Risk Assessment:

COMPARE and PCB-RISK Project: Integrated Risk Assessment of PCBs, their Metabolites and Halogenated Flame Retardants

Summary by Martin van den Berg and Lars Hagmar

In this session (oral presentations and posters) results will be presented from two large EU projects, PCB-RISK and COMPARE, that involve exposure, epidemiological, clinical and experimental studies related to possible effects of dioxin like compounds, PCBs and brominated flame retardants and their metabolites.

The EU PCB-RISK study involves a human population living in the Michalovce region of eastern Slovakia. In this area a chemical plant that manufactured the technical PCB mixture Delors contaminated the surrounding environment for decades. As a result PCB levels in samples from this population exceeded several times the background levels in subjects living in a comparable unexposed Slovakian province.

Th. Trnovec and his co-workers in this international collaboration come to the conclusion that this area belongs to the most heavily polluted areas with PCBs in the world. Several associations were found between exposure to PCB and other organo-chlorines with respect to health outcomes. Major findings included thyreopathies, diabetes mellitus, and signs of autoimmune processes. In children hearing impairment, dental enamel defects and neurobehavioral deficits were found, which will be presented in this session.

A. Kocan and co-workers determined the exposure to PCBs and selected organochlorine pesticide exposure in more 2000 adults and 400 children living in the contaminated Michalovce District and two other Slovakian districts with background PCB exposure. The health assessments within the PCB RISK project that will be presented in this session are based on this exposure data. Although the population living in the contaminated area had on average significantly higher levels of PCBs in their blood, individual variation in all three Slovakian districts was high.

L. Hovander and co-workers performed a study in which the levels of OH-PCBs and $MeSO_2$-PCBs were determined in plasma from humans living in the contaminated area and background areas of Slovakia. PCB methyl sulfones were detected and

quantified in all subjects from both cohorts. The most abundant PCB methyl sulfone in this study, 4-$MeSO_2$-CB149, is present at 0.5% of the CB-153 level making this type of PCB metabolites less dominant in humans than in certain species of wildlife.

M. Pliskova and an international group of co-workers studied dioxin-like, estrogenic and antiestrogenic activities in human blood samples collected in these two Eastern Slovakia regions using various in vitro bioassays. These in vitro data were compared with analytical data on concentrations of major classes of POPs. In blood samples from the background area a significantly higher ER-mediated activity was found, while in contrast anti-estrogenic activity was found more frequently in the contaminated Michalovce region. Overall, only weak associations between concentrations of PCBs and potential biomarkers of dioxin-like toxicity and estrogenicity were found in this study.

Janja Jan and co-workers evaluated the effects of long-term exposure to PCBs on developmental dental defects in children these Slovakia districts. This study showed a dose-response relationship between PCB exposure and developmental dental defects in children. These results confirm our previous findings by the same group, that long-term exposure to PCBs may indeed cause developmental dental defects. However, the mechanism of action by which these compounds cause dental effects is presently unknown.

The associations between exposure to PCBs and performance in neurobehavioral tests, thyroid hormones production and hearing status were evaluated by E. Sovcikova and co-workers. Selected confounding factors such as heavy metals and health/social background were also taken into consideration. These results indicate that exposure to PCBs and other POPs in the prenatal and perinatal period can have a significant effect on neuropsychological development of children.

A study by Z. Radikova and co-workers searched for relationships between long-term PCB pollution and disturbances in glucose homeostasis in populations from three districts of Eastern Slovakia. A relationship was found between degree of pollution and disorders of glucose metabolism indicating an increased frequency of diabetes and other dysglycemias concurring with higher levels of PCBs and other persistent pollutants. The authors suggest that interactive effects of compounds on human health cannot be excluded and therefore identification of the specific role of individual pollutants would be difficult.

Within the PCB RISK project P. Langer and co-workers examined the interrelations between long-term organochlorine pollution and fundamental markers of thyroid volume and function. Based on this epidemiological and clinical study it is concluded that several significant changes in thyroid parameters could be observed in subjects with high organochlorine levels. Based on these observed effects it may be suggested that such changes may contribute to the development of clinically overt disorders, especially in certain hereditary disposed individuals.

In the EU COMPARE project the major aim was to study the exposure-effect pathways to different kinds of organohalogen compounds. The main objective was to investigate comparative pathways of early life-stage exposure and long-term effects for several classes of organohalogens, including polychlorinated biphenyls (PCBs) and flame retardants, polybrominated bisphenols and –diphenylethers, and their hydroxylated metabolites. The COMPARE project involved both human exposure – effect studies as well as experimental studies with laboratory animals.

A. Bergman and co-workers will give a presentation that will highlight some of the results obtained within this project dealing with the chemical synthesis, characterisation and analytical aspects of these compounds. Information will also be given about the synthesis, physicochemical and toxicokinetic properties of polychlorobiphenylols (OH-PCBs). In addition, it reported that another BFR, hexabromocyclo-dodecane (HBCDD), can be detected in human blood of Dutch women in similar concentrations as PBDEs and can be is efficiently transferred to the foetus.

J. Weiss and co-workers studied various aspects of the clean up and detection methodology for hydroxylated PCBs. It was found that 4-OH-CB107 and 4-OH-CB146 concentrations decrease in both serum and plasma over time that is not caused by variation within the clean-up method. The extraction of OH-PCBs in plasma has a lower recovery than serum samples most likely due to the fact that plasma is a more protein rich matrix.

Chr. Buitenhuis and co-workers performed *in vivo* studies that involved prenatal exposure of rats to hydroxylated PCB metabolites and BFRs during critical stages of gonadal development. Effects that were studied included those on thyroid and sex steroid hormones, developmental landmarks, sexual and neurobehavioural development. Blood plasma and tissue levels were also analysed to determine

transplacental transfer. Results indicate that hydroylated PCB metabolites and BFRs are capable of placental transfer indicated an aging effect of some PCB metabolites on the estrous cycle of the female rats.

A. Sundberg and co-workers studied fetal and maternal kinetics and transplacental transport of phenolic environmental pollutants in pregnant TTR-deficient mice. The most conspicuous finding was that ^{14}C-BPA , ^{14}C-TBBPA and ^{14}C-TBP all gave rise to strong enrichment of radioactivity in the utero-luminal fluid and in the yolk sac epithelium at gestation day 14 and 17. A very low uptake both in fetal and maternal brains indicates an efficient blood-brain barrier for these compounds. The role of TTR binding is presently being explored using the TTR knock-out mice.

L. Meijer and co-workers studied a cohort of 90 pregnant women living in the northern part of the Netherlands. In this cohort a variety of POPs, including PCBs, PBDEs and their hydroxylated metabolites were determined in blood samples taken in the 20th and 35th week of pregnancy. Infants were followed for 1½ years to examine the influence of the compounds on their development. Most of the levels of contaminants in this Dutch cohort were higher than found in in Sweden, but lower than in Belgium and Spain. BDE-47 levels in our cohort are much lower compared to levels found in the USA.

L. Hagmar and co-workers performed an epidemiological study to assess whether a high dietary intake of POPs, including PCBs and BFRs, through fatty fish from the Baltic resulted in an increased incidence of osteoporotic fractures or decreased bone mineral density (BMD). However, up to now these data do not support the hypothesis that the relatively high exposure levels for POPs found in the Swedish fishermen populations have had any clear effects on neither fracture incidence nor bone mineral density in middle-aged and elderly subjects.