**Special session: Neurotoxicity and Other Effects**

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**SESSION SUMMARY:**

There are numerous hazardous contaminants in our environment. Many of these compounds are well-known persistent chemicals such as polychlorinated biphenyls (PCBs), methylmercury (MeHg), and 1,1,1-trichloro-2,2-bis[p-chlorophenyl]-ethane (DDT). These agents are known to be neurotoxic in laboratory animals and humans. Fetuses and neonates are among high-risk groups for exposure to these agents. There are some new chemicals such as polybrominated diphenyl ethers (PBDEs) entering into the environment. Although PCBs and DDT have been shown to be decreasing in the environment, PBDEs have been shown to be increasing rapidly. PBDEs are structurally similar to the known toxicants such as PCBs and dioxins. In addition to the individual effects, the effects related to the combination exposure to these chemicals need to be understood. In this special session, several studies on the neurotoxic effects of PCBs, MeHg, PBDEs, and dioxins would be presented. The results obtained from in vitro neuronal cultures as well as in vivo studies will be discussed.

The presentation by Eriksson et al (Paper # 625) compares the developmental neurotoxicity of flame-retardants, polybrominated flame-retardants, and organoposphoric compounds in mice. Neonatal NMRI male mice were exposed on days 3 or 10 to a single oral dose of either PBDE 183 (2,2',3,4,4',5',6'-heptabromodiphenyl ether; 15.2 mg or 21 umol/kg body weight), PBDE 203 (2,2',3',4,4',5,5',6-octabromodiphenyl ether; 16.8 mg or 21 umol/kg body weight) or PBDE 206 (2,2',3,3',4,4',5',6'-octabromodiphenyl ether; 18.5 mg or 21 umol/kg body weight). In addition, mice were also exposed on day 10 to a single oral dose of either triphenyl phosphate (0.4 to 40 mg/kg body weight) or tris(2-chloro-ethyl)phosphate (0.4 to 40 mg/kg body weight). Defects in spontaneous behavior (locomotion, rearing, and total activity) were observed in 2-month old mice, neonatally exposed to PBDEs 203 and 206, on postnatal day 10, and to PBDE 293 , on postnatal day 3. Furthermore, impairment in learning and memory were seen in mice exposed to PBDEs 203 and 206. These developmental effects are in agreement with earlier developmental neurotoxic effects for other PBDEs. On the other hand, mice exposed to either triphenyl phosphate or tris(2-chloro-ethyl)phosphate did not exhibit any significant changes in motor activity or learning and memory. The results indicated that phosphorus based flame retardants may not be developmentally neurotoxic while other brominated flame retardants are.

The presentation by Kodavanti et al (Paper # 419) reports the effects of several environmentally relevant PBDE congeners on PKC translocation, 14C-PBDE accumulation, and structure-activity relationships in cerebellar granule neurons. All the

tested congeners (PBDEs 47, 77, 99, 100, and 153) induced PKC translocation; the effect was greater with PBDE 47. In agreement with previous observations on PCBs, non-coplanarity seems to play a major role in the biological effect. Cerebellar granule neurons also accumulated all three tested PBDE congeners (PBDEs 47, 99, and 153). The accumulation of PBDEs either represented as percentage of control or nmoles, increased with time of exposure. There were distinct differences in the pattern of accumulation between PBDE congeners. The percentage accumulation was much lower for the 30 uM PBDE 99 and 10-30 uM PBDE 153 than at lower concentrations. The accumulation pattern with PBDE 47 did not vary with concentration. On a nanomole accumulation basis, PBDEs 47, 99, and 153 accumulation was linear with time, however, not linear with concentration. The pattern of PBDE accumulation seems to correlate with the effects on PKC translocation. Authors conclude that considering the structural similarity of PBDEs with PCBs and the known health effects of PCBs, these two groups of chemicals could work through the same mechanism to cause developmental neurotoxicity.

The presentation by Fisher et al (Paper # 624) deals with the interactive effects of PCBs and MeHg on spontaneous behavior and habituation capability when given to neonatal NMRI-mice during brain growth spurt (postnatal day 10). The results indicated that PCBs and MeHg, at low doses, could interact and enhance developmental neurotoxic effects. Animals exposed to combined low dose of 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153; 0.5 mg) + MeHg (0.4 mg)/kg body weight or PCB 153 (0.5 mg) + MeHg (4 mg)/kg body weight showed significantly impaired spontaneous motor behavior at the age of 2 months and 4 months. This altered spontaneous behavior was also seen in mice exposed to high dose of MeHg. Neither PCB 153 (0.5 mg) or MeHg (0.4 mg) alone affected the adult spontaneous behavior, but the combination caused an effect similar to the one seen with high dose of MeHg (4 mg/kg). Authors reported a similar interaction between other environmental agents and conclude that exposure to low doses of environmental agents can interact to enhance developmental neurotoxic effects.

The presentation by Bowers et al (Paper # 227) reports the developmental and neurobehavioral effects of perinatal exposure to a chemical mixture found in the blood of arctic populations. The mixture contains 14 PCB congeners, 12 organochlorine pesticides, and MeHg. Authors compared the effects of the complete mixture with the effects of the three major components of the mixture. The results indicate that, at least for this mixture of persistent chemicals, both developmental and neurobehavioral effects of the mixture cannot always be adequately characterized by the effects of the specific components of the mixture. Authors suggest that knowledge of the developmental and behavioral effects of specific components of the mixture do not necessarily provide reliable estimates of the effects of the mixture.

The presentation by Coburn et al (Paper # 605) reports the effects of commercial PCB mixture, Aroclor 1254 on osmoregulation by altering central vasopressin release. The results indicated that PCB exposure in rats (30 mg/kg/day for 15 days) attenuated the vasopressin (VP) release from supraoptic nucleus (SON). VP release is a normal response in control animals, however, virtually eliminated in PCB exposed rats. In

addition, PCB-exposed rats showed exaggerated increase in plasma VP of 500% over control. The stimulation of VP release seems to be mediated by nitric oxide synthase (NOS), since NO scavenger and NOS inhibitors have significantly reduced the compensatory release of VP within the SON in osmotically challenged animals. Authors speculate that reduced intra-SON release of VP during dehydration may compromise the capacity for osmoregulation during prolonged physiological demand.

The presentation by Fonnum et al (Paper # 232) deals with the effects of hydroxylated PCBs (OH-PCBs) on oxidative stress and cell death in cultured cerebellar granule cells. The results indicate that OH-PCBs (one of the metabolites of parent PCBs) increased dichlorofluoscein (DCF) fluorescence to levels several fold higher than controls suggesting increased reactive oxygen species formation by OH-PCBs. The increase observed with OH-PCBs was much higher than those seen with parent PCBs, brominated flame-retardants, fluorinated hydrocarobons, and hydrocarbon solvents. OH-PCBs also induced cell death. The cell death by OH-PCBs correlated with the induction of DCF fluorescence. Authors conclude that OH-PCBs induced both oxidative stress and cell death in rat cerebellar granule cells in culture.

The presentation by Kuroda et al (Paper # 109) describes the effects of two ortho-substituted OH-PCBs on thyroid hormone-dependent dendrite formation in Purkinje neurons in culture. The Purkinje cells in the absence of thyroxin (T4) showed poor or no dendritic growth. T4 addition resulted in large treelike elaborate dendrites. In the absence of T4, OH-PCB 106 or OH-PCB 165 did not affect the dendritic development, however, in the presence of T4, abnormal development of Purkinje cells were resulted by OH-PCBs. The effective dose was as low as 50 pM. These studies clearly indicate the effects of two ortho-substituted OH-PCBs on thyroid dependent function such as dendritic growth of Purkinje neurons.

The presentation by Yang et al (Paper # 313) reports the effects of TCDD on RACK-1 in rat cerebellar granule neurons as an attempt to identify the intracellular target of signaling pathway for the developmental effects of TCDD. RACK-1 (receptor for activated C-kinase) is one of the adaptor proteins that anchor the activated PKC at the site of translocation. PKC, which has a key role in learning and memory processes, has been altered by exposure to TCDD. The results indicate that TCDD increased the levels of RACK-1 in a dose- and time-dependent manner. Maximum increase was observed at 10 nM and >30 min exposure. The effects of TCDD on RACK-1 were blocked by a-naphthoflavone, an Ah-receptor blocker. Authors conclude that RACK-1 is possible target molecule for TCDD and other structurally related compounds and plays an important role in understanding PKC-isozyme specific mechanism of action and signaling pathways.

(This summary of the session does not necessarily reflect USEPA policy).