



Longitudinal Assessments: Challenges and Future Designs to Understand Exposure and Disease

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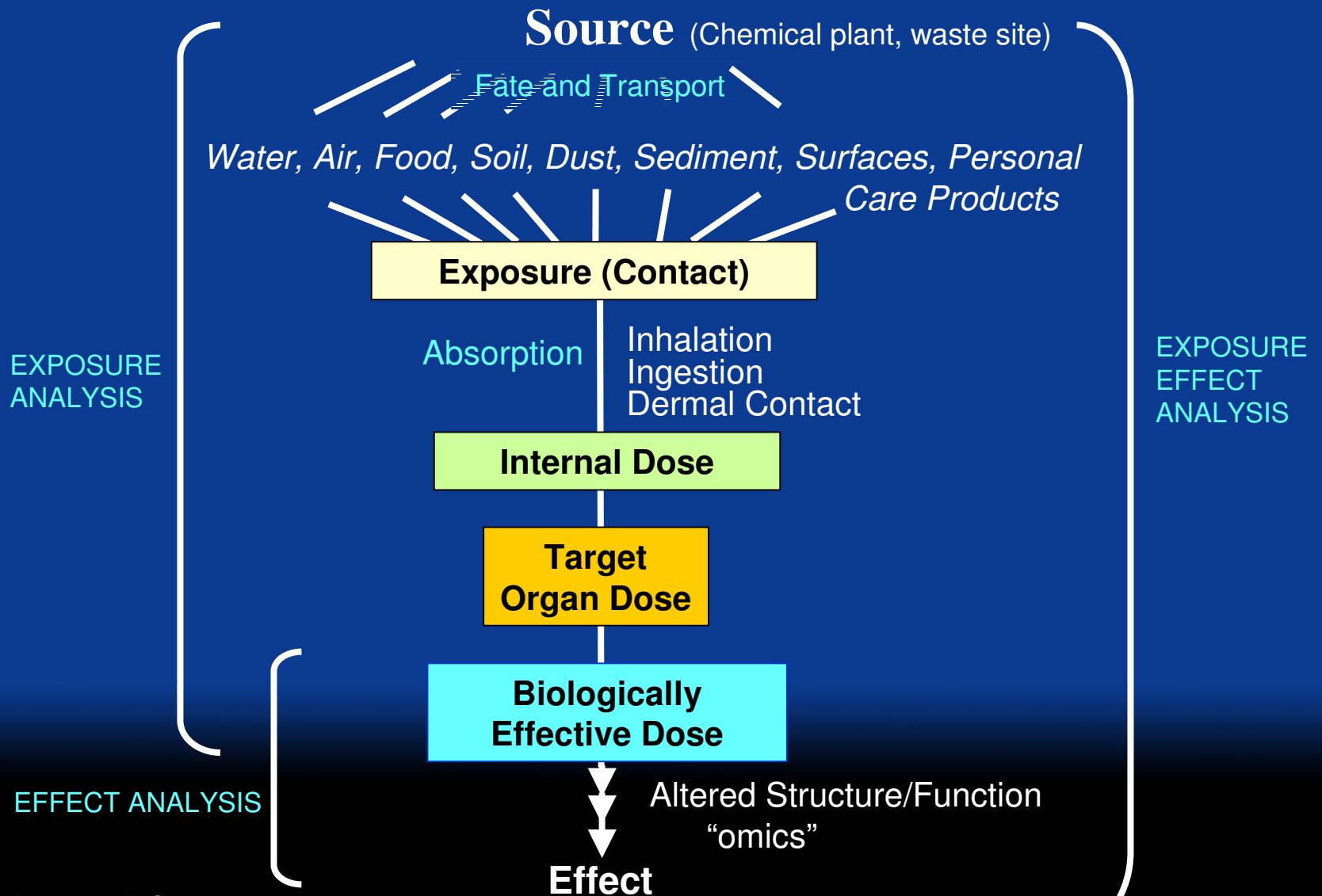
National Center for Environmental Health

Centers for Disease Control and Prevention

Atlanta, GA USA 30341

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Continuum: Understanding Relationship between Exposure and Disease



Adapted from: NRC 1987

Exposure Analysis for Disease Prevention



Adapted from: HESI's Biomonitoring Technical Committee

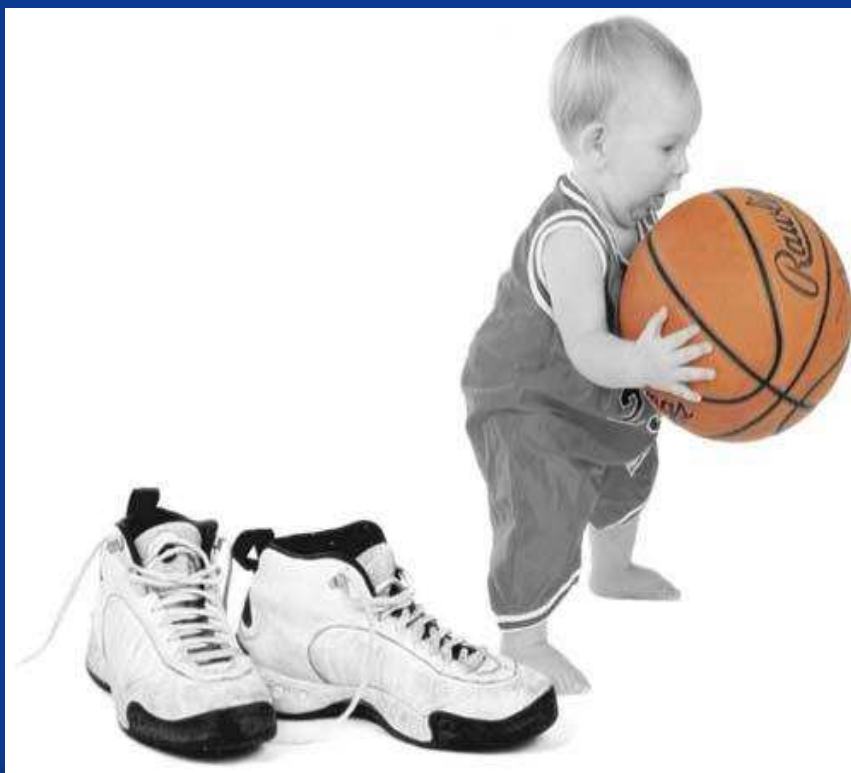
Longitudinal Assessments Imply Epidemiological Studies

- 1 Case Control
- 1 Cross Sectional
- 1 Longitudinal: assess exposure in population; follow population over time for disease development

Questions for Longitudinal Studies

- 1 What diseases? Generally hypotheses-driven for certain health endpoints
- 1 What stressors (including exposures to environmental chemicals) are “linked” to these diseases?
- 1 What population and its characteristics to study? Age; race; sex; other genetic differences that affect PK and PD; health status; exposure history; other exposures including medications

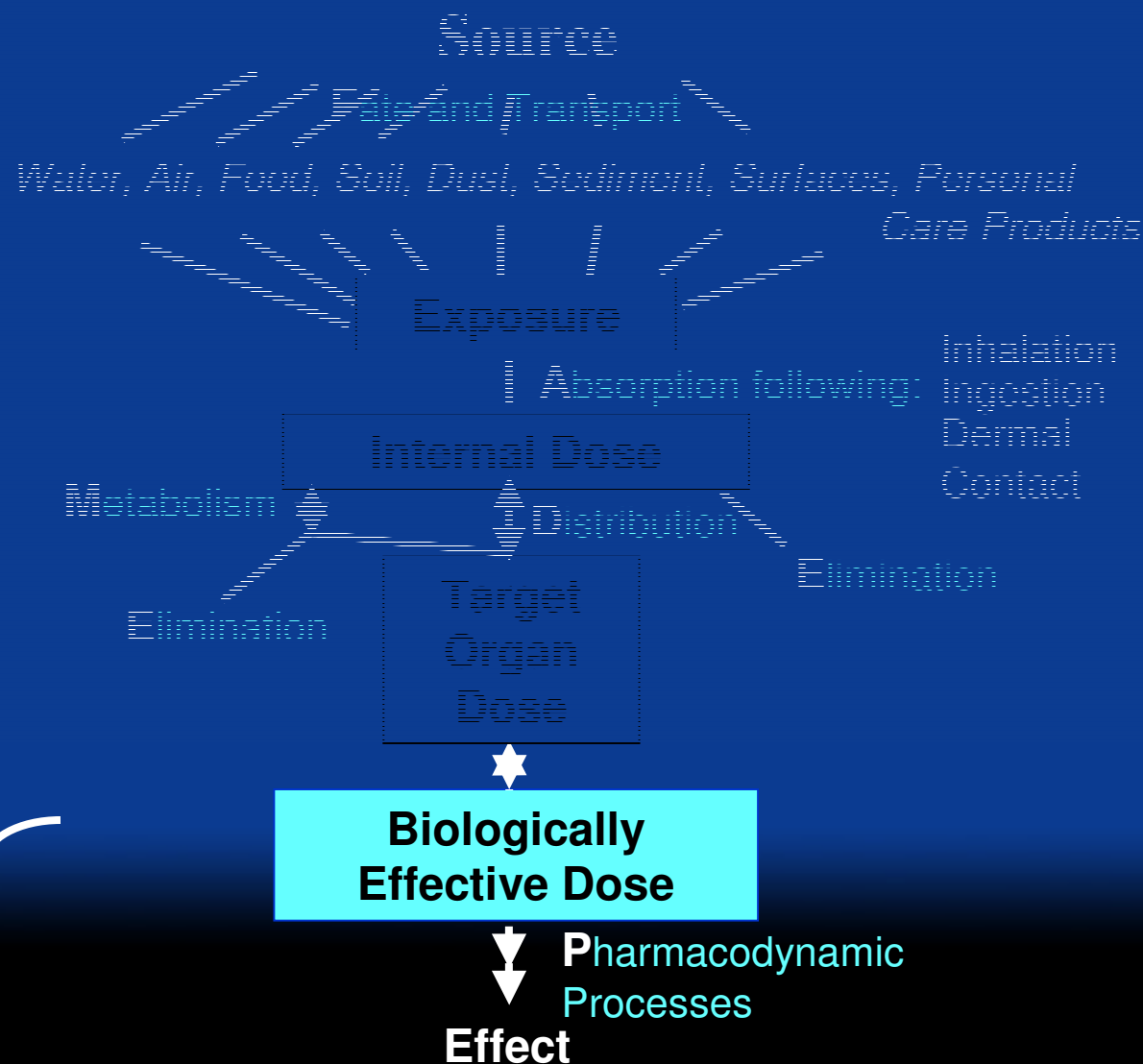
Exposure Assessment Approaches*



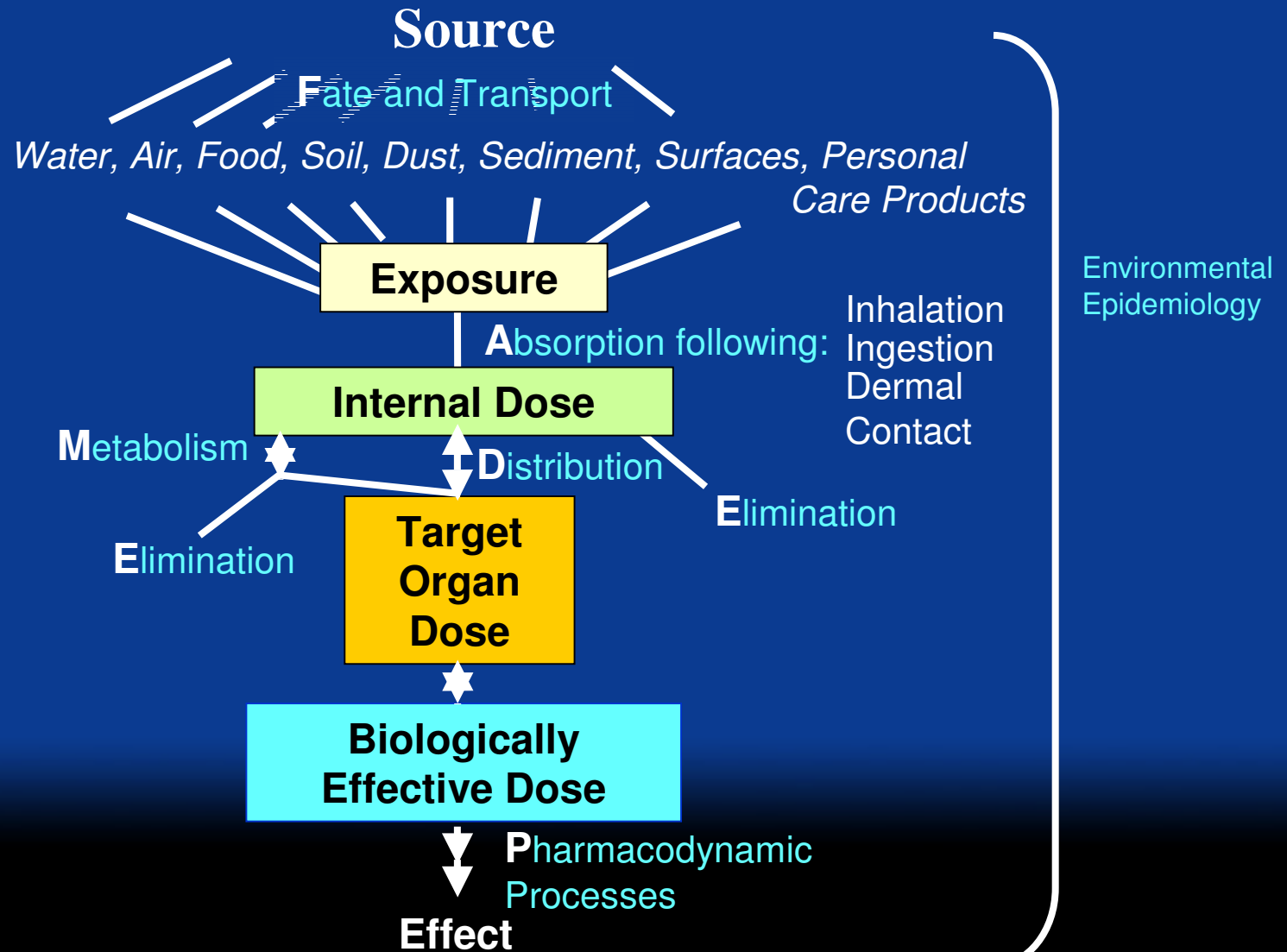
- 1 Preferred sampling time: at life stage of most susceptibility; real time
- 1 Biomonitoring
- 1 Personal Monitoring (air)
- 1 Environmental Monitoring
- 1 Questionnaire and other indirect means to complement all

* All these approaches need modeling to estimate internal dose or better yet the biologically effective dose. Validate and calibrate these models.

Exposure-Effect Continuum for Environmental Chemicals: Longitudinal Study



Exposure-Effect Continuum for Environmental Chemicals: Longitudinal Study



Choosing the Appropriate Matrix/Medium

- 1 Chemical dependent
- 1 Population dependent (age, race, health status, etc.)

Biomonitoring

Assessment of human exposure to an environmental chemical by measuring its exposure biomarker(s): the parent chemical (or its metabolite or reaction product) in human blood, urine, milk, saliva, adipose, or other tissue.

Integrates exposure/absorption over multiple pathways.

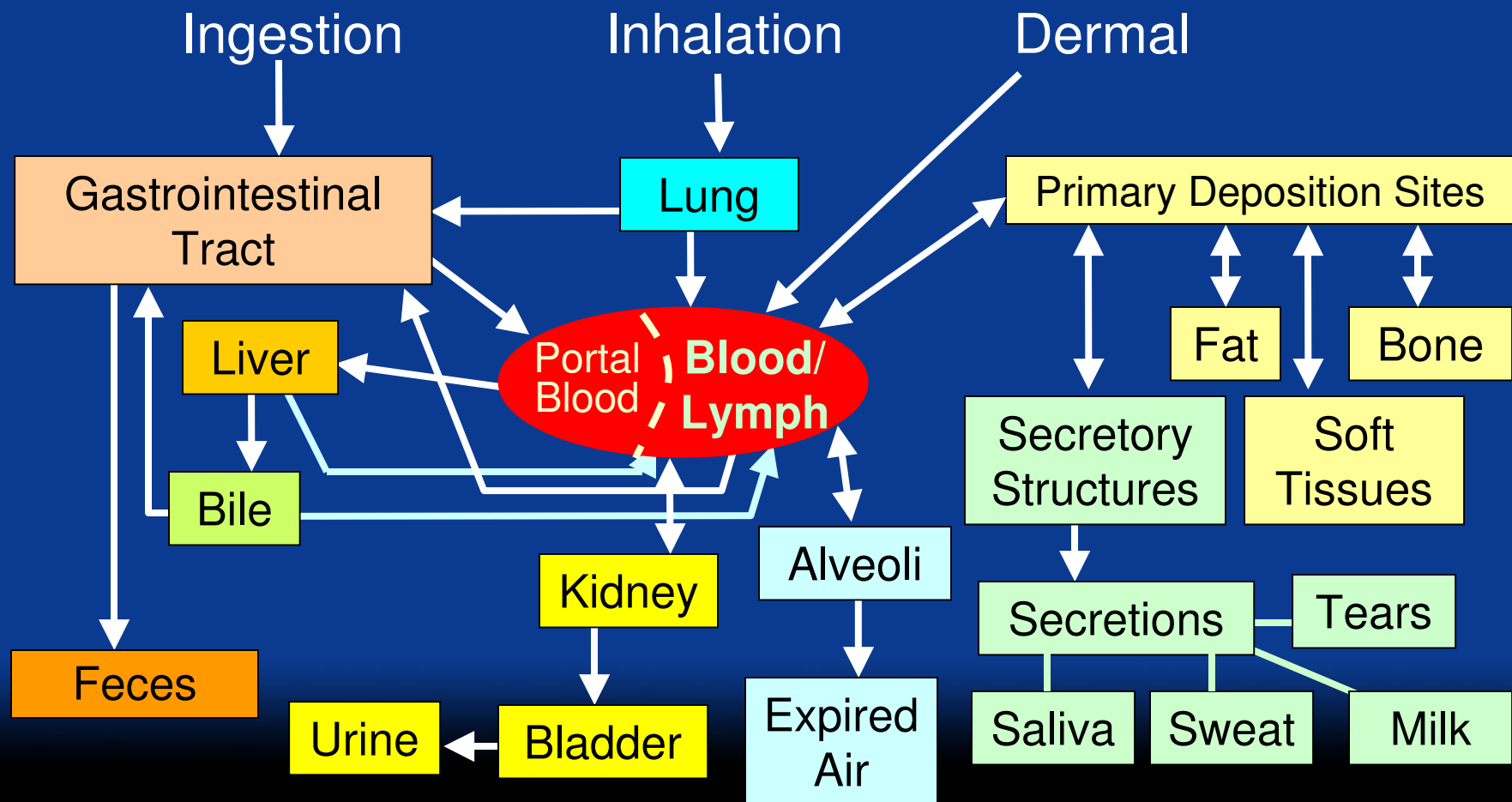
Selection of Biomonitoring Matrix: Environmental Chemical Dependent

1 Two primary classes of Environmental Chemicals

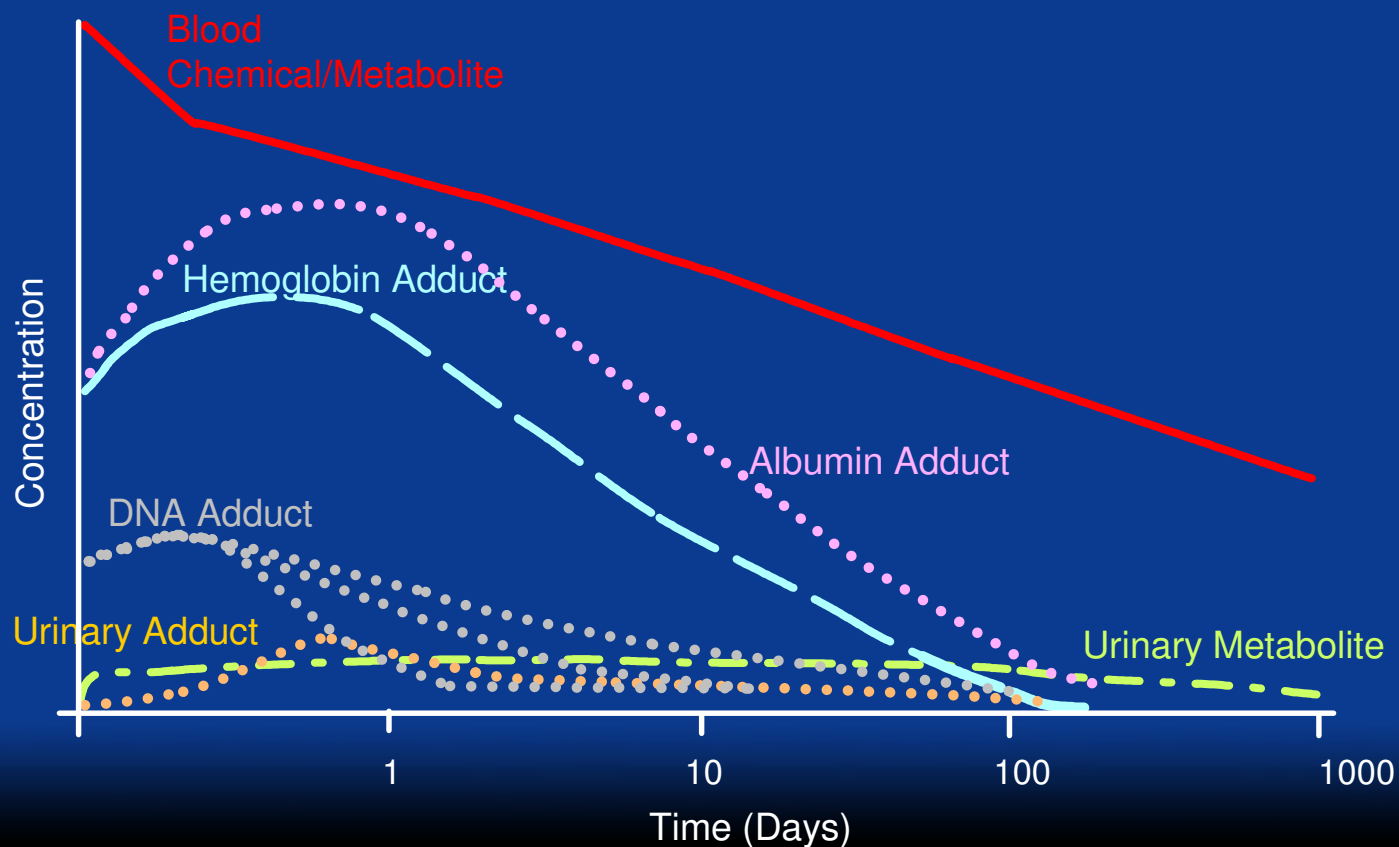
- u Persistent (half-lives in years)
 - « Exposures “Ceased” (PCDDs, PCDFs, PCBs, OCs)
 - « Exposures Continue (PBDEs, PFCs, Pb?)

- u Non Persistent (half-lives in minutes/hours)
 - « Form adducts (Aflatoxins, PAHs, Organophosphorous pesticides)
 - « Do not form adducts
 - Metabolites: Specific (Nicotine to Cotinine)
 - Metabolites: Nonspecific (Organophosphorous pesticides)

Selection of Biological Matrix: Absorption, Distribution, Metabolism, and Elimination of Environmental Chemicals in the Body



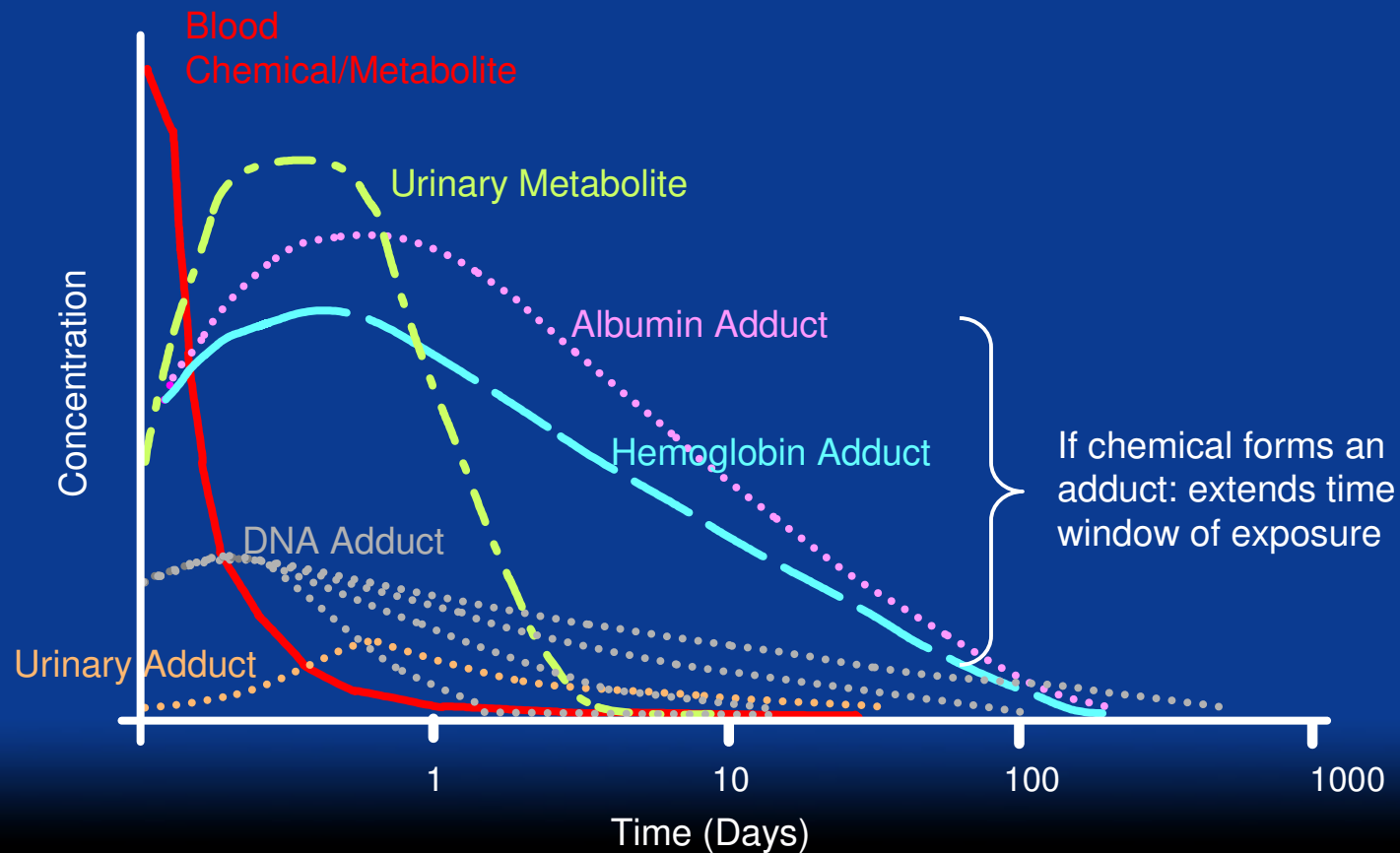
Selection of Biological Matrix: Post-Exposure Fate of a Persistent Chemical in Blood and Urine



Needham and Sexton. JEAEE 10: 611-629 (2000)

Adapted from: Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

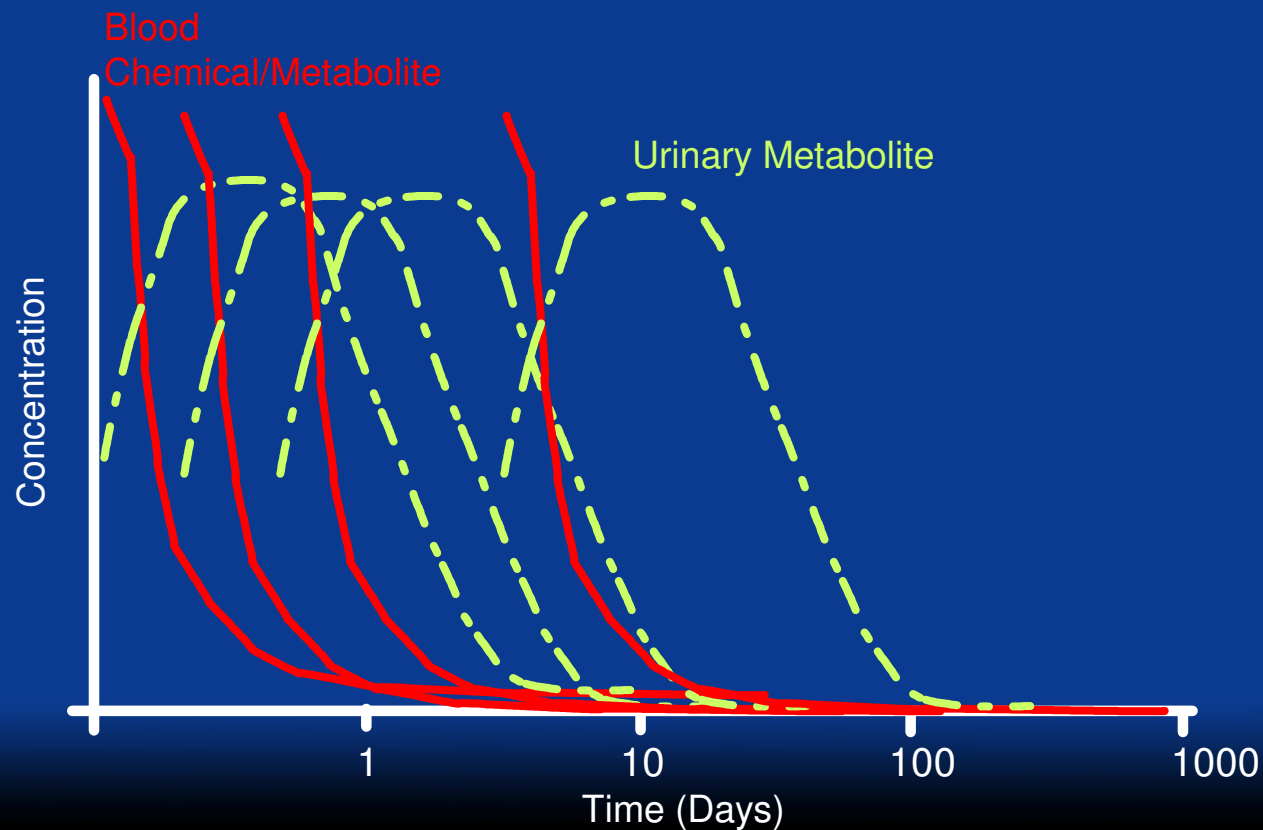
Selection of Biological Matrix: Post-Exposure Fate of a Nonpersistent Chemical in Blood and Urine



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Selection of Biological Matrix: Post-Exposure Fate of a Nonpersistent Chemical in Blood and Urine

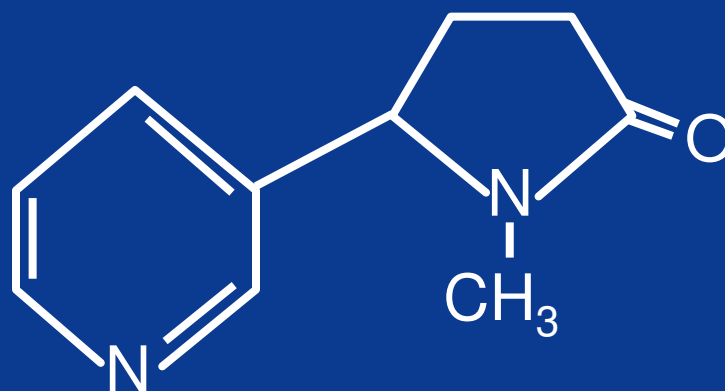


Barr et al. Environ Health Perspect **113**:1083-1091 (2005)

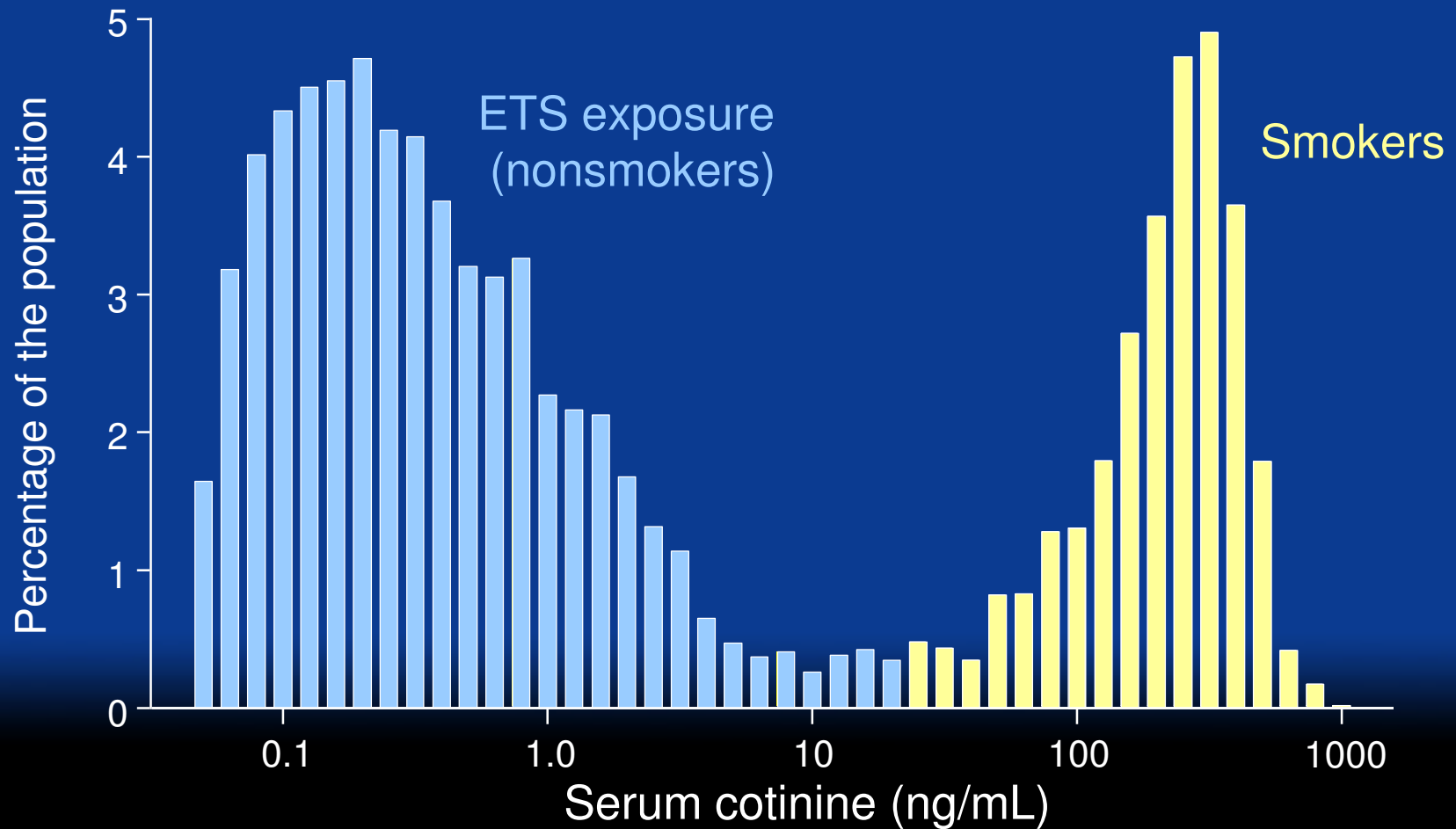
Needham, Barr, and Calafat. Neurotoxicology **26**:547-53 (2005)

Example of Nonpersistent Chemical that Forms Specific Metabolite: Nicotine to Cotinine

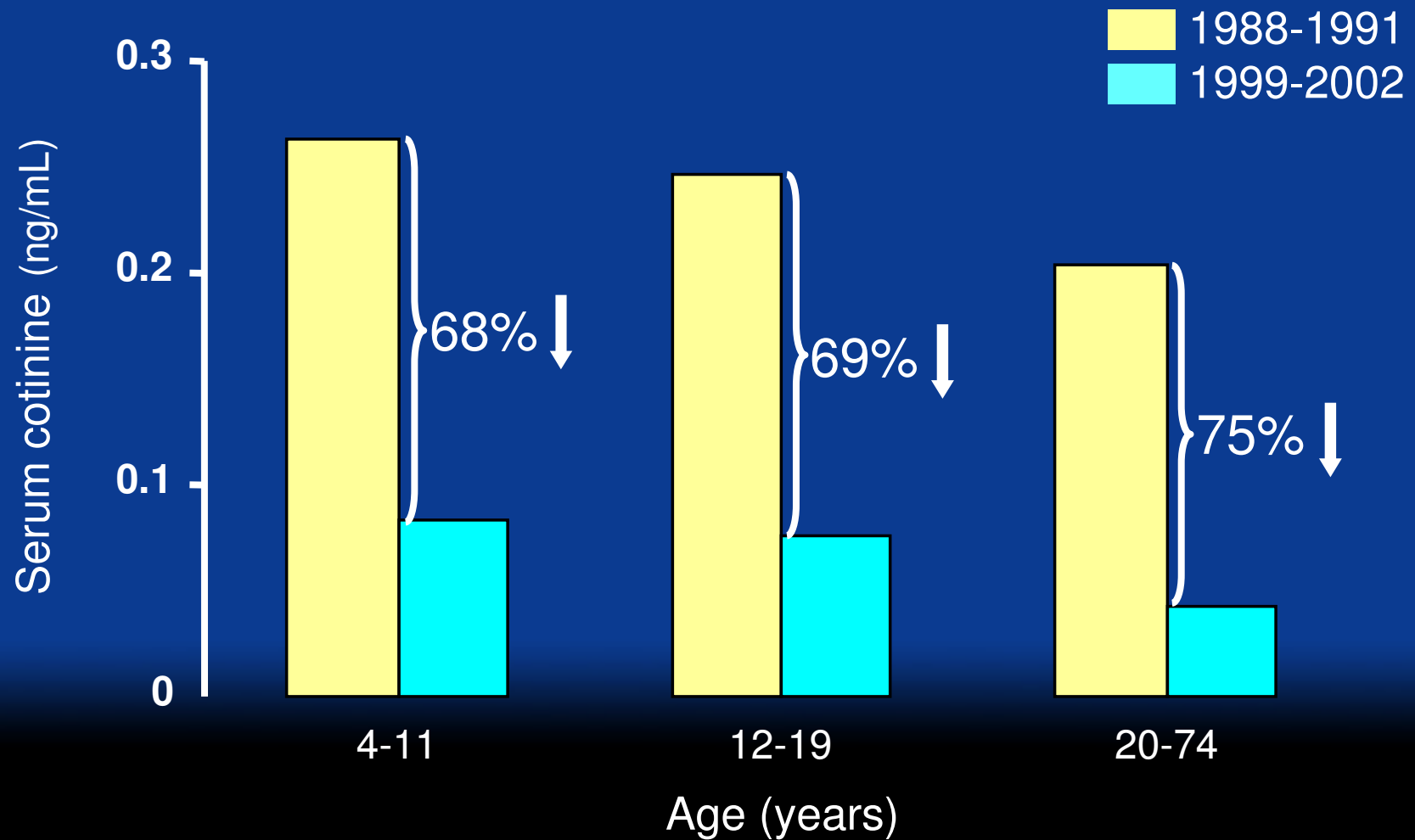
- 1 Cotinine is Nicotine metabolite that tracks exposure to tobacco smoke
- 1 For nonsmokers, cotinine tracks exposure to secondhand smoke



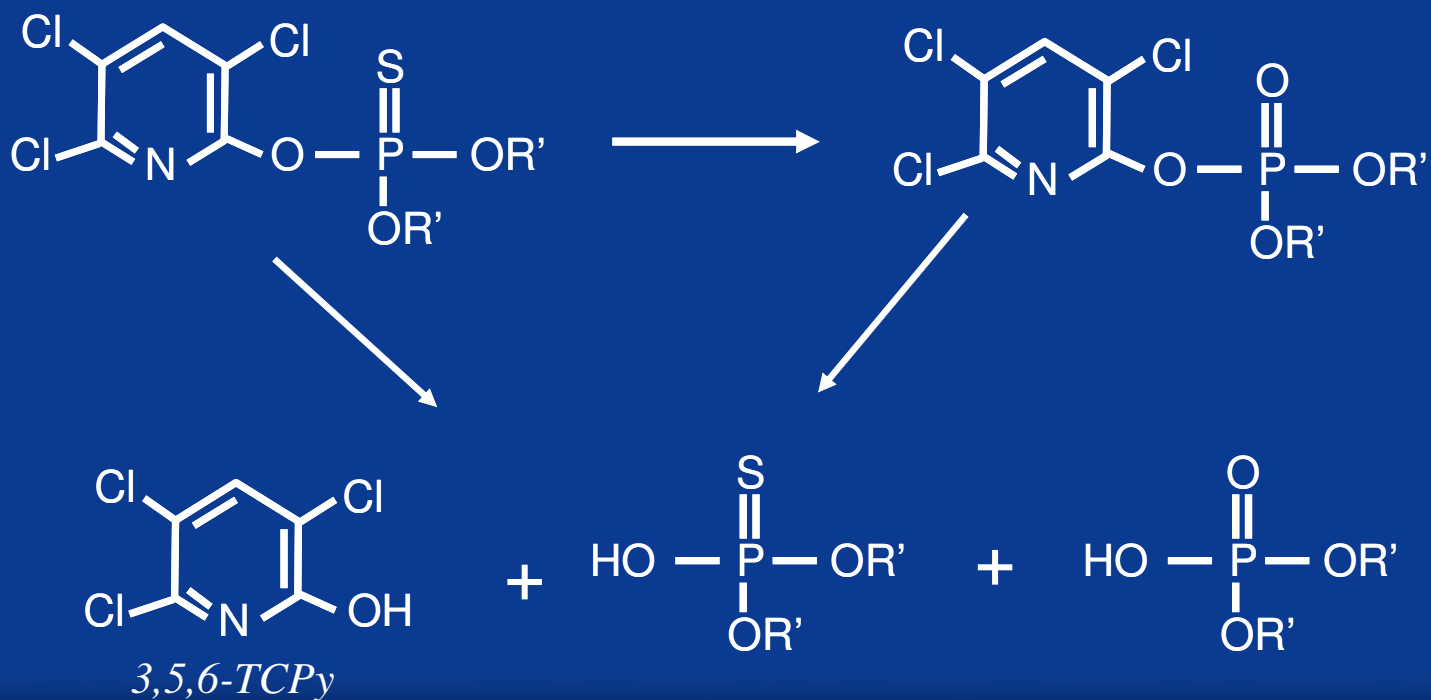
Exposure of the U.S. Population to Tobacco Smoke: Serum Cotinine Levels (NHANES III, 1988-1991)



Serum Cotinine Levels: Tracking Exposure to Secondhand Smoke in the Non-smoking U.S. Population



Example of Nonpersistent Chemical That Forms Nonspecific Metabolites and These Metabolites Are the Same Chemicals as Degradation Products: Chlorpyrifos



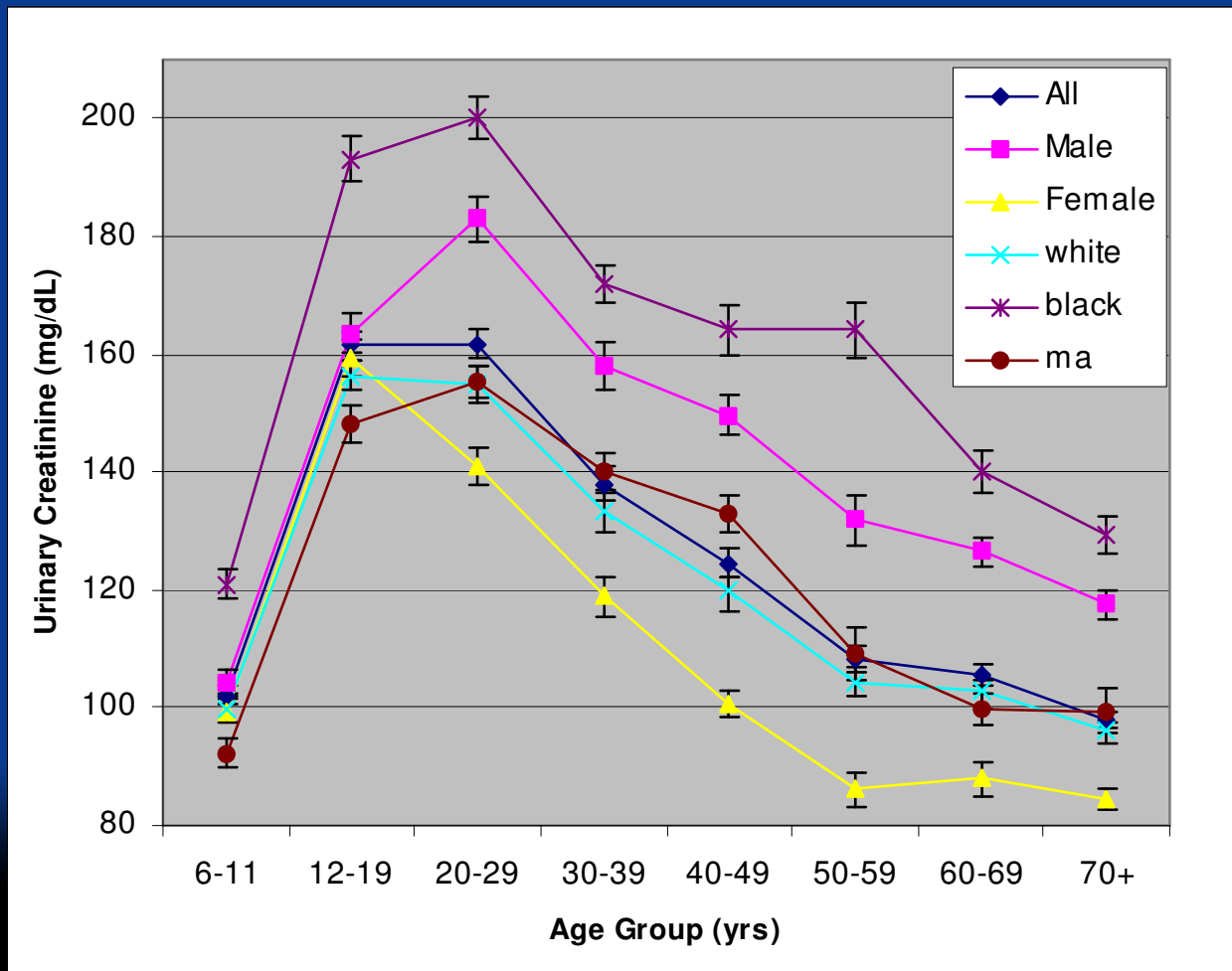
3,5,6-TCPy is “specific” metabolite

Dialkyl phosphates are “nonspecific” metabolites

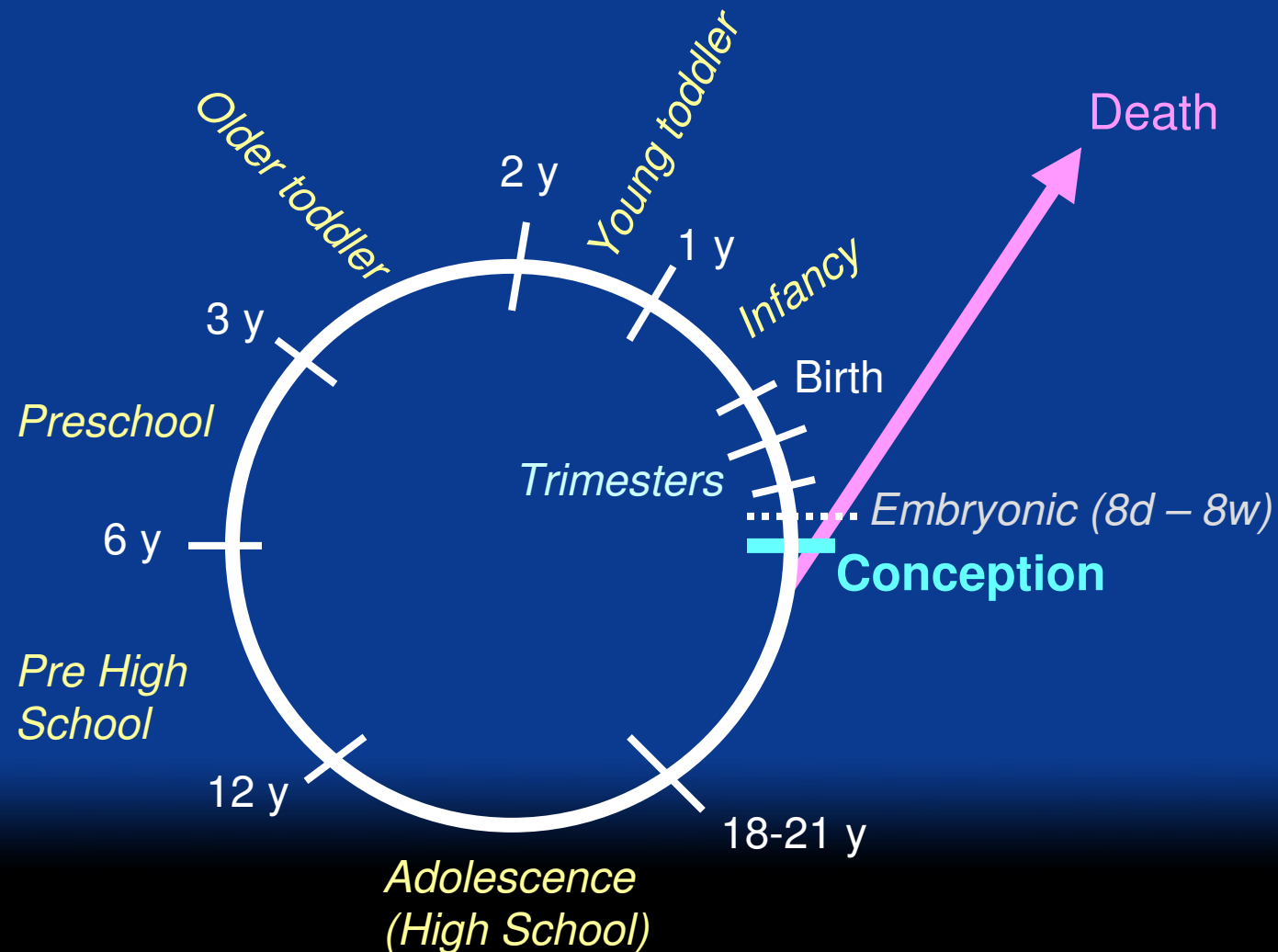
Other Issues Regarding Urine as Biomonitoring Matrix

- 1 Ease of sampling at different life stages
- 1 Collection times(s): spot, first morning void, 24 hour; i.e., temporal variability
- 1 “Nonregulated” matrix: hydration state
- 1 Concentration adjustment: creatinine

Creatinine Variability Among Populations: NHANES III



Life Stage of Population: A Primary Factor for Determining the Exposure Assessment Approach



Relative Importance of Various Biological Matrices for Measuring Exposure During the Different Life Stages

Matrices	Adult preconception	Fetal			0-1 year	2-3 years	4-11 years
		1st	2nd	3rd			
Persistent Organic Chemicals							
Blood (whole)	1				1	1	1
Blood (serum)	1				1	1	1
Blood (plasma)	1				1	1	1
Urine	3				3	3	3
Saliva	3				NA	3	3
Hair	3				3	3	3
Nails	3				3	3	3
Adipose Tissue	1				NA	NA	NA
Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	3				NA	3	3
Teeth	NA				NA	NA	3
Cord Blood	1	1	1	1	3	3	3
Meconium	3	2	2	2	3	3	3
Milk (maternal)	1	1	1	1	1	3	3
Blood (maternal)	1	1	1	1	1	3	3
Urine (maternal)	3	3	3	3	3	3	3
Hair (maternal)	3	3	3	3	3	3	3

Barr, Wang, and Needham. *Environ Health Perspect* **113**:1083-91 (2005)

Relative Importance of Various Biological Matrices for Measuring Exposure During the Different Life Stages

Matrices	Adult preconception	Fetal			0-1 year	2-3 years	4-11 years
		1st	2nd	3rd			
Nonpersistent Organic Chemicals							
Blood (whole)	1				1	1	1
Blood (serum)	1				1	1	1
Blood (plasma)	1				1	1	1
Urine	1				1	1	1
Saliva	2				NA	2	2
Hair	3				3	3	3
Nails	3				3	3	3
Adipose Tissue	3				NA	NA	NA
Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	3				NA	3	3
Teeth	3				NA	NA	3
Cord Blood	3	3	3	1	3	3	3
Meconium	3	3	2	2	3	3	3
Milk (maternal)	3	3	3	3	2	3	3
Blood (maternal)	3	1	1	1	3	3	3
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Matrices	Adult preconception	Fetal			0-1 year	2-3 years	4-11 years
		1st	2nd	3rd			
Volatile Organic Chemicals							
Blood (whole)	1				1	1	1
Blood (serum)	3				3	3	3
Blood (plasma)	3				3	3	3
Urine	2				2	2	2
Saliva	3				NA	3	3
Hair	3				3	3	3
Nails	3				3	3	3
Adipose Tissue	2				NA	NA	NA
Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	1				NA	1	1
Teeth	3				NA	NA	3
Cord Blood	3	3	3	1	3	3	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	2	3	3
Blood (maternal)	3	1	1	1	3	3	3
Urine (maternal)	3	3	3	3	3	3	3
Hair (maternal)	3	3	3	3	3	3	3

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Relative Importance of Various Biological Matrices for Measuring Exposure During the Different Life Stages

Matrices	Adult preconception	Fetal			0-1 year	2-3 years	4-11 years
		1st	2nd	3rd			
Bioaccumulative Inorganic Chemicals							
Blood (whole)	1				1	1	1
Blood (serum)	3				3	3	3
Blood (plasma)	3				3	3	3
Urine	2				2	2	2
Saliva	3				NA	3	3
Hair	2				2	2	2
Nails	2				2	2	2
Adipose Tissue	3				NA	NA	NA
Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	3				NA	3	3
Teeth	3				NA	NA	2
Cord Blood	2	2	2	1	3	3	3
Meconium	3	2	2	2	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
Blood (maternal)	1	1	1	1	3	3	3
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Nonbioaccumulative Inorganic Chemicals							
Blood (whole)	3				3	3	3
Blood (serum)	3				3	3	3
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Urine	1				1	1	1
Saliva	3				NA	3	3
Hair	2				2	2	2
Nails	2				2	2	2
Adipose Tissue	3				NA	NA	NA
Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	3				NA	3	3
Teeth	3				NA	NA	3
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Relative Importance of Various Biological Matrices for Measuring Exposure During the Different Life Stages

Matrices	Adult preconception	Fetal			0-1 year	2-3 years	4-11 years
		1st	2nd	3rd			
Criteria Pollutants							
Blood (whole)	1				1	1	1
Blood (serum)	3				3	3	3
Blood (plasma)	3				3	3	3
Urine	3				3	3	3
Saliva	3				NA	3	3
Hair	3				3	3	3
Nails	3				3	3	3
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Feces	3				3	3	3
Semen	3				NA	NA	NA
Breath	1				NA	1	1
Teeth	3				NA	NA	3
Cord Blood	3	3	3	3	3	3	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
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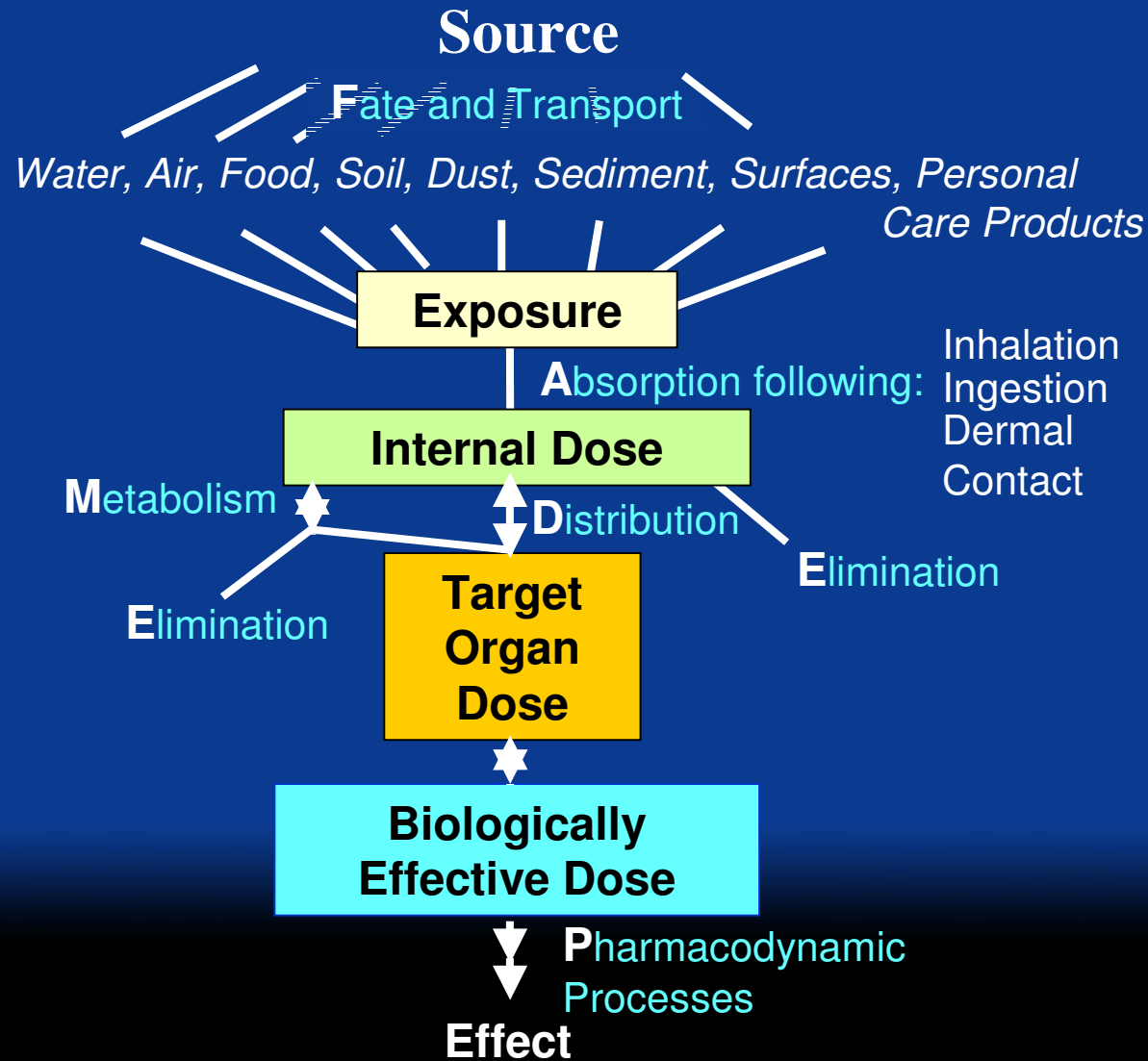
Strawman for Exposure Assessment to Various Chemical Classes for Longitudinal Studies

Again, exposure assessment should indicate "exposure status" at most susceptible period(s). If more than one susceptible period, exposure assessment should be done at least once per susceptible period.

All exposure assessments should include questionnaire (broadly defined) information.

- 1 Persistent Organic and Inorganic Chemicals
 - u Exposure "ceased": biomonitoring, one time
 - u Exposure continuing: biomonitoring, two times/susceptibility period
- 1 Nonpersistent, "Non- or Semi-Volatile" Organic Chemicals
 - u Form adducts: biomonitoring, two times/period
 - u Form specific metabolites but not adducts: biomonitoring, two times/period
 - u Form nonspecific metabolites but not adducts: needs work; biomonitoring and environmental monitoring; intraperson variability; multiple sampling/composite
- 1 Volatile Organic Chemicals
 - u Do not form adducts: personal air monitoring, two times/period
 - u Form Adducts: biomonitoring and personal air monitoring, two times/period
- 1 Nonbioaccumulative Inorganic Chemicals
 - u Biomonitoring, environmental monitoring (if not multimedia), two times/period
- 1 Criteria Pollutants
 - u Environmental monitoring, biomonitoring for carbon monoxide, two times/period or continuous monitoring data

Exposure-Effect Continuum for Environmental Chemicals: Longitudinal Study



Linkages Between Biologically Effective Dose and Effects

- 1 Acetylcholinesterase inhibition: lacks sensitivity
- 1 Chromosomal aberrations: lacks specificity
- 1 Markers of oxidative stress: lacks specificity
- 1 Biological signatures as defined by “omics” and other biological indicators
- 1 Data gap: specificity to targeted chemicals

Exposure-Effect Continuum for Environmental Chemicals: Longitudinal Study

