# Effect of Aroclor 1254 on thyroid hormone sulfation in fetal rats

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## Introduction

Polychlorinated biphenyls (PCBs) are known to affect thyroid hormone metabolism(1). Hydroxylated metabolites of PCBs (PCB-OHs) can compete with thyroid hormones for binding to transthyretin (2) and type I deiodinase (D1; 3). Recently, an inhibitory effect of PCB-OHs on iodothyronine sulfotransferase (SULT) activity was also demonstrated *in vitro*. Since 1) sulfation is suggested to be an important pathway in thyroid hormone metabolism during fetal development (4), and 2) PCB metabolites are found to accumulate in fetal tissues after maternal exposure (5), inhibition of thyroid hormone sulfation by PCB-OHs may play a role in the observed fetal thyroid hormone disturbances.

The aim of this study was to investigate if thyroid hormone sulfation is also inhibited by PCB-OHs *in vivo*. Since thyroid hormone sulfation is only one step in the integrate thyroid hormone metabolism, a wide spectrum of thyroid hormone parameters were tested.

## Materials and Methods

Pregnant Wistar rats were orally exposed to 25 mg Aroclor 1254/kg body weight from day 10 to day 18 of gestation. Fetal and maternal tissues were obtained on day 20 of gestation. Serum total T4 (TT4) and free T4 (FT4) levels were measured using Amerlite chemiluminescence kits. T4 sulfate (T4S) and rT3 were measured by specific RIA as described by Wu *et al.* (6) and Eelkman Rooda *et al.* (7). The different enzyme activity assays were performed as described earlier. In liver,

EROD activity (8), T4 UDP-glucuronyltransferase (T4 UGT; 9), D1 activity (9), and 3,3'-T2 SULT activity (10) were measured. In brain, type II deiodinase (D2; 9) and 3,3'-T2 SULT activity (10) were determined.

**Results and Discussion**

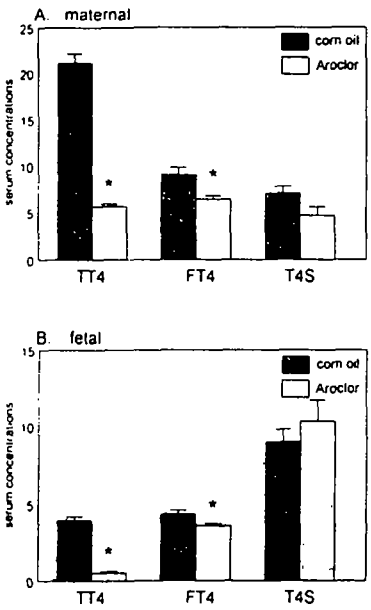


*Figure 1. Effects of prenatal exposure to Aroclor 1254 on maternal (A) and fetal (B) serum levels of TT4 (nmol/l), FT4 and T4S (pmol/l). *) significantly different from corn oil.*

TT4 and, to a lesser extent, FT4 levels were decreased after Aroclor 1254 treatment in fetal and maternal serum (Figure 1). Fetal T4S levels were very low in contrast to the high levels in human and sheep fetal serum reported previously (11-15). Treatment with Aroclor 1254 did not significantly change the T4S levels in both dams and fetuses.

In maternal and fetal liver and brain, 2 SULT activity was not statistically significant affected after treatment with Aroclor 1254 (Figure 2A-B). However, T2 SULT activity showed different results using a concentrations series of T2 together with pooled fetal liever cytosol. The results suggest a (competitive) inhibition of T2 SULT activity in the Aroclor 1254-exposed fetuses in liver cytosol (see Figure 2C).

Further data showed an induction of hepatic EROD and T4 UGT activity in dams after treatment with Aroclor 1254 (Table 1). D1 activity was low in fetal versus maternal liver, and was decreased in both dams and fetuses after treatment with Aroclor 1254. Brain D2 activity was increased in both dams and fetuses after exposure to Aroclor 1254 (Table 1).

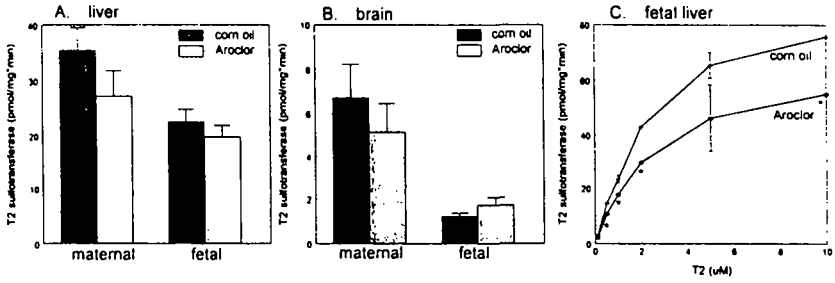


*Figure 2.* *Effects of prenatal exposure to Aroclor 1254 on T2 SULT activity in fetal and maternal liver (A) and brain cytosol (B). Cytosolic protein concentrations were 25 µg/ml for maternal liver and 100 µg/ml for fetal liver and brain, and the T2 concentration was 1.0 µM. In panel C, pooled samples of fetal liver cytosol and a T2 concentration series were used. *) significantly different from corn oil.*

*Table 1.* *Effects of prenatal exposure to Aroclor 1254 on hepatic EROD activity, T4 UGT, and D1 activity, and brain D2 activity in fetal and maternal tissues. N=9, * significantly different ($p<0.05$) from corn oil.*

| | | EROD activity (nmol/mg·min) | T4 UGT activity (pmol/mg·min) | D1 activity (pmol/mg·min) | D2 activity (fmol/mg·min) |
|---|---|---|---|---|---|
| DAMS | corn oil | 14.8 ±8.0 | 1.80±0.05 | 208.5±22.9 | 0.71±0.05 |
| | Aroclor 1254 | 2994.3 ±458.7 * | 8.37±0.60 * | 85.0±8.8 * | 0.91±0.09 |
| FETUSES | corn oil | 3.3±0.4 | 0.53±0.05 | 12.4±0.8 | 0.28±0.02 |
| | Aroclor 1254 | 15.0±5.6 * | 0.64±0.38 | 9.9±0.5 * | 0.44±0.06 * |

Our findings show that despite low hepatic D1 activity and considerable iodothyronine SULT activity in liver and brain, serum T4S levels in the fetal rat are much lower than those in fetal human or sheep, suggesting that sulfation is a less important pathway of fetal thyroid hormone metabolism in rats than in humans and sheep. Furthermore, the administration of (precursors of)

SULT inhibitors does not result is a decrease in fetal serum T4S levels, perhaps because degradation of T4S by hepatic D1 is simultaneously decreased.

**Acknowledgements**

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