Session: Kinetic, Enzyme Induction, Ah-Receptor
D. Schrenk and M. Wilhelm

The session comprises of 7 oral presentations and 5 posters.

The first oral presentation by Hennig and coworkers (51) deals with the effects of PCB on the cardiovascular system by modulating plasma and tissue lipids. In their in vivo study with LDL receptor deficient mice the authors showed that dietary fat consumption influenced PCB toxicity and that PCB-lipid interactions are dependent on the type of dietary fat. The expression of the vascular cell adhesion molecule-1, an important marker for endothelium cell dysfunction, was increased by PCB treatment at the vascular surface and cotreatment with corn oil but not with olive oil further increased PCB effects. Furthermore, PCB treatment of corn oil-fed but not olive oil-fed mice resulted in a marked decrease of major serum fatty acids. This may reflect increased uptake of linoleic acid within the vascular endothelium. PCB treatment also increased liver lipid accumulation in LDL-R-/- mice fed the corn oil- enriched diet which may be due to a down-regulation of the apolipoprotein A IV gene. The authors also showed that PCB treatment up-regulated genes involved in fatty acid uptake and catabolism while genes involved in fatty acid synthesis were down-regulated.

To date only few studies on accumulation and toxicity of PCBs in poultry have been performed. De Vos and De Schrijver (65) examined the long-term effects of low level dietary PCB contents in laying hens. Animal performance and egg quality parameters were not influenced by dietary PCB. PCB incorporation in egg yolk increased with the PCB dose. The amount of fat added to the diets did not influence faecal PCB digestibility and PCB retention. At doses of added 0-6 ng PCBs/g diet PCB concentrations in abdominal fat thigh tissue and breast tissue showed a dose-dependent uptake but never exceeded the legal maximum level of 200 ng PCBs/g fat. PCB profiles of 7 congeners in egg yolk and abdominal fat differed from those in the diet and faeces. The authors conclude that the maximum allowable PCB content in tissue fat may be reduced.

Kania-Korwel et al. (103) studied how different chlorination levels and the structure of PCB congeners influence their distribution and accumulation in rat tissues. The animals received single i.p. doses of soil PCB mixture or Aroclor 1254. PCB levels (after 7 days) were in general higher in tissues from soil extract-treated animals compared to Aroclor1254-treated animals. Lipid adjusted PCB levels were similar in all tissues except for much higher levels in the spleen. Principal component and hierarchical cluster analysis revealed that the composition of PCB mixtures is altered in biological matrices. The authors conclude that during the initial redistribution phase the chlorination level of PCB mixtures influence the total PCB concentrations in tissues such as the spleen. Furthermore, distribution, redistribution and metabolic processes of PCBs may depend on the degree of chlorination, and chlorine substitution pattern of individual congeners.

The tri-ortho-PCB CB 187 is one of the minor components in commercial PCB preparations and no TEF has been set for this congener. The 4-hydroxy-metabolite of CB 187 was found in blood at high concentrations. Koga et al. (187) studied the metabolism of CB 187 by liver microsomes of rats, hamster and guinea pigs. CB 187 was found to be easily metabolized to 3 metabolites by guinea pigs. These were a monohydroxy-hexaCB and two monohydroxy-hepta CB (4'-OH-CB178 and 4-OH-CB187). In contrast to findings in human blood, 4-OH-CB187 was not a major metabolite formed by animal liver. CB187 metabolism was accelerated by PB

treatment. Finally the authors postulate pathways of PCB187 in animals with CYP1A and CYP2B dependent metabolic processes.

Nishimura et al. (284) treated transthyretin (TTR)-deficient mice with PCB 114 or PCB 118 (50 mg/kg b.w.). Seven days after treatment, serum total T4 was significantly decreased in wild-type but not in TTR-null mice treated with PCB 118. PCB 118 but not PCB 114 led to a significant decrease in serum retinol, which was already markedly reduced in untreated TTR-null mice. The findings suggest that PCB 118 and/or its metabolites affect serum thyroid hormone or retinol homeostasis and that this effect is mediated via TTR.

Watanabe et al. (310) collected Jungle crows and analysed PCDD/F and non-ortho and mono-ortho PCBs in liver and breast muscle. In the liver higher concentrations of seven PCDD/F congeners, PCB 169 and PCB 123 were found. The authors observed a significant correlation between total hepatic TEQ and expression of CYP1A and 3A-like proteins in liver. The expression of CYP1A-like protein was correlated with a lower concentration ratio of certain congeners suggesting a role of this isozyme in their metabolism. Overall enzymatic/expression effects in the Jungle crow seem to represent a sensitive marker of TEQ exposure in that species.

Kubota et al. (331) investigated the TEq levels in liver and pectoral muscles of the common cormorant. They found a good correlation between hepatic TEq and the staining intensity for CYP1A-like protein analysed by Western blotting. For the concentration ratios of PCB 77 and PCB 169 negative correlations with the levels of CYP1A-like protein were found suggesting a role of this isozyme in metabolic elimination of both congeners. Comparison between levels in liver and muscle indicated a concentration-dependent hepatic sequestration of a number of congeners, CYP1A representing the most likely candidate for a binding protein involved in sequestration.

For young children ingestion of contaminated soil may be the major route for the intake of contaminants. Since data on bioavailability of contaminants from soil are rare, for risk assessment a complete bioavailability of contaminants from soil is often assumed. Wittsiepe et al. (466) studied the bioavailability of PCDD/F from a contaminated soil in young Goettingen minipigs. They found that soil reduced the PCDD/F bioavailability of about 70%. Furthermore, accumulation of PCDD/F from soil was only observed for congeners with 2378-chloro-substitution. Bioavailability of PCDD/F was congener- and tissue-specific. Since bioavailability expressed a I-TEq was 13.8%, the author conclude that by not considering bioavailability of PCDD/F the risk by the ingestion of PCDD/F contaminated soil might be overestimated.

Van Duursen et al. (509) analysed the expression and inducibility of CYP1A-catalysed EROD activity, and of CYP1A1 and CYP1B1 mRNAs in cultured human lymphocytes isolated from different individuals. Constitutive CYP1A1 expression was too low in most samples to be detected while CYP1B1 showed a high constitutive expression which was induced by TCDD treatment. No apparent influence of CYP1A1 m1 and CYP1B1 Val432Leu polymorphisms on inducibility of EROD activity or CYP1B1 mRNA levels was found. EC_{10} levels of induction were only about tenfold lower than background concentrations in human plasma suggesting a possible effect of background levels on AhR-dependent pathways in human lymphocytes.

Germer et al. (583) investigated the effects of various doses of the brominated flame retardant tetrabromobisphenol A (TBBPA), applied over 28 days via the feed, on the expression of

major phase I drug metabolising enzymes in rat liver. While no effects on CYP1A1, 1A2, 2B1/2 and 3A1 expression or activities were found in males, a non-significant trend towards higher levels was observed in female rats for CYP3A1 (on the protein level). In summary, the data suggest a lack of significant effects of TBBPA on major phase I drug metabolising enzymes in rat liver even at relatively high doses.

Bin Zhao et al. (659) investigated the ability of a series of flavonoids to activate a dioxin-responsive EGFP reporter gene in stably transfected mouse hepatoma cells. In parallel experiments effects on reporter gene expression in BG-1 cells stably transfected with an estrogen-responsive reporter construct were tested. The most active AhR activators were derivatives of the AhR antagonist alpha-naphthoflavone (ANF), while estrogen-receptor (ER)-driven reporter gene expression was markedly induced with derivatives of 6,7-naphthoflavone. A number of ANF derivatives and some flavone derivatives were identified as potent antagonists of ER-driven reporter gene expression.

Denison et al. (662) investigated the ability of extracts prepared from commercial and consumer products to induce Ah receptor(AhR)-dependent transformation and DNA binding in gel retardation analysis. Furthermore the effects of extracts to bind to the AhR and their capacity to induce the expression of an AhR-responsive firefly luciferase reporter gene in recombinant mouse, rat and Guinea pig cell lines were investigated. Results from all three assays were found to be in good agreement demonstrating the presence of AhR agonists in DMSO and ethanol extracts of a variety of plastic, rubber and paper products whereas the only active water extracts were form newspapers. The comparison between 4 h and 24 h incubations in reporter gene assays indicated that the inducers were labile and or degraded by metabolisms leading to a loss of their agonistic potency over time.