TOXICOLOGY SESSION I

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This session consists of papers on a wide spectrum of dioxin-related responses and symptoms, AhR mediated ligand binding characteristics, male and female reproductive toxicities and neurotoxicology, and risk assessment methodology. The following is a brief summary of this session.

1. **MECHANISM OF SIGNAL TRANSDUCTION BY THE DIOXIN (AH) RECEPTOR,** Poellinger L., Kazlauskas A., Andersson P., Hanberg A., McGuire J., Pongratz I., Kohle C., Bock KW.

Poellinger *et al.* summarized their studies on AhR function in terms of signal transduction, and showed requirement of abundant expression of hsp90, a molecular chaperone, to enhance ligand responsiveness. They also illustrate the function of XAP2, immunophilin-like protein, as a regulator for the subcellular localization of AhR by a cytoplasmic retention mechanism.

2. **DIOXIN-LIKE ACTIVITY IN HUMAN URINE AND MUNICIPAL SEWAGE.** ~~Matsuda T.,~~ Adachi J., Mori Y., Takigami H., Miller CA., Kato T., Saeki K., Matsui S.

Identifying an endogenous ligand for AhR is an extremely important subject that may open up a new avenue not only in toxicology but also in the physiological roles of AhR. Based on the finding, by the use of yeast reporter assay, that municipal sewage contained AhR ligands, Matsuda *et al.* thought that human urine might contain the ligands, and they screened human urine to detect endogenous AhR ligands. They have identified two potent endogenous AhR ligands, indigo and its metabolite, indirubin, the latter of which showed the equivalent affinity to AhR by the yeast assay.

3. ***IN UTERO* AND LACTATIONAL TCDD EXPOSURE IN THE MOUSE: IMPAIRED PROSTATE DEVELOPMENT AND FUNCTION.** Lin TM., Simanainen U., Rasmussen UT., Ko K., and ~~Peterson RE.~~

Impairment of growth and development of the prostate in experimental animals has been reported by many researchers as the most sensitive endpoint of TCDD toxicity when TCDD was administered *in utero* and lactationally. Lin TM., *et al.* reported *in utero* and lactational TCDD exposure in the mouse. They demonstrated clearly that GD 13-16 was the critical period in which TCDD causes impairment of prostate development, by using a cross-fostering study. And they also clarified the prostate lobe specific sensitivity to TCDD.

4. **ARYL HYDROCARBON RECEPTOR/DIOXIN RECEPTOR IN U937 CELLS AND HUMAN MACROPHAGES.** Komura K., Hayashi S., Okamoto K., Poellinger L., and Tanaka H.

Komura *et al.* tried to demonstrate the presence of endogenous AhR agonist using the human monocytic lymphoma-derived U937 cell line. They strongly suggested that endogenous ligands for AhR may exist in U937 cells because AhR DNA binding activities were inhibited in the presence of alpha-naphthoflavone, an AhR antagonist, in U937 cells.

5. **2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) AFFECTS GLUCOSE KINETICS IN RAT PLACENTA.** ~~Ishimura R.~~, Kawakami T., Aoki Y., Yonemoto J., Tohyama C., and Ohsako S.

Effects of TCDD on placenta have not been elucidated yet in spite of its extremely important functions in terms of fetal development. Ishimura *et al.* first revealed that TCDD administration to pregnant rats caused an increase in glycogen content and glycogen cell in junctional zone of placenta. The increase of glycogen content might be related to an increase in glucose transporter 3 gene expression.

6. ***IN UTERO* EXPOSURE TO 3,3',4,4',5-PENTACHLOROBIPHENYL (PCB 126) INDUCES HYPOSPADIAS IN FEMALE RATS.** ~~Yamamoto K.~~, Shirota M., Inoue K., Doyama A., Mukai M., Haishima A., Katoh C., Soda S., Kawabata A., Shirakura K., Sakurada Y., Akahori F., and Shirota K.

Malformation of external genitalia in female rat offspring *in utero* and lactationally exposed to TCDD has been well documented. Yamamoto *et al.* presented that 3,3',4,4',5-pentachlorobiphenyl (PCB 126) also induced hypospadias in female rat progenies as well as male. Additionally they showed that the gestational day (GD) 15 was a critical period to produce hypospadias in the female rat offspring, but not GD8 and postnatal day 1 onward.

7. **INTERACTIONS OF DIOXINS WITH NON-DIOXIN-LIKE CHEMICALS.** DeVito M. and Birnbaum LS.

DeVito and Birnbaum summarized their studies on interactions of TCDD with non-dioxin-like chemicals, especially PCB153. They showed in some cases, PCB153 inhibits TCDD response, such as enzyme induction (CYP1A1) or immunotoxicity. Since the TEF methodology is thought to underpredict the effect of mixtures of PCBs and dioxins in the thyroid, they suggested a need for more detailed studies on interactions of TCDD with PCBs in thyroid function, heme metabolism, developmental neurotoxicity and carcinogenesis.

8. **EXPLORING POSSIBLE DOSE-RESPONSE RELATIONSHIPS BETWEEN EXPOSURE TO PCDDs/Fs AND ACQUIRED DYSCHROMATOPSIA IN HUMANS.** ~~Edler L.~~, Muttray A., Jung D., Rose DM., Konietzko J., Portier C., and Heinzl H.

There is evidence that TCDD causes toxic neuropathy in rats whereas a causal relationship with human peripheral neuropathy and effects on the peripheral nervous system are still under discussion. Edler *et al.* explored possible neurotoxic effects of TCDD and its congeners

by several color vision tests for acquired dyschromatopsia in a German cohort occupationally exposed to PCDDs/Fs. Elder *et al.* demonstrated, for the first time, an association of higher PCDD/F body burden and moderate dyschromatopsia syndromes in heavily exposed workers in the chemical industry.

9. **INTERACTION PROFILES FOR A MIXTURE OF PERSISTENT CHEMICALS.** Pohl HR., Hansen H., and De Rosa CT.

Pohl et al. described interaction profiles for a mixture of five persistent chemicals: Chlorinated dibenzo-*p*-dioxins, hexachlorobenzene, p,p'-DDE, methylmercury, and PCBs. They described lack of data on joint toxic action of most of these chemicals in combination, and proposed two approaches: a component-based approach that assumes joint-toxic action, and a target-organ toxicity dose modification of the Hazard Index approach. The overall purpose of the profiles is to make recommendations for exposure-based assessments about the potential impact of joint toxic action of the mixture on public health.

10. **EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN ON SEXUAL DIFFERENTIATION—INFLUENCE OF THE *IN UTERO* EXPOSURE ON FETUS BRAIN AROMATASE ACTIVITY AND SEXUAL DIMORPHISMS IN RATS.** ~~Ikeda M.,~~ Mitsui T., Tamura M., Setani K., Kakeyama M., Sone H., Tohyama C., and Tomita T.

Feminization of the male rat by *in utero* and lactational exposure to TCDD has been well documented. However, precise mechanisms to induce feminization has not been explained yet. To investigate the changes in brain by TCDD exposure during fetal development, Ikeda *et al.* measured brain aromatase activity, saccharin preferences, and the volume of sexually dimorphic nucleus in the preoptic area (SDN-POA) in male rat offspring by maternal exposure to TCDD. TCDD decreased these three indices only in the male offspring.