

**Comments on the *OIG Scientific Analysis of Perchlorate*
(*External Review Draft*) dated December 30, 2008**

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General Comments

Rather than define the risk in terms of *low* total iodide uptake, consider defining the risk in terms of *a sustained, inhibitor-related decrease* in iodide uptake when dietary iodine is insufficient to make up the shortfall. Iodide uptake (IU) is measured as the accumulation of radioactive iodine by the thyroid over a fixed time period. Low IU values are associated with abundant iodine nutrition. Thus, low IU values are a normal homeostatic response to abundance and are not a risk factor. High IU values are associated with low or marginal iodine nutrition. Investigators in Birmingham, Alabama observed that between 1959 and the years 1967-1968 the average 24-hr radioiodine uptake measured in euthyroid patients dropped by nearly one-half and that this decline could be explained by the fact that the iodine content of commercial white bread had increased to approximately 150 µg per slice upon the introduction of a new bread-making process (Pittman, Jr. *et al.*, 1969). Eventually, the bread-making process that produced high iodine content in white bread became prevalent throughout the country. Studies conducted in a number of US cities in the early to mid-1970s reported decreased radioiodine uptake in euthyroid subjects and noted that population variation in dietary iodine, whether geographic, ethnic, or chronologic, must be considered when establishing a normal range of radioiodine uptake for diagnostic purposes (Caplan *et al.*, 1971; Sachs *et al.*, 1972; Nelson *et al.*, 1970; Robertson *et al.*, 1975). In Minneapolis, when the bread-making process changed a second time such that the average iodine content dropped to 26 µg per slice, this decrease in iodine content was accompanied by an increase of more than 75% in the average radioiodine uptake measured in euthyroid subjects between 1971 and 1975 (Wong and Schultz, 1977).

When dietary iodine is low or marginal over a period of time, the question is whether a given inhibitor-related decrease in IU might lead to depletion of iodine stores. The role of the risk assessment process is to identify, for a given range of inhibitor doses (and IU inhibition), the iodine intake below which a homeostatic increase in IU is unable to sufficiently compensate for the inhibition. The cumulative risk assessment process should carefully distinguish between low IU associated with high iodine intake (not a health risk) and a sustained, inhibitor-related decrease in IU from an initially high value in the presence of sustained dietary iodine insufficiency.

The word “total” does not appear to be especially helpful or informative in the context of iodide uptake. Consider instead identifying the uptake as thyroidal iodide uptake (TIU), iodide uptake by the thyroid (IUT) or just iodide uptake (IU).

Comments and Recommendations Based on New Analyses

New analyses from a perchlorate exposure study in 21 women and 16 men (the Greer study) provide overall support for a cumulative risk assessment approach to characterize the health risks of exposures to perchlorate and other inhibitors of iodide uptake in the most sensitive population subgroups, pregnant and lactating women.

A. The Greer Study and Acknowledgements

A perchlorate exposure study was conducted by Dr. Monte Greer (principal investigator, deceased), Dr. Gay Goodman (co-investigator) and Ms. Susan Greer (study coordinator). The radioiodine uptake (RAIU) results were published (Greer *et al.*, 2002) before data on urinary iodine, urinary perchlorate, and serum perchlorate were available.

Measurement of iodine in urine samples from all 37 study subjects was performed by Mr. Sam Pino and Mr. Michael Previti under the supervision of Dr. Lewis Braverman at Boston Medical Center. The present author calculated 24-hr urinary iodine excretion data based on these measurements and performed statistical and modeling analyses in an attempt to refine the dose response for perchlorate inhibition of iodide uptake. Several key results of those analyses are discussed in Section B of the present commentary.

Measurement of perchlorate in serum and urine samples from 8 or fewer subjects per group in the 0.02, 0.1, and 0.5 mg/kg-day dose groups was performed by scientists at the Air Force Research Laboratory (AFRL) under the supervision of Dr. David Mattie. The analytical method employed was not sensitive enough to allow measurement of serum perchlorate levels in the 0.02 mg/kg-day dose group. Urinary perchlorate was measured in 20 subjects, including 5 subjects in the 0.02 mg/kg-day group; these data were utilized by AFRL for pharmacokinetic modeling (Merrill *et al.*, 2005). The serum and urinary perchlorate data are not discussed further in the present commentary.

B. Summary of Study Results and Related Recommendations

1. Perchlorate has a greater inhibitory effect on radioiodine uptake (RAIU) in women and men with high baseline 24-hr radioiodine uptake ($RAIU_B$) than in those with low $RAIU_B$.
2. $RAIU_B$ decreases with increasing baseline 24-hr urinary iodine excretion (IE_B), a surrogate for the daily iodine intake. This relationship is more robust in the women than in the men.
3. In the women but not the men, the dose-related perchlorate inhibition of RAIU increases with increasing IE_B .
4. Describing the dose-dependence of perchlorate effects in terms of an absolute change in RAIU (post-exposure minus baseline) rather than as a relative change (ratio of post-exposure to baseline) facilitates correction for the modulating influences of $RAIU_B$ and IE_B and makes sense for other reasons (see below).
5. In the 37 subjects studied, IE_B values above 300 μg are associated with $RAIU_B$ values (measured as a fraction of the radioactive iodine ingested) between 0.10 and 0.23 (average = 0.155) and IE_B values below 200 μg are associated with $RAIU_B$ values between 0.13 and 0.34 (average = 0.243). Consider an absolute decrease of 0.031 from the average $RAIU_B$ values in the high- and low-IE subpopulations thus defined. This equates to 20% and 13% $RAIU_B$ decreases for the subpopulations with high IE and low IE, respectively. Thus, any description of effects in terms of relative rather than absolute change inconveniently weights the region of the IE distribution corresponding to people who are not at risk.

6. The results support taking account of the magnitude of iodide uptake as well as the daily iodine intake when assessing the health risks of exposures to perchlorate and other inhibitors of iodide uptake in a given female subpopulation.

C. Overview of Relevant Results

The effect of perchlorate can be described as the relative change in the 24-hr radioiodine uptake between baseline and exposure day 14 (the RAIU ratio) or the absolute change in the 24-hr radioiodine uptake between baseline and exposure day 14 (Δ RAIU). As shown in Figure 1A for the women and men considered separately and as reported by Greer *et al.* (2002) for the sexes combined, the RAIU ratio is linearly dependent on the logarithm of the perchlorate dose. Similarly, as shown in Figure 1B for both the women and the men, Δ RAIU is linearly dependent on the logarithm of the perchlorate dose. The results of applying linear regression analysis to the two models are shown in Tables 1 and 2 for the women and the men, respectively. For both sexes the multiple R-squared is greater and the p-value is smaller when the dependent variable is the RAIU ratio, indicating that this is a better metric than Δ RAIU for describing the dose-dependence of the uncorrected data. However, as discussed below, Δ RAIU appears appear to be a somewhat better metric when the data are corrected for the influence of the baseline 24-hr radioiodine uptake (RAIU_B).

In Figure 2, Δ RAIU is plotted against RAIU_B for the women at each of the four doses tested, 0.007, 0.02, 0.1, and 0.5 mg/kg-day. There is a negative linear trend (decrease in Δ RAIU with increasing RAIU_B) in the women at all four doses and the relationship achieves statistical significance in the 0.007 and 0.5 mg/kg-day groups ($p = 0.0007$ and $p = 0.006$, respectively).

Because only one man was assigned to the lowest dose group, statistical analysis is limited to the three remaining doses (0.02, 0.1, and 0.5 mg/kg-day). There is a negative linear trend in the men at all three doses and the relationship achieves statistical significance in the 0.02 and 0.5 mg/kg-day groups ($p = 0.05$ and $p = 0.03$, respectively; data not shown).

In the Greer study, the daily iodine intake was estimated as the baseline 24-hr urinary iodine excretion (IE_B). Figure 2 also shows, in a semi-quantitative fashion, the interaction between the baseline 24-hr iodine excretion (IE_B) and the RAIU_B in the women. It can be seen that the distribution of IE_B levels $< 300 \mu\text{g}$ is dramatically skewed to higher RAIU_B values. The median RAIU_B value in the women is 0.201. IE_B values are below $300 \mu\text{g}$ in 10 of the 11 women with RAIU_B values greater than or equal to 0.201 as compared to 4 of the 10 with RAIU_B values less than 0.201.

The distribution of IE_B values in the men is less skewed (data not shown). The median RAIU_B value in the men is 0.194. IE_B values are below $300 \mu\text{g}$ in 5 of the 8 men with RAIU_B values greater than 0.194 as compared to 3 of the 8 with RAIU_B values less than 0.194.

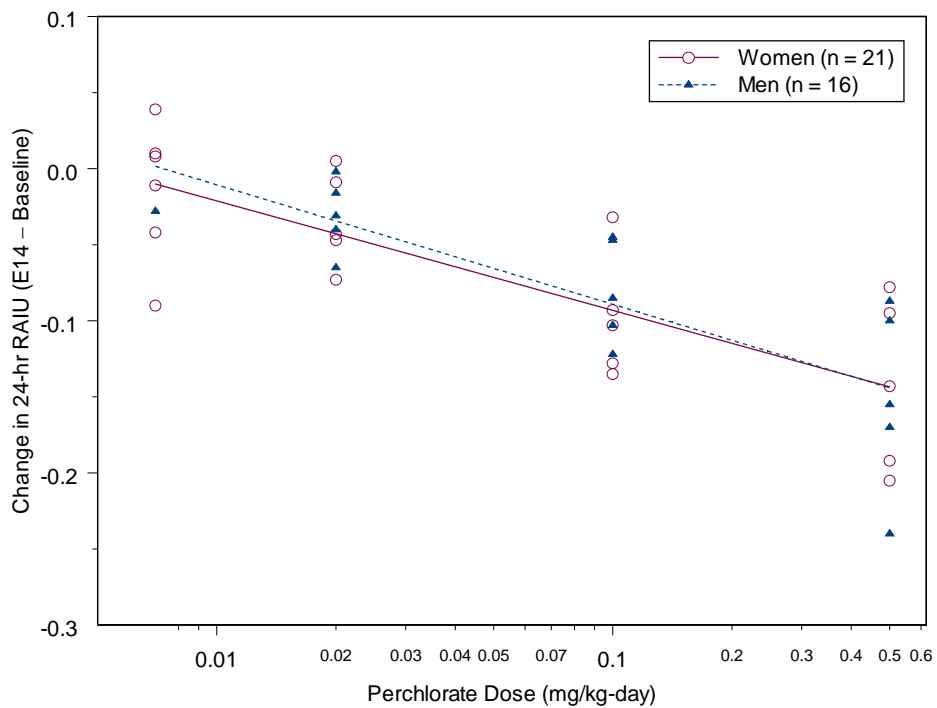
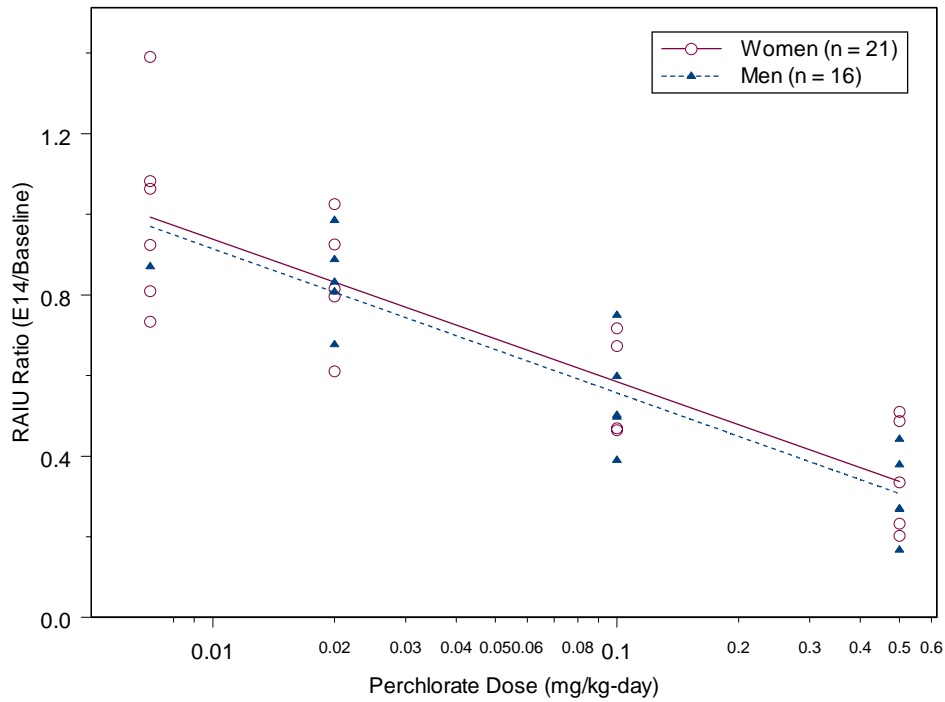


Figure 1. Dependence of the relative (A) and absolute (B) change in the 24-hr radioiodine uptake between baseline and exposure day 14 on the logarithm of the perchlorate dose, by sex. The lines are separate linear regression fits to the data for the women and the men.

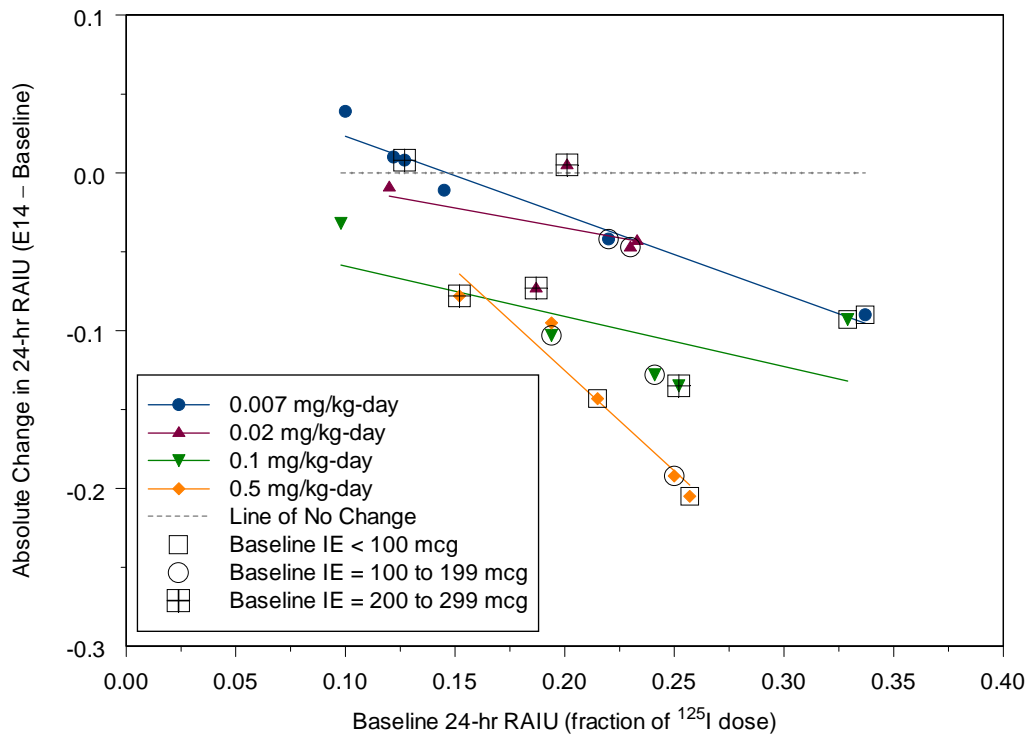


Figure 2. Dependence of the inhibitory effect of perchlorate in the women on the baseline radioiodine uptake. The absolute change in the 24-hr radioiodine uptake between baseline and exposure day 14 (Δ RAIU) is plotted against the baseline 24-hr radioiodine uptake ($RAIU_B$), by dose. The dashed line represents zero change in Δ RAIU. The solid lines are linear regression fits to the data (solid symbols) in each dose group. Data points with superimposed symbols represent subjects with baseline 24-hr iodine excretion (IE_B) values below 300 μ g, categorized according to the three ranges indicated. The remaining data points represent subjects with IE_B values above 300 μ g.

Figure 3 shows the dependence of the $RAIU_B$ on the IE_B separately in the women and the men. In both sexes there is a negative trend (decrease in $RAIU_B$ with increasing IE_B). In the women the slope is larger and the relationship stronger than in the men (slope = $-0.000314 \mu\text{g}^{-1}$, $p = 3 \times 10^{-5}$ in the women; slope = $-0.000148 \mu\text{g}^{-1}$, $p = 0.067$ in the men). The results suggest that in the women the IE_B was a good predictor of iodine status whereas this was not the case in the men.

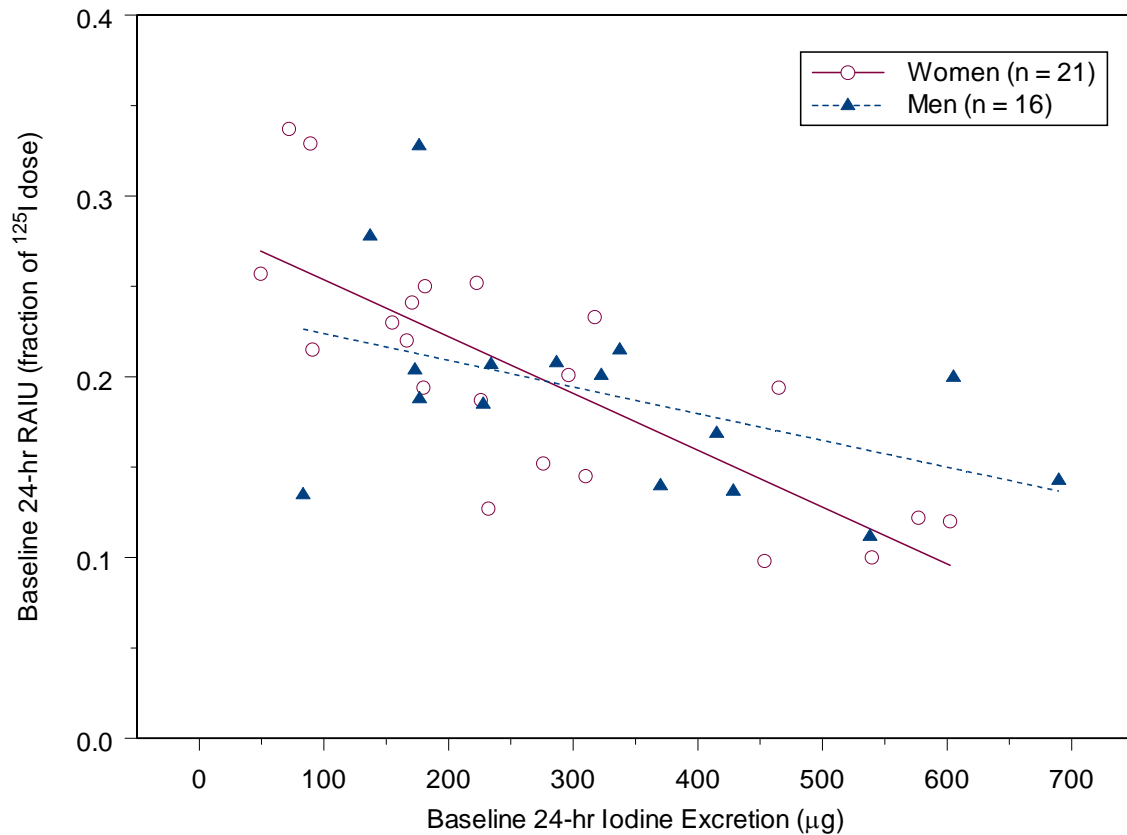


Figure 3. Dependence of the baseline 24-hr radioiodine uptake on the baseline 24-hr iodine excretion, by sex. The lines are separate linear regression fits to the data for the women and the men.

Consistent with the observed sex-related difference in the dependence of $RAIU_B$ on IE_B , the inhibitory effect of perchlorate in the women is more strongly dependent on IE_B than in the men. For the women the slope of the regression line for the dependence of $\Delta RAIU$ on IE_B was positive in all dose groups (0.00019, 0.00010, 0.00022, and 0.00025 from lowest to highest dose) and achieved statistical significance in the 0.007 mg/kg-day group ($p = 0.037$). For the men the slope was positive only in the 0.5 mg/kg-day dose group and was not statistically significant in any group. Comparison of the analyses in Tables 1 and 2 illustrate the differential influence of IE_B on the effect of perchlorate in the women *vs.* the men. Addition of IE_B to either of the univariate models in log dose improves the fit in the women more so than in the men, as revealed by larger decreases in residual standard error (RSE) and larger increases in multiple R-squared.

The models presented in Tables 1 and 2 express the exposure-related change in RAIU between baseline and E14 (the dependent variable) as either a relative or an absolute quantity. In the upper set of models the dependent variable is a relative quantity, the RAIU ratio. In the lower set of models the dependent variable is an absolute quantity, $\Delta RAIU$. To a large extent in the men (Table 2) and to some extent in the women (Table 1), the multivariate models reflect a greater improvement over the corresponding

univariate model in log dose when the dependent variable is Δ RAIU rather than the RAIU ratio.

Independent Variables	Degrees of freedom	Residual Standard Error	Multiple R-Squared	p value
<i>Models of the Relative Change in RAIU (E14/Baseline) in Women</i>				
Log dose	19	0.1657	0.7179	$<2 \times 10^{-6}$
Log dose + RAIU _B	18	0.1422	0.8031	$<5 \times 10^{-7}$
Log dose + IE _B	18	0.1279	0.8408	$<7 \times 10^{-8}$
Log dose + RAIU _B + IE _B	17	0.1310	0.8423	$<5 \times 10^{-7}$
<i>Models of the Absolute Change in RAIU (E14 – Baseline) in Women</i>				
Log dose	19	0.04261	0.6143	$<3 \times 10^{-5}$
Log dose + RAIU _B	18	0.02905	0.8301	$<2 \times 10^{-7}$
Log dose + IE _B	18	0.02997	0.8191	$<3 \times 10^{-7}$
Log dose + RAIU _B + IE _B	17	0.02777	0.8534	$<3 \times 10^{-7}$

Table 1. Comparison of linear regression models applied to the RAIU results in the women.

Independent Variables	Degrees of freedom	Residual Standard Error	Multiple R-Squared	p value
<i>Models of the Relative Change in RAIU (E14/Baseline) in Men</i>				
Log dose	14	0.1150	0.8091	$<3 \times 10^{-6}$
Log dose + RAIU _B	13	0.1164	0.8183	$<2 \times 10^{-5}$
Log dose + IE _B	13	0.1143	0.8248	$<2 \times 10^{-5}$
Log dose + RAIU _B + IE _B	12	0.1085	0.8542	$<3 \times 10^{-5}$
<i>Models of the Absolute Change in RAIU (E14 – Baseline) in Men</i>				
Log dose	14	0.04092	0.6177	0.0003
Log dose + RAIU _B	13	0.02069	0.9092	$<2 \times 10^{-7}$
Log dose + IE _B	13	0.04153	0.6344	0.0014
Log dose + RAIU _B + IE _B	12	0.01948	0.9257	$<5 \times 10^{-7}$

Table 2. Comparison of linear regression models applied to the RAIU results in the men.

D. References

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