

# Effect of Iodine Status and Gender on Perchlorate Inhibition of Iodide Uptake by the Thyroid in Adults: New Data from the Greer Study

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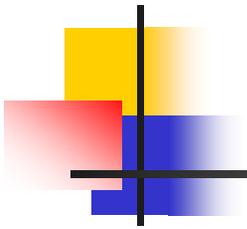
*Gay Goodman, Ph.D., D.A.B.T.*

Human Health Risk Resources, Inc., Seattle, WA

2008 Perchlorate Symposium

Seattle, March 20-21

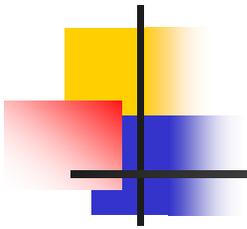
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# New and Improved

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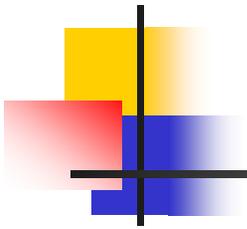
- This presentation has been expanded to address two questions raised during the Q & A period, as follows.
  - *To what extent does the effect of iodine on perchlorate inhibition of RAIU depend on the perchlorate dose metric?*
    - The dose-response model presented in the original was based simply on dose rate (units of mg/day). In the current version, model fits based on that metric are compared to those based on body-weight-adjusted dose rate (units of mg/kg-day).
  - *Is the observed effect of iodine statistically significant?*
    - The current version of the presentation provides the results of ANOVA with measures of 24-hr iodine excretion (IE) included as independent variables. A linearized version of the original model, likewise categorized by IE, is presented to facilitate statistical review of IE interaction effects.



# The Greer Study: Acknowledgements

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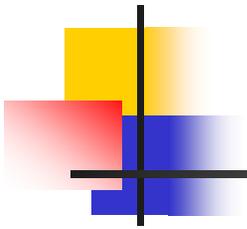
- Principal investigator: Prof. Monte A. Greer (deceased), OHSU.
- Co-investigator: Dr. Gay Goodman.
- Clinical coordinator: Ms. Susan E. Greer.
- Funding arranged by Dr. Richard C. Pleus.
- Greer *et al.* (2002), EHP 110: 927-937: written by Dr. Goodman and Prof. Greer; all data analyses by Dr. Goodman.
- As acknowledged in Greer *et al.* (2002): “The protocol was developed by G.G., M.A.G., and R.C.P. with the substantial contribution of D. Mattie and J. Fisher of the Air Force Research Laboratory and A. Jarabek of the U.S. Environmental Protection Agency.”



# The Greer Study: A Clinical Exposure Study

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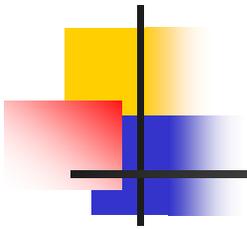
- Subjects: 37 adult volunteers.
- Perchlorate doses: 0.007, 0.02, 0.1, and 0.5 mg/kg-day.
- Perchlorate exposure duration and frequency:
  - Fourteen-day exposure via drinking water.
  - One-fourth dose at four fixed times each day.



# The Greer Study: RAIU

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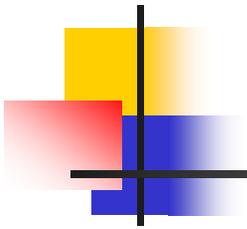
- In 24 subjects (main study):
  - 8-hr and 24-hr radioiodine uptake (RAIU) by the thyroid: baseline, exposure days 2 and 14, and 2 weeks post-exposure.
- In 13 additional subjects (add-on uptake study):
  - 8-hr RAIU: baseline and exposure day 14.
  - 24-hr RAIU: baseline, exposure day 14, and 2 weeks post-exposure.



# The Greer Study: Published Data; Unpublished Data

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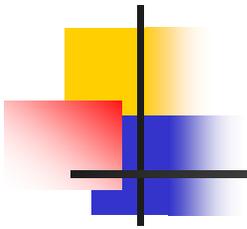
- Published in Greer *et al.* 2002 (EHP):
  - Thyroidal RAIU results.
  - Results of serum tests of thyroid function, clinical chemistry, and urinalysis.
- Unpublished as of March 2008:
  - Urinary perchlorate data; serum perchlorate data.
  - Urinary iodine data.



## Greer Study: post-2002 Analyses

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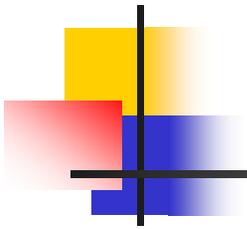
- Perchlorate analyses: Dr. David Mattie and colleagues at Air Force Research Laboratory.
- Iodine analyses: Prof. Lewis Braverman and colleagues at Boston Medical Center.
- Goodman's iodine-dependent model of perchlorate inhibition of RAIU in the Greer study:
  - Basis of Crump & Goodman (2004) benchmark dose analysis (submitted to NAS/NRC Committee).
  - Effect of sex not considered!



# Greer Study: Influence of Baseline RAIU on Perchlorate Inhibition of RAIU

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- *Earlier analysis submitted to the NAS/NRC Committee:*
  - In all subjects combined, the higher the baseline RAIU, the greater the inhibitory effect of perchlorate.
  - Linked to the overall dependence of the baseline RAIU on iodine intake.
- *The present analysis:* Categorization by sex.



# Greer Study: Framing the New Analyses

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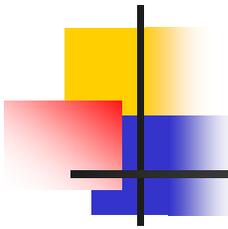
- Problem with sex as a covariate:
  - Low-dose group (0.007 mg/kg-day): 6 women, 1 man.
    - Cannot analyze effect of sex in low-dose group.
- However, can analyze:
  - Sex differences in baseline parameters for the entire study population (N = 37).
  - Exposure-related effects in women separately.
  - Influence of iodine on exposure-related effects in women separately.

*Background Basics:*

## Perchlorate and Iodide in the Thyroid: A Two-Way Street

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- Iodine (in the form of iodide) is taken up the thyroid for incorporation into thyroid hormone.
- Perchlorate inhibits iodide uptake by the thyroid.
- Iodide modulates perchlorate inhibition of iodide uptake.

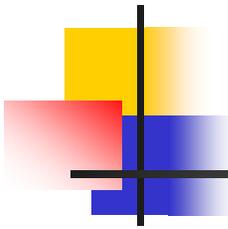


*Background Basics:*

## Perchlorate: Mechanism and Site of Action

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- Perchlorate ( $\text{ClO}_4^-$ ) and other monovalent anions that are structurally similar to iodide ( $\text{I}^-$ ):
  - Competitively inhibit the uptake of iodide by the thyroid and other tissues that concentrate iodide.
- The sodium-iodide symporter is the site of this inhibition in all tissues that concentrate iodide.

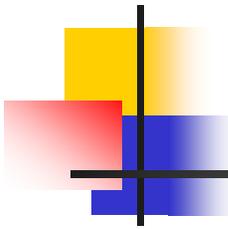


*Background Basics:*

## Effect of Iodide on Perchlorate Activity

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- Iodide modulates perchlorate inhibition of iodide uptake.
  - The nature of competitive inhibition is such that the inhibitory effect of perchlorate must be modified by the ratio of serum iodide to serum perchlorate.
    - Therefore, the dose-response for perchlorate inhibition of iodide uptake is expected to depend in some fashion on the ratio of serum iodide to serum perchlorate.

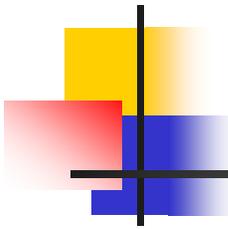


*Background Basics:*

## Urinary Iodine as a Measure of Iodine Status

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- The 24-hr urinary I excretion ( $\mu\text{g}$ ) is a useful surrogate for daily I intake.
- The 24-hr urinary I excretion is a more accurate and more precise measure of I intake than:
  - I concentrations in spot urine samples ( $\mu\text{g}/\text{L}$ ).
  - I concentrations in spot urine samples adjusted for creatinine to approximate 24-hr collection ( $\mu\text{g}$  per gram creatinine).

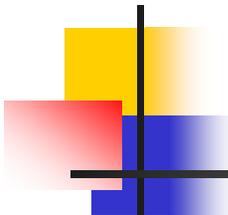


*Background Basics:*

## **RAIU Depends on Iodine Intake**

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- In sampled populations, the fraction of administered radioiodine taken up by the thyroid has been shown to decrease with increasing iodine in the food supply.
  - Explanation: With increasing levels of iodine in the diet, the thyroid requires a smaller proportion of the ingested iodine.

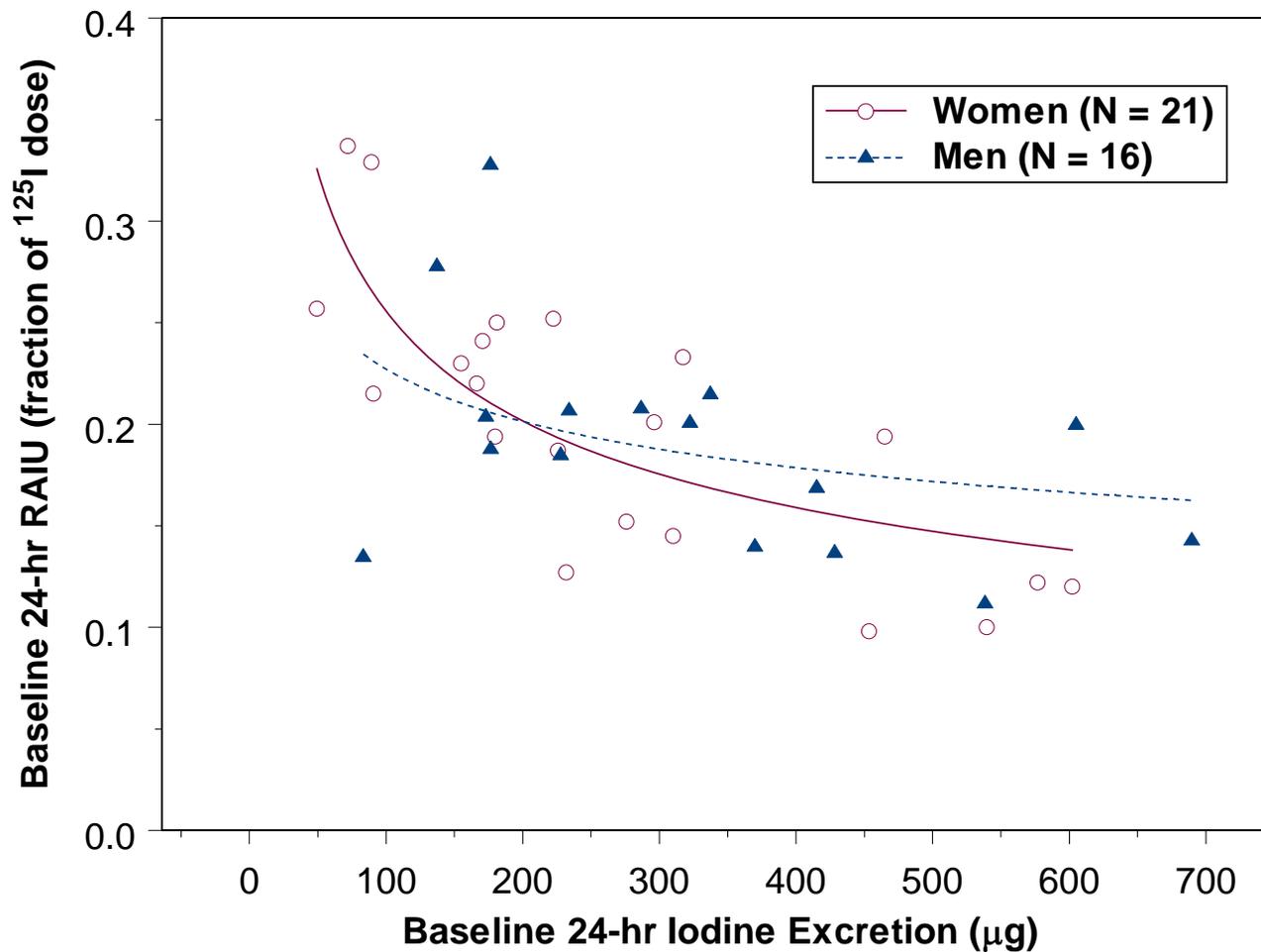


## Greer Study Pre-exposure: Effect of Iodine Excretion on RAIU at Baseline, by Sex

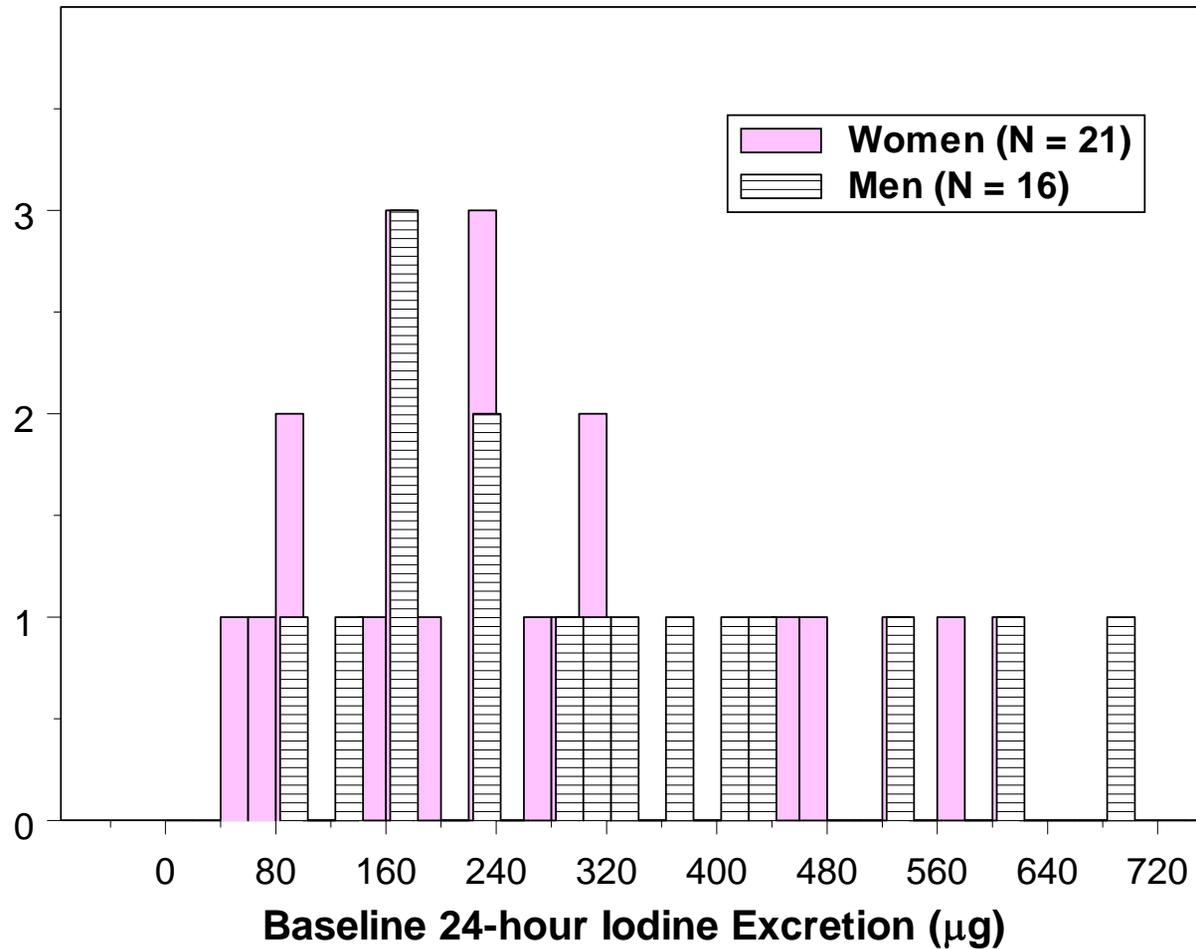
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- The new data show:
  - The dependence of the pre-exposure (baseline) radioiodine uptake ( $\text{RAIU}_b$ ) on the pre-exposure (baseline) iodine excretion ( $\text{IE}_b$ ) is stronger and less variable in the women than in the men.
- Data fitted to the model:  $\text{RAIU}_b = a (1/\text{IE}_b)^x$ 
  - Fitted values of  $a$  and  $x$  ( $\pm$  standard error):
    - In the women,  $a = 1.2 \pm 0.4$ ;  $x = 0.34 \pm 0.07$
    - In the men,  $a = 0.50 \pm 0.34$ ;  $x = 0.17 \pm 0.12$

## Baseline RAIU as a Function of Baseline Iodine Excretion



## Histogram Distribution of Subjects by Baseline Iodine Excretion

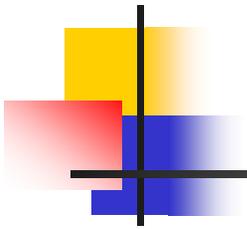


# Greer Study: Effect of Iodine on Perchlorate Inhibition of RAIU, by Sex: ANOVA

**ANOVA: Effect of perchlorate dose (mg/day or mg/kg-day), baseline iodine excretion ( $IE_b$ ), and exposure-day-14 iodine excretion ( $IE_{e14}$ ) on the 24-hr RAIU ratio (e14/baseline)**

	<i>Females</i> N = 21		<i>Males</i> N = 16	
Dose variable:	<u>mg/day</u>	<u>mg/kg-day</u>	<u>mg/day</u>	<u>mg/kg-day</u>
RSE <sup>§</sup>	0.180	0.172	0.167	0.161
	<u><i>p value</i></u>		<u><i>p value</i></u>	
1/dose	<0.00004	<0.00001	0.001	0.001
1/ $IE_b$	0.007	0.01	ns (>0.3)	ns (>0.2)
1/ $IE_{e14}$	ns (>0.6)	ns (>0.8)	0.05	0.05

<sup>§</sup>RSE, Residual standard error



## Greer Study: ANOVA Results for Perchlorate and Iodine Effects on RAIU, by Sex

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- Results of ANOVA in the women:
  - **The RAIU ratio (e14/baseline)** depends on baseline IE ( $IE_b$ ) but not on exposure-day 14 IE ( $IE_{e14}$ ).
- Results of ANOVA in the men:
  - The RAIU ratio (**e14/baseline**) depends on  $IE_{e14}$  but not on  $IE_b$ . The dependence of the RAIU ratio on  $IE_{e14}$  may reflect an effect of perchlorate on iodine absorption, excretion, or both.
  - Because the baseline RAIU was not dependent on  $IE_b$  in the men, is difficult to interpret the absence of an effect of  $IE_b$  on the RAIU ratio.
- The two dose metrics (mg/day and mg/kg-day) yielded similar ANOVA results.

## Greer Study:

### Dose-response (mg/day) for RAIU Inhibition in the Women, by IE<sub>b</sub>

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Perchlorate dose-response model:

$$24\text{-hr RAIU Ratio (e14/baseline)} = a (1/\text{dose})^x$$

where **a** and **x** are fitted parameters.

Dose in units of mg/day

Low IE<sub>b</sub>: 49 to 91 μg (n = 4):

$$a = 0.68 \pm 0.13; x = 0.17 \pm 0.09$$

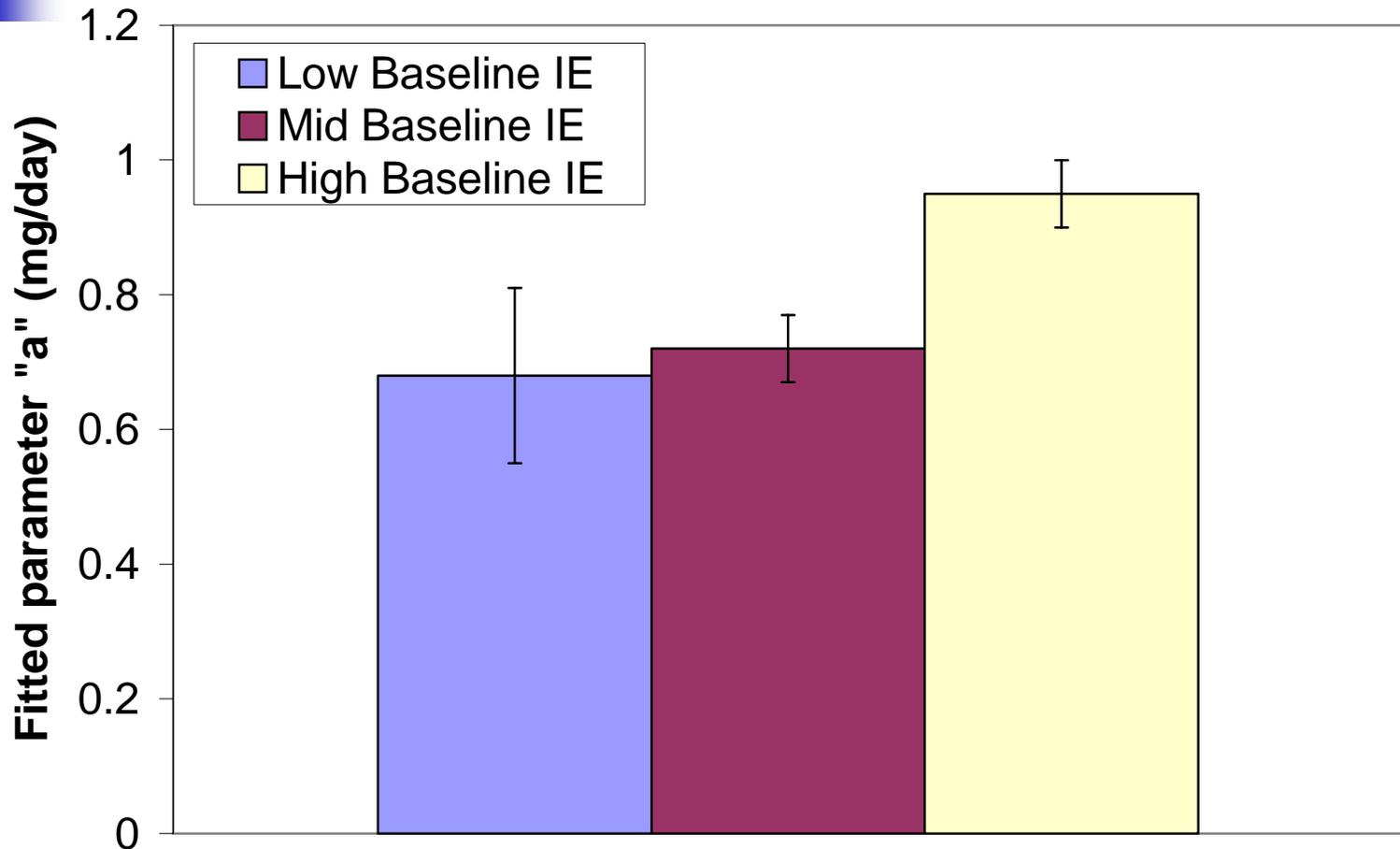
Mid IE<sub>b</sub>: 155 to 181 μg (n = 5):

$$a = 0.72 \pm 0.05; x = 0.22 \pm 0.05$$

High IE<sub>b</sub>: 222 to 602 μg (n = 12):

$$a = 0.95 \pm 0.05; x = 0.22 \pm 0.05$$

# Fit to Nonlinear Model in the Women, by Baseline IE: Dose in mg/day



## Greer Study:

### Dose-response (mg/kg-day) for RAIU Inhibition in the Women, by IE<sub>b</sub>

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Perchlorate dose-response model:

$$24\text{-hr RAIU Ratio (e14/baseline)} = a (1/\text{dose})^x$$

where **a** and **x** are fitted parameters.

Dose in units of mg/kg-day

Low IE<sub>b</sub>: 49 to 91 μg (n = 4):

$$a = 0.32 \pm 0.13; x = 0.18 \pm 0.10$$

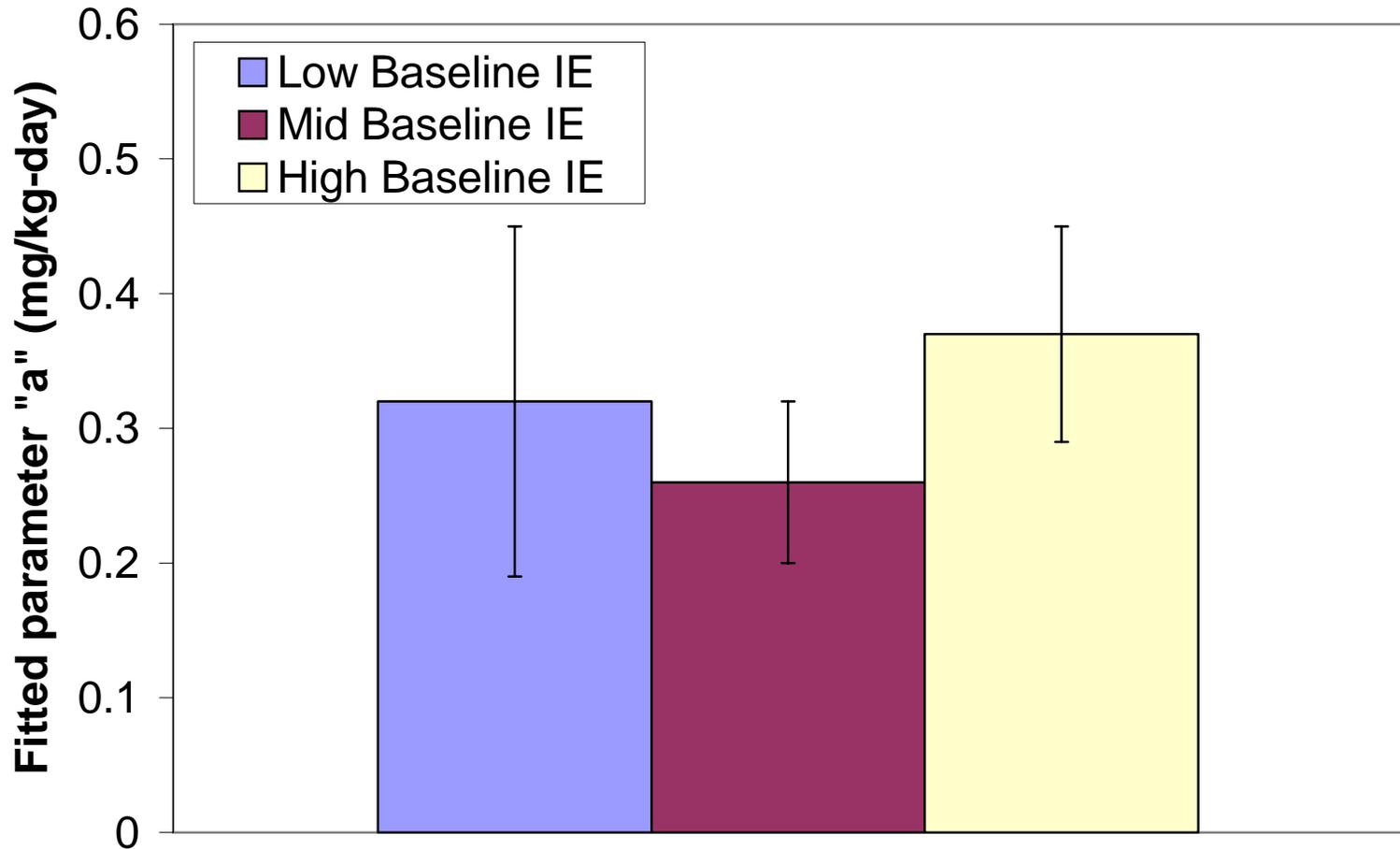
Mid IE<sub>b</sub>: 155 to 181 μg (n = 9):

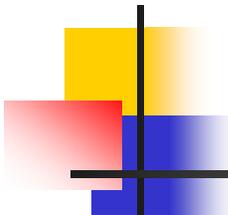
$$a = 0.26 \pm 0.06; x = 0.24 \pm 0.05$$

High IE<sub>b</sub>: 222 to 602 μg (n = 12):

$$a = 0.37 \pm 0.08; x = 0.22 \pm 0.05$$

## Fit to Nonlinear Model in the Women, by Baseline IE: Dose in mg/kg-day





## IE<sub>b</sub> Dependence of the Dose-response for RAIU Inhibition in the Women: Conclusions Regarding the Dose Metric

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- When the perchlorate dose is expressed in units of **mg/day**, nonlinear dose-response modeling of the women's data yields results *consistent with the ANOVA findings* (significant effect of IE<sub>b</sub> on the RAIU ratio).
- When the perchlorate dose is expressed in units of **mg/kg-day**, nonlinear dose-response modeling of the women's data yields results *inconsistent with the ANOVA findings* (no significant effect of IE<sub>b</sub> on the RAIU ratio).

## Greer Study:

### Dose-response for RAIU Inhibition in the Women, by $IE_b$ : Linearized Model

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Nonlinear perchlorate dose-response model:

$$y = a (1/\text{dose})^x$$

where  $y$  is the 24-hr RAIU Ratio (e14/baseline)  
and both  $a$  and  $x$  are fitted parameters.

Log transformation to linearize:

$$\ln y = \ln a + x \ln (1/\text{dose})$$

$$\text{Intercept} = \ln a$$

$$\text{Slope} = x$$

## Greer Study:

# Dose-response for RAIU Inhibition in the Women, by IE<sub>b</sub>: Linearized Model Results

$\ln y = \ln a + x \ln (1/\text{dose})$ , dose in units of mg/day

- *Note:* The dose-response for the low IE<sub>b</sub> group ( $\leq 91 \mu\text{g}$ ) was indistinguishable from that of the mid IE<sub>b</sub> group (155-181  $\mu\text{g}$ ).

Low + Mid IE<sub>b</sub>: 49 to 181  $\mu\text{g}$  (n = 9):

$$\ln a = -0.31 \pm 0.12 (p = 0.03) <====*$$

$$x = 0.25 \pm 0.05 (p = 0.001)$$

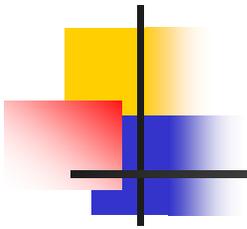
High IE<sub>b</sub>: 222 to 602  $\mu\text{g}$  (n = 12):

$$\ln a = -0.074 \pm 0.060 (\text{ns}, p > 0.2) <====*$$

$\Rightarrow a$  is indistinguishable from 1.

$$x = 0.20 \pm 0.03 (p = 0.0002)$$

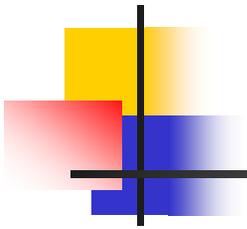
\* Significant difference in  $\ln a$  for these two IE categories



## Conclusions, I

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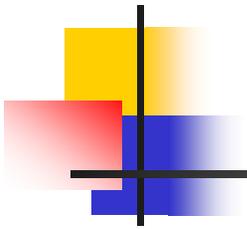
- Because perchlorate is a small charged molecule, is not metabolized, and is excreted quantitatively in the urine, when comparing exposure doses among same-sex adults of typical (or otherwise similar) height the simple exposure rate (mg/day) may be a better surrogate for perchlorate serum levels than the body-weight adjusted exposure rate.
- Much of the dose-response variability observed in the Greer study is attributable to sex differences in the dependence of the baseline radioiodine uptake on the baseline 24-hr urinary iodine excretion.



## Conclusions, II

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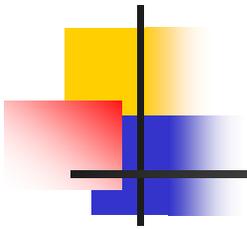
- Analyzing women separately and categorizing by baseline iodine excretion, it can be shown that lower iodine intake is associated with increased sensitivity to perchlorate inhibition of iodide uptake.
- Based on preliminary dose-response modeling of limited data, a perchlorate dose of 0.4 mg/day (0.007 mg/kg-day in a 60-kg woman) is predicted to inhibit iodide uptake by approximately 10 to 20% (depending on the model employed) in women with 24-hr iodine excretion (IE) of 50 to 180  $\mu\text{g}$ .
- No significant difference in the effect of iodine was found between women with 24-hr IE of 50 to 90  $\mu\text{g}$  and those with 24-hr IE between 155 and 180  $\mu\text{g}$ .



## Points to Consider, I

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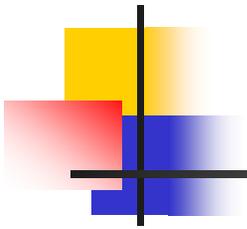
- Blount et al. (2006) performed spot urine collections whereas the Greer study performed 24-hr collections, which provide greater accuracy and precision in estimating daily iodine intake. Because of the greater variability of spot urines, it seems plausible that a large percentage of Blount et al.'s women with spot urine iodine concentrations  $< 100 \mu\text{g/L}$  had 24-hr urinary iodine excretion above  $150 \mu\text{g}$ .



## Points to Consider, II

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- When evaluating the potential health effects of perchlorate as a function of iodine intake, it is helpful to consider that inhibition of iodide uptake by naturally occurring goitrogens (including nitrate, thiocyanate, and perchlorate) has been built into the human requirement for iodine throughout our natural history.
  - With increasing concentrations of natural goitrogens in the diet or drinking water the dietary iodine requirement will increase, with no consequence as long as the need for iodine is met.



## Points to Consider, III

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- Ensuring iodine sufficiency in women of child-bearing age irrespective of their exposures to perchlorate or other goitrogens would be of great benefit to public health and at the same time eliminate any potential health risks related to perchlorate exposures.