Predicting drug metabolism-dependent toxicity

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In recent years, endogenous and xenobiotic metabolism has been one of the cutting edge topics of our journal (Hengstler and Bolt 2008; Bolt and Hengstler 2007, 2008a, b). Because of the dynamic progress in the field of drug metabolizing enzymes, we have initiated a new series of review articles that focus on nomenclature, substrate specificities, genetic organization, polymorphisms, clinical relevance and role in carcinogenesis (Pelkonen et al. 2008; Lankisch et al. 2008; Strassburg et al. 2008; Decker et al. 2009; Adam and Laufs 2008; Macdonald and Gledhill 2007). In order to give our readers a better overview over the numerous articles published in the field of drug metabolism in our journal during the past 2 years, we summarize their key messages and link them to the respective articles (Table 1).

Table 1 Take home messages of recent metabolism related publications in the *Archives of Toxicology*

Key message	Reference
Low doses of the organochlorine pesticide methoxychlor reduce activities of steroidogenic enzymes	Vaithinathan et al. (2008)
The expression of CYP and GST isoforms is strongly influenced by diet in rats and mice (amino acid based vs. egg-white diet, vs. standard laboratory chow)	Rudolf et al. (2008)

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Table 1 continued

Key message	Reference
The authors performed a systematic study with a set of 119 compounds comparing CYP1A1/1A2 induction and competition in rat and human cells; several so far unknown interspecies differences were identified	Westerink et al. (2008)
Test compound-induced gene expression patterns are similar in liver in vivo and in hepatocytes in vitro if optimized culture conditions are applied	Schug et al. (2008)
Potassium dichromate inhibits brush border enzymes of the intestine and causes lipid peroxidation	Arivarasu et al. (2008)
Non-alcoholic steatohepatitis (NASH) leads to increased PXR, Nqo1 and CYP4A14 expression	Fisher et al. (2008)
Some aromatic amines increase the influence of benzo[a]pyrene on Ah receptor dependent genes	Borza et al. (2008)
CYP2E1 mediates the formation of glycidamide, the ultimate carcinogenic metabolite of acrylamide	Settels et al. (2008)
Amitraz, a widely used formamidine pesticide, induces hepatic estrogen and testosterone metabolism	Chou et al. (2008)
Heavy metal exposure (cadmium, cobalt and lead) of bronchial epithelial cells leads to upregulation of steroid metabolism	Glahn et al. (2008)
Chronic exposure to low doses of 137 caesium influences testicular and adrenal steroid metabolism	Grignard et al. (2008)

Table 1 continued

Key message	Reference
This bio-distribution study of the neurotoxic substance 1,2-diethylbenzene shows that the parent compound and its metabolite 1-(2'-ethylphenyl) ethanol is found at higher concentrations in the brain than in the blood of rats	Payan et al. (2008)
A polymorphism of the microsomal epoxide hydrolase gene (exon 3 His genotype) is associated with urinary bladder cancer risk	Srivastava et al. (2008)
This review summarizes the state of the art concerning alternative methods to animal experiments including in vitro systems for metabolism	Lilienblum et al. (2008)
This study demonstrates large interspecies differences in CYP11B1-dependent bioactivation of the adrenocortical toxicant 3-methylsulphonyl-DDE. Bioactivation is high in adrenal tissue of hamsters and mice in contrast to guinea pigs and rats	Lindstrom et al. (2008)
Gene expression profiling of cultured human hepatocytes to Aroclor 1254 reveals a strong response of genes involved in xenobiotic defence	Thum and Borlak (2008)
This study systematically evaluates the metabolism of <i>N</i> -methyl- <i>N</i> -2,4,6-tetranitroaniline (tetryl) in rats	Myers and Spinnato (2007)
The insecticide profenofos induces genes related to steroidogenesis in rat testes, including CYP17A1, CYP11A1 and steroidogenic acute regulatory protein (StAR). The latter genes are suggested as new biomarkers of testicular toxicity	Moustafa et al. (2007)
CYP2C29 represents a novel hepatotoxicity biomarker	Spicker et al. (2007)
Histamine increases activity and protein levels of CYP1A1 and CYP2E1 in vivo, illustrating a role of CYPs in inflammation	Davila-Borja et al. (2007)
Genotype frequencies of CYP2E1*7B are similar in Turkish compared to other Caucasian populations	Ulusoy et al. (2007)
Microsomal epoxide hydrolase (EPHX1) is not significantly associated with risk of myocardial infarction	Cornelis et al. (2007)

Table 1 continued

Key message	Reference
Increased total levels of glutathione and decreased expression of multidrug-resistance protein2 (Mrp2) are involved in resistance of hepatocytes to ethacrynic acid toxicity	Parody et al. (2007)
Gene expression profiling in lung tissues of rats exposed to 5 and 10 ppm formaldehyde identifies expression alterations of cytochrome P450 isoenzymes	Sul et al. (2007)
Dehydrotarplatin, a new antineoplastic drug, causes a feminization of the pattern of CYP enzymes in male rat liver	Nannelli et al. (2007)
UGT1A9 is a key enzyme catalyzing the glucuronidation of dulcin. Dulcin, now banned, was a widely used sweetener	Uesawa et al. (2007)
This study presents a systematic comparison of CYP-induction in lung and liver	Elovaara et al. (2007)
This study systematically compares CYP1A induction by PAHs in the hepatoma cell line HepG2 and in the breast cancer cell line MCF-7	Skupinska et al. (2007)
Di (2-ethylhexyl) phthalate (DEHP) induces PPAR alpha in mice and rats but not in marmosets	Ito et al. (2007)
This article presents a PBPK model describing lactational transfer of PCB 153	Lee et al. (2007)
Cigarette smoking increases CYP1A1 expression in human urothelial cells	Dorrenhaus et al. (2007)

References

- Adam O, Laufs U (2008) Antioxidative effects of statins. Arch Toxicol 82:885–892
- Arivarasu NA, Fatima S, Mahmood R (2008) Oral administration of potassium dichromate inhibits brush border membrane enzymes and alters anti-oxidant status of rat intestine. Arch Toxicol 82:951–958
- Bolt HM, Hengstler JG (2007) The past and the future of toxicology. Arch Toxicol 81:1–3
- Bolt HM, Hengstler JG (2008a) A new series of review articles on drug metabolizing enzymes: nomenclature of isoenzyme families, genetic organization, polymorphisms, substrate specificities, clinical relevance and role in carcinogenesis. Arch Toxicol 82:413–414
- Bolt HM, Hengstler JG (2008b) Most cited articles in the Archives of Toxicology: the debate about possibilities and limitations of in vitro toxicity tests and replacement of in vivo studies. Arch Toxicol 82:881–883

- Borza A, Plottner S, Wolf A, Behm C, Selinski S, Hengstler JG, Roos PH, Bolt HM, Kuhlmann J, Follmann W (2008) Synergism of aromatic amines and benzo[a]pyrene in induction of Ah receptor-dependent genes. Arch Toxicol 82:973–980
- Chou CP, Lu SY, Ueng TH (2008) Modulation of serum concentrations and hepatic metabolism of 17 β -estradiol and testosterone by amitraz in rats. Arch Toxicol 82:729–737
- Cornelis MC, El-Soheily A, Campos H (2007) Microsomal epoxide hydrolase genotype and risk of myocardial infarction. Arch Toxicol 81:641–645
- Davila-Borja VM, Belmont JA, Espinosa JJ, Moreno-Sanchez R, Albores A, Montero RD (2007) Induction of CYP1A1 and CYP2E1 in rat liver by histamine: binding and kinetic studies. Arch Toxicol 81:697–709
- Decker M, Arand M, Cronin A (2009) Mammalian epoxide hydrolases in xenobiotic metabolism and signalling. Arch Toxicol 83:297–318
- Dorrenhaus A, Muller T, Roos PH (2007) Increased CYP1A1 expression in human exfoliated urothelial cells of cigarette smokers compared to non-smokers. Arch Toxicol 81:19–25
- Elovaara E, Mikkola J, Stockmann-Juvala H, Luukkanen L, Keski-Hynnä H, Kostianen R, Pasanen M, Pelkonen O, Vainio H (2007) Polycyclic aromatic hydrocarbon (PAH) metabolizing enzyme activities in human lung, and their inducibility by exposure to naphthalene, phenanthrene, pyrene, chrysene, and benzo(a)pyrene as shown in the rat lung and liver. Arch Toxicol 81:169–182
- Fisher CD, Jackson JP, Lickteig AJ, Augustine LM, Cherrington NJ (2008) Drug metabolizing enzyme induction pathways in experimental non-alcoholic steatohepatitis. Arch Toxicol 82:959–964
- Glahn F, Schmidt-Heck W, Zellmer S, Guthke R, Wiese J, Golka K, Hergenroder R, Degen GH, Lehmann T, Hermes M, Schormann W, Brulport M, Bauer A, Bedawy E, Gebhardt R, Hengstler JG, Foth H (2008) Cadmium, cobalt and lead cause stress response, cell cycle deregulation and increased steroid as well as xenobiotic metabolism in primary normal human bronchial epithelial cells which is coordinated by at least nine transcription factors. Arch Toxicol 82:513–524
- Grignard E, Gueguen Y, Grison S, Lobaccaro JMA, Gourmelon P, Souidi M (2008) In vivo effects of chronic contamination with 137 cesium on testicular and adrenal steroidogenesis. Arch Toxicol 82:583–589
- Hengstler JG, Bolt HM (2008) Failure in drug development: the role of inhibition and induction of cytochrome P450 enzymes. Arch Toxicol 82:665–666
- Ito Y, Yamanoshita O, Kurata Y, Kamijima M, Aoyama T, Nakajima T (2007) Induction of peroxisome proliferator-activated receptor α (PPAR α)-related enzymes by di(2-ethylhexyl) phthalate (DEHP) treatment in mice and rats, but not marmosets. Arch Toxicol 81:219–226
- Lankisch TO, Gillman TC, Erichsen TJ, Ehmer U, Kalthoff S, Freiberg N, Munzel PA, Manns MP, Strassburg CP (2008) Aryl hydrocarbon receptor-mediated regulation of the human estrogen and bile acid UDP-glucuronosyltransferase 1A3 gene. Arch Toxicol 82:573–582
- Lee SK, Ou YC, Andersen ME, Yang RSH (2007) A physiologically based pharmacokinetic model for lactational transfer of PCB 153 with or without PCB 126 in mice. Arch Toxicol 81:101–111
- Lilienblum W, Dekant W, Foth H, Gebel T, Hengstler JG, Kahl R, Kramer PJ, Schweinfurth H, Wollin KM (2008) Alternative methods to safety studies in experimental animals: role in the risk assessment of chemicals under the new European Chemicals Legislation (REACH). Arch Toxicol 82:211–236
- Lindstrom V, Brandt I, Lindhe O (2008) Species differences in 3-methylsulphonyl-DDE bioactivation by adrenocortical tissue. Arch Toxicol 82:159–163
- Macdonald N, Gledhill A (2007) Potential impact of ABCB1 (p-glycoprotein) polymorphisms on avermectin toxicity in humans. Arch Toxicol 81:553–563
- Moustafa GG, Ibrahim ZS, Hashimoto Y, Alkelch AM, Sakamoto KQ, Ishizuka M, Fujita S (2007) Testicular toxicity of profenofos in matured male rats. Arch Toxicol 81:875–881
- Myers SR, Spinnato JA (2007) Tissue distribution and elimination of *N*-methyl-*N*-2,4,6-tetranitroaniline (tetryl) in rats. Arch Toxicol 81:841–848
- Nannelli A, Messina A, Marini S, Trasciatti S, Longo V, Gervasi PG (2007) Effects of the anticancer dehydratraplatin on cytochrome P450 and antioxidant enzymes in male rat tissues. Arch Toxicol 81:479–487
- Parody JP, Alvarez MD, Quiroga A, Ronco MT, Francesc D, Carnovale C, Carrillo MC (2007) Hepatocytes isolated from preneoplastic rat livers are resistant to ethacrynic acid cytotoxicity. Arch Toxicol 81:565–573
- Payan JP, Binet S, Beydon D, Ferrari E (2008) Bio-distribution study of 1, 2-diethylbenzene and its main metabolites by whole-body autoradiography and tissue homogenates. Arch Toxicol 82:591–600
- Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H (2008) Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol 82:667–715
- Rudolf JL, Bauerly KA, Tchapanian E, Rucker RB, Mitchell AE (2008) The influence of diet composition on phase I and II biotransformation enzyme induction. Arch Toxicol 82:893–901
- Schug M, Heise T, Bauer A, Storm D, Blaszkewicz M, Bedawy E, Brulport M, Geppert B, Hermes M, Föllmann W, Rapp K, Maccoux L, Schormann W, Appel KE, Oberemm A, Gundert-Remy U, Hengstler JG (2008) Primary rat hepatocytes as in vitro system for gene expression studies: comparison of sandwich, Matrigel and 2D cultures. Arch Toxicol 82:923–931
- Settels E, Bernauer U, Palavinskas R, Klaffke HS, Gundert-Remy U, Appel KE (2008) Human CYP2E1 mediates the formation of glycidamide from acrylamide. Arch Toxicol 82:717–727
- Skupinska K, Misiewicz I, Kasprzycka-Guttman T (2007) A comparison of the concentration–effect relationships of PAHs on CYP1A induction in HepG2 and Mcf7 cells. Arch Toxicol 81:183–200
- Spicker JS, Pedersen HT, Nielsen HB, Brunak S (2007) Analysis of cell death inducing compounds. Arch Toxicol 81:803–811
- Srivastava DS, Mandhani A, Mittal RD (2008) Genetic polymorphisms of cytochrome P450 CYP1A1 (*2A) and microsomal epoxide hydrolase gene, interactions with tobacco-users, and susceptibility to bladder cancer: a study from North India. Arch Toxicol 82:633–639
- Strassburg CP, Lankisch TO, Manns MP, Ehmer U (2008) Family 1 uridine-5'-diphosphate glucuronosyltransferases (UGT1A): from Gilbert's syndrome to genetic organization and variability. Arch Toxicol 82:415–433
- Sul D, Kim H, Oh E, Phark S, Cho E, Choi S, Kang HS, Kim EM, Hwang KW, Jung WW (2007) Gene expression profiling in lung tissues from rats exposed to formaldehyde. Arch Toxicol 81:589–597
- Thum T, Borlak J (2008) Detection of early signals of hepatotoxicity by gene expression profiling studies with cultures of metabolically competent human hepatocytes. Arch Toxicol 82:89–101
- Uesawa Y, Staines AG, Lockley D, Mohri K, Burchell B (2007) Identification of the human liver UDP-glucuronosyltransferase involved in the metabolism of *p*-ethoxyphenylurea (dulcin). Arch Toxicol 81:163–168

- Ulusoy G, Arinc E, Adali O (2007) Genotype and allele frequencies of polymorphic *CYP2E1* in the Turkish population. Arch Toxicol 81:711–718
- Vaithinathan S, Saradha B, Mathur PP (2008) Transient inhibitory effect of methoxychlor on testicular steroidogenesis in rat: an in vivo study. Arch Toxicol 82:833–839
- Westerink WMA, Stevenson JCR, Schoonen WGEJ (2008) Pharmacologic profiling of human and rat cytochrome P450 1A1 and 1A2 induction and competition. Arch Toxicol 82:909–921