



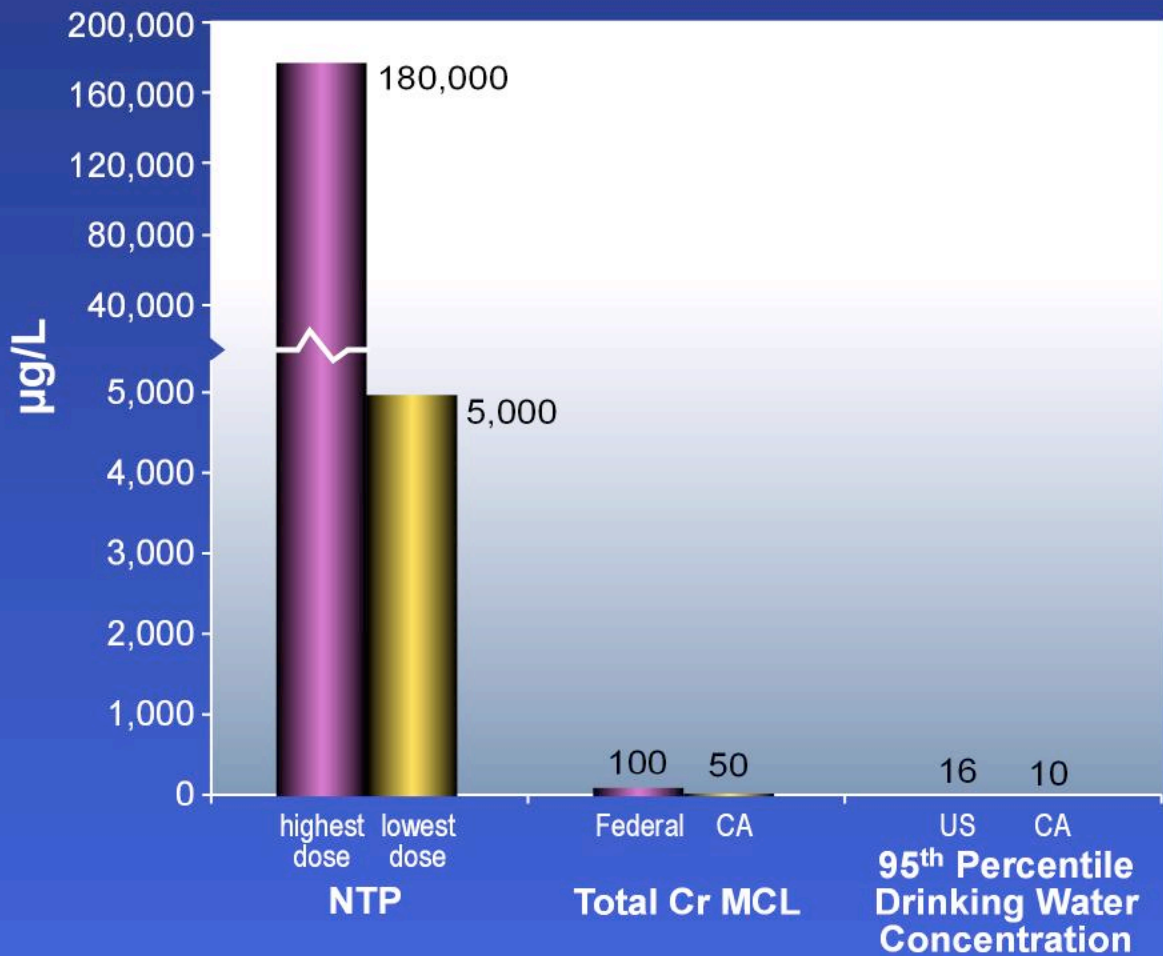
# Public Comments: Sodium Dichromate Dihydrate

**Deborah Proctor**

**Representing Tierra Solutions, Inc.**

**May 16, 2007**

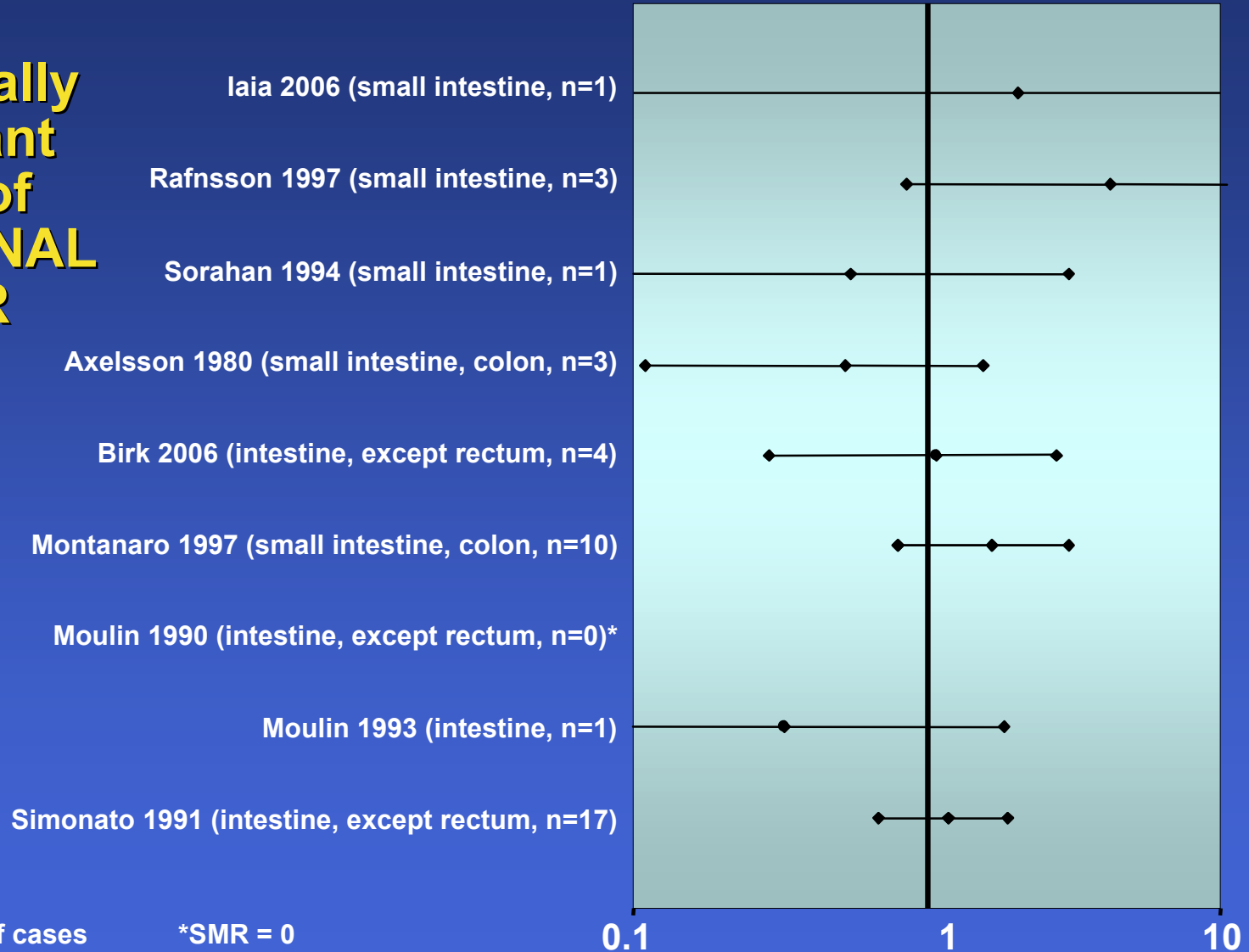
# Comparison of NTP Drinking Water Cr(VI) Concentrations with Potential Human Exposures



# Risk of Intestinal Cancers in Cr(VI)-Exposed Workers

Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals

**No  
Statistically  
Significant  
Excess of  
INTESTINAL  
CANCER  
in any  
Study**

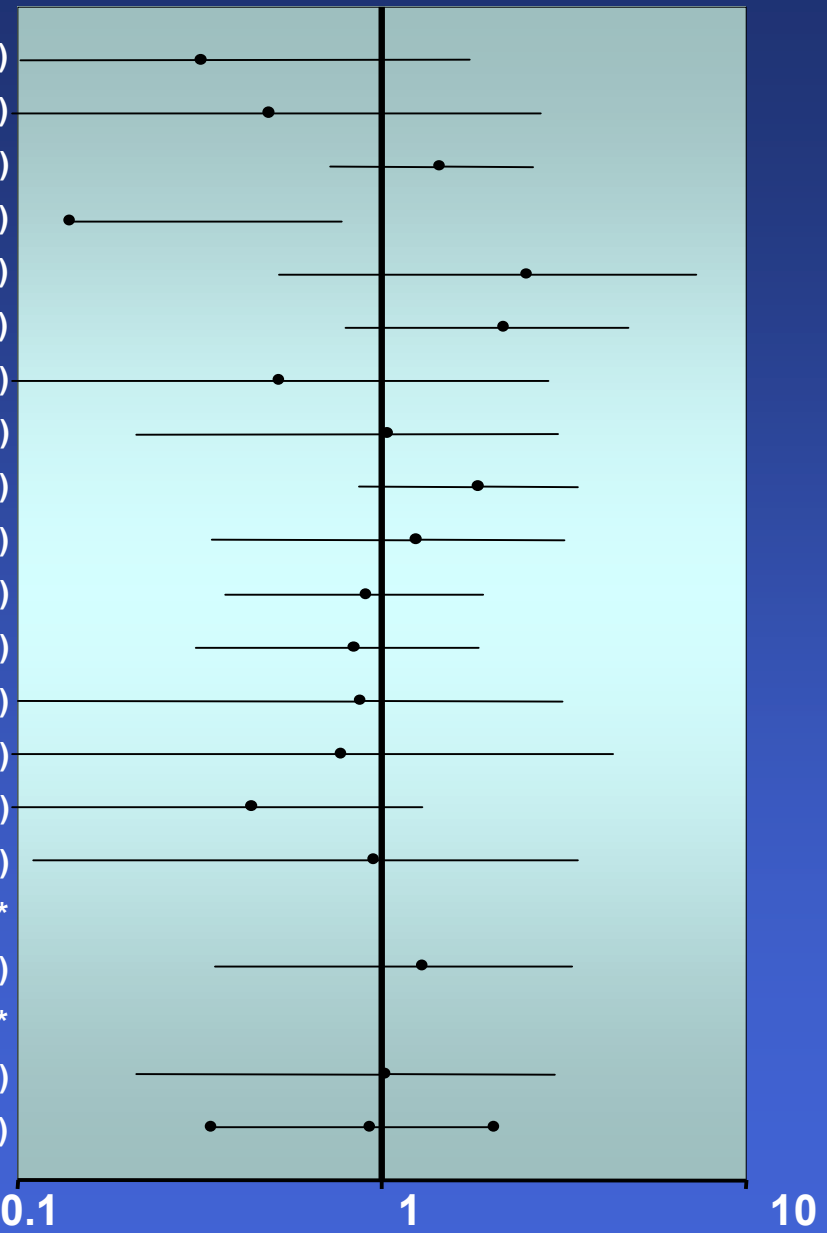


# Risk of Oral Cancers

Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals

**No  
Statistically  
Significant  
Excess of  
ORAL  
CAVITY  
CANCER  
in any  
Study**

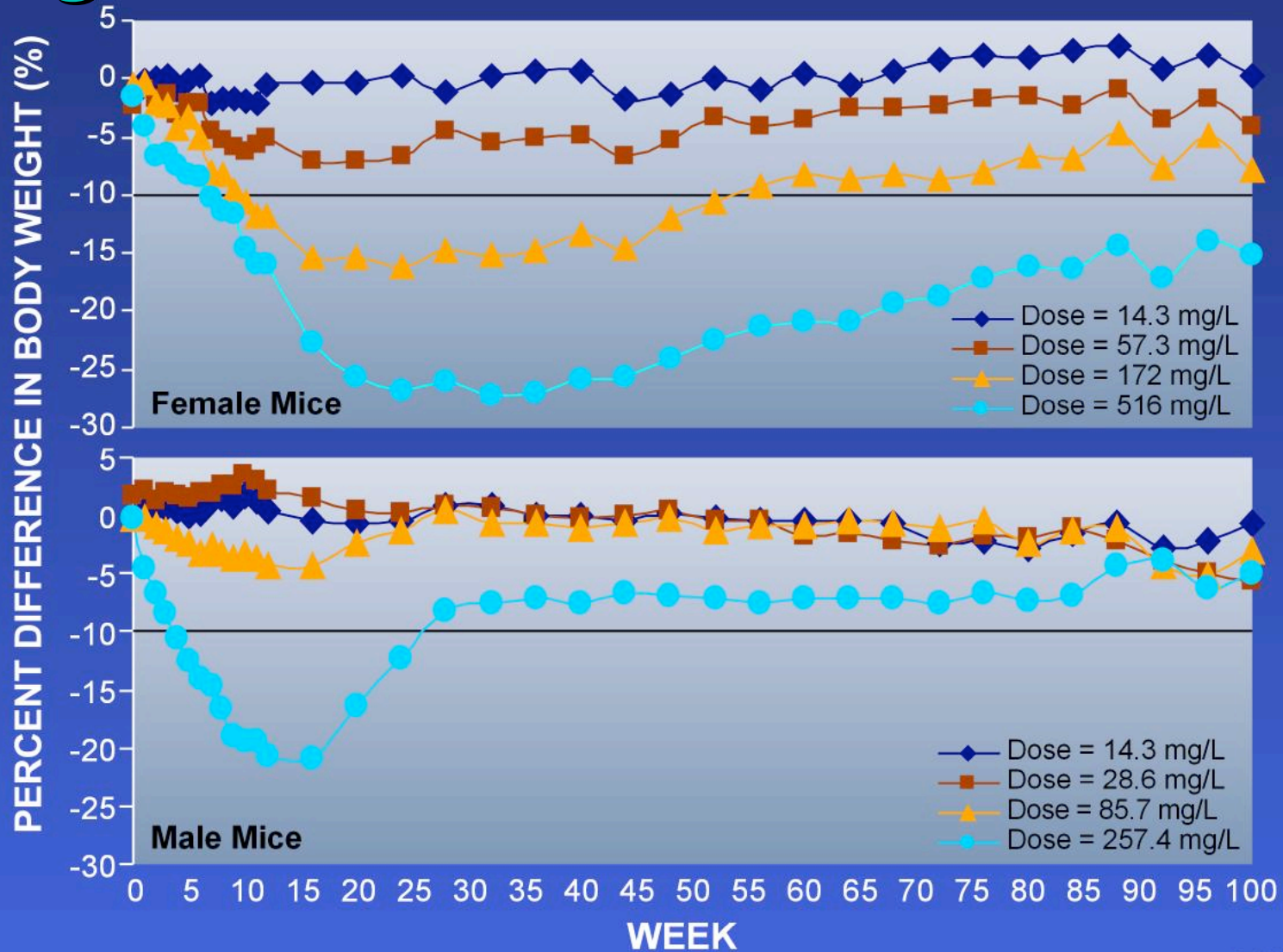
- Becker 1999 (lip, oral cavity, pharynx; n=1)
- Birk 2006 (oral cavity, pharynx; n=1)
- Blair 1980 (buccal cavity, pharynx; n=11)
- Boice 1999 (buccal cavity, pharynx; n=1)
- Dalager 1980 (buccal cavity, pharynx; n=3)
- Davies 1991 (mouth, pharynx; n=6)
- Deschamps 1995 (pharynx; n=1)
- Gibb 2000 (buccal cavity, peritoneum; n=8)
- Guberan 1989 (buccal cavity, pharynx; n=7)
- Montanaro 1997 (oral cavity, pharynx; n=4)
- Moulin 1993 (buccal cavity, pharynx; n=6)
- Moulin 1990 (buccal cavity, pharynx, larynx; n=7)
- Rafnsson 1997 (lips; n=2)
- Silverstein 1981 (buccal cavity, pharynx; n=1)
- Simonato 1991 (buccal cavity, pharynx; n=3)
- Sorahan 1987 (buccal cavity and throat; n=2)
- Sorahan 1994 (lip; n=0)\*
- Sorahan 1994 (tongue; n=4)
- Sorahan 1994 (salivary gland; n=0)\*
- Sorahan 1994 (mouth; n=3)
- Sorahan 1994 (pharynx; n=6)



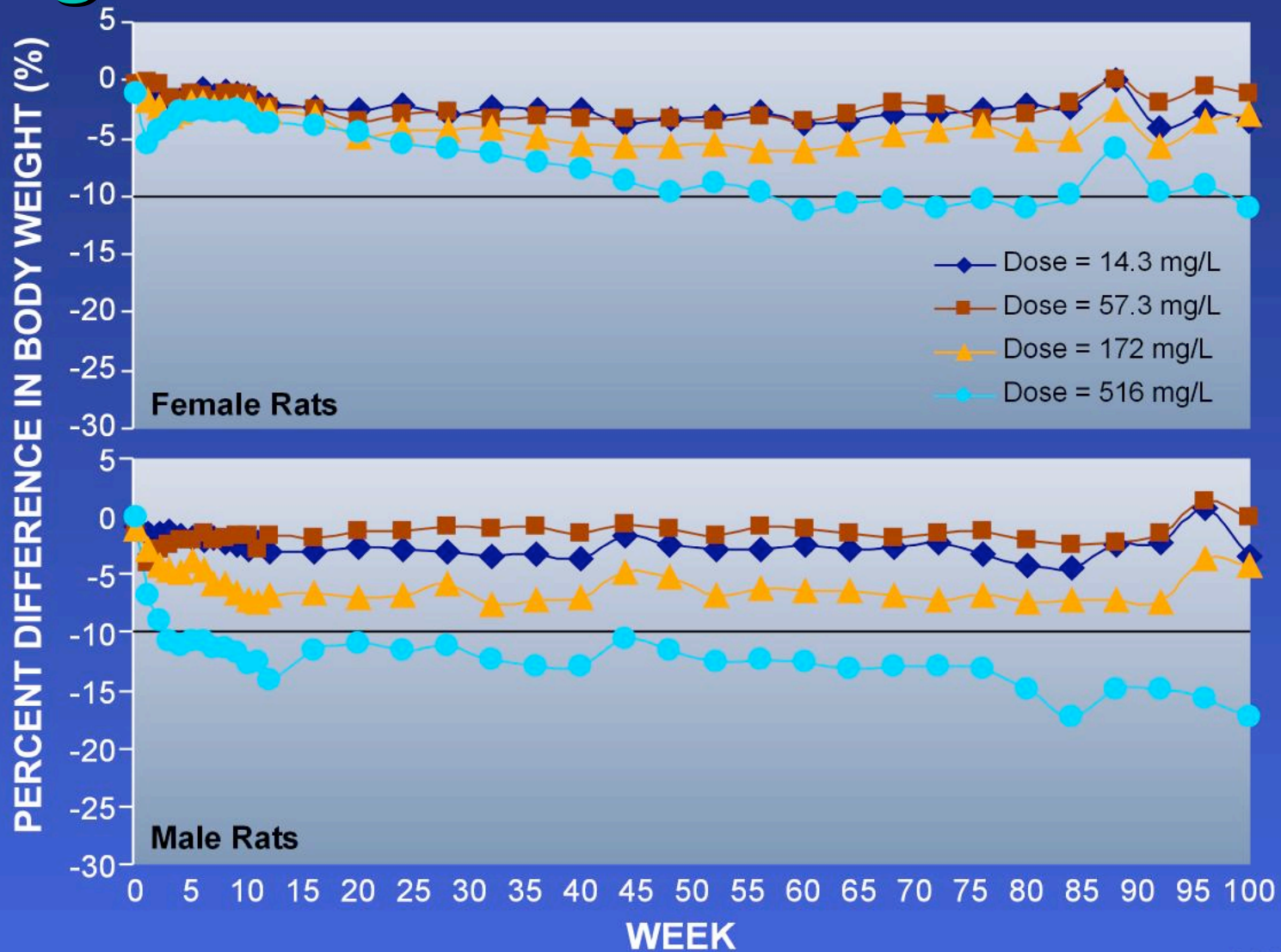
n=number of cases

\*SMR = 0

# Percent Difference in Body Weight from Control – Mice



# Percent Difference in Body Weight from Control – Rats



# Did the highest dose group exceed the maximum tolerable dose?

- Male and female rats, female mice had >10% decrease in body weight compared to controls
- Water consumption was markedly reduced (>20% rats and >30% mice)
- Poor palatability
- Dehydration affects normal physiology



# Interspecies Variability

|                      |  | <u>Human</u>  | <u>Rat</u>   | <u>Mouse</u>   |
|----------------------|--|---|--|--|
| <b>Buccal Cavity</b> | <u>Body weight</u> <sup>a</sup>              | 70 kg   | 500g   | 50 g   |
| <b>Esophagus</b>     | <u>Salivary Glands</u>                       |   |  |  |
|                      | pH   | 6.5–7.5 <sup>1,2</sup>  | 8.0–8.6 <sup>3</sup>   | 9.0–10.0 <sup>4</sup>  |
| <b>Stomach</b>       | Fraction of GI tract                         | ~33% <sup>5</sup>   | ~10% <sup>5</sup>  | ~10% <sup>5</sup>  |
|                      | Compartments                                 | <b>glandular</b>  | <b>forestomach + glandular</b>                                 | <b>forestomach + glandular</b>                                 |
|                      | pH   | 1.0–1.8 (fasting) <sup>6</sup><br>3.0–5.6 (meal) <sup>6</sup> | 5.0 (forestomach) <sup>6</sup><br>3.3 (glandular) <sup>6</sup> | 4.5 (forestomach) <sup>6</sup><br>3.1 (glandular) <sup>6</sup> |
|                      | Acid secretion rate (μEq/4h)                 | 8,000–20,000 <sup>6</sup>                                     | 440–1247 <sup>7-9</sup>  | 1–168 <sup>10-12</sup>   |
| <b>Duodenum</b>      | Indigenous microflora <sup>b</sup>           | none <sup>6</sup>   | ++ <sup>6</sup>  | +++ <sup>6</sup>   |
|                      | Emptying t <sub>1/2</sub> (min) <sup>c</sup> | 100 <sup>6</sup>  | 118 <sup>13</sup>  | 158 <sup>14</sup>  |
| <b>Jejunum</b>       | <u>Small Intestine</u>                       |   |  |  |
| <b>Ileum</b>         | Fraction of GI tract                         | ~33% <sup>5</sup>   | ~30% <sup>5</sup>  | ~30% <sup>5</sup>  |
|                      | pH   | 5–8 <sup>6</sup>  | 6.9–7.8 <sup>6</sup>   | 6.5–7.6 <sup>15</sup>  |
| <b>Cecum</b>         | <u>Large Intestine</u>                       |   |  |  |
|                      | Fraction of GI tract                         | ~33% <sup>5</sup>   | ~60% <sup>5</sup>  | ~60% <sup>5</sup>  |
| <b>Colon</b>         | pH   | 5.5–7.0 <sup>6</sup>  | 7.4–8.0 <sup>16</sup>  | 6.4–7.0 <sup>17,18</sup>                                       |
|                      |  |   |  |  |
| <b>Rectum</b>        |  |   |  |  |

a) Body weight of average adult male

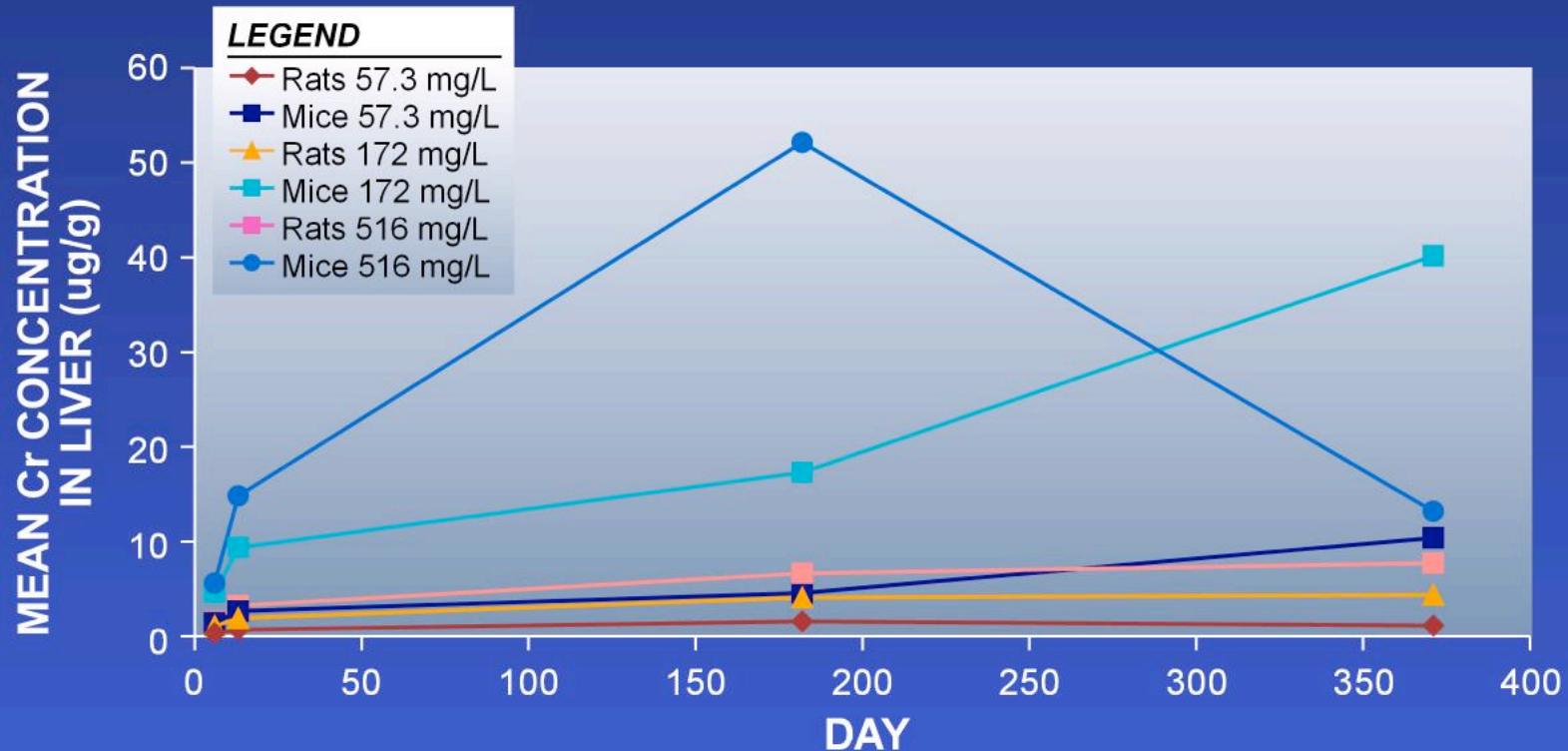
b) Log<sub>10</sub> cell viable count per gram contents of the stomach of different bacteria and protozoan species

c) Median values of gastric emptying time of solids

References provided on slides 15 and 16

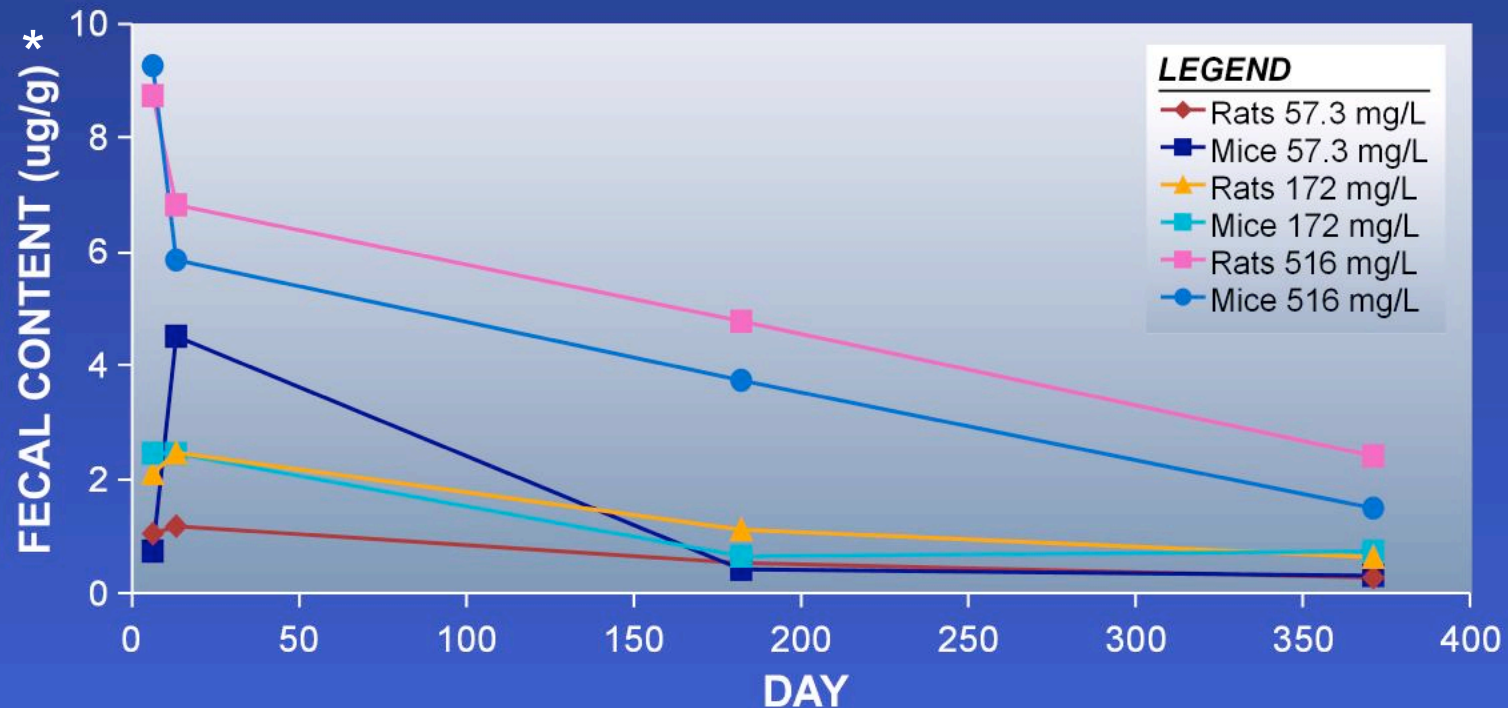


# Inter-species Variability: Mean Cr Concentrations in Liver – Female Mice and Male Rats



Demonstrates greater systemic uptake of Cr in mice than rats

# Inter-species Variability: Body-weight adjusted Cr Mass in Feces – Female Mice and Male Rats



Demonstrates greater reduction of Cr in rat GI than in mouse GI

\* Fecal Cr mass (ug) divided by mean body weight (g) throughout study to account for greater fecal mass in rats than mice

# Mode of Action for Tumor Development in Rats

- **Is dehydration a factor in the development of oral mucosa tumors in rats?**
  - Dehydration is associated with decreased saliva production (Ito et al. 2001)
  - Saliva protects oral cavity against cancer development (Dayan et al. 1997; Kaplan et al. 2002; Vered et al. 2003)
  - Lack of nonneoplastic lesions in oral mucosa suggests direct toxicity, and mutagenicity at the site of exposure is not the mode of action

# Mode of Action for Tumor Development in Mice

- **Is chronic irritation a mode of action for intestinal tumors in mice?**
  - Histiocytic infiltrations and epithelial hyperplasia are consistent with chronic irritation
  - Hyperplasia appeared consistent with adenomas
  - Relevant mode of action in other examples
    - Rodent forestomach (Poet et al. 2003, Wilkinson and Killeen 1996)
    - Human reflux esophagitis and esophageal cancer (Ribeiro et al. 1996)

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