

Composite Risk Benefit Curve Approach to Fish Consumption: Dispelling some myths

Michael Gochfeld
Joanna Burger
CRESP & EOHSI
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Public Health is Controversial

- Always has been
- John Snow vs prevailing miasma theory
- Public good vs individual autonomy
 - Quarantine vs freedom
 - Mandatory Vaccination (flu, thimerosal)
- Nutritional supplements
- Genetically modified organisms
- **Eat more or less or different fish**

Fish consumption

Balancing risks & benefits

- Good things in fish
 - Protein
 - Low cholesterol
 - High PUFA (EPA and DHA)
 - Selenium
- Bad things in fish
 - MeHg (methylmercury)
 - PCB (polychlorinated biphenyls)
 - Other organics

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 - MeHg (methylmercury)
 - PCB (polychlorinated biphenyls)
 - Other organics
- Eating fish as a surrogate for health conscious people
 - Healthy life styles
 - Avoiding red meat and twinkies
 - Exercise
 - Early prenatal care
 - Higher SES
 - Higher maternal education

Benefit domains

- Adult cardiovascular
 - Blood pressure
 - Arrhythmia
 - Non-fatal and fatal MI
- Fetal infant development
 - Including pregnancy outcomes
 - Developmental landmarks
 - IQ
- Adult cognitive (dementia, Alzheimer)
 - Is it an accident that several cultures consider fish “brain food”
 - Or is it that proximity to abundant fish sources was correlated with other demographic/SES benefits
 - Until 75 years ago the contaminants would have been negligible

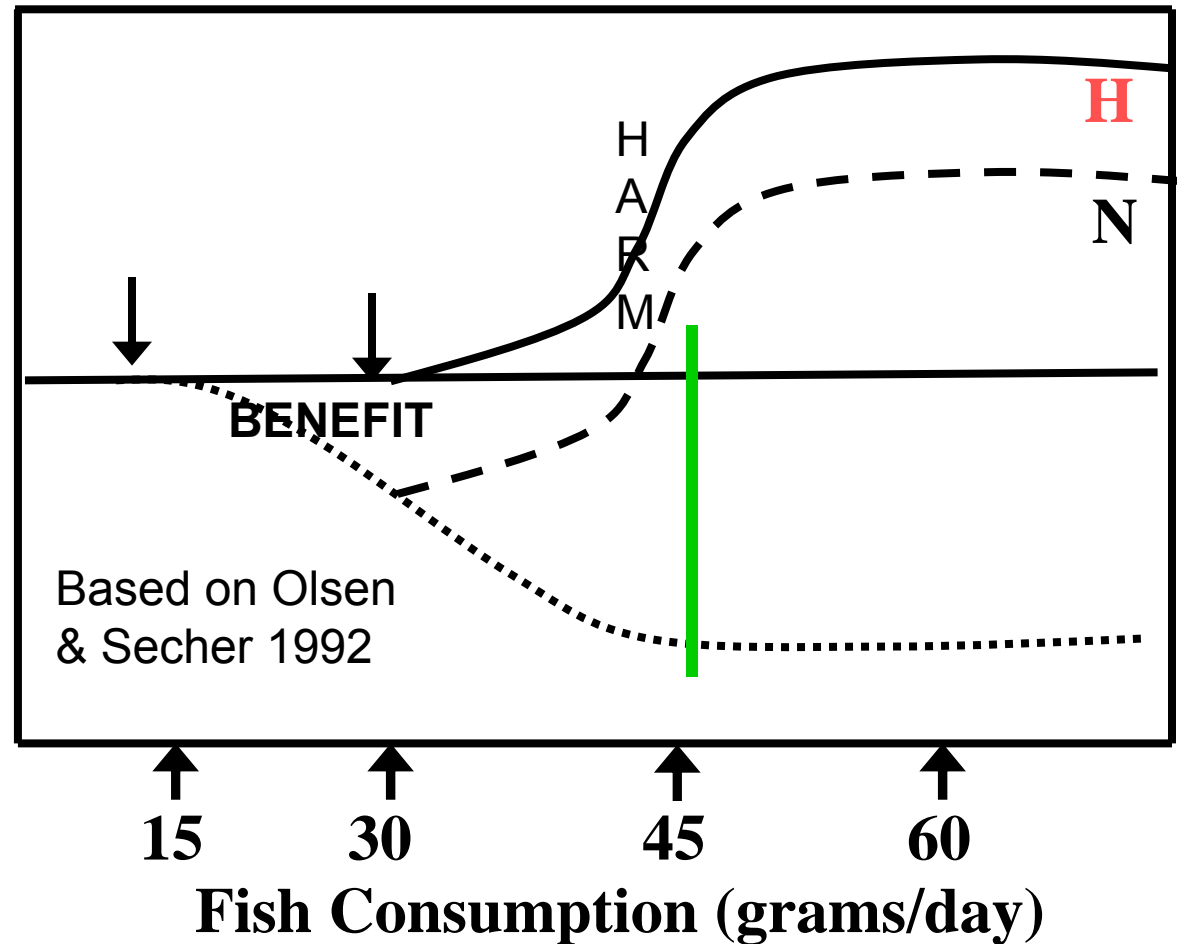
COMPOSITE DOSE-RESPONSE CURVES

Gochfeld & Burger (2005) Neurotoxicology 26:511

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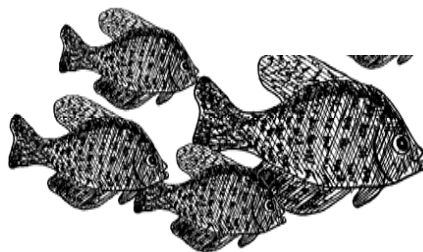
ACTUALLY NOT A LOT OF RELEVANT DATA

We come back to this graph later



BT=Benefit Threshold BA=Benefit Asymptote

NHT=Net Harm Threshold



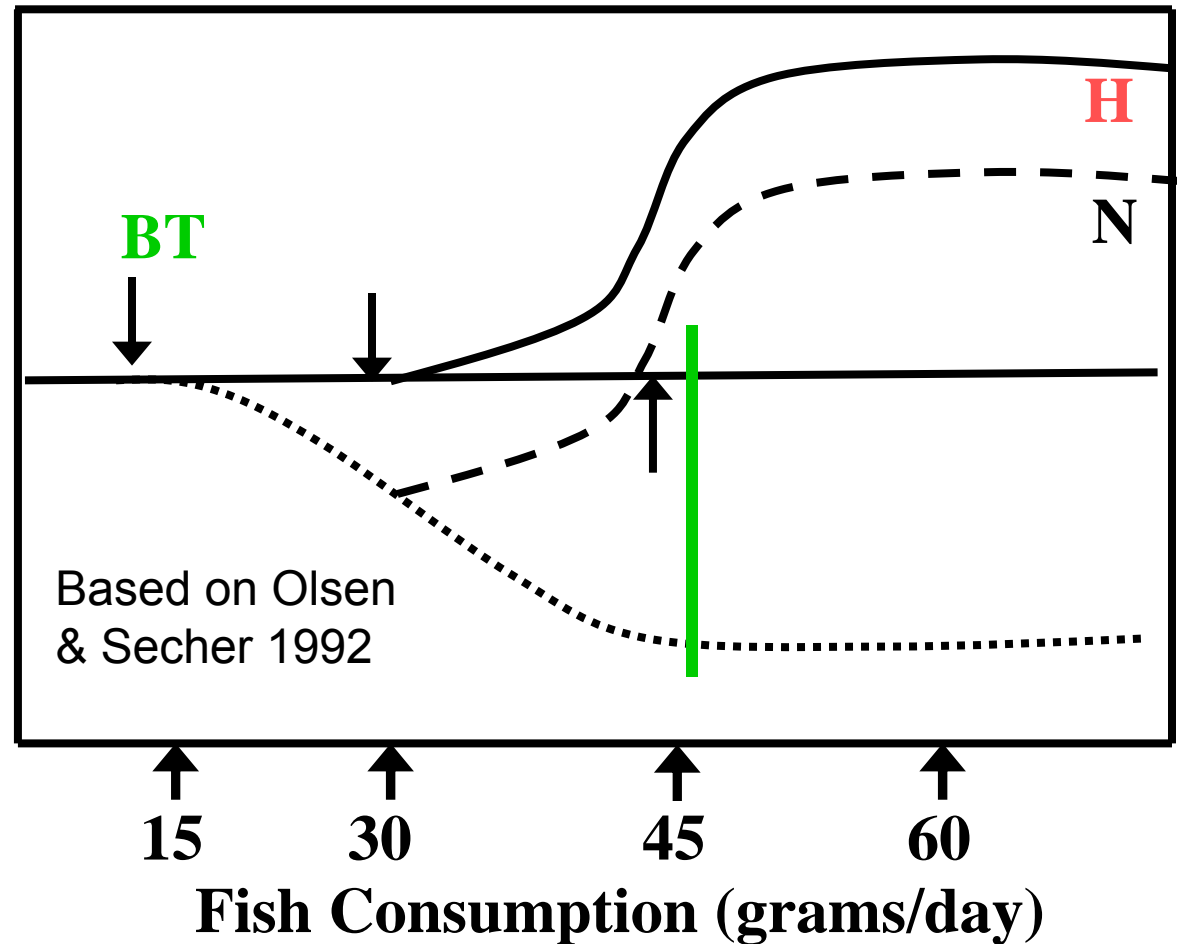
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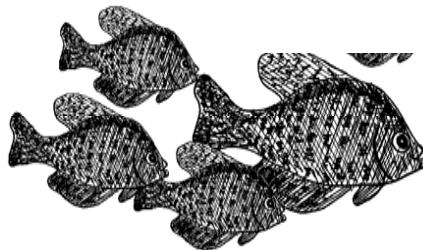
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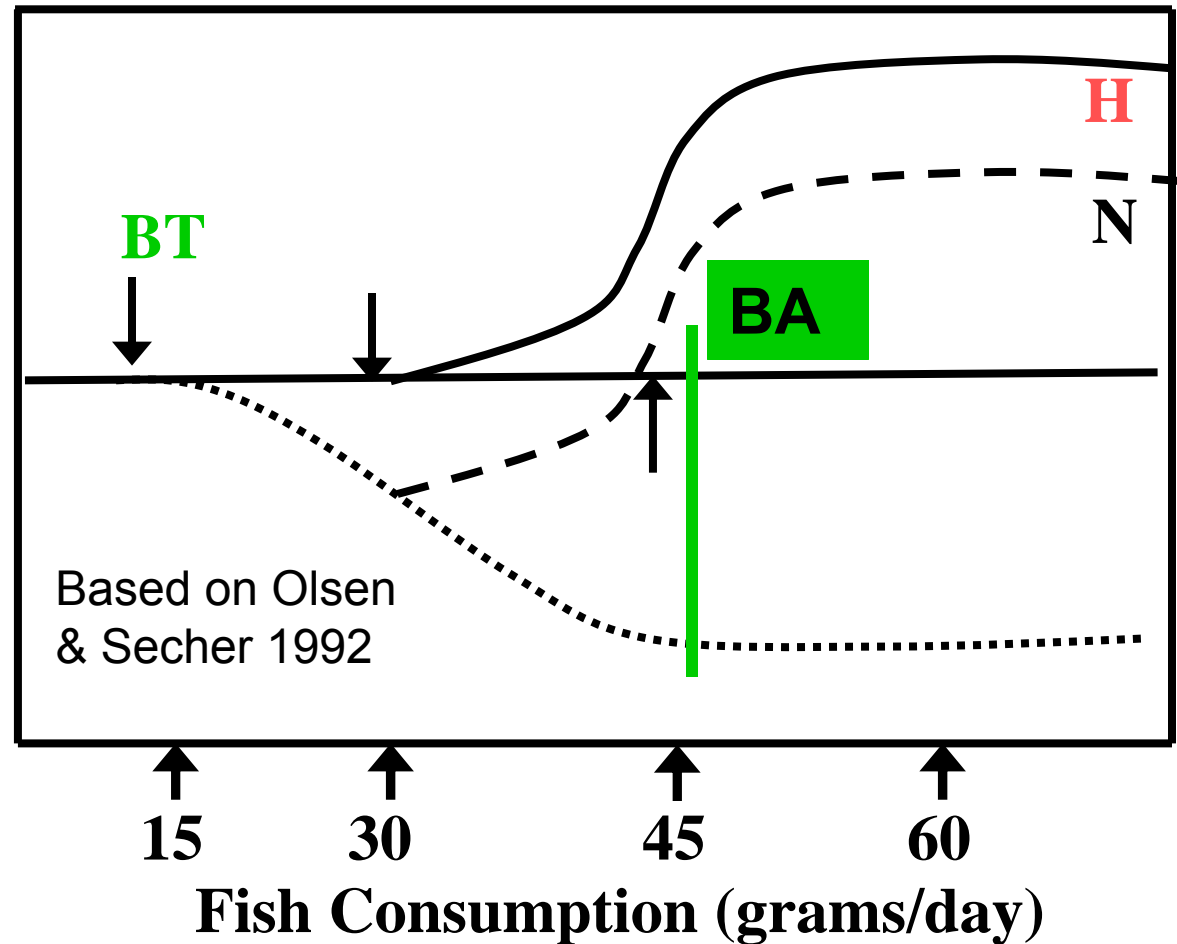
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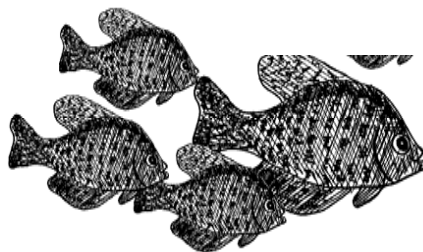
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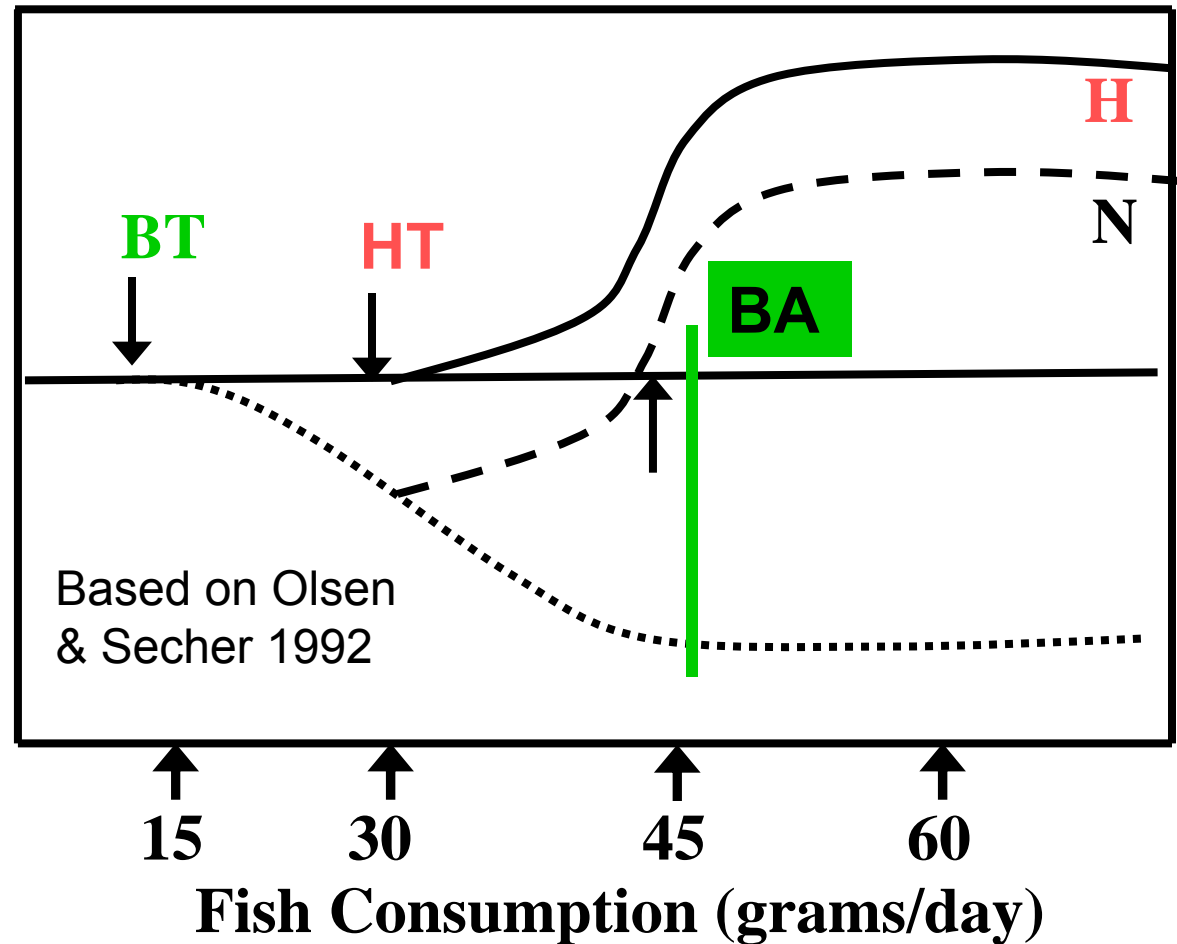
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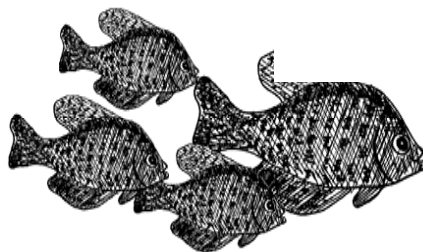
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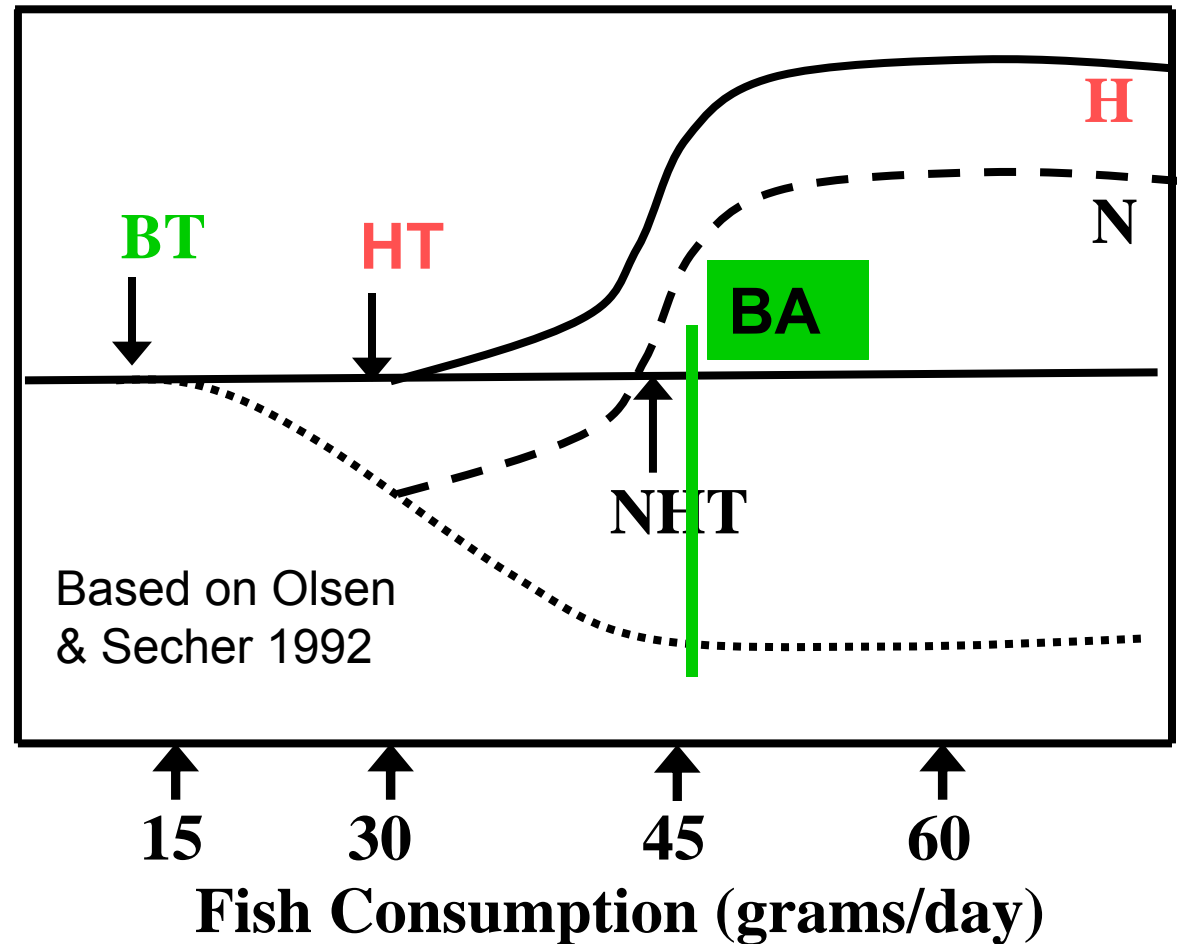
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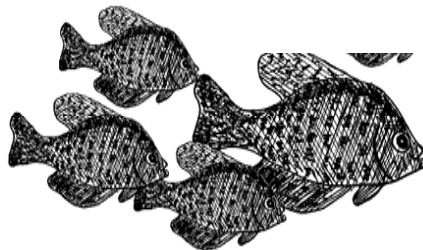
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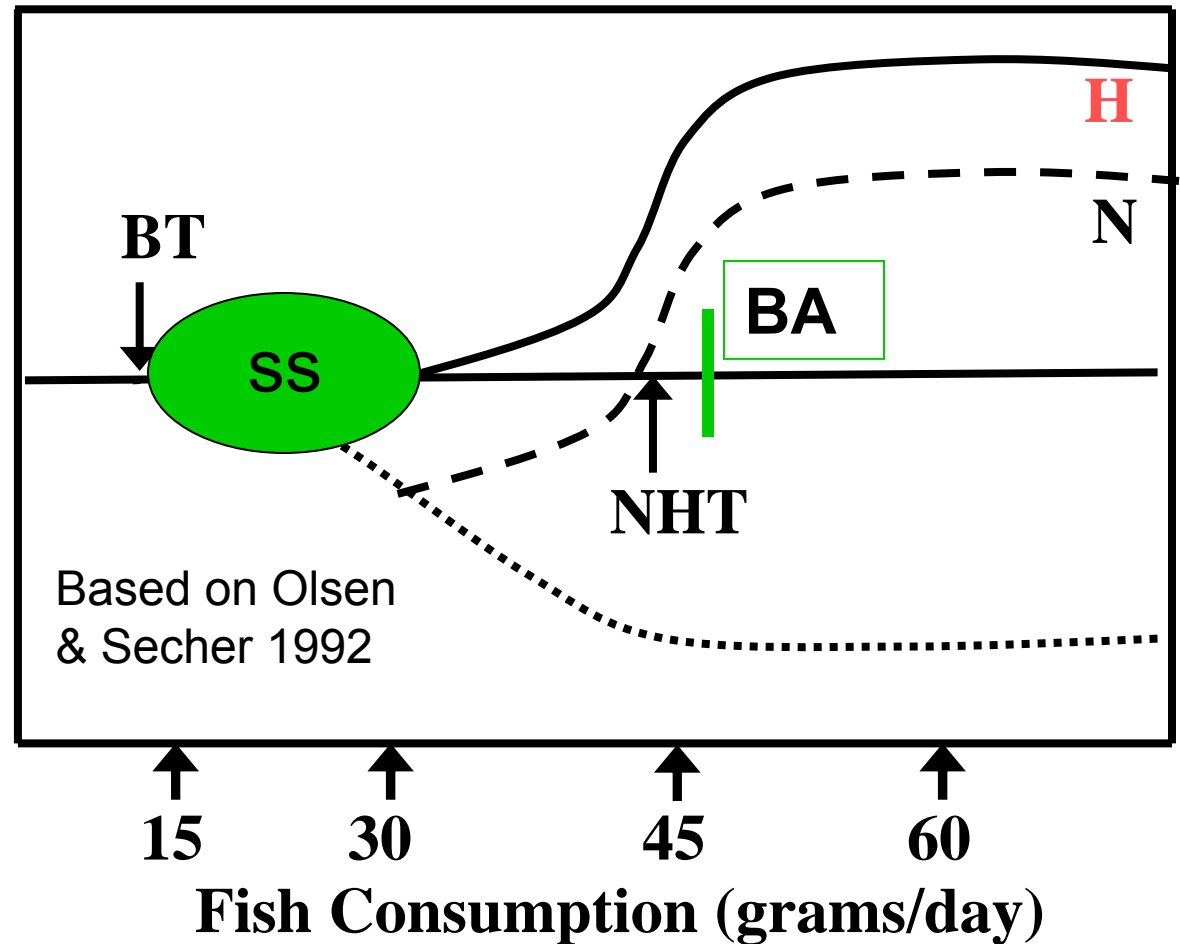
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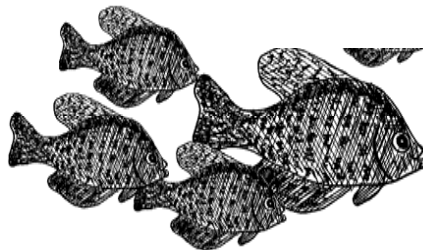
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Do we know enough already?

- Eat more fish low in bad things and high in good things
- Eat less fish high in bad things and low in good things

But as an academic

- I'm always going to say
- “more research is needed”
- Every discovery raises additional questions
- And with individualized medicine on the horizon there are domains of genomics, proteomics etc which certainly contribute to the benefits and harms from fish (or smoking or twinkies)
- Maybe we'll there will be a blood test to see if YOU need more or less fish than your neighbor

Common currency

- Increased risk per $\mu\text{g/day}$ of MeHg
- Decreased risk per mg/day of PUFA
- Decreased risk per g/day of fish or servings per week
- UNCOMMON CURRENCY
 - Fish consumption metric
 - PUFA intake metric
 - Endpoints assessed

Common currency

- Increased risk per $\mu\text{g/day}$ of MeHg
- Decreased risk per mg/day of PUFA
- Decreased risk per g/day of fish or servings per week
- UNCOMMON CURRENCY
 - Fish consumption metric
 - Semi-quantitative questionnaires, often historic recall
 - Grouped results in different ways
 - Or absent completely
 - PUFA intake metric
 - Sometimes measured in blood
 - Uncertain intake multiplied by variable concentration data
 - Endpoints assessed

IDEALIZED COMPOSITE CURVES

IS THERE A “Sweet Spot”
AT WHICH YOU GET ALL
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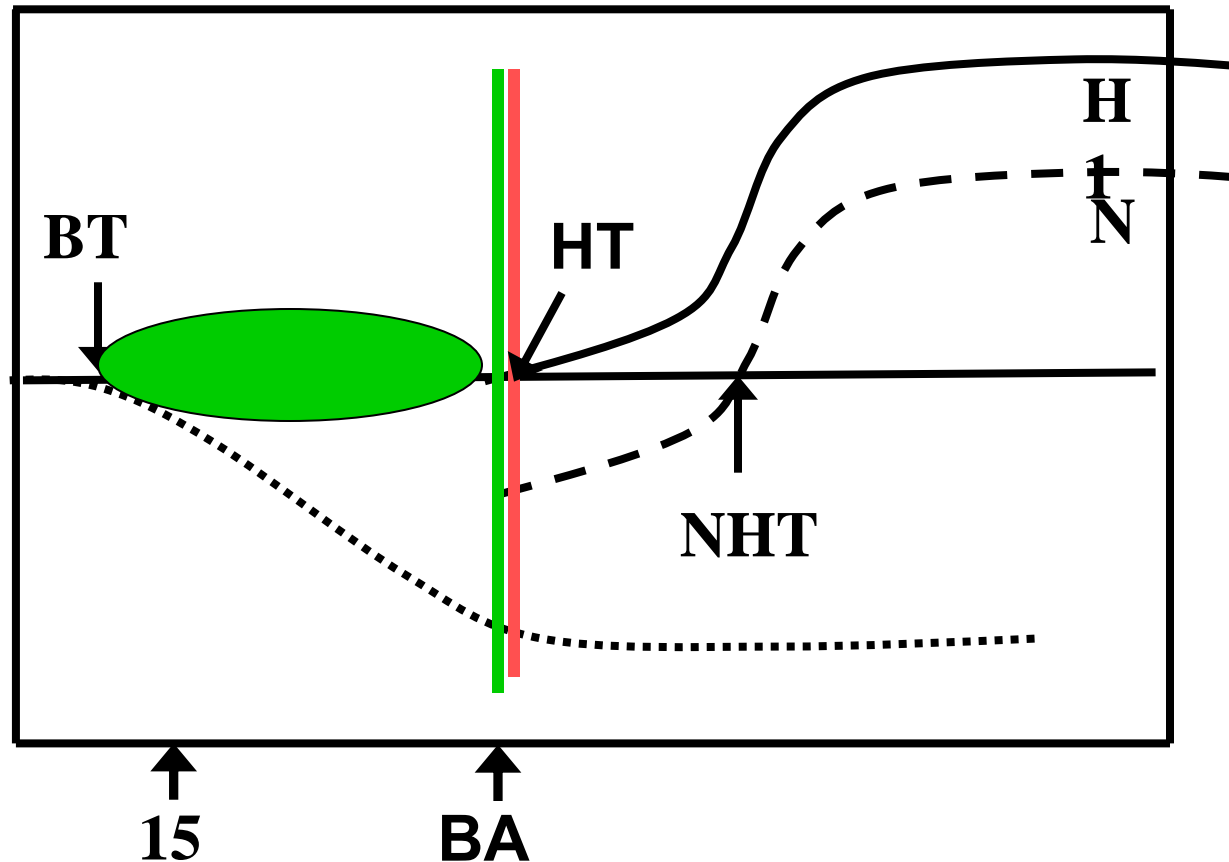
Here the Harm Threshold
LIES ABOVE the Benefit
Asymptote

H=Harm N=Net

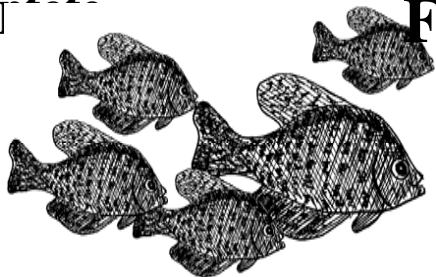
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Fish Consumption (grams/day)



Gochfeld & Burger (2005) Neurotoxicology 26:511

What Are the benefits due to?

- Good things in fish
 - High PUFA (EPA and DHA)
 - Which is what the literature seems emphasize
 - Selenium
 - Protein
 - Low cholesterol
 - All of the above
- Or to correlates of fish intake
 - Avoidance of red meat and twinkies
 - Other lifestyle correlates (particularly among those who eat fish frequently specifically for health reasons)

If PUFA benefits are so clear, why not just take supplements?

- It's a lot cheaper than fish
- \$1.50 to \$10 PER MONTH
- **BUT**
- Other supplement-only studies have not been reassuring
 - CARET* CHEMOPREVENTIVE STUDY FOR LUNG CANCER
 - found NEGATIVE impact of beta-carotene and vitamin A vs controls on lung cancer
- Are there downsides to MEGA-supplementation
 - lactation supplement and ↑BP in children
 - Increased risk of diabetes mellitus (Sept 2009)
- **beta-Carotene and Retinol Efficacy Study*

EPA Oral RfD

- **I.A. Reference Dose for Chronic Oral Exposure (RfD)**
- Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6
Last Revised — 07/27/2001

In **general**, the RfD is an **estimate** (with **uncertainty** spanning **perhaps** an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is **likely** to be without an **appreciable** risk of deleterious effects during a lifetime.

EPA Oral RfD

- **I.A. Reference Dose for Chronic Oral**

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EPA Oral RfD

- I.A. Reference Dose for Chronic Oral

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The National Flower of Risk Assessment -----THE HEDGE

MeHg RfD is based on

- **Critical Effect** Developmental neuropsychological impairment
- Human epidemiological studies
 - Grandjean et al., 1997;
 - Budtz-Jørgensen et al., 1999a)

Uncertainty for MeHg RfD

- Used benchmark dose
- Dose that would double the number of children below the 5th percentile
- Variation in toxicokinetics from ingested dose to blood level 3x
- Variation in toxicodynamics 3x
- Therefore overall UF $3 \times 3 = 10$
- Variation in cord blood was ignored
 - Cord assumed = maternal but in reality
 - Cord about 1.7 to 2x higher than maternal

Myth 1

- The RfD has a 10 fold margin of safety
- So we don't really have to worry about
 - 0.1 µg/kg/day
- This is based on protecting sensitive individuals.
- So there will be some individuals, who may be susceptible AT the RfD
- And some possibly below
- And if **they** also happen to eat a lot of fish.....

Myth 2

From various historic default assumptions

- “people don’t eat enough fish to get sick”
- “Oh that’s just the 99th percentile”
- But that small percentage above the 99% translates into a large number of people
- 1 % of 300,000,000 is 3 million
- In public health we worry about some conditions with lower occurrence rates

So part of the controversy is an illusion based on Myth 2

- Some people believe that you can't get mercury poisoning at the levels of fish consumption reported at these meetings.
- They point to Iraq and Minamata as the totem for MeHg poisoning
- With hair levels above 50 ppm

MW 57 yo guitarist

- Health conscious. No red meat for 15 year
- Ate fish almost daily
- 6-8 ounces per meal
- Mainly Swordfish and Tuna steaks
- Estimated fish intake 1140g/wk = 163 g/day
- Estimated MeHg intake about 850 µg/week
- For a 60 kg women = **2 µg/kg/day**
- Equivalent to a hair level about 20 µg/g (ppm)
- Basal hair samples was 13.3 ppm
- She noted tingling in face and fingers, tremor
- Faulty coordination and weakness in strumming guitar
- Hair falling out, trouble sleeping, irritable
- Neuropsych testing at the time of her visit 6 months after stopping fish
- Performed badly on grooved peg test and other neurobehavioral tests
- At 1 year, hair level was 6 ppm and strumming returned

More cases of MeHg poisoning

- Ed Groth published a report "Over the Limit"
- Lists 24 cases of very high fish consumption (including MW)
 - Some with typical MeHg symptoms
 - Some with atypical presentation
 - Some with still uncertain diagnosis
- <http://mercurypolicy.org/wp-content/uploads/2008/12/mppoverthelimit.pdf>
- Or google Groth "over the limit" Mercury Policy Project

Rollercoaster



How much of the benefit comes from PUFAs

- And not all the benefits have the same trajectory

Protective effect for “Heart” is well established

Hu et al (2002) Nurses Health Study n=84,688

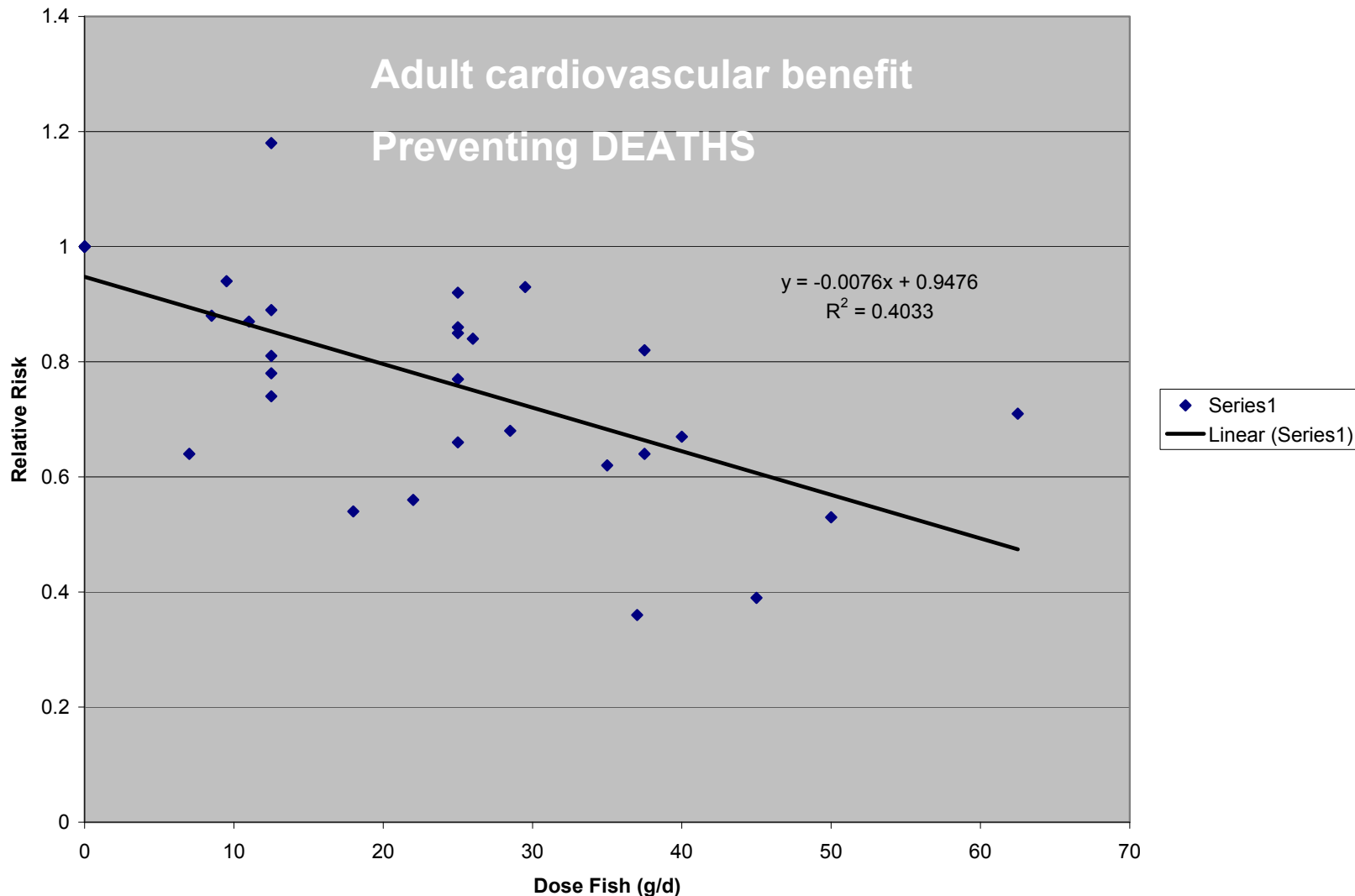
	<1/mo	1-3/mo	1/wk	2/wk	≥5 wk	Trend
Total CHD adj	1	.79 [.64-.97]	.71 [.51-.87]	.69 [.55-.88]	.66 [.50-.89]	P<.001
Non-fatal MI	1	.81 [.57-.15]	.66 [.47-.92]	.73 [.49-1.08]	.55 [.33-.90]	P=.01
ESTIMATED PUFA INTAKE BY QUINTILES						
% of energy	3%	5%	8%	14%	24%	
Total CHD	1	.93	.78	.68	.67	P<.001

Mozaffarian & Rimm 2006

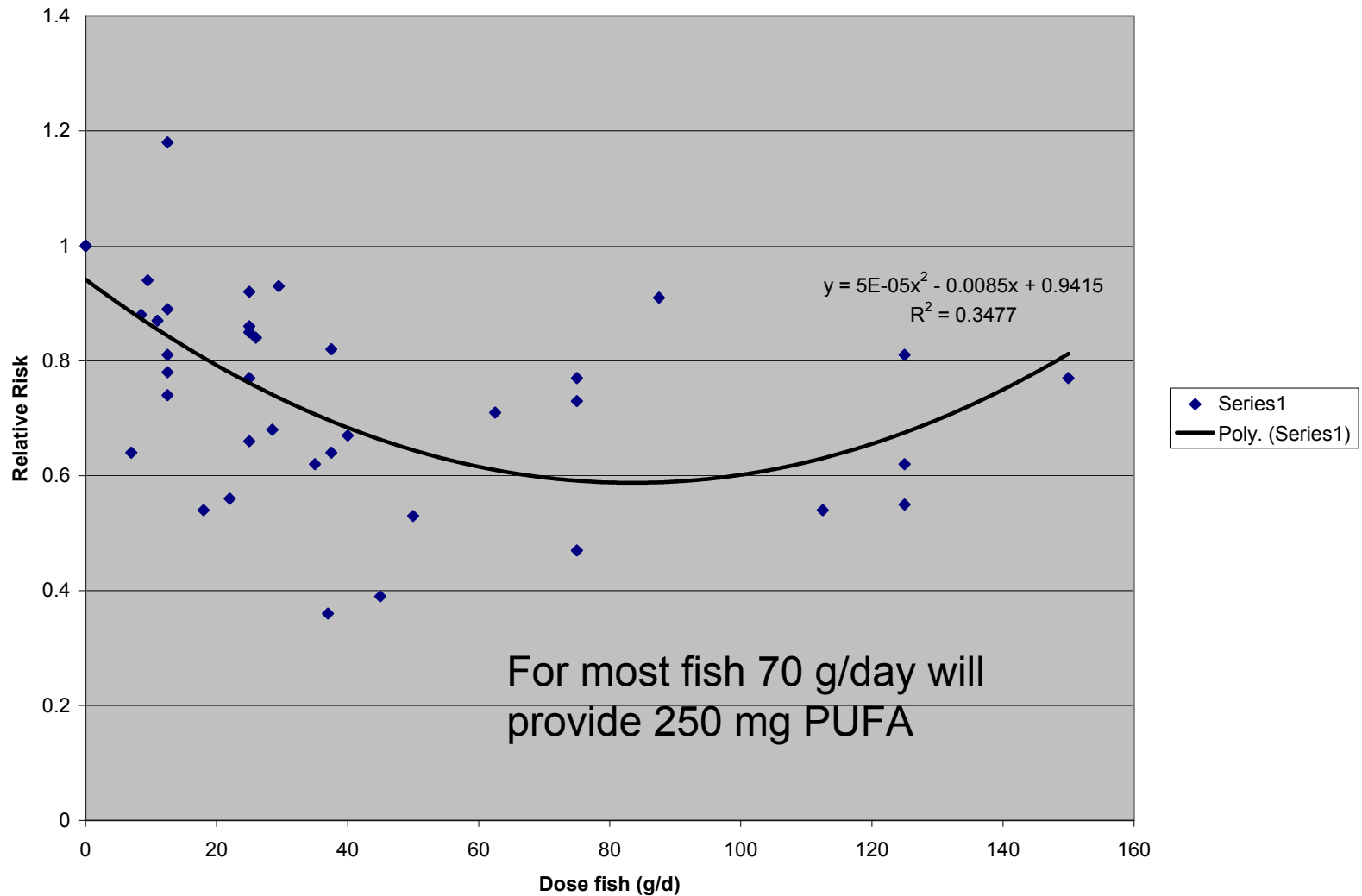
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Tina Goodwin analysis

One of the problems is that many papers censor intake data at 3+ meals/wk (small n)



Analysis of 10 studies with fish-consumption estimates
Goodwin & Gochfeld (MS)
Best site obtained with quadratic regression $r^2=.35$



Fish Intake Studies & CHD

		Fish intake	Highest category	Benefit threshold (midpoint)	Benefit asymptote
Hu et al 2002	84,688 nurses	5 categories	≥5/week (>120 g/day)	1/wk = 25 g/d HR=.66	none
Ascherio et al. 1995	44,895 men	6 categories	≥ 6/week	12 g/day HR=.74	Unclear ~110g/d
Albert et al. 1998	20,551 men Physicians	5 categories	≥ 5/week (>120 g/day)	37.5 g/day HR=.82	2-5x/wk=85g/d HR=.91
Krumhout et al 1985	852 men Zutphen	5 categories	≥ 45 g/day	7 g/day HR=.64	c45 g/day
Yuan et al 2001	18,244 men China	5 categories	≥200 g/day	18 g/day Not significant	unclear, Possibly 25 g/d
Daviglus et al 1997	1822 men Western Elect.	4 categories	≥ 35 g/day	8.5 g/day	None
Mozaffarian et al 2003	3910 Harvard	5 categories	≥ 3/week (>73 g/day)	11 g/day HR=.78	None
Oomen et al 2000	1097 men	4 categories	≥40 g/day	9.5 g/day HR=.94	none

(Bjerregaard et al 2009) Denmark

Prevention of Acute Coronary Syndrome

Lean vs Fatty Fish 57,053 men & women (Age=50 to 64 years) .

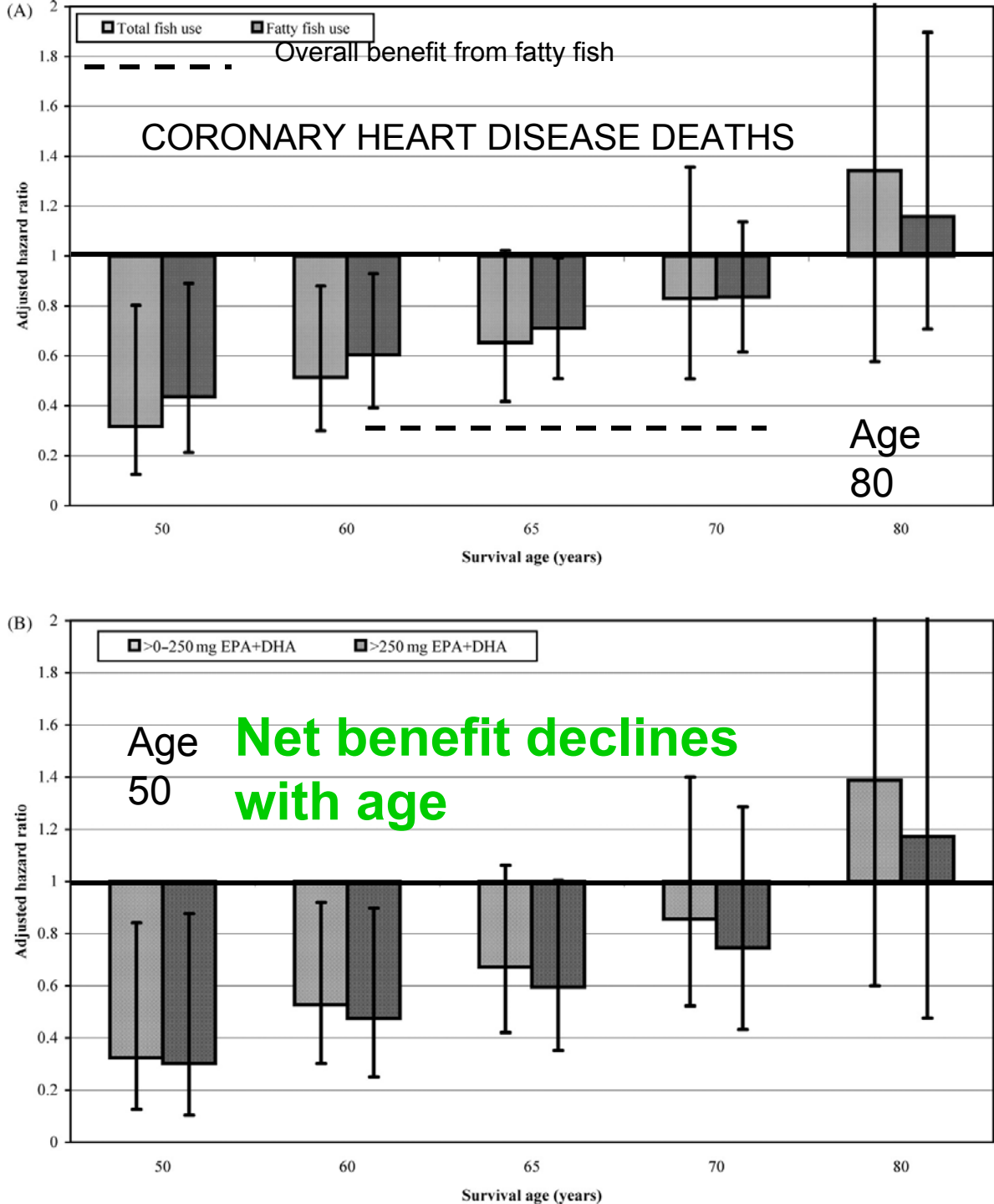
	Men	Women	
Fatty Fish	g/d >27 vs ≤6 OR=.67 33% decrease CI= [.53-.85]	g/d >23 vs ≤ 5g OR=.78 22% decrease CI=[.51-1.19]	Herring Mackerel Salmon Trout Char Caviar
Lean Fish	g/d >39 vs ≤14g OR=1.02 NO DECREASE CI=[.81-1.28]	g/d >33 vs ≤ 12 OR=.78 22% decrease CI=[.51-1.20]	Plaice Cod Shrimp Tuna

Oomen et al 2000 Fish intake and heart disease mortality (Europe)(n=2638)

- Lean fish consumption conferred no benefit in any country.
- Fatty fish compared with non-fatty-fish consumption was associated with lower CHD mortality;
- Pooled Relative Risk 0.66 [0.49-0.90]
- Am J Epidemiol 2000 151:999-1006

Streppel et al. 2008
Netherlands
Zutphen 40 year followup

Figure 1 Hazard ratios, with 95% confidence intervals, for long-term fish consumption (A) and eicosapentaenoic acid+docosahexaenoic acid intake from fish (B) in relation to coronary heart disease death at different ages and adjusted for energy intake, alcohol intake, wine use, fruit and vegetable consumption, saturated fat, *trans* unsaturated fatty acid, *cis* monounsaturated and *cis* polyunsaturated fat intake, serum cholesterol lowering diet, smoking, body mass index, prevalence of diabetes mellitus, systolic blood pressure, and socioeconomic status.



Mozaffarian found negative effect of fried fish

For men with heart disease

Those who ate baked/broiled fish mortality decreased with intake (up to a point)

Those who ate primarily fried fish mortality increased with intake.

Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus

Kaushik et al (Sept 2009)

Multivariate adjusted
Relative Risk by
Quintile of LCPUFA
intake estimated from
diet (mainly fish
frequenc)

Median daily intakes

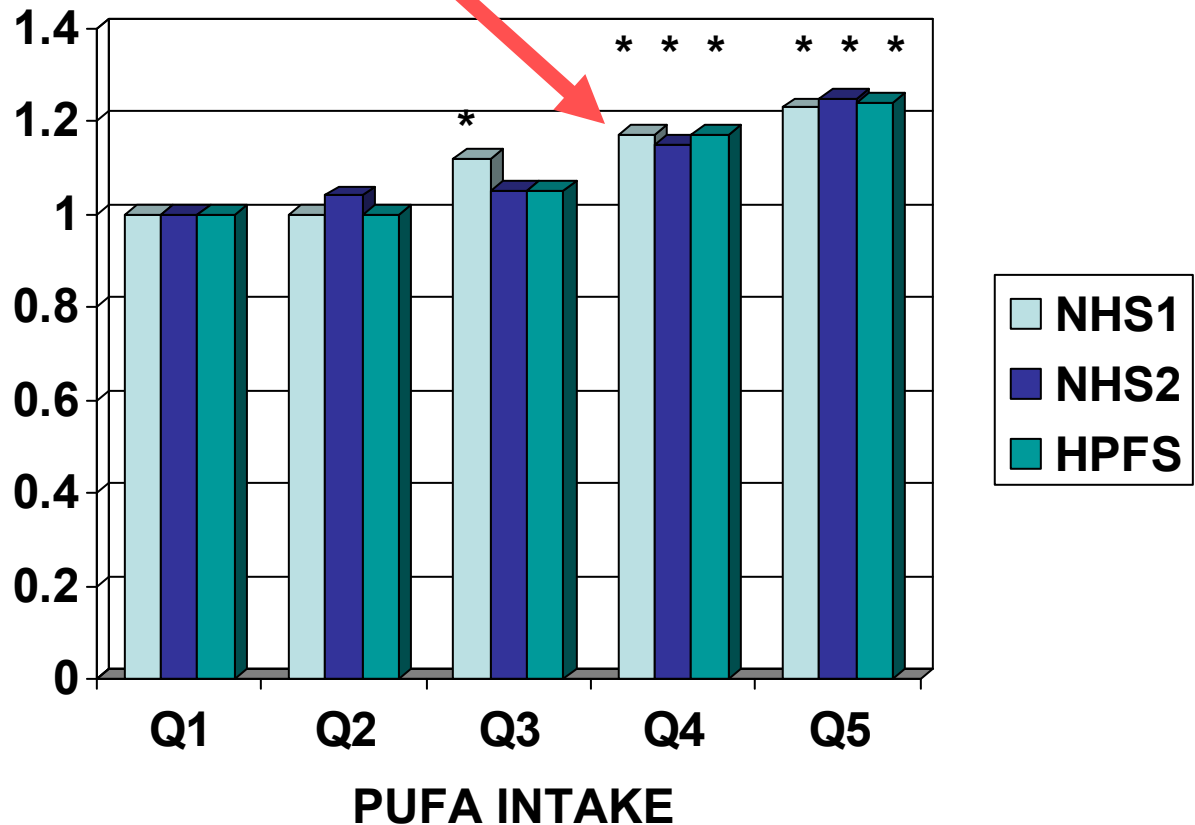
Q1 60 – 60 – 90 mg

Q2 120 – 100 – 180 mg

Q3 180 – 250 – 280 mg

Q4 270 – 320 – 390 mg

Q5 490 – 360 – 620 mg



NHS1=Nurses Health Study 1976 =121,700 female RNs

NHS2=Nurses Health Study II 1989 = 116,609 female RNs

HPFS=Health Professionals Study 1986 = 51,529 male health professionals

COMPOSITE CURVES: NURSES

Cardioprotection vs
Type II Diabetes

RR=1.25

Kaushik et al. Sept 2009

RR=1.15

NHS1

NHS2

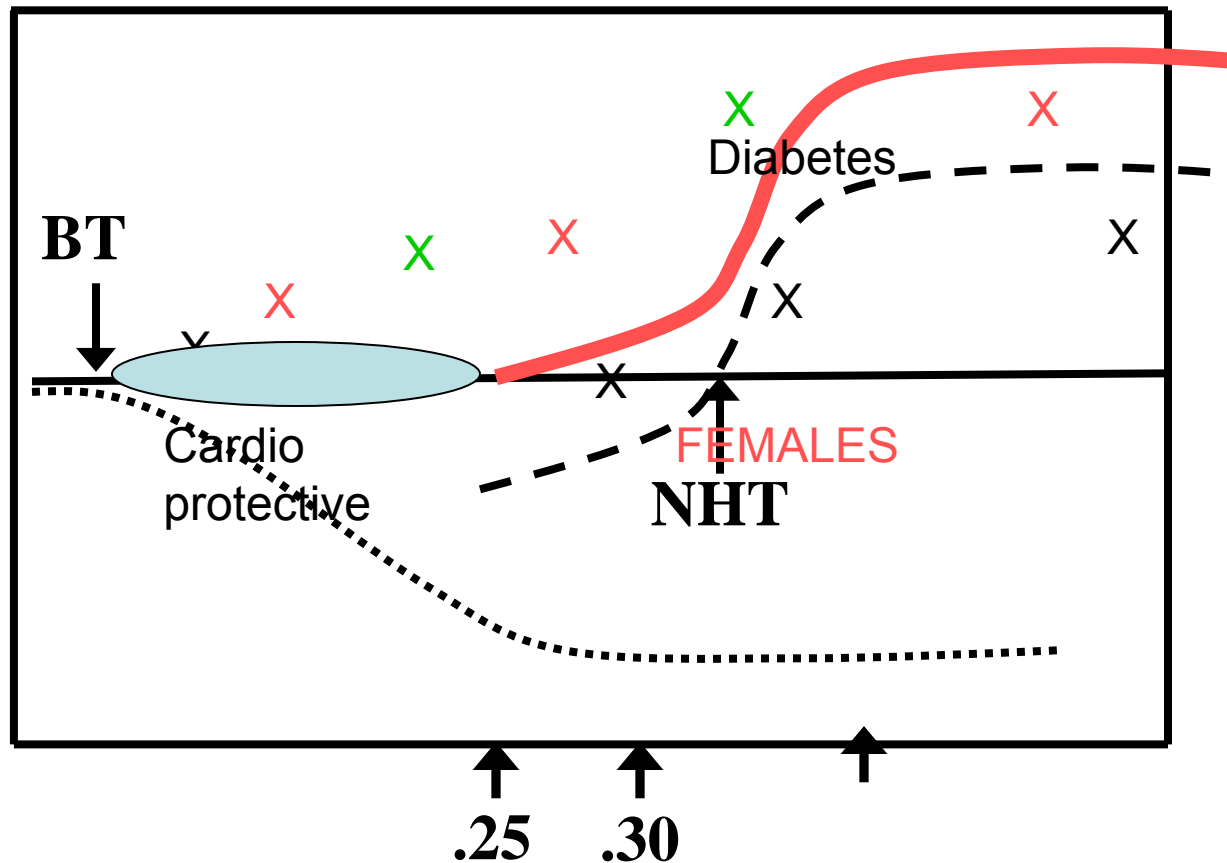
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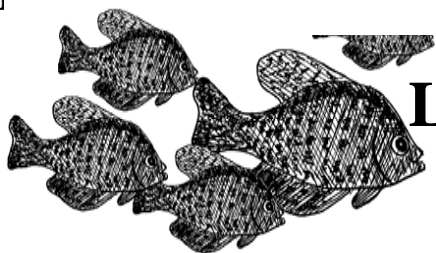
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Long-chain PUFA (grams/day)



Original graph Gochfeld & Burger (2005) Neurotoxicology 26:511

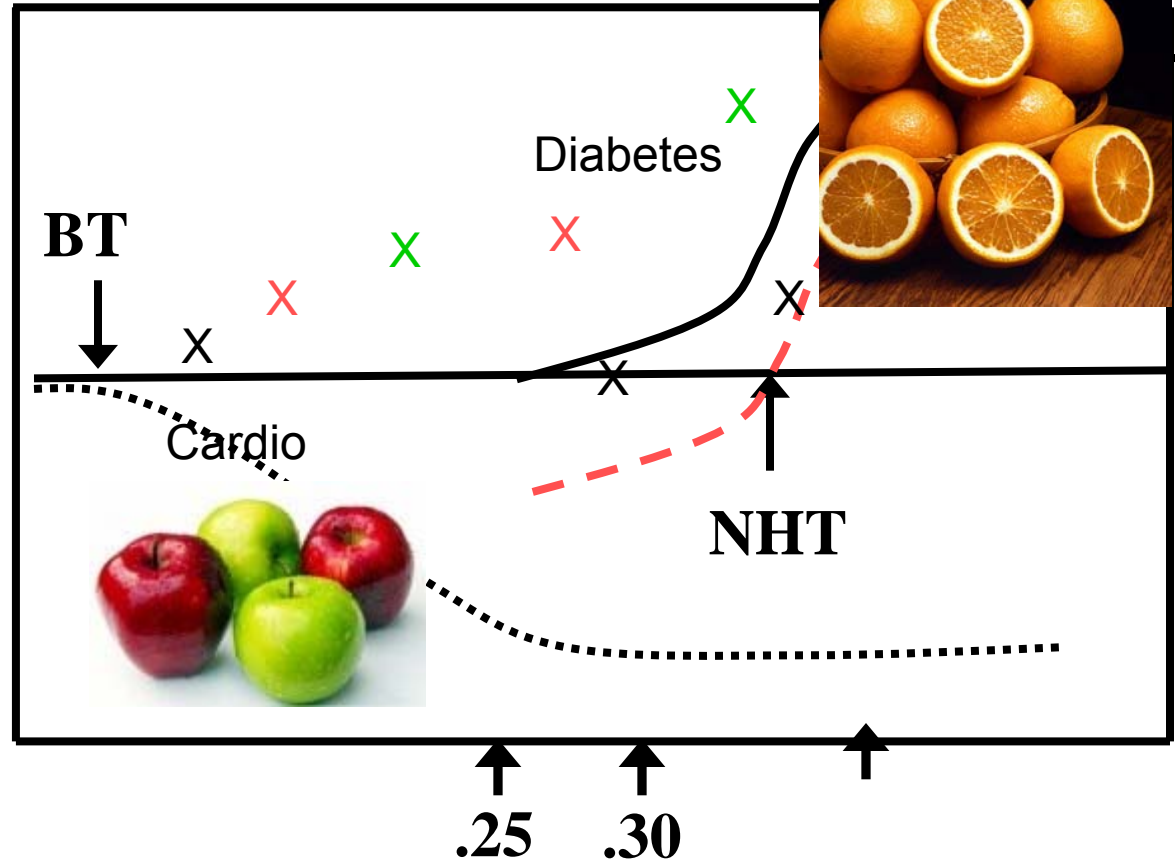
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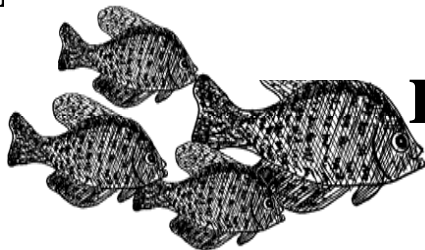
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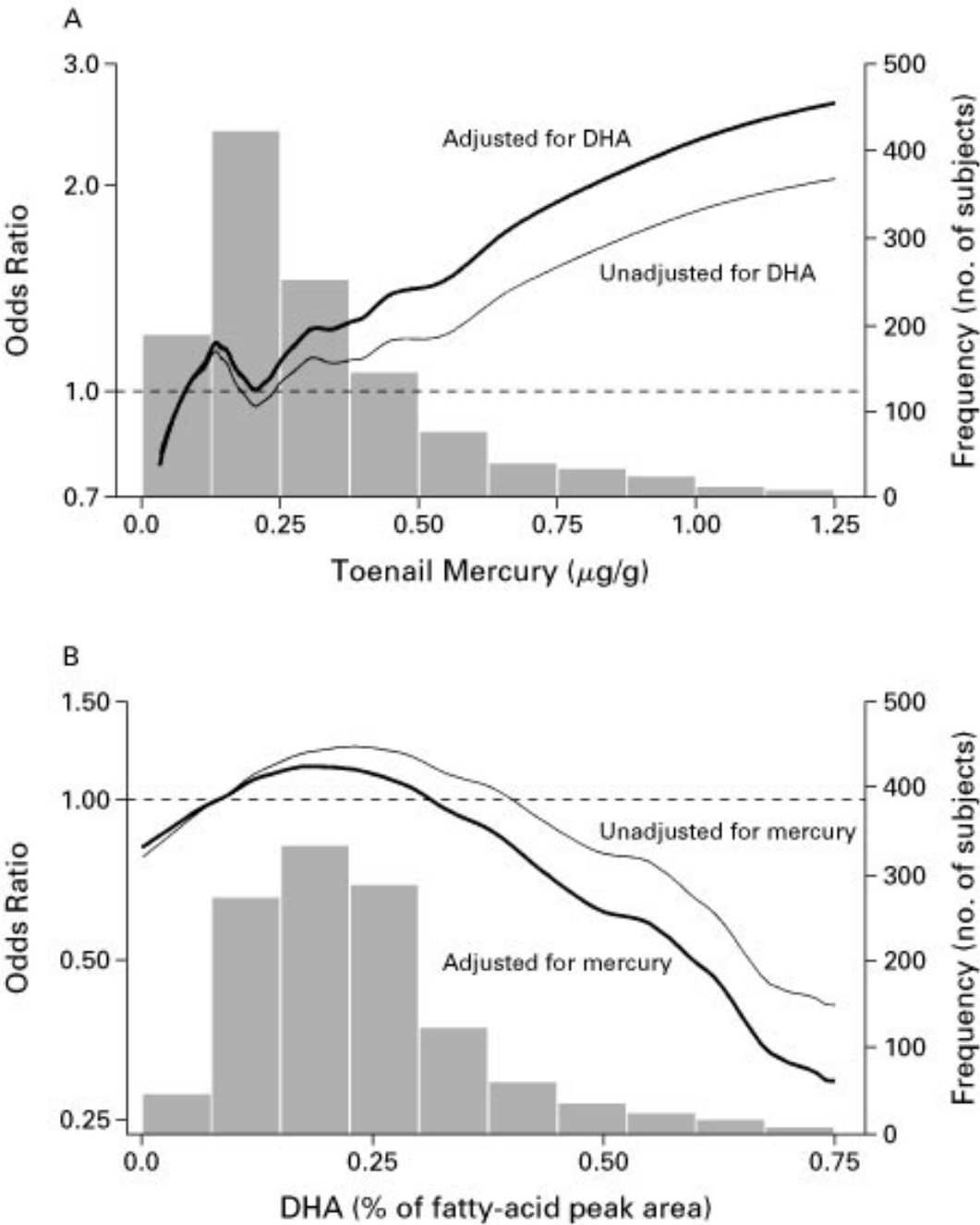
Long-chain PUFA (grams/day)

Original graph Gochfeld & Burger (2005) Neurotoxicology 26:511



MERCURY MUTES CARDIOPROTECTIVE EFFECTS

Figure 1. Nonparametric Estimates of the Risk of Myocardial Infarction According to the Levels of Mercury in the Toenails (Panel A) and of Docosahexaenoic Acid (DHA) in Adipose Tissue (Panel B).



Cohen, Bellinger & Shaywitz (2005) reviewed three prospective studies

- Faroes, Seychelles, New Zealand
- Faroes (7 yo study-Grandjean et al 1997)
 - 10x increase in MeHg delayed development by 5-8 months.
 - Some have accused Philippe Grandjean of over-analyzing
- Seychelles
 - Some have accused Philip Davidson of under-analyzing
- Cumulative estimate from Harvard analysis
 - 1 ug/g increase in maternal hair mercury
 - Loss of 0.7 [0-1.5] IQ points

Length of Gestation RCCT

- Olsen et al (1992) Denmark n=
 - Fish Oil 2.7 g/day vs olive oil and no oil
 - From week 30
 - Fish Oil → 4 days longer gestation & 107 g heavier
 - Effect greater in women with lower fish intake
- Smuts et al. (2003) US n=291
 - DHA from eggs (normal egg 33mg or high-DHA egg 133 mg) from 30 wks to delivery
 - 133mg → 6 days longer ($P=.009$). BW increased 83 g (NS)

Dunstan randomized trial

- 33 mothers received DHA(2.2g) & EPA (1.1g) during pregnancy
- 39 mothers received olive oil
- Evaluation at 30 months
 - Griffiths Mental Development Scales)
 - receptive language (Peabody Picture Vocabulary Test) and
 - behaviour (Child Behaviour Checklist).
- Eye-hand coordination improved
 - 114 vs 108 (P=0.012)
- Potential confounders
 - Many non-significant development scales
 - Possible harmful effects of olive oil
- *Dunstan et al. 2008*

PUFA Supplement Studies

Dunstan et al 2008 Australia	Pre-natal supplement	N=33 Fish Oil N=39 Olive Oil	DHA 2.2g/d EPA 1.1g/d	2.5 yrs	Eye-hand coordination
SanGiovanni et al 2000	Meta-analysis of DHA- formula			2 months 4 months	Visual acuity Improved Less difference
Asserhoj et al. 2009	Danish children with PUFA during lactation	Total N=98 FO=1.5g/d v Olive Oil		7 yrs	PUFA led to higher BP and lower physical activity

Oken et al. 2005 Boston Project Viva n=135
Change in Visual Recognition Memory
% novelty preference [95%CI]

Model	Effect/weekly serving	Effect / 1 ppm in hair
Fish intake only	+2.1	
Hair Hg only		-4.3
Fish + Hg	+ 3.9	-8.1
The multivariate model produced stronger and more significant independent effects than the individual regressions. No interaction term presented		

About 1 servings/week → 0.17 ppm in hair in this study isua

Is salmon the answer?

- Organic pollutants are NOT just in farmed fish
- Bad farming is profitable and harmful to environment
 - Escapes and genetic pollution
 - Sea lice and diseases
 - Habitat destruction
 - Some places still use fish meal
- Wild fishing would not be a problem IF? IF? IF?
 - the catches are kept within the bounds of production.
 - But wild Atlantics have collapsed, and
 - Pacific salmon have declined south of Canada,
 - are collapsing in Canada, and
 - remain strong only in Alaska.
- THOSE OF YOU FROM THE NORTHWEST PLEASE COMMENT?
- courtesy Carl Safina BLUE OCEAN INSTITUTE cellphone and mobile device users at fishphone.org.
info@blueocean.org

		MONTHLY	EPA	WEEKLY	12 oz/wk	2X/WEEK	DAILY	TRIBE
		7.5		32				549
PPM of MeHg (ug/g)		MICROGRAMS Mercury/DAY FOR 70 KG-ADULT						
0.05	Salmon	0.005	0.013	0.023	0.035	0.046	0.162	0.391
0.1	Lite Tuna	0.011	0.025	0.046	0.070	0.093	0.324	0.783
0.2	Canned Tuna	0.022	0.051	0.093	0.139	0.185	0.648	1.566
0.3		0.032	0.076	0.139	0.209	0.278	0.972	2.348
0.4		0.043	0.102	0.185	0.278	0.370	1.296	3.131
0.5		0.054	0.127	0.231	0.348	0.463	1.620	3.914
0.6		0.065	0.153	0.278	0.417	0.555	1.944	4.697
0.7		0.076	0.178	0.324	0.487	0.648	2.268	5.479
0.8		0.086	0.203	0.370	0.557	0.741	2.592	6.262
0.9		0.097	0.229	0.417	0.626	0.833	2.916	7.045
1	High Sushi tuna	0.108	0.254	0.463	0.696	0.926	3.240	7.828
1.2		0.130	0.305	0.555	0.835	1.111	3.888	9.393
1.4	Swordfish	0.151	0.356	0.648	0.974	1.296	4.536	10.959
2		0.216	0.509	0.926	1.391	1.851	6.480	15.656
4		0.432	1.017	1.851	2.783	3.703	12.960	31.311
	Shark							

Compute relative benefit/harm

How much fish do you need to reach the
250 mg/day benefit level

Fish	PUFA g/100 g variability	MeHg µg/g	Grams/wk needed to supply 250 mg/d	Ug/Hg in that amount of fish	HQ for RfD of 49ug/wk (.1)		
Salmon	1.59	.035	110	3.9	0.1		
Mackerel	1.79	.081	97.8	7.9	0.2		
Sardines	0.98	0.10	179	17.9	0.4		
Seabass	0.49	0.13	357	48.2	1.0		
Cod	0.24	0.12	729	88.2	1.8		
Tuna (ave)	0.7	0.4	257	103	2.1		
optimistic	1.2	0.4	146	58	1.2		
Swordfish	0.58	0.95	302	286	5.8		
Pike	0.14	0.31	1250	387	7.9		
Shark	0.22	1.33	795	1056	21		

COMPOSITE DOSE-RESPONSE CURVES

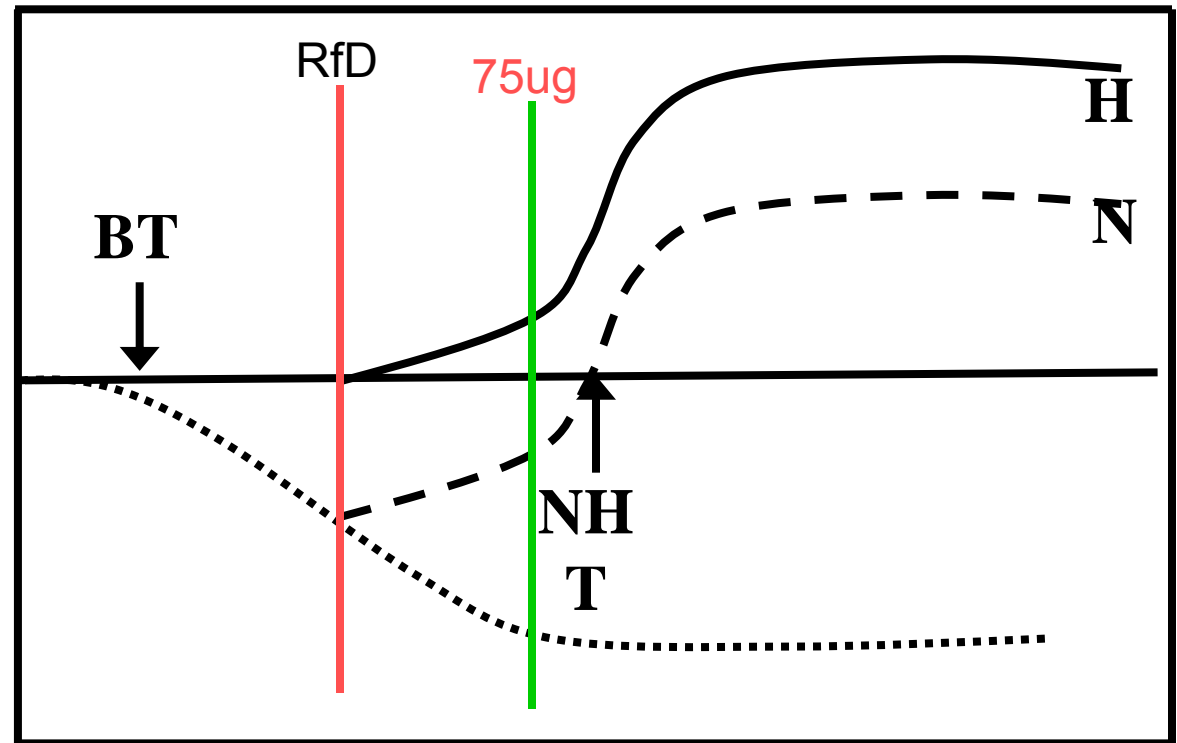
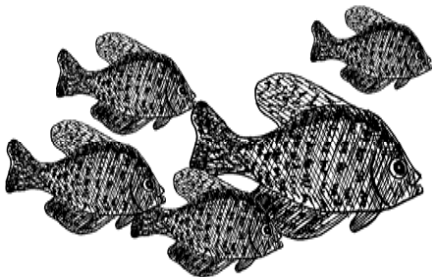
IS THERE A POINT AT WHICH YOU GET ALL THE BENEFITS BUT NONE OF THE RISKS?

ACTUALLY NOT A LOT OF RELEVANT DATA

We come back to this graph later

BT=Benefit Threshold

NHT=Net Harm Threshold



1143 1750mg
408g 625g

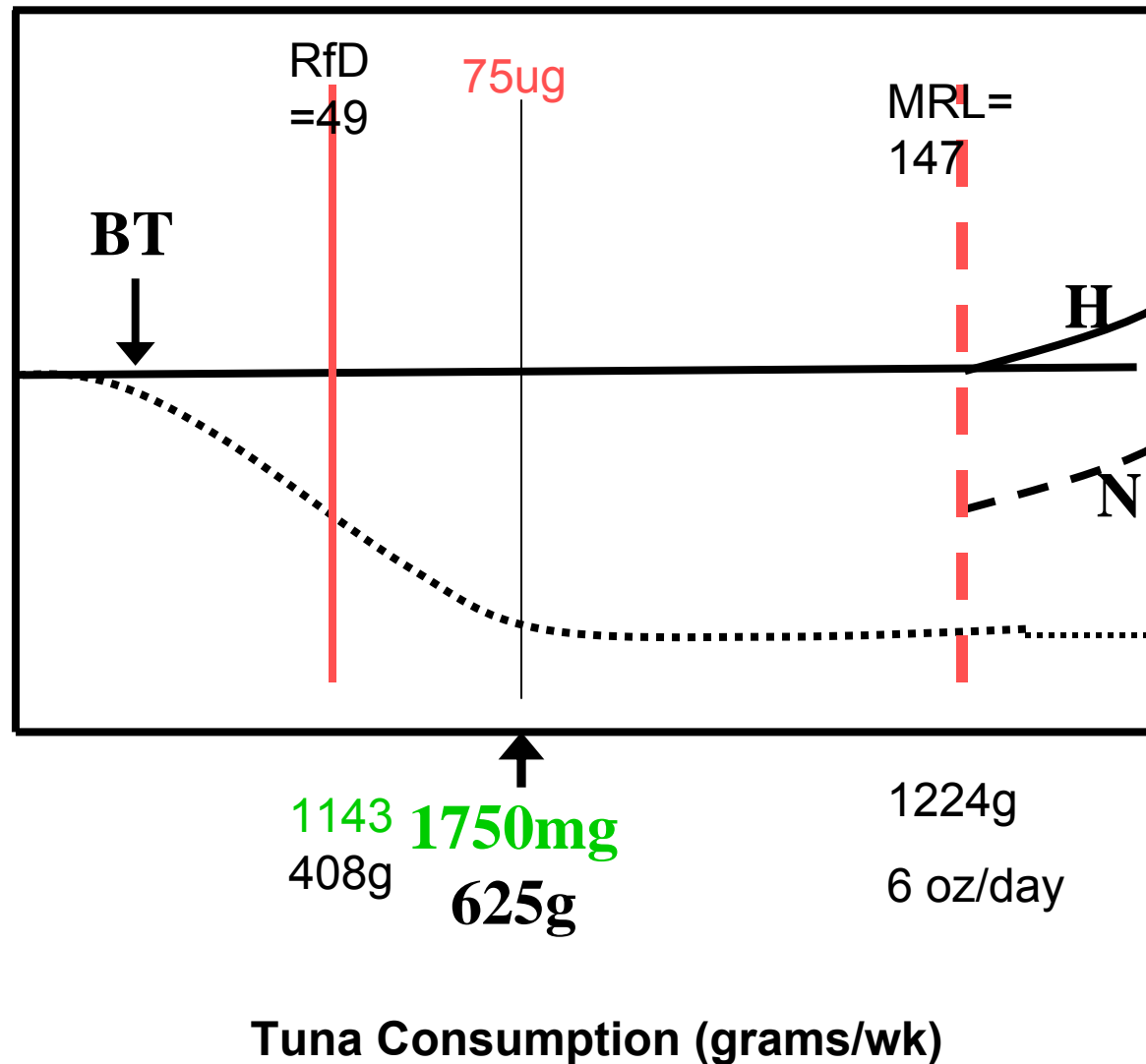
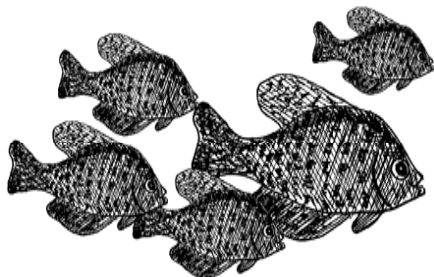
Tuna Consumption (grams/wk)

COMPOSITE DOSE-RESPONSE CURVES

**USE ATSDR MRL
instead of EPA RfD**

BT=Benefit Threshold

NHT=Net Harm Threshold



COMPOSITE (

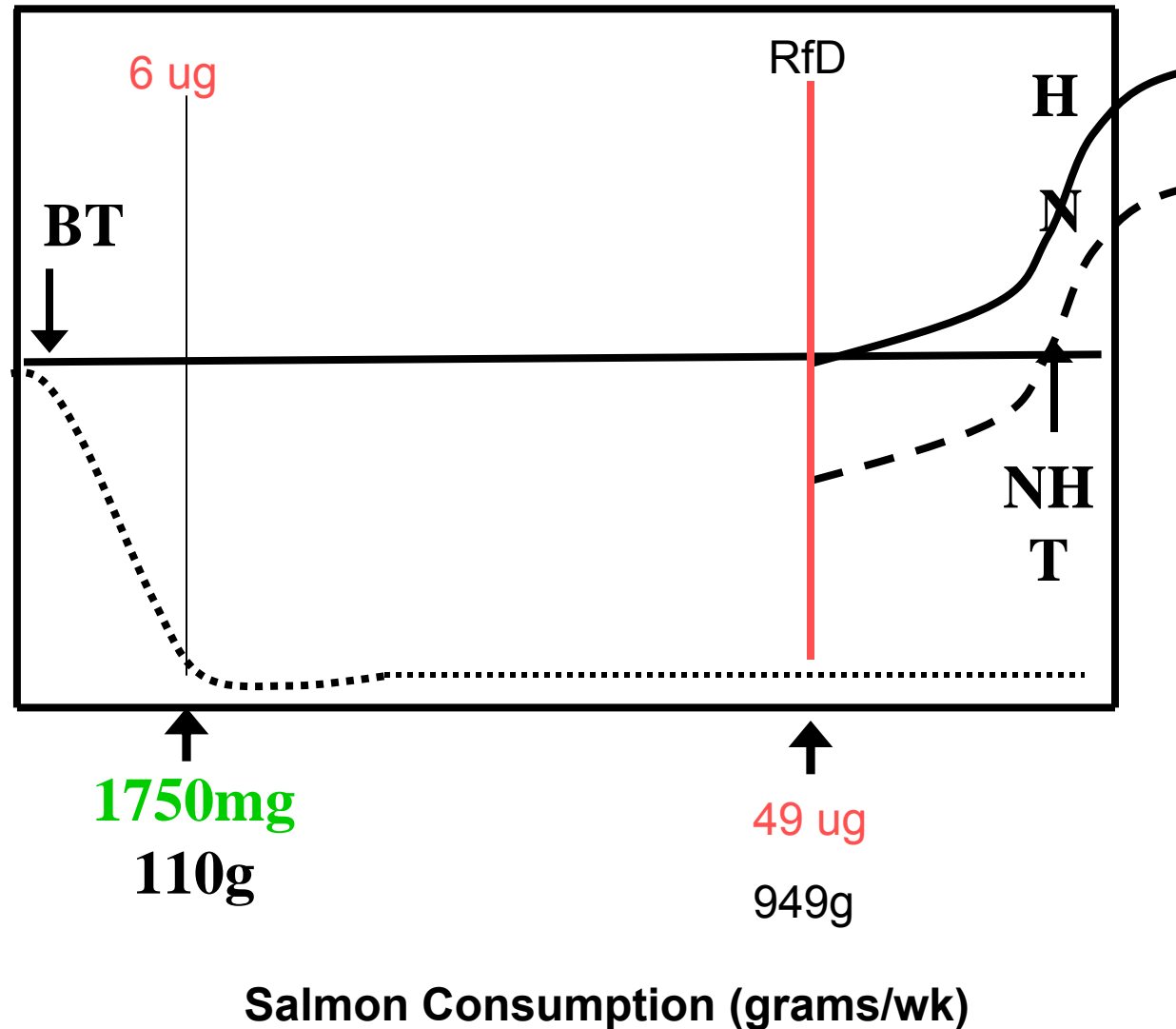
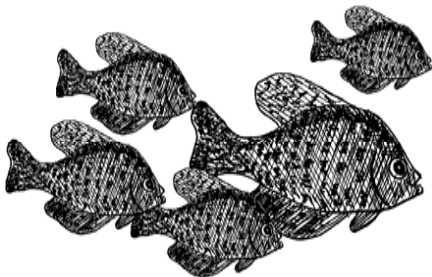
Salmon gives you better numbers

ACTUALLY NOT A LOT OF RELEVANT DATA

We come back to this graph later

BT=Benefit Threshold

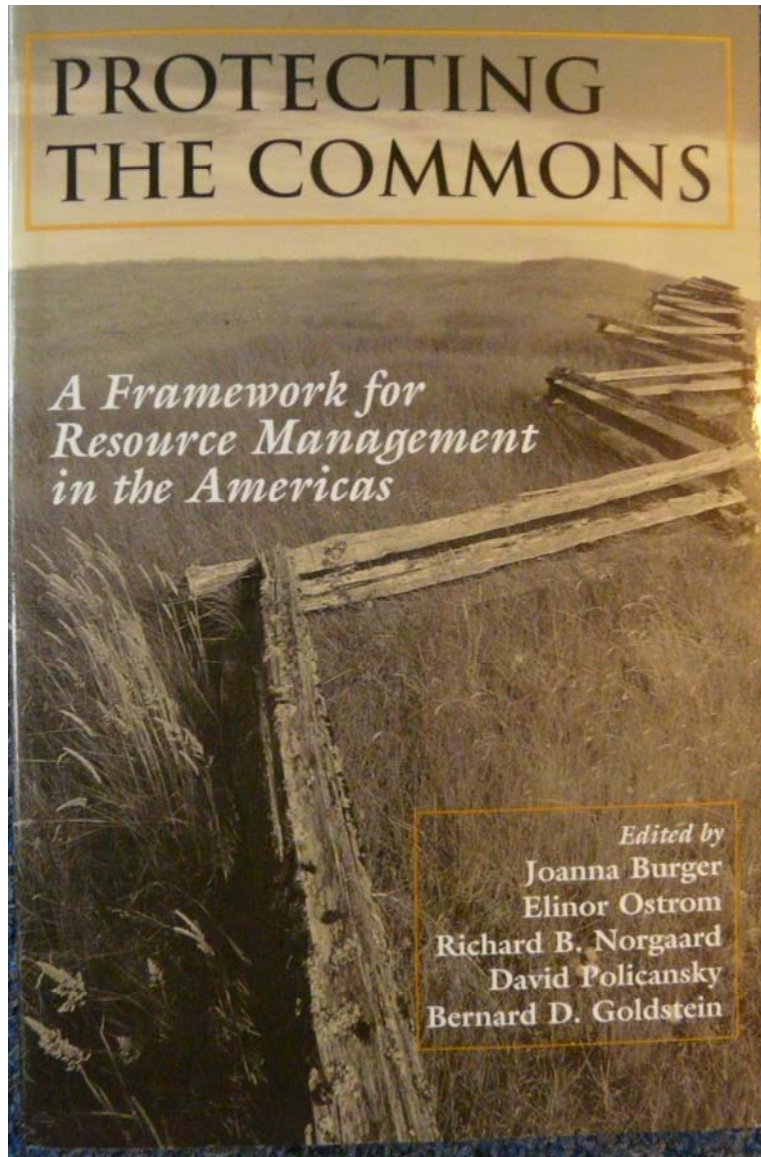
NHT=Net Harm Threshold



Just as we worry about climate

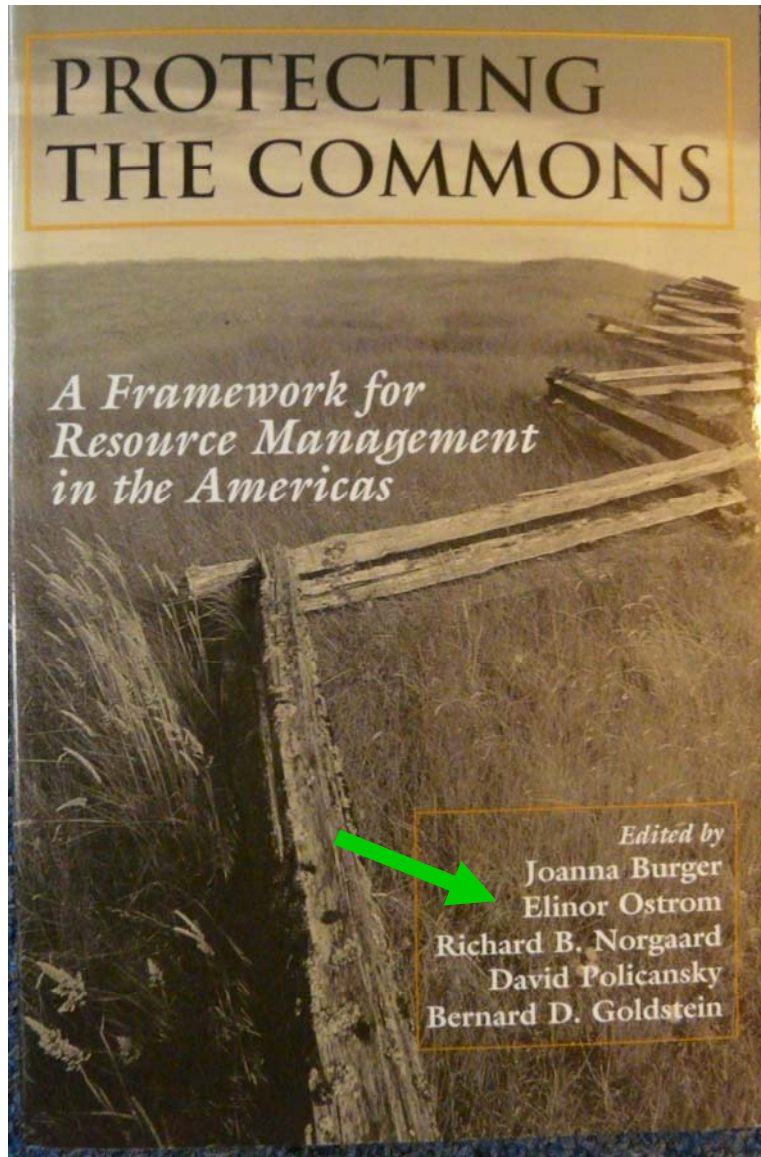
- We need to worry about fisheries
- Too many people wanting too much fish
 - The commercial fish that most of us eat
 - Come at a cost
 - Impact of fish farms and commercial fishers on coastal habitats and subsistence fishers
 - Global population predicted to “level off” at 9.5 billion by 2050

Ecologic Impact on fish stocks: It's not just a luxury for conservationists



- Global carrying capacity for biota
- Water carrying capacity for fish
- Competitive harvesting of fish
 - Non-food uses of fish
 - Non-efficient uses of fish energy/protein
- Fishing down the food chain
- By-catch
- Farming: bad practices more profitable
- Conflicts of interest in fishery management
 - Overfishing is widespread and growing
 - Despite better data and data processing
- **“Sustainability” is an oxymoron**
- **Protecting the Global Commons:**
 - **need for a comprehensive view**

Ecologic Impact on fish stocks: It's not just a luxury for conservationists

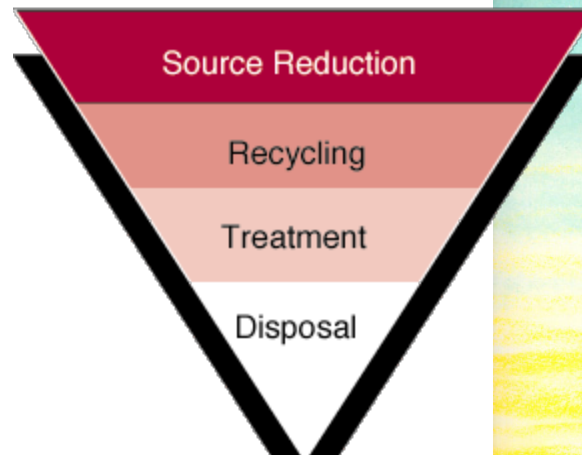


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Let's not lose site of Pollution Prevention

- <http://www.epa.gov/p2/>


Pollution Prevention Hierarchy



Pollution Prevention Primer

Compliance Division

California Environmental Protection Agency

 Air Resources Board



Let's not lose site of Pollution Prevention

- <http://www.epa.gov/p2/>

**LET'S BE SMART
ENOUGH TO
RESTORE THE
ENVIRONMENT
TO WHAT IT WAS
FOR OUR GREAT
GRANDPARENTS
WHO BELIEVED
THAT FISH WAS
A BRAIN FOOD**

