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Response to Comment on "Comparative Tissue Distribution, Biotransformation and Associated Biological Effects by Decabromodiphenyl Ethane and Decabrominated Diphenyl Ether in Male Rats after a 90-Day Oral Exposure Study"

We are responding to the comments made by Banasik and coauthors on our recent article "Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure study".[1]

Bioaccumulation occurs when the absorption rate of an organism is larger than the rate of loss. Thus, it depends on three factors; bioavailability, exposure dose, and systemic clearance. In our research, a 100 mg/kg bw/d dose of BDE-209 or decabrominated diphenyl ether (DBDPE) suspended in corn oil was fed to rats by oral gavage to determine whether bioaccumulation occurred at high exposure.[1] In the 1986 U.S. National Toxicology Program (NTP) recommended by Banasik et al., BDE-209 was fed in diets and its recovery from feces was used to determine bioaccumulation. In our study, however, the DBDPE amount retained in the organism as measured by liver concentration was used to determine bioaccumulation.[1] The fundamental differences between experimental methods indicate that it would not be appropriate to negate our results using this reference. Indeed, more recent research supports our conclusion.[2,3] The low concentration in rat tissues proved the poor biological availability of DBDPE, and suggested that it could still be detected in organisms, as has been demonstrated in wildlife.[4] We are confused by Banasik and coauthors use of a report from the U.K. Environment Agency (EA) to rebut our paper as this report does not disagree with our results, and its use of the word "poorly" does not mean "unable".[5] The question to ask is if BDE-209 is not bioaccumulative, then how can it be detected in rats and reach a steady-state?

Second, no changes in either liver weight or histopathology (data not shown) were observed. We did confirm, however, tissue distribution and biotransformation of the two compounds in the tissues and found biotransformation was possibly caused by different reasons. This is the first such report that we know of. In addition, rats were orally administrated in our study, with 1 986 152 ± 104 ng/g lw BDE-209 and 177 ± 111 ng/g lw DBDPE detected in the liver, respectively. Recently, we investigated alterations in the metabolic profiles of serum, liver, and liver extracts from rats after DBDPE and BDE-209 treatment using NMR-based metabonomics approach (data not shown). The changes in the metabolic profiles of DBDPE and BDE-209 treatment indicate that they perturbed fatty acid β-oxidation, glycolysis and energy metabolism. The comparison of BDE-209 and DBDPE from liver lipid extract, liver aqueous extract and serum proved that there were minor differences between BDE-209 and DBDPE. These results again proved that DBDPE can induce liver toxicity in rodents.

Third, we were not convinced that DBDPE affected thyroid hormone homeostasis for two reasons. One is that many researchers have demonstrated that PBDEs,[6,7] phenolic PCB metabolites,[7] and some $MeSO_2$−CBs [8] can disturb thyroid systems, shown mainly through reduced thyroid hormone levels in experimental animal models and several in vitro test systems. Biotransformation of DBDPE was tentatively proposed as $MeSO_2$-BDPE and $EtSO_2$-BDPE, and T_3 levels increased in DBDPE treatment in our study. Considering the fact that the chemicals quoted above can disturb thyroid systems, we concluded that DBDPE can disturb thyroid hormone levels and is worth deeper evaluation.

GC-MS is now applied as a routine technology for the screening of apparent or previously hidden metabolic phenotypes.[9] We totally agree with the fact that mass spectrum is an incomplete way to confirm the structure of unknown compounds without authentic standards, due to the uncertainty of physical-chemical properties and instrument settings. Consequently, we used the word "tentatively" in our previous paper.[1] We tried to further confirm using GC-MS-MS and HRMS, but found it difficult to do due to the low concentration of the DBDPE metabolites. We retained our conjecture because we think it is reasonable based on our knowledge, and the key point here is to indicate that DBDPE can be metabolized in organisms and to emphasize the metabolic differences between DBDPE and BDE-209. In addition, semiquantification is a common and accepted approach to qualify compounds without standards but which have structures similar to other known compounds. We used this method to compare metabolite concentration levels in different tissues. Thus, the response factor would not affect the conclusion.

In our study, the inductions of CYP3A2 and CYP2B1 after DBDPE and BDE-209 exposure, indicate that DBDPE and BDE-209 and/or their metabolites may have induced the corresponding mRNA expression. We did not confirm whether the protein levels and activities of the corresponding enzymes increased or not.

Despite the common use of BDE-209 and DBDPE, there is still much debate over their environmental fate, behavior, and possible toxic effects on wildlife and humans.

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REFERENCES

(1) Wang, F.; Wang, J.; Dai, J.; Hu, G.; Wang, J.; Luo, X.; Mai, B. Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure study. *Environ. Sci. Technol.* **2010**, *44*, 5655–5660.

(2) Huwe, J. K.; Smith, D. J. Accumulation, whole-body depletion and debromination of decabromodiphenyl ether in male Sprague-Dawley rats following dietary exposure. *Environ. Sci. Technol.* **2007**, *41*, 2371–2377.

(3) Covaci, A.; Harrad, S.; Abdallah, M. A.; Ali, N.; Law, R. J.; Herzke, D.; de Wit, C. A. Novel brominated flame retardants: A review of their analysis, environmental fate and behaviour. *Environ. Int.* **2011**, *37*, 532–556.

(4) Betts, K. Glut of data on "new" flame retardant documents its presence all over the world. *Environ. Sci. Technol.* **2009**, *43*, 236–237.

(5) Dungey, S.; Akintoye, L. *Environmental Risk Evaluation Report: 1,1′(Ethane-1,2 -diyl)bis[penta-bromobenzene] (CAS:84852-53-9)*; SCHO0507BMOR-E-P; Environment Agency: Bristol, UK, 2007.

(6) Meerts, I. A.; Van Zanden, J. J.; Luijks, E. A.; Leeuwen, B. I.; Marsh, G.; Jakobsson, E. Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro. *Toxicol. Sci.* **2000**, *56*, 95–104.

(7) Haraguchi, K.; Kato, Y.; Kimura, R.; Masuda, Y. Hydroxylation and methylthiolation of mono-ortho-substituted polychlorinated biphenyls in rats: identification of metabolites with tissue affinity. *Chem. Res. Toxicol.* **1998**, *11*, 1508–1515.

(8) Biesemeier, J. A.; Beck, M. J.; Silberberg, H.; Myers, N. R.; Ariano, J. M.; Bodle, E. S.; Sved, D. W.; Jacobi, S.; Stump, D. G.; Hardy, M.; Stedeford, T. Effects of dose, administration route, and/or vehicle on decabromodiphenyl ether concentrations in plasma of maternal, fetal, and neonatal rats and in milk of maternal rats. *Drug Metab. Dispos.* **2010**, *38*, 1648–1654.

(9) Kopka, J. Current challenges and development in GC-MS based metabolite profiling technology. *J. Biotechnol.* **2006**, *124*, 312–322.