LETTER TO THE EDITOR

Comment on: Effects of Decabrominated Diphenyl Ether (PBDE 209) Exposure at Different Developmental Periods on Synaptic Plasticity in the Dentate Gyrus of Adult Rats In Vivo

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Xing et al. (2009) exposed Wistar rats to decabromodiphenyl ether (PBDE 209; CASRN 1163-19-5) during five developmental periods: pregnancy, lactation via mother’s milk (indirect dosing), lactation via gavage (direct dosing), postweaning (direct dosing), and prenatal to life (indirect dosing during gestation and lactation and direct dosing postweaning). All animals were evaluated on postnatal day 60. The authors reported that exposure during lactation was the most sensitive period for causing effects on postsynaptic cell excitability.

In the Materials and Methods section, the authors stated: “[t]he animals in each group consisted of three to four litters with both sexes (the ratio of males to females was 1:1 to avoid the effects of litters and sexes.” For the input/output functions, paired-pulse reactions, long-term potentiation, and PBDE 209 concentrations in the hippocampus, however, the authors reported an “n” of 5, 7, 8, 9, 10, or 13 for the respective treatment groups (Xing et al., 2009). Thus, Xing et al. (2009) utilized an average of 1–2 (n = 5), 1–3 (n = 7), 2–3 (n = 8), 2–3 (n = 9), 2–4 (n = 10), or 3–4 (n = 13) litters as independent values per treatment group. This study is based on a clustered experimental design, and data analysis must control for litter effects.

The U.S. Environmental Protection Agency recently cosponsored two expert working groups on statistical considerations for use in developmental neurotoxicity testing and for direct dosing preweaning animals (Holson et al., 2008; Moser et al., 2005; Zoetis and Walls, 2003). These expert groups concluded that the litter must be used as the experimental and statistical unit regardless of whether animals are dosed indirectly or directly. Based on the number of litters used by Xing et al. (2009), their reported sample size should be an “n” of 3 or 4, with values from littersmates treated as replicates within each litter.

Failing to control for litter effects can have a profound impact on data analysis and resulting conclusions. For example, the rate of type I or false-positive errors has been reported to triple the nominal 0.05 alpha level when as few as two pups per litter were used as independent measures (Holson and Pearce, 1992). Because Xing et al. (2009) utilized varying numbers of pups from the same litter per treatment group as independent values, their results may be reflective of litter effects, inflating the significance of test article–related effects. It is noteworthy that the in vivo studies cited by Xing et al. (2009) as support that PBDEs cause developmental neurotoxicity also failed to control for litter effects (Eriksson et al., 2001, 2002; Fischer et al., 2008; Viberg et al., 2003a,b 2004, 2007, 2008). Furthermore, PBDE 209 was evaluated using the most recent validated test guideline for developmental neurotoxicity (OECD, 2007). This study utilized doses ranging from 1 mg/kg/day to 1000 mg/kg/day and was unable to replicate the effects reported by Viberg et al. (2003b, 2007) (Hardy et al., 2009).

In conclusion, Xing et al. (2009) failed to control for litter effects in analyzing data arising from a clustered experimental design. If the authors tracked which pups came from which litters per treatment group, their data may be reanalyzed to determine to what degree the effect they attributed to the treatment was a result of uncontrolled litter effects. In the absence of such a reanalysis, data by Xing et al. (2009) are of questionable relevance for risk assessment.

REFERENCES


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