

## Editorial:

### DRUG METABOLISM AND ENZYME INDUCTION

P. Godoy

Leibniz Research Centre for Working Environment and Human Factors (IfADo), Ardeystrasse 67, 44139 Dortmund, Germany

E-mail: godoy@ifado.de, Telephone: +49 231-1084-256, Fax: +49 231-1084-403

The prediction of metabolism-dependent toxicity is a cutting-edge topic in toxicology (Bolt and Hengstler, 2008). The shape of dose-response curves and toxic profiles are strongly dependent on activating or detoxifying metabolism. Most xenobiotic metabolizing enzymes include large numbers of isoenzymes with distinct substrate specificities. This diversity started to evolve 200 to 400 million years ago when reptiles and amphibians moved from sea to land and began to eat plants. The resulting co-evolution led to the establishment of phytotoxins which gave plants protection against herbivores, and herbivores responded with new detoxifying enzymes. A highlight in our partner journal is the initiation of a new series of review articles discussing nomenclature of isoenzyme families, genetic organization, polymorphisms, substrate specificities, clinical relevance and a role in carcinogenesis (Matés et al., 2008; Florl and Schulz, 2008; Strassburg et al., 2008; Beyersmann and Hartwig, 2008; Pelkonen et al., 2008; Verstraeten et al., 2008; Adam and Laufs, 2008). To give our readers an overview we summarize the key messages of articles on drug metabolism (Table 1A) and enzyme induction (Table 1B).

**Table 1A:** Recent studies in drug metabolism

Key Message	Reference
Human CYP2E1 is responsible for glycidamide formation from acrylamide. Similar results were obtained with human CYP2E1 superosomes, human liver microsomes and V79 cells expressing human CYP2E1.	Settels et al., 2008
Amitraz, a widely used formamidine pesticide, increases serum testosterone in male and decreases serum estradiol concentrations in female rats.	Chou et al., 2008
The human estrogen and bile acid UDP-glucuronosyltransferase gene UGT1A3 is regulated by the Ah receptor.	Lankisch et al., 2008
An association between an exon 3 His variant of microsomal epoxide hydrolase and risk of urinary bladder cancer was reported.	Srivastava et al., 2008
This review presents a comprehensive overview over the UGT1A family: genetic organization, nomenclature, polymorphisms and clinical relevance.	Strassburg et al., 2008
Primary cultures of human lung cells represent an adequate in vitro system to study activities of multidrug resistance protein related carriers.	Torky et al., 2008
Polymorphisms of sulfotransferase 1A1 and glutathione-S-transferase P1 are associated with urinary 8-hydroxy-2'-deoxyguanosine in humans who chew betel quid. Betel quid contains safrole, an inducer of oxidative DNA damage.	Wong et al., 2008

Key Message	Reference
A novel software allowed an unambiguous reconstruction of N-acetyltransferase 2 haplotypes in 2.920 of 2.921 cases.	Golka et al., 2008
The CYP11B1-activated adrenocortical toxicant 3-methylsulphonyl-DDE shows large interspecies differences in adrenal cortex binding of hamster, guinea pig, mouse and rat.	Lindström et al., 2008
Cultivated, metabolically competent primary human hepatocytes show characteristic alterations in gene expression patterns induced by Aroclor 1254.	Thum and Borlak, 2008

**Table 1B:** Recent results in research on **enzyme induction** by xenobiotics

Key message	Reference
Aromatic amines and PAHs act synergistically in inducing Ah receptor-dependent genes.	Borza et al., 2008
Screening of 119 compounds in human (HepG2) and rat (H4IIE) in vitro systems revealed major interspecies differences.	Westerink et al., 2008
Flavones in an amino acid based diet increased activities of phase I and II metabolizing enzymes in rats and mice.	Rudolf et al., 2008
Experimentally induced non-alcoholic steatohepatitis in mice is associated with increased mRNA levels of PXR, Cyp4A14 and Nqo1 in liver tissue. In contrast AhR, CAR, PPAR alpha and Nrf2 were not altered.	Fisher et al., 2008
This is a comprehensive review on inhibition and induction of human cytochrome P450 enzymes, including an overview over the most relevant compounds.	Pelkonen et al., 2008
Rats fed for 2 days with PAH-contaminated mussels sampled in coasts polluted by the Erika oil-tanker wreck showed induction of CYP1A1 in liver tissue.	Chaty et al., 2008

## REFERENCES

Adam O, Laufs U. Antioxidative effects of statins. *Arch Toxicol* 2008;82:885-92.

Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol* 2008;82:493-512.

Bolt HM, Hengstler JG: 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 (Editorial). *Arch Toxicol* 2008;82:413-4.

Borza A, Plöttner S, Wolf A, Behm C, Selinski S, Hengstler JG, Roos PH, Bolt HM, Kuhlmann J, Föllmann W. Synergism of aromatic amines and benzo[a]pyrene in induction of Ah receptor-dependent genes. *Arch Toxicol* 2008;82:973-80.

Chaty S, Rodius F, Lanhers MC, Burnel D, Vasseur P. Induction of CYP1A1 in rat liver after ingestion of mussels contaminated by Erika fuel oils. *Arch Toxicol* 2008;82:75-80.

Chou CP, Lu SY, Ueng TH. Modulation of serum concentrations and hepatic metabolism of 17beta-estradiol and testosterone by amitraz in rats. *Arch Toxicol* 2008;82:729-37.

- Fisher CD, Jackson JP, Lickteig AJ, Augustine LM, Cherrington NJ. Drug metabolizing enzyme induction pathways in experimental non-alcoholic steatohepatitis. *Arch Toxicol* 2008;82:959-64.
- Florl AR, Schulz WA. Chromosomal instability in bladder cancer. *Arch Toxicol* 2008;82:173-82.
- Golka K, Blaszkewicz M, Samimi M, Bolt HM, Selinski S. Reconstruction of N-acetyltransferase 2 haplotypes using PHASE. *Arch Toxicol* 2008;82:265-70.
- Lankisch TO, Gillman TC, Erichsen TJ, Ehmer U, Kalthoff S, Freiberg N, Munzel PA, Manns MP, Strassburg CP. Aryl hydrocarbon receptor-mediated regulation of the human estrogen and bile acid UDP-glucuronosyltransferase 1A3 gene. *Arch Toxicol* 2008;82:573-82.
- Lindström V, Brandt I, Lindhe O. Species differences in 3-methylsulphonyl-DDE bioactivation by adrenocortical tissue. *Arch Toxicol* 2008;82:159-63.
- Matés JM, Segura JA, Alonso FJ, Márquez J. Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. *Arch Toxicol* 2008;82:273-99.
- Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H. Inhibition and induction of human cytochrome P450 enzymes: current status. *Arch Toxicol* 2008;82:667-715.
- Rudolf JL, Bauerly KA, Tchapanian E, Rucker RB, Mitchell AE. The influence of diet composition on phase I and II biotransformation enzyme induction. *Arch Toxicol* 2008;82:893-901.
- Settels E, Bernauer U, Palavinskas R, Klaffke HS, Gundert-Remy U, Appel KE. Human CYP2E1 mediates the formation of glycidamide from acrylamide. *Arch Toxicol* 2008;82:717-27.
- Srivastava DS, Mandhani A, Mittal RD. 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* 2008;82:633-9.
- Strassburg CP, Lankisch TO, Manns MP, Ehmer U. Family 1 uridine-5'-diphosphate glucuronosyltransferases (UGT1A): from Gilbert's syndrome to genetic organization and variability. *Arch Toxicol* 2008;82:415-33.
- Thum T, Borlak J. Detection of early signals of hepatotoxicity by gene expression profiling studies with cultures of metabolically competent human hepatocytes. *Arch Toxicol* 2008;82:89-101.
- Torky A, Raemisch A, Glahn F, Foth H. Arachidonic acid pathway activates multidrug resistance related protein in cultured human lung cells. *Arch Toxicol* 2008;82:323-32.
- Verstraeten SV, Aimo L, Oteiza PI. Aluminium and lead: molecular mechanisms of brain toxicity. *Arch Toxicol* 2008;82:789-802.
- Westerink WM, Stevenson JC, Schoonen WG. Pharmacologic profiling of human and rat cytochrome P450 1A1 and 1A2 induction and competition. *Arch Toxicol* 2008;82:909-21.
- Wong RH, Hu CW, Yeh CY, Chao MR, Chen CC, Huang JH, Chang SH, Lee SI, Lee HS. Sulfotransferase 1A1 and glutathione S-transferase P1 genetic polymorphisms modulate the levels of urinary 8-hydroxy-2'-deoxyguanosine in betel quid chewers. *Arch Toxicol* 2008;82:313-21.