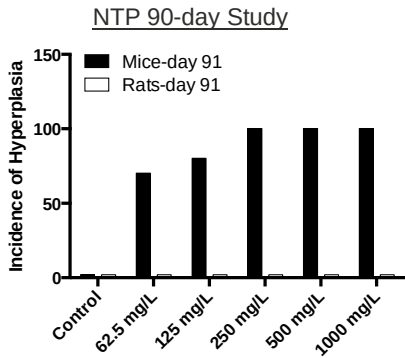


Science Question 3: Susceptibility of Mice to Gastrointestinal Toxicity

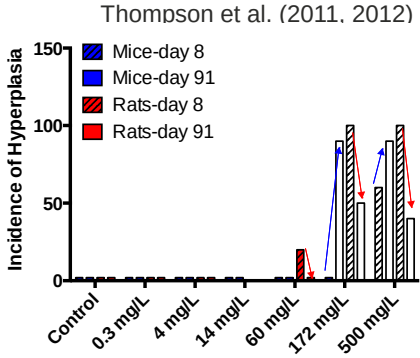
Chad Thompson, Ph.D.
ToxStrategies, Inc.
Supported by ACC
June 25, 2014

ToxStrategies

Incidence of Intestinal Hyperplasia in 90-Day Studies



Implication: mice are more susceptible than rats



Implications: mice and rats are qualitatively similar; effects in rats might have been subsiding...

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90-Day Rat Study Report Concluded:

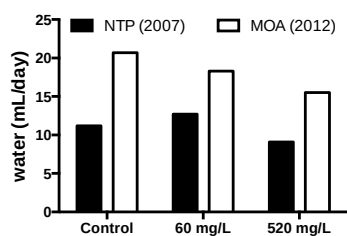
Southern Research:

"The microscopic lesions...were consistent with the type of **non-neoplastic lesions** that were observed in previous studies in... rats (histiocytic cellular infiltration) or mice (histiocytic cellular infiltration, diffuse epithelial hyperplasia) for 2 years...**In the current rat study, the intestinal lesions were more similar to lesions observed in the previous mouse study than to the previous rat study.** The reason for this discrepancy...is unknown."



- Blunting & thickening of villi
- Histiocytic cells in lamina propria of villus tips
- Elongation of crypts (regenerative hyperplasia)

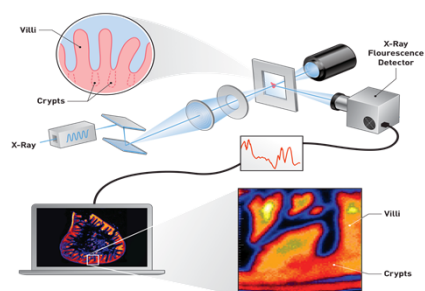
Source: Thompson et al. (2012)



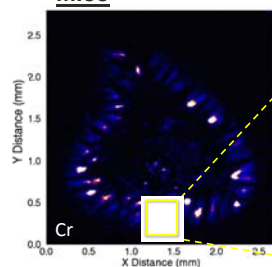
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Cr is Limited to Intestinal Villi in Both Species (Proliferation is Therefore Secondary to Villous Toxicity)

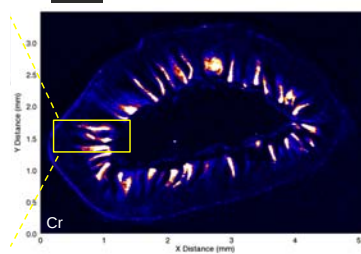
X-ray Fluorescence (Spectro)microscopy



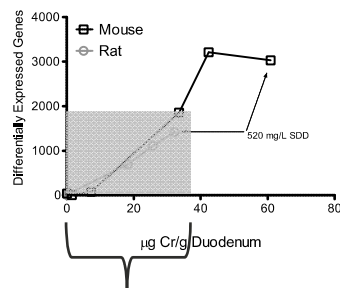
Mice



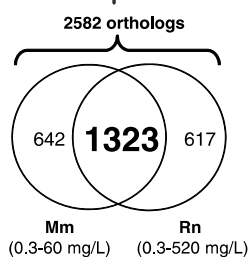
Rats



Gross Toxicogenomic Responses Similar in Both Species



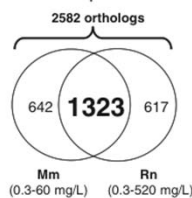
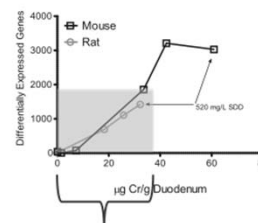
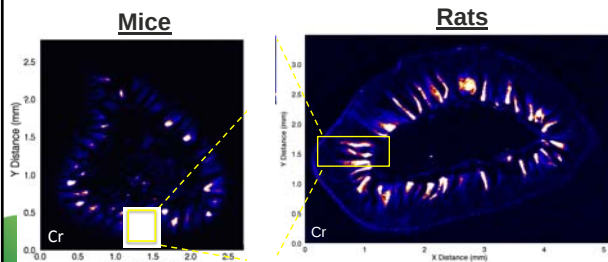
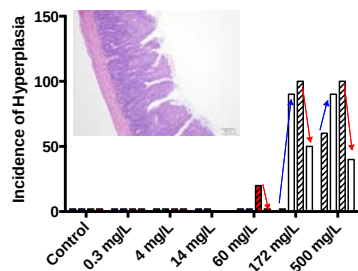
- On a tissue dose basis, Cr(VI) elicited similar number of significant differential gene changes



- Considering orthologous gene changes occurring at similar tissue dose levels, there was considerable overlap

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Rats and Mice May Be Qualitatively Similar



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