

Perchlorate on Thyroxine by Iodine Status:

Creatinine-Adjusted Urine Iodine vs. Unadjusted Urine Iodine

Steven H. Lamm, MD, Joseph G. Hollowell, MD,
Arnold Engel, MD, and Rusan Chen, PhD.

Consultants in Epidemiology & Occupational Health, LLC.

Washington, DC

Perchlorate Exposures, Iodine Modulation of Effect, and
Epidemiological Associations: Implications for Risk Analysis

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Iodine, Perchlorate, and Thyroxine

Conceptual Hypothesis:

Perchlorate and iodine are competitive inhibitors of the sodium iodide symporter (NIS) and thus for thyroxine production, thus:

- Does normal iodine supply protect thyroxine production from usual exposure to perchlorate?
- Is the thyroid more sensitive to NIS inhibition by perchlorate at low iodine status?

Iodine, Perchlorate, and Thyroxine

Working Analytic Hypothesis:

Is increasing urine perchlorate significantly associated with lower serum thyroxine levels for those with low iodine (nutrition, supply, status)?

Data source - NHANES 2001-2002

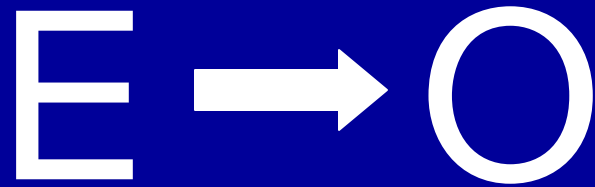
- Contains individualized measures of thyroxine (serum), iodine (urine), perchlorate (urine), and creatinine (urine).
- Only available dataset with these variables.
- Used by all three papers.

Question: Is the slope for perchlorate regressed on thyroxine level significantly negative for those with low iodine status?

Answers:

- Blount et al. (2006):
 - Yes, for women with UI < 100 ug/L.
- Lamm et al. (2007):
 - No, for women (15-44 y/o) with low UICr (< 100 ug/g)
(But yes, for women with high UICr (> 165 ug/g) and for thiocyanate.)
- Steinmaus, Miller and Howd (2007):
 - Yes, for women with UI < 100 ug/L,
and particularly for smokers (Thiocyanate, Cotinine)

Epidemiologic Model



Epidemiologic Model

- Population - Low Iodine Status
- Outcome - Serum Total Thyroxine
- Exposure - Urine Perchlorate (log)
- Mitigating factors (Co-variate)
 - Iodine Uptake Inhibitors (Thiocyanate, Nitrate)
 - Smoking (History, Thiocyanate, Cotinine)
 - Demographic and Medical (e.g., estrogenic)
 - Dilution (e.g., creatinine)

CDC Analysis (Blount, 2006)

Population:

- Women age 12-85(+) in NHANES 2001-2002
- Low iodine status < 100 ug/L (urine)

Finding:

Multivariate regression analysis shows a significant negative association between urine perchlorate level and serum total thyroxine level.

beta = - 0.89 p-value < 0.0001

CEOH Analysis (Lamm, 2007)

Population:

- Women age 15-44 in NHANES 2001-2002
- Low iodine status \leq 100 ug/gm creatinine (urine)

Finding:

Multivariate regression analysis shows no significant negative association between urine perchlorate level and serum total thyroxine level.*

beta = - 0.13 (0.25) p-value = 0.89 (0.72)

* Weighted (unweighted) beta and p-value for regression of urinary perchlorate on serum thyroxine for women age 15-44 in NHANES 2001-2002 and UICr <100 ug/gr creatinine.

Serum Thyroxine and Iodine Uptake Inhibitors, by Terciles of UICr*, unweighted Data, NHANES 2001-2002, WCBA***

UICr	Low Tercile <u>(<95.7 ug/g*)</u>	Middle Tercile <u>(95.7-167.4 ug/g)</u>	High Tercile <u>(> 167.4 ug/g)</u>
Perchlorate	0.25 (p=0.72)	-0.49 (p=0.42)	-1.09 (p=0.03)
Thiocyanate	-0.02 (p=0.94)	-0.04 (p=0.91)	-1.21 (p=0.01)
Nitrate	0.42 (p=0.52)	-0.63 (p=0.48)	1.14 (p=0.06)

- * Cr-Adj. Urine Iodine (ug iodine / gram creatinine)
- ** Regression coefficient (beta)
- *** Women of Childbearing Age

Serum Thyroxine and Iodine Uptake Inhibitors, by Terciles of UICr*, weighted Data, NHANES 2001-2002, WCBA***

UICr	Low Tercile (<u><92.0 ug/g*</u>)	Middle Tercile (<u>92.0-163.7 ug/g</u>)	High Tercile (<u>> 163.7 ug/g</u>)
Perchlorate	-0.13 (p=0.89)	-0.35 (p=.07)	-1.09 (p=0.01)
Thiocyanate	-0.30 (p=0.31)	0.71 (p=0.29)	-0.98 (p=0.02)
Nitrate	1.55 (p=0.06)	-2.31 (p=0.02)	0.06 (p=0.94)

* Cr-Adj. Urine Iodine (ug iodine / gram creatinine)

** Regression coefficient (beta)

*** Women of Childbearing Age

These results are not surprising:
Vanderver et al (2007) showed the same for
NHANES III (1986-1994)

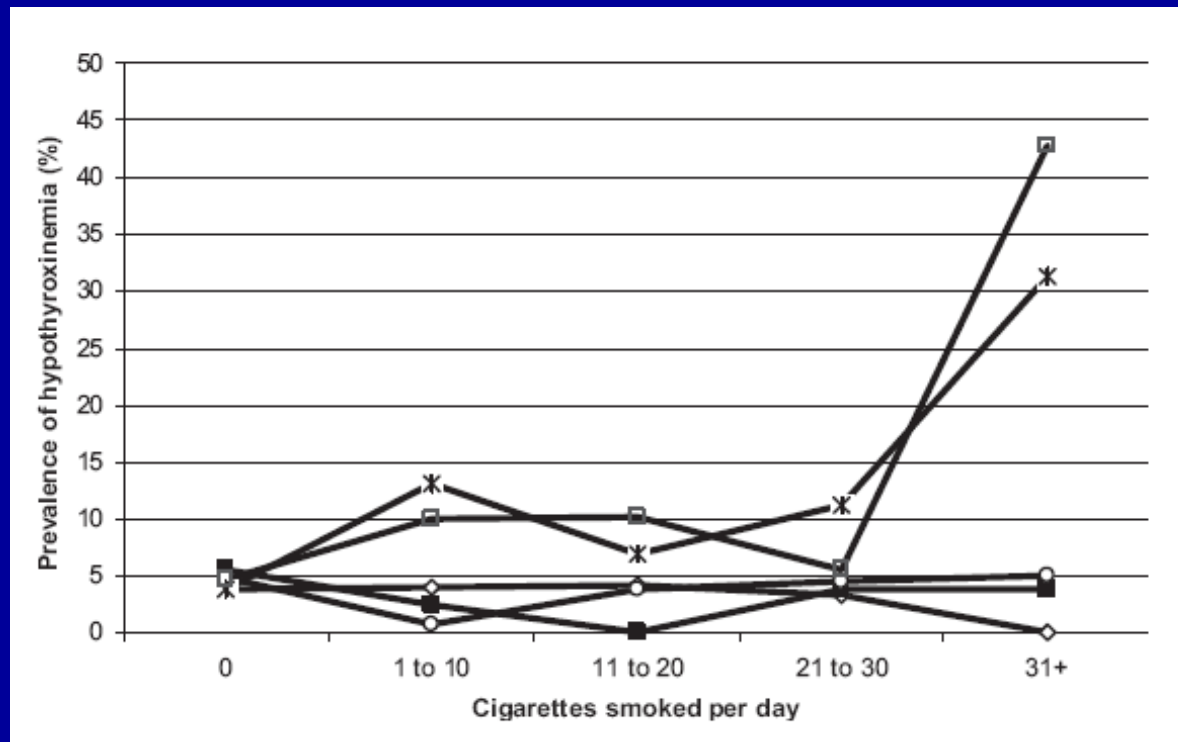


FIG. 3. Prevalence of hypothyroxinemia in women (age range: 15–44 years) stratified by urine iodine excretion. ◇: Urine iodine $< 50 \mu\text{g/L}$; ■: urine iodine $50-99 \mu\text{g/L}$; ○: urine iodine $100-199 \mu\text{g/L}$; ✱: urine iodine $200-299 \mu\text{g/L}$; □: urine iodine $300+ \mu\text{g/L}$.

Differences:

1. Definition of low iodine status.
2. Age group [12+ vs 15-44].
3. Weighted vs unweighted.
4. Possibly co-variates.

Co-Variates:

- Demographic – Age, Race/Ethnicity [Non-Hispanic White, Non-Hispanic Black, Mexican American, Other].
- Metabolic – Fasting time, Kilocalories, Serum Albumin, BMI, **C-reactive protein**.
- Iodine Uptake Inhibitors (IUI) – Urinary Perchlorate, Thiocyanate, Nitrate.
- Other Urinary – Creatinine, Iodine, Cotinine.
- Estrogenic – Estrogen use, Pregnancy, Postmenopausal, Premenarche.
- Other Drugs – Furosemide, Glucocorticoids/Androgens, Beta-blockers, others.

Population Weighting:

- CEOH Analysis for Urinary Perchlorate:

Low UI:

- Unweighted beta = - 0.91 p-value = 0.04
- Weighted beta = - 0.84 p-value = 0.14

Low UICr:

- Unweighted beta = 0.25 p-value = 0.72
- Weighted beta = - 0.13 p-value = 0.89

Age-Group:

Women with UI < 100 ug/L

<u>Age</u>	<u>N</u>	<u>Beta</u>	<u>p-value</u>
15-44	625	- 0.91	0.04
12-85(+)	1111	- 0.89	< 0.001

Significant Definitional Differences

- What is the Metric of Iodine Status?
 - Urine Iodine (UI, ug/L)
 - Urine Iodine, Creatinine-Adjusted (UICr, ug/g)
 - 24- hour Urine Iodine (ug/day) [“Gold standard”]
 - Plasma Iodine (exclude protein-bound)
- What is the Measure of Low?
 - WHO population median (< 100 ug/L)
 - Low Tercile
 - Below Interquartile Range

Caveats

- Not appropriate to use population characteristic as individual characteristic.
- Anderson demonstrated that individuals with low iodine measures do not have a population of low measures.

Analogy

- To find risk factors for the poorly performing students in a school system.
 1. Identify all schools with median score at or above national average.
 2. Identify all students in those school with a score below the national average.
- Are the risk factors for the poorer students at the good schools the same as for the students at the poor schools or of the poorer students at the poor schools?

Urinary Iodine Excretion (UI or UIE)

- This is not a primary measure, but a ratio of iodine excretion to water excretion:

i.e., ug iodine per liter urine

measured in an aliquot of an untimed urine specimen.

UI Creatinine-Adjusted (UICr)

- For an individual, the hourly rate of creatinine excretion is constant.
- UICr relates iodine excretion to creatinine excretion and thus converts it to a pseudo-timed rate.

i.e., ug iodine per gm creatinine.

Therefore, the measure is the amount of iodine excreted during the time a gram of creatinine is excreted, a surrogate for an iodine excretion rate.

Does it make a Difference – Literature?

- Hopton Cann (2007) NHANES I, Age 25-74, 1971-75, M+F
 - “Measurement of the urinary iodine/creatinine ratio is one of the most widely used methods of estimating iodine intake and was used as the surrogate measure of iodine status”
 - “Participants were stratified into terciles according to the urinary iodine/creatinine ratio, as a marker of iodine exposure.”
- Manz (2000) Six European Countries, Age 3-5, 1991-96 M+F
 - “The urinary iodine-creatinine ratio appears to be a much better parameter for assessing iodine supply than urinary iodine.”
- Thompson (2001) New Zealand, Age 18-49, 1997-98, M+F
 - “Thyroid volume correlates significantly with 24-hr iodine excretion and iodine/creatinine ratio, but not with urinary iodine.”

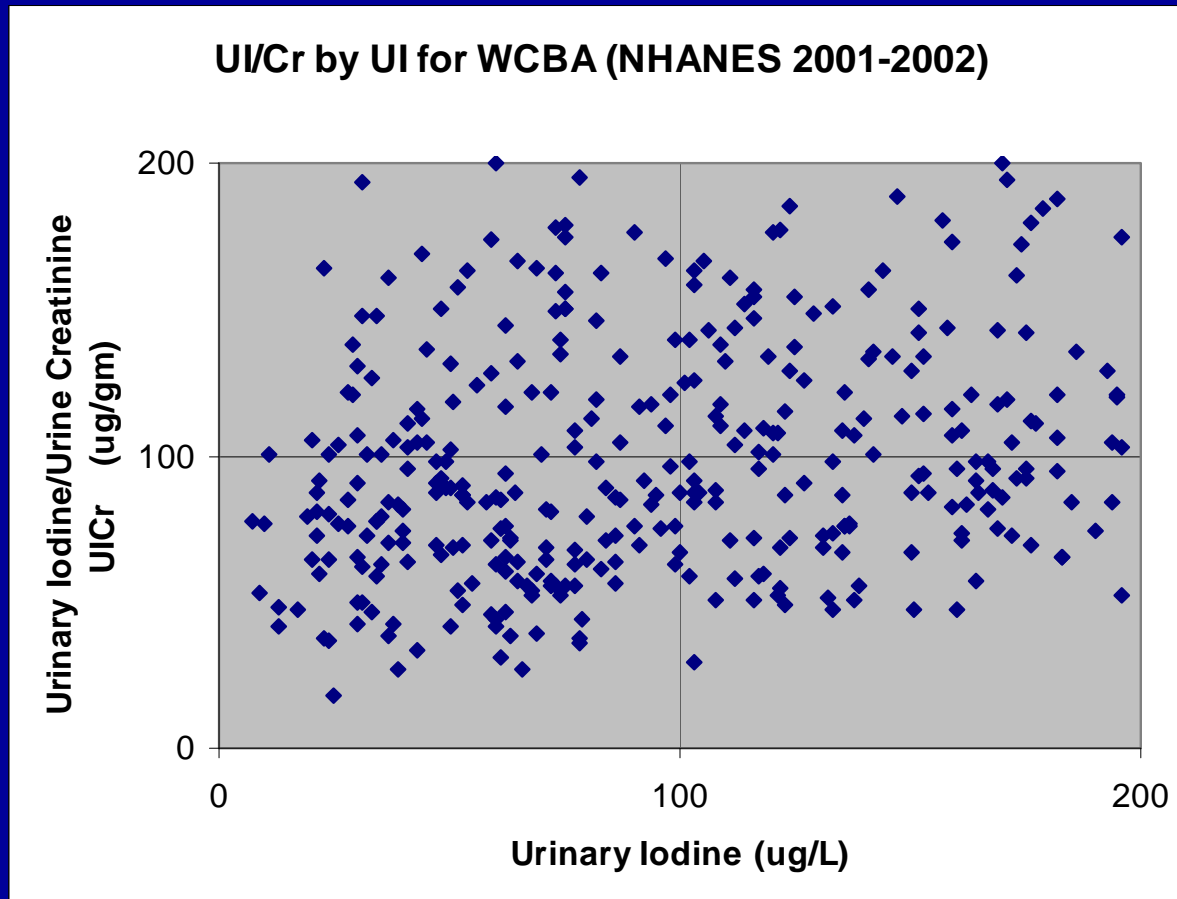
Does it make a Difference – Individuals?

	<u>UICr < 100</u>	<u>UICr > 100</u>	<u>Sum</u>
UI < 100	20%	13%	33%
<u>UI > 100</u>	<u>16%</u>	<u>51%</u>	<u>67%</u>
Sum	36%	64%	100%

Only half the subjects remain not low.

Only 42% of the ever low remain low.

Does it make a Difference – Who stays low?



Generic Approach to Biomonitoring

- Urine measurements are expressed both directly as a concentration (ug/L) and as a relative concentration (ug/gm creatinine).
- Distributions are presented as percentiles
 - Median, quartiles, extreme deciles.
- A reasonable definition of high and low is outside of the interquartile range.

Presentation of Biomonitoring Data

Example of mono-ethyl phthalate

	<u>N</u>	<u>GM</u>	<u>10th</u>	<u>25th</u>	<u>50th</u>	<u>75th</u>	<u>90th</u>
ug/L	1,024	176.0	27.7	61.5	171	424	1160
ug/g	1,024	151.5	30.8	63.9	134	337	892

Analytic proposal – Compare findings for those below, above, and within the interquartile range.

Biomonitoring

Barr (2005) NHANES III, age 6+, 1988-94, M+F

“Urinary biomonitoring data typically are adjusted to a constant creatinine concentration to correct for variable dilutions among spot samples.”

“For multiple regression analysis of population groups, we recommend that the analyte concentration (unadjusted for creatinine) should be included in the analysis with urinary creatinine added as a separate independent variable.”

Analytic Proposals

1. Find or develop a second data set.
2. Define iodine status on the basis of creatinine-adjusted urinary iodine (UICr).
3. Define “Low” on a percentile basis, either tercile [N = 370] or quartile [N = 278] (below interquartile range).

Summary

- Iodine/Creatinine ratio is a population definer.
- Iodine and creatinine (and perchlorate, etc.) are independent exposure (risk) factors.