A COMPARISON ON DEVELOPMENTAL NEUROTOXIC EFFECTS OF HEXABROMOCYCLODODECAN, 2,2´,4,4´,5,5´-HEXABROMODIPHENYL ETHER (PBDE 153) AND 2,2´,4,4´,5,5´-HEXACHLOROBIPHENYL (PCB 153)

P. Eriksson, H. Viberg, C. Fischer, M. Wallin and A. Fredriksson

Department of Environmental Toxicology, Uppsala University, Norbyvägen 18A, S-752 36 Uppsala, Sweden

Introduction

Brominated flame-retardants (BFR) are a novel 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. Although HBCDD is increasing in the environment there is very little known about its toxic effects and especially concerning its potency as an environmental developmental neurotoxic agent.

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 2,2´,4,4´,5- pentabromodiphenyl ether (PBDE 99) can cause developmental neurotoxic effects when given to neonatal mice[10]. Induction of permanent aberration in spontaneous behaviour was found to be induced during limited period of the neonatal brain development[11]. This altered behaviour was also seen to worsen with age and also to affect learning and memory[10]. Furthermore, adult mice showed an increased susceptibility at adult age to nicotine, indicating that the cholinergic transmitter system was affected[12].

In our present studies we have seen that neonatal exposure to HBCDD, PBDE 153 or PCB 153 can induce developmental neurotoxic effects, such as changes in spontaneous behaviour, learning and memory defects, and reduced amounts of nicotinic receptors, effects that worsen with age. Neonatal NMRI-male mice were exposed on day 10 to PBDE 153 [0.45- 9.0 mg (0.7-14) ìmol/kg body weight], HBCDD [0.9-13.5 mg (1.4-21 ìmol)/kg body weight] or PCB 153 [0.51-5.1 mg (1.4-14 ìmol)/kg body weight]. In mice exposed to PBDE 153 and PCB 153 the spontaneous behaviour was observed in 2-, 4-, and 6-month-old mice, and performance in Morris water maze at an age of 6 months. In mice exposed to HBCDD the behavioural studies were conducted at an age of 3 months. The behavioural tests

showed that the effects were dose-response related. In mice neonatally exposed to PBDE 153 or PCB 153 the effects were also time-response related. Animals exposed to PBDE 153 and showing defects in learning and memory the amounts of nicotinic receptors in hippocampus were reduced.

These results indicate that HBCDD can cause developmental neurotoxic effects similar to that of PBDEs, and that both HBCDD and PBDE can induce developmental neurotoxic effects in the same dose range as those observed for PCB. This, and the facts that PBDEs and HBCDD are increasing in the environment and that PCBs are still found in mother's milk and in the environment, calls for further investigations of certain BFR as neurotoxicants. Possible interactive neurotoxic effects between these BFR and PCBs also constitute an interesting approach for the future. Their role as possible environmental toxicants involved in the processes of neurodegeneration and aging also calls for further studies.

Acknowledgements

Financial support by grants from the Foundation for Strategic Environmental Research and the Swedish Environmental Protection Board.

References

1. de Boer J., Wester P.G., Klamer H.J.C., Lewis W.E. and Boon J.P. (1998) Nature, 394, 28.
2. Sellström, U(1999), Determination of some polybrominated flame retardants in biota, sediment and sewage sludge (PhD thesis) Stockholm University, Department of Environmental Chemistry and Institute of Applied Environmental Research.
3. Sjödin A., Hagmar L., Klasson-Wehler E., Kronholm-Diab K., Jakobsson E. and Bergman Å. (1999) Environ Health Crit, 107, 643.
4. Norén K. and Meironyté D. (2000*)* Chemosphere , 40, 1111
5. Meironyté D., Norén K. and Bergman Å. (1999) Toxicol. Environ. Health , 58, 329
6. Davison A.N. and Dobbing J. (1968) Applied Neurochemistry*;* Blackwell, Oxford, pp. 178, 253.
7. Eriksson P. (1997) Neurotoxicology, 18, 719.
8. Eriksson P. and Talts U. (2000) Neurotoxicology, 21, 37.
9. Eriksson P., Ankarberg E. and Fredriksson A. (2000) Brain Res., 853, 41
10. Eriksson P., Jakobsson E. and Fredriksson A. (2001) Environ. Health Perspec., 9, 903.
11. Eriksson P., Viberg H., Jakobsson E., Örn U. and Fredriksson A. (2002) Toxicol. Sci.,(in press)
12. Viberg H., Fredriksson A. and Eriksson P. (2002) Toxicol. Sci., (in press)