

An Overview of the Toxicology and Pharmacology of Perchlorate

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Regulatory Checkbook

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REGULATORY
CHECKBOOK

Where to Start?

- **Almost everything you read or hear about perchlorate health effects is wrong.**
 - It is not carcinogenic, mutagenic, immunotoxic.
 - It does not cause reproductive harm.
 - It cannot cause hypothyroidism or developmental harm at environmental levels observed in the U.S.
- **U.S. exposure is well below the no-effect threshold.**
 - Nothing at all happens below about 200 ppb.
 - U.S. exposure is 0 to 15 ppb.
- **USEPA's 2002 draft risk assessment is unreliable.**
 - Based on low-quality science interpreted incorrectly.
 - Dismisses epidemiology showing no effects at high doses.
 - Ignores human clinical trial data identifying the threshold.

What About Lettuce?

EWG's *Suspect Salads* Report

- **Riddled with misrepresentation and factual errors.**
 - EPA 'standards' differ from EWG claims.
 - All thyroid ill's falsely attributed to perchlorate.
- **EWG gets 'F' in Scientific Methods 101.**
 - Unreliability of test methods suppressed.
 - Data suppressed, then invented, then manipulated.
 - 18 of 22 (82%) samples suppressed (no detects).
 - Only 1 of 4 'detects' had measurable perchlorate.
 - EWG invented values for 3 others reported by lab as 'trace'.
- **Level of perchlorate detected was trivial.**
 - Biochemical effect from nitrate in average EWG serving is 225 times greater than effect from 1 ppb perchlorate.
 - If nitrate in lettuce is safe, how can perchlorate be risky?

Why Does Nitrate Matter?

- **Perchlorate and nitrate have same mode of action on the thyroid.**
 - Perchlorate is about 300 times as potent as nitrate.
 - Nitrate exposure in diet is thousands of times greater.
 - Equivalent 'protection' requires nitrate MCL of about 300 ppb.
 - Current nitrate MCL is 10,000 ppb.
- **USEPA risk assessment leads to bizarre implied risk messages:**
 - Nitrate MCL is severely under-protective.
 - Green, leafy vegetables are dangerous

Single Serving Vegetable	Average Nitrate Content	Estimated Perchlorate Drinking Water Equivalent Level
Broccoli	740,000 ppb	100 ppb
Turnip greens	6,600,000 ppb	800 ppb

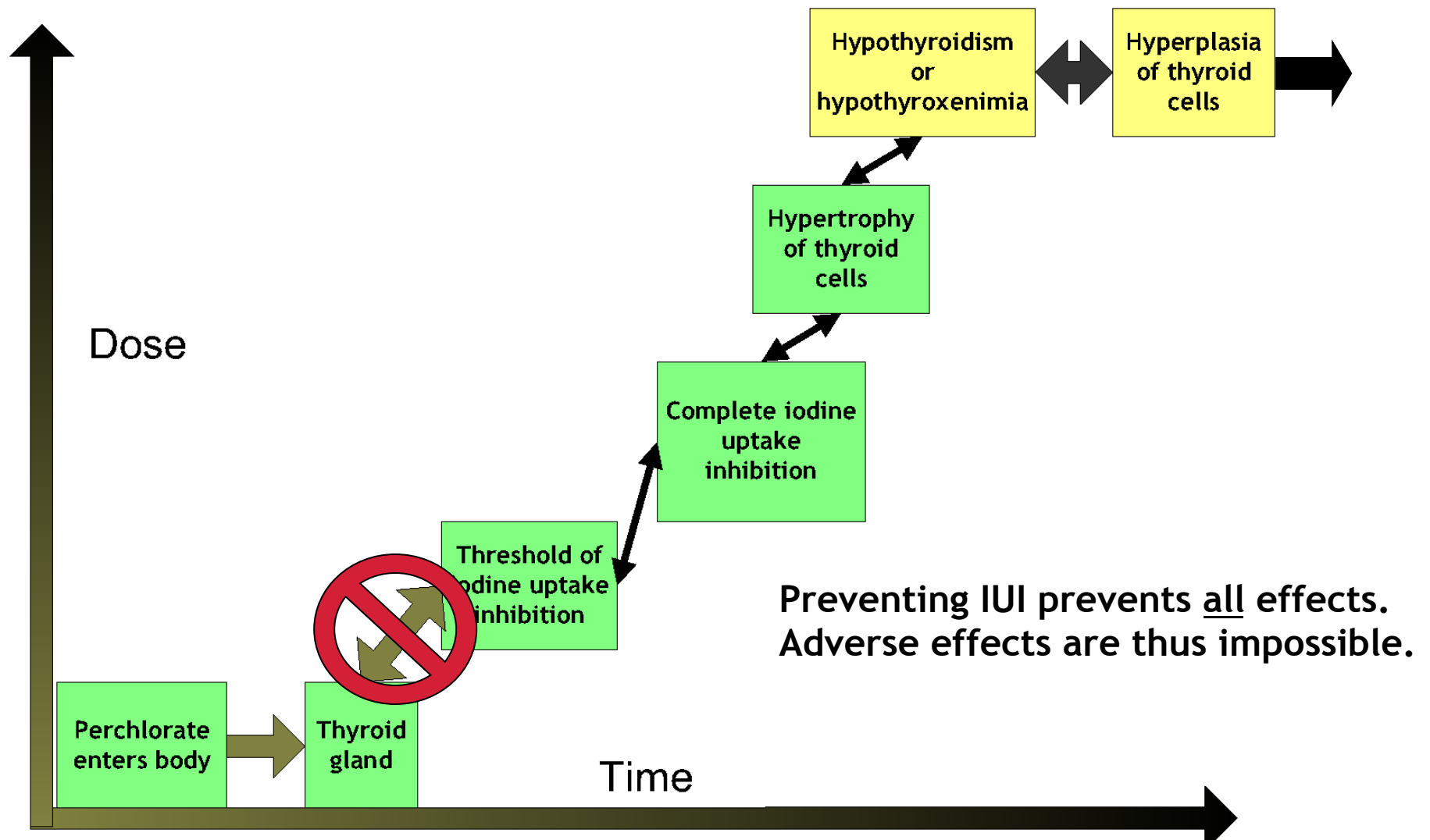
Where Does USEPA Perchlorate Risk Assessment Lead Us?

- **Fosters activists' demand for dramatic reduction in nitrate MCL.**
 - Same activists who claim perchlorate is 'toxic' also want very low nitrate standards.
 - Equivalent level of 'protection' for nitrate means:
 - Reduce MCL from 10,000 ppb to 300 ppb.
 - Staggeringly expensive costs for public water systems.
 - Paralysis in U.S. agriculture.
 - Zero public health benefits.
- **Sets precedent for setting other standards based on mere exposure, not risk.**
- **Exacerbated by impending Prop 65 listing.**

What is Perchlorate?

- Used as an oxidizer in solid rocket fuel.
- Found in fertilizer, natural deposits.
- For 50 years, a therapeutic agent for Graves Disease.
- Not an endocrine disruptor that mimics hormones.
- **Affects the thyroid by iodide uptake inhibition**
 - Several reversible steps required to reduce thyroid hormones
 - Iodide uptake inhibition is merely the first of these steps
 - Adverse effects require all of these steps to occur
 - Mundane things cause iodide uptake inhibition
- **Central nervous system can be adversely affected if thyroid hormones are reduced a lot and for a long time**

Sequence of Biochemical Events Required to Lead to an Adverse Effect



Toxicology and Pharmacology of Perchlorate

- **Toxicological and pharmacologic database is robust.**
- **Mechanism of action**
 - Known for perchlorate
 - Unknown for many drugs and environmental contaminants
 - Known for perchlorate
 - Unknown for many drugs and environmental contaminants
- **Human data**
 - Clinical studies
 - Occupational studies
 - Epidemiological studies
- **Animal data: Full battery of tests completed, including...**
 - Cancer (no effects)
 - Reproductive harm (no effects)
 - Immunotoxicity (no effects)
 - Developmental harm

What Do We Know?

- Human and rat thyroid glands operate differently.
- Clinical studies have determined a NEF for IUI uptake.
- Occupational studies show no long term effects to workers despite exposures 10,000 times higher.
- Well-conducted epi studies show no adverse effects of perchlorate at doses greater than levels in US.
- Animal studies show that perchlorate...
 - Is not carcinogenic.
 - Is not mutagenic.
 - Is not immunotoxic.
 - Does not cause reproductive toxicity.
 - Does not accumulate in body, and is excreted in hours.


Human Studies Show No Risk at US Exposure Levels

- No effect level (NEF) for IUI: equivalent to 200 ppb perchlorate in drinking water.
- No Observable Effect Level (NOEL) for thyroid hormones: is unknown but must exceed 17,000 ppb for healthy men and women.
- No Observable Adverse Effect Level (NOAEL) for thyroid hormones: is unknown but must exceed 17,000 ppb for healthy men and women.
- Lowest Observable Adverse Effect Level (LOAEL) for first signs of clinical hypothyroidism: is unknown but must be substantially greater than NOEL or NOAEL.

Why the NEF Means No Risk for Everyone

- **The NEF is a threshold below which IUI does not occur.**
- **Why IUI is not risky?**
 - IUI is fully reversible and mundane daily event.
 - Substantial and sustained IUI is needed to cause transient TH changes.
 - Transient TH changes are normal and regulated by homeostasis.
 - Sustained TH changes may lead to adverse effects if untreated.
- **Evidence that below the threshold, nothing happens.**
 - Greer *et al.* estimated the threshold for IUI at 180-220 ppb.
 - Results consistent with studies by Boston Univ Medical School.
 - A dose equivalent to 17,000 ppb causes 70% IUI.
 - Lamm, *et al.* found no change in thyroid hormones, blood chemistry, thyroid parameters—even after years of exposure and despite 70% IUI.

EPA's 2002 Draft Risk Assessment Deconstructed

 EPA
United States Environmental Protection Agency
Office of Research and Development
Washington, DC 20460
NCEA-1-0503
January 16, 2002
External Review Draft
Perchlorate Environmental Contamination:
Toxicological Review and Risk Characterization
External Review Draft
(Do Not Cite or Quote)

Notice
This document is an external review draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



✓ Rat study suggests ‘potential’ for neurodevelopmental harm.

✓ “Critical effect” in humans is iodide uptake inhibition.

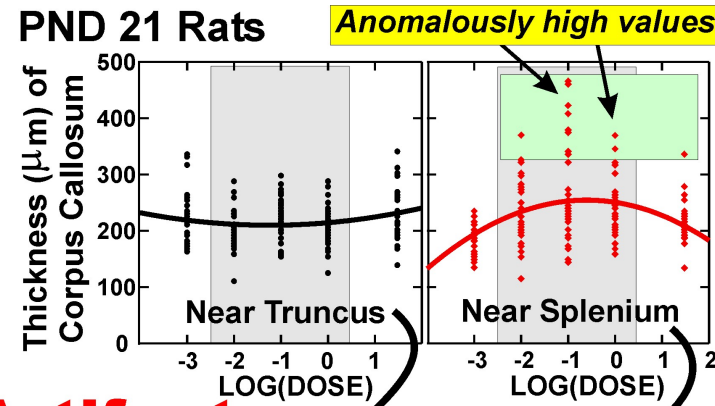
✓ Composite ‘uncertainty factor’ = 300

Thus, the DWEL for perchlorate RfD = 1 ppb.

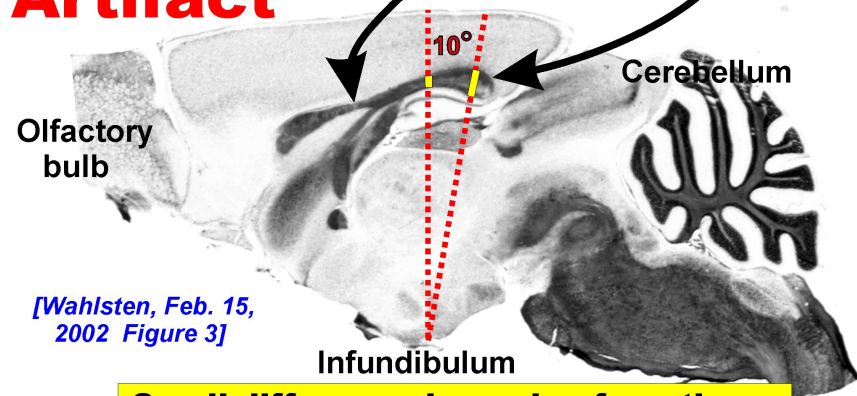
Why the Rat Study EPA Relies on Has No Value for Risk Assessment

Top Right Graph

- Obvious signs of trouble:
 - Inverse U-shaped dose-response curve implies no risk at very low AND very high doses
 - Outliers are in the intermediate doses



Artifact



[Wahlsten, Feb. 15, 2002 Figure 3]

Small difference in angle of section creates a large difference in apparent thickness of the corpus callosum

Bottom Graph

- How lab errors happened
- Why coronal sectioning is wrong (thickness varies)

Top Left Graph

- Excludes lab errors
- Dose-related trend vanishes

Epidemiology Studies

- Studies with perchlorate measurements consistently show no effects.
- Studies that claim to show effects did not actually measure perchlorate exposure.
 - What did they really measure?
 - Control for multiple confounders is very hard but essential before inferring a real effect.

Nitrate inhibits iodide uptake
Perchlorate inhibits iodide uptake

- Same mechanism of action makes direct comparisons possible and highly relevant.
- Much nitrate is found in common foods—especially green, leafy vegetables.
- Nitrate in vegetables is normal.
- These foods are considered safe and healthy.

Nitrate MCL and Perchlorate RfD/DWELs differ by 10,000x

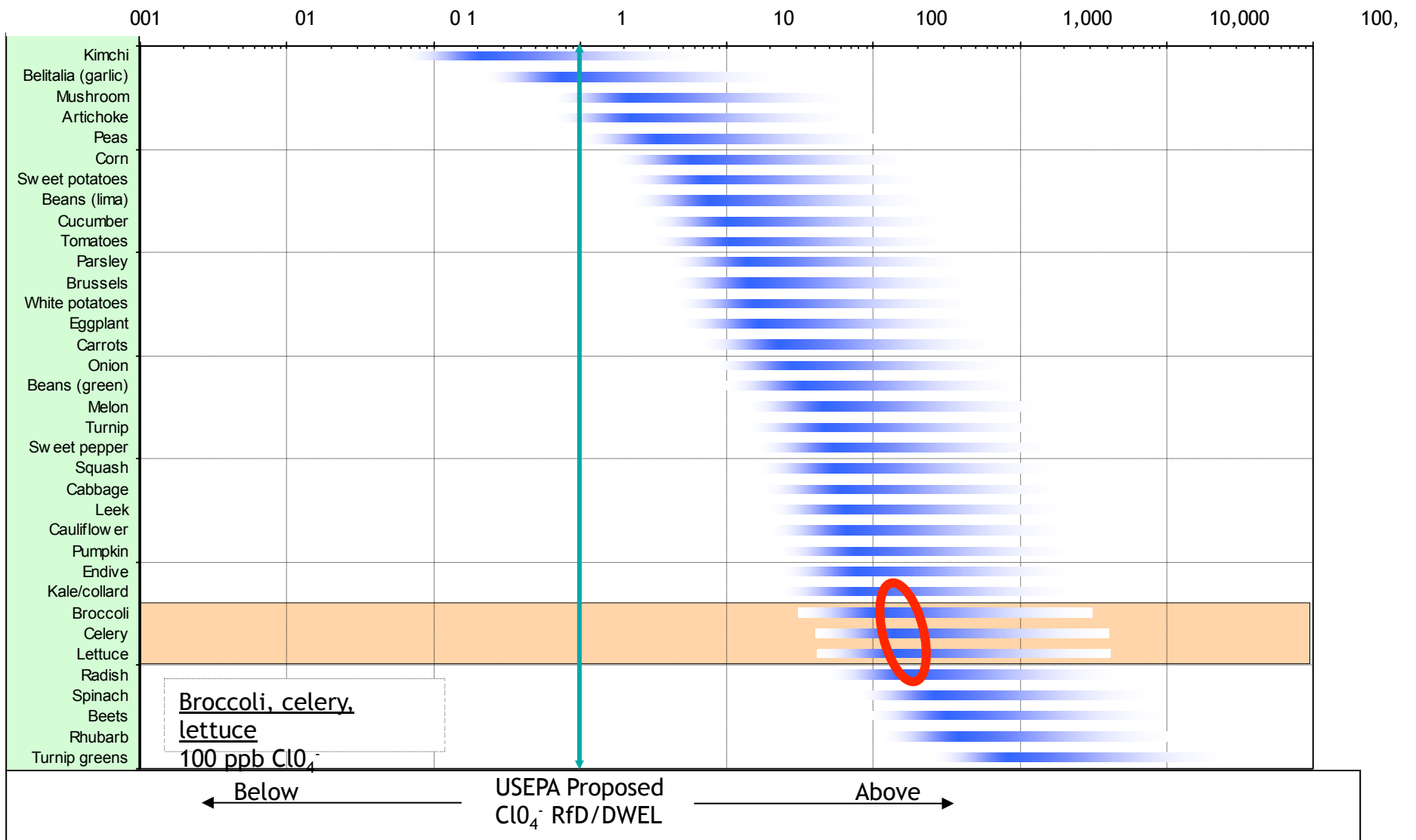
- **Nitrate MCL = 10 ppm = 10,000 ppb**
 - Based on methemoglobinemia
- **Perchlorate RfD/DWEL = 1 ppb**
 - Based on iodide uptake inhibition

Common Foods Containing Nitrate

- ✓ Milk
- ✓ Bacon
- ✓ Sausage
- ✓ Pepperoni
- ✓ Beef
- ✓ Ham
- ✓ Broccoli
- ✓ Celery
- ✓ Lettuce
- ✓ Radish
- ✓ Spinach
- ✓ Beets
- ✓ Rhubarb
- ✓ Garlic
- ✓ Artichoke
- ✓ Peas
- ✓ Corn
- ✓ Sweet potatoes
- ✓ Lima Beans
- ✓ Cucumber
- ✓ Tomatoes
- ✓ Parsley
- ✓ Brussels sprouts
- ✓ White potatoes
- ✓ Eggplant
- ✓ Carrots
- ✓ Onion
- ✓ Green Beans
- ✓ Melon
- ✓ Turnip
- ✓ Sweet pepper
- ✓ Squash
- ✓ Cabbage
- ✓ Leek
- ✓ Cauliflower
- ✓ Pumpkin
- ✓ Endive
- ✓ Kale
- ✓ Turnip Greens

Iodide Uptake Inhibition from Single Servings of Vegetables Expressed in ppb Perchlorate in Drinking Water

Best Professional Judgment Scenario Highlighted



Risk Communication Issues

- **Revealing comparisons with vegetables:**

Single Serving	Perchlorate DWEL Equivalent
Broccoli	100 ppb
Turnip greens	800 ppb

- **Implications:**

- Current nitrate MCL is severely unprotective, equal 'protection' at about 300 ppb nitrate.
- All vegetables are 'unsafe'.

What About Lettuce?

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Other Information

- **Media reports of public health ‘crisis’ .**
 - Generated by activist groups and EPA staff.
 - Contain, perpetuate and magnify scientific errors:
 - Cancer, tumors.
 - Graves Disease (hyperthyroidism).
 - Hypothyroidism (unrelated auto-immune disorders).
- **Ongoing human and animal studies.**
- **UNMC State of the Science Symposium.**
 - Summer/Fall 2003.
 - Blue ribbon panel of scientists.
 - Output will be consensus reports submitted for publication in a peer reviewed journal.

Conclusions

- **1 ppb RfD/DWEL significantly understates how much perchlorate exposure is 'safe' .**
- **200-500 ppb RfD/DWEL protects even sensitive subpopulations.**
- **If EPA risk assessment prevails...**
 - Nitrate MCL is 30 times too high.
 - All vegetables are unsafe.

Where to Go from Here?

Risk Assessment Issues

- **Scientific peer review problems at EPA:**
 - Three external peer reviews have been performed so far.
 - Upcoming National Academy review supposed to be the 'final' one.
 - New peer review system needed.

Where to Go from Here?

Risk Assessment Issues

- **Policy biases in EPA risk assessment need to be identified and removed :**
 - Many other examples of systemic, embedded policy bias include dioxin, TCE, butadiene, atrazine)
 - Can EPA produce unbiased, policy-neutral risk assessments?
 - Evidence for optimism is limited.
 - NAS can't be relied on to fix every EPA risk assessment.
 - Errors stand unless rescinded.
 - New procedures needed, but are hard to craft.

Where to Go from Here?

Regulatory Policy

- **Decisions based on USEPA 2002 risk assessment easily challenged in court.**
 - Risk assessment applies 2001 policy nixing '3rd-party' human data.
 - USEPA policy declared illegal and vacated in *CropLife v. EPA* (6/4/03).
 - Jan 2003 EPA 4-18 ppb 'guidance' on perchlorate is equally vulnerable to challenge.
- **Cal OEHHA draft PHG relies heavily on 2002 USEPA risk assessment (but not USEPA 2001 policy).**

Questions?

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