Common viral infection alters pentabromodipenyl ether (BDE-99) distribution and plasma thyroxine levels in mice

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Polybrominated diphenyl ethers (PBDEs) have become widely distributed in the environment because of their large volume use for fire protection, the persistence against degradation and ability to accumulate in biota. In time trend studies increased concentrations have been observed at several biological levels.

The role of infections as modulators of effects of environmental chemicals is largely unknown. However, earlier studies from our lab have shown that TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) distribution is altered during a viral infection [1], and that the infection becomes aggravated [2]. In the case of PBDEs, nothing is known whether infections could change metabolism and distribution. As infections will affect most persons now and then, and as they sometimes could be long-lasting, increased knowledge in these matter may improve the risk assessment of PBDEs as well as of other persistent organic pollutants.

Earlier studies have shown that tetra- and pentabrominated PBDE are efficiently absorbed from the gastro-intestinal tract and distributed to the fat depots, liver, adrenal cortex, ovary, lungs and brain (unpublished observations). We also know that PBDEs are able to induce microsomal enzymes, such as CYP 1A1/2 and CYP 2B [3]. Results from in vitro-experiments suggest that these enzymes, and probably chiefly CYP 2B, could be responsible for phase I metabolism of PBDEs [4]. In this way, changes in enzyme activities could affect the distribution of PBDEs in the body, and the distribution may also be related to the biological effects of the PBDEs, depending on the target organ localisation, concentration and rate of elimination. In earlier studies from our lab, effects of PBDE mixture of pure congeners on CYP activities and on thyroid hormone concentration have been studied in mice and rats.

In the present study female Balb/d mice were infected (day 0) with coxsackievirus B3 (CB3), and on day 1 of infection orally dosed with approx. 200 µg/kg (ca 0.5 µCi) of ^{14}C-labelled 2,2',4,4',5-pentabromodiphenyl ether (^{14}C-BDE-99) and subsequently sacrified on day 3 of the infection for studies of ^{14}C-BDE 99 distribution. At the same time tissue samples were dissected for monitoring of ^{14}C-distribution, serum samples were also taken for measurement of free thyroxine (FT4). Infected mice developed expected clinical signs of disease. In comparison with control values, the infection increased the ^{14}C-BDE 99 concentration in the liver to 186% of control, and decreased

the concentration in the lungs to 47% and in the pancreas to 51% of control (Table 1). However, the infection caused no change in the concentration of ^{14}C-BDE 99 in the blood, brain, heart, spleen and kidneys. The present infection-induced distribution changes are different from other environmental pollutants, such as dioxin, acryl amide and cadmium. In addition, infection changes FT4 levels in serum, and in infected mice the FT4 levels are about 35% of those in control mice (data not shown). Note that the BDE 99-dose used in this study is too low to cause effects on T4 levels in the mouse. As earlier discussed [5,6] the decrease in T4 levels could be coupled to an increase in CYP-activities, as metabolites of PBDEs generally will have higher affinity to TTR, the major serum T4-transport protein in rodents, than have the unmetabolised PBDE compounds. Therefore, it is suggested that the change in tissue distribution of ^{14}C-BDE 99 as a result of the infection may have been caused by an infection-induced specific change in the liver metabolism capacity of the PBDE congener. Ongoing preliminary studies indeed suggest that ethoxyresorufin-*O*-deethylase (EROD) activities (mirroring CYP 1A1/2) are changed in infected mice compared to control, and that the direction of change may be dependent on the phase in the infection.

To conclude, a viral infection in mice alters the distribution of ^{14}C-labelled PBDE congener BDE 99, resulting in increased levels in the liver and decreased levels in pancreas and lung. In the serum samples, free thyroxin levels in infected mice are decreased to about 35% of those in control mice. Ongoing studies suggest that CYP-changes will occur during infection and both distribution and thyroxin changes may be a result of infection-induced alterations of microsomal CYP-activities.

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Table 1. BDE 99 distribution (c.p.m./mg fresh wt)

Treatment	Animal code	Brain	Heart	Liver	Lung	Spleen	Kidney	Pancreas	Blood
PBDE	1	1.25	2.04	1.85	19.5	1.87	4.31	9.88	0.70
PBDE	2	0.98	2.45	1.58	11.5	1.27	3.80	4.40	0.52
PBDE	3	2.40	2.81	2.35	25.0	2.45	4.89	5.22	2.40
PBDE	4	1.04	2.00	2.05	7.01	1.29	3.75	6.58	0.63
PBDE	5	1.18	2.25	1.39	20.0	1.71	3.34	8.25	0.72
mean ± SD		**1.37 ± 0.58**	**2.31 ± 0.34**	**1.85 ± 0.38**	**16.6 ± 7.22**	**1.72 ± 0.49**	**4.02 ± 0.59**	**6.86 ± 2.23**	**0.99 ± 0.79**
PBDE + infection	6	1.17	3.83	1.92	6.54	1.95	4.84	4.70	1.34
PBDE + infection	7	1.09	2.87	4.57	7.33	1.15	4.61	1.87	0.56
PBDE + infection	8	1.65	3.18	4.04	11.5	1.36	5.97	5.46	0.75
PBDE + infection	9	1.30	3.08	3.00	9.22	1.84	4.73	3.65	0.83
PBDE + infection	10	1.19	2.09	3.70	4.19	1.07	2.89	1.68	0.68
mean ± SD		**1.28 ± 0.22**	**3.01 ± 0.63**	**3.44 ± 1.03**	**7.75 ± 2.75**	**1.47 ± 0.40**	**4.61 ± 1.10**	**3.47 ± 1.68**	**0.83 ± 0.30**
p-value		n.s	n.s	0.01	0.03	n.s	n.s	0.03	n.s