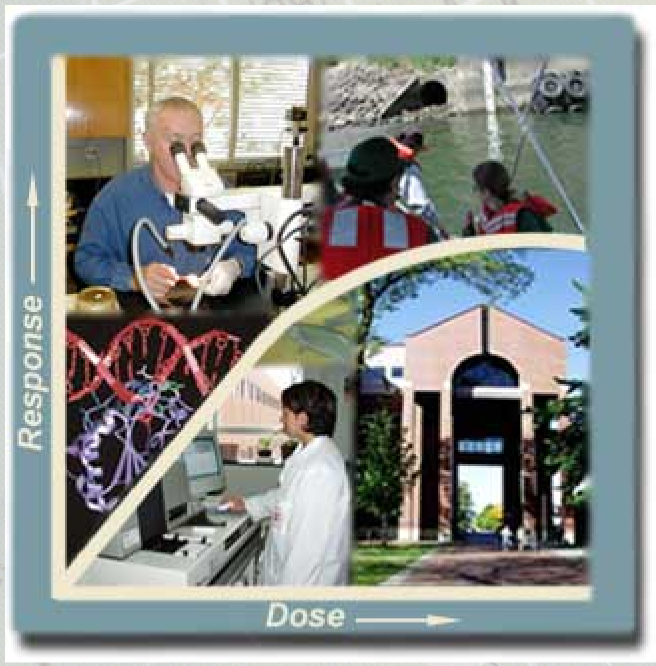
Pesticide Toxicology and Risk Assessment



http://emt.orst.edu

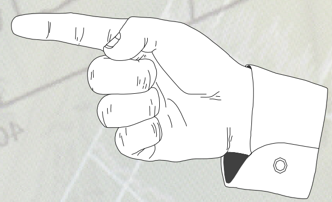
Jeffrey J Jenkins

Department of Environmental & Molecular Toxicology

Oregon State University

Toxicology

- The science of poisons
- The study of adverse effects of chemicals on living systems

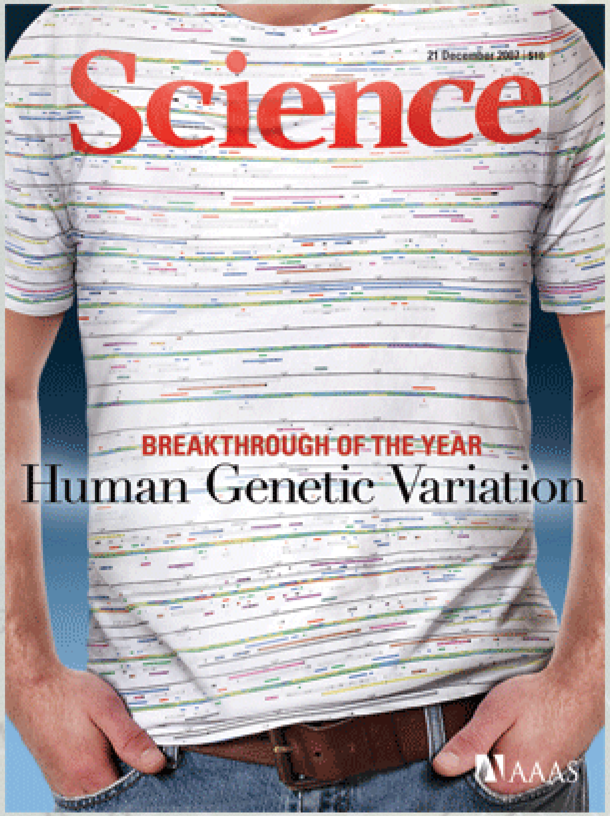


Bag of chemicals

(You)

Toxicology studies how external chemicals interact with your body’s chemicals to cause damage or illness

Science Breakthrough of the Year: Human Genetic Variation



2001: Human genome project – DNA sequence (~3 billion bases; ~30,000 genes) for a few individuals

2007: faster, cheaper technologies for sequencing DNA and assessing variation in genomes;

much more is known about how different we are from one another.

23andMe.com – understand your DNA for ~$1000

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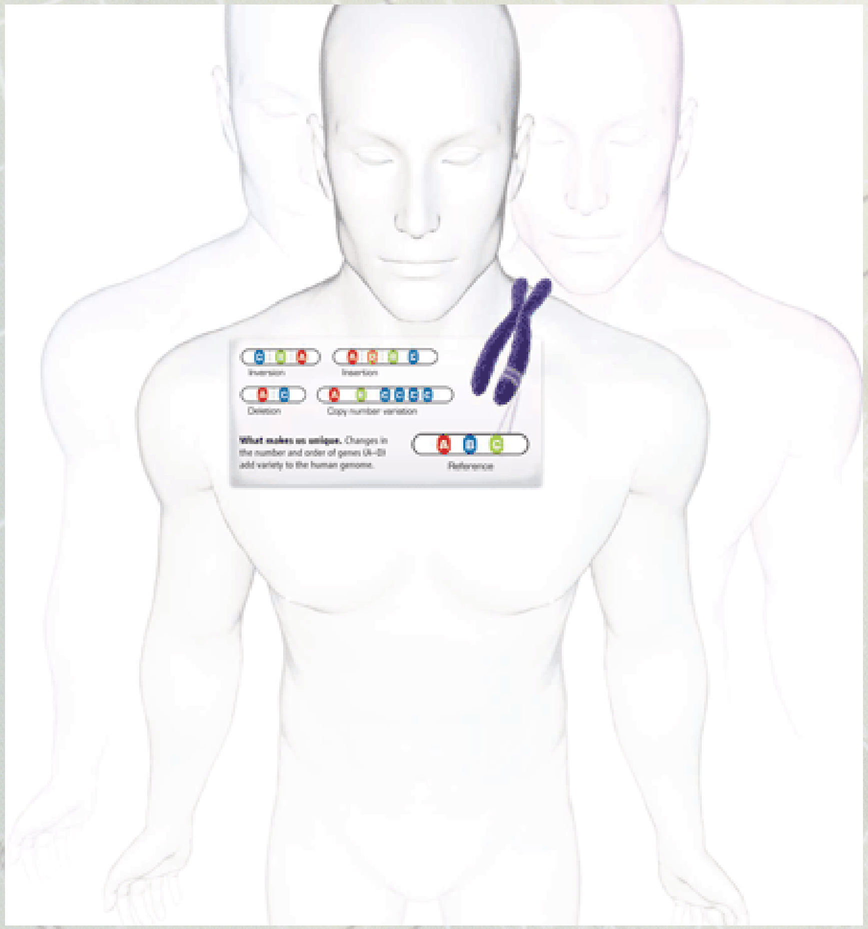
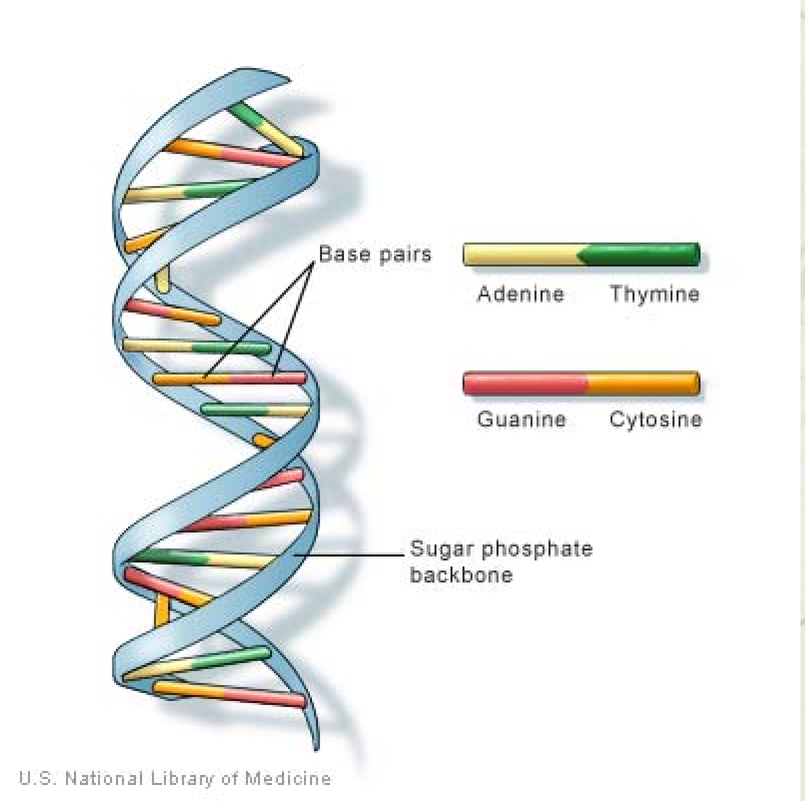
What makes us unique. Changes in the number and order of genes add variety to the human genome



Composite: K. Krause/Science (Human: 3D4 medical.com; Chromosome: C. Bickel/Science)



Gene – region of the DNA strand that codes for proteins that result in gene expression.

Chromosome – bundle of genes that replicates as a unit

In humans two single nucleotide polymorphisms (SNPs) occur in about 2,200 nucleotides (~15 million differences between individuals, ~3 million charted).

Nucleotide (base pair) differences

www.hapmap.org

SNPs – single letter (base pair) differences

Does not account for missing, deleted, repetitive DNA sequences

Used to determine common genetic variants that occur in humans

Link genetic variants to risk (disease, chemical exposure)

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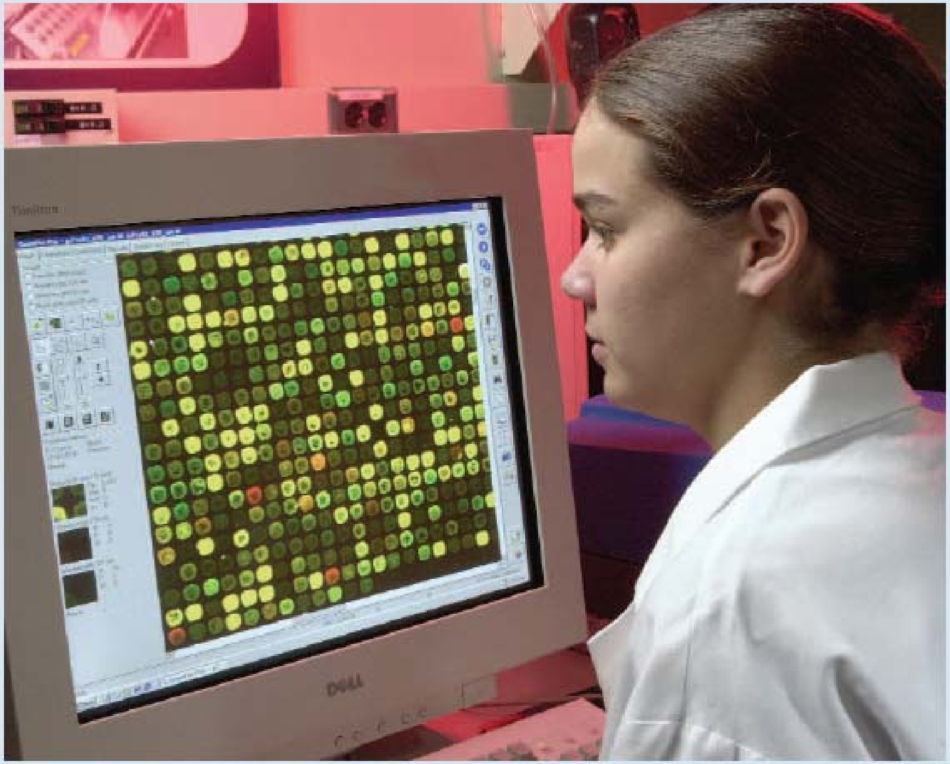
Microarray Demystified

One goal of toxicogenomics is to use gene expression as a highly sensitive and informative marker for toxicity. Using microarrays, researchers can quickly and accurately screen for large numbers of gene expression responses to toxic substances, determine if toxic effects occur at low-dose exposures, highlight vulnerable tissue or cell types, begin to extrapolate effects from one species to another, and eventually identify genes associated with the development of environmentally caused diseases.



Connecting the dots. Since 1997, scientists in the NIEHS Microarray Group have processed more than 12,000 microarray "chips" in the search for better knowledge of how environmental factors affect gene expression.

Microarray chips contain up to 20,000 complementary DNAs (cDNAs) or oligonucleotides that are spotted onto a small glass substrate.

Laser scanners detect the red and/or green fluorescent signals of the spotted gene fragments.

The resulting patterns of color form a gene expression profile that points out a possible toxic condition.

Centre of Bioinformatics
Peking University

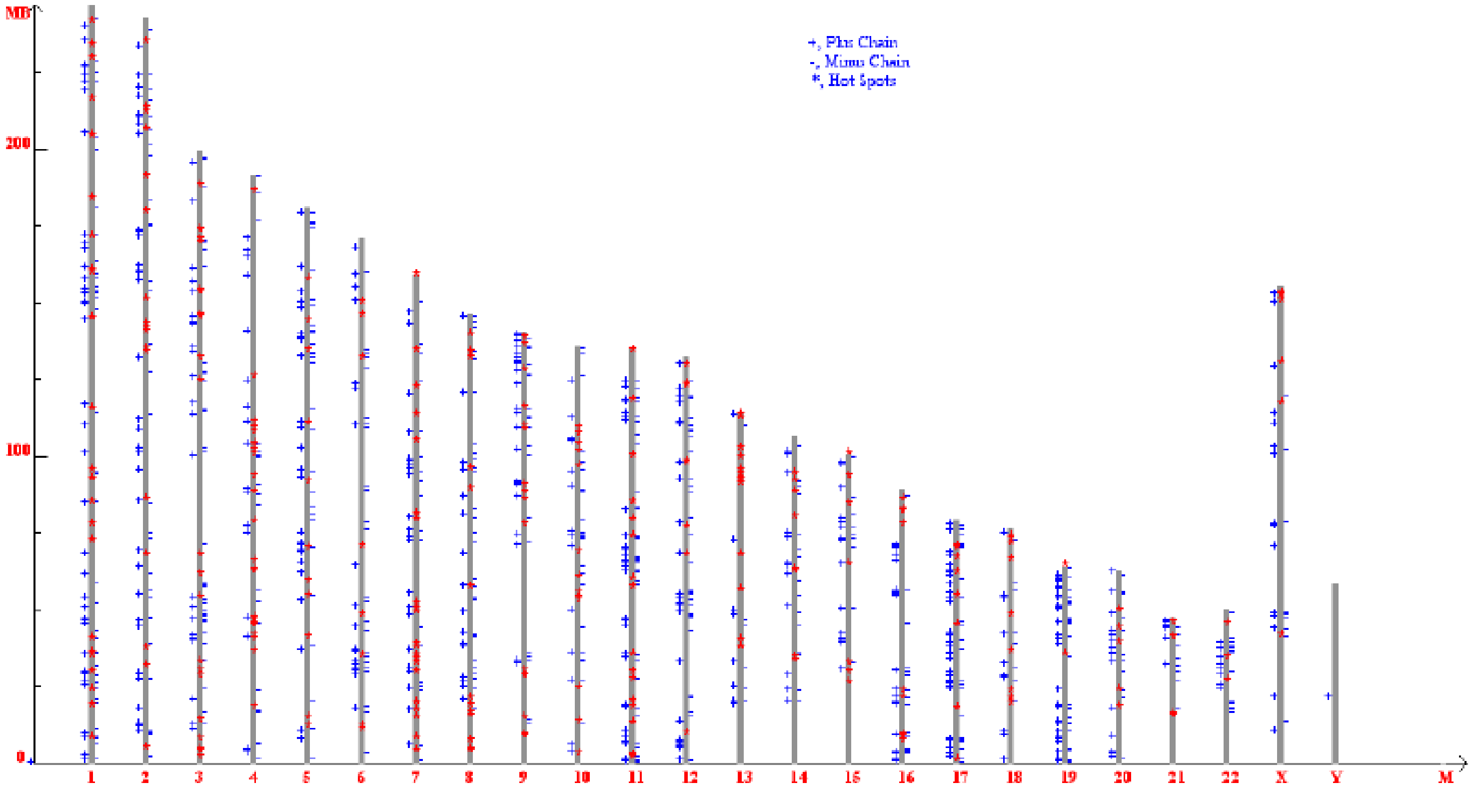
HOME | Score View | Chromosome View | Pathway View | Advanced Search | BLAST | Download | Publications

Quick Search By Entrez Gene ID (example:9252) : Quick Search!

KARG >> Addiction Related Genes And Sensitive Points On Chromosome (Homo Sapiens)

Chromosome overview of addiction related genes and sensitive points for Homo Sapies. To cite this work, please refer to: **Li CY, Mao X, Wei L (2008) Genes and (common) pathways underlying drug addiction. PLoS Comput Biol 4(1): e2. doi:10.1371/journal.pcbi.0040002**

Mouse over or click '+/-'...



Any Comments and suggestions to : KARG GROUP.

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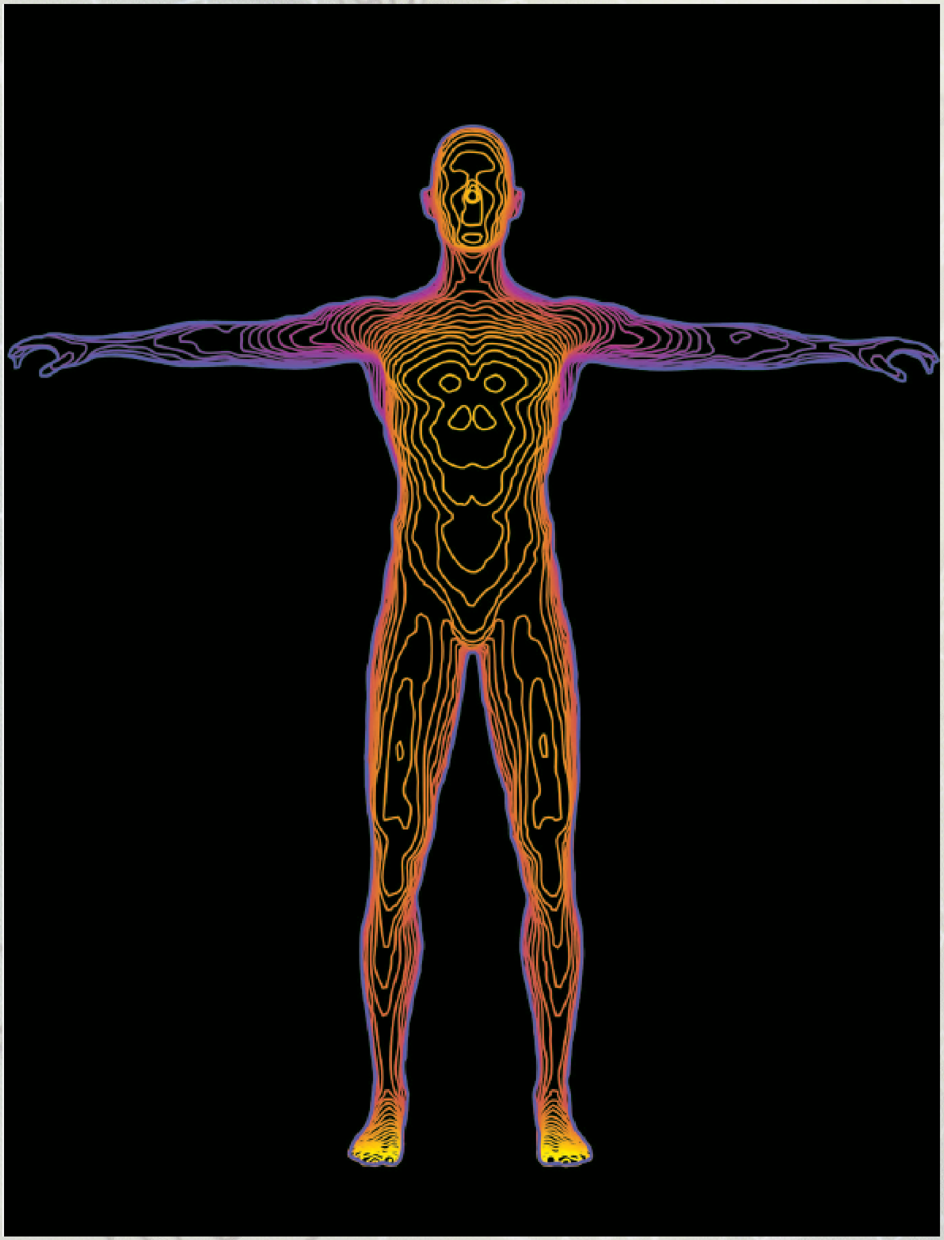

Understanding you as a bag of chemicals

Systems Biology and the "omics"

Genomics
Epigenomics
Transcriptomics
Proteomics
Metabolomics
Metabonomics

Pharmacogenomics
Toxicogenomics

Bioinformatics

Systems Biology Glossary

- Systems biology: understanding of the function of a biological system–tissue, organ, or organism–as a whole.

Genomics – study of gene expression, protein and metabolite profiles
Epigenomics – DNA methylation (cells turn genes on/off)
Transcriptomics – mRNA profile (functional genomics; microarrays)
Proteomics – cell proteins (proteome)
Metabolomics – cellular metabolites (products of gene expression)
Metabonomics – organismal metabolites; metabolic profiling

Pharmacogenomics – drug effects at the gene expression level
Toxicogenomics – toxicity at the gene expression level

Bioinformatics – genomic data acquisition, analysis, interpretation

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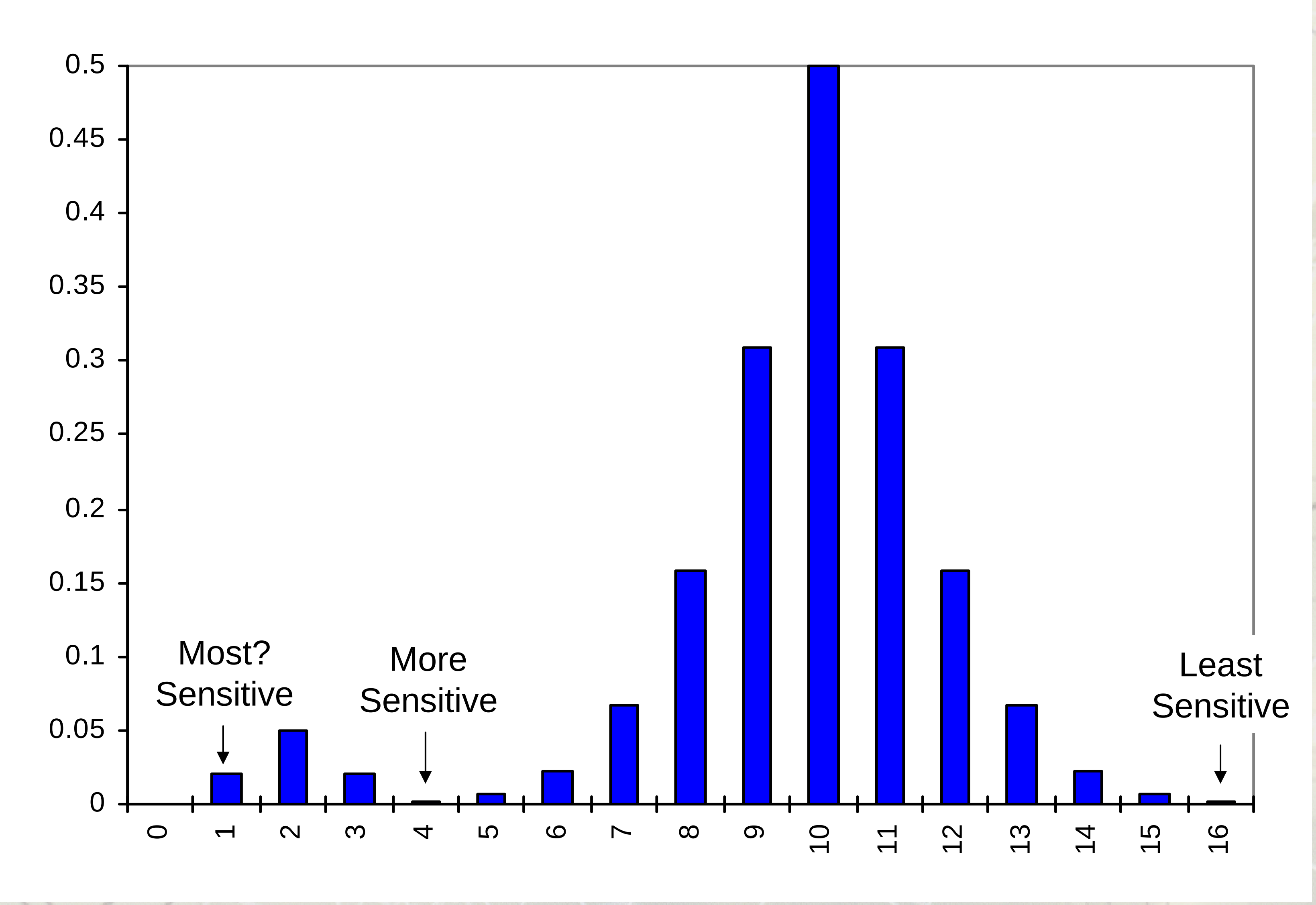
Sensitive populations: Bimodal Frequency Distribution



Expressions of Toxicity

- Modify existing body functions
- Change speed of cellular reactions
- Reversible injury
- Irreversible injury
- Death

Future – gene expression and genotoxicity

All substances are poisons; there is none that is not a poison.

The right DOSE differentiates a poison from a remedy

(the dose makes the poison)

Areolus Phillipus Theophrastus Bombastus von Hohenheim

Paracelsus (1493-1541)

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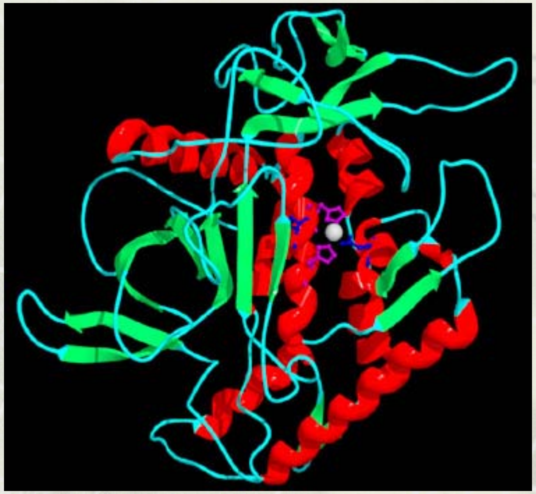
New Yorker magazine 6-11-01

Botulinum A Toxin:
Food Poison or Wrinkle Remover?



- **Botulinum A toxin is:**
- produced by the bacterium *Clostridium botulinum*
- the <u>most potent known biologic neurotoxin</u>
- a neuromuscular agent; inhibits acetylcholine release
- a drug administered by intramuscular injection
- marketed as BOTOX®

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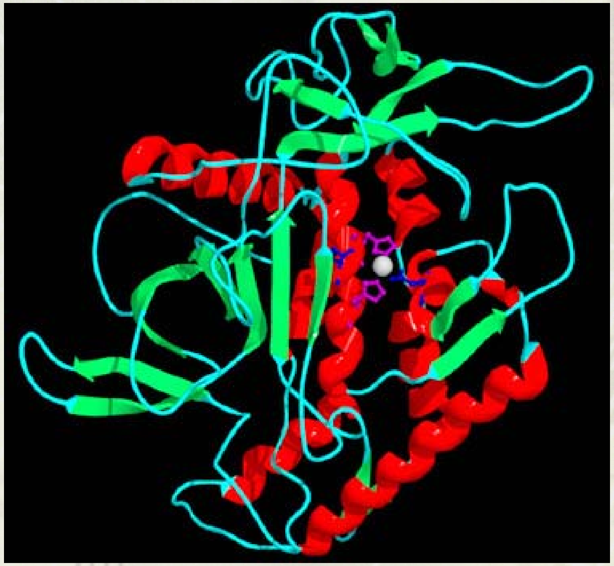
Botulinum A Toxin:



Food poison or wrinkle remover?

It depends on the dose

Chemicals of Concern

~84,000 chemical substances regulated in the USA.

~1000-1500 new chemicals manufactured each year.

How many pesticide active ingredients?

~1000

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EPA Pesticide Risk Assessment

Source: Purdue University Pesticides Program

Risk = f (exposure, toxicity)

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Toxicity Testing

- Animal models will predict adverse effects in humans.
- High dose, short term, exposure of animals will predict adverse effects of low dose, long term, exposure in humans.

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TABLE 4-1 Battery of Tests Required by EPA for New Pesticide Chemicals

Tests	Food Uses	Nonfood Uses
Acute tests		
Acute oral toxicity—rat	R	R
Acute dermal toxicity	R	R
Acute inhalation toxicity—rat	R	R
Primary eye irritation—rabbit	R	R
Primary dermal irritation	R	R
Dermal sensitization	R	R
Delayed neurotoxicity—hen	R	R
Subchronic testing		
90-day feeding studies—rodent and nonrodent	R	C
21-day dermal toxicity	C	C
90-day dermal toxicity	C	C
90-day inhalation—rat	C	C
90-day neurotoxicity—hen or mammal	C	C
Chronic tests		
Chronic feeding of two species—rodent and nonrodent	R	C
Oncogenicity study of two species—rat and mouse preferred	R	C
Teratogenicity in two species	R	C
Reproduction—two-generation	R	C
Mutagenicity tests		
Gene mutation	R	R
Structural chromosomal aberration	R	R
Other genotoxic effects	R	R
Special tests		
General metabolism	R	C
Dermal penetration	C	C
Domestic animal safety	C	C

Note: R = required data; C = conditionally required data on the basis of special pesticide characteristics, potential use and exposure patterns, or results of routinely required studies.
Source: Adapted from 40 CFR 158.340.

NAS Toxicity Testing for Assessment of Environmental Agents: Interim Report (2006)

Chemical Risk Assessment :

Human Health risks

Threshold

There is some dose, below which there will be no effect.

Non-threshold (cancer)

Potency estimated from the probability of developing cancer over a lifetime of exposure.

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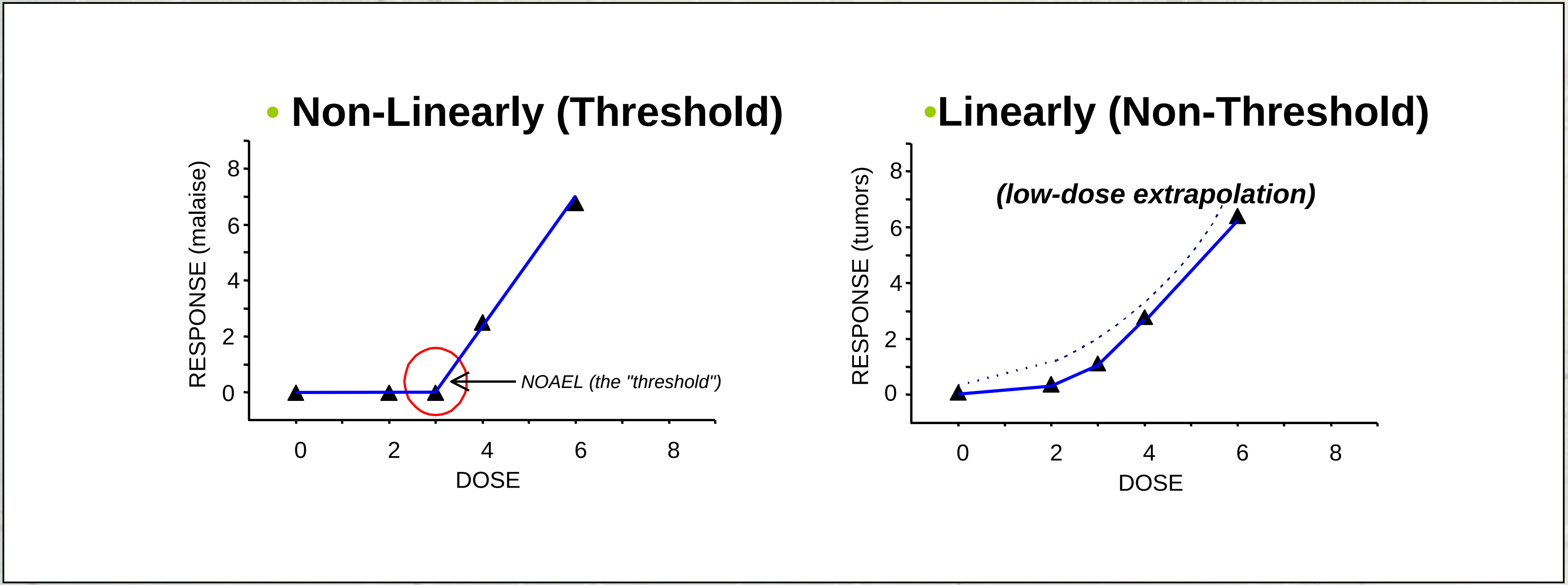
Toxicological effects are believed to occur either:



NOAEL: No Observable Adverse Effect Level

National Academy of Sciences four-step risk assessment paradigm

Hazard Identification

- What are the toxicological effects (endpoints)? For example, cholinesterase inhibition.

Dose-Response Assessment

- At what dose level do the effects occur? For example, what's the NOAEL?

Exposure Assessment

- How much chemical is a person being exposed to?

Risk Characterization

- Combine the hazard, dose-response, and exposure information to describe the overall magnitude of the risk

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Pesticide Risk Assessment

- **NOAEL**: EPA scientists examine the results of tests exposing laboratory animals to various doses of a pesticide.
- The highest dose which caused no observable harm or side effects is the <u>*No-Observable Adverse Effect Level*</u> *or NOAEL*.

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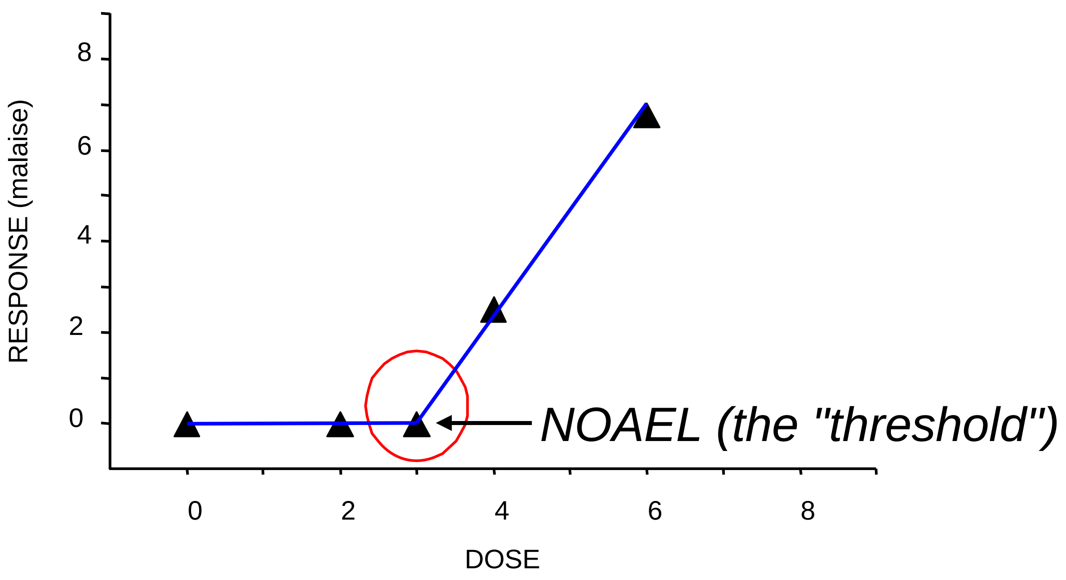
No Observable Adverse Effect Level (NOAEL)



How Is Dose-Response Assessed?

- How depends on:
  - Duration of exposure (acute, chronic)
  - Type of toxic effect (cancer; non-cancer)
  - Route of exposure (inhalation, dermal, oral)
  - Type of risk assessment (dietary; residential; occupational)

NOAELs from 90-day rat, 24-month rat, 90-day dog, and 12-month dog studies compared with the lowest NOAEL excluding the 12-month dog study (SABRE data)

Active ingredient	Chemical class	90-Day rat NOAEL (mg/kg/day)	90-Day dog NOAEL (mg/kg/day)	1-Year dog NOAEL (mg/kg/day)	2-Year rat NOAEL (mg/kg/day)	Lowest NOAEL all studies	Lowest NOAEL excluding chronic dog
2,4-D	Phenoxyacid	15	1	1	5	1	1
Acetochlor	Acetanilide	80	10	2	10	2	10
Atrazine	Triazine	1	6	5	3.5	1	1
Butylate	Carbamate	32	45	5	100	5	32
Carbaryl	Carbamate	125	1	3.1 (LOAEL)	10	1	1
Cyprodinil	Anilinopyrimidine	3	46	—	2.7	2.7	2.7
Diazinon	Organophosphorothioate	0.3 (LOAEL)	0.02 (LOAEL)	0.004	20	0.004	0.006 (LOAEL/3)
Glufosinate ammonium	Phosphinic analogue of glutamic acid	3.2 (LOAEL)	2	5	2	2	2
Hexaconazole	Triazole	3	5	2	4.7	2	3
Mevinphos	Organophosphate	0.25 (LOAEL)	0.0625 (LOAEL)	0.025	0.025	0.025	0.025
Prallethrin	Pyrethroid	24	3	5	16.3	3	3
Tebuconazole	Triazole	9	73	2.9	5	2.9	5
Triallate	thiocarbamate	3	2	1.275	NA (0.5 = LOAEL)	0.5 (LOAEL)	0.5 (LOAEL)
Vinclozoline	Dicarboximide	4	3	2.4	1	1	1
Dicamba	Dichlorobenzoate	250	6	52	≥125	6	6
Dimethoate	Organophosphate	2	<0.25	<0.18	0.05	0.05	0.05
Chlorfenapyr	Pyrrole	24	4	4	No study	4	4
MCPA	Dithiocarbamate	7	3	1.75	4.38	1.75	3
Metolachlor	Acetanilide	23	10	9.7	15	9.7	10
Benomyl	Benzimidazole	25	13	12.5	>125	12.5	13
Propachlor	Acetanilide	75	38	6.25	2.4	2.4	2.4
2,4-DB	Phenoxyacid	16	8	<2.39	3	2.39	3
Fosetyl-AL	Organophosphate	365	274	250	400	250	274

Critical Reviews in Toxicology, 36:37–68, 2006

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No-observable Adverse Effect Levels (NOAELs)

	90 day rat NOAEL (mg/kg/day)	90 day dog NOAEL (mg/kg/day)	1-year dog NOAEL (mg/kg/day)	2-year rat NOAEL (mg/kg/day)	Lowest NOAEL (mg/kg/day)
2,4 D	15	1	1	5	1
Acetochlor	80	10	2	10	2
Atrazine	1	6	5	3.5	1
Carbaryl	125	1	3.1	10	1

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Threshold-based Risk Assessment

Threshold: there is some dose, below which there will be no effect.

- **RFD**: *The Reference Dose* is the amount of a pesticide residue a person could consume daily for 70 years with no harmful non-cancer effects.
- **RFD** (EPA) = Allowable daily intake (EU[1])

[1]And other developed countries

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Pesticide Risk Assessment

- The RFD is determined by dividing the NOAEL by a uncertainty factor (UF), usually between 100 and 1000

- 10X – uncertainty in extrapolating from animal studies to humans (interspecies).
- 10X – to account for variation in human susceptibility (intraspecies).
- 2-10X – to account for sensitive sub-populations (infants and children)[1].
- 2-10X – optional factor for inconsistent data

[1] FQPA requires EPA to make determination if additional factor necessary.

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Reference Dose (Non-cancer risk)

- Start with the NOAEL (mg/kg BW/day)
- Calculate a reference dose (RfD):

$$RfD = \frac{NOAEL}{UF}$$

UF: ***10X for Interspecies***

10X for Intraspecies

Other (as needed) Uncertainty Factors

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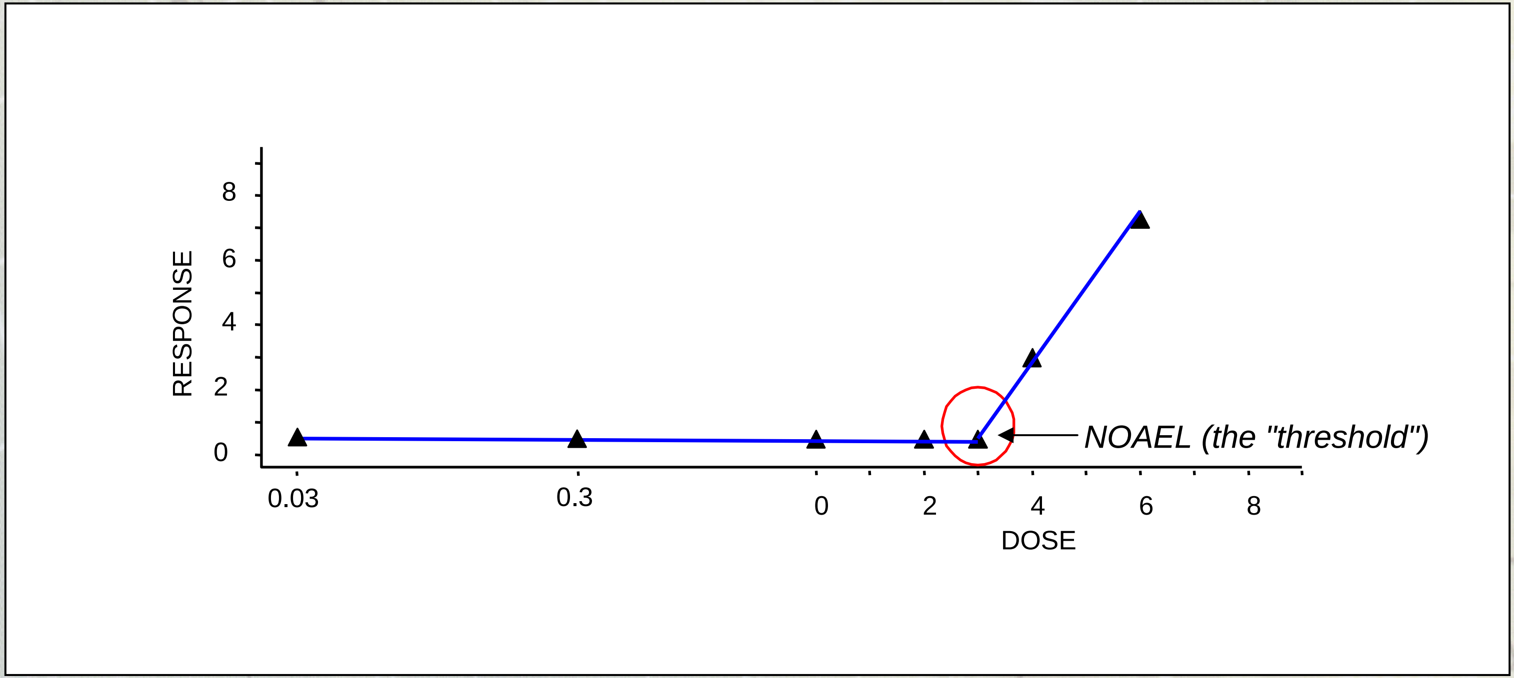
Reference Dose relative to NOAEL



$$RfD = \frac{NOAEL}{UF}$$

$$RfD = \frac{3}{10 \times 10} = 0.03 \text{ mg/kg/day}$$

Reference Dose (Non-cancer risk)

Pesticide	Reference dose[1]
Naled	0.002
chlorpyrifos	0.003
malathion	0.02
resmethrin	0.03
permethrin	0.05
glyphosate	0.10

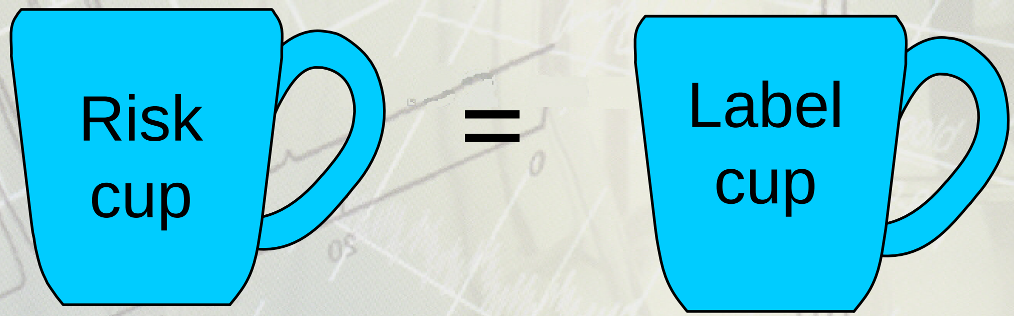
[1] mg/kg/day

Pesticide Risk Assessment

- **RFD**: *The Reference Dose* is the amount of a pesticide residue a person could consume daily for 70 years with no harmful non-cancer effects.

RFD =

Pesticide Label Cup



The lower the risk associated with each use, the greater the number of potential registered uses

Minor uses: last in/first out?

Pesticide Risk Assessment: Cancer

- Cancer risk: The amount of a pesticide residue a person could consume daily for 70 years that would result in no more than 1-in-a-million (10^{-6}) increased chance of developing cancer as a direct result of consumption of (exposure to) that chemical.

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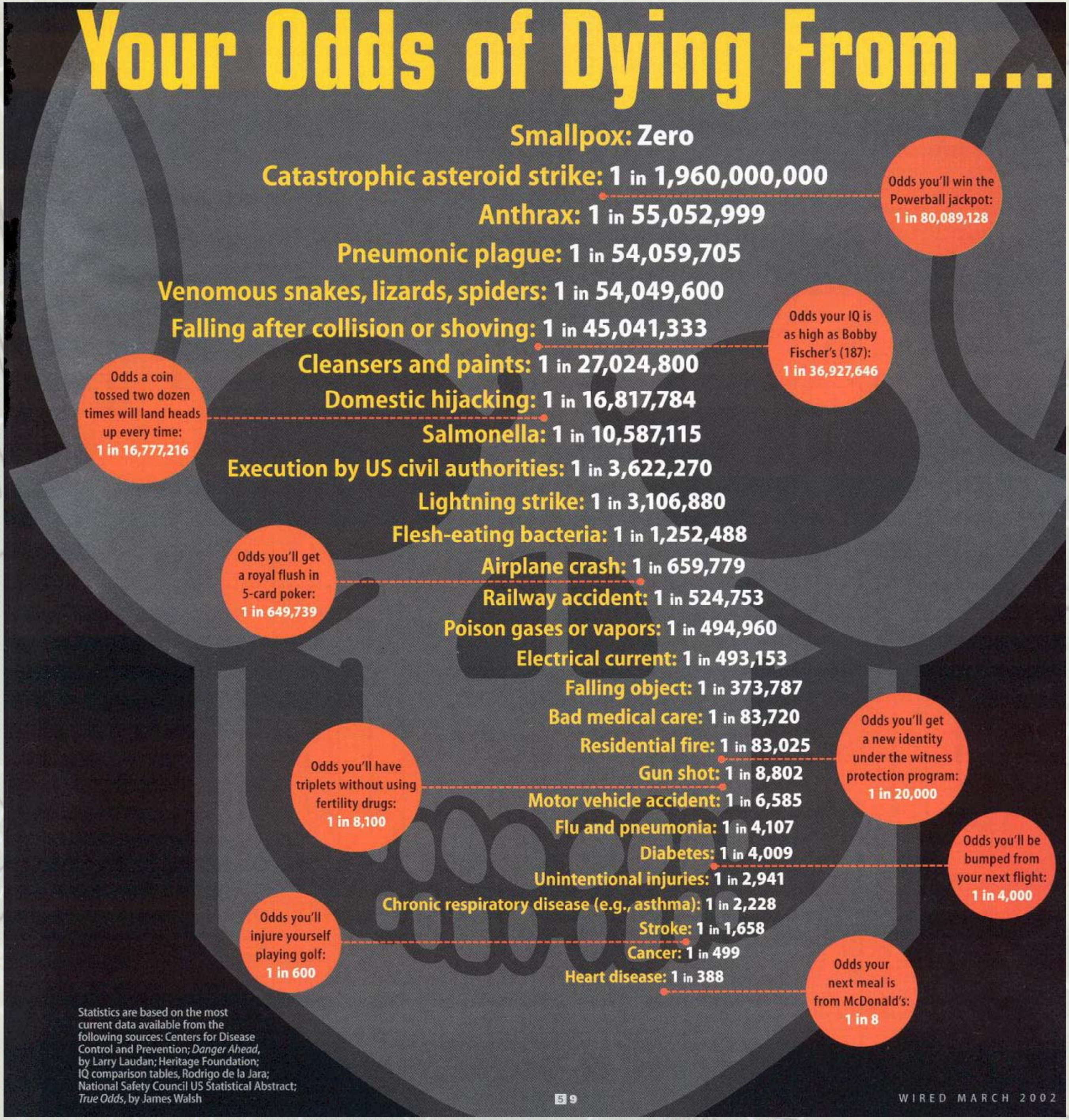
Odds of cancer during lifetime ~ 1 in 4



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“The odds of winning Powerball’s huge Jackpot were high enough - 1 in 146.1 million.”

OregonLive.com
Everything Oregon

The Oregonian

A secret worth $340 million

Friday, October 21, 2005

JAMES MAYER and DAVID AUSTIN
The Oregonian

JACKSONVILLE -- Bank teller Robin Bell knew one thing for sure: "It wasn't my ticket, I can tell you that."

But someone bought the winning $340 million Powerball ticket in this Southern Oregon gold mining-turned tourist town and as of Thursday night, no one had come forward to claim the prize.

It could have been someone passing through. But for the folks here, it's much more entertaining to speculate that one of the town's 2,410 residents became an overnight megamillionaire.

"I hope it's someone who comes in here a lot," said Andy Gough, co-owner of the J'Ville Tavern, one of only two places in town where the ticket could have been bought. "I hope it's someone who really needs it."

Oregon Lottery officials said they won't know who the winner is until someone contacts them. The jackpot winner will get either an average annual payment of $7.59 million a year for 30 years or a lump-sum payment of $110.1 million after state and federal taxes. It was the largest jackpot in the history of the Powerball game played in 28 states across the United States.

In Oregon, the Powerball jackpot winner was one of six who had big days Wednesday. Four players matched five of the white balls in the drawing to collect $200,000, plus a bonus jackpot take of $653,000 each. In addition, a Portland couple won a $2.6 million Megabucks jackpot Wednesday night.

The odds of winning Powerball's huge jackpot were high enough -- 1 in 146.1 million. But to have so many winners in one drawing is nearly unprecedented, said Chuck Baumann, a spokesman for the Oregon Lottery. The odds of matching five numbers and not the Powerball are 1 in 3.56 million.

"Having someone win the Megabucks jackpot alone is great," Baumann said. "These other things happening are just amazing. Everything else is gravy. When it rains, it pours."

The last time a Powerball jackpot was won in Oregon was six years ago.

If Wednesday's winner was a Jacksonville resident, the secret held up throughout the day.

"We know who it isn't, by all the people who came in here and said it wasn't them," Gough said.

Gough later went home to check her car, because her husband, who was hunting, always buys a five-pack of tickets.

In fact the theory that the winning ticket might be in the woods with a hunter who doesn't know he's rich was a favorite theory at antler-festooned J'Ville.

Gough has more than sentimental reasons to hope the winner bought the ticket in her place. The retailer who sold it will get $100,000.

The odds are, that's more likely to be a few blocks away at Ray's Food Place. The market sold 4,317 Powerball tickets, compared with 407 at the tavern.

But what do the odds mean when lightning strikes twice in the same town on the same day?

Todd and Beth Zitzner of Jacksonville bought a Powerball ticket at Ray's and won more than $853,000 for matching five numbers. Todd Zitzner said he never buys lottery tickets but decided to purchase $20 worth recently. "I'm just lucky," he said while picking up their check Thursday in Salem. "It's a lucky town today."

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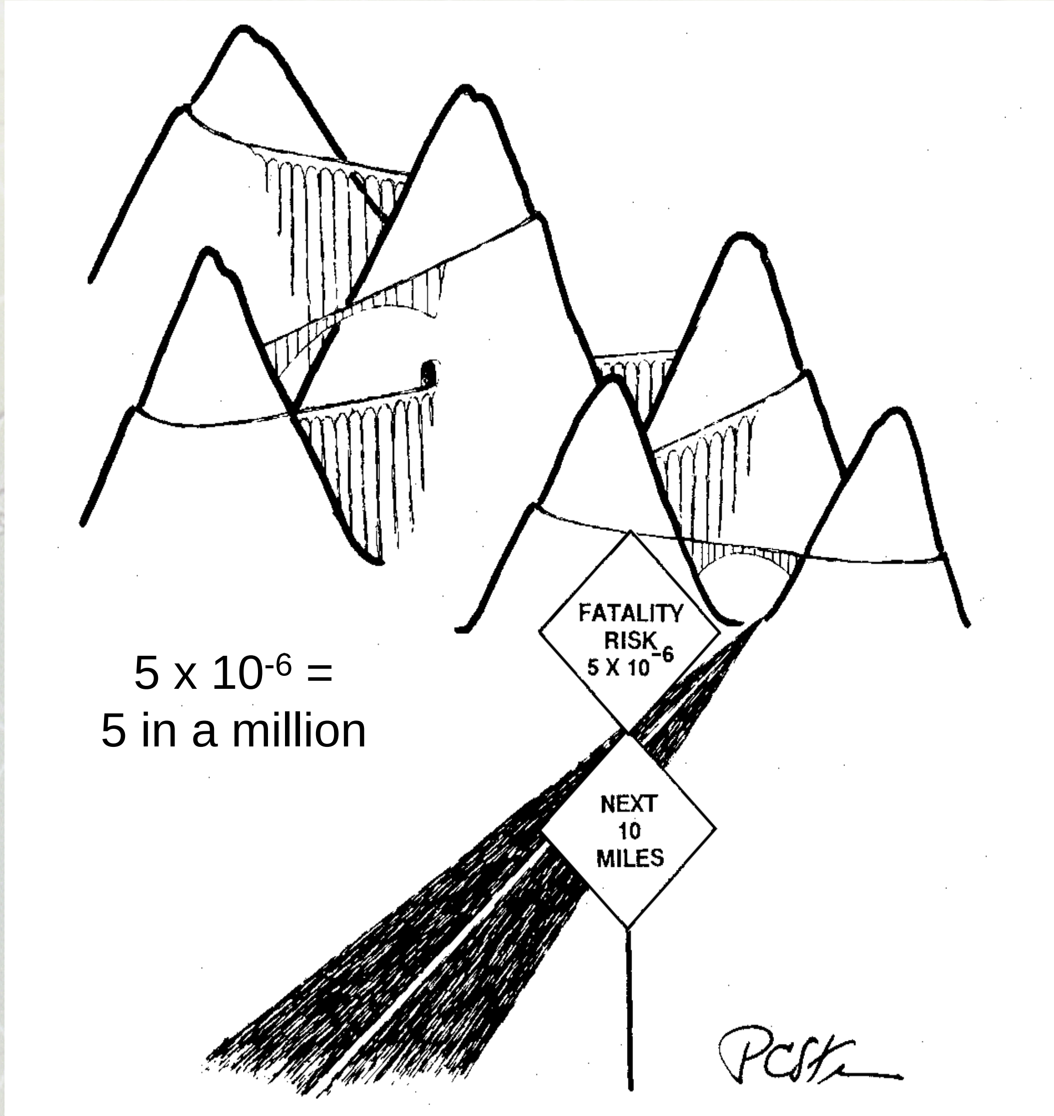
Actuarial Risk: predict future events based upon past occurrences

Population Risk: probability of injury from well defined random events

Individual Risk: better explained with plausibility rather than probability



5×10^{-6} =
5 in a million

Cancer "Prevention"

EPA cancer risk assessment goal:

prevent excess cancers due to chemical exposure

- Often assumes a lifetime daily dose (mg/kg/day)
- Excess cancer: >1 in 4 U.S. population

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Excess Cancer Risk Terminology

- U.S. cancer rate: 1 in 4 or ¼ or 0.25
- Acceptable excess cancer rate for each chemical exposure = 0.25 + ?
- How about 0.25 + 0.000001=.250001*
- 0.000001 = 1.0 x 10^{-6}, often referred to as 10^{-6} cancer risk, this means that assuming daily exposure over a 70 year lifetime that an individual would have a 1 in 1 million risk of cancer above normal probability.

*Population risk, individual risk will vary with genetic predisposition to cancer, lifestyle, and other factors.

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EPA Residential Risk Assessment

- Start with the NOAEL (mg/kg BW/day)
- Determine the uncertainty factors:
  - Intraspecies (10X)
  - Interspecies (10X)
  - Other (e.g. FQPA Safety Factor)
- Multiply uncertainty factors to determine target margin of Exposure (MOE).

MOE = 10 x10 x other UF

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EPA Residential Risk Assessment

- Estimates of exposure are derived from:
  - Available exposure data
  - Pesticide Handlers Exposure Database (PHED)
  - Knowledge of consumer practices (e.g., typical application rate, how often, etc.)

EPA Risk Characterization

Risk = f (toxicity, exposure)

- Threshold Risk Assessment

$$\text{MOE} = \frac{\text{NOAEL (mg/kg BW day)}}{\text{Exposure (mg/kg BW day)}}$$

- Non-threshold (cancer) Risk Assessment

Risk (probability) = q_1* X exposure

q_1^*= cancer slope factor, usually expressed in units of proportion (of a population) affected per unit exposure (e.g. mg/kg/day)

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EPA Risk Characterization: *Level of Concern*

- Threshold risk: values less than the MOE or greater than the RfD are of concern.

- Cancer (non-threshold)
  – expressed as a probability
  – $>10^{-6}$ increased chance of developing cancer

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EPA Risk Assessment: FPQA

Reasonable certainty of no harm

"Safety is defined as a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

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Pesticide aggregate exposure and cumulative risk

- A cumulative risk assessment incorporates aggregate exposure data (from multiple pathways), for example:
  - food
  - drinking water
  - residential/non-occupational exposure

- for those chemicals with a <u>common mechanism of toxicity</u>
  (such as the OP insecticides).

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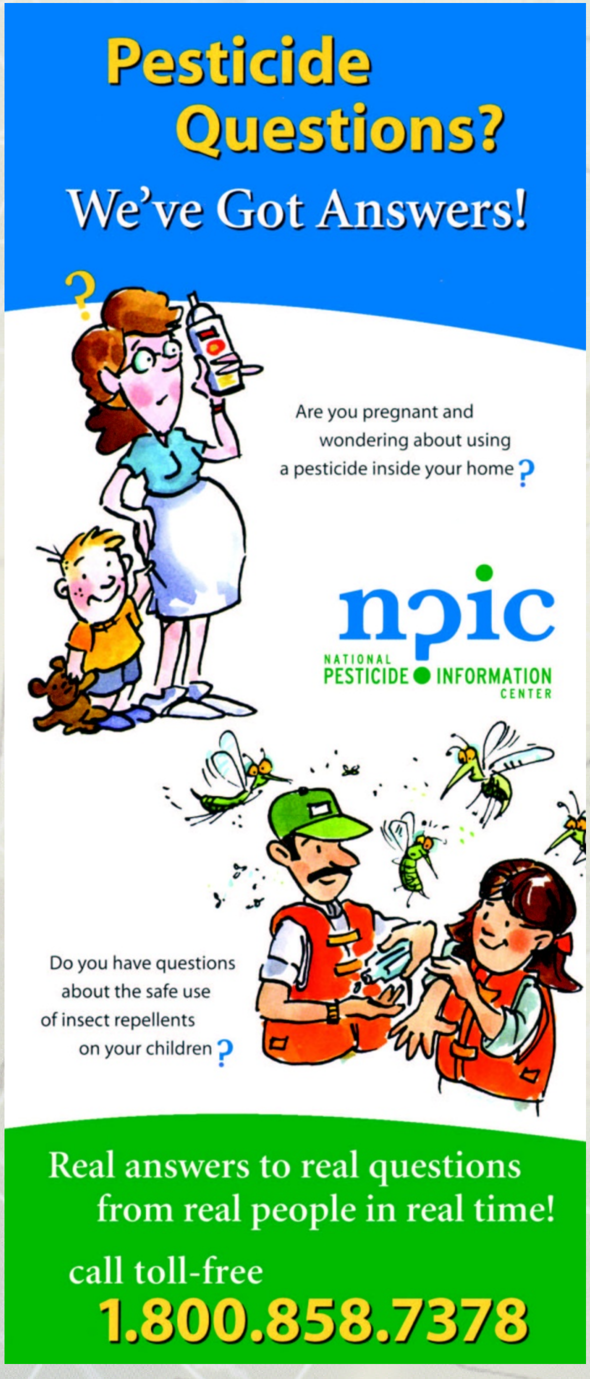
National Pesticide Information Center (http://npic.orst.edu/)

an effort of Oregon State University and the U.S. Environmental Protection Agency**.**

a toll-free telephone service that provides pesticide information to any caller in the United States, Puerto Rico, or the Virgin Islands.

a service that provides objective, science-based information about a wide variety of pesticide-related subjects.



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