

Exposure to Perchlorate and Dietary Nitrate and Thiocyanate

RB Belzer,¹ RC Pleus,² GM Bruce,² and MK Peterson²

¹ Regulatory Checkbook, Mt. Vernon VA

² Intertox, Seattle WA

2004 Water Quality Conference, Ontario CA
27 October 2004



Background on Perchlorate (ClO_4^-)

- Perchlorate is both natural and manufactured.
 - Oxidizer in solid rocket propulsion systems, munitions, road flares, fireworks
 - Historically FDA-approved pharmaceutical for Graves' Disease; amiodarone-induced thyrotoxicosis, adjuvant for medical imaging
 - Constituent in NOP-approved fertilizers

Background on Perchlorate (ClO_4^-)

- Perchlorate is both natural and manufactured.
- Perchlorate inhibits iodide uptake.
 - Several reversible steps required to reduce thyroid hormones.
 - Iodide uptake inhibition is the first of these of these reversible steps.
 - Adverse effects require all of these steps to occur.
 - Other, mundane things cause iodide uptake inhibition.

Background on Perchlorate (ClO_4^-)

- Perchlorate is both natural and manufactured.
- Perchlorate inhibits iodide uptake.
- High exposure may adversely affect neurodevelopment.
 - If thyroid hormones are reduced a lot.
 - If thyroid hormones are reduced a lot for a long time.

Logic Behind this Analysis

- Assume US EPA 2002 draft risk assessment is correct and proposed 1 ppb drinking water equivalent level is reasonable.

Logic Behind this Analysis

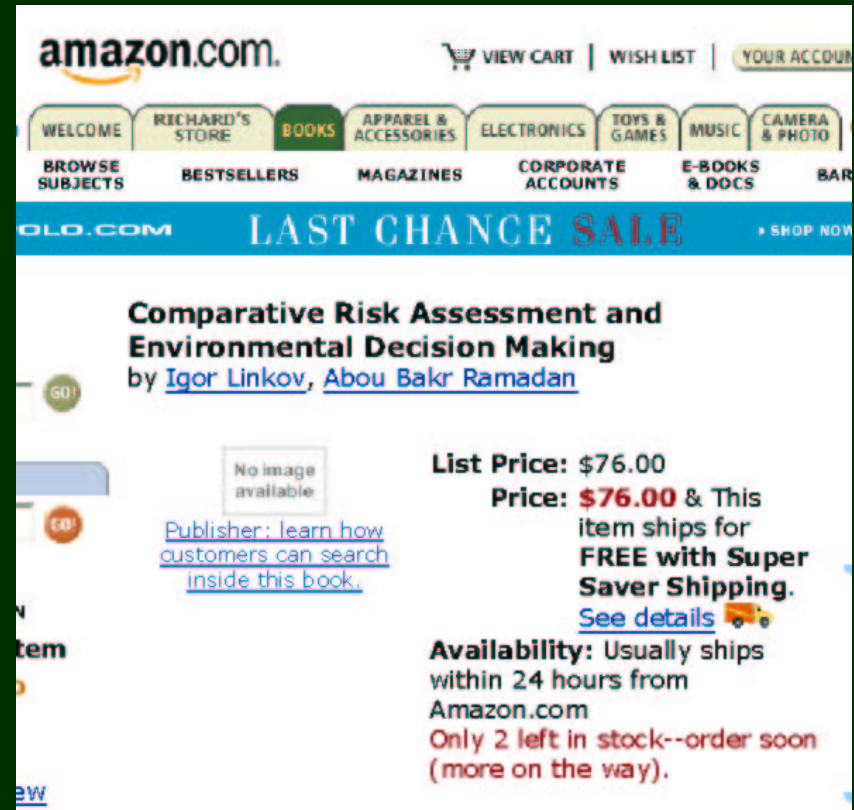
- Assume US EPA 2002 draft risk assessment is correct and proposed 1 ppb drinking water equivalent level is reasonable.
- Indirectly test the plausibility of these assumptions.

Logic Behind this Analysis

- Assume US EPA 2002 draft risk assessment is correct and proposed 1 ppb drinking water equivalent level is reasonable.
- Indirectly test the plausibility of these assumptions. How?
- Compare perchlorate ingestion with anti-thyroid agents found in common foods.
 - Nitrate and thiocyanate
 - Potencies, bioavailability, amounts ingested differ

Nitrate Comparison Is Published

Belzer, RB, Bruce, GM,
Peterson, MK, Pleus, RC,
*Using Comparative
Exposure Analyses to
Validate Low-Dose Human
Health Risk Assessment:
The Case Of Perchlorate*, in
Linkov, I. and Ramadan, A.
eds. Comparative Risk
Assessment and
Environmental Decision
Making. Kluwer, 2004.



Amazon.com sales rank: 2,732,307
“Only 2 left in stock--order soon (more on the way).”

Relative Potencies across NO_3 and ClO_4^-

- Derived from Wyngaarden *et al.* 1953 study directly relevant to this issue
- Biphasic dose-response curve creates uncertainty
 - Best professional judgment = 300
 - High value increases relative weight of ClO_4^-

Relative potencies across
middle of dose-response range: 10x to 330x
(Adapted from Wyngaarden 1953)

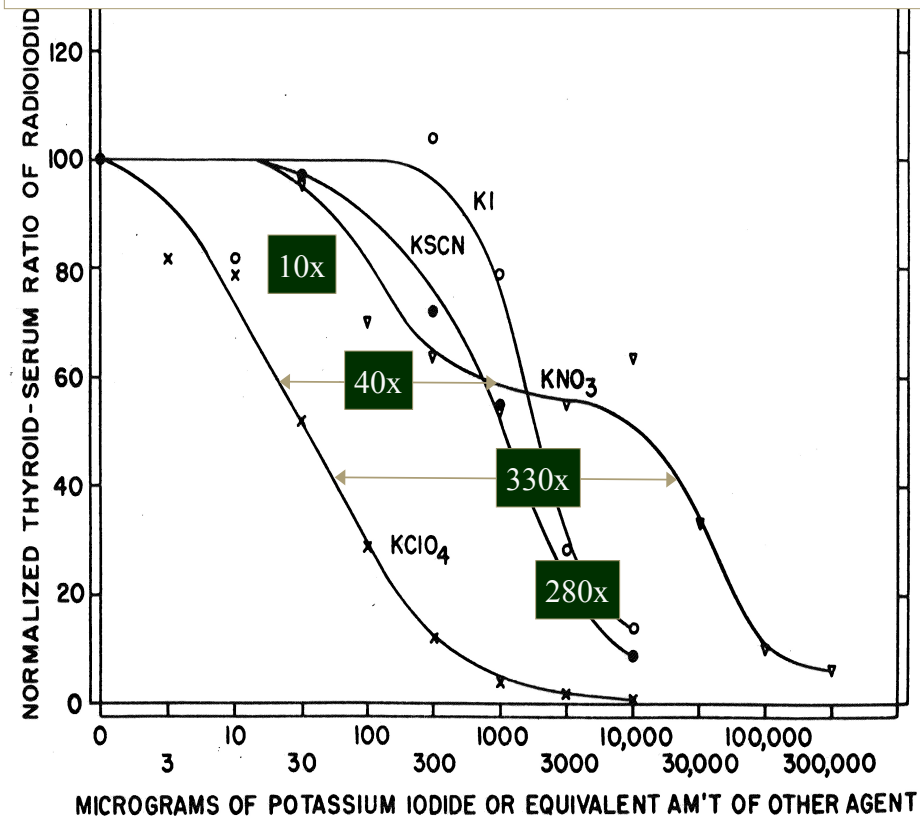


FIG. 1. The effects of iodide, thiocyanate, perchlorate, and nitrate ions upon the concentration gradient of I^{131} , when these agents were given in increasing doses, accompanying a constant dose of I^{131} . The ordinate is thyroid-serum I^{131} ratio, normalized to express the control gradient for each group as 100, and averaged for each agent. The abscissa is the dose of potassium iodide or equivalent dose of thiocyanate, perchlorate, or nitrate, plotted logarithmically.

Perchlorate Equivalency Ratio (PER) to Nitrate

- Calculate ratio of goitrogen to perchlorate exposure using Perchlorate Equivalency Ratios (PERs)
 - $PER = 10 \rightarrow$ perchlorate is 10 times as potent
 - $PER = 300 \rightarrow$ perchlorate is 300 times as potent
 - $PER = 1,000 \rightarrow$ perchlorate is 1,000 times as potent

Perchlorate Equivalency Ratio (PER) to Nitrate

- Calculate ratio of goitrogen to perchlorate exposure using Perchlorate Equivalency Ratios (PERs).
 - $PER = 10 \rightarrow$ perchlorate is 10 times as potent
 - $PER = 300 \rightarrow$ perchlorate is 300 times as potent
 - $PER = 1,000 \rightarrow$ perchlorate is 1,000 times as potent
- Evidence from rat studies for NO_3 ranges from 10 to 330.

Perchlorate Equivalency Ratio (PER) to Nitrate

- Calculate ratio of goitrogen to perchlorate exposure using Perchlorate Equivalency Ratios (PERs)
 - PER = 10 → perchlorate is 10 times as potent
 - PER = 300 → perchlorate is 300 times as potent
 - PER = 1,000 → perchlorate is 1,000 times as potent
- Evidence from rat studies for NO₃ ranges from 10 to 330.
- Tonacchera et al. 2001 *in vitro* study: PER = 240.

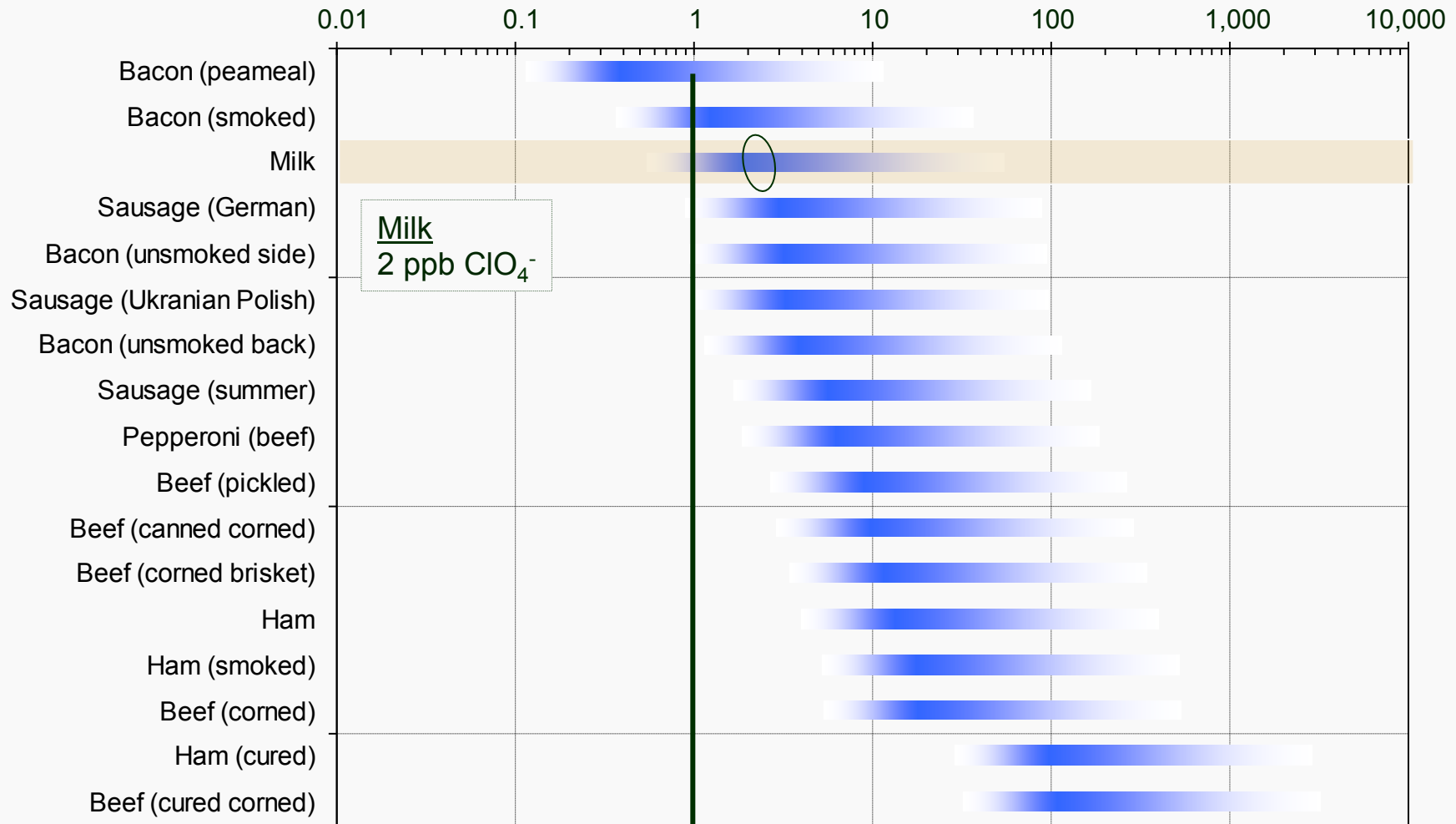
Perchlorate Equivalency Ratio (PER) to Nitrate

- Calculate ratio of goitrogen to perchlorate exposure using Perchlorate Equivalency Ratios (PERs)
 - PER = 10 → perchlorate is 10 times as potent
 - PER = 300 → perchlorate is 300 times as potent
 - PER = 1,000 → perchlorate is 1,000 times as potent
- Evidence from rat studies for NO_3^- ranges from 10 to 330.
- Tonacchera et al. 2001 *in vitro* study: PER = 240.
- Our BPJ appears to overstate potency of ClO_4^- by 25%

Methods

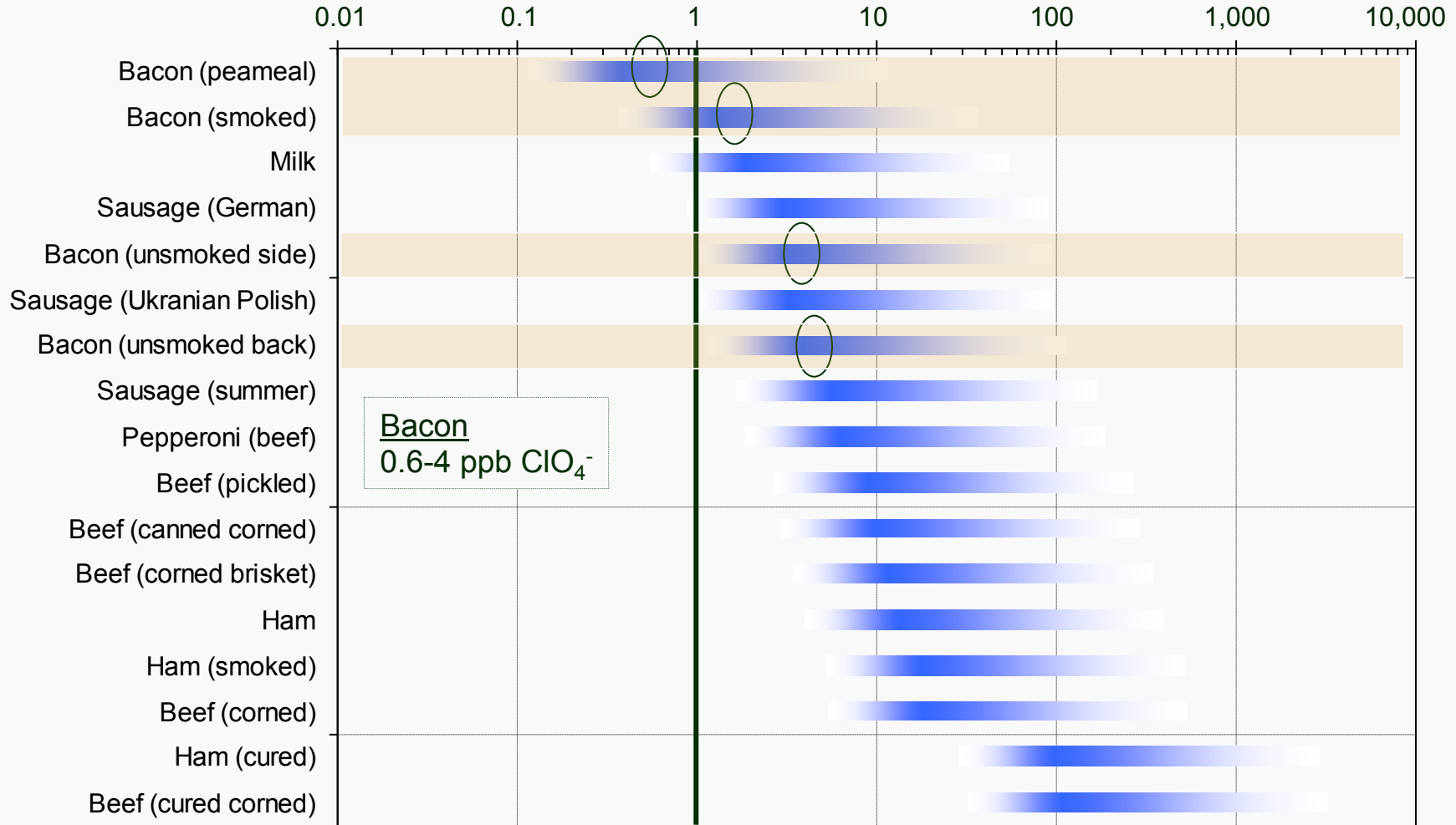
- Convert RfD into a daily dose (0.002 mg/day)
 - Based on a 64.2 kg reference woman
 - The developing baby is the presumed sensitive subpopulation via exposure through her mother
- Calculate nitrate or thiocyanate exposure from foods based on standard references
- Focus on single servings, not complete diet
 - Makes comparisons very simple
 - Underestimates the effects of NO_3 and SCN^-

Iodide Uptake Inhibition from Nitrate in Single Servings of Dairy or Processed Meats Expressed in ppb ClO_4^- in Drinking Water



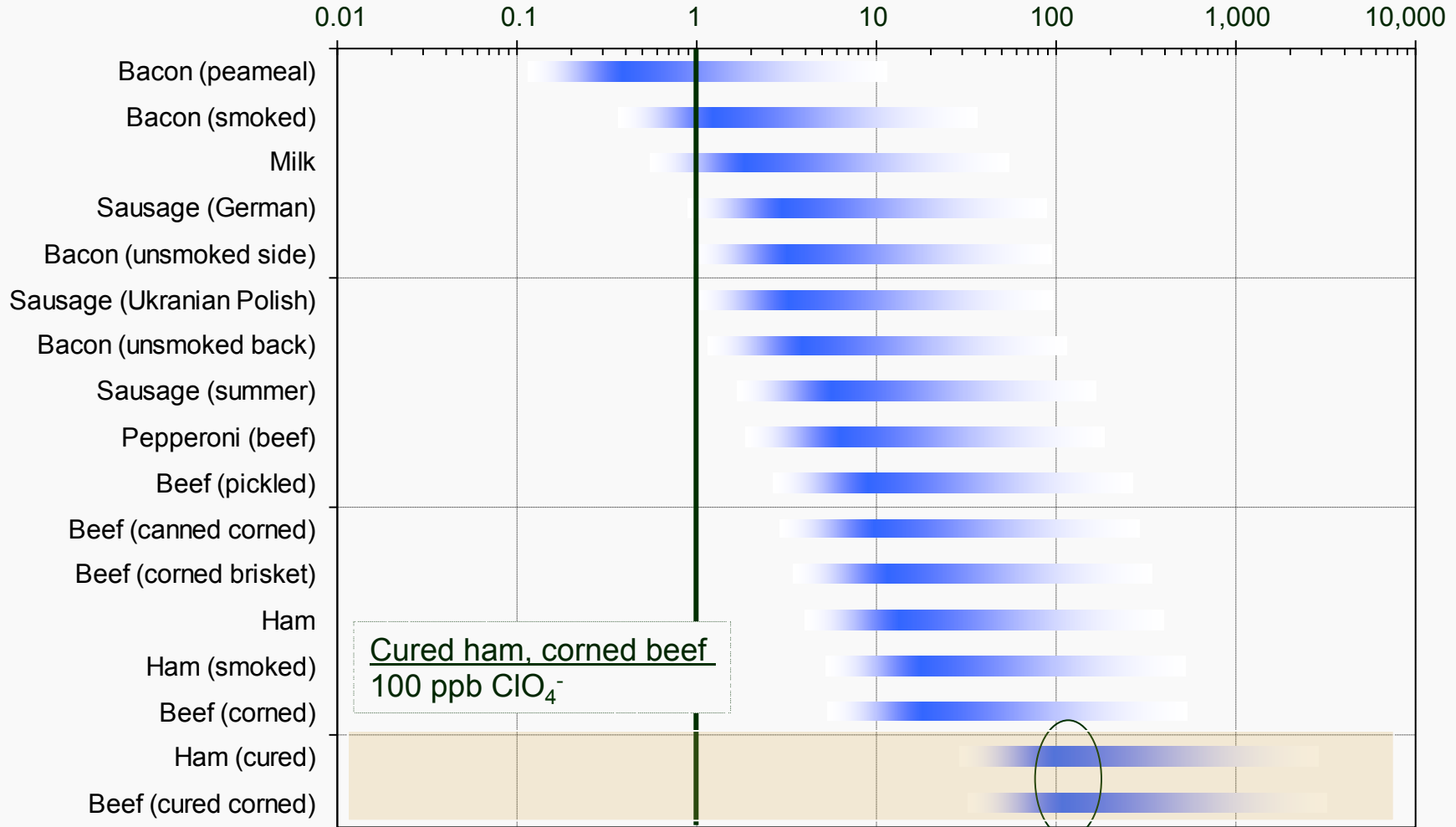
← Below USEPA Proposed ClO_4^- RfD DWEL Above →

Iodide Uptake Inhibition from Nitrate in Single Servings of Dairy or Processed Meats Expressed in ppb ClO_4^- in Drinking Water



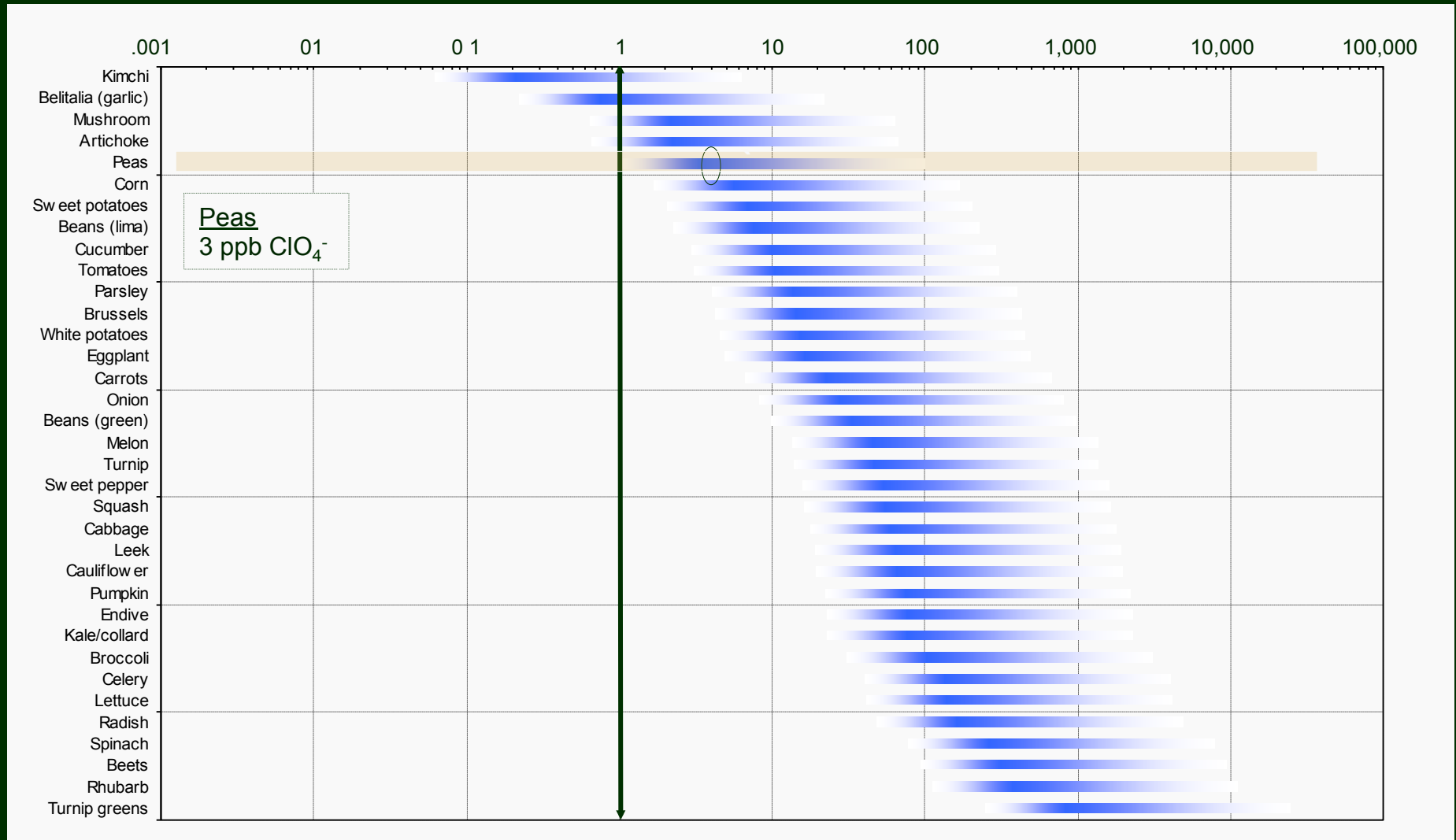
← Below USEPA Proposed ClO_4^- RfD DWEL Above →

Iodide Uptake Inhibition from Nitrate in Single Servings of Dairy or Processed Meats Expressed in ppb ClO_4^- in Drinking Water



Below ← USEPA Proposed ClO_4^- RfD DWEL → Above

Iodide Uptake Inhibition from Nitrate in Single Servings of Vegetables Expressed in ppb ClO_4^- in Drinking Water

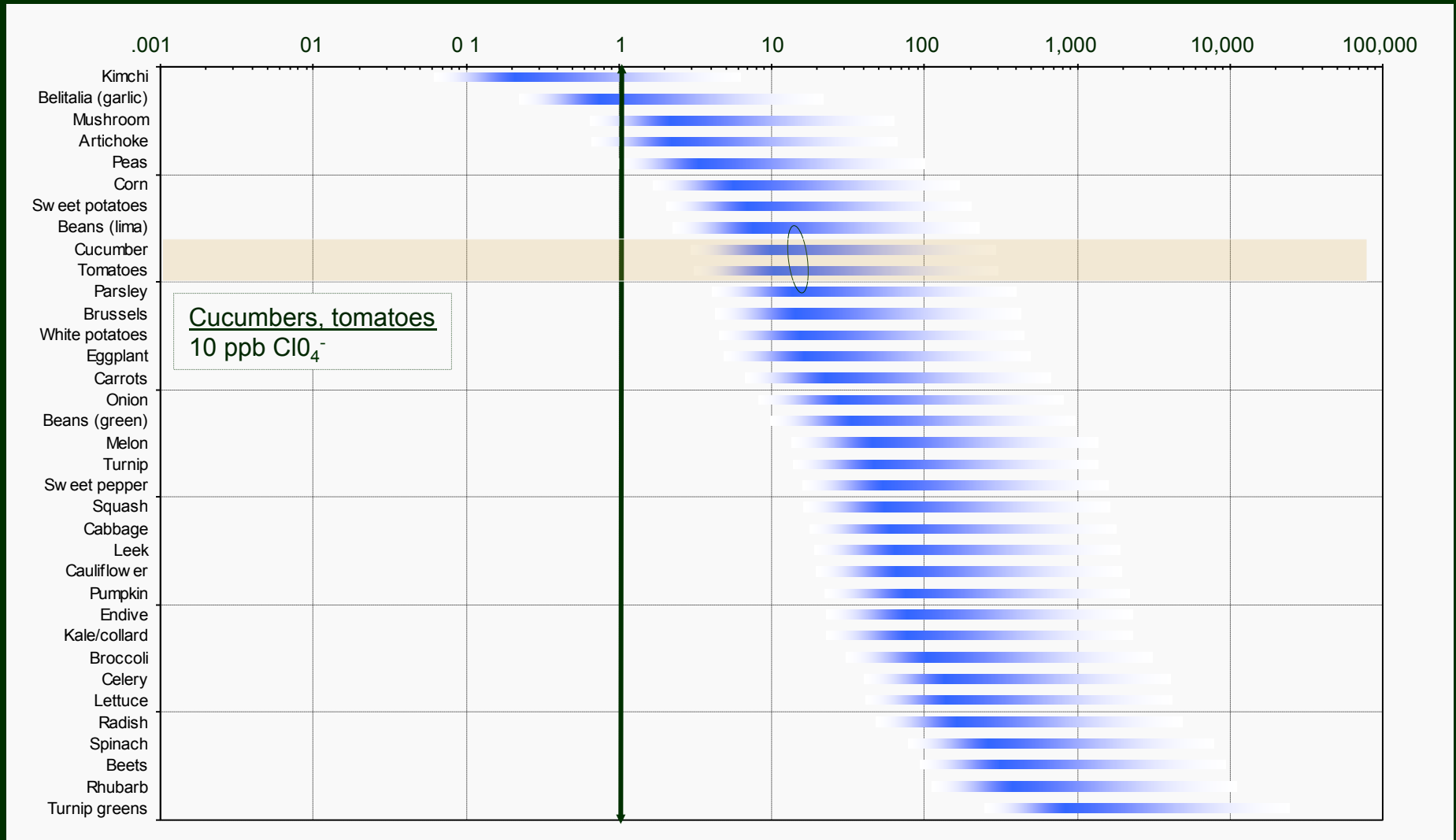


Below

USEPA Proposed
 ClO_4^- RfD DWEL

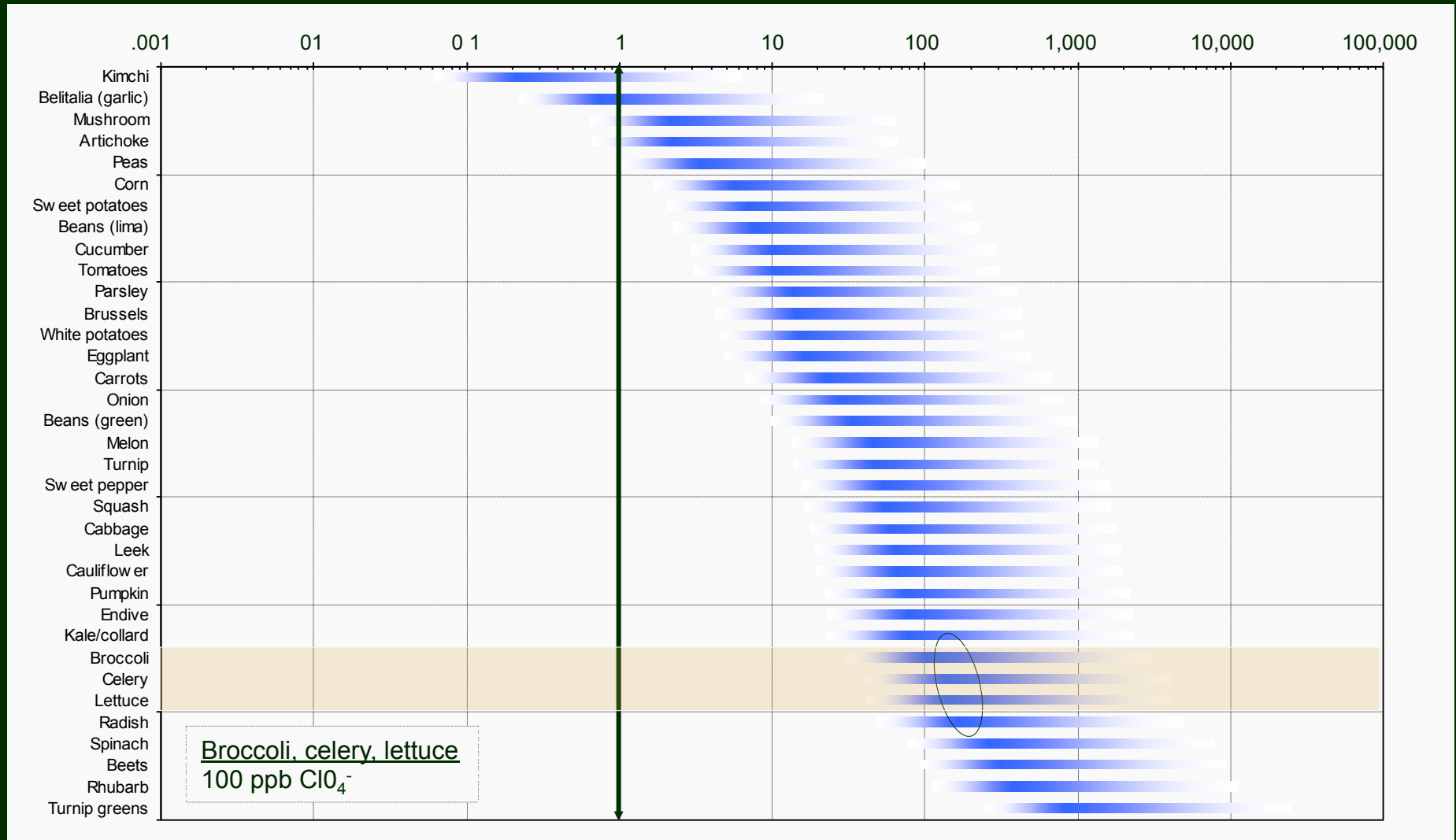
Above

Iodide Uptake Inhibition from Nitrate in Single Servings of Vegetables Expressed in ppb ClO_4^- in Drinking Water



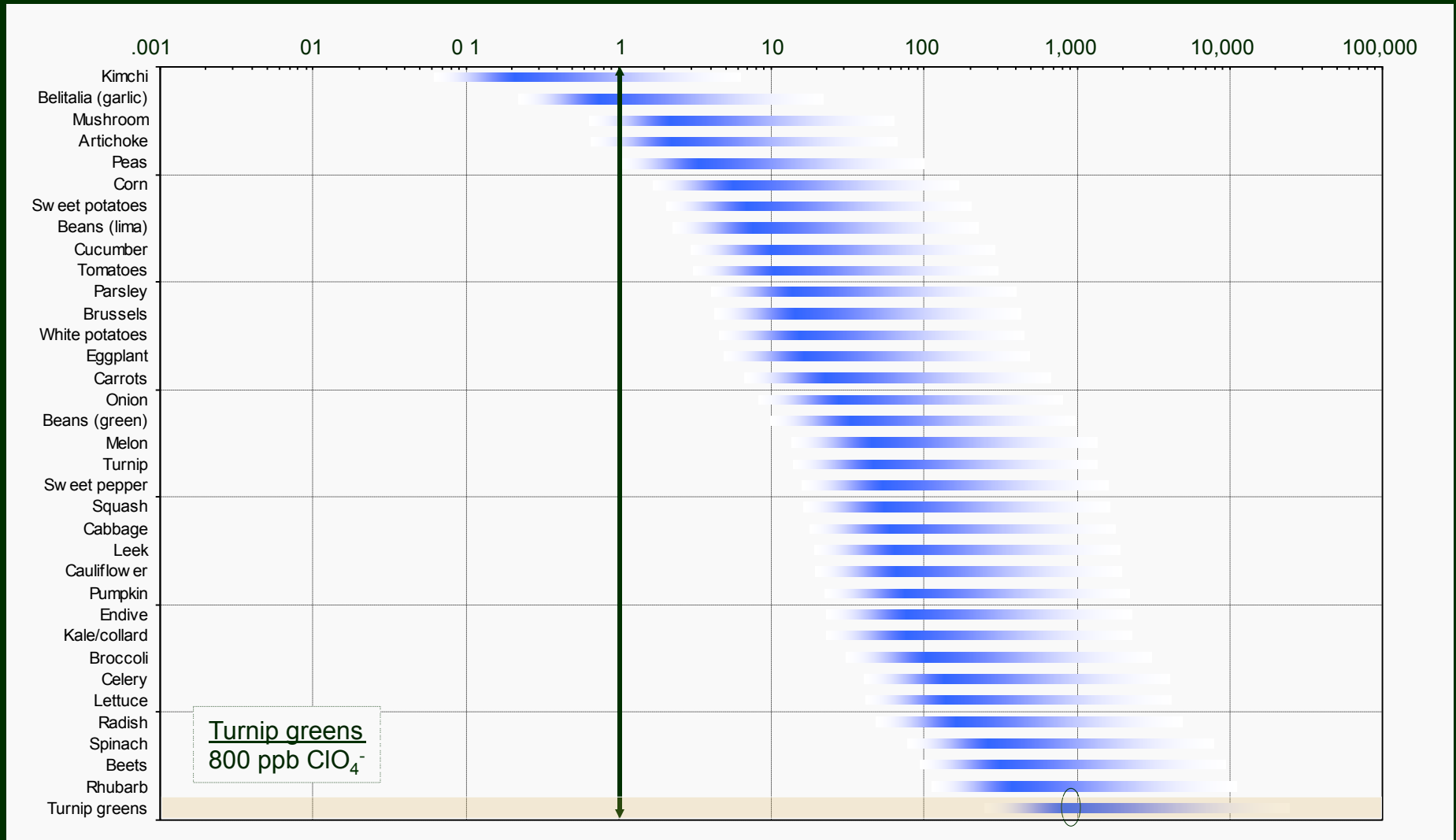
Below ← USEPA Proposed ClO_4^- RfD DWEL → Above

Iodide Uptake Inhibition from Nitrate in Single Servings of Vegetables Expressed in ppb ClO_4^- in Drinking Water



Below ← USEPA Proposed ClO_4^- RfD DWEL → Above

Iodide Uptake Inhibition from Nitrate in Single Servings of Vegetables Expressed in ppb ClO_4^- in Drinking Water



Below ← USEPA Proposed ClO_4^- RfD DWEL → Above

Communicating Risk Information

- What is the “Reference Dose” (really)?
- How is the RfD routinely (mis)interpreted?
- What are its risk communication implications?

What is the 'Reference Dose' (really)? 'Safety' as Defined by Lawyers

- “An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”
-

Scientific Uncertainty in the RfD is Ambiguous

- ‘Uncertainty spanning perhaps an order of magnitude’ means it may exceed 10-fold.
- It could be above or below the RfD.

Scientific Uncertainty in the RfD is Ambiguous

- ‘Uncertainty spanning perhaps an order of magnitude’ means it may exceed 10-fold.
- It could be above or below the RfD.
- What does this mean for perchlorate?
 - U.S. EPA says uncertainty is 10-fold and bisected by the RfD, but the basis for this assertion is not transparent.
 - EPA admits 4-18 ppb interim guideline is really 1-54 ppb.
 - By definition, all values within this range are indistinguishable.
 - There is no scientific basis to believe that uncertainty is only 10-fold.

How is the RfD Routinely (Mis)interpreted?

- Critical policy choices are hidden within the RfD definition.
 - What is an “appreciable” risk?
 - What does “likely to be without” risk mean?
 - What effects are “deleterious”?

How is the RfD Routinely (Mis)interpreted?

- Critical policy choices are hidden within the RfD definition.
- The RfD is well-misunderstood by the public.
 - “The RfD applies to less-than-lifetime exposures.” No.
 - “The RfD is a ‘bright line’ separating ‘safety’ from ‘risk’ .” No.
 - “Exposures above the RfD are ‘unsafe’ .” No.

How is the RfD Routinely (Mis)interpreted?

- Critical policy choices are hidden within the RfD definition.
- The RfD is well-misunderstood by the public.
- The RfD delivers a false, dichotomous risk message.
 - Any exposure below the RfD is “safe”.
 - Any exposure above the RfD is “unsafe”.

Implied Risk Communication Message:

Nitrate in
Dairy and
Processed Meats

Perchlorate-equivalent exposure in ppb, per serving
Green = "safe"
Red = "unsafe"

- Very few are "safe"
 - They are "safe" only under very high PER scenarios
- Most are "unsafe"
 - The true PER doesn't matter

PER Value	10	30	100	300	1000
Bacon (peameal)	10.	4.	1.	.4	.1
Bacon (smoked)	40.	10.	4.	1.	.4
Milk	60.	20.	6.	2.	.6
Sausage (German)	90.	30.	9.	3.	.9
Bacon (unsmoked side)	100.	30.	10.	3.	1.
Sausage (Ukrainian Polish)	100.	30.	10.	3.	1.
Bacon (unsmoked back)	100.	40.	10.	4.	1.
Sausage (summer)	200.	60.	20.	6.	2.
Pepperoni (beef)	200.	60.	20.	6.	2.
Beef (pickled)	300.	90.	30.	9.	3.
Beef (canned corned)	300.	100.	30.	10.	3.
Beef (corned brisket)	300.	100.	30.	10.	3.
Ham	400.	100.	40.	10.	4.
Ham (smoked)	500.	200.	50.	20.	5.
Beef (corned)	500.	200.	50.	20.	5.
Ham (cured)	3,000.	1,000.	300.	100.	30.
Beef (cured corned)	3,000.	1,000.	300.	100.	30.

Implied Risk Communication Message:

Low-nitrate
Vegetables

Perchlorate-equivalent exposure in ppb, per serving
Green = "safe"
Red = "unsafe"

PER Value	10	30	100	300	1000
Kimchi	6.	2.	1.	.2	.1
Belitalia (garlic)	20.	7.	2.	.7	.2
Mushroom	60.	20.	6.	2.	.6
Artichoke	70.	20.	7.	2.	.7
Peas	100.	30.	10.	3.	1.

- Very few are "safe"
 - They are "safe" only under very high PER scenarios
- Most are "unsafe"
 - The true PER doesn't matter

Implied Risk Communication Message:

Intermediate-nitrate

Vegetables

- All are “unsafe”
- The true PER does not matter

Perchlorate-equivalent exposure in ppb, per serving
Green = “safe” Red = “unsafe”

PER Value	10	30	100	300	1000
Corn	200.	60.	20.	6.	2.
Sweet potatoes	200.	70.	20.	7.	2.
Beans (lima)	200.	80.	20.	8.	2.
Cucumber	300.	100.	30.	10.	3.
Tomatoes	300.	100.	30.	10.	3.
Parsley	400.	100.	40.	10.	4.
Brussels sprouts	400.	100.	40.	10.	4.
White potatoes	500.	200.	50.	20.	5.
Eggplant	500.	200.	50.	20.	5.
Carrots	700.	200.	70.	20.	7.
Onion	800.	300.	80.	30.	8.
Beans (green)	1,000.	300.	100.	30.	10.
Melon	1,000.	500.	100.	50.	10.
Turnip	1,000.	500.	100.	50.	10.
Sweet pepper	2,000.	500.	200.	50.	20.

Comparing Perchlorate with Nitrate

High-nitrate
Vegetables

Perchlorate-equivalent exposure in ppb, per serving
Green = "safe" Red = "unsafe"

- All are "unsafe"
- Green, leafy vegetables are the "worst"

PER Value	10	30	100	300	1000
Squash	2,000.	600.	200.	60.	20.
Cabbage	2,000.	600.	200.	60.	20.
Leek	2,000.	700.	200.	70.	20.
Cauliflower	2,000.	700.	200.	70.	20.
Pumpkin	2,000.	800.	200.	80.	20.
Endive	2,000.	800.	200.	80.	20.
Kale/collard	2,000.	800.	200.	80.	20.
Broccoli	3,000.	1,000.	300.	100.	30.
Celery	4,000.	1,000.	400.	100.	40.
Lettuce	4,000.	1,000.	400.	100.	40.
Radish	5,000.	2,000.	500.	200.	50.
Spinach	8,000.	3,000.	800.	300.	80.
Beets	10,000.	3,000.	1,000.	300.	100.
Rhubarb	10,000.	4,000.	1,000.	400.	100.
Turnip greens	30,000.	8,000.	3,000.	800.	300.

Comparing Perchlorate with Thiocyanate

- Thiocyanates are well-known dietary goitrogens.
- Epidemiological studies have shown thyroidal effects.
 - Cassava consumption elevated TSH, decreased T4 levels compared to control populations with lower thiocyanate (Akindahunsi et al., 1998, Biassoni et al., 1991).
 - Like nitrate, iodine deficiency may be a confounder.
 - Adequate iodine may be protective for all such agents.

PER Estimates for Thiocyanate

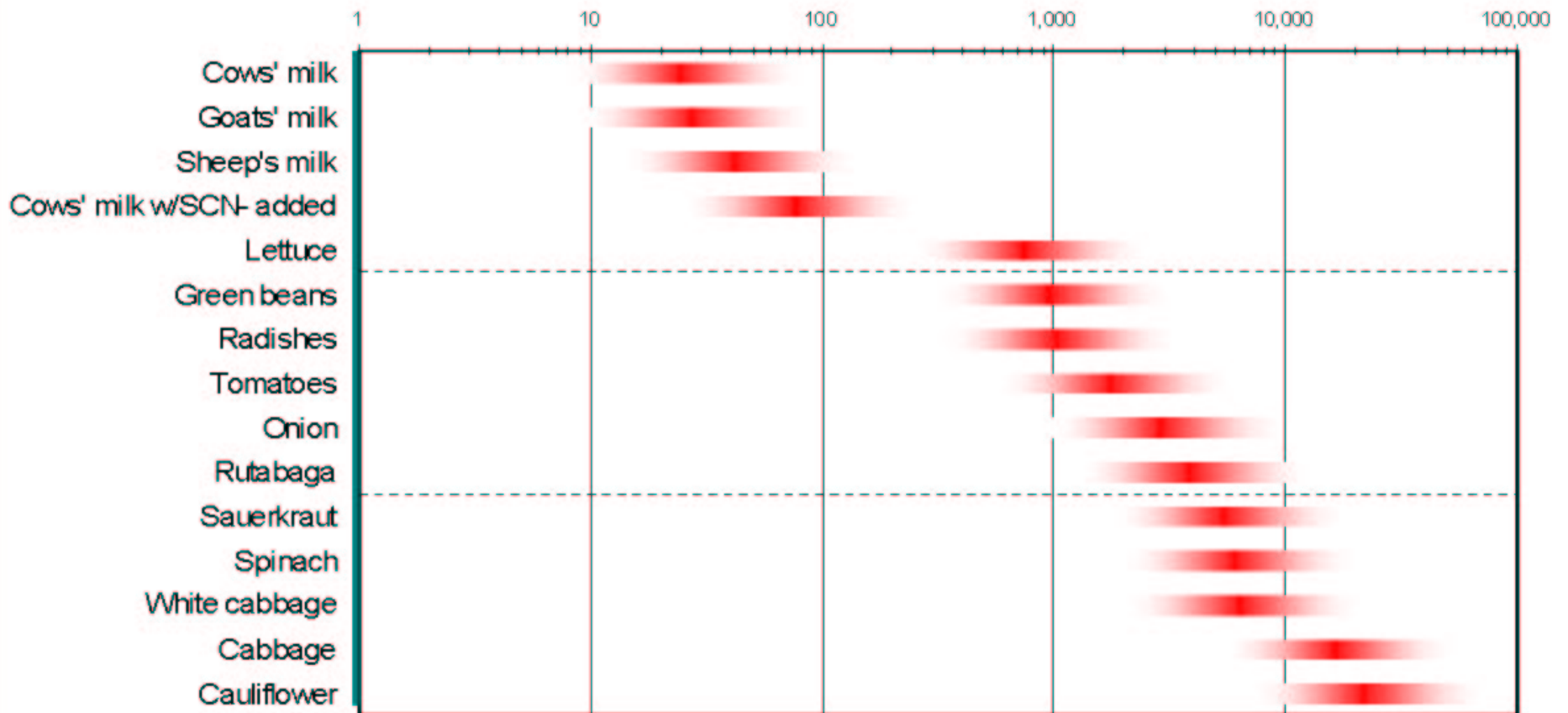
Study	PER Estimate	Notes
Greer et al. (1966)	12	Based on 50% iodide uptake inhibition
Wyngaarden et al. (1953)	23	Used Figure 1 from study; based on average normalized thyroid-serum ratio of 20, 50, and 80
Wyngaarden et al. (1952)	10	Data not presented in study; derived from text
Tonacchera et al. (2001)	10	Data from Figure 4 of paper Human NIS transfected in Chinese hamster ovary cells
Low PER	3	BPJ bisects 10x uncertainty No empirical data support 3 or 30
BPJ PER	10	
High PER	30	

Iodide Uptake Inhibition from SCN⁻ in Single Servings of Various Foods Expressed in ppb ClO₄⁻ in Drinking Water*

Food	Minimum	BPJ	Maximum
Cows' milk	80	20	10
Goats' milk	90	30	10
Sheep's milk	100	40	10
Cows' milk w/SCN ⁻ added	300	100	30
Lettuce	2,000	1,000	200
Green beans	3,200	1,000	300
Radishes	3,000	1,000	300
Tomatoes	6,000	1,800	600
Onion	10,000	3,000	1,000
Rutabaga	10,000	4,000	1,300
Sauerkraut	20,000	5,000	1,800
Spinach	20,000	6,000	2,000
White cabbage	20,000	6,000	2,000
Cabbage	50,000	20,000	5,000
Cauliflower	70,000	20,000	7,000

* 1 significant figure, adult drinking water consumption assumed to be 2 L/day

Estimated Iodide Uptake Inhibition from SCN^- in Single Servings of Various Foods Expressed in ppb ClO_4^- in Drinking Water



USEPA Proposed ClO_4^- RfD → Above

Conclusions:

If $\text{ClO}_4^- > 1$ ppb is 'unsafe', then...

- 1 serving of common foods is 10s to 100s of times more "unsafe" from nitrate.
- 1 serving of common foods is 100s to 1000s of times more "unsafe" from thiocyanate.
- If single servings of common foods are 'safe', then the US EPA risk assessment for perchlorate is wrong.

Questions?

Richard B Belzer, PhD.

Belzer@RegulatoryCheckbook.Org

703.780-1850 v

202.478.1626 f