Characterization of maternal and fetal bisphenol A disposition in a physiologically-based sheep model

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15.6. Abstract Title: Characterization of maternal and fetal bisphenol A disposition in a physiologically-based sheep model

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Introduction: Bisphenol A (BPA) is one of the most highly produced chemicals worldwide and the human exposure to BPA is thought to be ubiquitous. As fetal period represents a critical BPA exposure window, an integrative model of pregnant ewe based on physiological considerations was developed to determine if the pregnancy-associated physiological changes and the metabolic specificities of the feto-placental unit can influence BPA toxicokinetic. The aims of this study were to determine the toxicokinetic parameters of BPA and its inactive metabolite BPA-Glucuronide (BPA-G) in the feto-maternal compartments and to characterize the placental transfer of BPA and BPA-G.
Materials and Methods: In a first longitudinal study, four ewes were infused IV for 24 hours with BPA (2 mg/(kg.d)) at four physiological stages: one month before breeding, one and four month of pregnancy, and one month after lambing. Blood samples were collected at each period during the three last hours of the infusion and during 48 h after the end of infusion. Percentage of unbound BPA was evaluated for each period by equilibrium dialysis. In a second study, BPA (2 mg/(kg.d) and 5 mg/(kg.d) for ewes and fetus respectively) and BPA-G (3.54 mg/(kg.d) were infused IV for 24 hours to 7 pregnant ewes or to 5 fetus at 4 month of gestation. Maternal and fetal plasma and amniotic fluid were collected during the three last hours of infusion thereafter for several days until lambing. BPA, BPA-G and BPA-Sulfate (BPA-S) concentrations were assayed by UPLC/MS/MS.
Results: The pregnancy stage modified neither maternal internal exposure to BPA and its metabolites nor plasma clearance of BPA. The BPA clearance was 5-fold higher in fetus than in adults (150 mL/kg.min versus 30 mL/kg.min), with values in adult very closed to the human one.3% of the BPA dose infused to the pregnant ewe was transferred across the placenta to the fetus. The feto-placental unit appeared to be highly efficient to conjugate BPA. The conjugated metabolites (BPA-G and BPA-S) remained trapped in the feto-placental compartment. The BPA fraction not bound to plasma protein *i.e* the bioactive BPA form, was two-fold higher in the fetus than in the adults (11% versus 6 %), suggesting that for the same dose (total BPA) fetus is 2-fold more exposed than ewes.
Conclusions: For a BPA maternal exposure of 2 mg/(kg.d), the fetus received in late pregnancy a BPA dose of about 1 mg/(kg.d) when adjusted to its bodyweight. The resulting fetal plasma concentrations of BPA-G and BPA-S were 5 to 10-fold higher than the maternal ones and these metabolites remained trapped in amniotic fluid until lambing. This high internal exposure to BPA metabolites raises the question of a possible local deconjugation and reactivation of these conjugated forms in target organs (gonads, brain, [3DOTS]) and provides new insights for human risk assessment.

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ABSTRACTS