Comments for the EPA SAB Perchlorate Advisory Panel

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A global consultancy, working with clients to manage their most challenging environmental, health and safety issues and attain their sustainability goals.

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A trade association supporting the chlor-alkali industry and serve the public by fostering continuous improvements to safety and the protection of human health and the environment connected with the production, distribution and use of chlorine, sodium and potassium hydroxides, and sodium hypochlorite

Existing drinking water advisory and standards for ClO_4 are all based on the assumption that a perchlorate higher than the NOEL observed over a 2-week exposure (Greer et al. (2002)) could result in chronic reduction in thyroid hormone production.

Since publication of the NAS (2005) report and the EPA reference dose (RfD) for perchlorate, clinical, occupational, and epidemiological studies have been published which indicate evidence of non-adverse thyroidal compensation for perchlorate-induced inhibition of iodide uptake.

In these studies, chronic exposure to perchlorate at doses higher than the Greer at al (2002) NOEL resulted in no change in iodide uptake (measured by RAIU) and/or thyroid hormone homeostasis.

A new RfD should be derived, based on chronic human data published since the NAS report. It should be based on a different critical toxic endpoint, resulting in a more scientifically defensible drinking water standard.

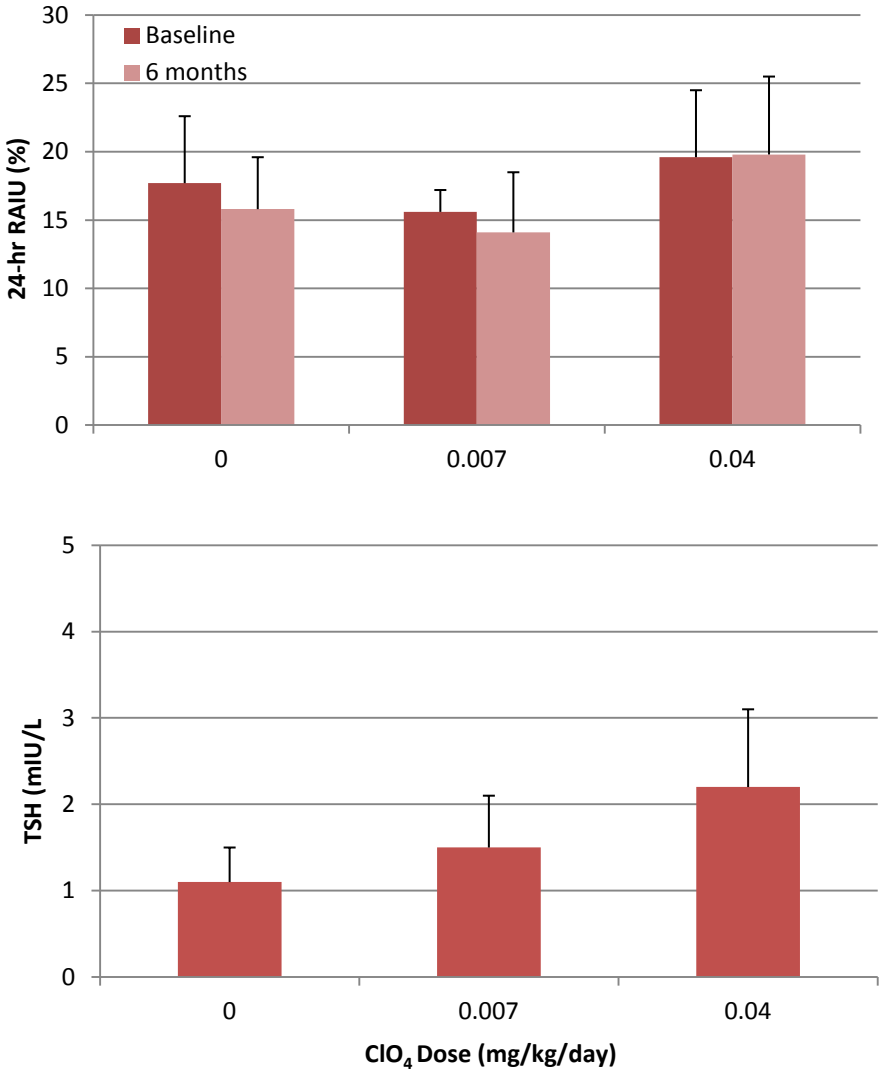
Braverman et al. (2006): 6 Month Exposure

Four to five subjects given 0, 0.007, or 0.04 mg/kg/d ClO4 for six months.

High doses were 6x the NOEL used as basis of NAS and EPA RfDs

RAIU, TSH, free T4 index, T3, and thyroglobulin measured.

Daily capsule doses for 6 months resulted in no change in RAIU, TSH or free T4 index.



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Braverman et al. (2005): 1.7+ Year Exposure

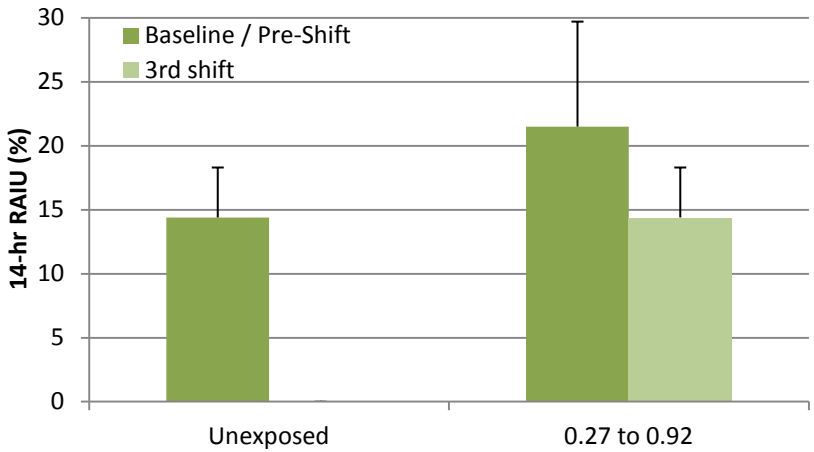
Forty-one workers exposed to approximately 0.27-0.92 mg/kg/d ClO_4 for at least 1.7 years.

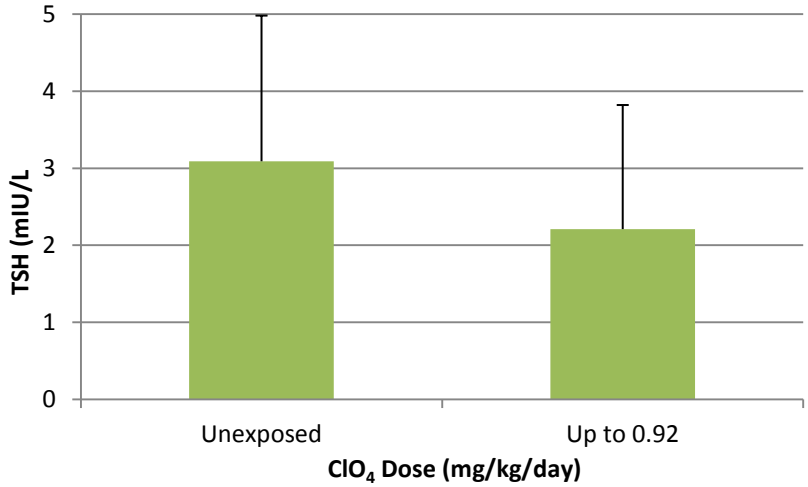
ClO4 exposure 40-130x higher than the NOEL used as basis of NAS and EPA RfDs

Pre-shift RAIU higher (21.5%) in exposed group vs. non-exposed (13.5%), indicating NIS upregulation.

Post-shift RAIU in exposed group (14.3%) same as non-exposed group.

TSH, T4, and thyroid morphometry in exposed group not affected by ClO_4.





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Ecological Epidemiological Studies of ClO4 and Thyroid Function in Pregnant Women and Fetuses

Study	Subjects	Urinary ClO_4 (µg/L)	Serum TSH (mIU/L)	Statistical Analysis	Association Between ClO_4 and Thyroid Hormone
Tellez et al. (2005)	181 pregnant & post-partum women, Northern Chile	mean range 24.5-132.9	mean range 2.61-8.25	multivariate regression	Negative (TSH, T_3, free T_4 index)
Pearce et al. (2010)	854 pregnant women Cardiff, Wales	2.4 (0.03-368)	2.3 (0.02-29.8)	Spearman rank correlation; multivariate regression	Negative (TSH, T_3, free T_4 index)
Pearce et al. (2010)	787 pregnant women Turin, Italy	5.1 (0.04-168)	1.5 (0.005-3.3)	Spearman rank correlation; multivariate regression	Negative (TSH, T_3, free T_4 index)
Pearce et al. (2011)	102 pregnant women Cordoba, Argentina	13.5 (1-676)	2.27 ± 4.4 SD	Spearman rank correlation; multivariate regression	Negative (TSH, T_3, free T_4 index)
Pearce et al. (2011)	102 pregnant women Los Angeles, CA, USA	7.8 (0.4-284)	1.58 ± 1.6 SD	Spearman rank correlation; multivariate regression	Negative (TSH, T_3, free T_4 index)
		µg/g creatinine	mIU/g creatinine		
Cao et al. (2010)	92 infants Philadelphia, PA, USA	mean range 2.5 - 28	mean range 23 - 41	multivariate regression	Positive (ClO_4 modeled alone) Negative (when modeled with nitrate and thiocyanate)

Recommendations

A new RfD should be derived, based on chronic human data published since the NAS report, which will result in a more scientifically defensible drinking water standard.

Consider chronic human data to identify new critical endpoint. These data demonstrate non-adverse, compensatory upregulation of iodide transport and maintenance of thyroid hormone homeostasis at doses higher than 2-week NOEL of current EPA RfD.

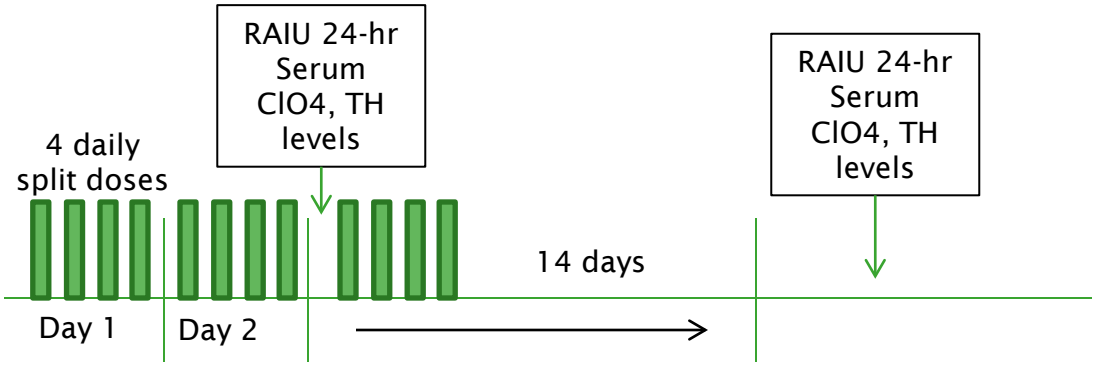
Explore modifying existing PBPK pregnancy model for ClO_4 to account for upregulation of NIS and iodide transport.

Validate modified PBPK model using iodide/ClO_4 serum and urine data from occupational and epidemiology studies.

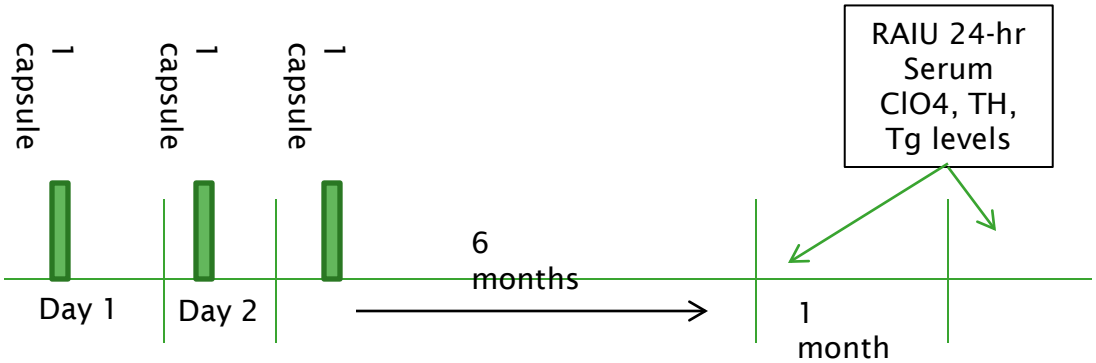
New life-stage RfDs can be derived using NOAEL/UF approach or PBPK model extrapolation (if model is adequately validated).

Appendix

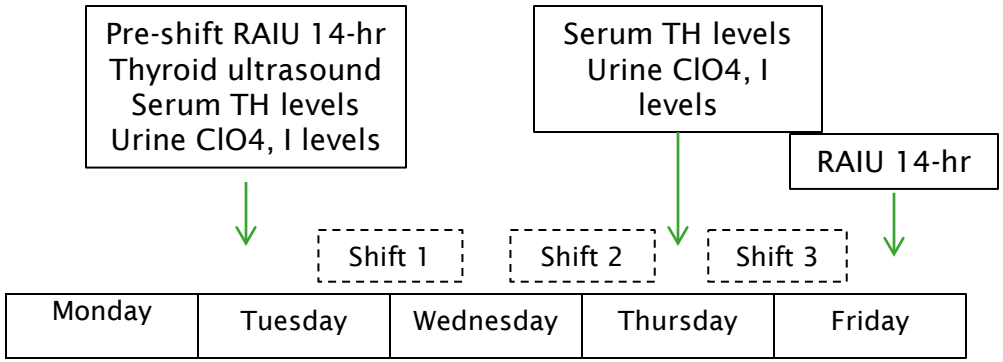
Greer et al. (2002)
- 7-10 adults
- 0.007 – 0.5 mg/kg/day in water (split doses) for 14 days



Braverman et al. (2006)
- 4-5 adult men
- 0, 0.007, or 0.42 mg/kg/day in capsules for 6 months



Braverman et al. (2005)
- 12 adult controls
- 29 exposed ClO4 workers
- 0 or up to 0.92 mg/kg/day in air for 1.7+ years



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