

Risks from multiple chemicals in polluted communities



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November 2011

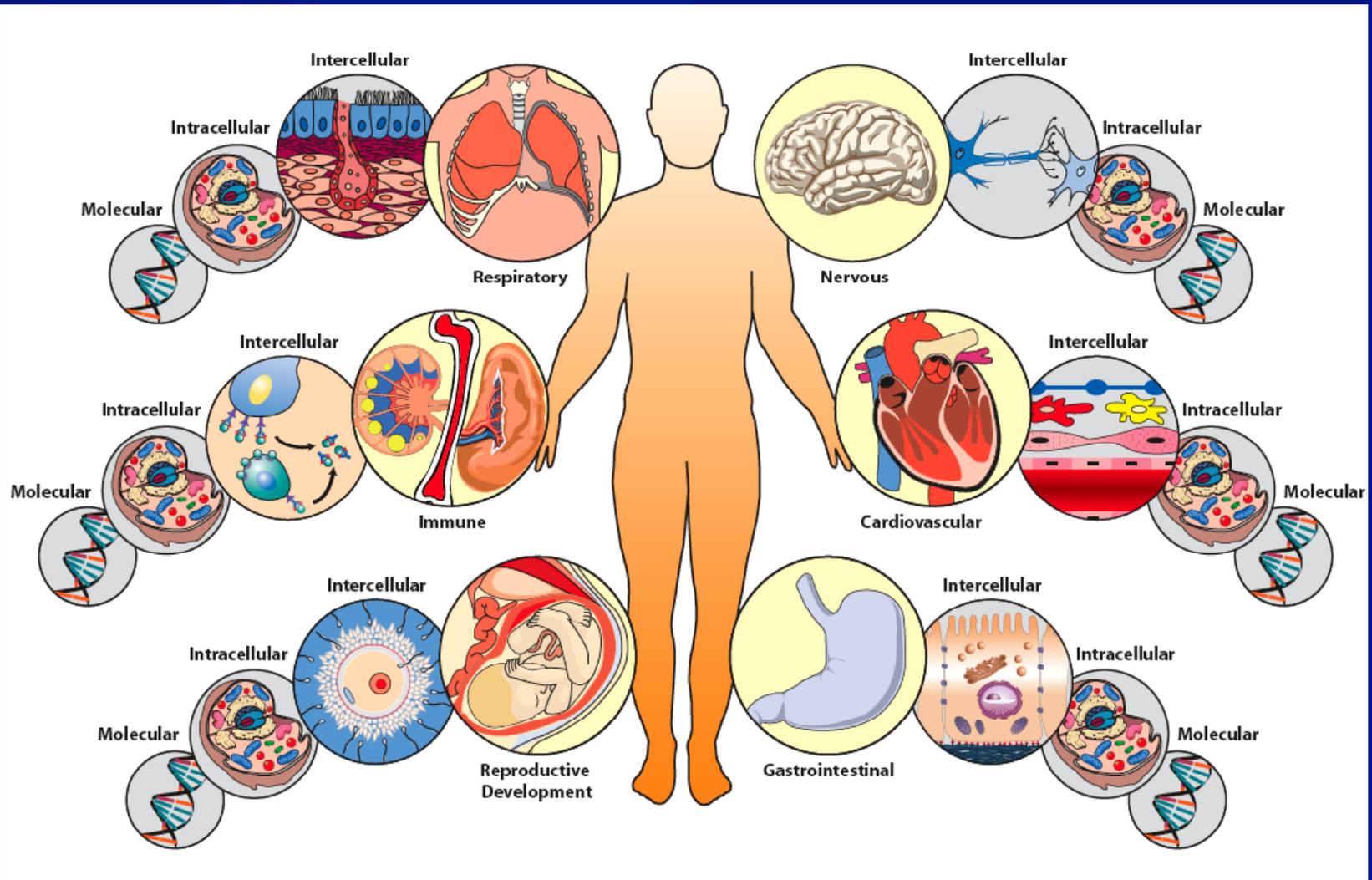
National Center for Environmental Health
Agency for Toxic Substances and Disease Registry



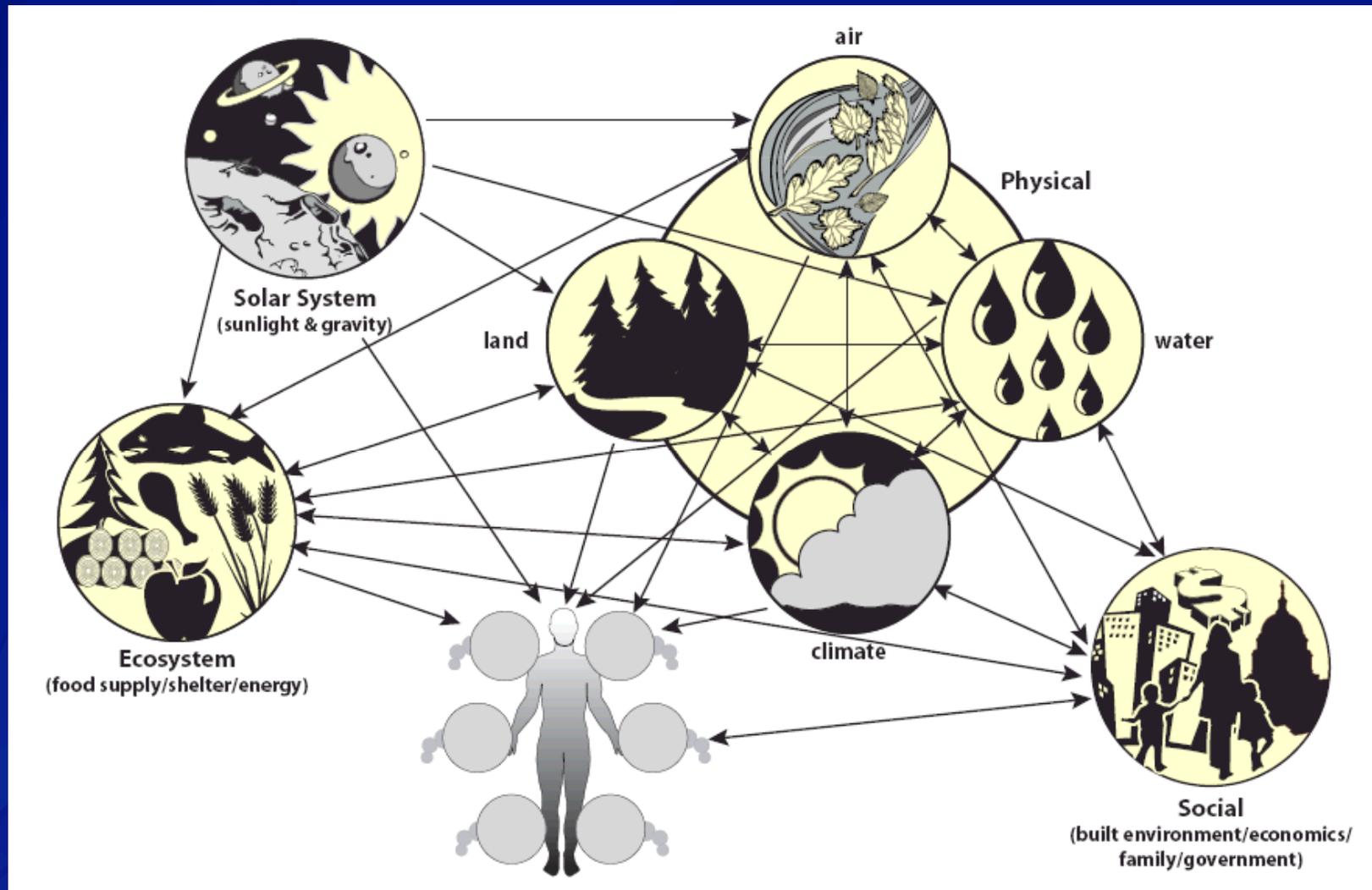
Major Themes

- ❑ **Measurement of multiplexed signals**
 - Environmental
 - Ecological
 - Biological
- ❑ **Greater acquisition and use of data from humans**
- ❑ **Systems thinking (ecological frame of mind)**
- ❑ **Complex analyses of complex systems**
 - Ability to predict
- **Does this mean simplicity cannot work?**

Systems Biology for the Individual



Interaction Network: Our Environment and Our Health

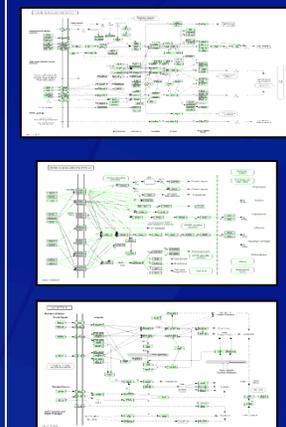


Gohlke and Portier (2007)

Identifying Important Disease Pathways

Human Genetics
+
Human Disease

+

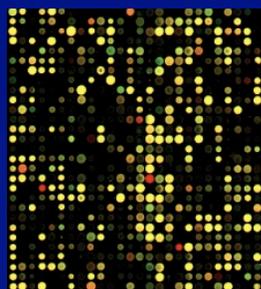


Sets of Pathways

Identify Pathways
Related to Human
Disease

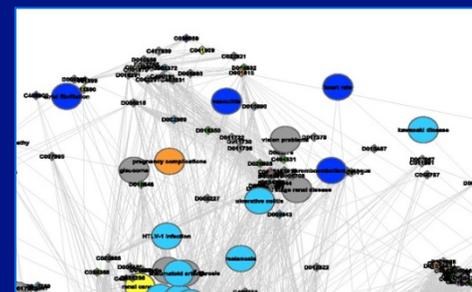


+



High Throughput
High Content
Chemical-Specific
Data

Predict
Chemical-Gene-
Disease Interactome



Predict
Risks

Develop
Screens

Set
Priorities

Fingerprint
Toxicants

Develop
Hypotheses

New
'omics &
HTS Data

Genetic Association Database

geneticassociationdatabase.nih.gov

- The Genetic Association Database is a gene-centered archive of published scientific papers on human genetic association studies.
- Database Contents
 - 28347 records on human gene-phenotype (mostly complex disease) relationships
- Data used in our analysis
 - Manual phenotype grouping and better annotation
 - 8,825 unique associations between 2088 genes and 208 disease phenotypes

Becker et al. (2004) *Nature Genetics* 36(5)

Comparative Toxicogenomics Database

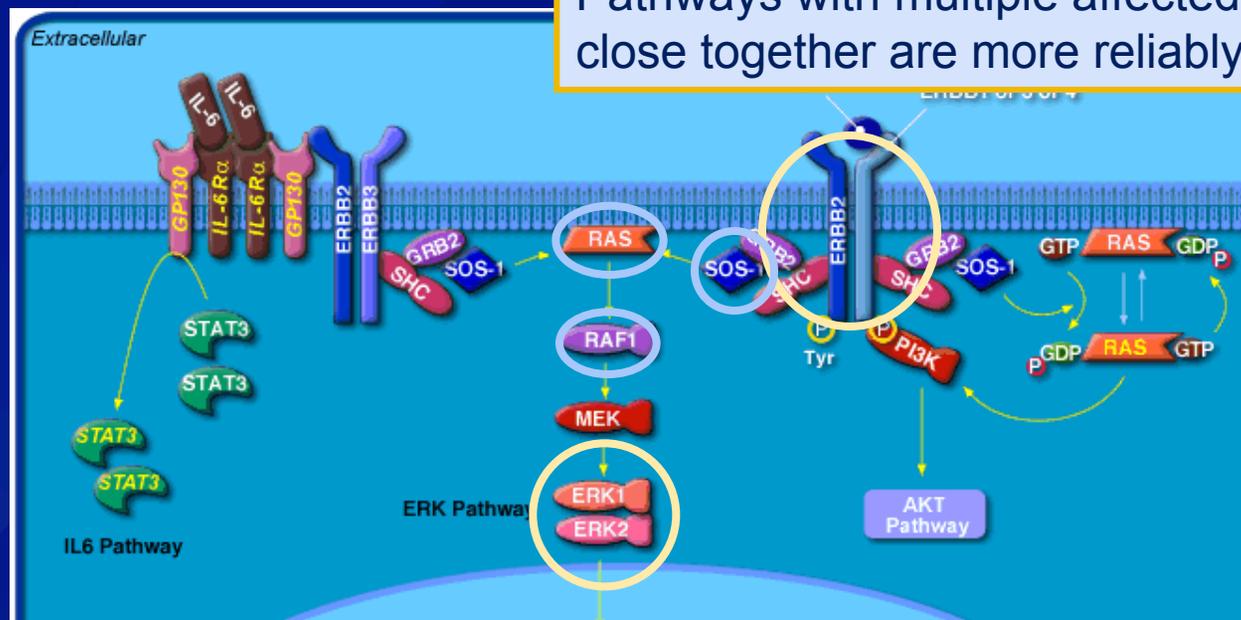
<http://ctd.mdibl.org/>

- Interactions between environmental factors and genes/proteins in diverse organisms are curated from the published literature using both algorithm based methods as well as manual curation.
- Environmental factor identifiers used in the literature are annotated using MeSH chemical terms.

Mattingly et al. 2006. *Toxicol Sci.* 92(2):587-95.

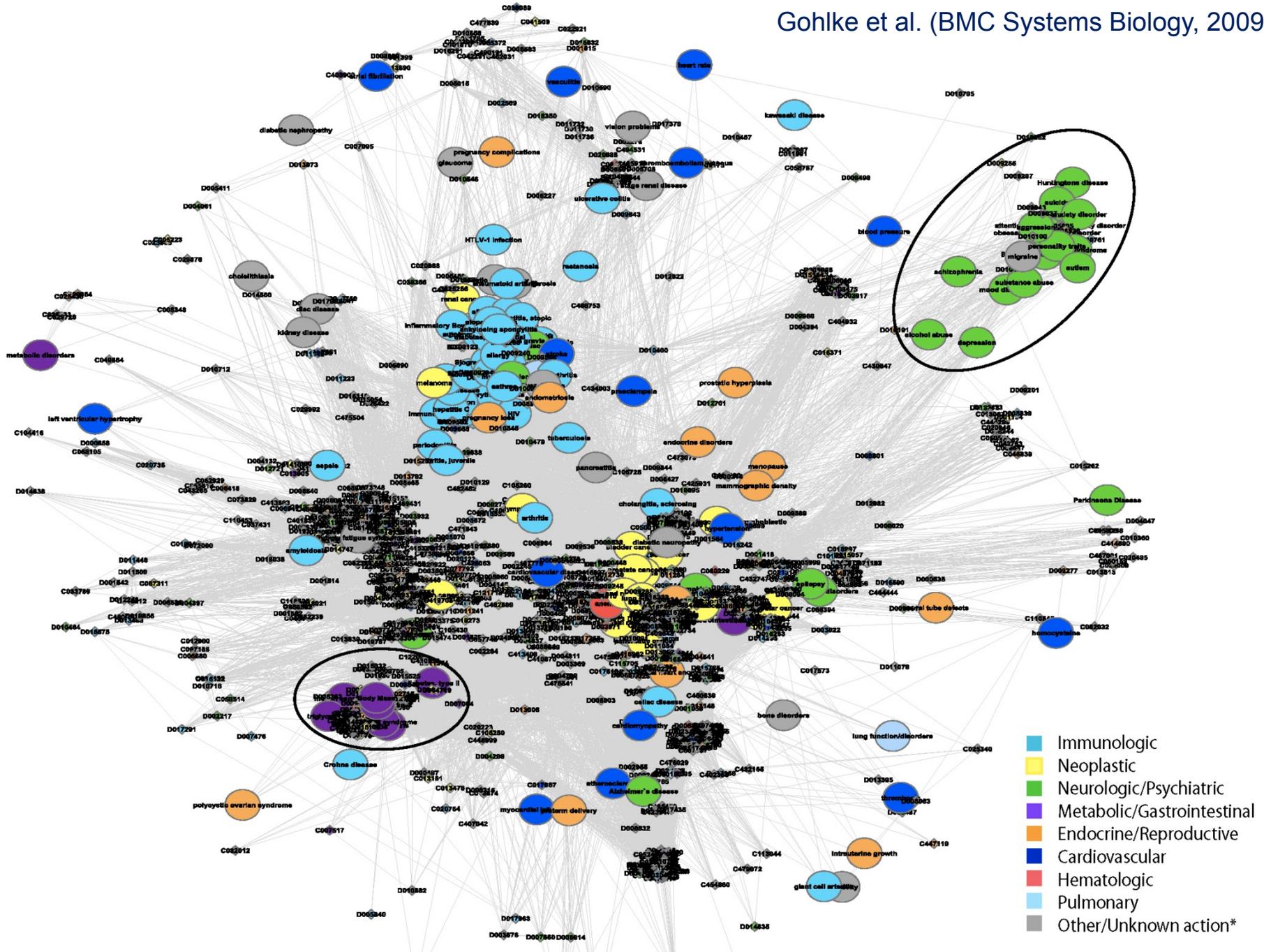
Structurally-Enhanced Pathway Enrichment Analysis (SEPEA) Thomas et al. (Genome Biology 2009)

Sequential Best Rule
Pathways with multiple affected components
close together are more reliably linked

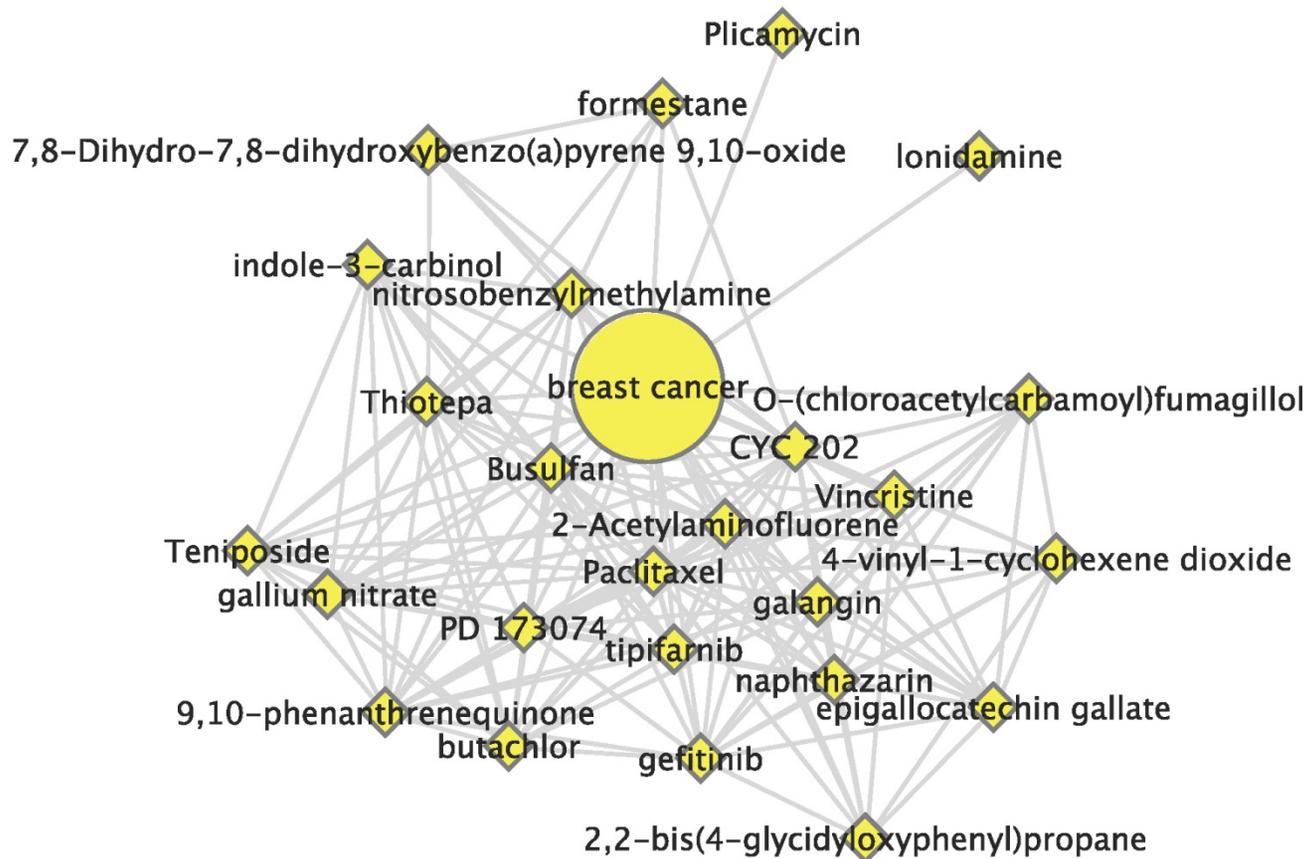


Heavy Ends Rule
Specificity of the pathway at the receptor end
Ultimate response by downstream components
Intermediate components typically shared between pathways

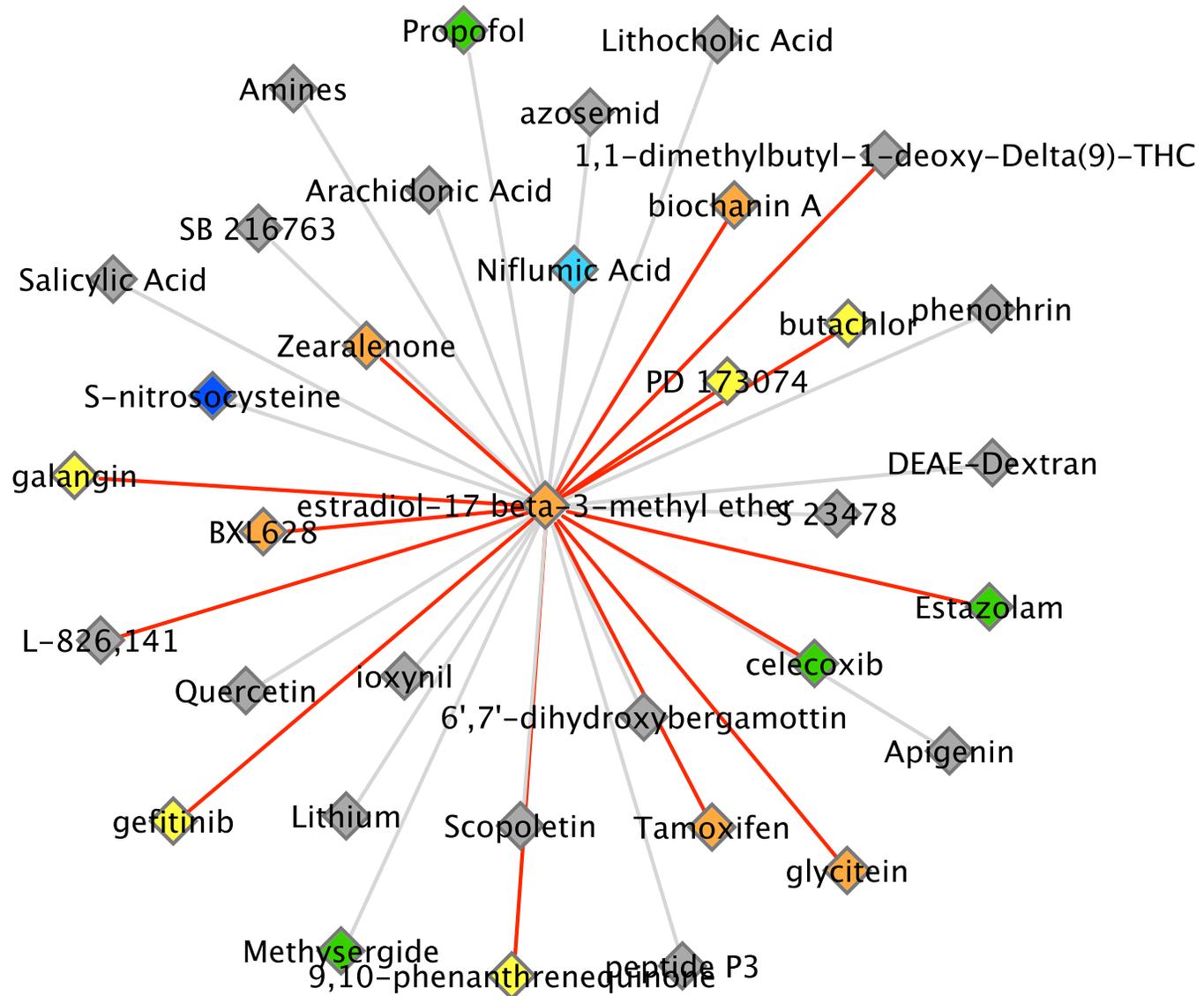




Breast Cancer & Environment Interactome

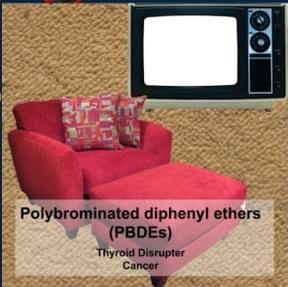
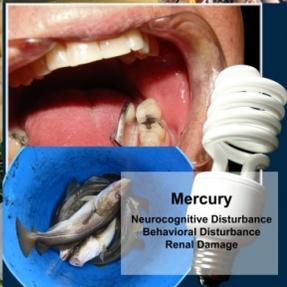
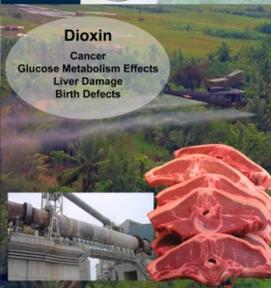
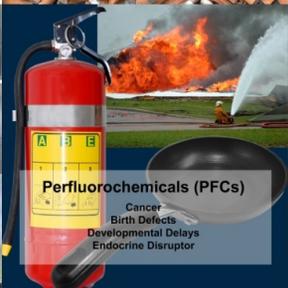
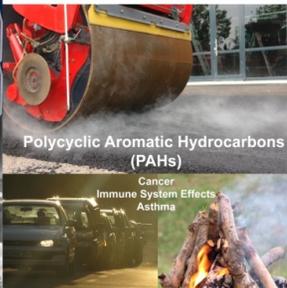
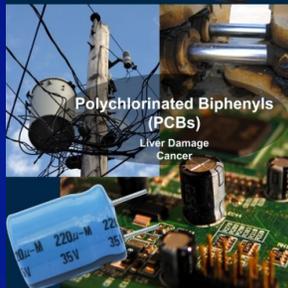
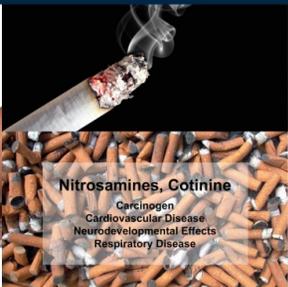
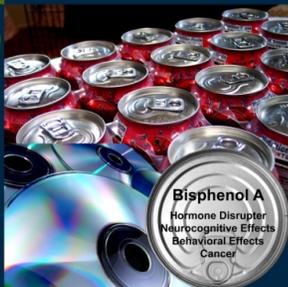
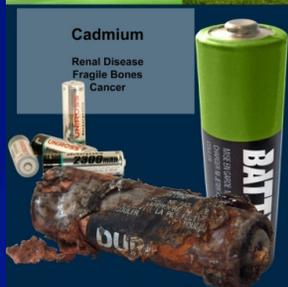
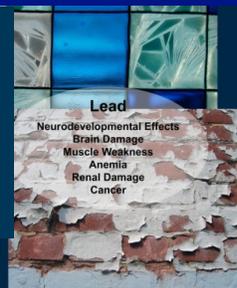
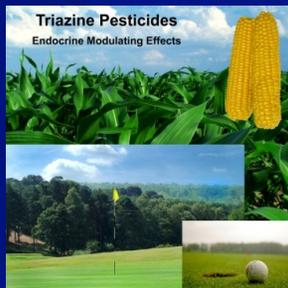


Estradiol Interactome



National Biomonitoring Program

400 environmental chemicals measured in blood or urine



National Biomonitoring Program targets both the general population and special groups

General population



- *National Exposure Report* (NHANES measurements)
- *National Children's Study*

Higher exposed or vulnerable groups



Higher or potentially higher exposed groups



Newborns



Women of childbearing age



Elderly

- 50-75 studies each year

CDC can currently measure more than 400 environmental chemicals in blood or urine

Metals

lead

cadmium

arsenic

speciated arsenic

mercury

methyl mercury

ethyl mercury

antimony

uranium

cobalt

cesium

tungsten

thallium

platinum

molybdenum

barium

beryllium

Chemicals currently measured at CDC

Environmental phenols

bisphenol A

benzophenone-3

4 tert octyl phenol

methyl paraben

ethyl paraben

propyl paraben

butyl paraben

others...

Chemicals currently measured at CDC

Perfluorinated compounds

perfluorooctanoic acid

perfluorooctane sulfonic acid

10 other perfluorinated compounds

Chemicals currently measured at CDC

Phthalates

monomethyl phthalate

mono-ethyl phthalate

16 other phthalates

Chemicals currently measured at CDC

Polybrominated diphenyl ethers

2,2',4'-Tribromodiphenyl ether (BDE 17)

2,2',4,4',5,5'-hexabromodiphenyl ether (BDE 153)

21 other PBDEs and related compounds

Chemicals currently measured at CDC

Tobacco smoke

cotinine

nicotine

NNAL

2 other tobacco smoke markers

Chemicals currently measured at CDC

Perchlorate, thiocyanate, nitrate

Polycyclic aromatic hydrocarbons (63)

Volatile organic compounds (43)

Halogenated phenol compounds (12)

Chemicals currently measured at CDC

Fungicides (8)

Organophosphate insecticides (24)

Other pesticides (17)

Chemicals currently measured at CDC

Hydroxylated polychlorinated biphenyls (4)

Polychlorinated naphthalenes (6)

Toxaphenes (6)

Chemicals currently measured at CDC

Acrylamide hemoglobin adduct

Glycidamide hemoglobin adduct

Chemicals currently measured at CDC

Phytoestrogens (6)

Trans Fatty Acids (9)

Omega 3 and 6 Fatty Acids (10)

Table 11. Cadmium in urine (creatinine corrected)

Geometric mean and selected percentiles of urine concentrations (in $\mu\text{g/g}$ of creatinine) for the U.S. population aged 6 years and older, National Health and Nutrition Examination Survey, 1999-2002.

	Survey years	Geometric mean	Selected percentiles				Sample size
		(95% conf. interval)	(95% confidence interval)				
			50th	75th	90th	95th	
Total, age 6 and older	99-00	.181 (.157-.209)	.219 (.199-.238)	.423 (.391-.446)	.712 (.645-.757)	.933 (.826-1.07)	2257
	01-02	.199 (.181-.218)	.212 (.194-.232)	.404 (.377-.440)	.690 (.630-.754)	.917 (.813-.998)	2689
Age group							
6-11 years	99-00	*	.085 (.063-.107)	.147 (.123-.182)	.210 (.171-.316)	.300 (.184-.607)	310
	01-02	.075 (.059-.094)	.100 (.083-.112)	.166 (.136-.192)	.233 (.206-.281)	.291 (.221-.440)	368
12-19 years	99-00	.071 (.051-.098)	.093 (.084-.106)	.147 (.130-.163)	.215 (.204-.240)	.283 (.222-.404)	648
	01-02	.078 (.067-.091)	.091 (.085-.101)	.136 (.123-.143)	.191 (.175-.234)	.280 (.234-.321)	762
20 years and older	99-00	.267 (.247-.289)	.288 (.261-.304)	.484 (.433-.545)	.769 (.727-.818)	1.07 (.927-1.17)	1299
	01-02	.261 (.236-.289)	.273 (.247-.303)	.481 (.426-.518)	.776 (.691-.850)	.979 (.874-1.12)	1559
Gender							
Males	99-00	.154 (.131-.182)	.174 (.158-.191)	.329 (.293-.382)	.617 (.537-.700)	.788 (.696-.929)	1121
	01-02	.159 (.143-.177)	.168 (.157-.182)	.334 (.304-.364)	.532 (.491-.653)	.757 (.690-.856)	1334
Females	99-00	.211 (.170-.261)	.267 (.239-.308)	.473 (.423-.551)	.783 (.690-.917)	1.09 (.813-1.38)	1136
	01-02	.245 (.216-.278)	.263 (.228-.297)	.479 (.414-.541)	.792 (.687-.884)	.985 (.876-1.16)	1355
Race/ethnicity							
Mexican Americans	99-00	.175 (.137-.223)	.181 (.144-.225)	.331 (.266-.418)	.612 (.441-.828)	.843 (.674-1.13)	780
	01-02	.156 (.136-.178)	.170 (.150-.184)	.282 (.263-.340)	.501 (.388-.614)	.693 (.507-.839)	682
Non-Hispanic blacks	99-00	.183 (.140-.240)	.201 (.168-.241)	.414 (.343-.472)	.658 (.516-.827)	.873 (.722-.962)	546
	01-02	.190 (.156-.232)	.195 (.174-.225)	.385 (.336-.449)	.676 (.559-.850)	.917 (.725-1.08)	667
Non-Hispanic whites	99-00	.175 (.146-.209)	.219 (.191-.250)	.432 (.387-.470)	.729 (.666-.783)	1.00 (.826-1.16)	760
	01-02	.205 (.184-.229)	.224 (.208-.242)	.421 (.382-.470)	.719 (.668-.784)	.931 (.806-1.05)	1132

* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

Study: young children may receive higher PBDE exposure than adults



- ❑ DLS showed that serum levels of PBDEs increase with age from newborns to children between the ages of 4 and 6, then decrease with increasing age
- ❑ These findings suggest young children may receive higher exposure to PBDEs compared to adults, especially ages 4-6 years

NCEH: Division of Laboratory Sciences

Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population

- ❑ **Assess and monitor the nutritional status of the U.S. population every two years**
- ❑ **Improve measurements of nutritional status**
- ❑ **58 biochemical indicators**
 - Water-soluble vitamins.
 - Fat-soluble vitamins and nutrients.
 - Trace elements.
 - Isoflavones and lignans.
 - Acrylamide adducts.



Detecting Human Exposure to Chemical Agents

An Efficient Protocol for Laboratory Response Following An Exposure Event



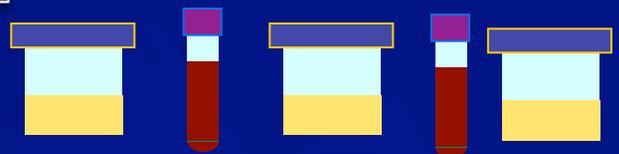
* Chemical * Military Exposure * CWA * Industrial *



Chemical Emergency Response Team

24/7

Rapid deployment



Aliquot & Track Samples

Rapid Toxic Screen
40 persons
25 aliquots/person
150 analytes evaluated



Large Scale Response
1000+ persons
1-2 aliquots/person
1-2 analytes evaluated

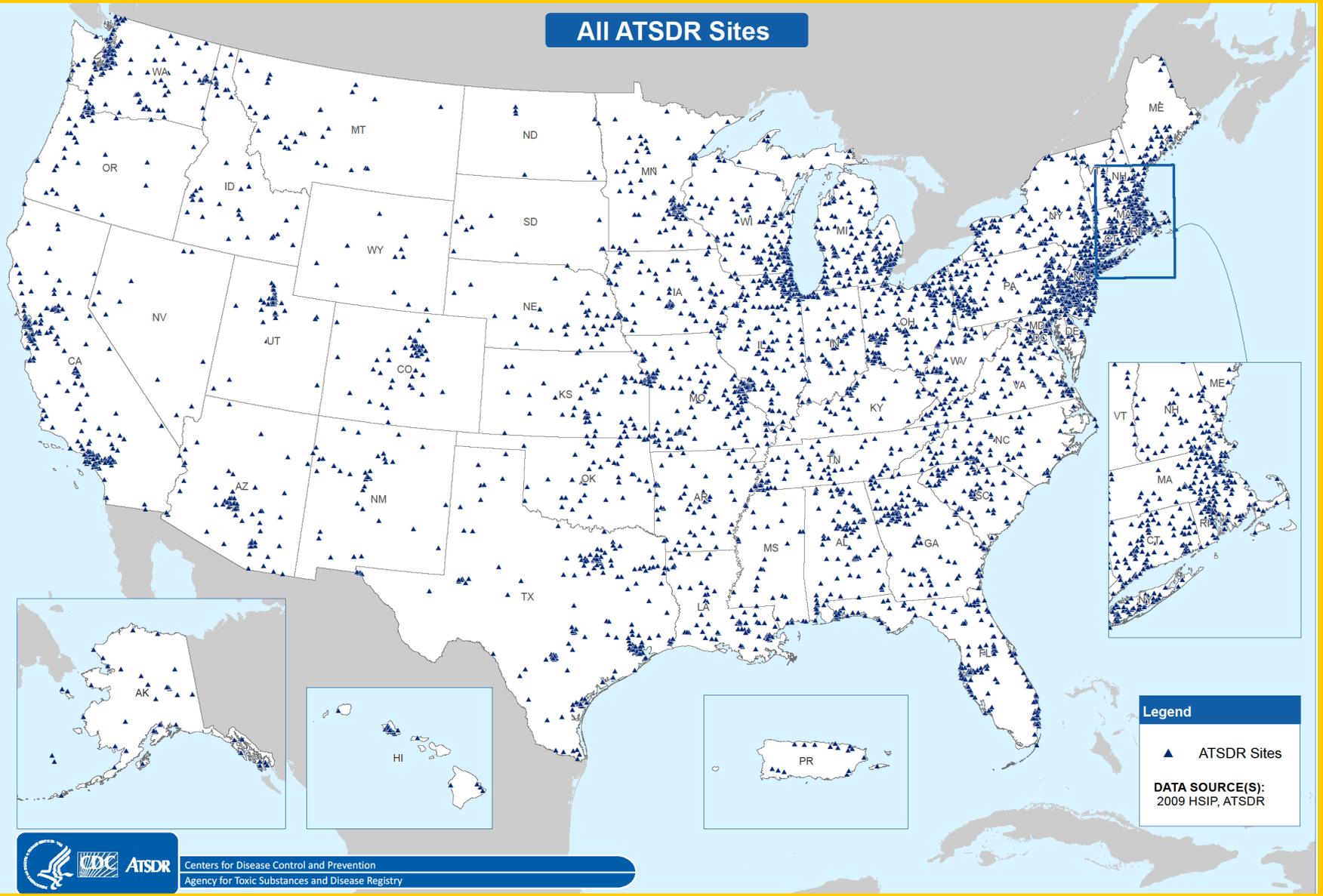
Experimental Mixtures Strategy



The Problem

- ❑ **People are exposed to more than one substance in communities visited by NCEH and ATSDR**
- ❑ **Action levels are expressed as exposures that are not associated with a stated risk**
 - **Example:**
 - Water contamination in a community includes four agents all 10% above the MRL
 - While no one contaminant is at a level requiring action, the aggregate risk to the community may be unacceptable
 - Multiple chemicals may interact to increase risk
 - Multiple methods exist to address this question

All ATSDR Sites



Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

Investigating Chemical Exposure



Corpus Christi, TX

- Exposure Investigation finds participants' exposure to benzene and other VOCs not higher than those of the US population



Saufley C&D Landfill, FL

- Health investigation with environmental sampling for H₂S and PM, personal sampling for H₂S.
- Community respiratory health survey

ATSDR: Division of Health Assessment and Consultation

The Experimental Solution

- ❑ **Assign risk to the action level**
 - I will use MRL for this as this is ATSDR's action level
- ❑ **Draw a smooth curve between 0 added risk at 0 exposure and the risk at the point of departure (LOAEL, BMD, etc.) that runs through the risk at the MRL for each chemical**
- ❑ **Use this curve to evaluate risks at the actual exposures for each chemical**
- ❑ **Aggregate the risks to come up with estimated risks for the population**

How would this work?

□ Some background

- MRLs are derived by dividing the point of departure (POD) by safety and uncertainty factors
- The POD can be derived in numerous ways
 - Benchmark Dose Method (preferred method)
 - Lowest Observed Adverse Effect Level (LOAEL)
 - No Observed Adverse Effect Level (NOAEL)
- Modifying and Uncertainty Factors are based upon scientific judgment and are guided by several documents
 - They are both context and POD type specific

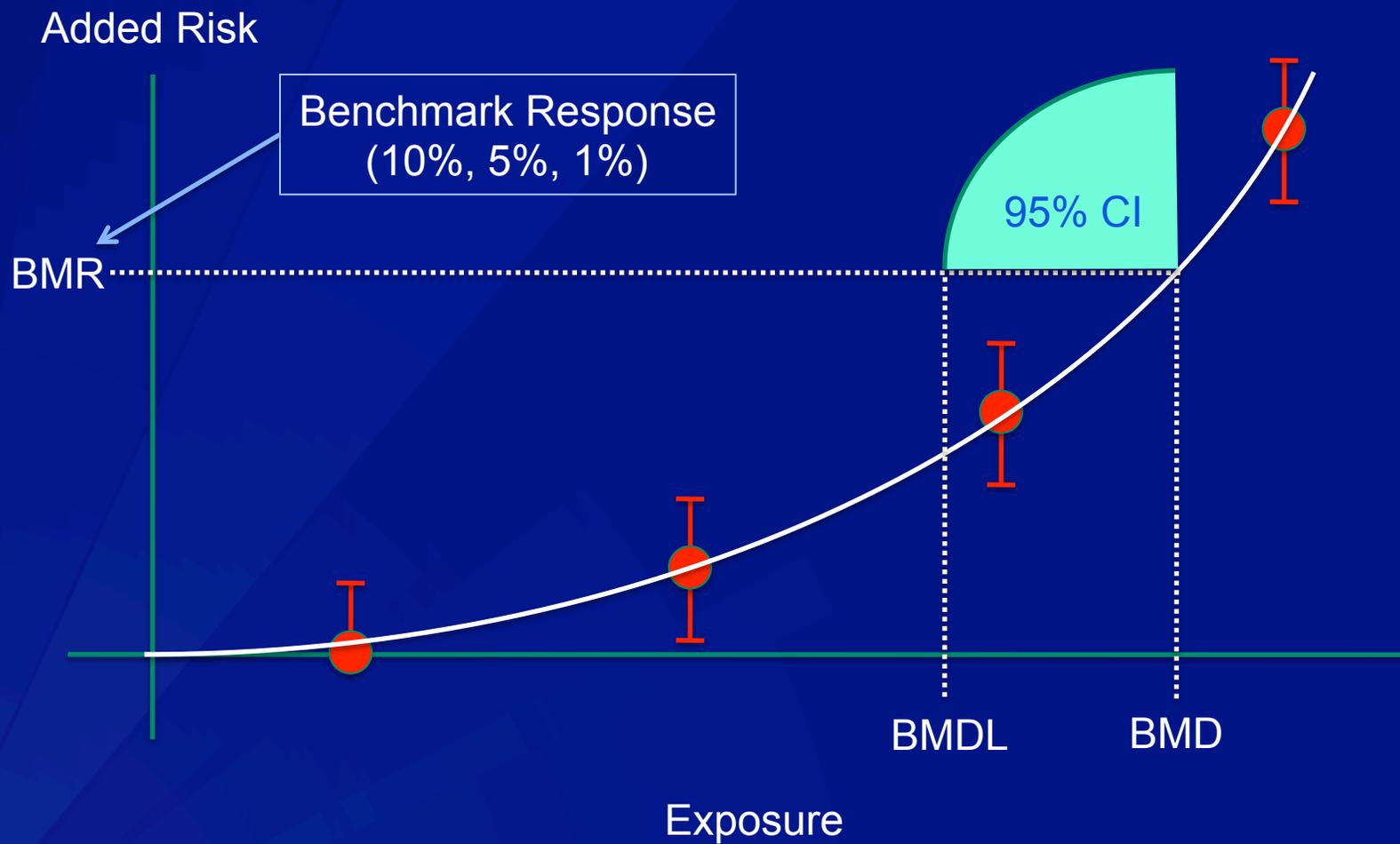
Benchmark Dose (BMD) Method

Added Risk

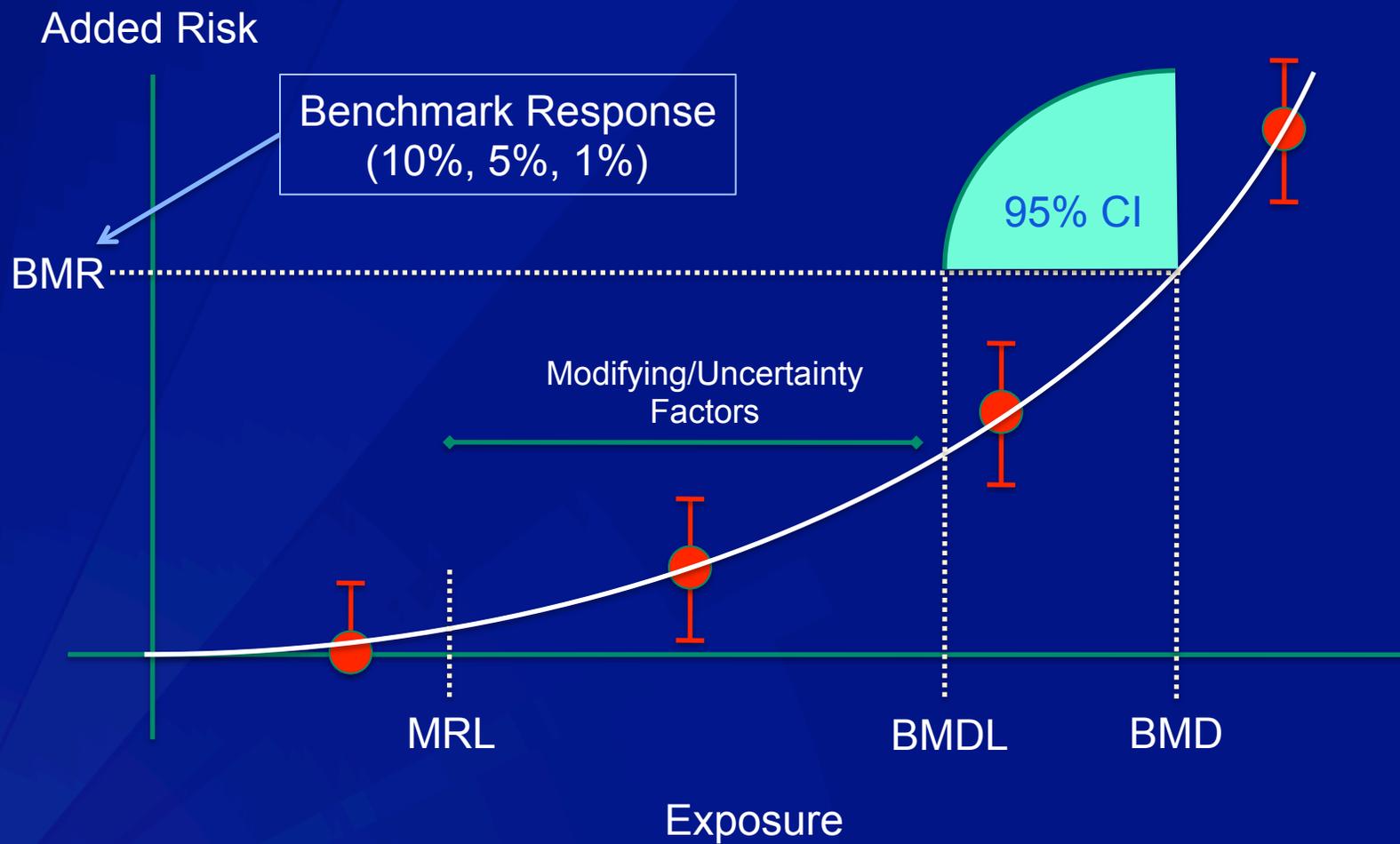


Exposure

Benchmark Dose (BMD) Method



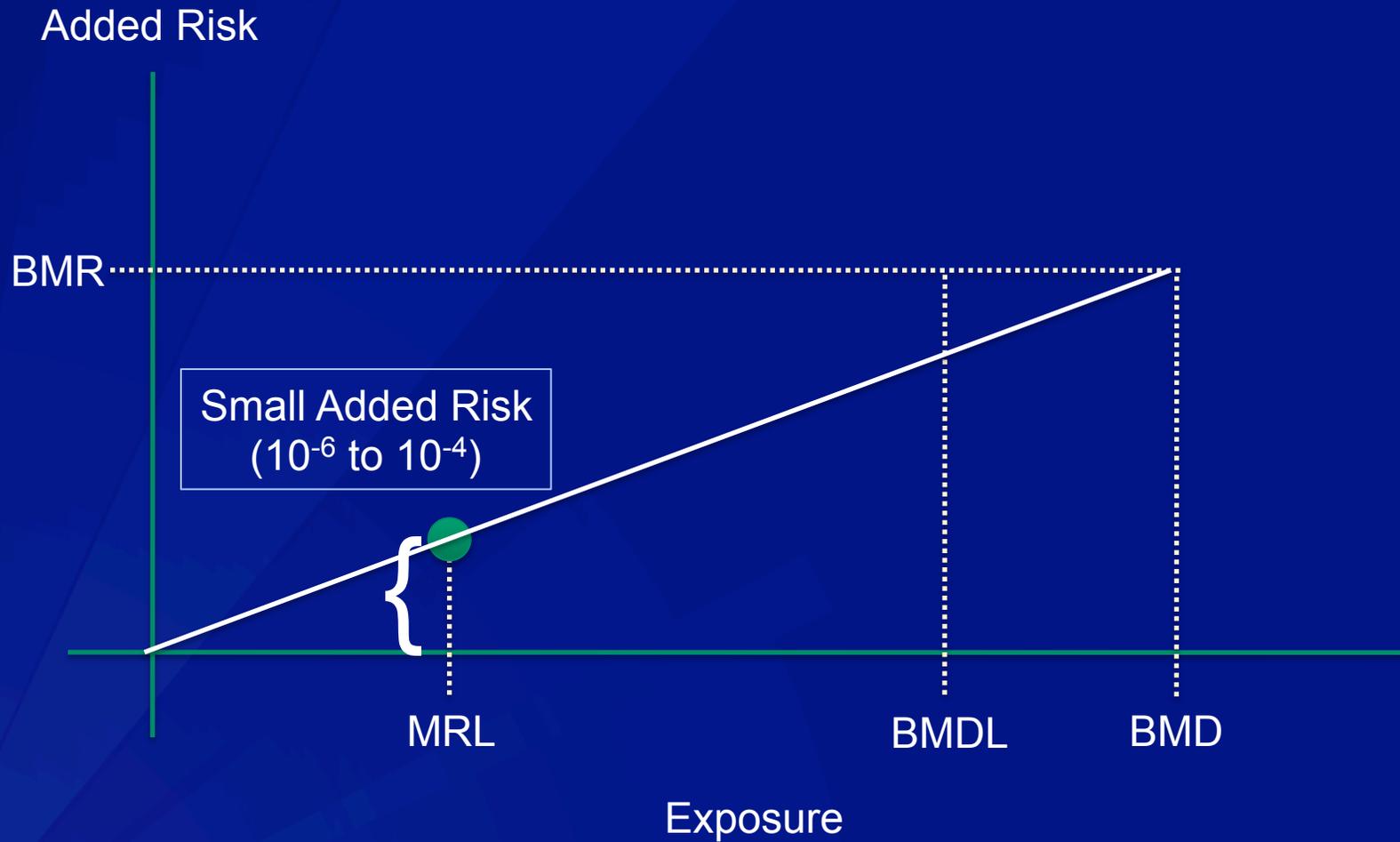
Benchmark Dose (BMD) Method



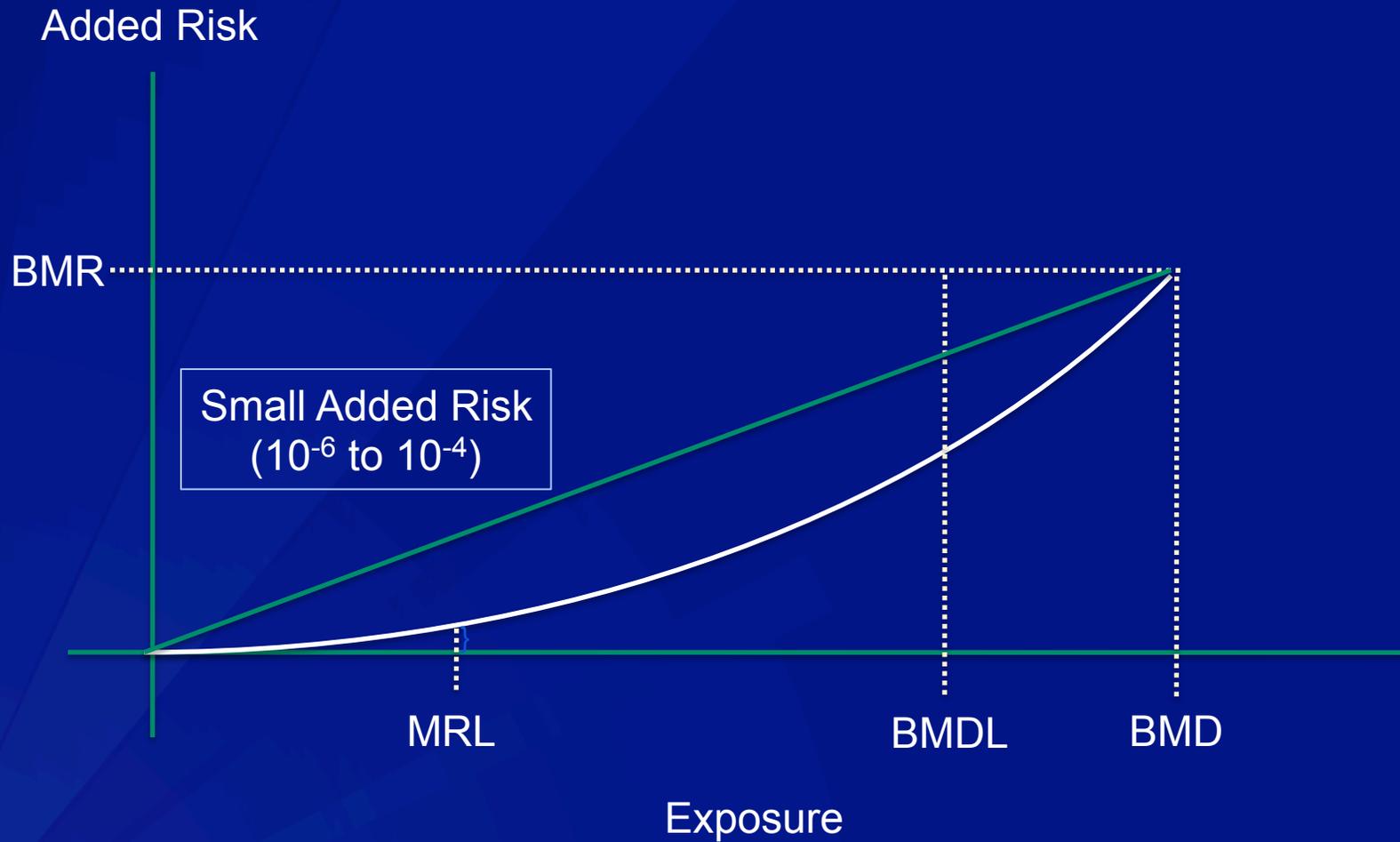
Experimental Risk Estimation



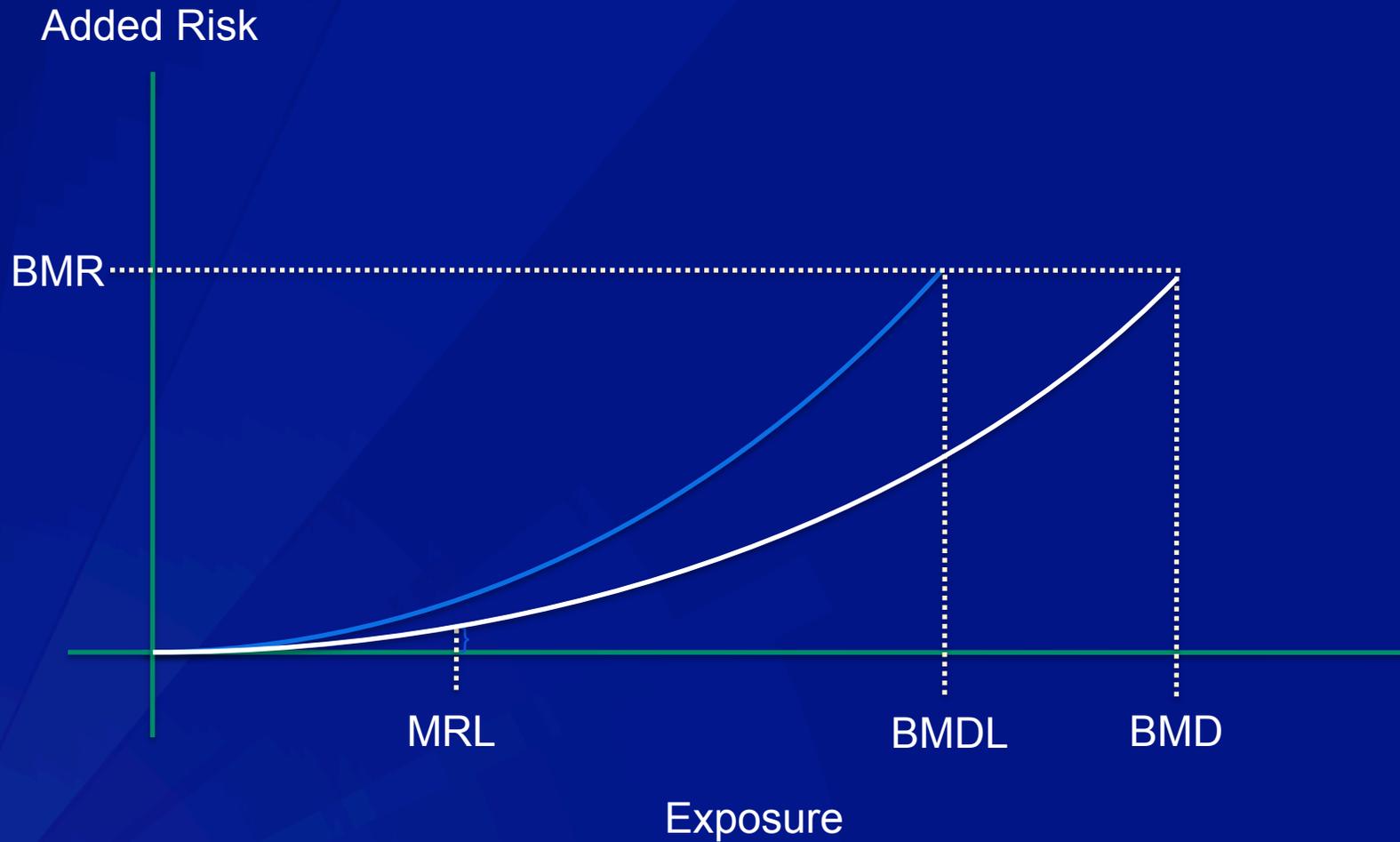
Experimental Risk Estimation



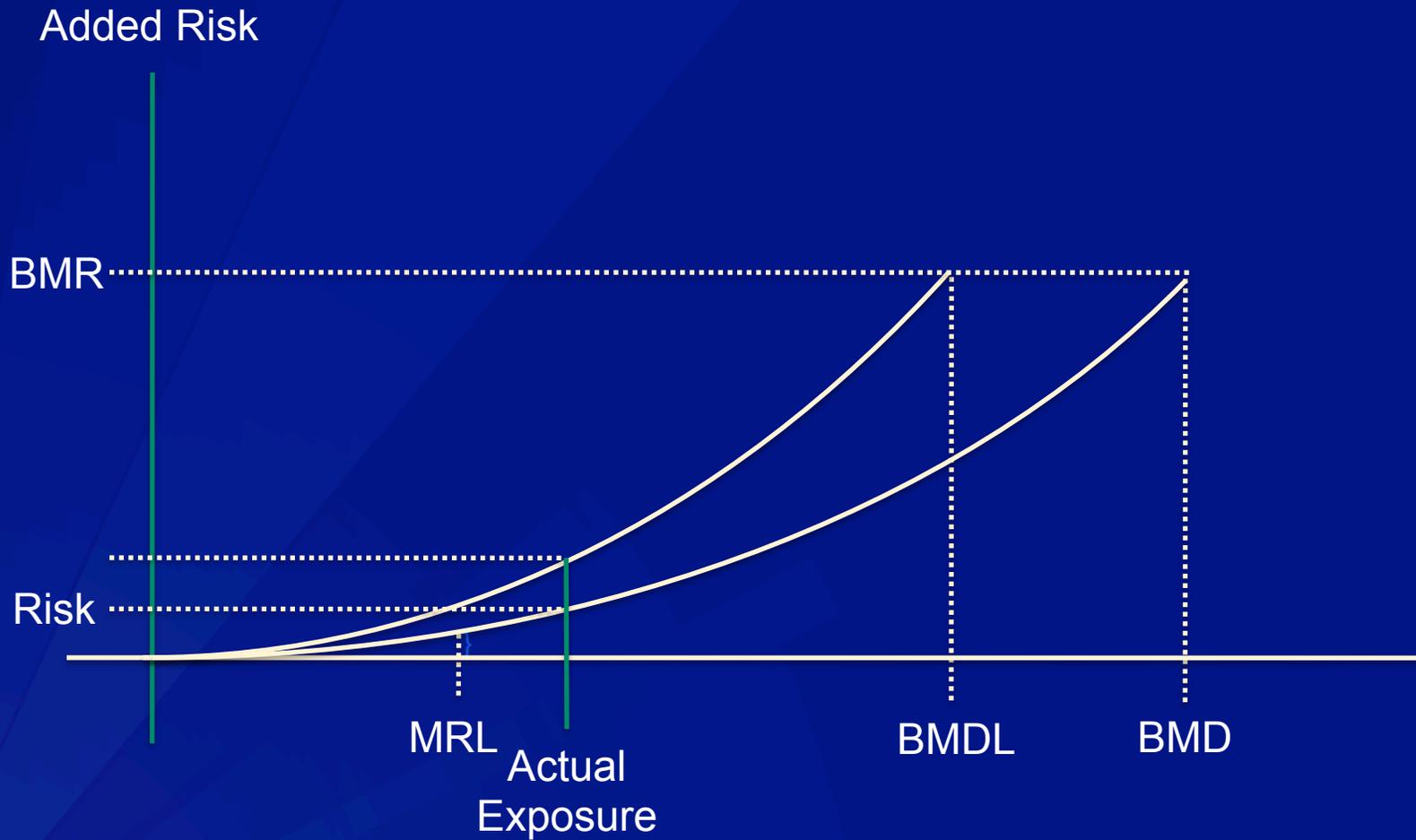
Experimental Risk Estimation



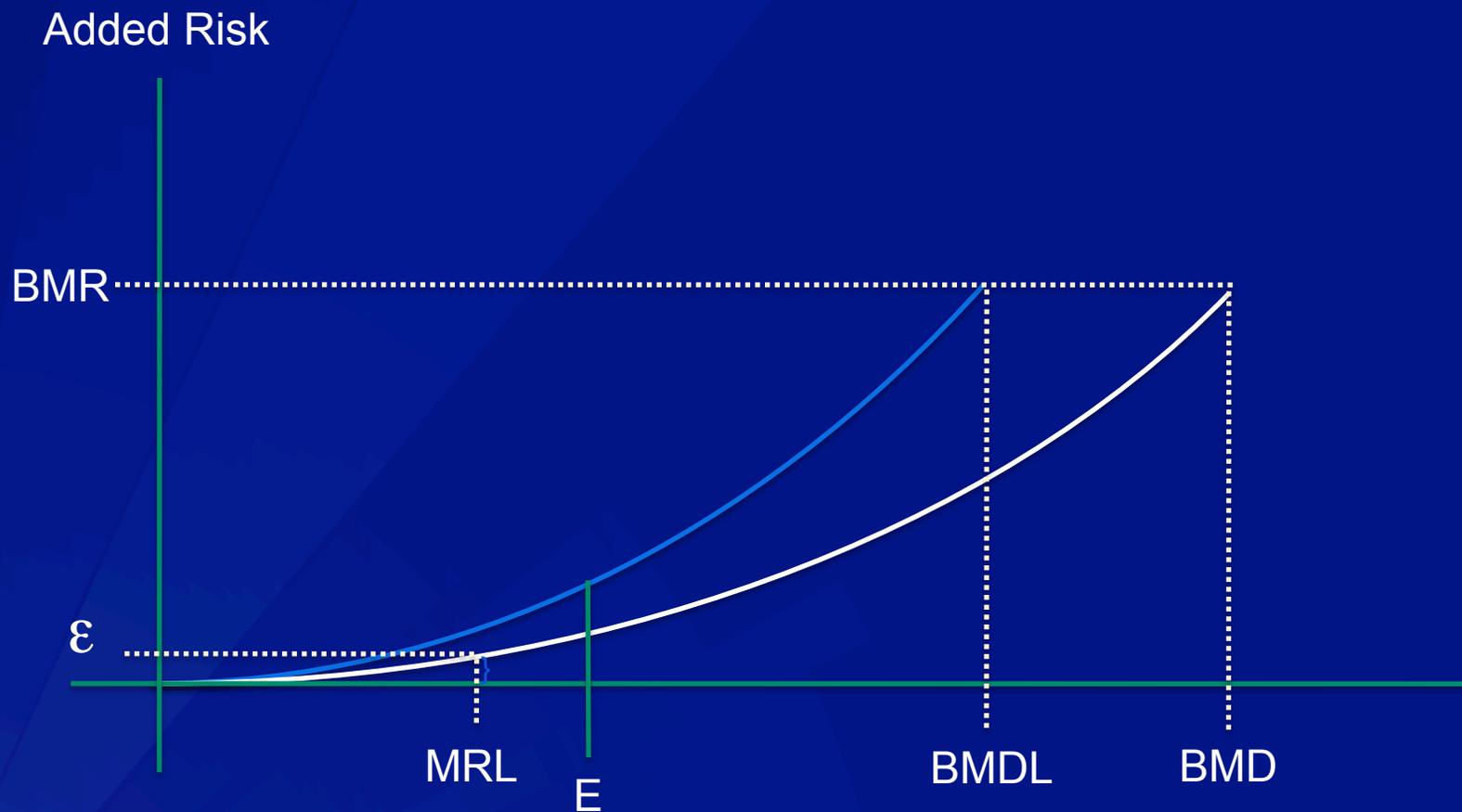
Experimental Risk Estimation



Experimental Risk Estimation



Mathematical Description



Mathematical Description

The function we are using to interpolate between the BMD and 0 added risk is:

$$R_D = (1 - \exp(-\alpha * D^k)) \approx \alpha * D^k \quad (1)$$

so at the BMD the risk is:

$$R_{BMD} = \alpha BMD^k \quad (2)$$

And the response at the MRL is given by:

$$\varepsilon = \alpha MRL^k \quad (3)$$

where ε is very small

Mathematical Description

- Since the value of α is the same for equation [2] and [3], it follows that:

$$k = \frac{\log\left(\frac{R_{BMD}}{\varepsilon}\right)}{\log\left(\frac{BMD}{MRL}\right)}$$

which allows us to solve for α :

$$\alpha = \frac{R_{BMD}}{BMD^k} = \frac{\varepsilon}{MRL^k}$$

Mathematical Description

- The upper bounds are calculated from the following two formulae:

$$\alpha_{ub} = \frac{R_{BMD}}{BMDL^k}$$

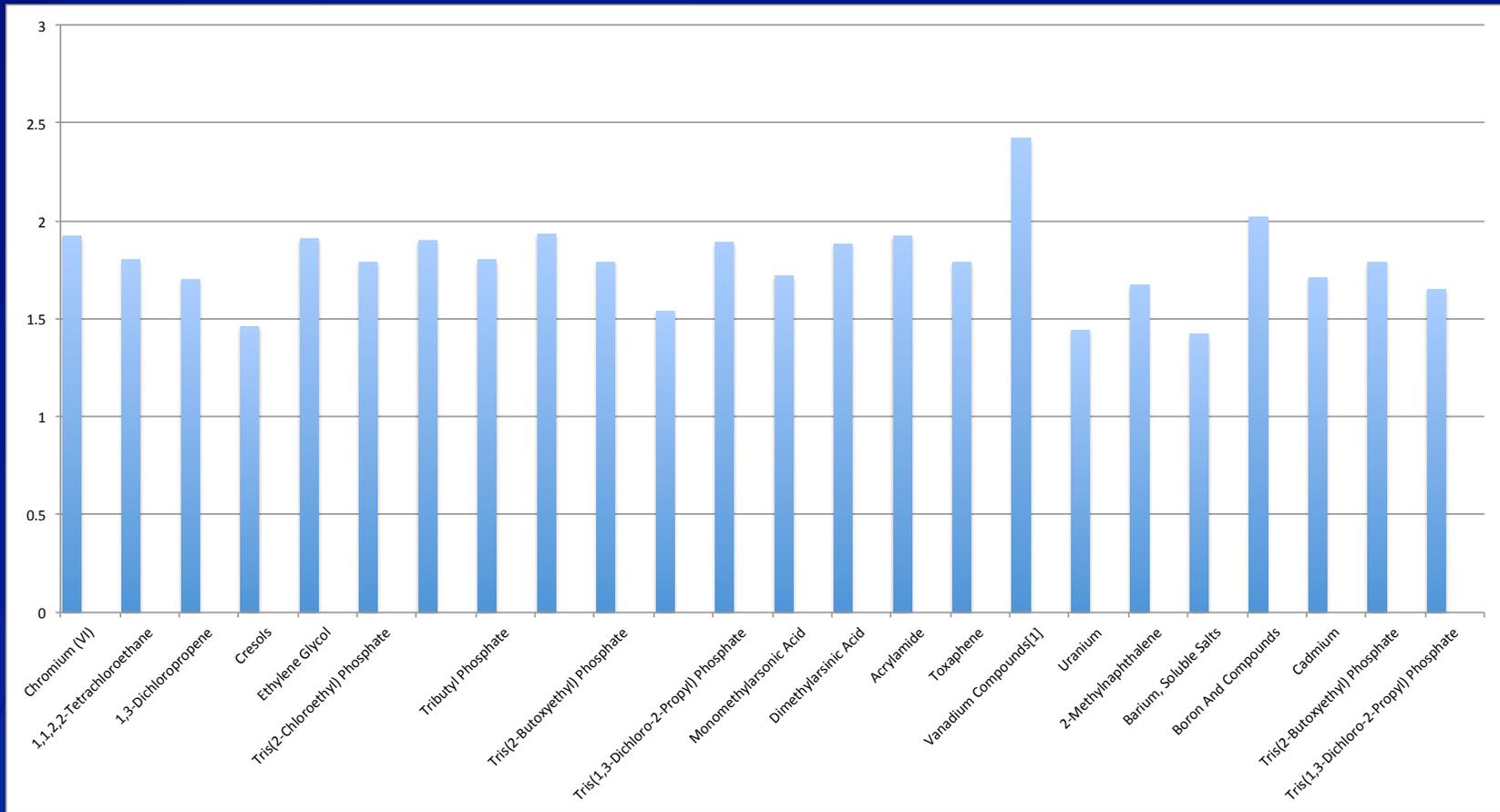
$$R_{MRLub} = \alpha_{ub} MRL^k$$

Substance	Type ¹	MRL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)	UF	BMR	K	Upper Bound Risk @MRL	α	α_{ub}
Chromium (VI)	O,C,Q	0.001	0.12	0.09	100	0.1	1.92	1.74E-05	5.91E+00	1.03E+01
1,1,2,2-Tetrachloroethane	O,I,Q	0.5	82.89	53.88	100	0.1	1.80	2.17E-05	3.49E-05	7.58E-05
1,3-Dichloropropene	O,I,Q	0.04	9.00	3.57	100	0.1	1.70	4.82E-05	2.38E-03	1.15E-02
Cresols	O,I,Q	0.1	55.89	13.94	100	0.1	1.46	7.55E-05	2.86E-04	2.16E-03
Ethylene Glycol	O,A,Q	0.8	99.35	75.56	100	0.1	1.91	1.69E-05	1.53E-05	2.58E-05
Tris(2-Chloroethyl) Phosphate	O,I,Q	0.6	102.44	60.76	100	0.1	1.79	2.55E-05	2.50E-05	6.37E-05
	O,C,Q	0.3	37.92	25.78	100	0.1	1.90	2.08E-05	9.89E-05	2.06E-04
Tributyl Phosphate	O,I,Q	0.02	3.30	1.96	100	0.1	1.80	2.56E-05	1.16E-02	2.97E-02
	O,A,Q	1.1	130.32	111.47	100	0.1	1.93	1.35E-05	8.32E-06	1.12E-05
Tris(2-Butoxyethyl) Phosphate	O,A,Q	4.8	824.97	477.25	100	0.1	1.79	2.66E-05	6.04E-07	1.61E-06
	O,I,Q	0.2	80.62	21.92	100	0.1	1.54	7.38E-05	1.18E-04	8.74E-04
Tris(1,3-Dichloro-2-Propyl) Phosphate	O,C,Q	0.02	2.60	1.94	100	0.1	1.89	1.74E-05	1.64E-02	2.85E-02
Monomethylarsonic Acid	O,C,Q	0.01	2.09	1.09	100	0.1	1.72	3.07E-05	2.81E-02	8.62E-02
Dimethylarsinic Acid	O,C,Q	0.02	2.68	1.80	100	0.1	1.88	2.11E-05	1.57E-02	3.31E-02
Acrylamide	O,A,Q	0.02	2.44	1.78	100	0.1	1.92	1.83E-05	1.81E-02	3.31E-02
Toxaphene	O,I,Q	0.002	0.34	0.22	100	0.1	1.79	2.18E-05	6.92E-01	1.51E+00
Vanadium Compounds ²	I,C,Q	0.0001	0.0045	0.003	30	0.1	2.42	2.70E-05	4.57E+04	1.23E+05
Uranium	O,A,Q	0.002	0.75	0.20	100	0.05	1.44	6.68E-05	7.56E-02	5.05E-01
2-Methylnaphthalene	O,C,Q	0.04	6.47	4.30	100	0.05	1.67	1.98E-05	2.19E-03	4.35E-03
Barium, Soluble Salts	O,C,Q	0.2	80.06	61.13	300	0.05	1.42	1.47E-05	9.85E-05	1.45E-04
Boron And Compounds	O,I,Q	0.2	13.70	10.30	66	0.05	2.02	1.78E-05	2.56E-04	4.55E-04
Cadmium	O,I,C	0.0005	0.11	0.05	100	0.1	1.71	3.84E-05	3.27E-02	1.26E-01
Tris(2-Butoxyethyl) Phosphate	O,A,C	4.8	824.97	477.25	100	0.1	1.79	2.66E-05	6.04E-07	1.61E-06
Tris(1,3-Dichloro-2-Propyl) Phosphate	O,I,C	0.05	13.36	4.49	100	0.1	1.65	6.03E-05	1.39E-03	8.41E-03

¹ Entries are Route,Length,Data where route is oral (O), inhalation (I); length is acute (A), intermediate (I), chronic (C); data is quantal (Q), continuous (C)

² Exposure entries here are mg/cubic meter

Values for K

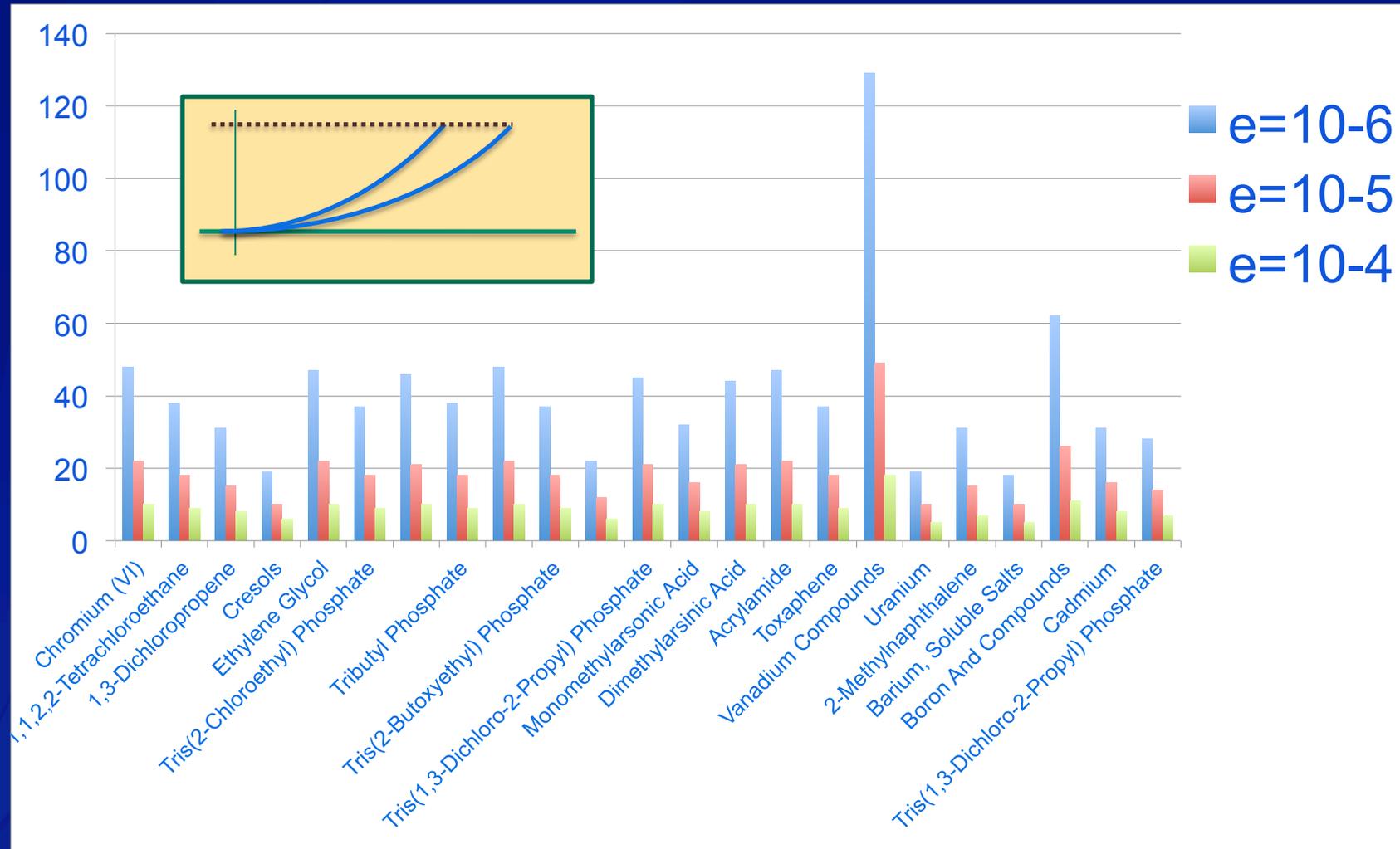


Relative Risk at Twice the MRL to Risk at MRL

Substance	Type ¹	κ	$\epsilon=10^{-6}$	κ	$\epsilon=10^{-5}$	κ	$\epsilon=10^{-4}$
Chromium (VI)	O,C,Q	2.40	5.27	1.92	3.78	1.44	2.71
1,1,2,2-Tetrachloroethane	O,I,Q	2.25	4.77	1.80	3.49	1.35	2.55
1,3-Dichloropropene	O,I,Q	2.13	4.36	1.70	3.25	2.13	4.36
Cresols	O,I,Q	1.82	3.53	1.46	2.74	1.09	2.13
Ethylene Glycol	O,A,Q	2.39	5.23	1.91	3.76	1.43	2.70
Tris(2-Chloroethyl) Phosphate	O,I,Q	2.24	4.72	1.79	3.46	1.34	2.54
	O,C,Q	2.38	5.20	1.90	3.74	1.43	2.69
Tributyl Phosphate	O,I,Q	2.25	4.77	1.80	3.49	1.35	2.55
	O,A,Q	2.41	5.32	1.93	3.81	1.45	2.73
Tris(2-Butoxyethyl) Phosphate	O,A,C	2.24	4.71	1.79	3.46	1.34	2.54
	O,I,Q	1.92	3.78	1.54	2.90	1.15	2.22
Tris(1,3-Dichloro-2-Propyl) Phosphate	O,C,Q	2.37	5.15	1.89	3.71	1.42	2.67
	O,I,C	2.06	4.17	1.65	3.13	1.24	2.36
Monomethylarsonic Acid	O,C,Q	2.16	4.45	1.72	3.30	1.29	2.45
Dimethylarsinic Acid	O,C,Q	2.35	5.10	1.88	3.68	1.41	2.66
Acrylamide	O,A,Q	2.40	5.27	1.92	3.78	1.44	2.71
Toxaphene	O,I,Q	2.24	4.73	1.79	3.47	1.35	2.54
Vanadium Compounds	I,C,Q	3.02	8.10	2.42	5.33	1.81	3.51
Uranium	O,A,Q	1.83	3.54	1.44	2.71	1.05	2.07
2-Methylnaphthalene	O,C,Q	2.13	4.37	1.67	3.19	1.22	2.33
Barium, Soluble Salts	O,C,Q	1.81	3.50	1.42	2.68	1.04	2.05
Boron And Compounds	O,I,Q	2.56	5.90	2.02	4.04	1.47	2.77
Cadmium	O,I,C	2.13	4.39	1.71	3.27	1.28	2.43

¹ Entries are Route,Length,Data where route is oral (O), inhalation (I); length is acute (A), intermediate (I), chronic (C); data is quantal (Q), continuous (C)

Relative Risk at 5X the MRL to Risk at MRL



So how do we do mixtures?

$$R_{E_i} = \Pr[\text{Disease} | \text{Exposure} = E_i]$$

$$\text{So } 1 - R_{E_i} = \Pr[\text{No Disease} | \text{Exposure} = E_i]$$

What we want to calculate is:

$$\begin{aligned} & \Pr[\text{Disease} | \text{Exposures} = E_1 \text{ and } E_2 \text{ and } E_3] \\ &= 1 - (\Pr[\text{No Disease} | \text{Exposures} = E_1 \text{ and } E_2 \text{ and } E_3]) \end{aligned}$$

Assuming independent action between chemicals, then we have:

$$\begin{aligned} &= 1 - \Pr[\text{D} | E = E_1] \times \Pr[\text{D} | E = E_2] \times \Pr[\text{D} | E = E_3] \\ &= 1 - (1 - \Pr[\text{D} | E = E_1]) \times (1 - \Pr[\text{D} | E = E_2]) \times (1 - \Pr[\text{D} | E = E_3]) \\ &= 1 - (1 - R_{E_1}) (1 - R_{E_2}) (1 - R_{E_3}) \end{aligned}$$

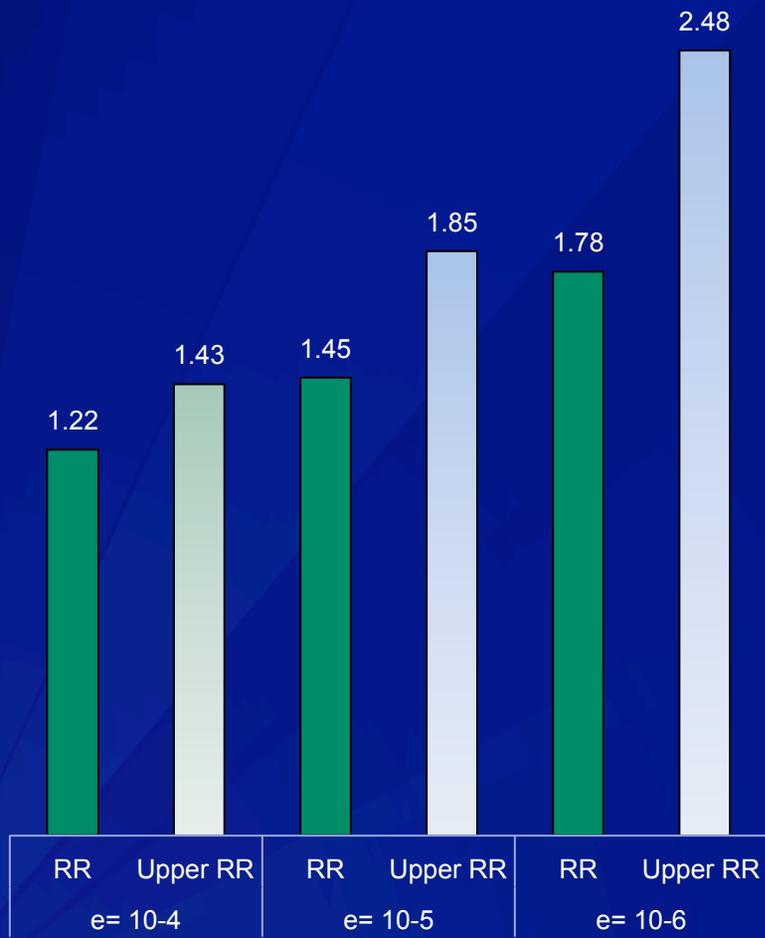
Summary

- ❑ Estimate α , K and α_{ub} for each chemical
- ❑ Evaluate population and estimate exposures to population for each compound
- ❑ Calculate a risk for each exposure for the population
- ❑ Combine the risks using the formula given previously
- ❑ Compare this to the target risk for the population

A Mixture Example ($\epsilon=10^{-5}$)

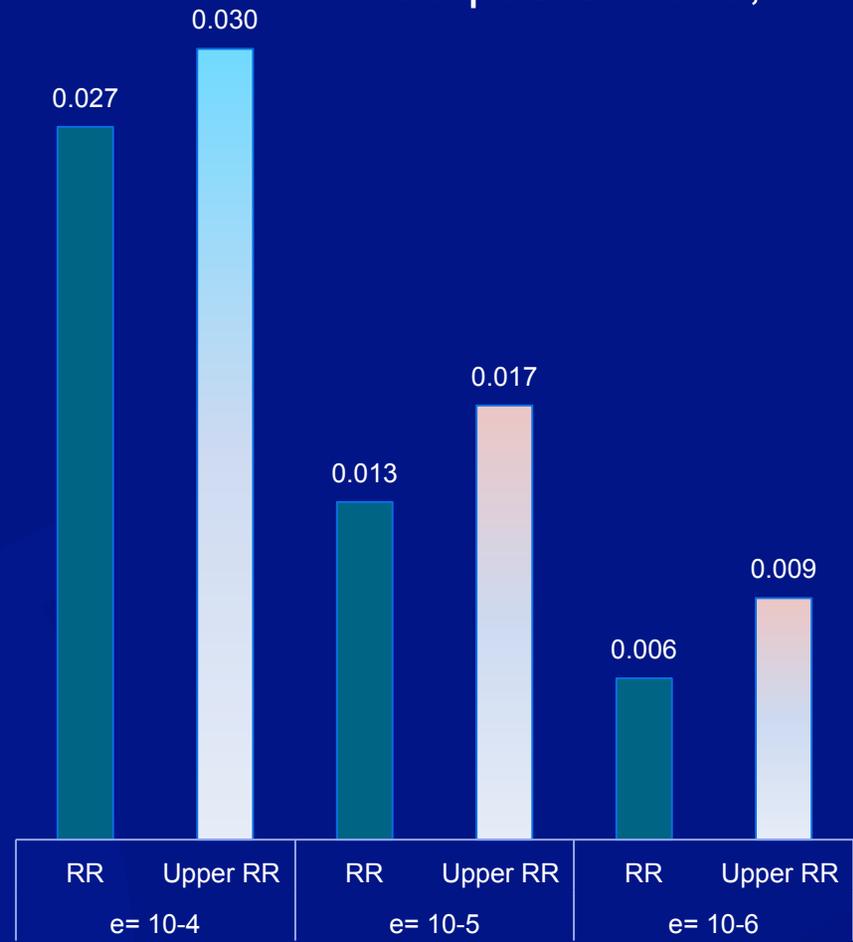
- ❑ **A population is exposed as follows:**
 - 0.001 mg/kg/day of cadmium (twice the MRL)
 - 0.018 mg/kg/day of tributyl phosphate (slightly below the MRL)
 - 0.1 mg/kg/day of Barium Salts (half the MRL)
- ❑ **Risk for Cadmium = 3.3×10^{-5}**
 - Upper bound = 1.3×10^{-4}
- ❑ **Risk for Tributyl phosphate = 8.3×10^{-6}**
 - Upper bound = 2.1×10^{-5}
- ❑ **Risk for Barium Salts = 2.3×10^{-6}**
 - Upper bound = 4.4×10^{-6}
- ❑ **Combined Risk = 4.4×10^{-5}**
 - Upper bound = 1.9×10^{-4}

**Figure 8a. Risk Ratio:
Mixture Cd, B, TnBP**



**Figure 8b. Risk Ratio: Mixture
BTEX (benzene, toluene,
ethylbenzene, xylenes)**

Corpus Christie, Tx.



Remaining Issues

- ❑ **Risks derived from LOAELS**
 - Already have this worked out
- ❑ **Sensitivity to choice of ϵ**
- ❑ **Similar mode of action**
 - Dose-additivity occurs in this case
- ❑ **Appearance of accuracy**
 - Greater scientific certainty implied than real
- ❑ **Advantage?**

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