Safety of Vitamin D

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safety

1: the condition of being safe from undergoing or causing hurt, injury, or loss

IOM August 4 2009

Safety = Toxicity

For vitamin D, the classic criteria for harm pertain to excessive calcium in serum or urine.

No other harmful outcomes are known... except for some epidemiologic relationships that relate higher serum 25(OH)D to higher risk of prostate and pancreatic cancers.

Safety = Toxicity

The context of calcium excess:

Vitamin D3 Poisoning by Table Sugar.

DOSE: 1.7 MILLION UNITS/DAY FOR 7 MONTHS!

Reinhold Vieth PhD[b], Tanya R Pinto BSc[b], Bajinder S Reen MD[a], and Min M Wong MD[a]

Lancet 2002 359: 672

June 1999, a 29-year-old man admitted to emergency with symptoms of:

- **extreme right-sided flank pain**
- **conjunctivitis** (a sign of dehydration)
- **increased thirst**
- **vomiting**
- **in acute renal failure**
- **anorexia**
- **fever, chills**

Initially treated with steroids and discharged:
presumed gastroenteritis

Vitamin D3 Poisoning by Table Sugar.
DOSE: 1.7 MILLION UNITS/DAY FOR 7 MONTHS!

October 1999, his 63-year-old father was admitted to emergency with similar complaints.

He was also in acute renal failure, and no history of stones.

Calcium VERY HIGH 3.82 mmol/L (normal, 2.20-2.65 mmol/L),

25(OH)D HIGH 1555 nmol/L (normal 20-80 nmol/L)

1,25(OH)$_2$D NEAR NORMAL 151 pmol/L (normal, 30-140 pmol/L

Elevated "free" 1,25(OH)2D causing toxicity.

Lancet 2002 359: 672

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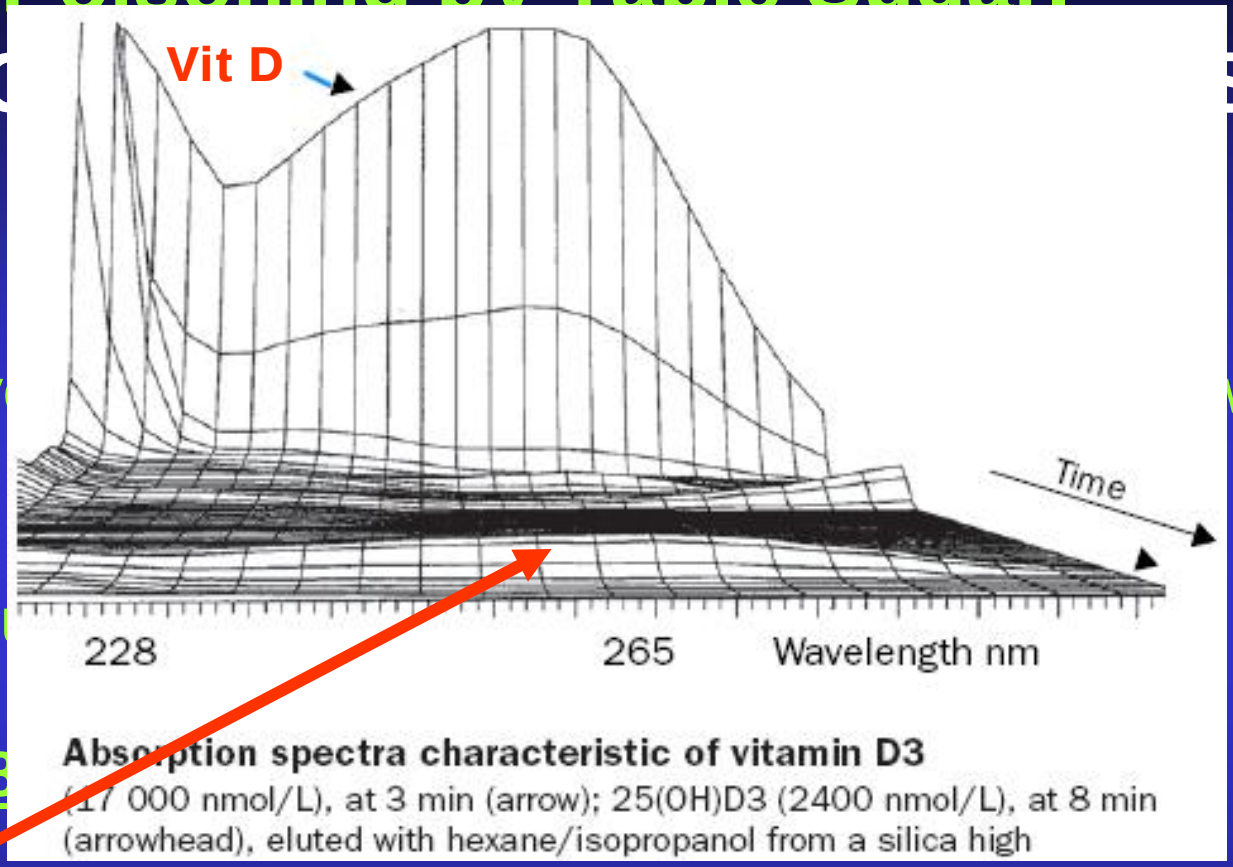
October 1999, his 63-y… with

He was also in ac…

Calcium VERY HIGH 3.8…



Absorption spectra characteristic of vitamin D3
(17 000 nmol/L), at 3 min (arrow); 25(OH)D3 (2400 nmol/L), at 8 min (arrowhead), eluted with hexane/isopropanol from a silica high

25(OH)D HIGH 1555 nmol/L (normal 20-80 nmol/L)

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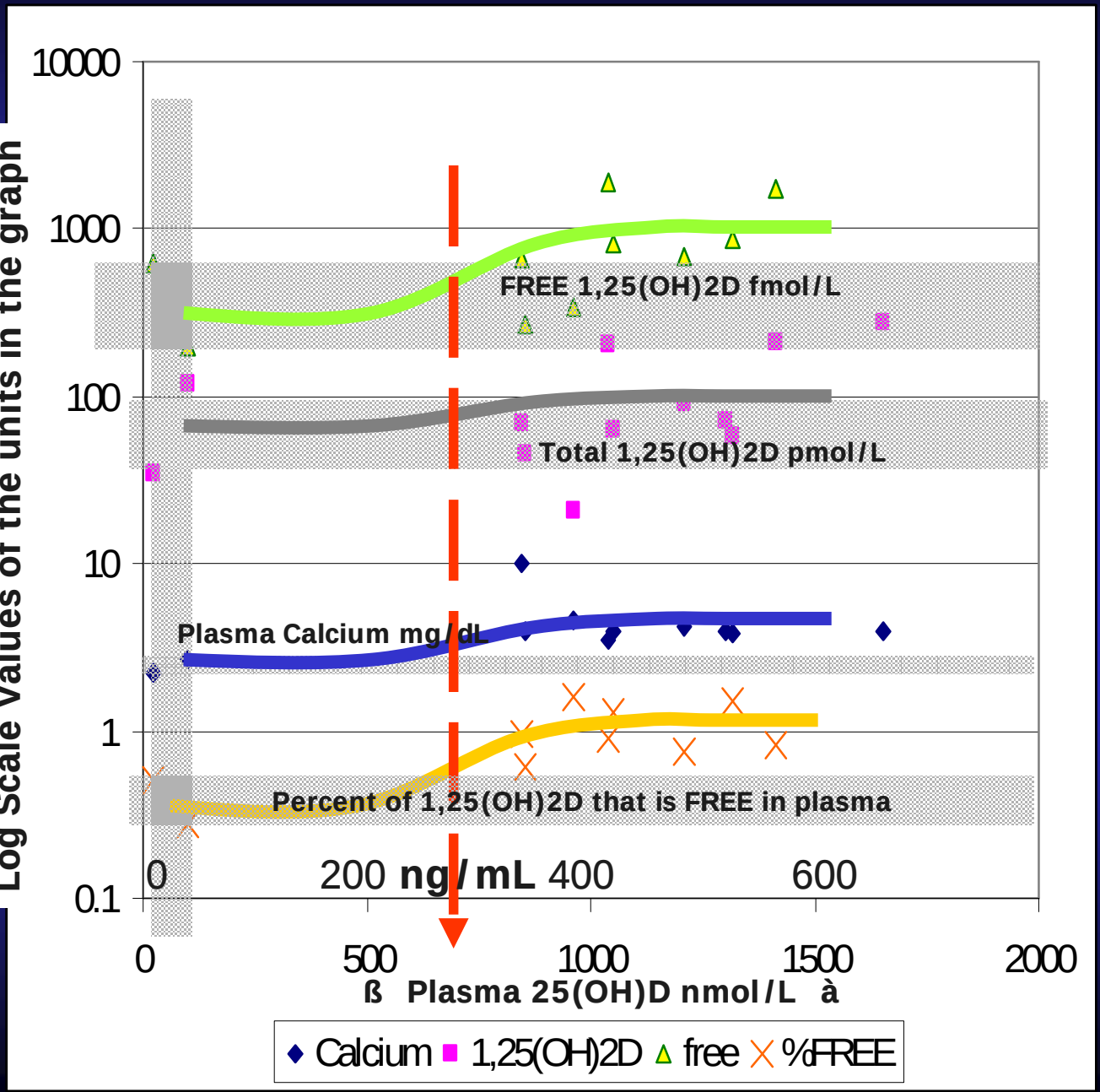
Lancet 2002 359: 672

2. Saturability: 25(OH)D > 600 nmol/L



Toxic mechanism involves FREE 1,25(OH)2D

Pettifor, J. M. et. al. Ann Inter Med 1995;122:511-513

SATURABILITY OF DBP

PLASMA

D-Binding

Protein

(capacity

4300 nmol/L

1800 ng/mL)

PLASMA

VITAMIN D

METABOLITES

BOUND

PLASMA
1,25(OH)2D
BOUND

Excessive calcium in blood and urine

PLASMA

1,25(OH)2D

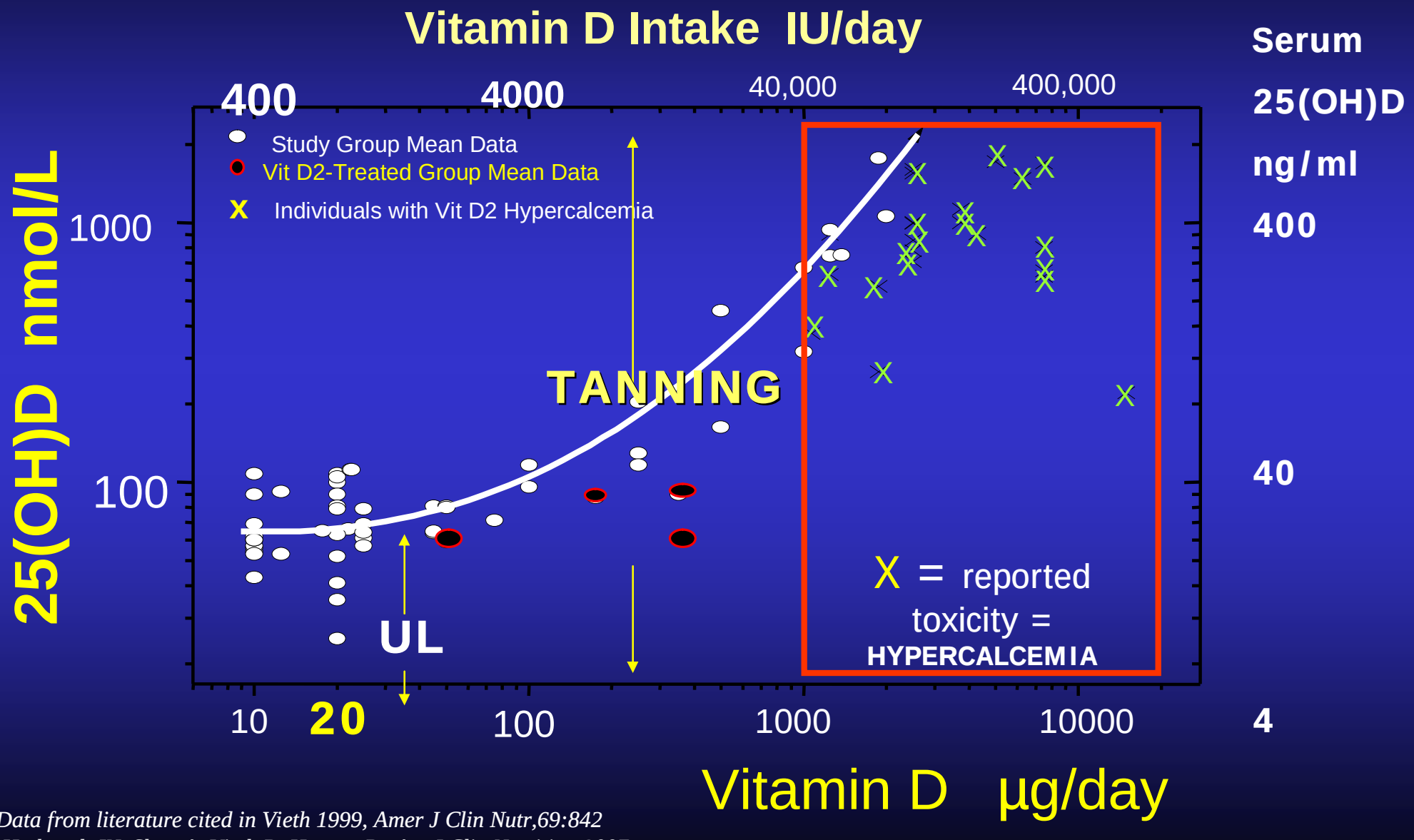
FREE

INTESTINE CALCIUM ABSORPTION

BONE CALCIUM RESORPTION

Vieth *Bone and Mineral, 11* (1990) 267-272

Human Dose Response for vitamin D



Data from literature cited in Vieth 1999, Amer J Clin Nutr,69:842
Hathcock JN, Shao A, Vieth R, Heaney R. Am J Clin Nutrition 2007

Safety of vitamin D_3 in adults with multiple sclerosis[1–3]

Samantha M Kimball, Melanie R Ursell, Paul O'Connor, and Reinhold Vieth

ABSTRACT

Background: Vitamin D_3 may have therapeutic potential in several diseases,including multiple sclerosis. High doses of vitamin D_3 may be required for therapeutic efficacy, and yet tolerability—in the present context, defined as the serum concentration of 24-hydroxyvitamin D [25(OH)D] that does not cause hypercalcemia—remains poorly characterized.

Objective: The objective of the study was to characterize the calcemic response to specific serum 25(OH)D concentrations.

Design: In a 28-wk protocol, 12 patients in an active phase of multiple sclerosis were given 1200 mg elemental Ca/d along with progressively increasing doses of vitamin D_3: from 700 to 7000 μg/wk (from 28 000 to 280 000 IU/wk).

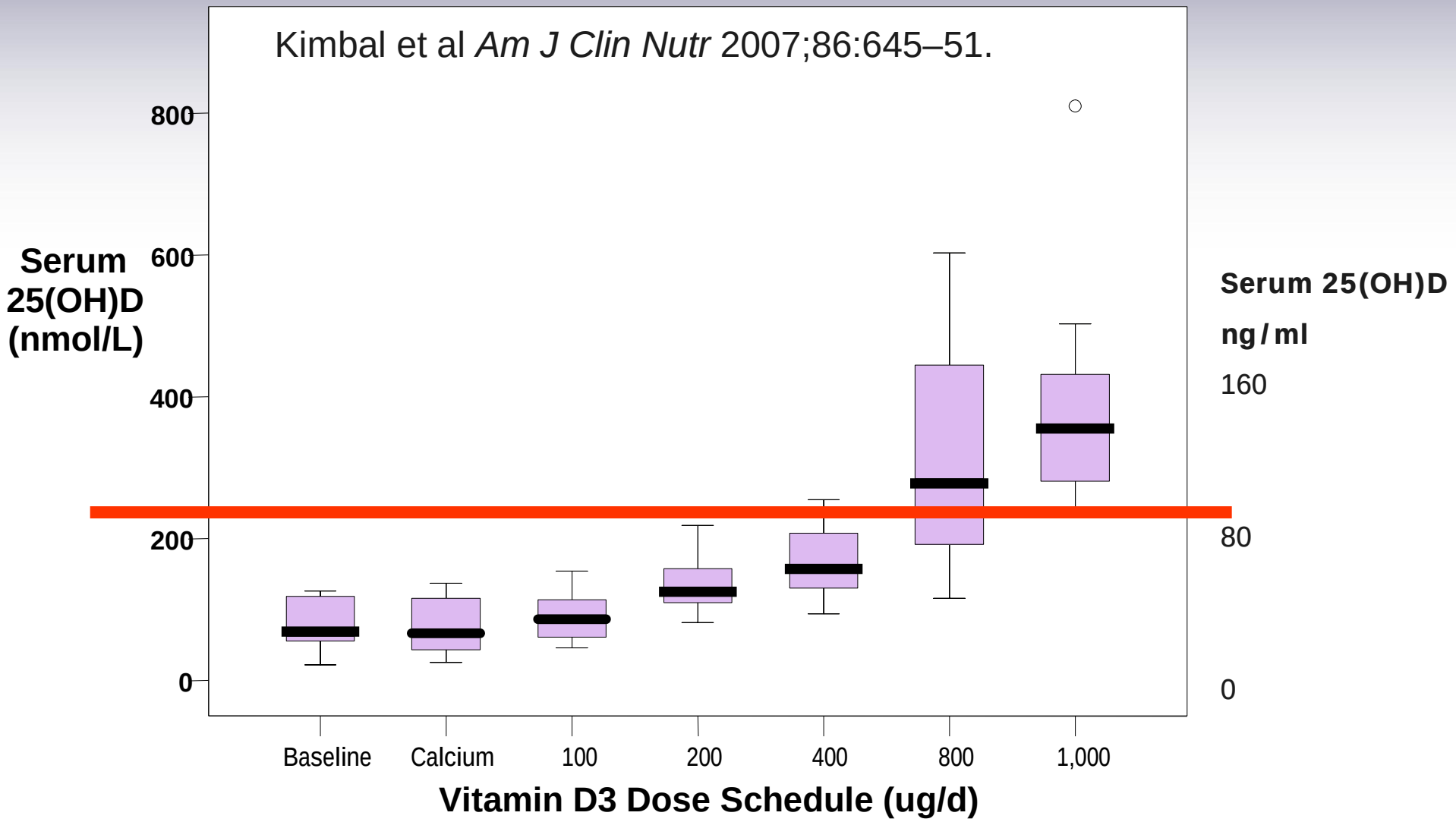
Intakes of 100 μg/d (4000 IU/d) (5) (6) have been shown to be safe. studies suggest that the desirable s [25(OH)D] concentration exceeds and sustain these concentrations adults require vitamin D intakes o IU/d) (10, 11).

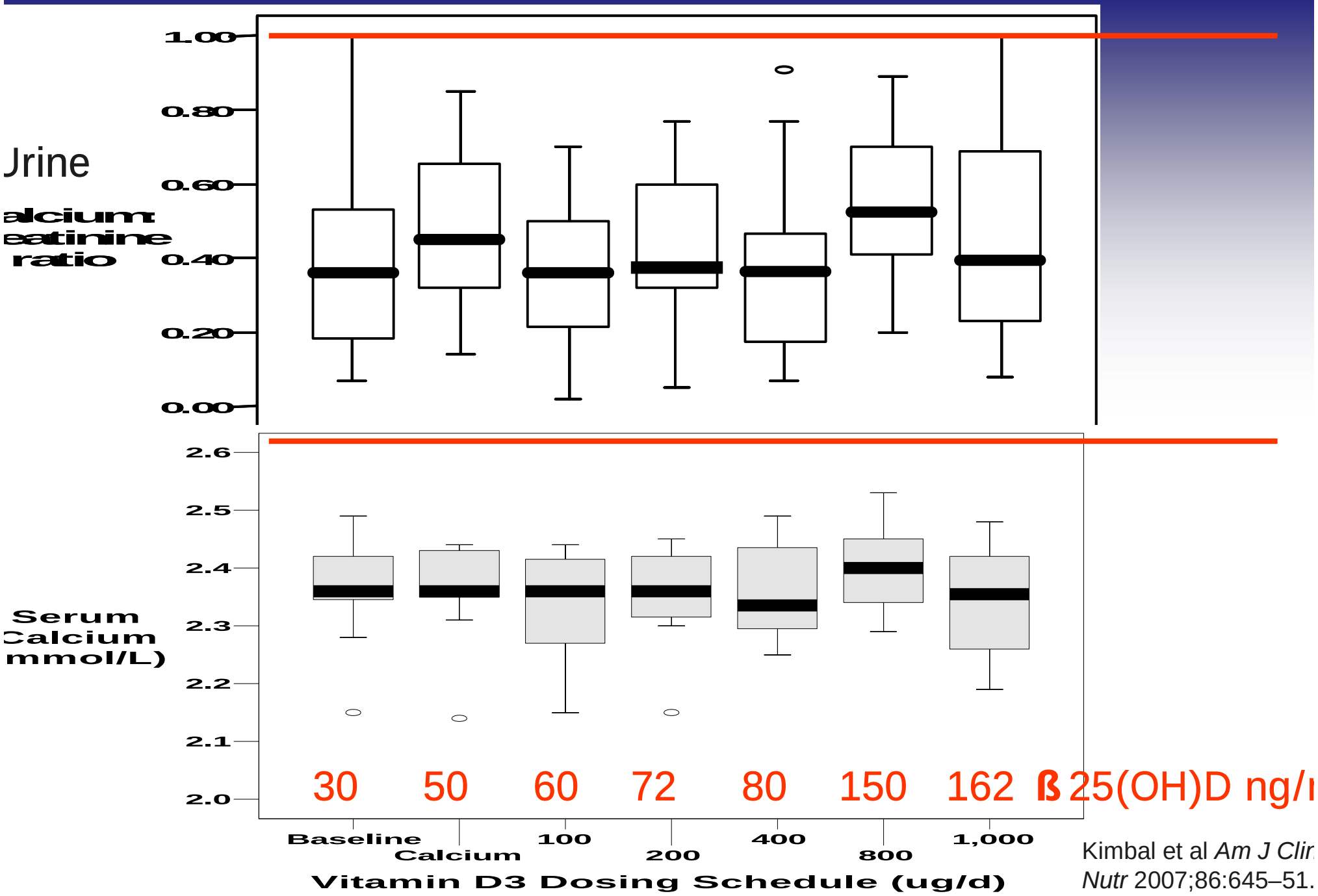
There is much interest in the role o of health and disease. The rationale multiple sclerosis (MS) is that metab as paracrine immune modulators (1 tion of proinflammatory T lymphoc duction of cytokines, both of which

Am J Clin Nutr 2007;86:645–51.

Doses of vitamin D pertinent to the UL and LOAEL, and their effects on serum calcium

MS Patients on 1200 mc Ca. EVERY MONTH THE VITAMIN D3 DOSE WAS INCREASE
N A STUDY TO CHARACTERIZE TOLERABILITY TO SPECIFIC SERUM 25(OH)D LEVEL





Kimbal et al *Am J Clir*
Nutr 2007;86:645–51.

ABSORPTION OF CALCIUM FROM DIET

The effect of vitamin D nutrition (based on serum 25(OH)D reaches a plateau at about 80 nmol/L)

R Heaney, *Journal of Steroid Biochemistry & Molecular Biology* xxx (2005)

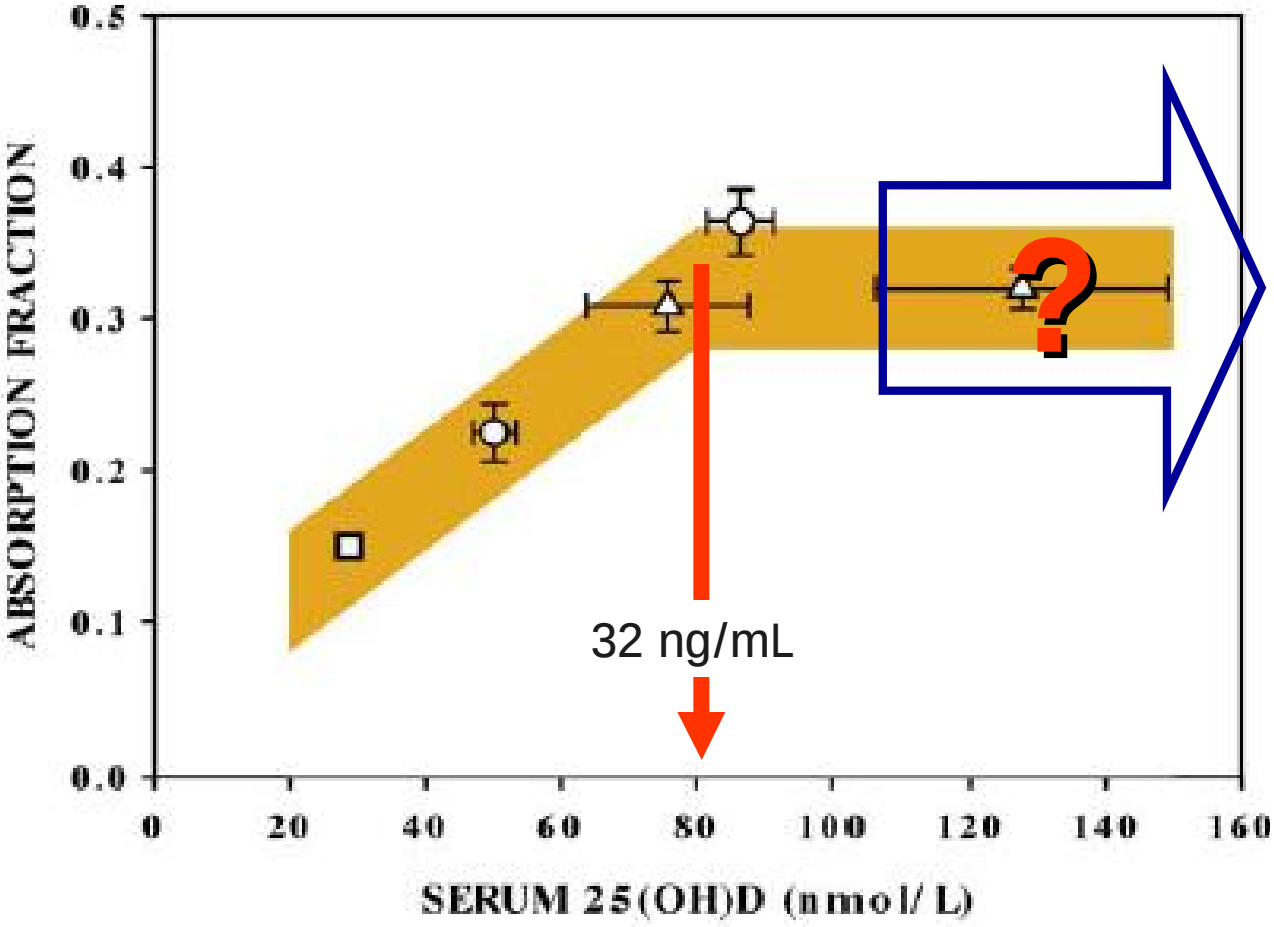
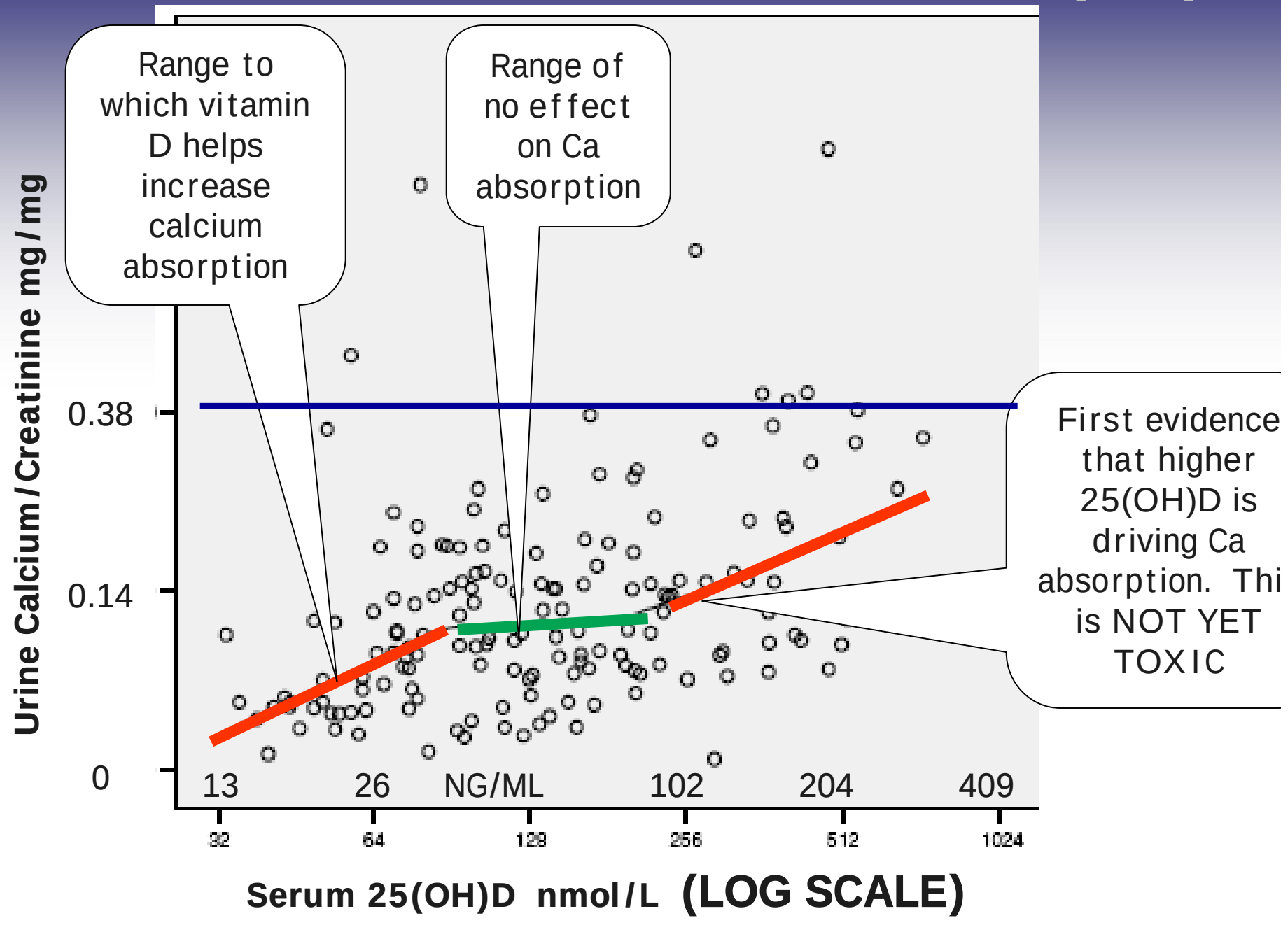


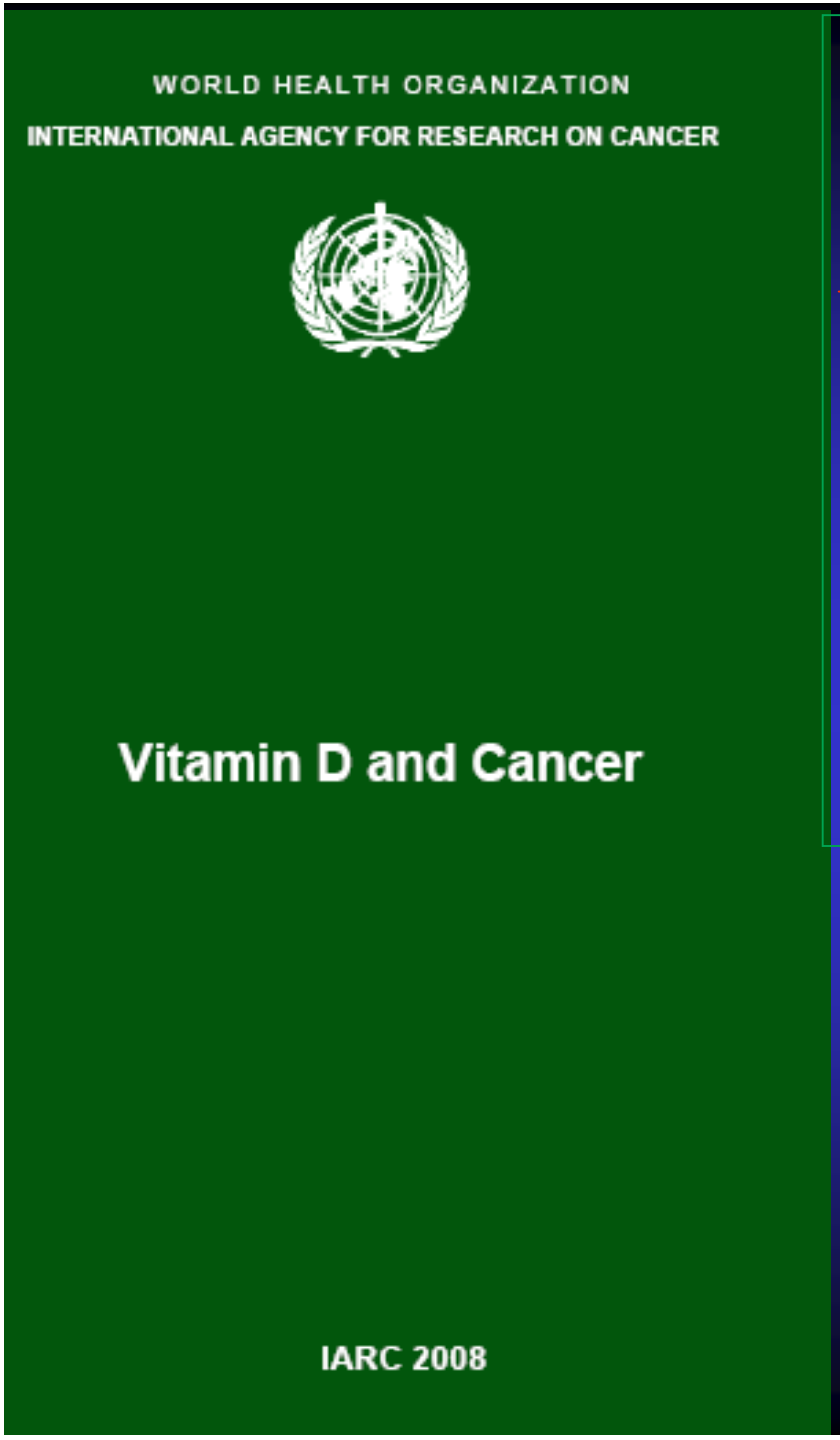
Fig. 2. Calcium absorption fraction plotted as a function of serum 25OHD concentration in three studies. The paired ○ symbols represent the data of one study [11]; the paired △ symbols, a second [12], and the □ symbol is the estimated absorption for the subjects not treated with Vitamin D in the study of Bischoff et al. [13,14]. (Copyright Robert P. Heaney, 2003. Used with permission.)

Urine calcium / creatinine ratio vs 25(OH)D



Safety = Toxicity

The context of Higher 25(OH)D and Higher Cancer risk



Overall conclusion 6: adverse events

There is no data available on the health hazards of long□term maintenance of high 25□hydroxyvitamin D serum levels in healthy subjects over long periods.

Past experiences with other compounds (e.g., **several anti□oxidants** and **hormone replacement therapies**) have shown serious adverse effects of the chronic use of supplements or long□term maintenance of high serum levels.

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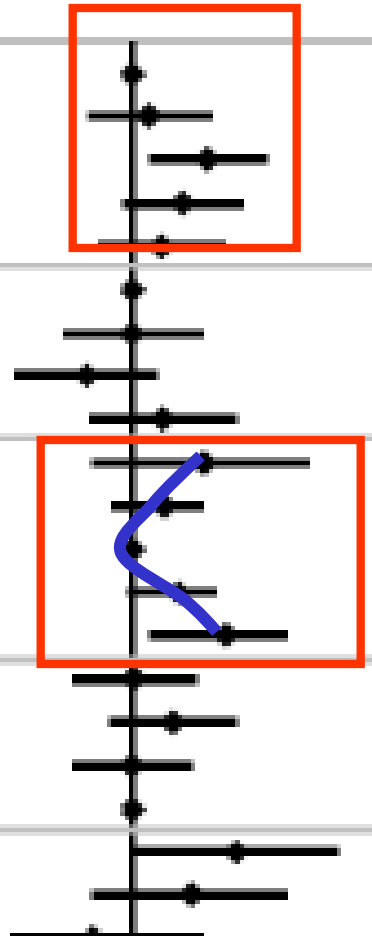
Number 183 Vitamin D and Calcium: A Systematic Review of Health Outcomes
Prepared for: Agency for Healthcare Research and Quality

Figure 7. Prostate cancer risk stratified by vitamin D concentration

Study	Category	25(OH)D concentration (nmol/L)	P for trend	Quality
Ahn 2008 (n=1530)	Q1 (ref)	13 - 43	0.20	B
	Q2	43 - 51		
	Q3	51 - 61		
	Q4	61 - 72		
	Q5	72 - 129		
Platz 2004 (n=920)	Q1 (ref)	nd	0.59	B
	Q2	nd		
	Q3	nd		
	Q4	nd		
Tuohimaa 2004 (n=2073)	Cat1	<19	nd	C
	Cat2	20 - 39		
	Cat3 (ref)	40 - 49		
	Cat4	50 - 79		
	Cat5	>80		
Li 2007 (n=1156)	Q1	nd	0.91	C
	Q2	nd		
	Q3	nd		
	Q4 (ref)	nd		
Ahonen 2000 (n=715)	Q1	<30	0.01	C
	Q2	31 - 40		



le 29. Vitamin D and pancreatic cancer: Results of observational studies

or Year y Name	Life Stage, y	Outcome (no. of cases; no. of control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of cases	No. of control	Adjusted OR	95% CI	P for trend
enberg-Solomon 77 nd l) 17067]	51-70, male only	Exocrine pancreatic cancer (200; 400)	11.8 (median)						0.001
				<32	27	80	1	Reference	
				32-41.1	34	80	1.30	0.70, 2.40	
				41.1-51.1	47	80	2.12	1.15, 3.90*	
				51.1-65.5	35	81	1.50	0.81, 2.76	
				>65.5	57	79	2.92	1.56, 5.48*	
enberg-Solomon 78) ius) 18842]	51-70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y						0.49
				≤45.9	44	74	1	Reference	
				>45.9 to ≤60.3	40	74	0.97		
				>60.3 to ≤69.5	27	73	0.86		
				>69.5 to ≤82.3	31	74	0.84		
				>82.3	42	73	1.45		
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd						
				<49.3	22	44	1		
				>49.3 to <65.2	22	42	2.52		
				>65.2 to <78.4	21	43	2.33		
				>78.4	26	38	4.03		
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd						
				<49.3	33	48	1.97		
				>49.3 to <65.2	15	50	0.66		
				>65.2 to <78.4	18	49	0.91		
				>78.4	24	54	1.45		

listically significant (P<0.05)

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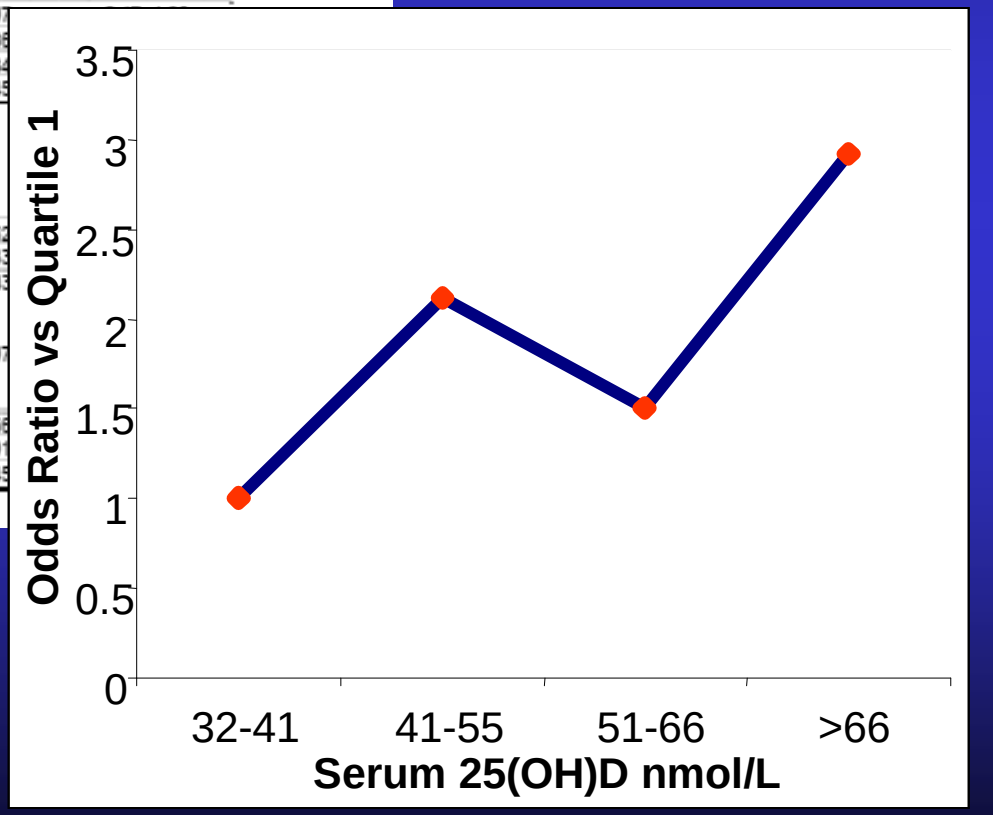

Stolzenberg-Solomon 2006

29. Vitamin D and pancreatic cancer: Results of observational studies

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				>60.3 to ≤69.5	27	73	0.86	0.40, 1.84	
42]				>69.5 to ≤82.3	31	74	0.84	0.39, 1.80	
				>82.3	42	73	1.45	0.66, 3.15	
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd						P for interaction between low and moderate/high residential sun exposure = 0.015
				<49.3	22	44	1	Reference	
				>49.3 to <65.2	22	42	2.52	0.92, 6.90	
				>65.2 to <78.4	21	43	2.33	0.83, 6.48	
				>78.4	26	38	4.03	1.38, 11.79*	
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd						
				<49.3	33	48	1.97	0.80, 4.82	
				>49.3 to <65.2	15	50	0.66	0.22, 2.01	
				>65.2 to <78.4	18	49	0.91	0.31, 2.71	
				>78.4	24	54	1.45	0.53, 3.96	

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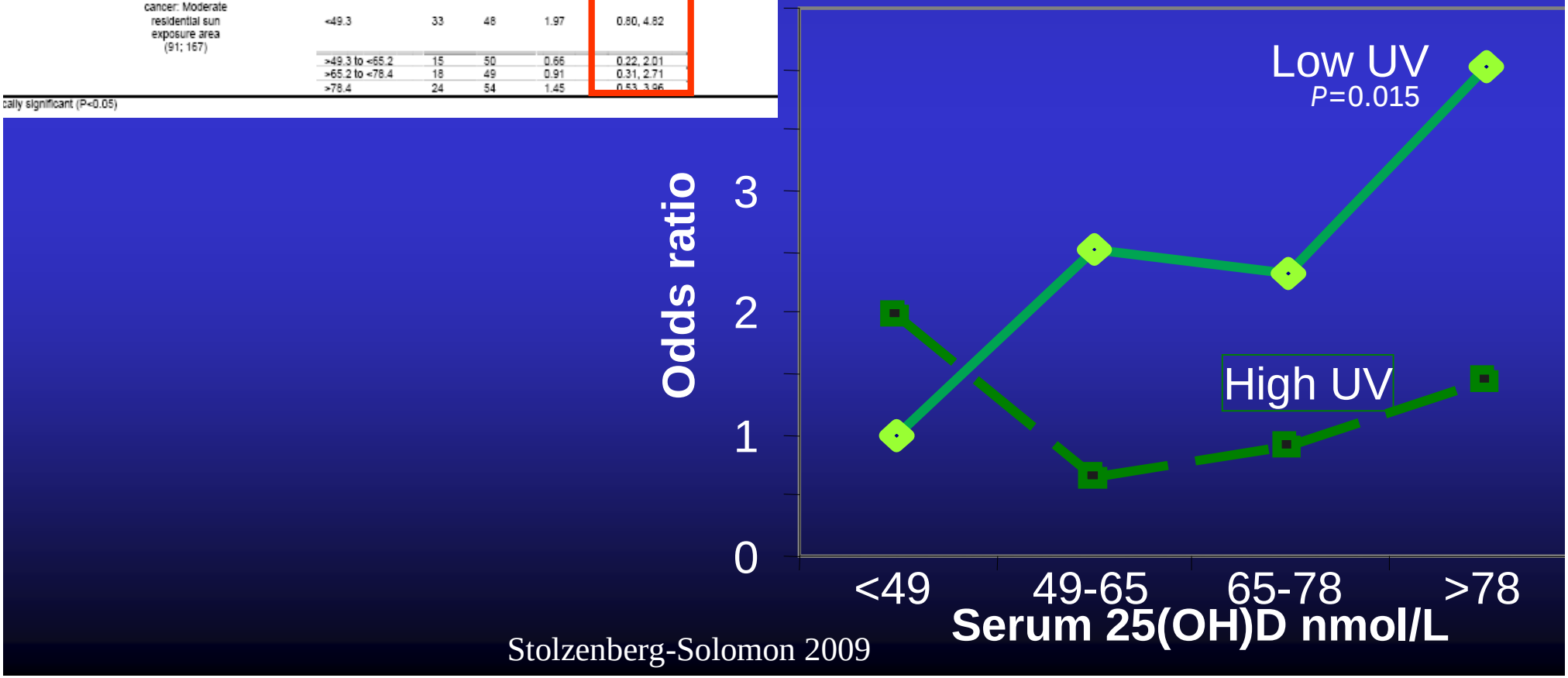
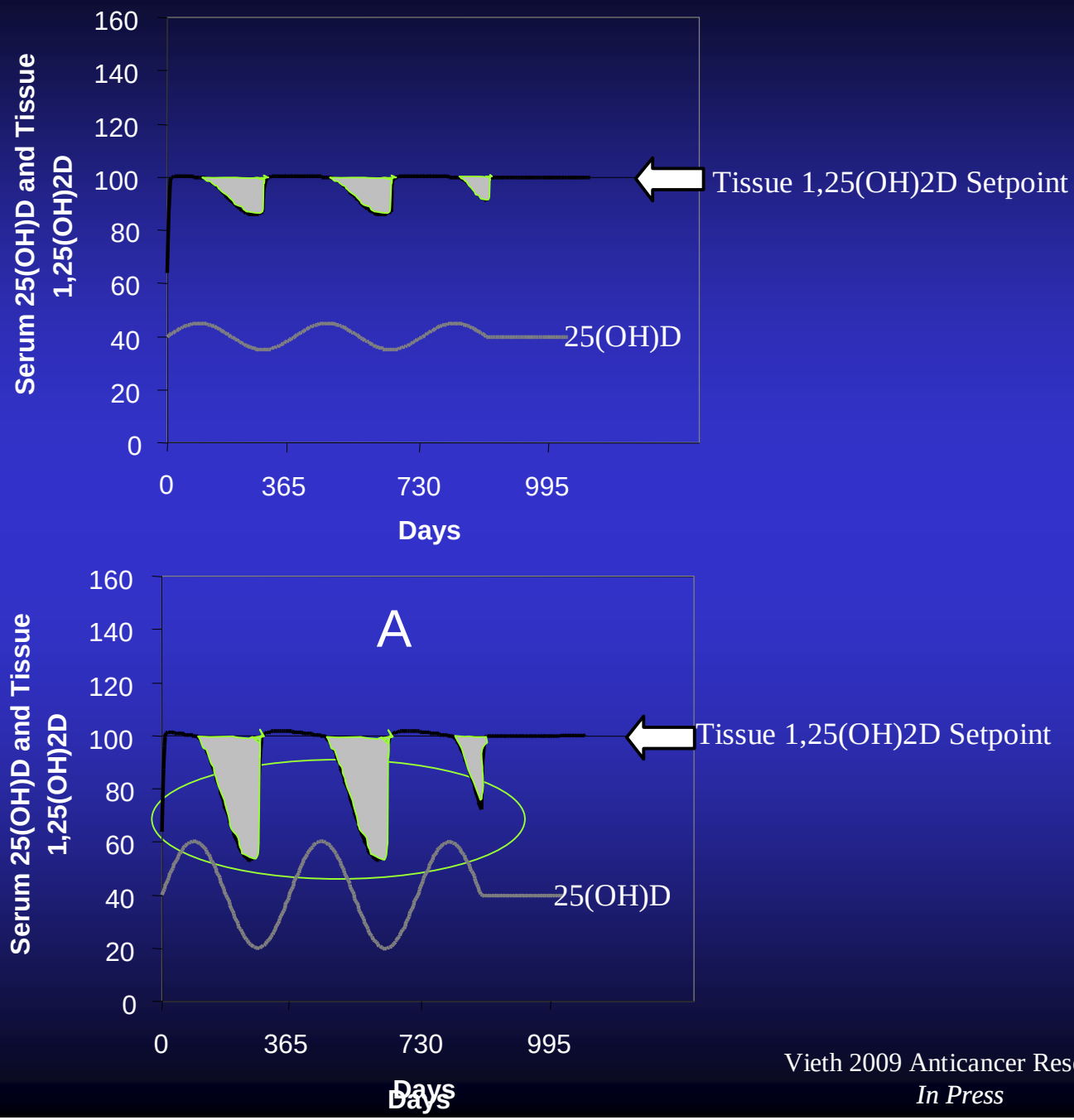


Stolzenberg-Solomon 2009

SAME AVERAGE 25(OH)D BUT
Larger amplitude results in larger below-setpoint phase in tissue 1,25(OH)2D

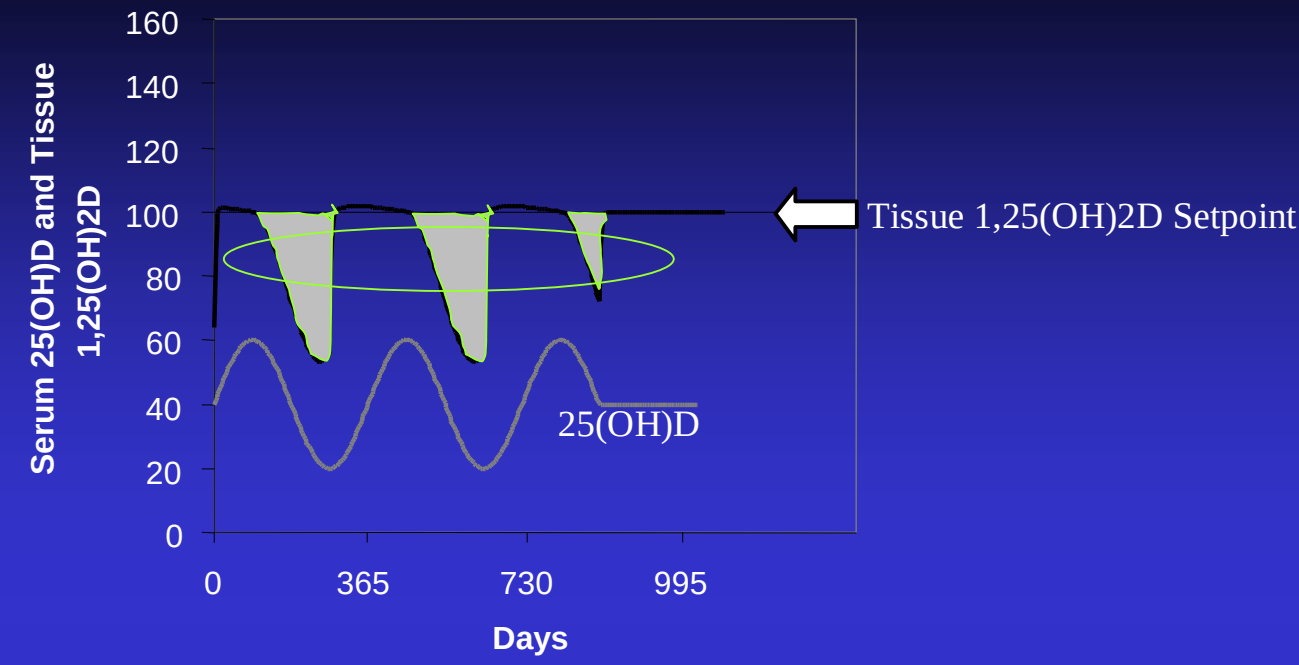
Shaded area highlights the sub-setpoint phases in tissue 1,25(OH)2D.

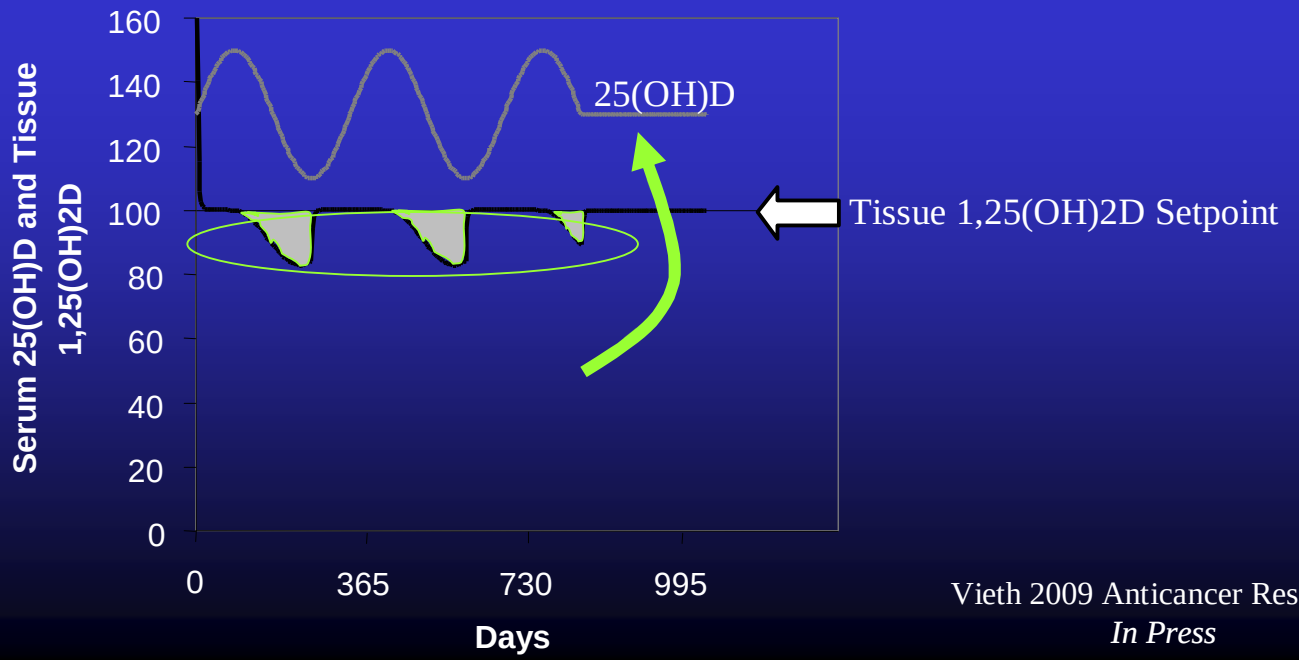


Vieth 2009 Anticancer Resear
In Press

Higher 25(OH)D would **dampen negative effects of seasonal variation**:

Shaded area highlights the sub-setpoint phases in tissue 1,25(OH)2D.





Vieth 2009 Anticancer Resear
In Press

Safety = Toxicity

For vitamin D, the classic criteria for harm pertain to excessive calcium in serum or urine. **TOXICITY REQUIRES AVERAGE DAILY INTAKES WELL BEYOND 10,000 IU**

Northern or low-UV environments: epidemiologic relationships with higher serum 25(OH)D and higher risk of prostate and pancreatic cancers. These may be due to **seasonal high/low fluctuations in 25(OH)D** that may be alleviated with vitamin D supplementation.