COMPARATIVE DEVELOPMENTAL NEUROTOXICITY OF FLAME-RETARDANTS, POLYBROMINATED FLAME-RETARDANTS AND ORGANOPHOSPHOROUS COMPOUNDS, IN MICE

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Brominated flame-retardants (BFR) are a new group of global environmental contaminants[1,2]. Within this group the polybrominated diphenyl ethers (PBDE) constitute a class that are found in electrical appliances, building materials, and textiles. PBDEs are persistent compounds that appear to have an environmental dispersion similar to that of polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT)[2]. While there is a decrease for PCBs and DDT the PBDEs have been found to increase in the environment and in human mother's milk[3,4,5]. Hexabromocyclododecane (HBCDD) is also used as an additive BFR that is mainly used in different polystyrene resins and in textiles. Tetra-bromo-bis-phenol –A (TBBPA) also belongs to the BFRs and is used as additive or reactive BFR.

Another group of flame retardants (FR) are the phosphorous flame-retardants, where organophosphorous esters are the most commonly used. Several organophosphorous compounds are well known neurotoxic insecticides affecting the cholinergic system by inhibiting acetylcholinesterase. OPs such as triphenyl phosphate and tris(2-chloro-ethyl)phosphate are used as FR and as plasticizer.

In several studies we have shown that low-dose exposure of environmental toxic agents such as PCBs, DDT, as well as well-known neurotoxic agents such as nicotine, organophosphorous compounds and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), during the period of rapid brain growth, known as the "brain growth spurt" ("BGS")[6], in neonatal mice can lead to disruption of the adult brain function, and to an increased susceptibility to toxic agents as adults[7,8]. These studies have also shown that there is a critical phase in the neonatal development, when the maturational processes of the developing CNS are at a stage of critical vulnerability, during which these persistent effects are induced[7,9]. In humans, this period begins during the third trimester of pregnancy and continues throughout the first 2 years of life; in mice and rats this period is neonatal, spanning the first 3-4 weeks of life.

Recently we have reported that certain PBDEs, such as 2,2',4,4'-tetrabromodiphenyl ether (PBDE 47), 2,2′,4,4′,5- pentabromodiphenyl ether (PBDE 99), 2,2',4,4',5,5'-hexabromodiphenyl ether (PBDE153) and 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (PBDE 209) can cause

developmental neurotoxic effects when given to neonatal mice[10,11,12]. The developmental neurotoxic effects after neonatal exposure to PBDE 209 are suggested to be caused by a metabolite (possible de-brominated one). Neonatal exposure HBCDD has also been shown to cause developmental neurotoxic effects[13]. Neonatal exposure to PBDE 99, PBDE 153 and HBCDD was also found to affect learning and memory in the adult animal. The induction of permanent aberration in spontaneous behaviour was induced during limited period of the neonatal brain development[12,14]. The altered spontaneous behaviour was also seen to worsen with age[10,11]. In these studies we have also found that the cholinergic system is one target that is affected, observed as changes in the response of the cholinergic system and a decrease in cholinergic receptors, and is one of the mechanisms underlying the observed behavioural changes. BFRs so far studied TBBPA appears not to cause developmental neurotoxic effects when administered at the same dose levels to neonatal mice[10].

In the present studies we have investigated whether neonatal exposure to three highly brominated dipehenyl ethers, 2,2',3,4,4',5',6'-heptabromodiphenyl ether (PBDE183), 2,2',3'4'4',5,5',6-octabromodiphenyl ether (PBDE 203) and 2,2',3,3',4,4',5',6'-nonabromodiphenyl ether (PBDE 206) can induce developmental neurotoxic effects, such as aberrations in spontaneous behaviour and in learning and memory. Furthermore, neonatal developmental neurotoxicity effects were also studied for two OPs used as FR, triphenyl phosphate and tris(2-chloro-ethyl)phosphate.

Developmental exposure to PBDEs: Neonatal NMRI-male mice were exposed on day 3 or day 10 to an single oral dose of either PBDE 183 [15.2 mg (21) μmol/kg body weight], PBDE 203 [16.8mg (21μmol)/kg body weight] or PBDE 206 [18.5 mg (21μmol)/kg body weight]. Mice serving as controls received 10 ml/kg body weight of a 20% fat emulsion vehicle. Mice were observed for spontaneous behaviour at an age of 2 months. Learning and memory was observed in Morris water maze at an age of 3 months. PBDE 183, PBDE 203, PBDE 206 were synthesized at the Wallenberg Laboratory, Stockholm University, Sweden, and kindly donated by the research group of Åke Bergman.

Developmental exposure to OPs: Neonatal NMRI-male mice were exposed on day 10 to a single oral dose of either triphenyl phosphate [0.4 mg – 40 mg/kg body weight] or tris(2-chloro-ethyl)phosphate[0.4 mg – 40 mg/kg body weight]. Mice serving as controls received 10 ml/kg body weight of a 20% fat emulsion vehicle. Mice were observed for spontaneous behaviour at an age of 2 and 4 months.

Defects in spontaneous behavior (locomotion, rearing and total activity) was observed in 2-month-old mice, neonatally exposed to PBDE 203 and PBDE 206, on postnatal day 10, and to PBDE 203, on postnatal day 3. A minor change in spontaneous behaviour was seen in mice exposed to PBDE 183 on postnatal day 3. Furthermore, impairment in learning and memory, were seen in mice exposed to PBDE 203 and PBDE 206, on postnatal day 10. The developmental neurotoxic effects were most pronounced in mice exposed to the octa-brominated diphenyl ether, PBDE 203. These developmental effects are in agreement with earlier developmental neurotoxic effects for other PBDEs[10,11,12].

In mice neonatally exposed to either triphenyl phosphate or tris(2-chloro-ethyl)phosphate were any significant change seen in mice, neither in 2-month-old nor in 4-month-old mice.

The present results indicate that PBDE 203 and PBDE 206 can cause developmental neurotoxic effects similar to those earlier seen for PBDE 47, PBDE 99, PBDE 153, PBDE 209 and HBCDD. However, either triphenyl phosphate or tris(2-chloro-ethyl)phosphate appears not to as potent developmental neurotoxic agents as the PBDEs or HBCDD since no effect were seen on spontaneous behaviour in mice exposed to a dose of 40 mg/kg body weight.

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