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Addressing Temporally Varying Exposures in Toxicity Characterizations

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Presentation to

***Temporal Exposure Issues for Environmental Pollutants:
Health Effects and Methodologies for Estimating Risk***

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Outline

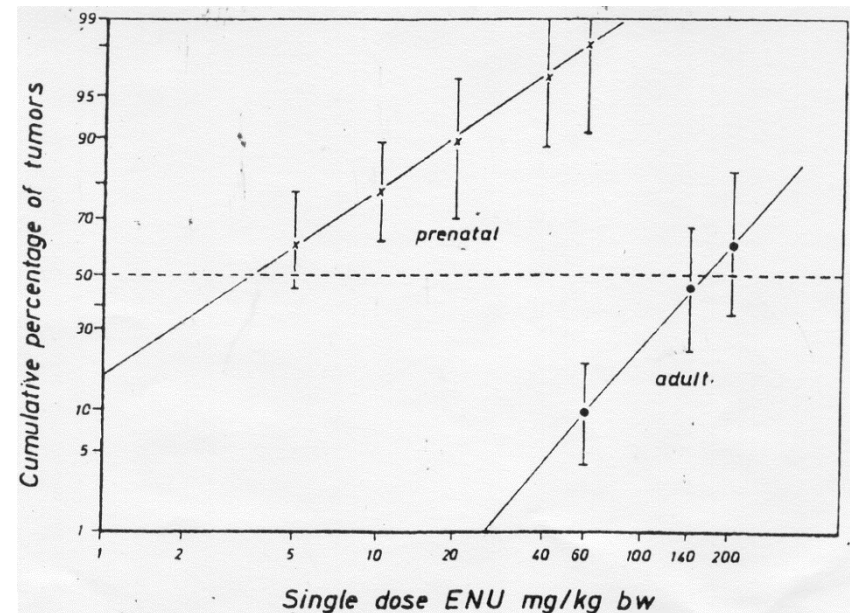
- Carcinogenicity
 - Early Life Exposure
 - Discontinuous exposure scenarios
- Time-varying exposure and vulnerable groups

Carcinogenicity

Examples of data and analyses

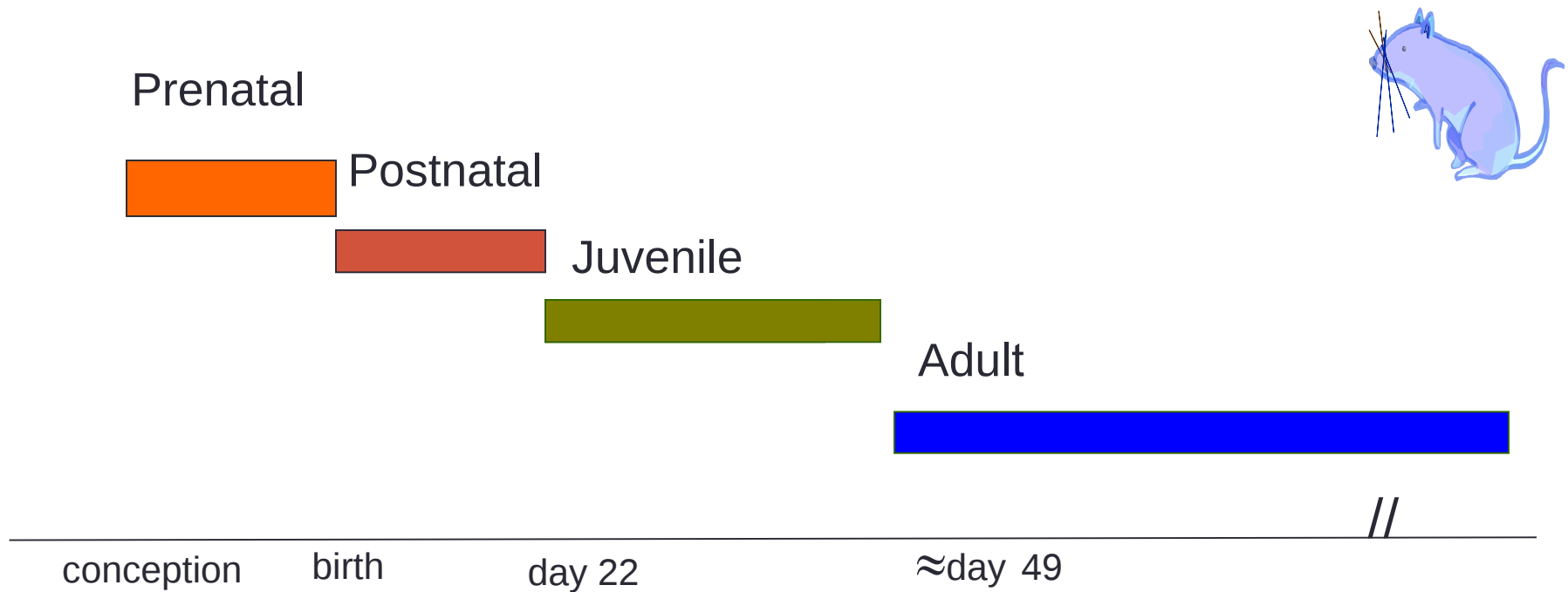
Early-life susceptibility to carcinogens

- Human examples
 - Diethylstilbestrol (DES) *in utero*
 - Radioactive iodine early childhood
 - Immunosuppressive agents during childhood
 - X-irradiation during adolescence
- Animals
 - Many examples
 - Systematic study of literature (e.g., EPA, CalEPA)

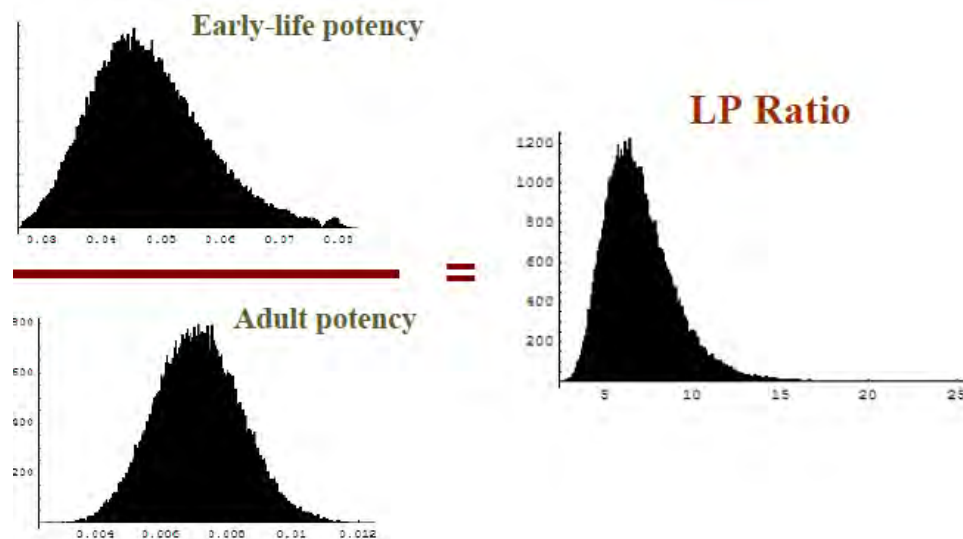


TEXT-FIGURE 3.—Dose-response relationships for the induction of neurogenic tumors in BD rats by single doses of ENU. *Prenatal*: during fetal development, on day 15 post coitum; *adult*: in 90-day-old rats.

Age windows evaluated

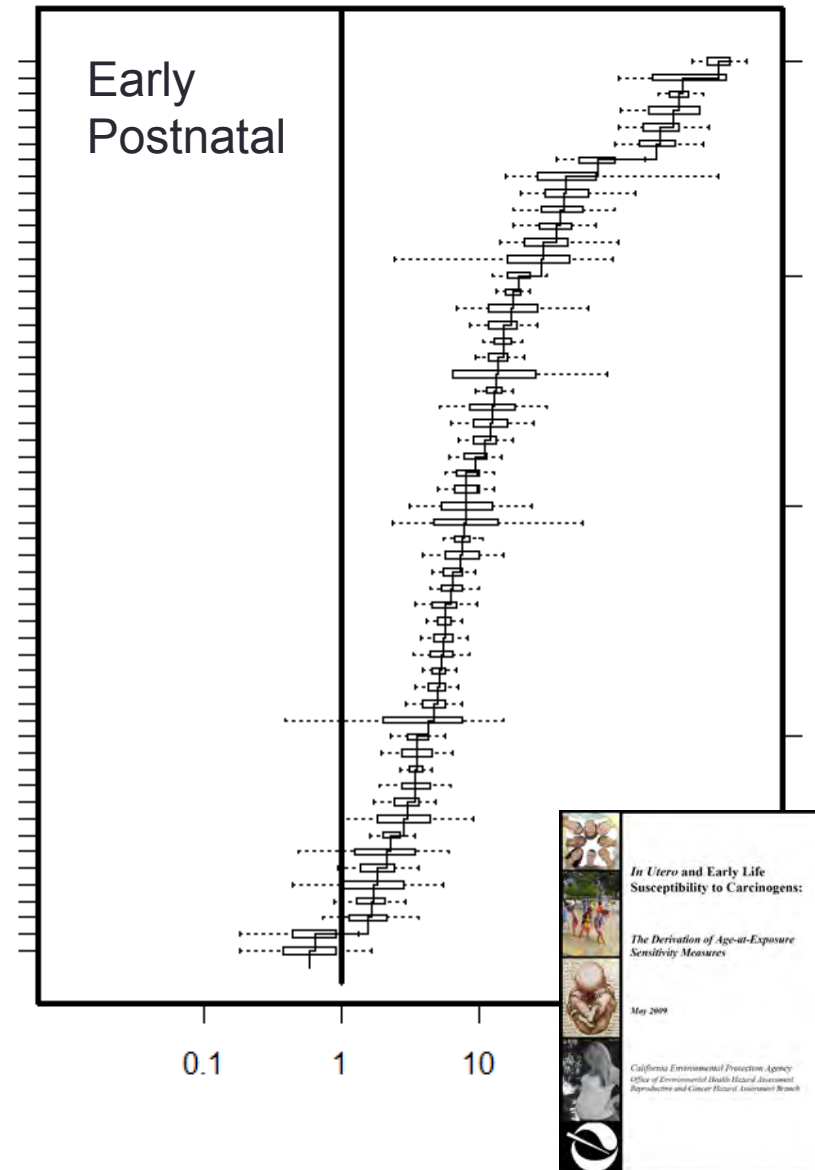
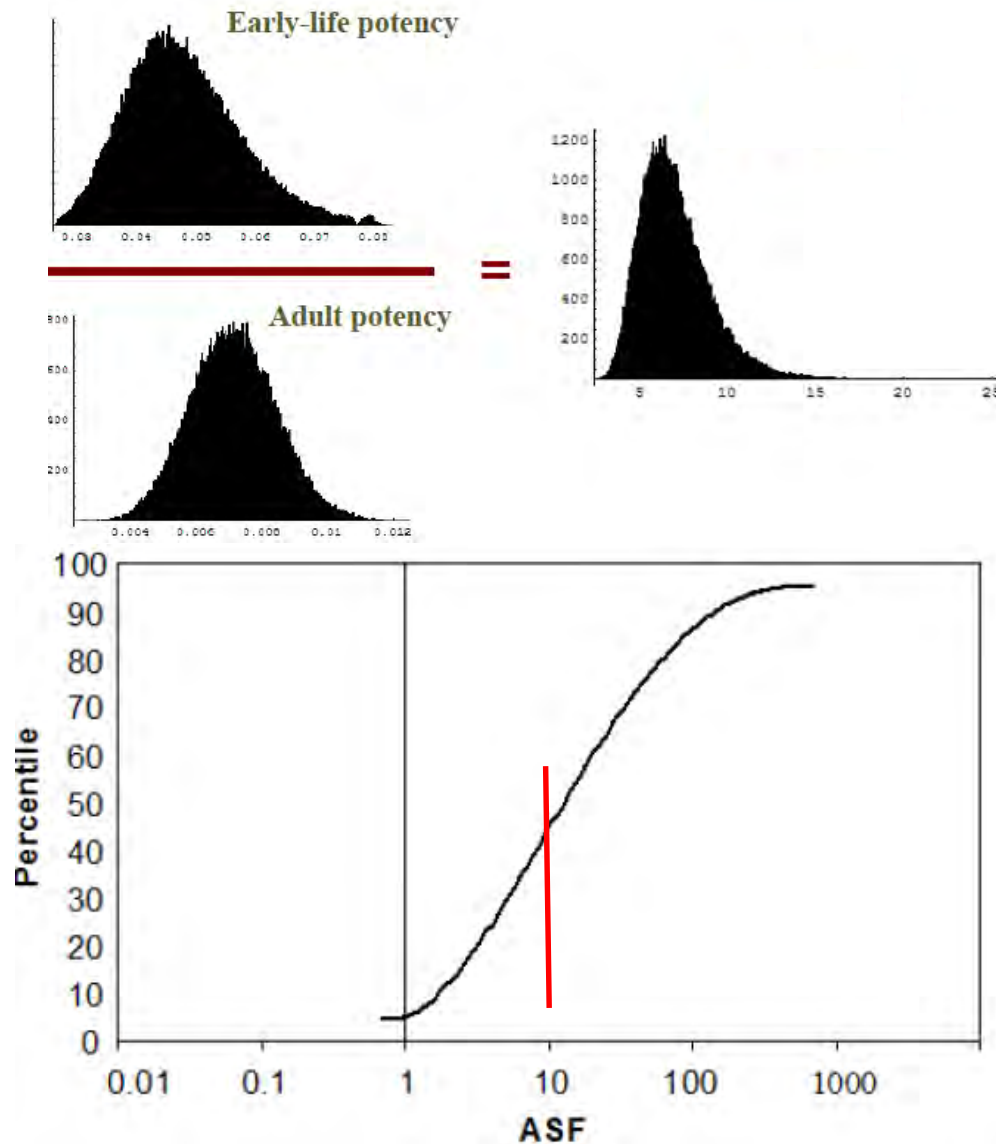


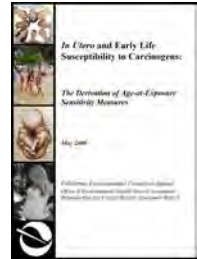
23 Chemicals to Evaluate Cancer Age-Susceptibility



- Benzidine
- Benzo[a]pyrene
- Butylnitrosourea
- DDT
- Dibutylnitrosamine
- Diethylnitrosamine
- Diethylstilbesterol (DES)
- 7,12-Dimethylbenz[a]anthracene (DMBA)
- 1,2-Dimethylhydrazine
- Dimethylnitrosamine
- Di-*n*-propylnitrosamine
- 1-Ethylnitrosobiuret
- Ethylnitrosourea
- 2-Hydroxypropylnitrosamine
- 3-Hydroxyxanthine
- 3-Methylcholanthrene
- 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
- Methylnitrosourea
- β -Propiolactone
- Safrole
- Tetrachlorodibenzodioxin (TCDD)
- Urethane
- Vinyl chloride

Carcinogenic activity ratio – Early Postnatal : Adult





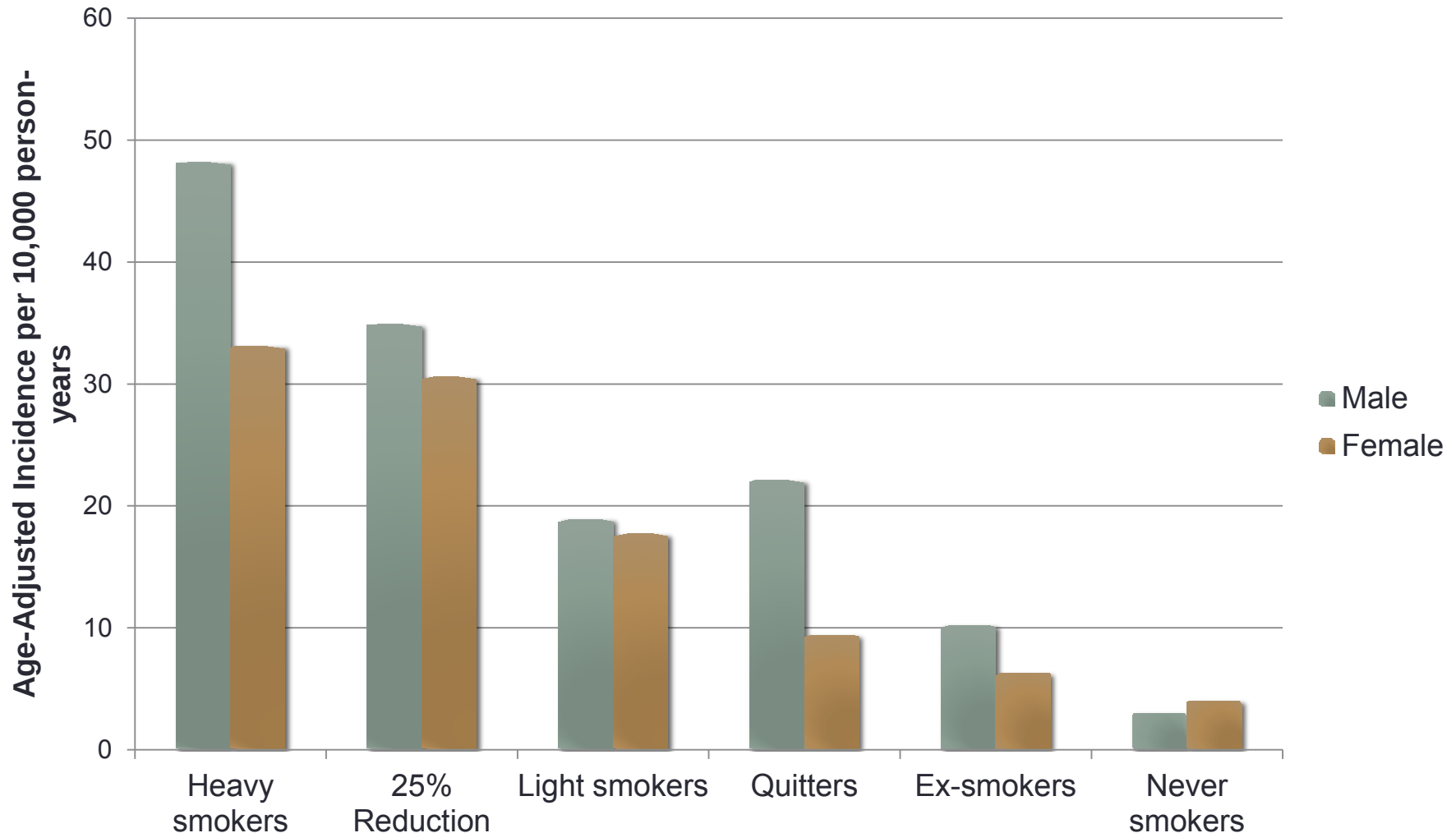
Early-life increased sensitivity to cancer

Lifestage	Fold Increase more than adult			
	Mean	Percentile		
		50 th	70 th	95 th
Prenatal	21	3	10	115
Postnatal	79	13	28	350
Juvenile	7	5	7	20

Source: OEHHA, 2009

Stopped Exposure: Smoking and Lung Cancer

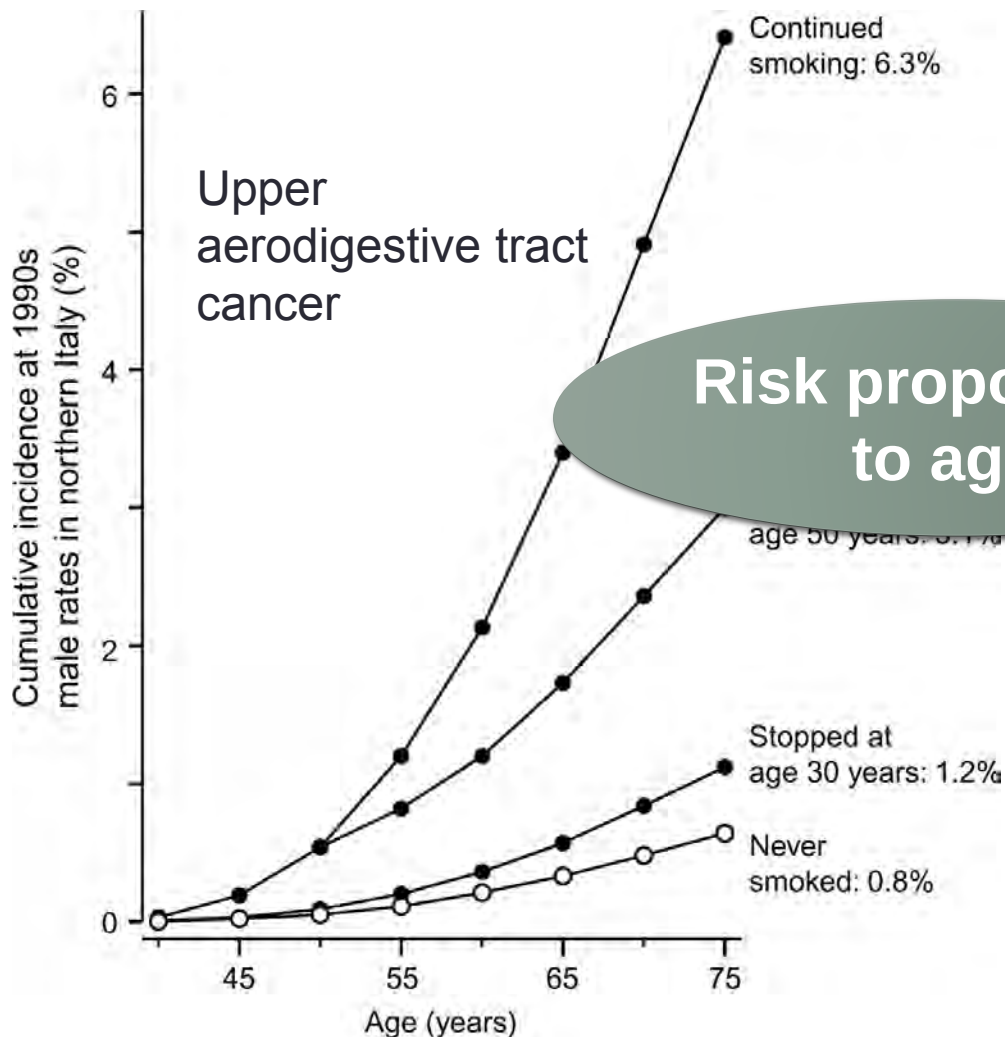
(Godtfredsen et al. 2005)



Stopped exposure

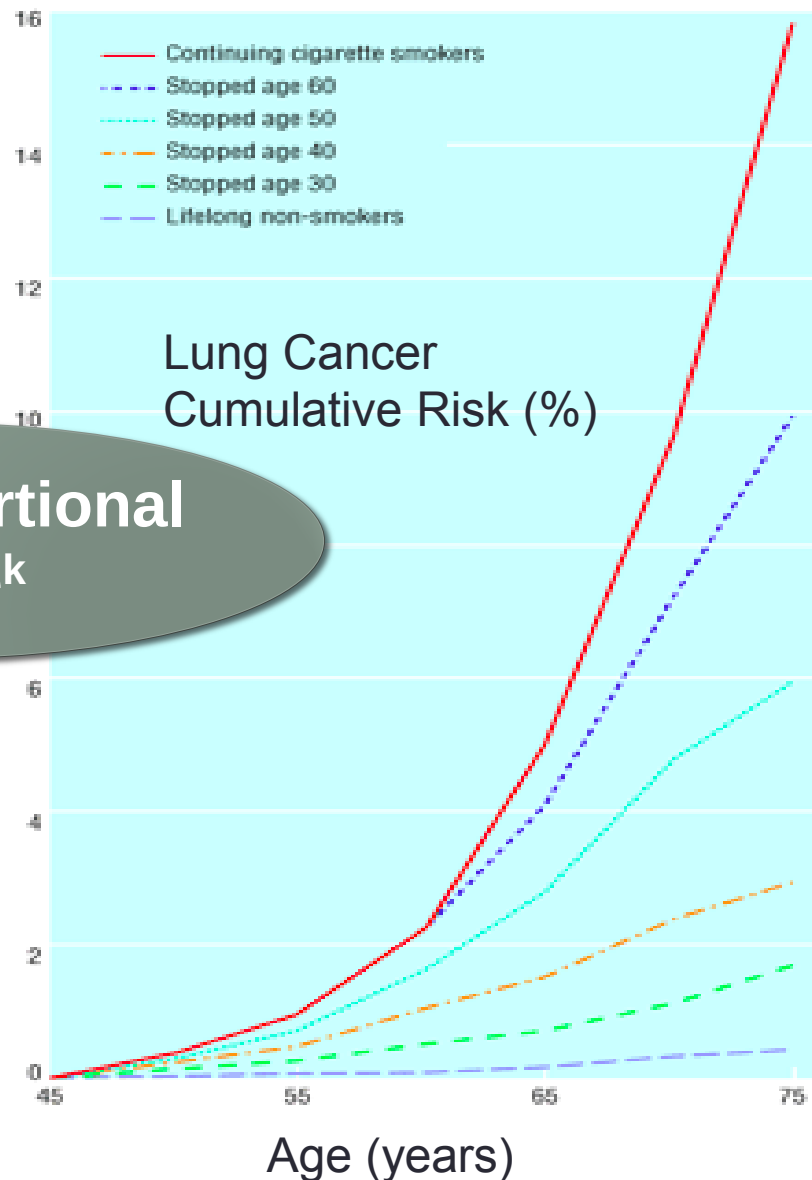
1990s incidence rates for Italian men.

Cristina Bosetti et al. Am. J. Epidemiol. 2007;167:468-473



1950 and 1990 Case Control studies in the UK

Peto et al. BMJ 2000; 321:323-329



One time acute exposures: Cancer findings reported by Calabrese and Blaine (1999)

Chemical	# strains with positive results		
	Mice	Rats	Other
Benzo(a)pyrene	39	11	16
Dibenzanthracene	49	1	2
Diethylnitrosamine	69	10	3
Dimethylnitrosamine	32	10	3
DMBA	93	59	19
Ethylnitrosourea	66	36	13
Methylcholanthrene	155	16	22
Methylnitrosourea	39	32	1
Radiation	12	11	1
Urethane	123	1	0

Time-dependent models to account for discontinuous or varying exposures

Example: Single exposure at age λ

Tumor incidence at age t for a single dose $\mathcal{D}$

$$= 1 - \exp [-(t/T_0)^k \cdot (A + (B \cdot \mathcal{D}/t \cdot \mathcal{F}))],$$

where

$$\mathcal{F} = (1 - \lambda/t)^{k-j} (\lambda/t)^{j-1} \div \beta(k-j+1, j)$$

k reflects whether it is assumed the carcinogen is affected early or late in the process

j reflects the increase of cancer with age

Benzo(a)pyrene experiments



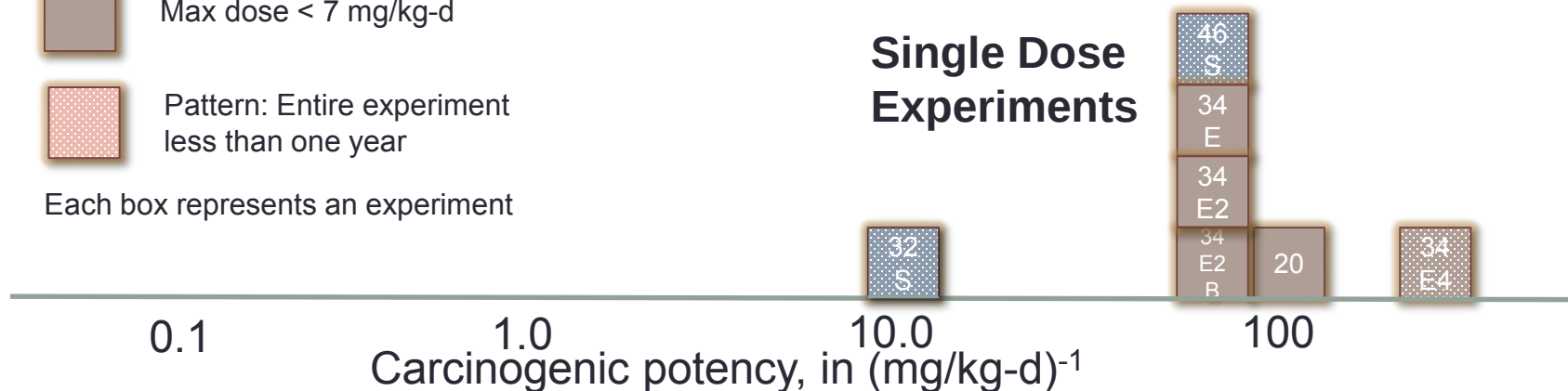
Max dose < 7 mg/kg-d



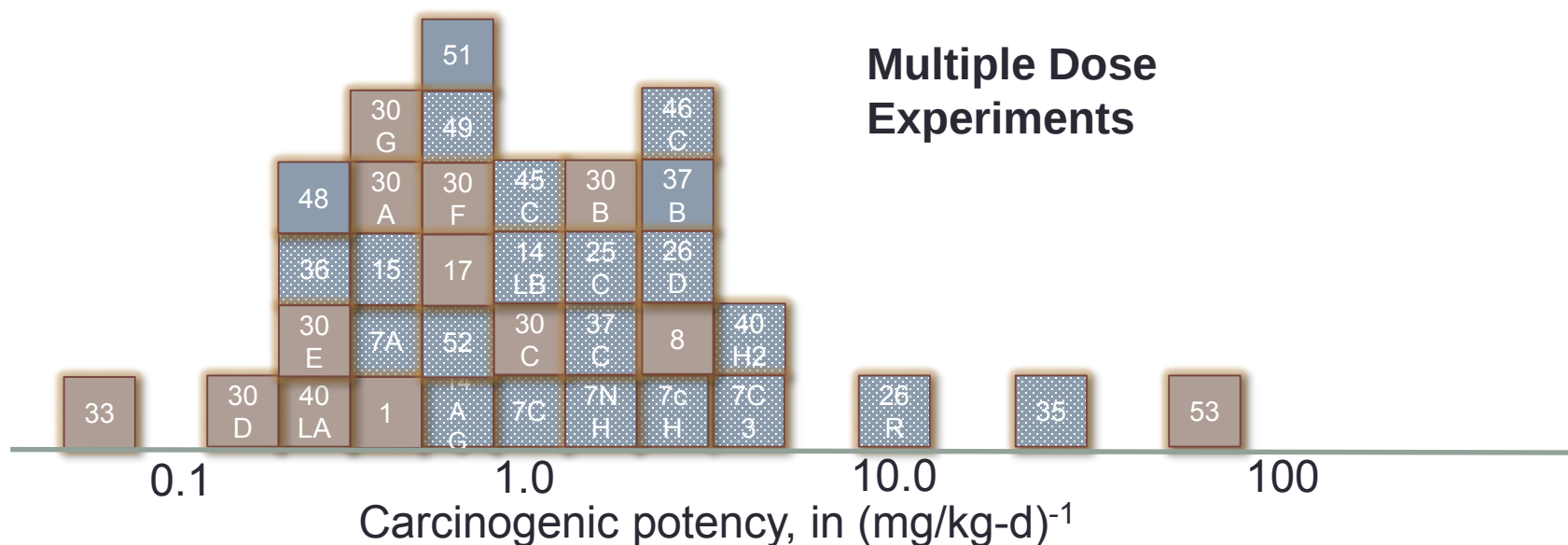
Pattern: Entire experiment
less than one year

Each box represents an experiment

Single Dose Experiments

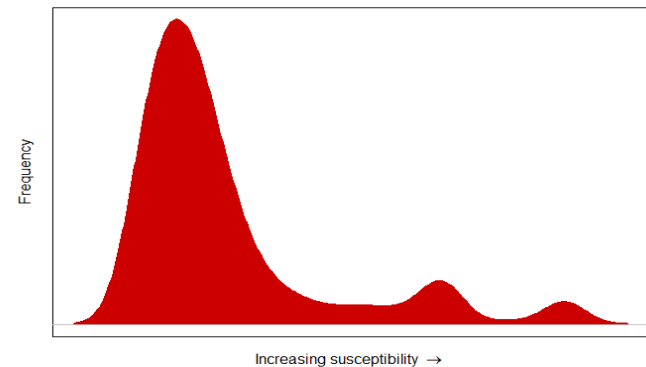


Multiple Dose Experiments



Time varying exposure and vulnerable populations

Case examples



- California's Proposition 65 list of chemicals "known to cause reproductive toxicity"
 - Covers male & female reproductive and developmental toxicity
 - Mandatory 1000 fold factor applied to NOEL or BMD
 - Business warns if causes exposure $> \text{NOEL}/1000$ or $\text{BMD}/1000$
 - Pre-regulatory concept - no averaging of exposure over time (more than one day) for existing safe harbor levels except lead
- Copper in drinking water, Wilson's heterozygotes and the bottle fed infant (NAS 200x)
- Perchlorate interference of I- uptake in bottle fed infants (CalEPA OEHHA 2014)
- Acute exposure to older adults from domoic acid in contaminated sea food
- Cadmium and renal toxicity in older adults (OEHHA 2006)
 - Accumulation of dose in drinking water throughout life
 - ⇒ High internal exposure of older adults

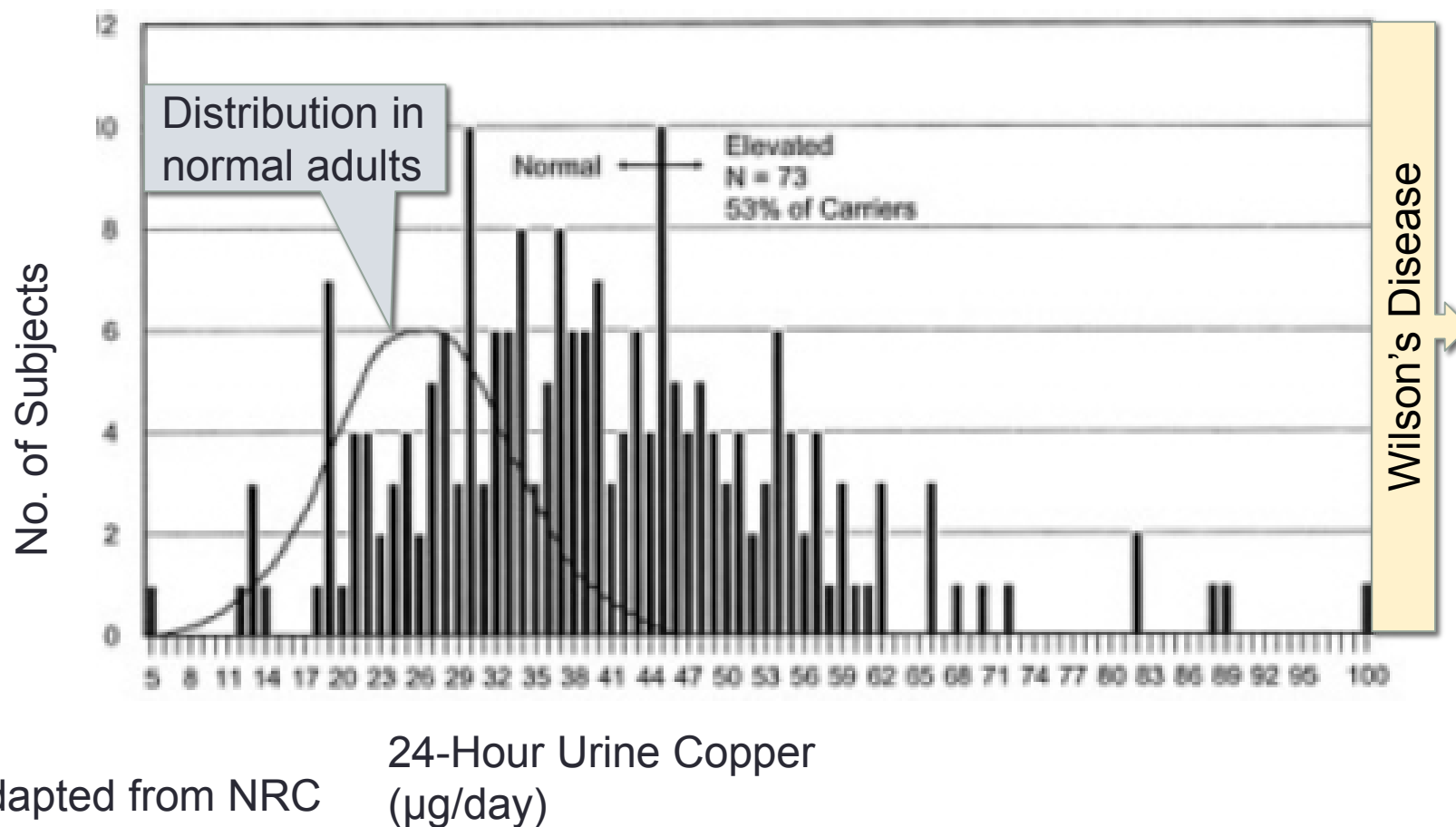


Wilson's heterozygotes, copper toxicity and the bottle fed infant

- Wilson's disease
 - Autosomal recessive disorder
 - Defective biliary excretion of copper
 - Copper accumulation in brain and liver leads to chronic cirrhosis and neuropsychiatric disorder
 - Frequency: at least 1 in 40,000 births
- Wilson's heterozygotes
 - Abnormal biliary excretion observed in 50% of heterozygotes
 - Cases of liver toxicity also observed
 - Frequency: at least 1% of general population



Urinary copper in 206 Wilson's disease siblings



Adapted from NRC
(2000)

Water consumption by formula fed infant



Copper from infant formula powder alone:

75 $\mu\text{g/kg-d}$

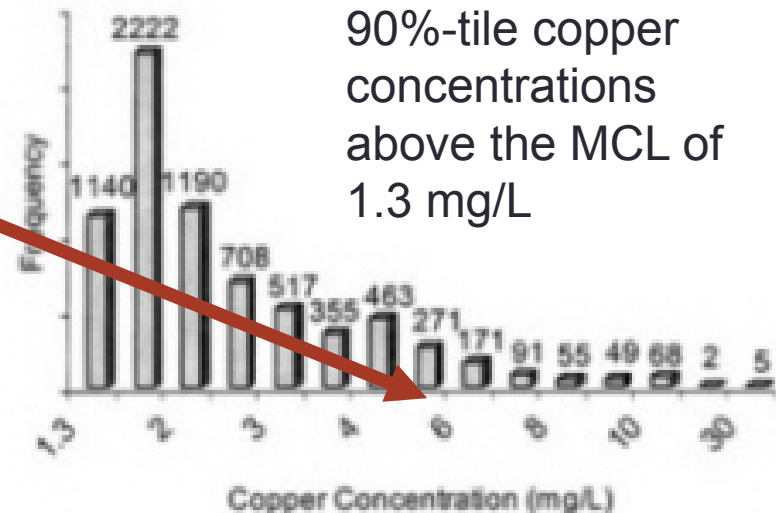
Copper from infant formula + water at MCL of 1.3 mg/L:

267 $\mu\text{g/kg-d}$

WHO upper limit on safe range for infants:

150 $\mu\text{g/kg-d}$

Can calculate at 6 mg/L a dose for formula fed infants that has been associated with liver toxicity in sensitive infants



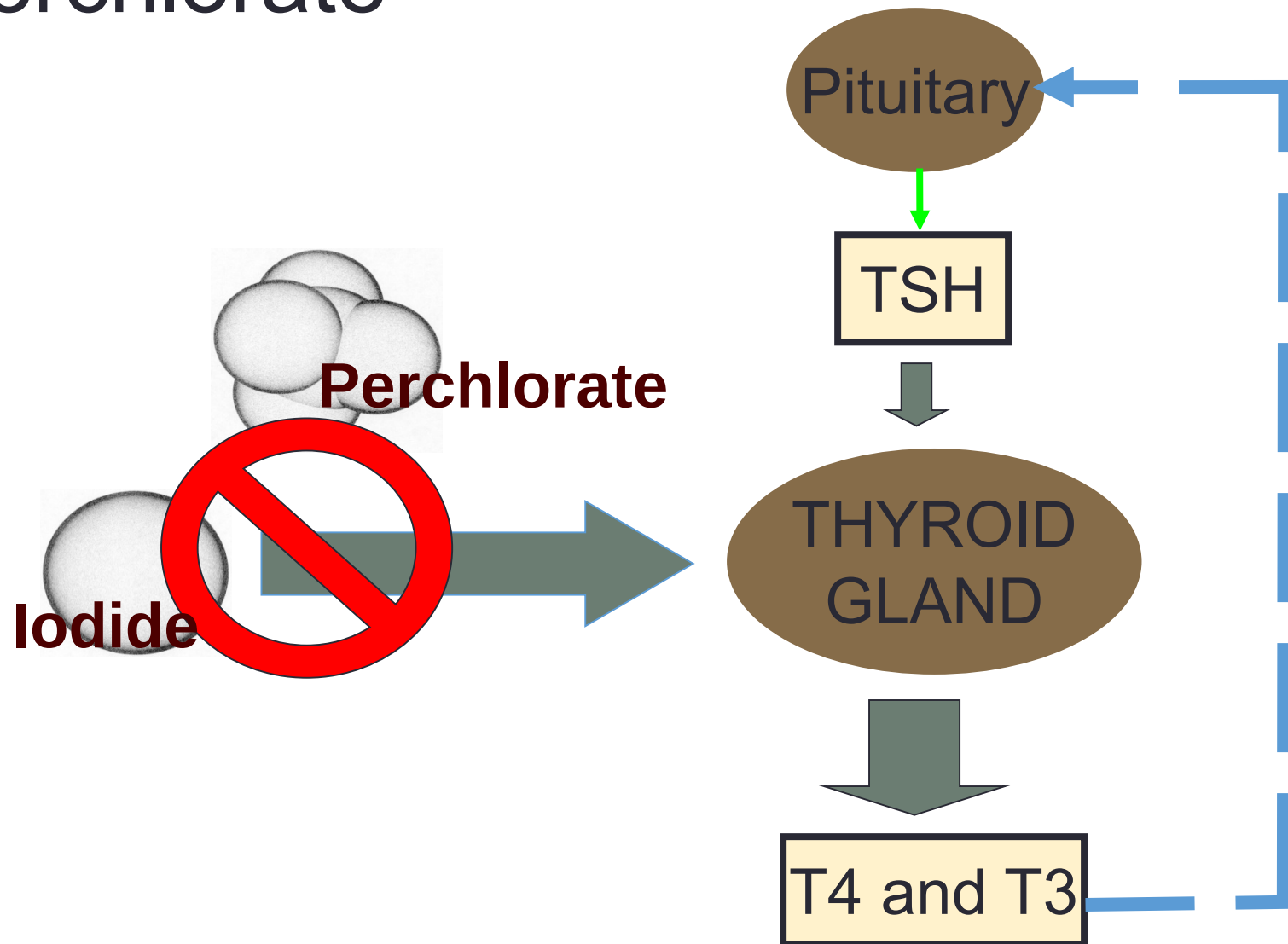
NAS Committee on Copper in Drinking Water



Concern for infants with altered copper metabolism

- High drinking water consumption compared to adults
 - Bottle fed infant with several fold higher consumption
- Factor of 3 higher levels of liver copper compared to adults
- Liver toxicity from in Wilson's heterozygotes or other genetic factors that affect copper elimination
- Concern supported by experimental animal strains sensitive to copper due to genetic alterations
 - Models provide insights on effects and mechanisms

Perchlorate



Considerations



- **Thyroid hormone-dependent brain and neurodevelopment** (Haddow et al., 1999; Klein et al., 2001; Kooistra et al., 2006; Pop et al., 2003; Pop et al., 1999; Vermiglio et al., 2004)
- **Low stores of thyroid hormone** (van den Hove, 1999)
- **Low iodine intakes** (Pearce et al., 2007: 47% women with breast milk iodine levels below Institute of Medicine recommendations for infant intake)

Maternal influences on infant susceptibility

- About 2.5% of pregnant women in U.S. suffering from subclinical hypothyroidism
- About 15% women had low iodide excretion in NHANES III
- Mother is infant's major source of iodine if she is breast-feeding
- Perchlorate excreted in milk if mother is consuming it in food and water
- If mother is a smoker, she delivers less iodine in milk

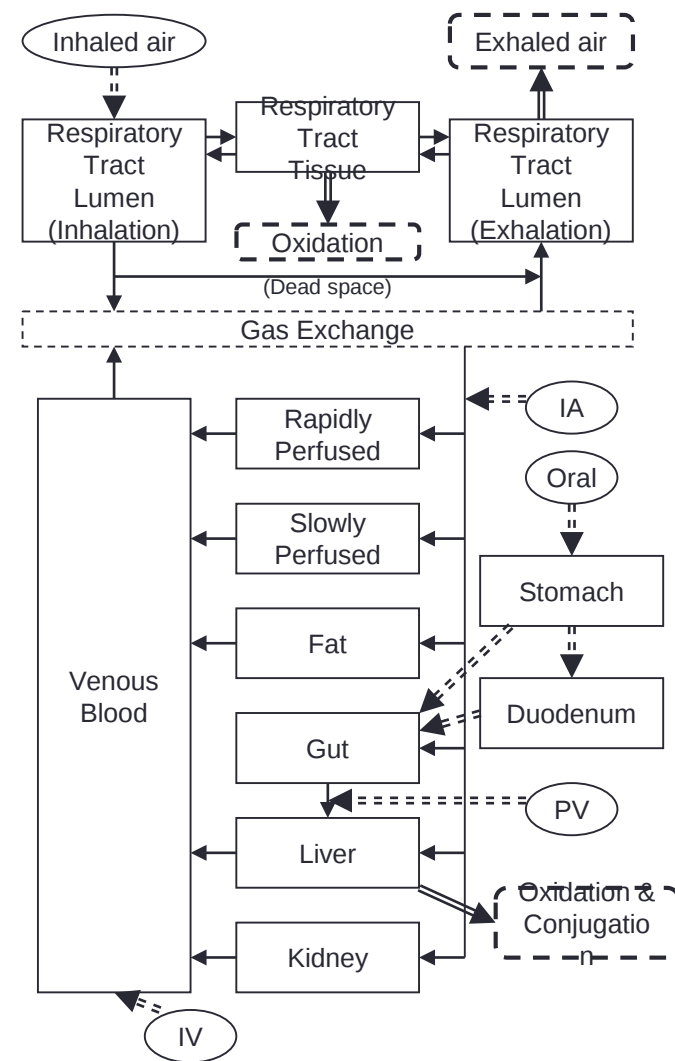
California Drinking Water Goal for Perchlorate

- Upstream adverse event
 - Interference of I- uptake
 - Measured in healthy adults exposed to perchlorate
- Identifiable subgroups at risk
 - Infants, pregnant women and fetus via mom's exposure
- Exposure estimate to ensure adequate margin of safety
 - 95th %tile water intake : body weight ratio
 - Addresses bottle fed infant
- Other exposures to perchlorate
 - Food
 - Infant formula
- Inter-individual variability factor of 10
 - Extrapolation from healthy adults (basis for BMD) to young infant

California's consideration of sensitivity

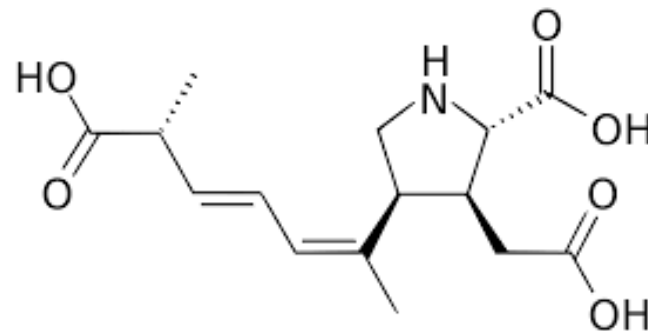
Evidence based adoption of defaults

- Revised default intra-species adjustment, absent data:
 - Pharmacokinetics
 - 10, if no model and no specific data
 - Pharmacodynamics
 - 3, if no additional child susceptibility
 - 10, otherwise: (e.g., asthma exacerbation or neurotoxicity)
- Infant and child specific exposure intakes
 - food, water, breast feeding, home grown food consumption, ...



Domoic Acid

- Produced by *Pseudo-nitzschia* algae
- Annual summer closing of muscle collection
- Unprecedented 2015 algal bloom on West Coast
- High levels in crabs, which slowly eliminate domoic acid
- Recreational fisheries closed in California through winter holidays. Still closed north of San Luis Obispo County



Binds to glutamate receptors in the brain

Prince Edward Island 1987 Outbreak Amnesic Shellfish Poisoning “ASP”

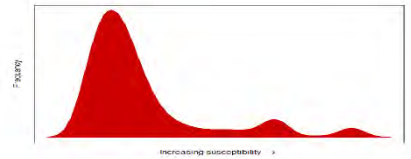
Cases

- Within 24 hours of exposure
- 107 (47 men, 60 women) met definition of ASP
- 19 severe cases hospitalized, 12 in intensive care
- 4 deaths
 - Autopsy showed brain damage – neuronal necrosis and astrogliosis particularly in the hippocampus
- Greater severity in
 - Men with reduced kidney function
 - Those with pre-existing conditions (weakened blood brain barrier)

Amnesic Shellfish Poisoning

- Within 24 hours vomiting, and other GI symptoms
- Within 48 hours neurological symptoms
- Symptoms include: GI, unstable blood pressure, cardiac arrhythmias, neurological dysfunction (e.g., disorientation, coma, seizures, memory loss)
- Long term: memory loss, learning impairment and seizures

Concluding remarks



- Acute exposures to carcinogens
 - Increased risks to children and in utero are a special concern
 - Further work to establish good practice in calculating risks is needed
- Methods are in place to address cancer risks from early life exposures. California and EPA differ in the types of carcinogens addressed.
- Special consideration of susceptible subgroups is critical in evaluating the effects of acute exposures
- Further work is needed on methods to characterize risks from exposures during windows of susceptibility.