Presentation 10 – Wayne Briner

Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure

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Animal Findings

- DU accumulates in brain as well as skeleton, muscle, spleen, liver, heart, lung, lymph nodes, testes (Pellmar et al., 1999).
- DU accumulates in hippocampus & striatum, as well as cortex & striatum (Barber et al., 2005)
- DU pellets inhibited spike formation in the hippocampus of rats, no evidence of renal damage (Pellmar et al., 1998 & 1999).
- Rats given high doses of U exhibit tremors (Domingo et al., 1987).
- U may compete with calcium at the cellular level, in particular the neuromuscular endplate (Lin et al., 1988)

- No effect of U on DA or 5-HT or catabolite levels in a variety of brain structures (Houpert et al., 2004).
- No behavioral effects seen after 6 months DU pellet implantation (Pellmar et al., 1998)

- Developmental Effects
- U produces variety of adverse effects when administered prenatally on litter size and viability. Some teratogenic effects, esp. skeletal (native U, Domingo et al, 1989; Bosque et al, 1993; Paternian et al, 1989)
- Gestational day 10 (neural tube formation) most vulnerable time (Domingo, 1994)
- DU implanted rats demonstrated no effect on pregnancy or rat pups. DU does cross placental barrier and fetal tissue accumulates DU (Benson, 1998)

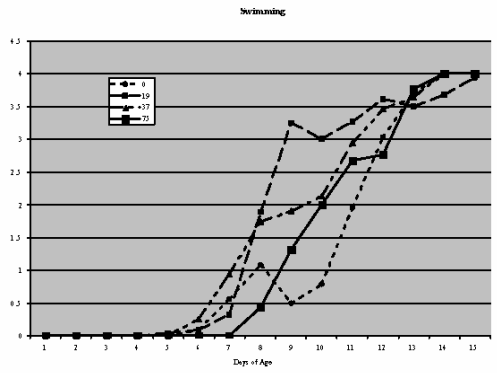
Human Findings

- DU found in urine of those exposed (Hooper et al., 1999; McDiarmid et al, 1999, 2000, 2001; Hodge et al, 2001). Issues concerning utility.
- Relationship between urinary DU and computerized neurocognitive testing (McDiarmid et al, 2000).
- Relationship between urinary DU elevated serum prolactin levels (McDiarmid et al, 2000).

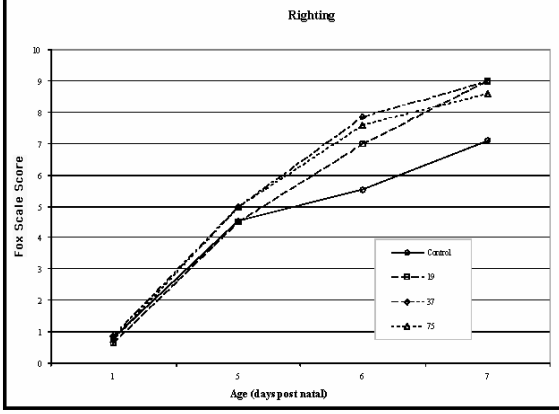
Developmental Research

Female mice were exposed to 0, 19, 37, or 75 mg/L of uranium acetate for two weeks, then mated. Exposure of dams and pups continued until sacrifice. Mice were assessed using the Fox Developmental Scale until age 21 days. At 21 days of age the pups were assessed with a Functional Observation Battery after-which the brains were removed for study.

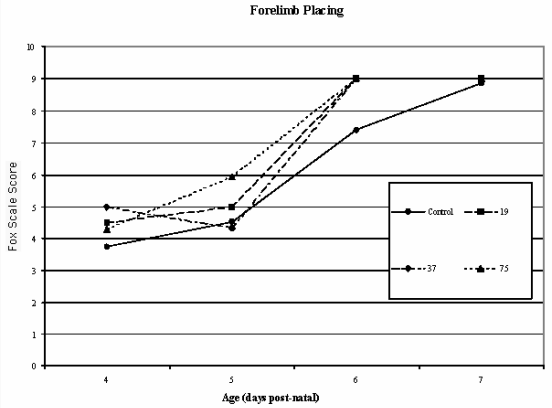
Swimming



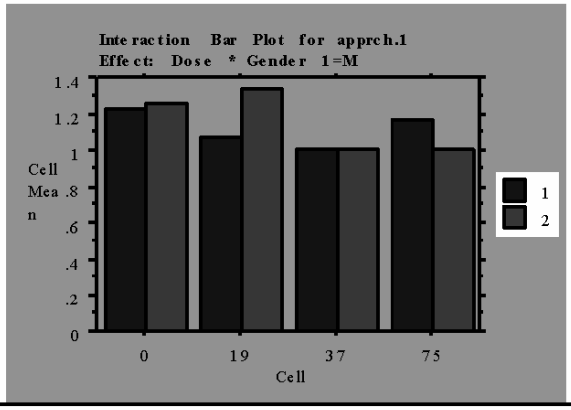
Righting



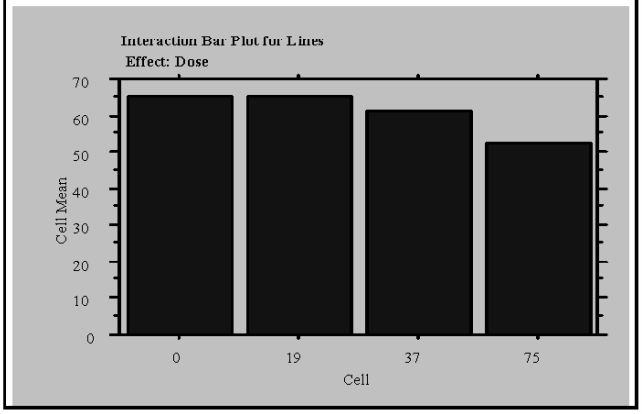
Forelimb Placing



Approach



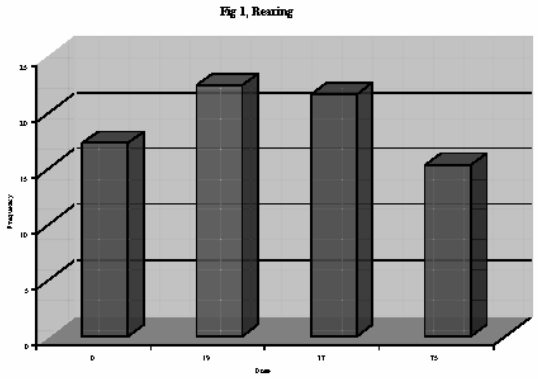
OF, Line Crossing



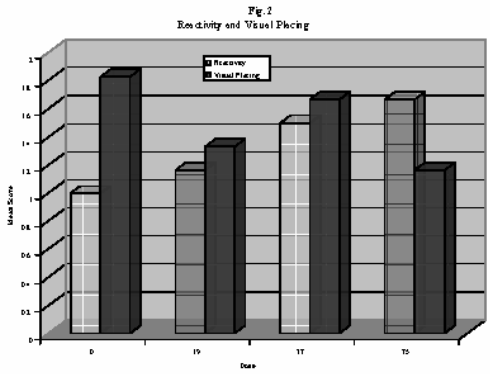
Adult Mice

- Male adult mice were reared under standard laboratory conditions and exposed to DU acetate in drinking water at 4 dosage levels (0, 19, 37, and 75 mg/L) for 2 weeks.

Rearing



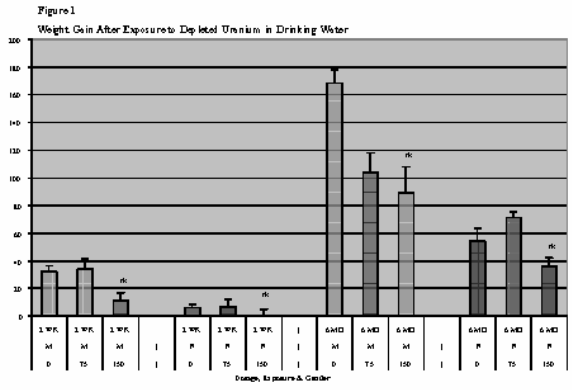
Reactivity & Visual Placing



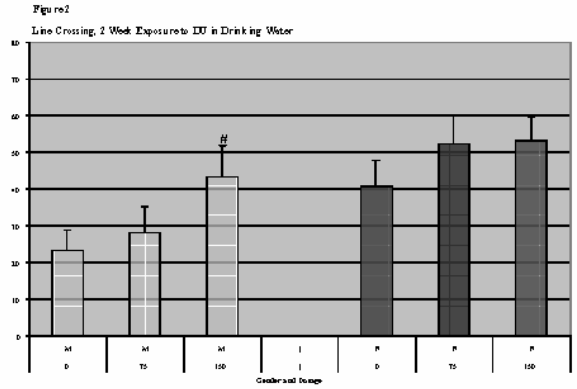
Rat Behavior (adult)

- Rats were were exposed to depleted uranium acetate dihydrate in drinking water at doses of 0, 75, or 150mg/L for 2 weeks or for 6 months. At the conclusion of exposure, animals were tested in the open-field maze.
- Lipid oxidation levels determined using TBA method.

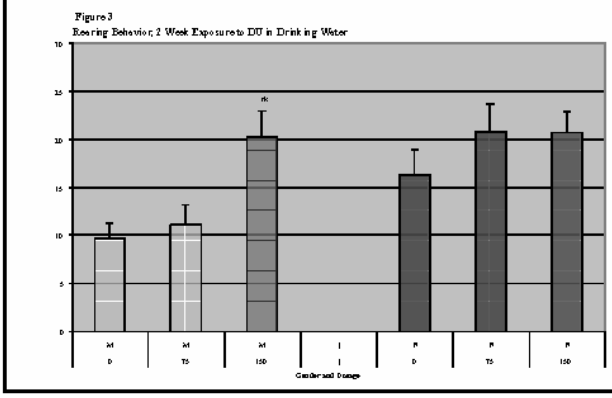
Weight Gain



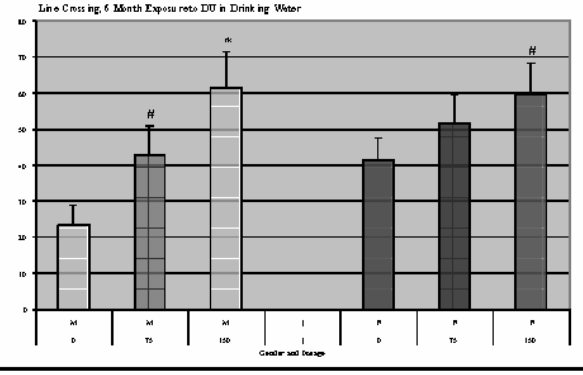
Line Crossing, 2 weeks



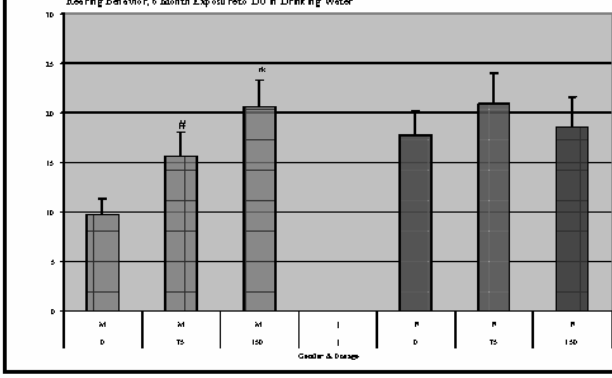
Rearing, 2 weeks



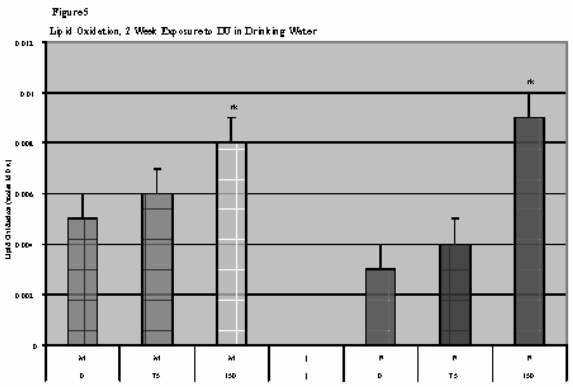
Line Crossing, 6 months



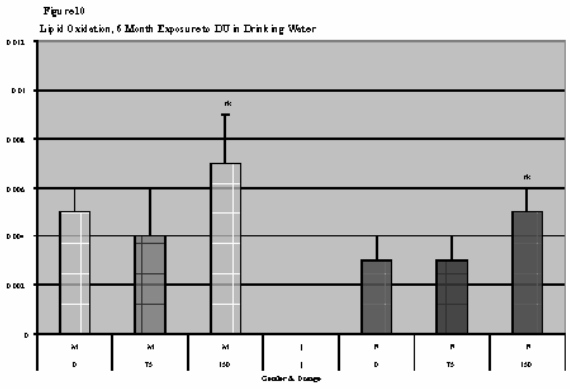
Rearing, 6 months



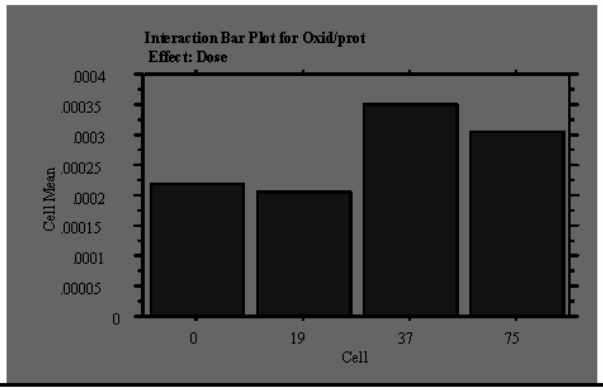
Lipid Oxidation (adult, 2 weeks)



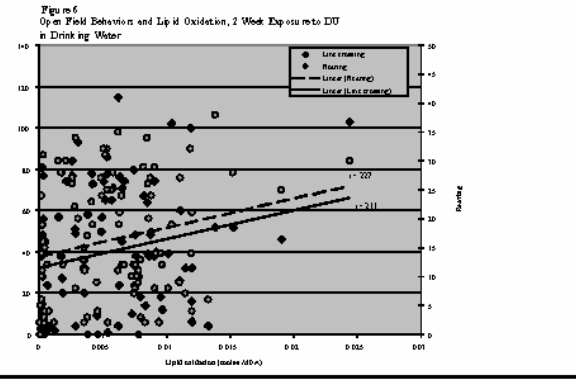
Lipid Oxidation (adult, 6 months)



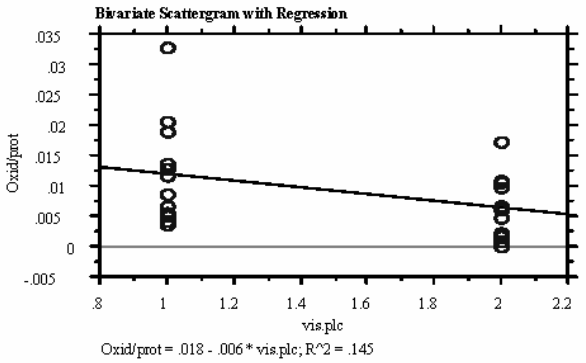
Lipid Oxidation Seen in Mice



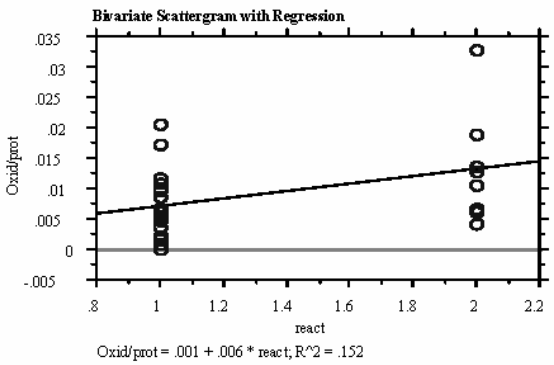
Lipid Oxidation & Behavior



Lipid Ox & Behavior (mice)



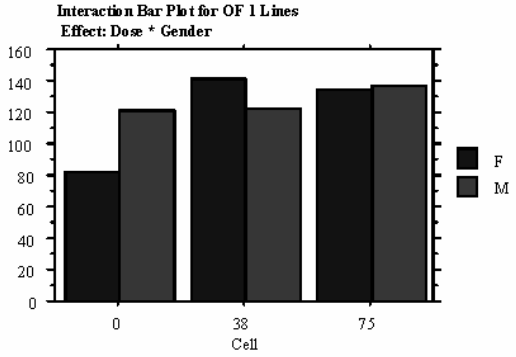
Lipid Ox & Mice (cont)



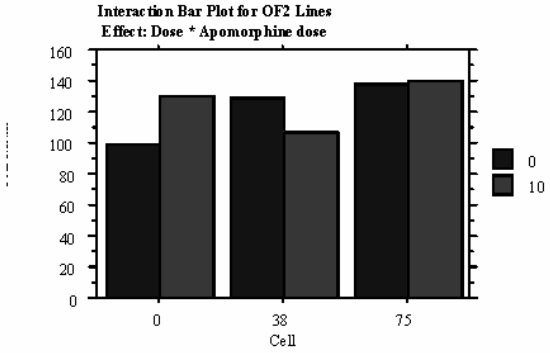
Neurotransmitter Studies

- Mice exposed to 0, 39, 75 mg/L DU acetate dihydrate for 2 weeks.
- Open field followed by repeat with apomorphine trial.
- HPLC determination of monoamines using an ion-pairing method with UV detection. Midbrain.
- PRELIMINARY FINDINGS!!

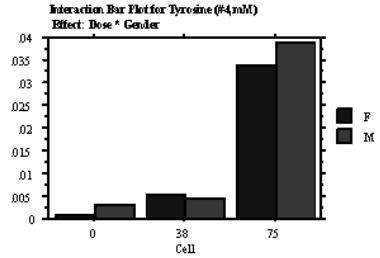
OF Behavior



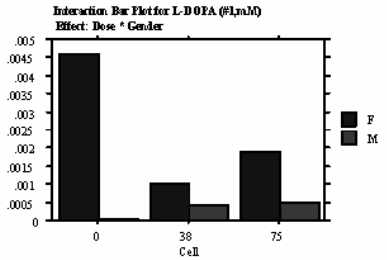
Apomorphine Effect



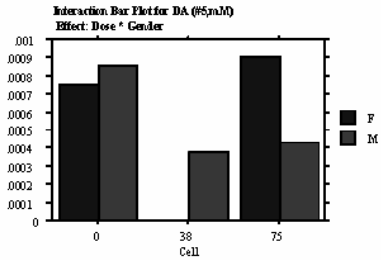
Tyrosine



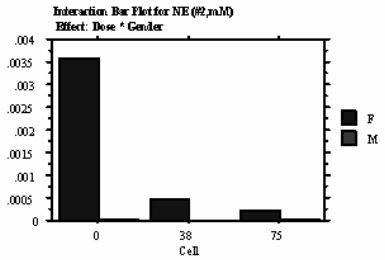
DOPA



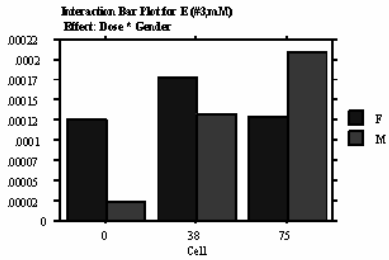
Dopamine Levels



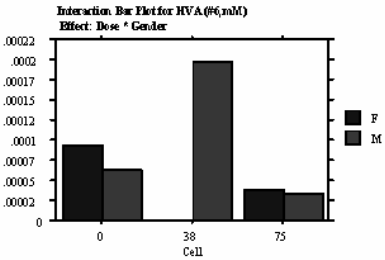
Norepinephrine



Epinephrine



HVA



Overview

- Behavioral changes in adults and developing animals
- Changes seen in two species
- Produces lipid oxidation in CNS (direct/indirect?)
- Lipid oxidation related to behavioral alterations
- Complex effects on midbrain neurotransmitter profile

Thanks

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