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TISSUE DISTRIBUTION AND MACROMOLECULAR BINDING OF EXTREMELY LOW DOSES OF [^{14}C]- BENZENE IN MICE.

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The tissue distribution and macromolecular binding dose-response of [^{14}C]-benzene (500 mg/kg to 700 pg/kg) is being studied in B6C3F$_1$ and DBA mice to determine if macromolecular adducts can be detected at human-relevant exposures and how dose influences bioactivation. [^{14}C]-Benzene is being measured by accelerator mass spectrometry. Radiocarbon from [^{14}C]-benzene is measurable in tissues, DNA and protein to doses of 700 pg/kg. [^{14}C]-Benzene is rapidly absorbed at a dose of 628 ng/kg with peak tissue concentrations occurring at 1 hr. Peak liver DNA adduct levels are also reached within 1 hr (7 adducts/10^{11} nucleotides) while peak bone marrow DNA adduct levels are reached at 24 hr (21 adducts/10^{11} nucleotides). Absorbed dose and adduct formation is linear with administered dose between doses of 700 pg/kg - 16 mg/kg. Saturation occurs above the 16 mg/kg dose for absorbed dose and liver protein adducts. Bone marrow DNA adducts are 5 times those in the liver. Protein adducts were factors of 15 and 50 greater than DNA adduct levels in liver and bone marrow, respectively. Single rate constant elimination's are seen for all tissues except bone marrow, which is best described as multi-phasic, with $t_{1/2}$s of 0.8 and 7 hr These data show that benzene is rapidly absorbed at human-relevant doses and that adducts to macromolecules are present. The data suggest that greater levels of reactive metabolites may form and accumulate in the bone marrow relative to liver. Finally, these data suggest protein binding at low dose may be an important benzene target *in vivo*. Work in progress is addressing how metabolite profiles change with dose in bone marrow and how metabolism in the DBA and B6C3F$_1$ mice differ at low dose. This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under contract no. W-7405-ENG-48 and supported by NIH grant ES04705 and HEI #95-4.