### Title

Levels of Kras Codon 12 Mutations in Mouse Ovary Measured by ACB-PCR Were Not Increased by Transplacental Exposure to benzo[a]pyrene or Impacted by Gclm Genotype




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**Levels of *Kras* Codon 12 Mutations in Mouse Ovary Measured by ACB-PCR Were Not Increased by Transplacental Exposure to benzo[*a*]pyrene or Impacted by *Gclm* Genotype.** Parsons BL[1], Banda M[1], Myers MB[1], McKim KL[1], Ortiz L[2], Luderer U[2]. [1]National Center for Toxicological Research, US FDA, Jefferson, AR, United States, [2]University of California, Irvine, Irvine, CA, United States.

ACB-PCR, a sensitive DNA-based method for quantifying cancer-driver mutations, has been used to demonstrate: 1) relatively high levels of *KRAS* mutations are frequently present in normal rodent and human tissues, 2) human tumors frequently carry *KRAS* mutant subpopulations, thus *KRAS* mutation contributes to a greater fraction of human cancers than is recognized, and 3) increased levels of *Kras* mutation may occur following short-term exposure to carcinogens. *KRAS* is the fourth most frequently mutated gene in ovarian cancer, with two specific mutations accounting for 73% of those reported (G12D, 41%; G12V, 32%). This study investigated the utility of ACB-PCR in evaluating the transplacental mutagenesis of benzo[*a*]pyrene, in the presence and absence of Gclm-deficiency. Our prior study showed *Gclm-/-* mice have increased sensitivity to ovarian tumorigenesis induced by prenatal benzo[*a*]pyrene exposure. Gclm is the modifier subunit of glutamate cysteine ligase, which catalyzes the rate limiting step in glutathione biosynthesis. C57Bl/6J (*Gclm* heterozygous) dams were gavaged with 2 mg/kg/day benzo[*a*]pyrene or the sesame oil vehicle on gestational days 6.5-15.5. Ovaries of female offspring (*Gclm*+/+, *Gclm* +/-, and *Gclm*-/-) were harvested at first vaginal estrus (postnatal day 34-46) and *Kras* codon 12 GAT and GTT mutations (G12D and G12V, respectively) were quantified. Measureable levels of *Kras* mutation were present in all ovarian DNA samples, with geometric mean mutant fractions (MFs) of $6.11 \times 10^{-5}$ and $1.07 \times 10^{-4}$ for G12D and G12V in *Gclm*+/+ vehicle control mice, respectively. No significant changes in *Kras* MF were observed due to benzo[*a*]pyrene-treatment, *Gclm* genotype, or their interaction.