, Jr. (2012) *p*-Anilinoaniline enhancement of dioxin-induced *CYP1A1* transcription and aryl hydrocarbon receptor occupancy of *CYP1A1* promoter: role of the cell cycle. *Drug Metab Dispos* **40:**1032-1040.

Elovaara E, Mikkola J, Luukkanen L, Antonio L, Fournel-Gigleux S, Burchell B, Magdalou J, and Taskinen J (2004) Assessment of catechol induction and glucuronidation in rat liver microsomes. *Drug Metab Dispos* **32:**1426-1433.

Elves RG, Ueng TH, and Alvares AP (1985) Regulation of hepatic monooxygenases by phenobarbital, 3-methylcholanthrene, and polychlorinated biphenyls in rapid and slow acetylator mice. *Drug Metab Dispos* **13:**354-358.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Ema M, Sogawa K, Watanabe N, Chujoh Y, Matsushita N, Gotoh O, Funae Y, and Fujii-Kuriyama Y (1992) cDNA cloning and structure of mouse putative Ah receptor. *Biochem Biophys Res Commun* **184:**246-253.

Falkner KC, McCallum GP, and Bend JR (1993) Effects of arsenite treatment on NAD(P)H-quinone acceptor oxidoreductase activity in liver, lung, kidney, and heart of the rat: comparison to induction by the polyaromatic hydrocarbon, ß-naphthoflavone. *Drug Metab Dispos* **21:**334-337.

Falkner KC, Ritter JK, and Prough RA (2008) Regulation of the rat UGT1A6 by glucocorticoids involves a cryptic glucocorticoid response element. *Drug Metab Dispos* **36:**409-417.

Fernandez-Salguero P, Pineau T, Hilbert DM, McPhail T, Lee SST, Kimura S, Nebert DW, Rudikoff S, Ward JM, and Gonzalez FJ (1995) Immune system impairment and hepatic fibrosis in mice lacking the dioxin-binding Ah receptor. *Science* **268:**722-726.

Forkert PG, Vessey ML, Park SS, Gelboin HV, and Cole SP (1989) Cytochromes P-450 in murine lung: an immunohistochemical study with monoclonal antibodies. *Drug Metab Dispos* **17:**551-555.

Forster U, Luippold G, and Schwarz LR (1986) Induction of monooxygenase and UDP-glucuronosyltransferase activities in primary cultures of rat hepatocytes. *Drug Metab Dispos* **14:**353-360.

Foth H, Molliere M, Kahl R, Jahnchen E, and Kahl GF (1984) Covalent binding of benzo[*a*]pyrene in perfused rat lung following systemic and intratracheal administration. *Drug Metab Dispos* **12:**760-766.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Frueh FW, Hayashibara KC, Brown PO, and Whitlock JP, Jr. (2001) Use of cDNA microarrays to analyze dioxin-induced changes in human liver gene expression. *Toxicol Lett* **122:**189-203.

Fu ZD, Csanaky IL, and Klaassen CD (2012) Effects of aging on mRNA profiles for drug-metabolizing enzymes and transporters in livers of male and female mice. *Drug Metab Dispos* **40:**1216-1225.

Fu ZD, Selwyn FP, Cui JY, and Klaassen CD (2016) RNA sequencing quantification of xenobiotic-processing genes in various sections of the intestine in comparison to the liver of male mice. *Drug Metab Dispos* **44:**842-856.

Fu ZD, Selwyn FP, Cui JY, and Klaassen CD (2017) RNA-Seq profiling of intestinal expression of xenobiotic processing genes in germ-free mice. *Drug Metab Dispos* **45:**1225-1238.

Fujita S, Masuda M, Shimamoto Y, Hoshi H, Kariya S, Kazusaka A, and Suzuki T (1996) Effect of 3-methylcholanthrene on bunitrolol metabolism: kinetics and immunological studies on 4-hydroxylation of bunitrolol catalyzed by two species of cytochromes P450 in rat liver microsomes. *Drug Metab Dispos* **24:**254-259.

Fukunaga BN, Probst MR, Reisz-Porszasz S, and Hankinson O (1995) Identification of functional domains of the aryl hydrocarbon receptor. *J Biol Chem* **270:**29270-29278.

Gasiewicz TA and Bauman PA (1987) Heterogeneity of the rat hepatic Ah receptor and evidence for transformation in vitro and in vivo. *J Biol Chem* **262:**2116-2120.

Gasiewicz TA, Geiger LE, Rucci G, and Neal RA (1983) Distribution, excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in C57BL/6J, DBA/2J, and B6D2F1/J mice. *Drug Metab Dispos* **11:**397-403.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Gasiewicz TA and Henry EC (2012) History of research on the AHR, in *The AH Receptor in Biology and Toxicology* (Pohjanvirta R, ed) pp 3-32, John Wiley & Sons, Inc., Hoboken NJ.

Gharavi N and El-Kadi AOS (2005) *tert*-Butylhydroquinone is a novel aryl hydrocarbon receptor ligand. *Drug Metab Dispos* **33:**365-372.

Gibson CR, Lin C, Singh R, Brown CM, Richards K, Brunner J, Michel K, Adelsberger J, Carlini E, Boothe-Genthe C, Raab C, Luu M, Michael A, Parikh M, Ciecko P, Subramanian R, Krolikowski P, Rodrigues AD, Baillie TA, and Rushmore TH (2005) Induction of CYP1A in the beagle dog by an inhibitor of kinase insert domain-containing receptor: differential effects in vitro and in vivo on mRNA and functional activity. *Drug Metab Dispos* **33:**1044-1051.

Gielen JE, Goujon FM, and Nebert DW (1972) Genetic regulation of aryl hydrocarbon hydroxylase induction. *J Biol Chem* **247:**1125-1137.

Girault I, Rougier N, Christophe C, Lidereau R, Beaune P, Bieche I, and de Waziers I (2005) Simultaneous measurement of 23 isoforms from the human cytochrome P450 families 1 to 3 by quantitative reverse transcriptase-polymerase chain reaction. *Drug Metab Dispos* **33:**1803-1810.

Goddard KA, Schultz RJ, and Stegeman JJ (1987) Uptake, toxicity, and distribution of benzo[*a*]pyrene and monooxygenase induction in the topminnows *Poeciliopsis monacha* and *Poeciliopsis lucida*. *Drug Metab Dispos* **15:**449-455.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Goldstein JA, Hass JR, Linko P, and Harvan DJ (1978) 2,3,7,8-Tetrachlorodibenzofuran in a commercially available 99% pure polychlorinated biphenyl isomer identified as the inducer of hepatic cytochrome P-448 and aryl hydrocarbon hydroxylase in the rat. *Drug Metab Dispos* **6:**258-264.

Gonzalez FJ and Fernandez-Salguero P (1998) The aryl hydrocarbon receptor: studies using the *Ahr*-null mice. *Drug Metab Dispos* **26:**1194-1198.

Graham RA, Downey A, Mudra D, Krueger L, Carroll K, Chengelis C, Madan A, and Parkinson A (2002) In vivo and in vitro induction of cytochrome P450 enzymes in beagle dogs. *Drug Metab Dispos* **30:**1206-1213.

Granberg L, Ostergren A, Brandt I, and Brittebo EB (2003) CYP1A1 and CYP1B1 in blood-brain interfaces: CYP1A1-dependent bioactivation of 7,12-dimethylbenz[*a*]anthracene in endothelial cells. *Drug Metab Dispos* **31:**259-265.

Griffeth LK, Rosen GM, and Rauckman EJ (1984) Effects of model traumatic injury on hepatic drug metabolism in the rat. III. Differential responses of cytochrome P-450 subpopulations. *Drug Metab Dispos* **12:**588-595.

Groen K, Breimer DD, and van Bezooijen CF (1992) Metabolism of simultaneously administered antipyrine and theophylline in male BN/BiRij rats before and after induction with 3-methylcholanthrene. *Drug Metab Dispos* **20:**502-506.

Gruszczyk J, Grandvuillemin L, Lai-Kee-Him J, Paloni M, Savva CG, Germain P, Grimaldi M, Boulahtouf A, Kwong HS, Bous J, Ancelin A, Bechara C, Barducci A, Balaguer P, and Bourguet W (2022) Cryo-EM structure of the agonist-bound Hsp90-XAP2-AHR cytosolic complex. *Nat Commun* **13:**7010.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Guengerich FP (1993) The 1992 Bernard B. Brodie Award Lecture. Bioactivation and detoxication of toxic and carcinogenic chemicals. *Drug Metab Dispos* **21:**1-6.

Haarmann-Stemmann T, Bothe H, Kohli A, Sydlik U, Abel J, and Fritsche E (2007) Analysis of the transcriptional regulation and molecular function of the aryl hydrocarbon receptor repressor in human cell lines. *Drug Metab Dispos* **35:**2262-2269.

Halpaap-Wood K, Horning EC, and Horning MG (1981) The effect of phenobarbital and ß-naphthoflavone induction on the metabolism of biphenyl in the rat and mouse. *Drug Metab Dispos* **9:**97-102.

Hariparsad N, Carr BA, Evers R, and Chu X (2008) Comparison of immortalized Fa2N-4 cells and human hepatocytes as in vitro models for cytochrome P450 induction. *Drug Metab Dispos* **36:**1046-1055.

Hartley DP and Klaassen CD (2000) Detection of chemical-induced differential expression of rat hepatic cytochrome P450 mRNA transcripts using branched DNA signal amplification technology. *Drug Metab Dispos* **28:**608-616.

Hassan HE, Myers AL, Lee IJ, Mason CW, Wang D, Sinz MW, Wang H, and Eddington ND (2013) Induction of xenobiotic receptors, transporters, and drug metabolizing enzymes by oxycodone. *Drug Metab Dispos* **41:**1060-1069.

Helmig S, Hadzaad B, Dohrel J, and Schneider J (2009) Influence of the CYP1B1 L432V gene polymorphism and exposure to tobacco smoke on CYP1B1 mRNA expression in human leukocytes. *Drug Metab Dispos* **37:**1490-1495.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Henderson CJ, Kapelyukh Y, Scheer N, Rode A, McLaren AW, MacLeod AK, Lin D, Wright J, Stanley LA, and Wolf CR (2019) An extensively humanized mouse model to predict pathways of drug disposition and drug-drug interactions, and to facilitate design of clinical trials. *Drug Metab Dispos* **47:**601-615.

Hines RN, Luo Z, Cresteil T, Ding X, Prough RA, Fitzpatrick JL, Ripp SL, Falkner KC, Ge NL, Levine A, and Elferink CJ (2001) Molecular regulation of genes encoding xenobiotic-metabolizing enzymes: mechanisms involving endogenous factors. *Drug Metab Dispos* **29:**623-633.

Hubbard TD, Murray IA, and Perdew GH (2015) Indole and tryptophan metabolism: endogenous and dietary routes to Ah receptor activation. *Drug Metab Dispos* **43:**1522-1535.

Hunter SR, Vonk A, Mullen Grey AK, and Riddick DS (2017) Role of glucocorticoid receptor and pregnane X receptor in dexamethasone induction of rat hepatic aryl hydrocarbon receptor nuclear translocator and NADPH-cytochrome P450 oxidoreductase. *Drug Metab Dispos* **45:**118-129.

Iba MM, Fung J, Pak YW, Thomas PE, Fisher H, Sekowski A, Halladay AK, and Wagner GC (1999) Dose-dependent up-regulation of rat pulmonary, renal, and hepatic cytochrome P-450 (CYP) 1A expression by nicotine feeding. *Drug Metab Dispos* **27:**977-982.

Ingelman-Sundberg M, Zhong XB, Hankinson O, Beedanagari S, Yu AM, Peng L, and Osawa Y (2013) Potential role of epigenetic mechanisms in the regulation of drug metabolism and transport. *Drug Metab Dispos* **41:**1725-1731.

Jackson JA, Birnbaum LS, and Diliberto JJ (1998) Effects of age, sex, and pharmacologic agents on the biliary elimination of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in F344 rats. *Drug Metab Dispos* **26:**714-719.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

James MO, Altman AH, Morris K, Kleinow KM, and Tong Z (1997) Dietary modulation of phase 1 and phase 2 activities with benzo[*a*]pyrene and related compounds in the intestine but not the liver of the channel catfish, *Ictalurus punctatus*. *Drug Metab Dispos* **25:**346-354.

Jemnitz K, Veres Z, Monostory K, and Vereczkey L (2000) Glucuronidation of thyroxine in primary monolayer cultures of rat hepatocytes: in vitro induction of UDP-glucuronosyltranferases by methylcholanthrene, clofibrate, and dexamethasone alone and in combination. *Drug Metab Dispos* **28:**34-37.

Jerina DM (1983) The 1982 Bernard B. Brodie Award Lecture. Metabolism of aromatic hydrocarbons by the cytochrome P-450 system and epoxide hydrolase. *Drug Metab Dispos* **11:**1-4.

Jigorel E, Le Vee M, Boursier-Neyret C, Parmentier Y, and Fardel O (2006) Differential regulation of sinusoidal and canalicular hepatic drug transporter expression by xenobiotics activating drug-sensing receptors in primary human hepatocytes. *Drug Metab Dispos* **34:**1756-1763.

Jilek JL, Tian Y, and Yu AM (2017) Effects of microRNA-34a on the pharmacokinetics of cytochrome P450 probe drugs in mice. *Drug Metab Dispos* **45:**512-522.

Joiakim A, Mathieu PA, Palermo C, Gasiewicz TA, and Reiners JJ, Jr. (2003) The Jun N-terminal kinase inhibitor SP600125 is a ligand and antagonist of the aryl hydrocarbon receptor. *Drug Metab Dispos* **31:**1279-1282.

Joiakim A, Mathieu PA, Shelp C, Boerner J, and Reiners JJ, Jr. (2016) Epidermal growth factor receptor kinase inhibitors synergize with TCDD to induce CYP1A1/1A2 in human breast epithelial MCF10A cells. *Drug Metab Dispos* **44:**665-671.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Josse R, Aninat C, Glaise D, Dumont J, Fessard V, Morel F, Poul JM, Guguen-Guillouzo C, and Guillouzo A (2008) Long-term functional stability of human HepaRG hepatocytes and use for chronic toxicity and genotoxicity studies. *Drug Metab Dispos* **36:**1111-1118.

Juchau MR, Namkung J, and Chao ST (1982) Mono-oxygenase induction in the human placenta: interrelationships among position-specific hydroxylations of 17ß-estradiol and benzo[*a*]pyrene. *Drug Metab Dispos* **10:**220-224.

Kaminsky LS and Zhang QY (2003) The small intestine as a xenobiotic-metabolizing organ. *Drug Metab Dispos* **31:**1520-1525.

Kanebratt KP and Andersson TB (2008a) Evaluation of HepaRG cells as an in vitro model for human drug metabolism studies. *Drug Metab Dispos* **36:**1444-1452.

Kanebratt KP and Andersson TB (2008b) HepaRG Cells as an in vitro model for evaluation of cytochrome P450 induction in humans. *Drug Metab Dispos* **36:**137-145.

Kapelyukh Y, Henderson CJ, Scheer N, Rode A, and Wolf CR (2019) Defining the contribution of CYP1A1 and CYP1A2 to drug metabolism using humanized *CYP1A1/1A2* and *Cyp1a1/Cyp1a2* knockout mice. *Drug Metab Dispos* **47:**907-918.

Karlgren M, Simoff I, Keiser M, Oswald S, and Artursson P (2018) CRISPR-Cas9: a new addition to the drug metabolism and disposition tool box. *Drug Metab Dispos* **46:**1776-1786.

Kasai N, Sakaki T, Shinkyo R, Ikushiro S, Iyanagi T, Kamao M, Okano T, Ohta M, and Inouye K (2004) Sequential metabolism of 2,3,7-trichlorodibenzo-*p*-dioxin (2,3,7-triCDD) by cytochrome P450 and UDP-glucuronosyltransferase in human liver microsomes. *Drug Metab Dispos* **32:**870-875.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Katchamart S, Stresser DM, Dehal SS, Kupfer D, and Williams DE (2000) Concurrent flavin-containing monooxygenase down-regulation and cytochrome P-450 induction by dietary indoles in rat: mplications for drug-drug interaction. *Drug Metab Dispos* **28:**930-936.

Kato Y, Haraguchi K, Kubota M, Seto Y, Okura T, Ikushiro S, Koga N, Yamada S, and Degawa M (2010) A possible mechanism for the decrease in serum thyroxine level by a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-like polychlorinated biphenyl congener, 3,3',4,4',5-pentachlorobiphenyl in mice. *Drug Metab Dispos* **38:**150-156.

Kato Y, Ikushiro S, Takiguchi R, Haraguchi K, Koga N, Uchida S, Sakaki T, Yamada S, Kanno J, and Degawa M (2007) A novel mechanism for polychlorinated biphenyl-induced decrease in serum thyroxine level in rats. *Drug Metab Dispos* **35:**1949-1955.

Katoh M, Matsui T, Nakajima M, Tateno C, Soeno Y, Horie T, Iwasaki K, Yoshizato K, and Yokoi T (2005) In vivo induction of human cytochrome P450 enzymes expressed in chimeric mice with humanized liver. *Drug Metab Dispos* **33:**754-763.

Kawasaki Y, Sakuma T, Goto Y, and Nemoto N (2010) Regulatory xenobiotic responsive elements in the distal 5'-flanking region of the mouse *Cyp1a2* gene required for transcriptional activation by 3-methylcholanthrene and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Drug Metab Dispos* **38:**1640-1643.

Kazlauskas A, Poellinger L, and Pongratz I (1999) Evidence that the co-chaperone p23 regulates ligand responsiveness of the dioxin (aryl hydrocarbon) receptor. *J Biol Chem* **274:**13519-13524.

Kellermann G, Luyten-Kellermann M, Horning M, and Stafford M (1975) Correlation of aryl hydrocarbon hydroxylase activity of human lymphocyte cultures and plasma elimination rates for antipyrine and phenylbutazone. *Drug Metab Dispos* **3:**47-50.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Khan IU, Bickers DR, Haqqi TM, and Mukhtar H (1992) Induction of CYP1A1 messenger RNA in rat epidermis and cultured human epidermal keratinocytes by benz[*a*]anthracene and ß-naphthoflavone. *Drug Metab Dispos* **20:**620-624.

Kim H, Reddy S, and Novak RF (1995) 3-Methylcholanthrene and pyridine effects on CYP1A1 and CYP1A2 expression in rat renal tissue. *Drug Metab Dispos* **23:**818-824.

Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, and Diefenbach A (2011) Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science* **334:**1561-1565.

Kitamura R, Asanoma H, Nagayama S, and Otagiri M (2008) Identification of human liver cytochrome P450 isoforms involved in autoinduced metabolism of the antiangiogenic agent (Z)-5-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-propanoic acid (TSU-68). *Drug Metab Dispos* **36:**1003-1009.

Klaassen CD and Cui JY (2015) Review. Mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. *Drug Metab Dispos* **43:**1505-1521.

Kocarek TA and Reddy AB (1996) Regulation of cytochrome P450 expression by inhibitors of hydroxymethylglutaryl-coenzyme A reductase in primary cultured rat hepatocytes and in rat liver. *Drug Metab Dispos* **24:**1197-1204.

Korashy HM and El-Kadi AOS (2006) Transcriptional regulation of the NAD(P)H:quinone oxidoreductase 1 and glutathione S-transferase Ya genes by mercury, lead, and copper. *Drug Metab Dispos* **34:**152-165.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Koyano S, Saito Y, Fukushima-Uesaka H, Ishida S, Ozawa S, Kamatani N, Minami H, Ohtsu A, Hamaguchi T, Shirao K, Yoshida T, Saijo N, Jinno H, and Sawada JI (2005) Functional analysis of six human aryl hydrocarbon receptor variants in a Japanese population. *Drug Metab Dispos* **33:**1254-1260.

Kozak KR, Abbott B, and Hankinson O (1997) *Arnt*-deficient mice and placental differentiation. *Dev Biol* **191:**297-305.

Larsen-Su S and Williams DE (1996) Dietary indole-3-carbinol inhibits FMO activity and the expression of flavin-containing monooxygenase form 1 in rat liver and intestine. *Drug Metab Dispos* **24:**927-931.

Lee C, Ding X, and Riddick DS (2013a) Downregulation of mouse hepatic CYP3A protein by 3-methylcholanthrene does not require cytochrome P450-dependent metabolism. *Drug Metab Dispos* **41:**1782-1786.

Lee C, Ding X, and Riddick DS (2013b) The role of cytochrome P450-dependent metabolism in the regulation of mouse hepatic growth hormone signaling components and target genes by 3-methylcholanthrene. *Drug Metab Dispos* **41:**457-465.

Lee C, Hutson JR, Tzau VKF, and Riddick DS (2006) Regulation of constitutive mouse hepatic cytochromes P450 and growth hormone signaling components by 3-methylcholanthrene. *Drug Metab Dispos* **34:**1530-1538.

Lee C, Watt KC, Chang AM, Plopper CG, Buckpitt AR, and Pinkerton KE (1998) Site-selective differences in cytochrome P450 isoform activities: comparison of expression in rat and rhesus monkey lung and induction in rats. *Drug Metab Dispos* **26:**396-400.

Levin W (1990) The 1988 Bernard B. Brodie Award Lecture. Functional diversity of hepatic cytochromes P-450. *Drug Metab Dispos* **18:**824-830.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Li AP (2020) In vitro human cell-based experimental models for the evaluation of enteric metabolism and drug interaction potential of drugs and natural products. *Drug Metab Dispos* **48:**980-992.

Li CY, Renaud HJ, Klaassen CD, and Cui JY (2016) Age-specific regulation of drug-processing genes in mouse liver by ligands of xenobiotic-sensing transcription factors. *Drug Metab Dispos* **44:**1038-1049.

Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, Wilhelm C, and Veldhoen M (2011) Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **147:**629-640.

Lim JJ, Suh Y, Faustman EM, and Cui JY (2022) Perfluorinated carboxylic acids with increasing carbon chain lengths upregulate amino acid transporters and modulate compensatory response of xenobiotic transporters in HepaRG cells. *Drug Metab Dispos* **50:**1396-1413.

Liu D, Qin S, Ray B, Kalari KR, Wang L, and Weinshilboum RM (2018) Single nucleotide polymorphisms (SNPs) distant from xenobiotic response elements can modulate aryl hydrocarbon receptor function: SNP-dependent CYP1A1 induction. *Drug Metab Dispos* **46:**1372-1381.

Liu J, Cui JY, Lu YF, Corton JC, and Klaassen CD (2021) Sex-, age-, and race/ethnicity-dependent variations in drug-processing and Nrf2-regulated genes in human livers. *Drug Metab Dispos* **49:**111-119.

Lu D, Zhao M, Chen M, and Wu B (2020) Circadian clock-controlled drug metabolism: implications for chronotherapeutics. *Drug Metab Dispos* **48:**395-406.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Lund J, Devereux T, Glaumann H, and Gustafsson JA (1988) Cellular and subcellular localization of a binding protein for polychlorinated biphenyls in rat lung. *Drug Metab Dispos* **16:**590-599.

Ma Q and Lu AYH (2007) CYP1A induction and human risk assessment: an evolving tale of in vitro and in vivo studies. *Drug Metab Dispos* **35:**1009-1016.

Ma Q and Whitlock JP, Jr. (1997) A novel cytoplasmic protein that interacts with the Ah receptor, contains tetratricopeptide repeat motifs, and augments the transcriptional response to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J Biol Chem* **272:**8878-8884.

MacPherson L, Tamblyn L, Rajendra S, Bralha F, McPherson JP, and Matthews J (2013) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin poly(ADP-ribose) polymerase (TiPARP, ARTD14) is a mono-ADP-ribosyltransferase and repressor of aryl hydrocarbon receptor transactivation. *Nucleic Acids Res* **41:**1604-1621.

Madan A, Graham RA, Carroll KM, Mudra DR, Burton LA, Krueger LA, Downey AD, Czerwinski M, Forster J, Ribadeneira MD, Gan LS, Lecluyse EL, Zech K, Robertson P, Koch P, Antonian L, Wagner G, Yu L, and Parkinson A (2003) Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. *Drug Metab Dispos* **31:**421-431.

Madhu C, Mitchell DY, and Klaassen CD (1993) Effect of P-450 inducers on biliary excretion of glutathione and its hydrolysis products: correlation between hepatic γ-glutamyl-transpeptidase activity and the proportion of glutathione hydrolysis products in bile. *Drug Metab Dispos* **21:**342-349.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Maher JM, Cheng XG, Slitt AL, Dieter MZ, and Klaassen CD (2005) Induction of the multidrug resistance-associated protein family of transporters by chemical activators of receptor-mediated pathways in mouse liver. *Drug Metab Dispos* **33:**956-962.

Malliou F, Andriopoulou CE, Gonzalez FJ, Kofinas A, Skaltsounis AL, and Konstandi M (2021) Oleuropein-induced acceleration of cytochrome P450-catalyzed drug metabolism: central Role for nuclear receptor peroxisome proliferator-activated receptor α. *Drug Metab Dispos* **49:**833-843.

Maltepe E, Schmidt JV, Baunoch D, Bradfield CA, and Simon MC (1997) Abnormal angiogenesis and responses to glucose and oxygen deprivation in mice lacking the protein ARNT. *Nature* **386:**403-407.

Manchester DK, Gordon SK, Golas CL, Roberts EA, and Okey AB (1987) *Ah* receptor in human placenta: stabilization by molybdate and characterization of binding of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, 3-methylcholanthrene, and benzo[*a*]pyrene. *Cancer Res* **47:**4861-4868.

Mannering GJ (1986) The 1984 Bernard B. Brodie Award Lecture. From morphine to interferon: an odyssey of drug metabolism. *Drug Metab Dispos* **14:**1-4.

Martin LA, Wilson DT, Reuhl KR, Gallo MA, and Klaassen CD (2012) Polychlorinated biphenyl congeners that increase the glucuronidation and biliary excretion of thyroxine are distinct from the congeners that enhance the serum disappearance of thyroxine. *Drug Metab Dispos* **40:**588-595.

Massey TE, Devereux TR, and Fouts JR (1986) Biotransformation of xenobiotics in individual rabbit hepatocytes: application of microspectrofluorometry. *Drug Metab Dispos* **14:**319-324.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Masubuchi N, Hakusui H, and Okazaki O (1997) Effects of pantoprazole on xenobiotic metabolizing enzymes in rat liver microsomes: a comparison with other proton pump inhibitors. *Drug Metab Dispos* **25:**584-589.

Matsunawa M, Akagi D, Uno S, Endo-Umeda K, Yamada S, Ikeda K, and Makishima M (2012) Vitamin D receptor activation enhances benzo[*a*]pyrene metabolism via CYP1A1 expression in macrophages. *Drug Metab Dispos* **40:**2059-2066.

Mays DC, Hecht SG, Unger SE, Pacula CM, Climie JM, Sharp DE, and Gerber N (1987) Disposition of 8-methoxypsoralen in the rat: induction of metabolism in vivo and in vitro and identification of urinary metabolites by thermospray mass spectrometry. *Drug Metab Dispos* **15:**318-328.

McGuire J, Okamoto K, Whitelaw ML, Tanaka H, and Poellinger L (2001) Definition of a dioxin receptor mutant that is a constitutive activator of transcription: delineation of overlapping repression and ligand binding functions within the PAS domain. *J Biol Chem* **276:**41841-41849.

McNeilly AD, Woods JA, Ibbotson SH, Wolf CR, and Smith G (2012) Characterization of a human keratinocyte HaCaT cell line model to study the regulation of CYP2S1. *Drug Metab Dispos* **40:**283-289.

Meneses-Lorente G, Pattison C, Guyomard C, Chesne C, Heavens R, Watt AP, and Sohal B (2007) Utility of long-term cultured human hepatocytes as an in vitro model for cytochrome P450 induction. *Drug Metab Dispos* **35:**215-220.

Meyer BK, Pray-Grant MG, Vanden Heuvel JP, and Perdew GH (1998) Hepatitis B virus X-associated protein 2 is a subunit of the unliganded aryl hydrocarbon receptor core complex and exhibits transcriptional enhancer activity. *Mol Cell Biol* **18:**978-988.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, and Bradfield CA (2010) An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol* **185:**3190-3198.

Mimura J, Yamashita K, Nakamura K, Morita M, Takagi TN, Nakao K, Ema M, Sogawa K, Yasuda M, Katsuki M, and Fujii-Kuriyama Y (1997) Loss of teratogenic response to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in mice lacking the Ah (dioxin) receptor. *Genes to Cells* **2:**645-654.

Minchin RF, McManus ME, Thorgeirsson SS, Schwartz D, and Boyd MR (1985) Metabolism of 2-acetylaminofluorene in isolated rabbit pulmonary cells: evidence for the heterogeneous distribution of monooxygenase activity in lung tissue. *Drug Metab Dispos* **13:**406-411.

Miners JO, Attwood J, Wing LM, and Birkett DJ (1985) Influence of cimetidine, sulfinpyrazone, and cigarette smoking on theobromine metabolism in man. *Drug Metab Dispos* **13:**598-601.

Modly CE, Das M, Don PS, Marcelo CL, Mukhtar H, and Bickers DR (1986) Capsaicin as an in vitro inhibitor of benzo[*a*]pyrene metabolism and its DNA binding in human and murine keratinocytes. *Drug Metab Dispos* **14:**413-416.

Mohutsky MA, Petullo DM, and Wrighton SA (2005) The use of a substrate cassette strategy to improve the capacity and throughput of cytochrome P450 induction studies in human hepatocytes. *Drug Metab Dispos* **33:**920-923.

Monteiro P, Gilot D, Langouet S, and Fardel O (2008) Activation of the aryl hydrocarbon receptor by the calcium/calmodulin-dependent protein kinase kinase inhibitor 7-oxo-*7H*-benzimidazo[2,1-*a*]benz[de]isoquinoline-3-carboxylic Acid (STO-609). *Drug Metab Dispos* **36:**2556-2563.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Moody DE, Taylor LA, Smuckler EA, Levin W, and Thomas PE (1983) Immunohistochemical localization of cytochrome P-450a in liver sections from untreated rats and rats treated with phenobarbital or 3-methylcholanthrene. *Drug Metab Dispos* **11:**339-343.

Morgan ET, Dempsey JL, Mimche SM, Lamb TJ, Kulkarni S, Cui JY, Jeong H, and Slitt AL (2018) Physiological regulation of drug metabolism and transport: pregnancy, microbiome, inflammation, infection, and fasting. *Drug Metab Dispos* **46:**503-513.

Morgan ET, Sewer MB, Iber H, Gonzalez FJ, Lee YH, Tukey RH, Okino S, Vu T, Chen YH, Sidhu JS, and Omiecinski CJ (1998) Physiological and pathophysiological regulation of cytochrome P450. *Drug Metab Dispos* **26:**1232-1240.

Moriguchi T, Motohashi H, Hosoya T, Nakajima O, Takahashi S, Ohsako S, Aoki Y, Nishimura N, Tohyama C, Fujii-Kuriyama Y, and Yamamoto M (2003) Distinct response to dioxin in an aryl hydrocarbon receptor (*AHR*)-humanized mouse. *Proc Nat Acad Sci USA* **100:**5652-5657.

Mukhtar H and Bickers DR (1983) Age-related changes in benzo[*a*]pyrene metabolism and epoxide-metabolizing enzyme activities in rat skin. *Drug Metab Dispos* **11:**562-567.

Mullen Grey AK and Riddick DS (2011) The aryl hydrocarbon receptor pathway and the response to 3-methylcholanthrene are altered in the liver of adrenalectomized rats. *Drug Metab Dispos* **39:**83-91.

Munzel PA, Schmohl S, Heel H, Kalberer K, Bock-Hennig BS, and Bock KW (1999) Induction of human UDP glucuronosyltransferases (UGT1A6, UGT1A9, and UGT2B7) by *t*-butylhydroquinone and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Caco-2 cells. *Drug Metab Dispos* **27:**569-573.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Murphy PJ (2008a) The development of drug metabolism research as expressed in the publications of ASPET: Part 2, 1959-1983. *Drug Metab Dispos* **36:**981-985.

Murphy PJ (2008b) The development of drug metabolism research as expressed in the publications of ASPET: Part 3, 1984-2008. *Drug Metab Dispos* **36:**1977-1982.

Myers MJ, Farrell DE, Howard KD, and Kawalek JC (2001) Identification of multiple constitutive and inducible hepatic cytochrome P450 enzymes in market weight swine. *Drug Metab Dispos* **29:**908-915.

Nakano M and Nakajima M (2022) Adenosine-to-inosine RNA editing and N^6-methyladenosine modification modulating expression of drug metabolizing enzymes. *Drug Metab Dispos* **50:**624-633.

Neavin DR, Lee JH, Liu D, Ye Z, Li H, Wang L, Ordog T, and Weinshilboum RM (2019) Single nucleotide polymorphisms at a distance from aryl hydrocarbon receptor (AHR) binding sites influence AHR ligand-dependent gene expression. *Drug Metab Dispos* **47:**983-994.

Nebert DW (1988) The 1986 Bernard B. Brodie Award Lecture. The genetic regulation of drug-metabolizing enzymes. *Drug Metab Dispos* **16:**1-8.

Nebert DW (2017) Aryl hydrocarnon receptor (AHR): "pioneer member" of the basic-helix/loop/helix *per-Arnt-sim* (bHLH/PAS) family of "sensors" of foreign and endogenous signals. *Prog Lipid Res* **67:**38-57.

Nebert DW, Considine N, and Kon H (1973) Genetic differences in cytochrome P-450 during induction of mono-oxygenase activities. *Drug Metab Dispos* **1:**231-238.

Neumann CM, Steppan LB, and Kerkvliet NI (1992) Distribution of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in splenic tissue of C57BL/6J mice. *Drug Metab Dispos* **20:**467-469.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Nguyen LP and Bradfield CA (2008) The search for endogenous activators of the aryl hydrocarbon receptor. *Chem Res Toxicol* **21:**102-116.

Okey AB (2007) Special contribution. An aryl hydrocarbon receptor odyssey to the shores of toxicology: the Deichmann lecture, International Congress of Toxicology-XI. *Toxicol Sci* **98:**5-38.

Okey AB, Bondy GP, Mason ME, Kahl GF, Eisen HJ, Guenthner TM, and Nebert DW (1979) Regulatory gene product of the *Ah* locus: characterization of the cytosolic inducer-receptor complex and evidence for its nuclear translocation. *J Biol Chem* **254:**11636-11648.

Okey AB, Vella LM, and Harper PA (1989) Detection and characterization of a low affinity form of cytosolic Ah receptor in livers of mice nonresponsive to induction of cytochrome P_1-450 by 3-methylcholanthrene. *Mol Pharmacol* **35:**823-830.

Omura T (2022) Perspective of the induction of liver microsomal cytochrome P450s by chemical compounds. *Drug Metab Dispos* **50:**1000-1001.

Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, Jugold M, Guillemin GJ, Miller CL, Lutz C, Radlwimmer B, Lehmann I, von Deimling A, Wick W, and Platten M (2011) An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* **478:**197-203.

Oravec CT, Samuel MJ, and D'Ambrosio SM (1985) Metabolism of 7,12-dimethyl-benz[*a*]anthracene and its DNA adduct formation in human fetal kidney and intestinal cells in culture. *Drug Metab Dispos* **13:**76-80.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Osabe M, Sugatani J, Fukuyama T, Ikushiro S, Ikari A, and Miwa M (2008) Expression of hepatic UDP-glucuronosyltransferase 1A1 and 1A6 correlated with increased expression of the nuclear constitutive androstane receptor and peroxisome proliferator-activated receptor α in male rats fed a high-fat and high-sucrose diet. *Drug Metab Dispos* **36:**294-302.

Pande P, Zhong XB, and Ku WW (2020) Histone methyltransferase G9a regulates expression of nuclear receptors and cytochrome P450 enzymes in HepaRG cells at basal level and in fatty acid induced steatosis. *Drug Metab Dispos* **48:**1321-1329.

Papac DI and Franklin MR (1988) N-Benzylimidazole, a high magnitude inducer of rat hepatic cytochrome P-450 exhibiting both polycyclic aromatic hydrocarbon- and phenobarbital-type induction of phase I and phase II drug-metabolizing enzymes. *Drug Metab Dispos* **16:**259-264.

Paroli L, Lee C, and Rifkind AB (1994) Identification of hepatocytes as the major locus of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced CYP1-related P450s, $TCDD_{AA}$ and $TCDD_{AHH}$,in chick embryo liver. *Drug Metab Dispos* **22:**962-968.

Paszek M and Tukey RH (2020) Nrf2-independent regulation of intestinal constitutive androstane receptor by the pro-oxidants cadmium and isothiocyanate in *hUGT1* mice. *Drug Metab Dispos* **48:**25-30.

Patel A, Zhang S, Paramahamsa M, Jiang W, Wang L, Moorthy B, and Shivanna B (2015) Leflunomide induces pulmonary and hepatic CYP1A enzymes via aryl hydrocarbon receptor. *Drug Metab Dispos* **43:**1966-1970.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Pelkonen O, Sotaniemi E, Tokola O, and Ahokas JT (1980) Correlations between cytochrome P-450 and oxidative metabolism of benzo[*a*]pyrene and 7-ethoxycoumarin in human liver in vitro and antipyrine elimination in vivo. *Drug Metab Dispos* **8:**218-222.

Perdew GH (1988) Association of the Ah receptor with the 90-kDa heat shock protein. *J Biol Chem* **263:**13802-13805.

Petrick JS and Klaassen CD (2007) Importance of hepatic induction of constitutive androstane receptor and other transcription factors that regulate xenobiotic metabolism and transport. *Drug Metab Dispos* **35:**1806-1815.

Pfeifer A and Neumann HG (1988) Modulation of *trans*-4-acetylaminostilbene metabolism in the rat by methylcholanthrene and phenobarbital and its relevance for acute toxicity. *Drug Metab Dispos* **16:**276-284.

Pichard-Garcia L, Weaver RJ, Eckett N, Scarfe G, Fabre JM, Lucas C, and Maurel P (2004) The olivacine derivative S 16020 (9-hydroxy-5,6-dimethyl-N-[2-(dimethylamino)ethyl)-*6H*-pyrido(4,3-*b*)-carbazole-1-carboxamide) induces CYP1A and its own metabolism in human hepatocytes in primary culture. *Drug Metab Dispos* **32:**80-88.

Pillai UA, Ziegler TL, Wang DX, Kattnig MJ, McClure T, Liebler DC, Mayersohn M, and Sipes IG (1996) 3,3',4,4'-Tetrachloroazobenzene absorption, disposition, and metabolism in male Fischer 344 rats. *Drug Metab Dispos* **24:**238-244.

Pohjanvirta R, Tuomisto J, Vartiainen T, and Rozman K (1987) Han/Wistar rats are exceptionally resistant to TCDD. I. *Pharmacol Toxicol* **60:**145-150.

Poland A and Glover E (1974) Comparison of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, a potent inducer of aryl hydrocarbon hydroxylase, with 3-methylcholanthrene. *Mol Pharmacol* **10:**349-359.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Poland A and Glover E (1980) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: segregation of toxicity with the *Ah* locus. *Mol Pharmacol* **17:**86-94.

Poland A, Glover E, and Bradfield CA (1991) Characterization of polyclonal antibodies to the Ah receptor prepared by immunization with a synthetic peptide hapten. *Mol Pharmacol* **39:**20-26.

Poland A, Glover E, and Kende AS (1976) Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by hepatic cytosol: evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase. *J Biol Chem* **251:**4936-4946.

Poland AD (1996) Meeting report. Receptor-acting xenobiotics and their risk assessment. *Drug Metab Dispos* **24:**1385-1388.

Poppers PJ, Levin W, and Conney AH (1975) Effect of 3-methylcholanthrene treatment on phenacetin O-dealkylation in several inbred mouse strains. *Drug Metab Dispos* **3:**502-506.

Pratt-Hyatt M, Lickteig AJ, and Klaassen CD (2013) Tissue distribution, ontogeny, and chemical induction of aldo-keto reductases in mice. *Drug Metab Dispos* **41:**1480-1487.

Preiss LC, Liu R, Hewitt P, Thompson D, Georgi K, Badolo L, Lauschke VM, and Petersson C (2021) Deconvolution of cytochrome P450 induction mechanisms in HepaRG nuclear hormone receptor knockout cells. *Drug Metab Dispos* **49:**668-678.

Puga A, Maier A, and Medvedovic M (2000) The transcriptional signature of dioxin in human hepatoma HepG2 cells. *Biochem Pharmacol* **60:**1129-1142.

Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, Caccamo M, Oukka M, and Weiner HL (2008) Control of T_{reg} and T_H17 cell differentiation by the aryl hydrocarbon receptor. *Nature* **453:**65-71.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Ramsden D, Wu JT, Zerler B, Iqbal S, Jiang J, Clausen V, Aluri K, Gu Y, Dennin S, Kim J, and Chong S (2019) In vitro drug-drug interaction evaluation of GalNAc conjugated siRNAs against CYP450 enzymes and transporters. *Drug Metab Dispos* **47:**1183-1194.

Rannug A, Rannug U, Rosenkranz HS, Winqvist L, Westerholm R, Agurell E, and Grafstrom AK (1987) Certain photooxidized derivatives of tryptophan bind with very high affinity to the Ah receptor and are likely to be endogenous signal substances. *J Biol Chem* **262:**15422-15427.

Reiners JJ, Jr., Cantu AR, Thai G, and Scholler A (1992) Differential expression of basal and hydrocarbon-induced cytochrome P-450 monooxygenase and quinone reductase activities in subpopulations of murine epidermal cells differing in their stages of differentiation. *Drug Metab Dispos* **20:**360-366.

Reisdorph R and Lindahl R (2007) Constitutive and 3-methylcholanthrene-induced rat ALDH3A1 expression is mediated by multiple xenobiotic response elements. *Drug Metab Dispos* **35:**386-393.

Reyes H, Reisz-Porszasz S, and Hankinson O (1992) Identification of the Ah receptor nuclear translocator protein (Arnt) as a component of the DNA binding form of the Ah receptor. *Science* **256:**1193-1195.

Riddick DS, Ding X, Wolf CR, Porter TD, Pandey AV, Zhang QY, Gu J, Finn RD, Ronseaux S, McLaughlin LA, Henderson CJ, Zou L, and Fluck CE (2013) NADPH-Cytochrome P450 oxidoreductase: roles in physiology, pharmacology, and toxicology. *Drug Metab Dispos* **41:**12-23.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Riddick DS, Lee C, Bhathena A, Timsit YE, Cheng PY, Morgan ET, Prough RA, Ripp SL, Michael Miller KK, Jahan A, and Chiang JYL (2004) Transcriptional suppression of cytochrome P450 genes by endogenous and exogenous chemicals. *Drug Metab Dispos* **32:**367-375.

Rieger JK, Klein K, Winter S, and Zanger UM (2013) Expression variability of absorption, distribution, metabolism, excretion-related microRNAs in human liver: influence of nongenetic factors and association with gene expression. *Drug Metab Dispos* **41:**1752-1762.

Roberts BJ and Whitelaw ML (1999) Degradation of the basic helix-loop-helix/Per-ARNT-Sim homology domain dioxin receptor via the ubiquitin/proteasome pathway. *J Biol Chem* **274:**36351-36356.

Roberts EA, Xie ZW, Yang S, and Lipa J (1993) Inducibility of enzyme activities associated with the cytochrome P-450 1A family, ethoxyresorufin O-deethylase, and methoxyresorufin O-demethylase in human hepatocyte lines derived from normal liver tissue. *Drug Metab Dispos* **21:**56-61.

Rockwell CE, Jin Y, Boss AP, Kaiser LM, and Awali S (2022) The complicated role of nuclear factor erythroid-derived 2-like 2 in allergy and asthma. *Drug Metab Dispos* **50:**500-507.

Rondini EA, Fang H, Runge-Morris M, and Kocarek TA (2014) Regulation of human cytosolic sulfotransferases 1C2 and 1C3 by nuclear signaling pathways in LS180 colorectal adenocarcinoma cells. *Drug Metab Dispos* **42:**361-368.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao CC, Patel B, Yan R, Blain M, Alvarez JI, Kebir H, Anandasabapathy N, Izquierdo G, Jung S, Obholzer N, Pochet N, Clish CB, Prinz M, Prat A, Antel J, and Quintana FJ (2016) Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat Med* **22:**586-597.

Roy M, Monsarrat B, Cros S, Lecointe P, Rivalle C, and Bisagni E (1985) Cytochrome P-450-mediated O-demethylation of two ellipticine derivatives: differential effect of the murine *Ah* locus phenotype. *Drug Metab Dispos* **13:**497-502.

Roymans D, Annaert P, Van Houdt J, Weygers A, Noukens J, Sensenhauser C, Silva J, Van Looveren C, Hendrickx J, Mannens G, and Meuldermans W (2005) Expression and induction potential of cytochromes P450 in human cryopreserved hepatocytes. *Drug Metab Dispos* **33:**1004-1016.

Rush WR, Smith SA, Mulvey JH, Graham DJ, and Chaplin MD (1987) Inhibition and induction of hepatic drug metabolism in rats and mice by nafimidone and its major metabolite nafimidone alcohol. *Drug Metab Dispos* **15:**571-578.

Rysz M, Bromek E, Haduch A, Sadakierska-Chudy A, and Daniel WA (2015) Damage to the brain serotonergic system increases the expression of liver cytochrome P450. *Drug Metab Dispos* **43:**1345-1352.

Safe S (1990) Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit Rev Toxicol* **21:**51-88.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Sakuma T, Ohtake M, Katsurayama Y, Jarukamjorn K, and Nemoto N (1999) Induction of CYP1A2 by phenobarbital in the livers of aryl hydrocarbon-responsive and -nonresponsive mice. *Drug Metab Dispos* **27:**379-384.

Salhab AS, James MO, Wang SL, and Shiverick KT (1986) Positional metabolism of benzo[*a*]pyrene in rat placenta and maternal liver: comparison of induction effects. *Drug Metab Dispos* **14:**471-476.

Sawaya RM and Riddick DS (2008) Cytochrome P450 2C11 5'-flanking region and promoter mediate in vivo suppression by 3-methylcholanthrene. *Drug Metab Dispos* **36:**1803-1811.

Schaefer O, Ohtsuki S, Kawakami H, Inoue T, Liehner S, Saito A, Sakamoto A, Ishiguro N, Matsumaru T, Terasaki T, and Ebner T (2012) Absolute quantification and differential expression of drug transporters, cytochrome P450 enzymes, and UDP-glucuronosyl-transferases in cultured primary human hepatocytes. *Drug Metab Dispos* **40:**93-103.

Schebb NH, Muvvala JB, Morin D, Buckpitt AR, Hammock BD, and Rice RH (2014) Metabolic activation of the antibacterial agent triclocarban by cytochrome P450 1A1 yielding glutathione adducts. *Drug Metab Dispos* **42:**1098-1102.

Schiering C, Wincent E, Metidji A, Iseppon A, Li Y, Potocnik AJ, Omenetti S, Henderson CJ, Wolf CR, Nebert DW, and Stockinger B (2017) Feedback control of AHR signalling regulates intestinal immunity. *Nature* **542:**242-245.

Schlezinger JJ and Stegeman JJ (2000) Dose and inducer-dependent induction of cytochrome P450 1A in endothelia of the eel, including in the swimbladder rete mirabile, a model microvascular structure. *Drug Metab Dispos* **28:**701-708.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Schmidt JV, Su GHT, Reddy JK, Simon MC, and Bradfield CA (1996) Characterization of a murine *Ahr* null allele: involvement of the Ah receptor in hepatic growth and development. *Proc Natl Acad Sci USA* **93:**6731-6736.

Schreiber TD, Kohle C, Buckler F, Schmohl S, Braeuning A, Schmiechen A, Schwarz M, and Munzel PA (2006) Regulation of CYP1A1 gene expression by the antioxidant *tert*-butylhydroquinone. *Drug Metab Dispos* **34:**1096-1101.

Schrenk D and Bock KW (1990) Metabolism of benzene in rat hepatocytes: influence of inducers on phenol glucuronidation. *Drug Metab Dispos* **18:**720-725.

Selwyn FP, Cui JY, and Klaassen CD (2015) RNA-Seq quantification of hepatic drug processing genes in germ-free mice. *Drug Metab Dispos* **43:**1572-1580.

Shelby MK and Klaassen CD (2006) Induction of rat UDP-glucuronosyltransferases in liver and duodenum by microsomal enzyme inducers that activate various transcriptional pathways. *Drug Metab Dispos* **34:**1772-1778.

Shen ES and Olson JR (1987) Relationship between the murine Ah phenotype and the hepatic uptake and metabolism of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Drug Metab Dispos* **15:**653-660.

Shiizaki K, Kawanishi M, and Yagi T (2014) Microbial metabolites of omeprazole activate murine aryl hydrocarbon receptor in vitro and in vivo. *Drug Metab Dispos* **42:**1690-1697.

Shively CA and Vesell ES (1987) In vivo and in vitro biotransformation of theobromine by phenobarbital- and 3-methylcholanthrene-inducible cytochrome P-450 monooxygenases in rat liver: role of thiol compounds. *Drug Metab Dispos* **15:**217-224.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Shiverick KT (1981) In vivo and in vitro effects of ß-naphthoflavone on cytochrome P-450-dependent testosterone hydroxylase activities in liver microsomes. *Drug Metab Dispos* **9:**545-550.

Siest G, Jeannesson E, Marteau JB, Samara A, Marie B, Pfister M, and Visvikis-Siest S (2008) Transcription factor and drug-metabolizing enzyme gene expression in lymphocytes from healthy human subjects. *Drug Metab Dispos* **36:**182-189.

Sinclair PR, Gorman N, Walton HS, Sinclair JF, Lee CA, and Rifkind AB (1997) Identification of CYP1A5 as the CYP1A enzyme mainly responsible for uroporphyrinogen oxidation induced by AH receptor ligands in chicken liver and kidney. *Drug Metab Dispos* **25:**779-783.

Smith SH, Jayawickreme C, Rickard DJ, Nicodeme E, Bui T, Simmons C, Coquery CM, Neil J, Pryor WM, Mayhew D, Rajpal DK, Creech K, Furst S, Lee J, Wu D, Rastinejad F, Willson TM, Viviani F, Morris DC, Moore JT, and Cote-Sierra J (2017) Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol* **137:**2110-2119.

Smolowitz RM, Hahn ME, and Stegeman JJ (1991) Immunohistochemical localization of cytochrome P-450IA1 induced by 3,3',4,4'-tetrachlorobiphenyl and by 2,3,7,8-tetrachlorodibenzofuran in liver and extrahepatic tissues of the teleost *Stenotomus Chrysops* (scup). *Drug Metab Dispos* **19:**113-123.

Soars MG, Petullo DM, Eckstein JA, Kasper SC, and Wrighton SA (2004) An assessment of UDP-glucuronosyltransferase induction using primary human hepatocytes. *Drug Metab Dispos* **32:**140-148.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Spink DC, Katz BH, Hussain MM, Spink BC, Wu SJ, Liu N, Pause R, and Kaminsky LS (2002) Induction of CYP1A1 and CYP1B1 in T-47D human breast cancer cells by benzo[*a*]pyrene is diminished by arsenite. *Drug Metab Dispos* **30:**262-269.

Spivack SD, Hurteau GJ, Reilly AA, Aldous KM, Ding XX, and Kaminsky LS (2001) CYP1B1 expression in human lung. *Drug Metab Dispos* **29:**916-922.

Stevens EA, Mezrich JD, and Bradfield CA (2009) The aryl hydrocarbon receptor: a perspective on potential roles in the immune system. *Immunology* **127:**299-311.

Stiborova M, Dracinska H, Hajkova J, Kaderabkova P, Frei E, Schmeiser HH, Soucek P, Phillips DH, and Arlt VM (2006) The environmental pollutant and carcinogen 3-nitro-benzanthrone and its human metabolite 3-aminobenzanthrone are potent inducers of rat hepatic cytochromes P450 1A1 and-1A2 and NAD(P)H:quinone oxidoreductase. *Drug Metab Dispos* **34:**1398-1405.

Stresser DM, Bailey GS, and Williams DE (1994a) Indole-3-carbinol and ß-naphthoflavone induction of aflatoxin B_1 metabolism and cytochromes P-450 associated with bioactivation and detoxication of aflatoxin B_1 in the rat. *Drug Metab Dispos* **22:**383-391.

Stresser DM, Sun J, and Wilson SS (2021) Evaluation of tissue stem cell-derived human intestinal organoids, a physiologically relevant model to evaluate cytochrome P450 induction in gut. *Drug Metab Dispos* **49:**245-253.

Stresser DM, Williams DE, Griffin DA, and Bailey GS (1995) Mechanisms of tumor modulation by indole-3-carbinol: disposition and excretion in male Fischer 344 rats. *Drug Metab Dispos* **23:**965-975.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Stresser DM, Williams DE, McLellan LI, Harris TM, and Bailey GS (1994b) Indole-3-carbinol induces a rat liver glutathione transferase subunit (Yc2) with high activity toward aflatoxin B_1 exo-epoxide: association with reduced levels of hepatic aflatoxin-DNA adducts in vivo. *Drug Metab Dispos* **22:**392-399.

Stuchal LD, Kleinow KM, Stegeman JJ, and James MO (2006) Demethylation of the pesticide methoxychlor in liver and intestine from untreated, methoxychlor-treated, and 3-methylcholanthrene-treated channel catfish (*Ictalurus punctatus*): evidence for roles of CYP1 and CYP3A family isozymes. *Drug Metab Dispos* **34:**932-938.

Sugawara M, Okamoto K, Kadowaki T, Kusano K, Fukamizu A, and Yoshimura T (2009) Inoculation of human tumor cells alters the basal expression but not the inducibility of cytochrome P450 enzymes in tumor-bearing mouse liver. *Drug Metab Dispos* **37:**2244-2254.

Sun D, Lu J, Zhang Y, Liu J, Liu Z, Yao B, Guo Y, and Wang X (2021) Characterization of a novel *CYP1A2*-knockout rat model constructed by CRISPR-Cas9. *Drug Metab Dispos* **49:**638-647.

Swanson HI (2015) Drug metabolism by the host and gut microbiota: a partnership or rivalry? *Drug Metab Dispos* **43:**1499-1504.

Swanson HI, Njar VC, Yu Z, Castro DJ, Gonzalez FJ, Williams DE, Huang Y, Kong AN, Doloff JC, Ma J, Waxman DJ, and Scott EE (2010) Targeting drug-metabolizing enzymes for effective chemoprevention and chemotherapy. *Drug Metab Dispos* **38:**539-544.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Takano H, Yamaguchi JI, Kato S, Hamada M, Tada M, and Endo H (2021) Downregulation of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes by prolyl hydroxylase domain 2 inhibitors via hypoxia-inducible factor-α stabilization. *Drug Metab Dispos* **49:**20-30.

Tang C, Lin JH, and Lu AYH (2005) Metabolism-based drug-drug interactions: what determines individual variability in cytochrome P450 induction? *Drug Metab Dispos* **33:**603-613.

Tanner N, Kubik L, Luckert C, Thomas M, Hofmann U, Zanger UM, Bohmert L, Lampen A, and Braeuning A (2018) Regulation of drug metabolism by the interplay of inflammatory signaling, steatosis, and xeno-sensing receptors in HepaRG cells. *Drug Metab Dispos* **46:**326-335.

Taylor RE, Bhattacharya A, and Guo GL (2022) Environmental chemical contribution to the modulation of bile acid homeostasis and farnesoid X receptor signaling. *Drug Metab Dispos* **50:**456-467.

Thiebaud N, Sigoillot M, Chevalier J, Artur Y, Heydel JM, and Le Bon AM (2010) Effects of typical inducers on olfactory xenobiotic-metabolizing enzyme, transporter, and transcription factor expression in rats. *Drug Metab Dispos* **38:**1865-1875.

Thomas RS, Rank DR, Penn SG, Zastrow GM, Hayes KR, Pande K, Glover E, Silander T, Craven MW, Reddy JK, Jovanovich SB, and Bradfield CA (2001) Identification of toxicologically predictive gene sets using cDNA microarrays. *Mol Pharmacol* **60:**1189-1194.

Tochigi Y, Yamashiki N, Ohgiya S, Ganaha S, and Yokota H (2005) Isoform-specific expression and induction of UDP-glucuronosyltransferase in immunoactivated peritoneal macrophages of the rat. *Drug Metab Dispos* **33:**1391-1398.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Vakharia DD, Liu N, Pause R, Fasco M, Bessette E, Zhang QY, and Kaminsky LS (2001) Polycyclic aromatic hydrocarbon/metal mixtures: effect on PAH induction of CYP1A1 in human HepG2 cells. *Drug Metab Dispos* **29:**999-1006.

van de Kerkhof EG, de Graaf IA, de Jager MH, Meijer DK, and Groothuis GM (2005) Characterization of rat small intestinal and colon precision-cut slices as an in vitro system for drug metabolism and induction studies. *Drug Metab Dispos* **33:**1613-1620.

van de Kerkhof EG, de Graaf IAM, de Jager MH, and Groothuis GMM (2007) Induction of phase I and II drug metabolism in rat small intestine and colon in vitro. *Drug Metab Dispos* **35:**898-907.

van de Kerkhof EG, de Graaf IA, Ungell AL, and Groothuis GM (2008) Induction of metabolism and transport in human intestine: validation of precision-cut slices as a tool to study induction of drug metabolism in human intestine in vitro. *Drug Metab Dispos* **36:**604-613.

Vansell NR (2022) Mechanisms by which inducers of drug metabolizing enzymes alter thyroid hormones in rats. *Drug Metab Dispos* **50:**508-517.

Vansell NR and Klaassen CD (2002) Increase in rat liver UDP-glucuronosyltransferase mRNA by microsomal enzyme inducers that enhance thyroid hormone glucuronidation. *Drug Metab Dispos* **30:**240-246.

van Veld PA, Stegeman JJ, Woodin BR, Patton JS, and Lee RF (1988) Induction of monooxygenase activity in the intestine of spot (*Leiostomus xanthurus*), a marine teleost, by dietary polycyclic aromatic hydrocarbons. *Drug Metab Dispos* **16:**659-665.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Vermillion Maier ML, Siddens LK, Uesugi SL, Choi J, Leonard SW, Pennington JM, Tilton SC, Smith JN, Ho E, Chow HHS, Nguyen BD, Kolluri SK, and Williams DE (2021) 3,3'-Diindolylmethane exhibits significant metabolism after oral dosing in humans. *Drug Metab Dispos* **49:**694-705.

Walle T, Otake Y, Galijatovic A, Ritter JK, and Walle UK (2000) Induction of UDP-glucuronosyltransferase UGT1A1 by the flavonoid chrysin in the human hepatoma cell line HepG2. *Drug Metab Dispos* **28:**1077-1082.

Walle T, Walle UK, Sedmera D, and Klausner M (2006) Benzo[*a*]pyrene-induced oral carcinogenesis and chemoprevention: studies in bioengineered human tissue. *Drug Metab Dispos* **34:**346-350.

Walle UK and Walle T (2002) Induction of human UDP-glucuronosyltransferase UGT1A1 by flavonoids: structural requirements. *Drug Metab Dispos* **30:**564-569.

Wang H, Zhang L, Xia Z, and Cui JY (2022) Effect of chronic cadmium exposure on brain and liver transporters and drug-metabolizing enzymes in male and female mice genetically predisposed to Alzheimer's disease. *Drug Metab Dispos* **50:**1414-1428.

Wang HW, Chen TL, Yang PC, and Ueng TH (2001) Induction of cytochromes P450 1A1 and 1B1 by emodin in human lung adenocarcinoma cell line CL5. *Drug Metab Dispos* **29:**1229-1235.

Wang J, Yu L, Jiang H, Zheng X, and Zeng S (2020) Epigenetic regulation of differentially expressed drug-metabolizing enzymes in cancer. *Drug Metab Dispos* **48:**759-768.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Wang P, Chen S, Wang Y, Wang X, Yan L, Yang K, Zhong XB, Han S, and Zhang L (2021) The long noncoding RNA hepatocyte nuclear factor 4α antisense RNA 1 negatively regulates cytochrome P450 enzymes in Huh7 cells via histone modifications. *Drug Metab Dispos* **49:**361-368.

Wang SL, He XY, and Hong JY (2005) Human cytochrome P4502S1: lack of activity in the metabolic activation of several cigarette smoke carcinogens and in the metabolism of nicotine. *Drug Metab Dispos* **33:**336-340.

Watkins JB and Klaassen CD (1983) Chemically-induced alteration of UDP-glucuronic acid concentration in rat liver. *Drug Metab Dispos* **11:**37-40.

Wells PG, Mackenzie PI, Chowdhury JR, Guillemette C, Gregory PA, Ishii Y, Hansen AJ, Kessler FK, Kim PM, Chowdhury NR, and Ritter JK (2004) Glucuronidation and the UDP-glucuronosyltransferases in health and disease. *Drug Metab Dispos* **32:**281-290.

White RD, Shea D, and Stegeman JJ (1997) Metabolism of the aryl hydrocarbon receptor agonist 3,3',4,4'-tetrachlorobiphenyl by the marine fish scup (*Stenotomus chrysops*) in vivo and in vitro. *Drug Metab Dispos* **25:**564-572.

Wilkening S, Stahl F, and Bader A (2003) Comparison of primary human hepatocytes and hepatoma cell line HepG2 with regard to their biotransformation properties. *Drug Metab Dispos* **31:**1035-1042.

Wroblewski VJ and Olson JR (1988) Effect of monooxygenase inducers and inhibitors on the hepatic metabolism of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the rat and hamster. *Drug Metab Dispos* **16:**43-51.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Xiao GH, Pinaire JA, Rodrigues AD, and Prough RA (1995) Regulation of the *Ah* gene battery via Ah receptor-dependent and independent processes in cultured adult rat hepatocytes. *Drug Metab Dispos* **23:**642-650.

Yajima K, Uno Y, Murayama N, Uehara S, Shimizu M, Nakamura C, Iwasaki K, Utoh M, and Yamazaki H (2014) Evaluation of 23 lots of commercially available cryopreserved hepatocytes for induction assays of human cytochromes P450. *Drug Metab Dispos* **42:**867-871.

Yang SK, Chou MW, Evans FE, and Fu PP (1984) Metabolism of 8-hydroxymethyl-benz[*a*]anthracene by rat liver microsomes: stereochemistry of dihydrodiol metabolites and the effect of enzyme induction. *Drug Metab Dispos* **12:**403-413.

Yoshinari K, Okino N, Sato T, Sugatani J, and Miwa M (2006) Induction of detoxifying enzymes in rodent white adipose tissue by aryl hydrocarbon receptor agonists and antioxidants. *Drug Metab Dispos* **34:**1081-1089.

Yost GS and Finley BL (1985) Stereoselective glucuronidation as a probe of induced forms of UDP-glucuronyltransferase in rabbits. *Drug Metab Dispos* **13:**5-8.

You D, Richardson JR, and Aleksunes LM (2020) Epigenetic regulation of multidrug resistance protein 1 and breast cancer resistance protein transporters by histone deacetylase inhibition. *Drug Metab Dispos* **48:**459-480.

Youdim KA, Tyman CA, Jones BC, and Hyland R (2007) Induction of cytochrome P450: assessment in an immortalized human hepatocyte cell line (Fa2N4) using a novel higher throughput cocktail assay. *Drug Metab Dispos* **35:**275-282.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Young RA and Mehendale HM (1987) Effect of cytochrome P-450 and flavin-containing monooxygenase modifying factors on the in vitro metabolism of amiodarone by rat and rabbit. *Drug Metab Dispos* **15:**511-517.

Yu AM, Tian Y, Tu MJ, Ho PY, and Jilek JL (2016) MicroRNA pharmacoepigenetics: posttranscriptional regulation mechanisms behind variable drug disposition and strategy to develop more effective therapy. *Drug Metab Dispos* **44:**308-319.

Zhang QY, Dunbar D, and Kaminsky LS (2003) Characterization of mouse small intestinal cytochrome P450 expression. *Drug Metab Dispos* **31:**1346-1351.

Zhang QY, Wikoff J, Dunbar D, Fasco M, and Kaminsky L (1997) Regulation of cytochrome P4501A1 expression in rat small intestine. *Drug Metab Dispos* **25:**21-26.

Zhang QY, Wikoff J, Dunbar D, and Kaminsky L (1996) Characterization of rat small intestinal cytochrome P450 composition and inducibility. *Drug Metab Dispos* **24:**322-328.

Zhang Y, Cheng X, Aleksunes L, and Klaassen CD (2012) Transcription factor-mediated regulation of carboxylesterase enzymes in livers of mice. *Drug Metab Dispos* **40:**1191-1197.

Zhang Y, Yan T, Sun D, Xie C, Zheng Y, Zhang L, Yagai T, Krausz KW, Bisson WH, Yang X, and Gonzalez FJ (2018) Structure-activity relationships of the main bioactive constituents of *Euodia rutaecarpa* on aryl hydrocarbon receptor activation and associated bile acid homeostasis. *Drug Metab Dispos* **46:**1030-1040.

Zhang YK, Saupe KW, and Klaassen CD (2010) Energy restriction does not compensate for the reduced expression of hepatic drug-processing genes in mice with aging. *Drug Metab Dispos* **38:**1122-1131.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Zhang YK, Yeager RL, and Klaassen CD (2009) Circadian expression profiles of drug-processing genes and transcription factors in mouse liver. *Drug Metab Dispos* **37:**106-115.

Zhao P, Fan S, Gao Y, Huang M, and Bi H (2022) Nuclear receptor-mediated hepatomegaly and liver regeneration: an update. *Drug Metab Dispos* **50:**636-645.

Zhong Z, Goto M, Hijioka T, Oide H, Kauffman FC, and Thurman RG (1994) Role of Kupffer cells in storage and metabolism of benzo[*a*]pyrene in the liver. *Drug Metab Dispos* **22:**680-687.

Zhou S and Shu Y (2022) Transcriptional regulation of solute carrier (SLC) drug transporters. *Drug Metab Dispos* **50:**1238-1250.

Ziegler TL, Pillai UA, Smith RL, Kattnig MJ, Liebler DC, Mayersohn M, and Sipes IG (1996) Absorption and disposition kinetics of 3,3',4,4'-tetrachloroazoxybenzene in the male Fischer 344 rat. *Drug Metab Dispos* **24:**1009-1014.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Footnotes

Funding: This work received no external funding.

Financial disclosure: No author has an actual or perceived conflict of interest with the contents of this article.

Address correspondence to: Dr. David S. Riddick, Department of Pharmacology and Toxicology, Medical Sciences Building, University of Toronto, Toronto, ON, Canada M5S 1A8. E-mail: david.riddick@utoronto.ca

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Figure Legends

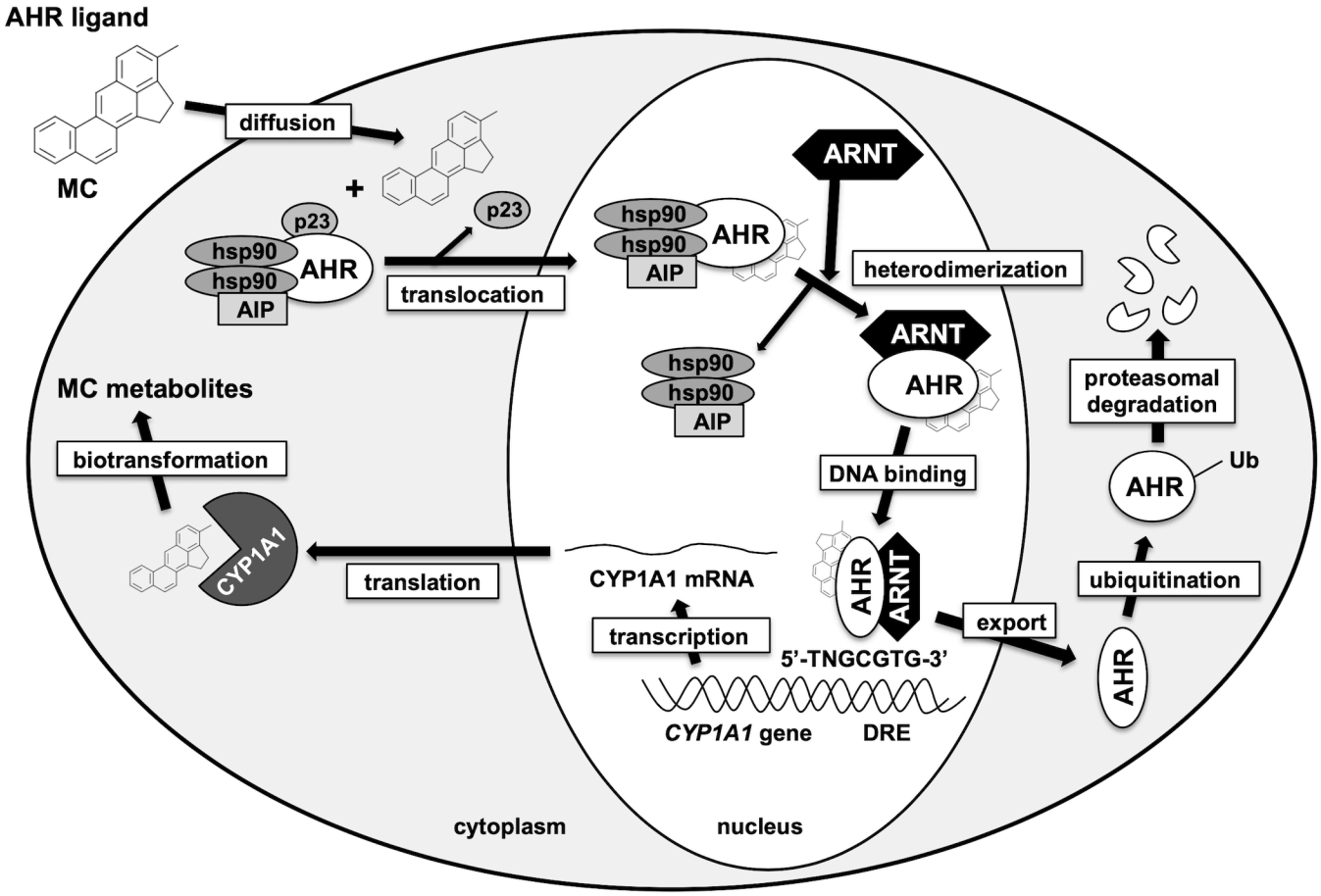
Fig. 1. The classic mechanistic paradigm for AHR-mediated induction of *CYP1A1*. Steps are described in the text and include: entry of an agonist ligand (MC shown here) into the cell by diffusion; binding of ligand to the cytoplasmic AHR complex; nuclear translocation and chaperone dissociation; heterodimerization with ARNT; heterodimer binding to DRE sequences and transcriptional regulation of *CYP1A1*; translation of mRNA into functional CYP1A1 protein that biotransforms the inducing ligand; export of AHR from the nucleus and its ubiquitination and proteasomal degradation.

Fig. 2. A year-by-year timeline showing the total DMD pages published and the number of DMD articles related to AHR. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 50, Issue 12 (December 2022), inclusive.

Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

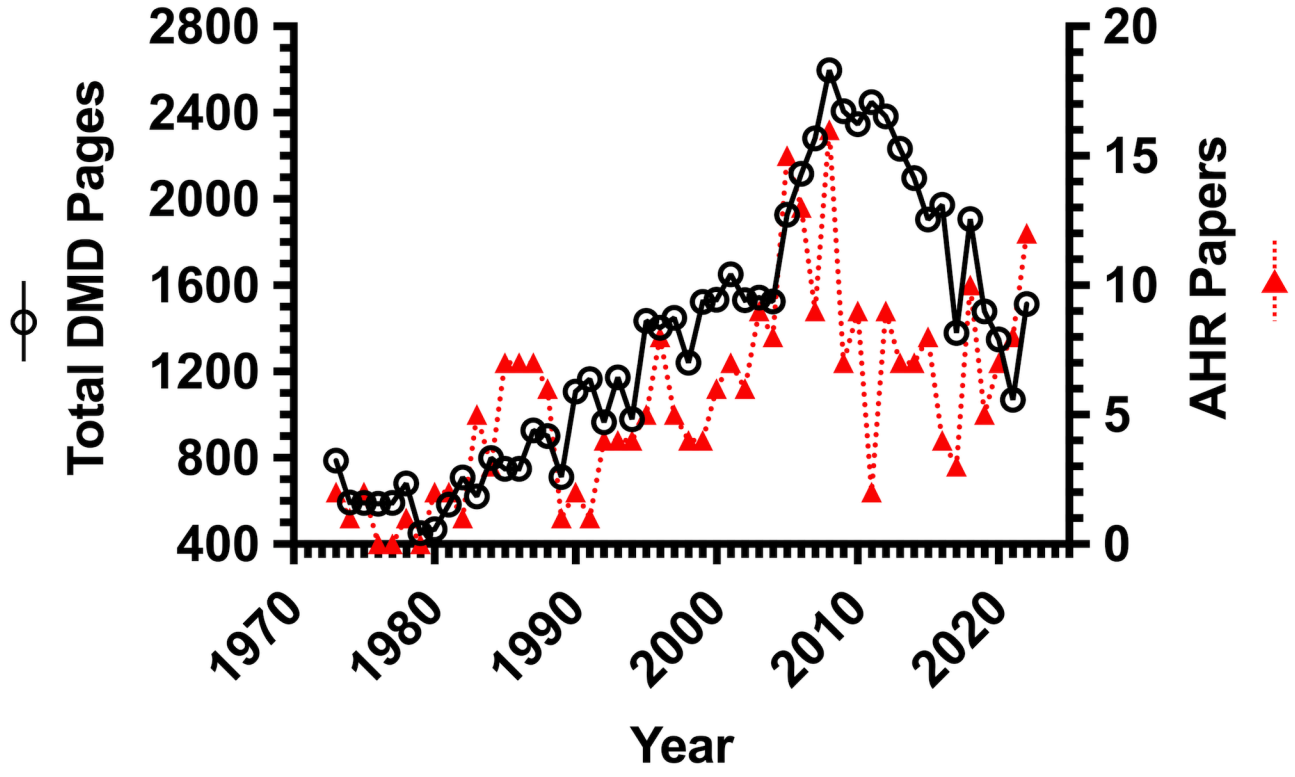
Figure 1



Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024

DMD Fast Forward. Published on January 18, 2023 as DOI: 10.1124/dmd.122.001009
This article has not been copyedited and formatted. The final version may differ from this version.

Figure 2



Downloaded from dmd.aspetjournals.org at ASPET Journals on April 23, 2024