The background of the slide features a series of concentric circles in a light blue color, centered on a dark blue background. The circles are of varying diameters and are arranged in a way that they overlap, creating a ripple effect across the entire slide.

Pharmacovigilance of Prescription Drugs: Misuse, Abuse and Diversion in the RADARS[®] System

Richard C. Dart, MD, PhD

October 22, 2008

Outline

- What is the RADARS System?
 - Owned by Denver Health and Hospital Authority
 - Relationship to subscribers
 - RADARS System concepts
- Application of RADARS System Data
- Application of Prescription Monitoring Program Data

The background of the slide is dark blue with several concentric circles in a lighter blue color, creating a radar-like effect. A yellow rectangular border is centered on the slide, containing the text "RADARS®" and "SYSTEM" in yellow serif font.

RADARS[®] SYSTEM

What is the RADARS System?

- History of the RADARS System
 - Purdue Pharma, 2002
 - Transfer to Denver Health and Hospital Authority, 2006
 - Independent program
 - Public Safety Net hospital
 - Not for Profit
 - State sanctioned independent authority

What does the RADARS System Do?

- Gather data related to prescription drug misuse, abuse, and diversion
- Conduct research
- Publish research
- Sell data to subscribers

Relationship to Subscribers

- Provide surveillance data to pharmaceutical manufacturers for risk management activities
 - Quarterly reporting – brand or drug specific
 - In-depth custom analyses for specific issues
 - Data may be used only for risk management

Product Specificity

RADARS System Opioid Drugs

Hydrocodone

Oxycodone

Morphine

Fentanyl

Methadone

Hydromorphone

Buprenorphine

Oxymorphone

Tramadol

Scientific Advisory Board

- Consult with RADARS System staff
 - Oversee research
 - Recommend new research
 - Review manuscripts
- Consult with subscribers
 - Anticipate issues regarding misuse, abuse or diversion of their product.

Scientific Advisory Board

Substance Abuse Experts

- Herbert D. Kleber, MD
Columbia University
- Sidney Schnoll, MD, PhD
Pinney Associates
- Edward Senay, MD
University of Chicago
- George E. Woody, MD
University of Pennsylvania

Law Enforcement

- John Burke
National Association of Drug Diversion Investigators

Prescription Monitoring Programs

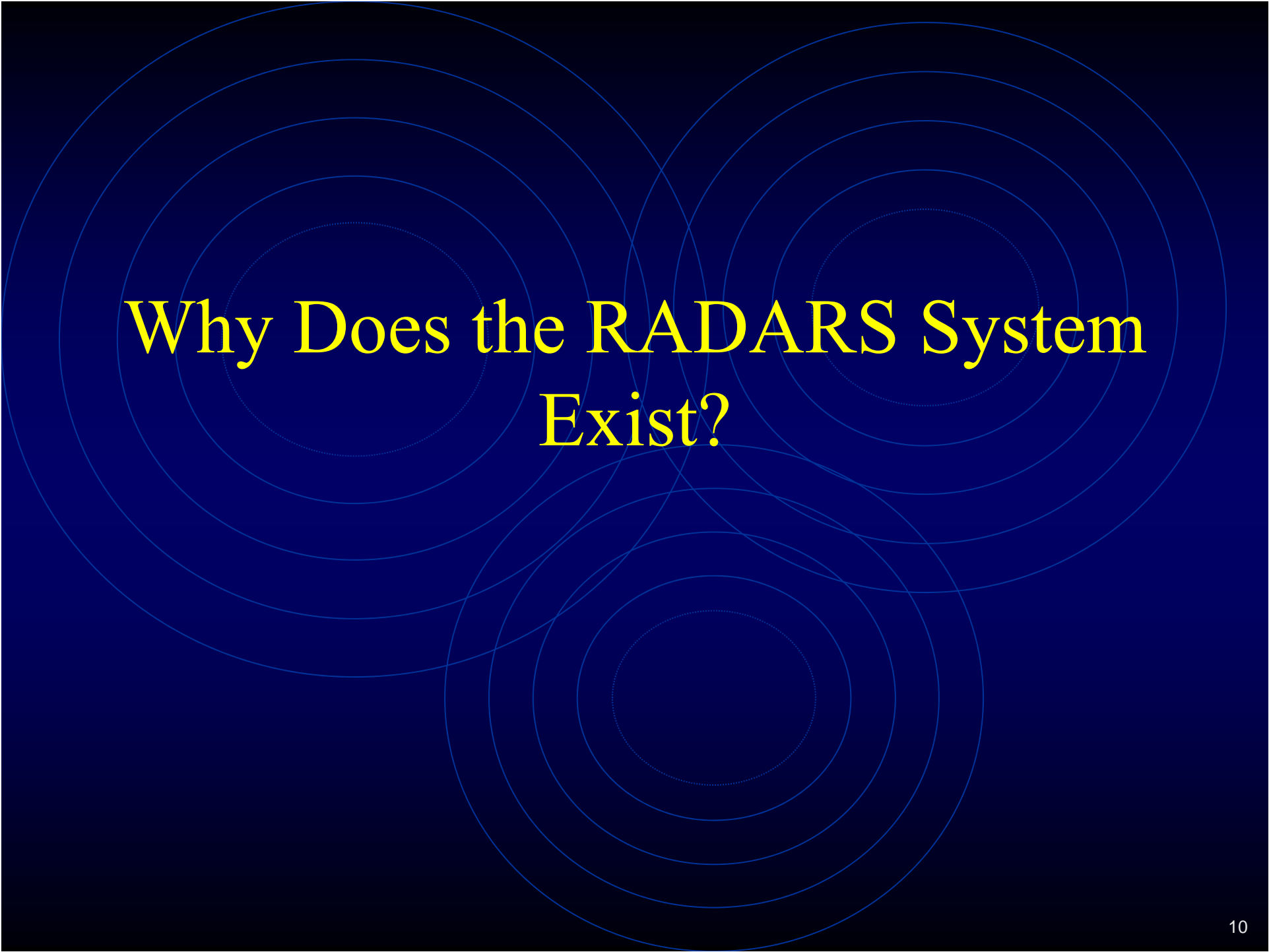
- Danna Droz, RPh, JD
Ohio State Board of Pharmacy

Epidemiologists/Biostatisticians

- Edgar Adams, ScD
Covance
- Alvaro Muñoz, PhD
Johns Hopkins University

Principal Investigators

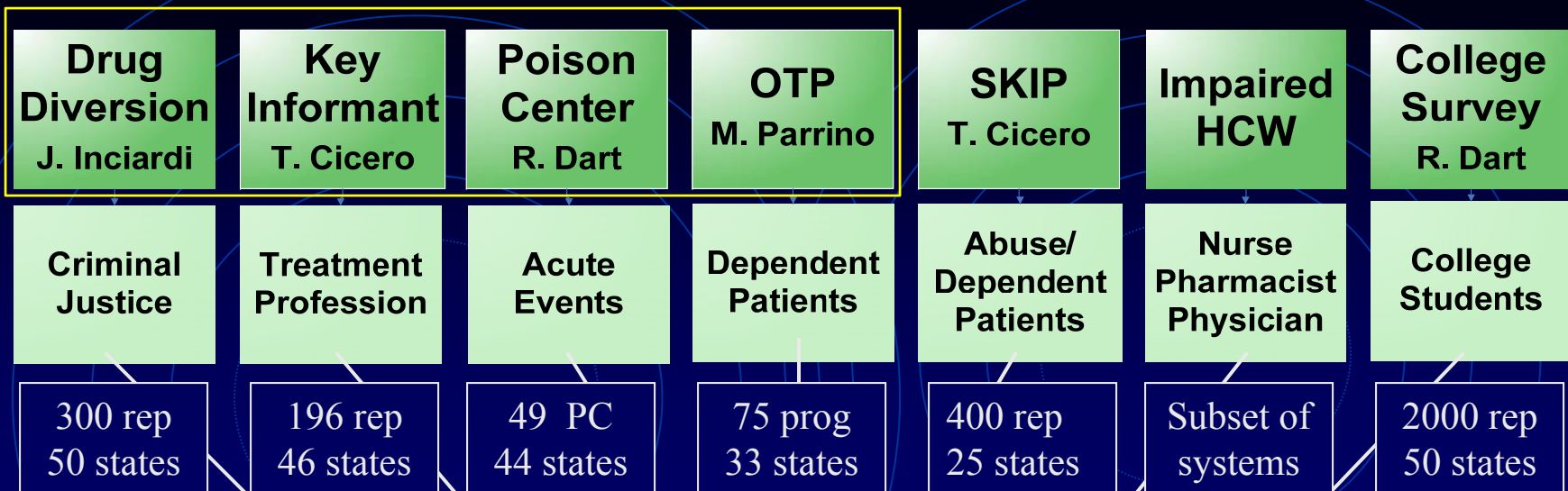
- Theodore J. Cicero, PhD
Washington University at St. Louis
- Richard C. Dart, MD, PhD
Denver Health and Hospital Authority
- James A. Inciardi, PhD
University of Delaware
- Mark W. Parrino, MPA
American Assoc. for the Treatment of Opioid Dependence



Why Does the RADARS System Exist?

Surveillance of Prescription Medication Misuse, Abuse and Diversion

Prescription drug abuse
can't be measured by
traditional adverse event systems
such as DAWN, NSDUH, MTF



Prescription Medication Issues

- Hidden events & motives
- Indications
- Formulations

RADARS System Process

Adding the Denominator

**Drug
Diversion**

**Key
Informant**

**Poison
Center**

**Opioid Tx
Programs**

SKIP

**Impaired
HCW**

**College
Survey**

Numerators compiled by each signal detection system

Two Denominators:

- 1. Population and**
- 2. Unique Recipients of Dispensed Drug (URDD)**

RADARS System Organization

Drug
Diversion

Key
Informant

Poison
Center

Opioid Tx
Programs

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Impaired
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Survey

Numerators compiled by each signal detection system

Two Denominators:
1. Population and
2. Unique Recipients of Dispensed Drug (URDD)

RADARS System calculation of rates

Review by Scientific Advisory Board

RADARS System Organization

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Diversion

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Numerators compiled by each signal detection system

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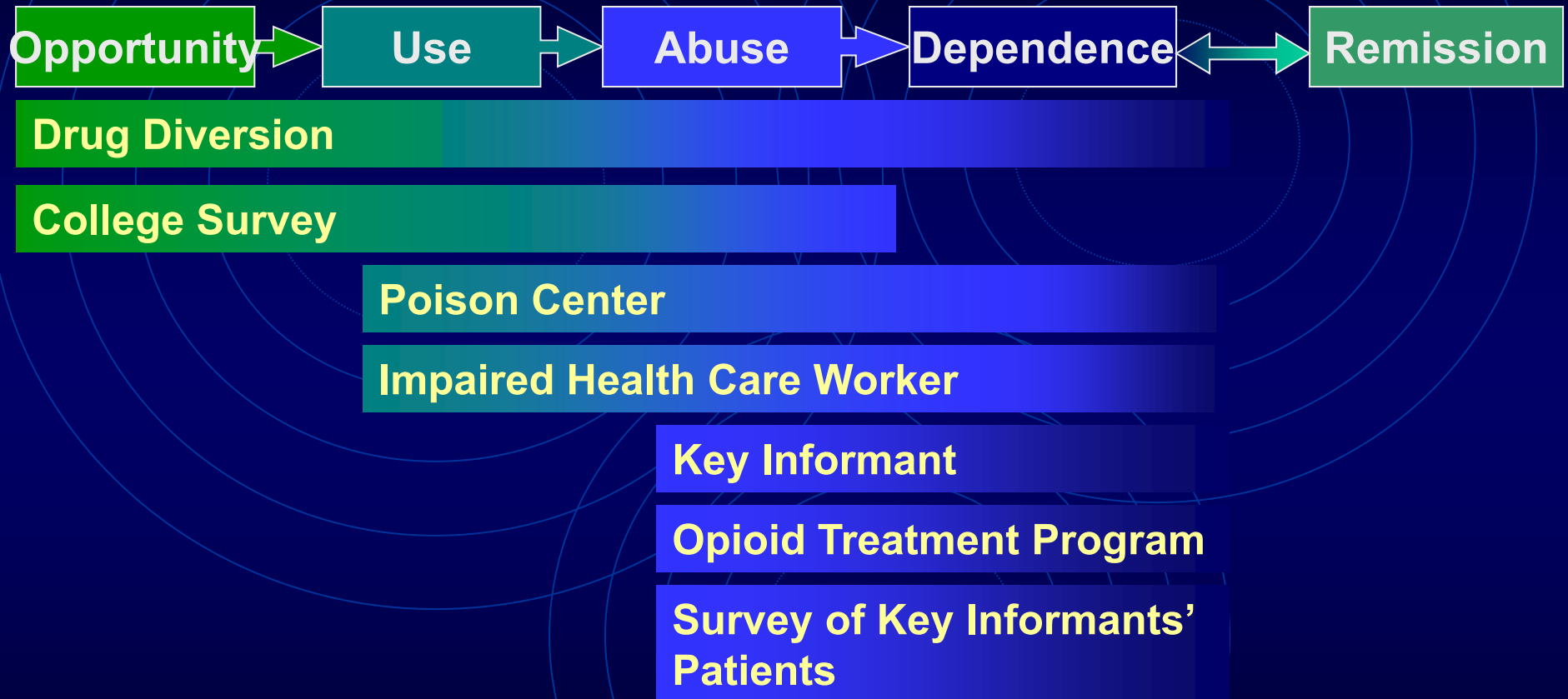
RADARS System calculation of rates

Review by Scientific Advisory Board

Reports sent to subscribers
Quarterly, Annual, Special Issue

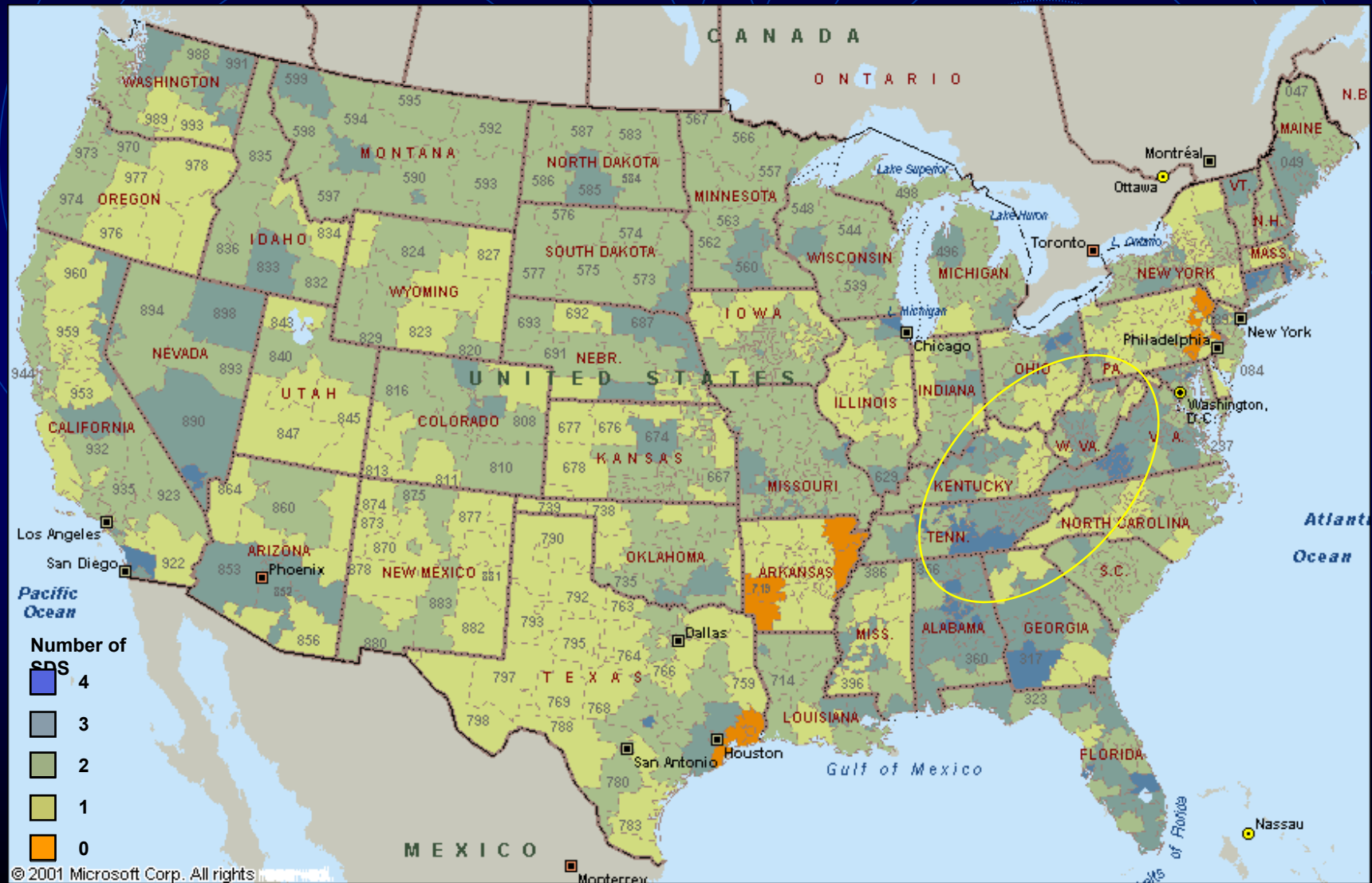
Results are submitted for publication (17)

Drug Dependence Pathway

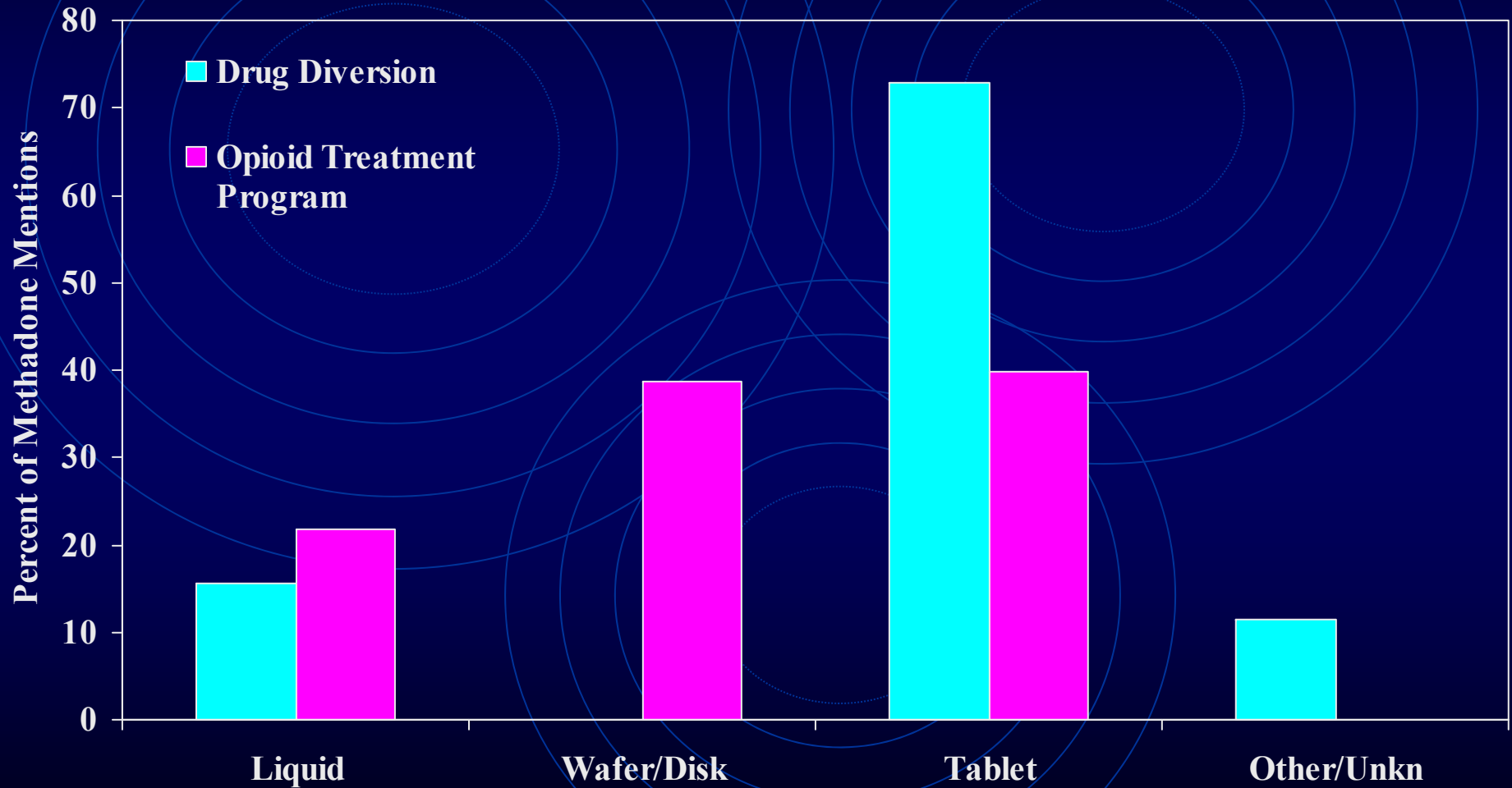


Source: Chilcoat HD, Johanson CE. Vulnerability to Cocaine Abuse. Higgins ST, Ed. *Cocaine Abuse: Behavior, Pharmacology, and Clinical Applications*. San Diego, CA: Academic Press; 1998: 313-341.
Institute of Medicine – Committee on Opportunities in Drug Abuse Research. *Pathways of Addiction*. Washington, DC: National Academy Press; 1996.

RADARS System, Signal Detection Systems by 3 Digit ZIP Code, Q3 2008

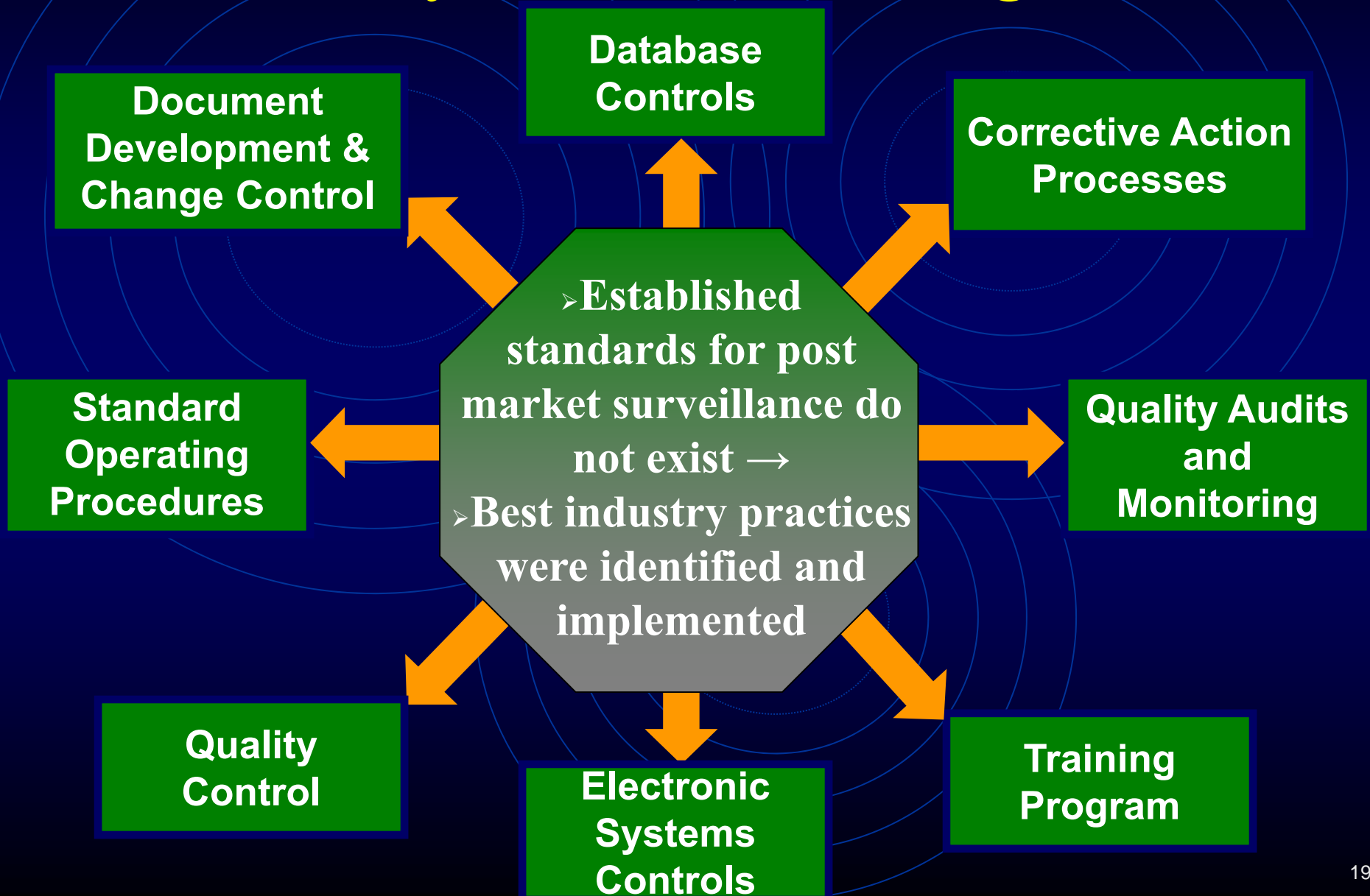


Methadone Formulations



Drug Diversion, 2003-2007; Opioid Treatment Program, 2005-2007

Quality Assurance Program





Application of RADARS System

Standard Reports

Issue Analysis

Standard Report

CONFIDENTIAL
RADARS® System
1st Quarter 2008 [REDACTED] Report
[REDACTED] Data

1. RADARS® System Report

SIGNAL DETECTION Drug Diversion Signal Detection System

CONFIDENTIAL
RADARS® System
1st Quarter 2008 – [REDACTED] Report
[REDACTED] Data

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Buprenorphine

Sample Signal Site and Associated Rates 1st Quarter 2008

City, State*	3 Digit ZIP Code	Signal System	20072	20073	20074	20081
New Bedford, MA	027	DD	13.6	0	20.4	20.4
		KI	No Data	No Data	No Data	No Data
		PC	0.2	0.2	0.2	0.6
		OTP	No Data	0.2	0.4	0.2

* Largest city identified in given 3-digit ZIP code.

DD = Drug Diversion; signal threshold = ≥ 5 Cases per 100,000 Population/Quarter

KI = Key Informant; signal threshold = ≥ 5 Cases per 100,000 Population/Quarter

PC = Poison Center; signal threshold = ≥ 2 Cases per 100,000 Population/Quarter

OTP = Opioid Treatment Program; signal threshold = ≥ 2 Cases per 100,000 Population/Quarter

Methadone

Sample Signal Site and Associated Rates 1st Quarter 2008

City, State*	3 Digit ZIP Code	Signal System	20072	20073	20074	20081
Warwick, RI	028	DD	0	6.2	6.2	3.1
		KI	0	0	No Data	No Data
		PC	0.3	0	0.3	0.2
		OTP	No Data	No Data	0	0.2

* Largest city identified in given 3-digit ZIP code.

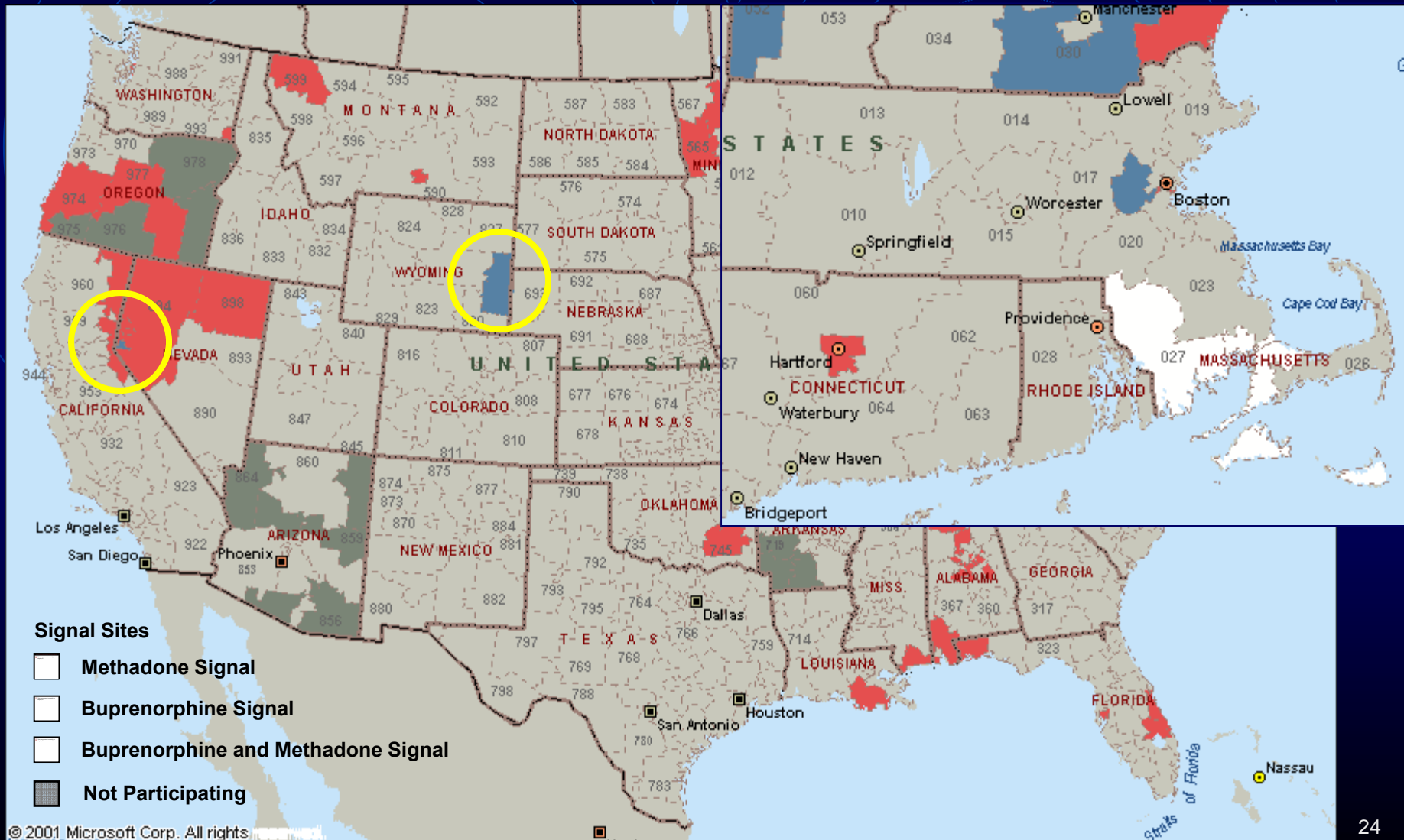
DD = Drug Diversion; signal threshold = ≥ 5 Cases per 100,000 Population/Quarter

KI = Key Informant; signal threshold = ≥ 5 Cases per 100,000 Population/Quarter

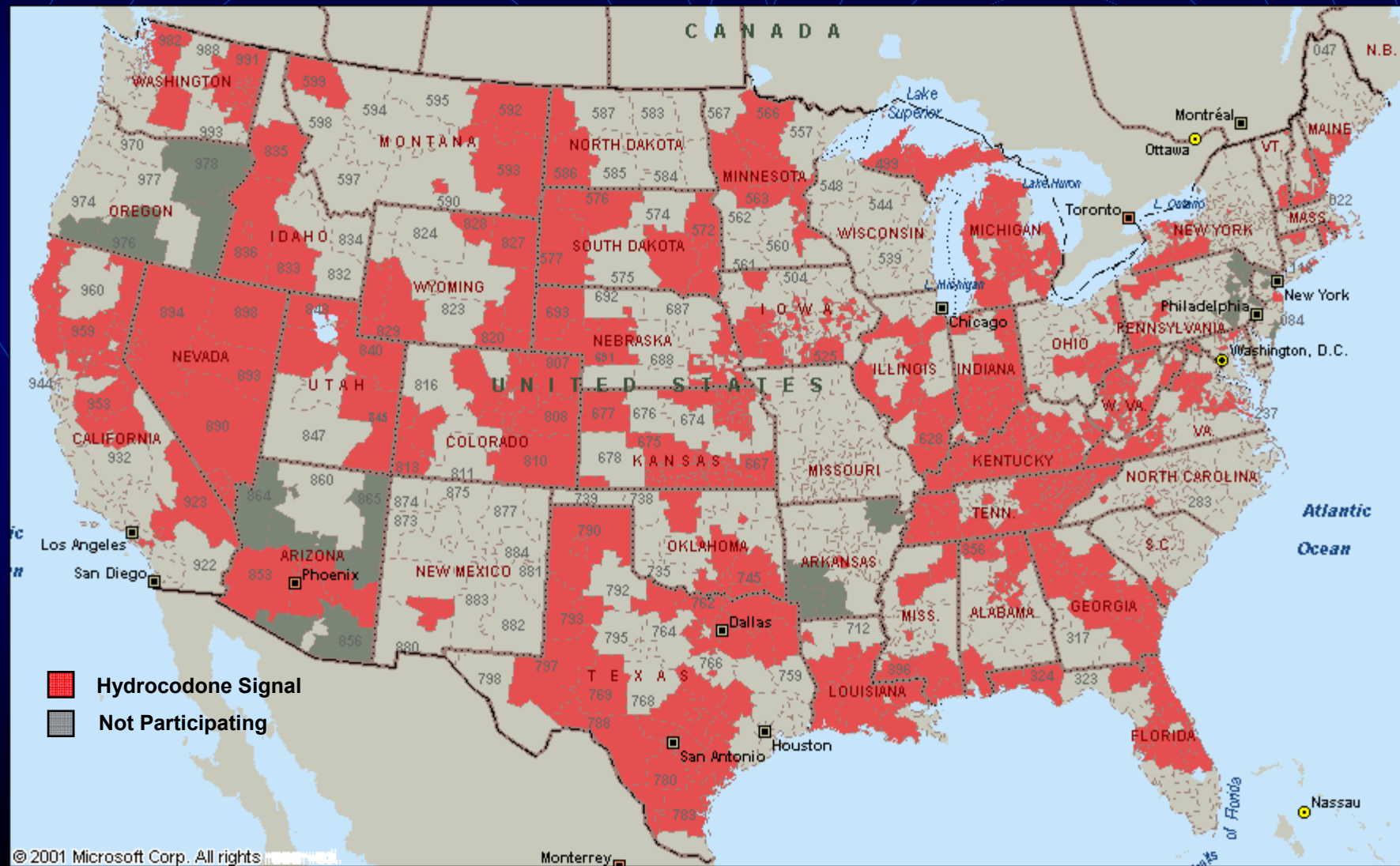
PC = Poison Center; signal threshold = ≥ 2 Cases per 100,000 Population/Quarter

OTP = Opioid Treatment Program; signal threshold = ≥ 2 Cases per 100,000 Population/Quarter

Buprenorphine and Methadone Signal Sites, All SDS, Q1 2008



Hydrocodone Signal Sites, All Signal Detection Systems, Q1 2008



Issue Evaluation

System-Wide Studies

- Intervention Analysis
- Product, Formulation, or Drug Class Comparisons
- Geographic Analyses
- Analysis of Trends Over Time

Drug Diversion

- Rapid Assessment Studies
- Characterization of Drug Using Populations
- Focus Group & Individual Interview
- Street Prices of Diverted Drugs
- Diversion of Drugs with Limited Abuse Liability
- Route of Exposure Studies

Opioid Treatment Program & SKIP

- Demographics
- Drug Source
- Injection Use
- Pain as a Reason for Seeking Treatment

Key Informant

- Profile of Key Informants

Poison Center

- Demographics
- Pediatric Exposures
- Associated Medical Outcomes
- Root Cause Analyses
- Route of Exposure
- Product Dose
- Polysubstance
- Product Identification Calls

College Survey

- Demographics
- Drug Source
- Reason for Non-Medical Use
- Frequency of Non-Medical Use
- Illicit Drug Use
- Route of Non-Medical Use

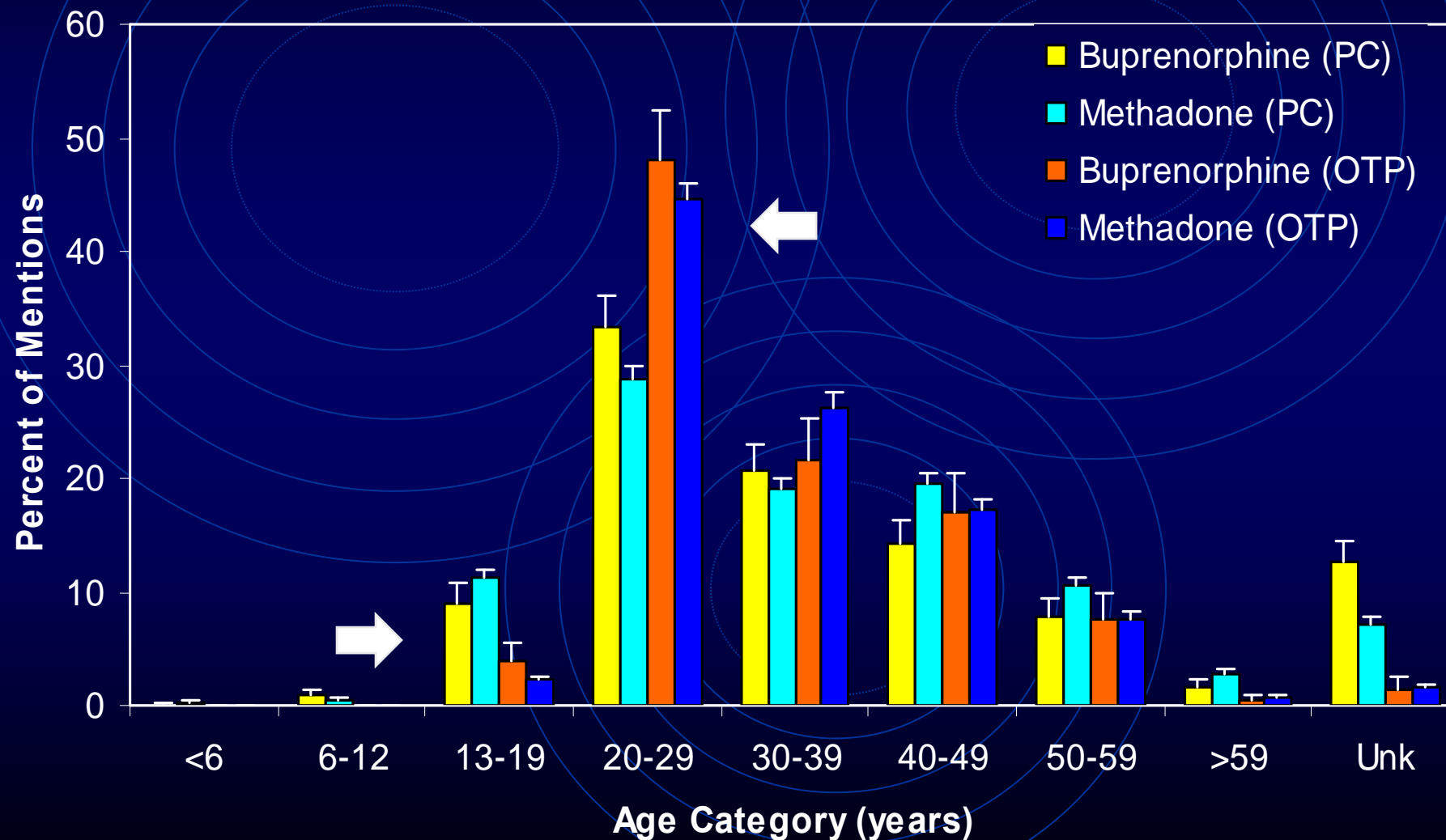
Impaired Health Care Worker

- Health Care Worker Discipline
- As a subset of other systems, studies include those listed for the other systems

Issue Evaluation

- “In order to design interventions, we need more detail about who, what and where our drug is misused, abused or diverted...”
- Potential actions
 - Phased launch
 - Limited marketing
 - Future clinical trial site selection

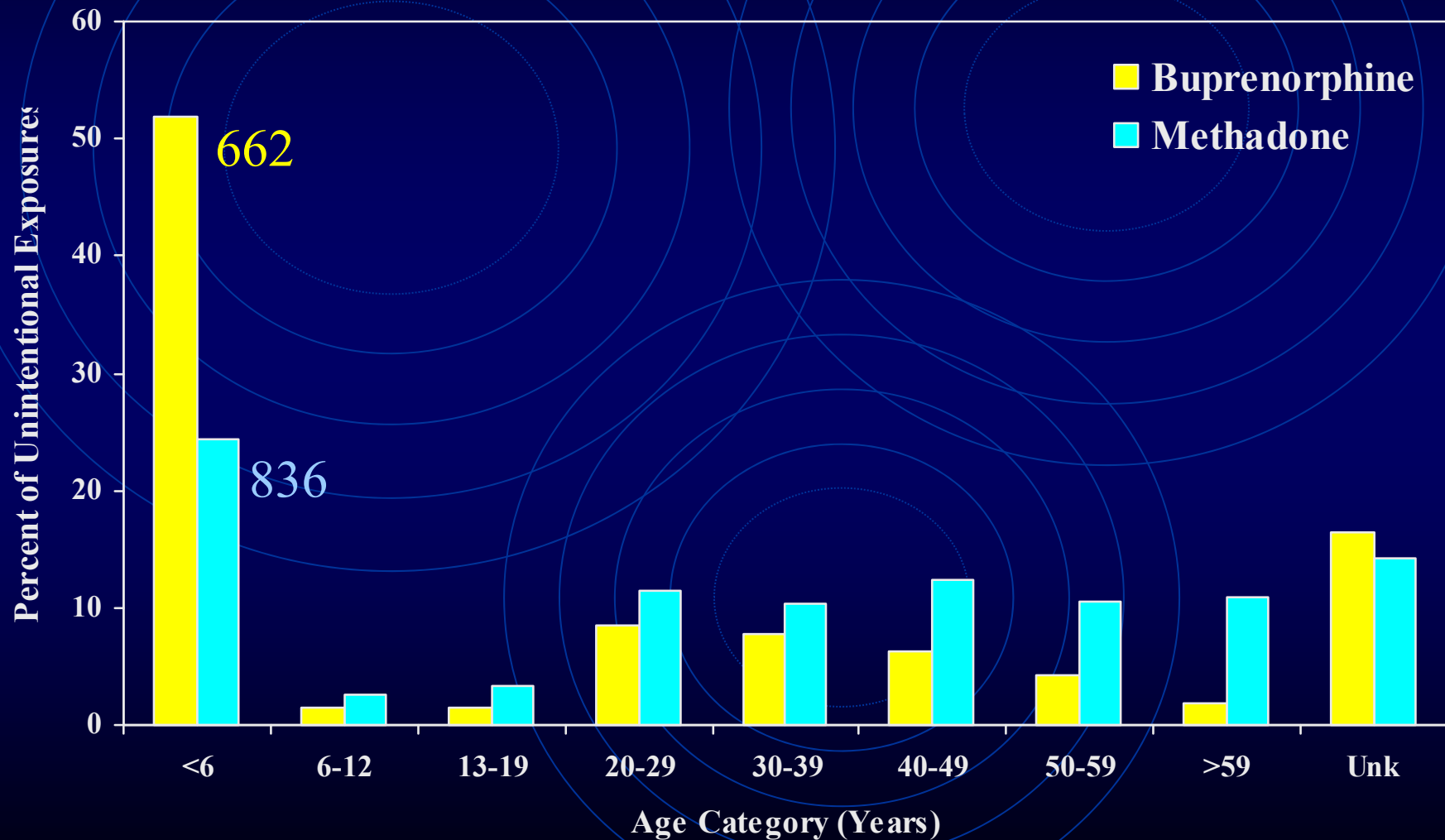
Poison Center and Opioid Treatment Program Data by Age Category



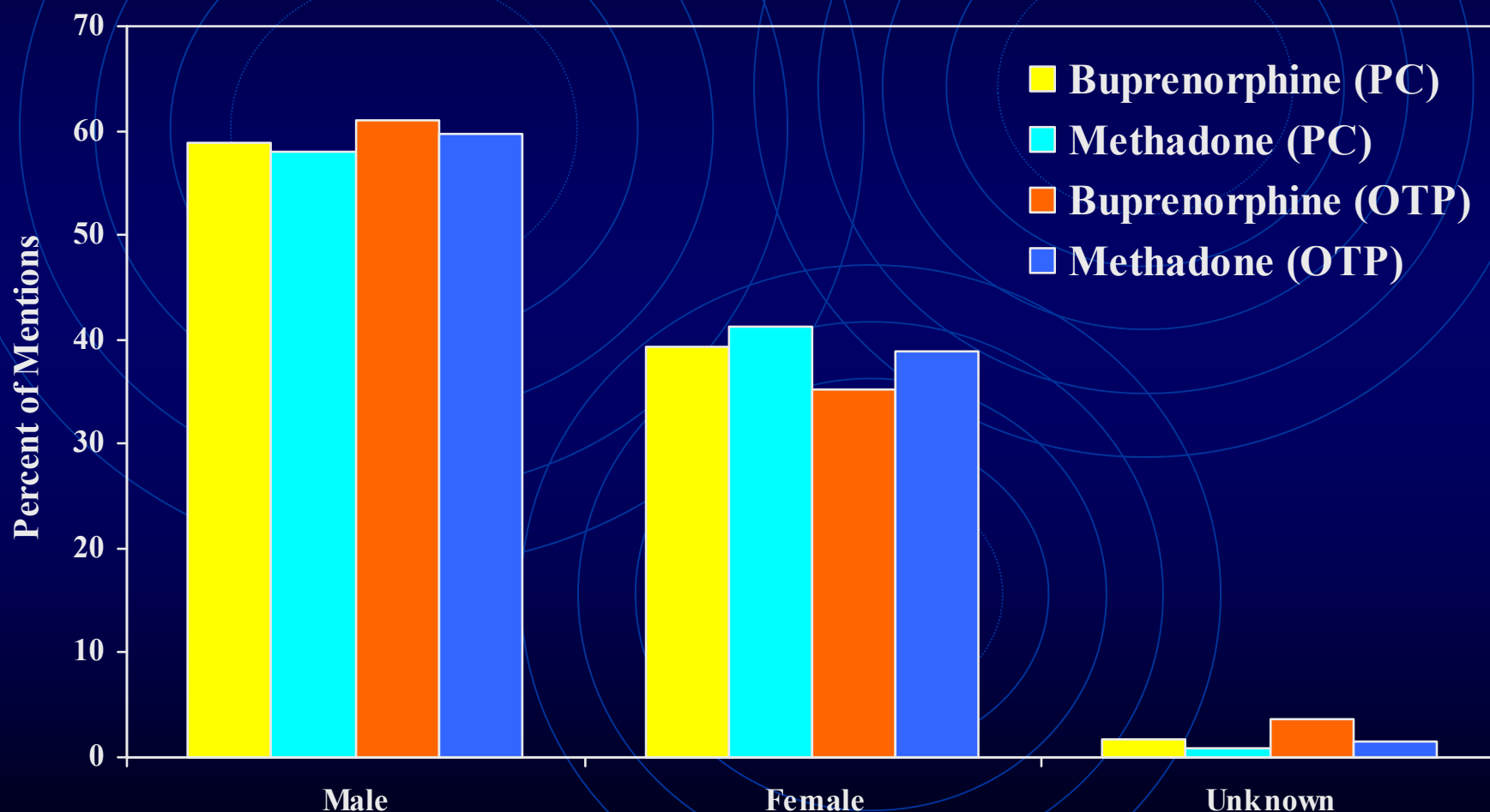
Poison Center: Intentional Exposures, 2003-2007; Opioid Treatment Program: 2005-2007

Issue Evaluation – Pediatrics

Poison Center Unintentional Exposures, 2003 – 2007



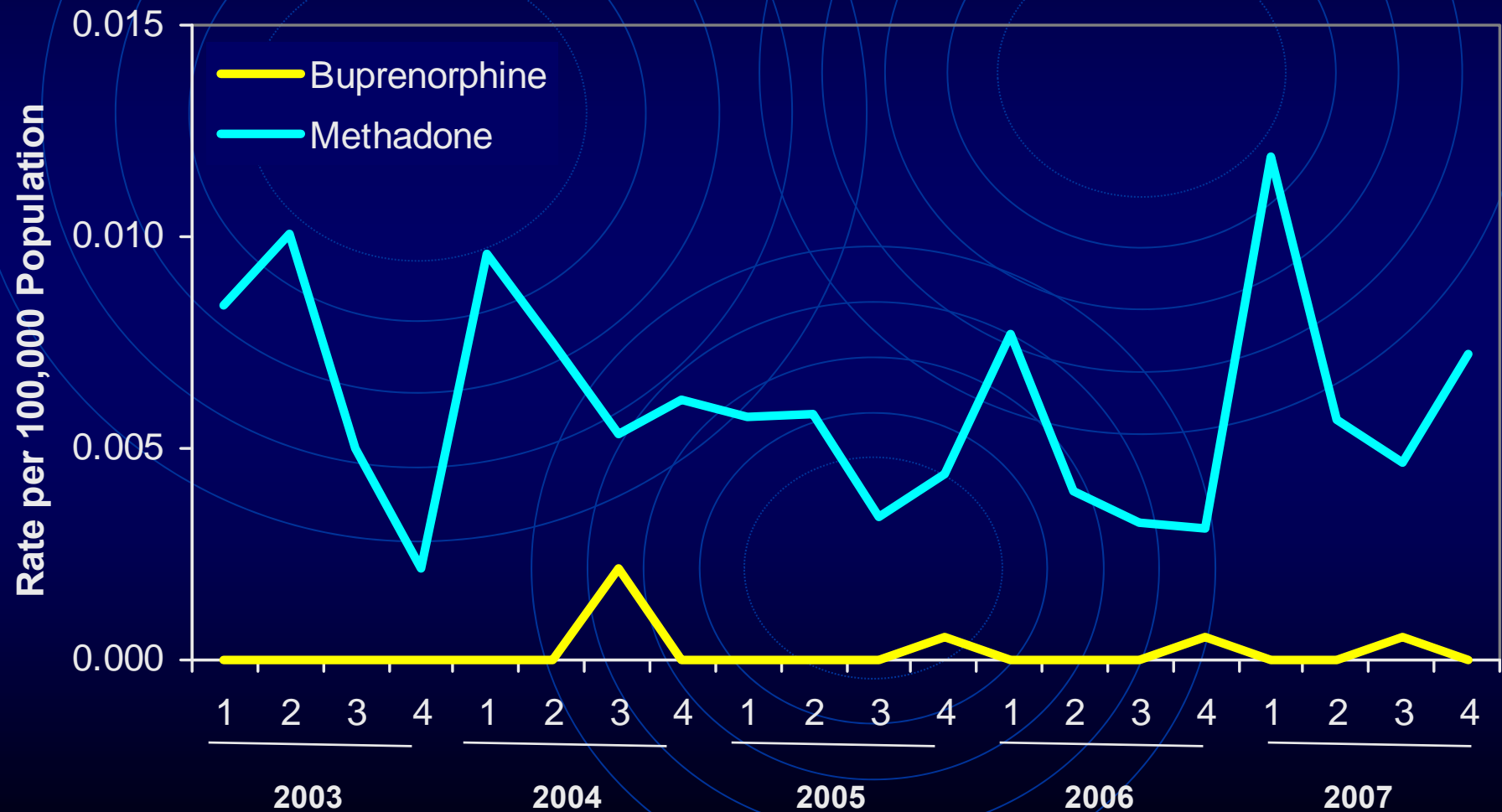
Poison Center and Opioid Treatment Program Data by Gender



Issue Analysis

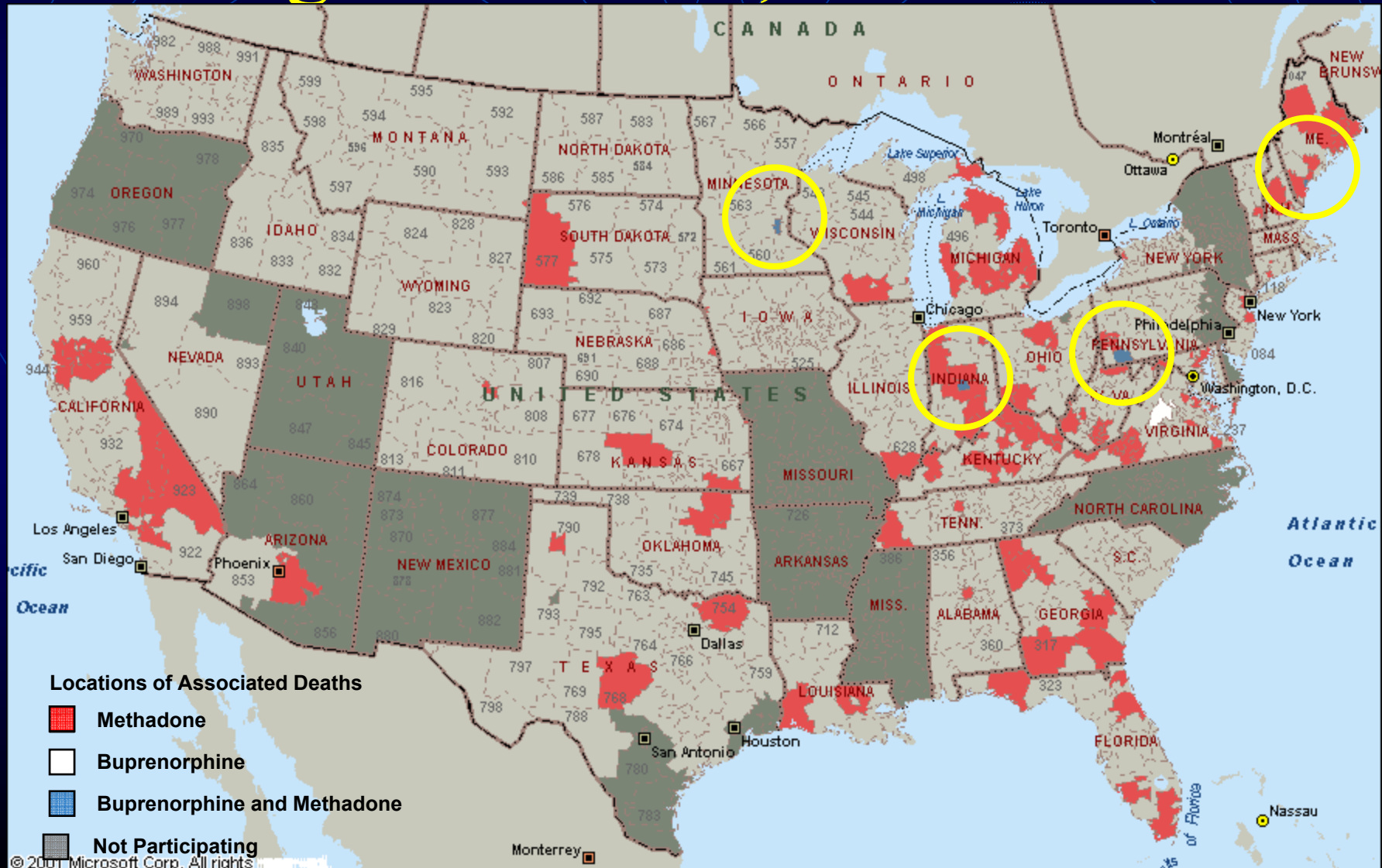
- “We need to understand deaths caused by our product’s drug class”
 - Poison center signal detection system provides indicator of associated deaths and root cause analysis

Poison Center Associated Death Rates 2003 – 2007



Poison Center Associated Deaths

3-Digit ZIP Code, 2003 – 2007



Limitations

Not measuring prevalence

- Complete case detection not required for surveillance
- Incomplete coverage / convenience sample
 - System expansion plans, statistical extrapolation
 - Good established understanding of sampling frame
- Complex system requires user familiarity
 - Interpretations by SAB
 - Training sessions available for subscribers, federal agencies

Future Directions

- Monitor additional medications
- Abuse deterrent formulations
- Change method for determining signals
- Explore new groups for study



Application of Prescription Monitoring Program Data

Possible Applications

- Scientific Publications
 - PMP data are invaluable
 - Help reinforce value of PMP data nationwide
- Development of Signal Detection System
- Combination of both above
- Others?

Scientific Publications: Possible Research Questions

- States with PMPs have higher overall prescription opioid abuse rates but decreasing prescription opioid abuse rates over time relative to states without PMPs
 - Comparing nationwide PMP status to RADARS System data and NSDUH data

Scientific Publications: Possible Research Questions

- How should an “abuser” be defined using PMP data?
 - Rx from ≥ 20 prescribers AND ≥ 16 pharmacies??
 - Also referred to as “doctor shoppers”
- What is the proportion of “abusers” by drug?

Data from OH, 10/1/2006 – 6/30/2008

Drug	Abusers (N)	Total Patients (N)	Abusers (%)
Tramadol	1,176	537,092	0.22
Carisoprodol	346	58,886	0.59
Hydrocodone	1,538	2,383,503	0.06
Pentazocine	85	8,259	1.03
Oxycodone	1,497	1,150,755	0.13
Alprazolam	618	438,420	0.14
Propoxyphene	962	744,426	0.13

Data from OH, 10/1/2006 – 6/30/2008

Drug	Abusers (N)	Total Abusers (N)	Abusers (%)
Tramadol	1,176	1,554	75.68
Carisoprodol	346	1,554	22.27
Hydrocodone	1,538	1,554	98.97
Pentazocine	85	1,554	5.47
Oxycodone	1,497	1,554	96.33
Alprazolam	618	1,554	39.77
Propoxyphene	962	1,554	61.90

Scientific Publications: Possible Research Questions

- How many “abusers” are obtaining quantities that suggest abuse or diversion?
 - 639 total days in the 7 quarter time period
 - > 639 days of supply Rx from ≥ 20 prescribers AND ≥ 16 pharmacies is highly suggestive of diversion

Data from OH, 10/1/2006 – 6/30/2008

Drug	Abusers w/ > 639 d supply (N)	Abusers (N)	Abusers w/ > 639 d supply (%)
Tramadol	92	1,176	7.82
Carisoprodol	32	346	9.25
Hydrocodone	155	1,538	10.08
Pentazocine	0	85	0
Oxycodone	223	1,497	14.90
Alprazolam	83	618	13.43
Propoxyphene	10	962	1.04

RADARS System Contacts

Elise Bailey, MSPH

RADARS System Manager

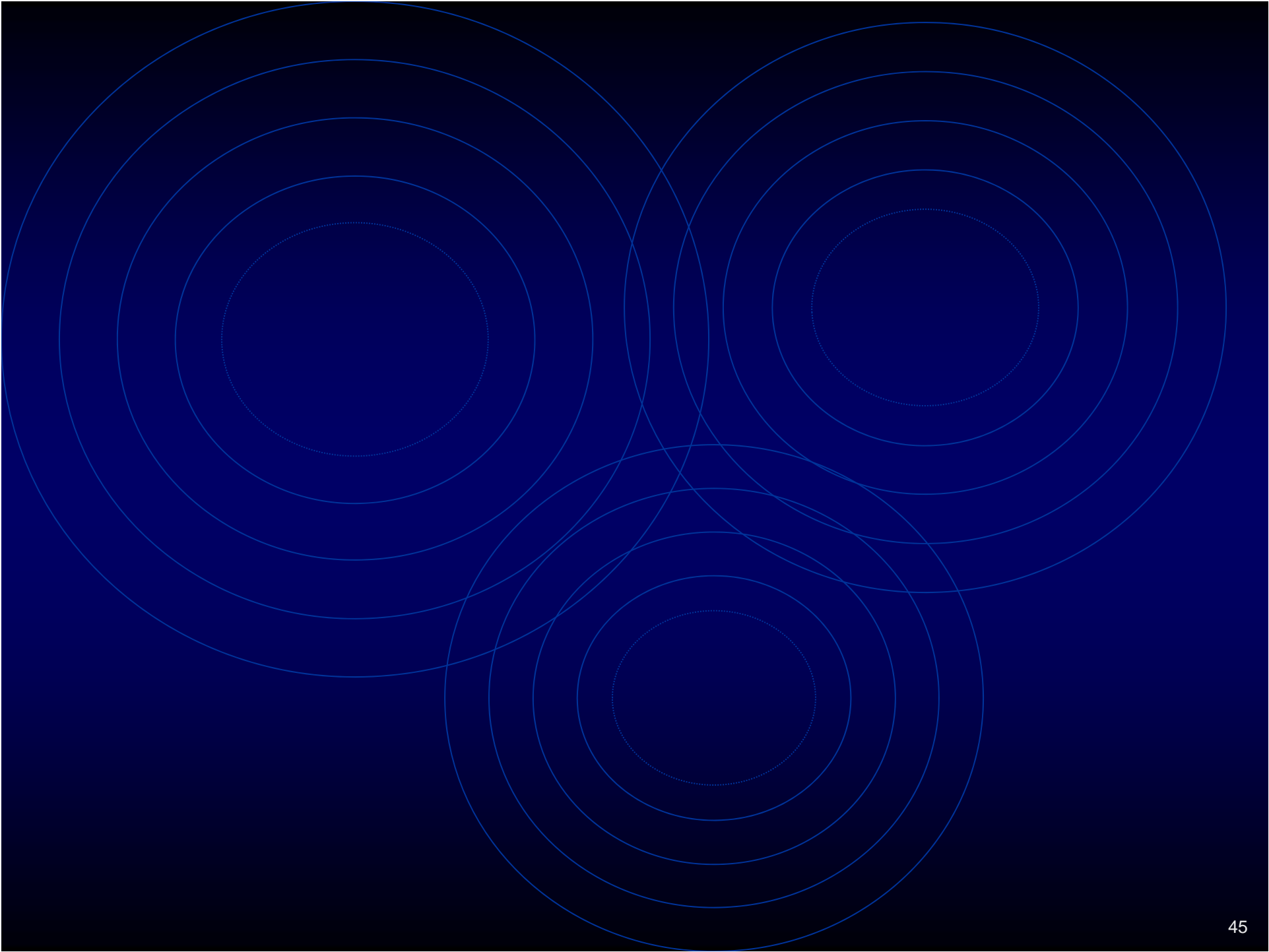
(303) 739-1297

Elise.Bailey@rmpdc.org

Richard C. Dart, MD, PhD

RADARS System Executive Director

Richard.Dart@rmpdc.org



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RADARS System 2009 Annual Meeting

*Thursday, April 23, 2009
Bethesda, Maryland*

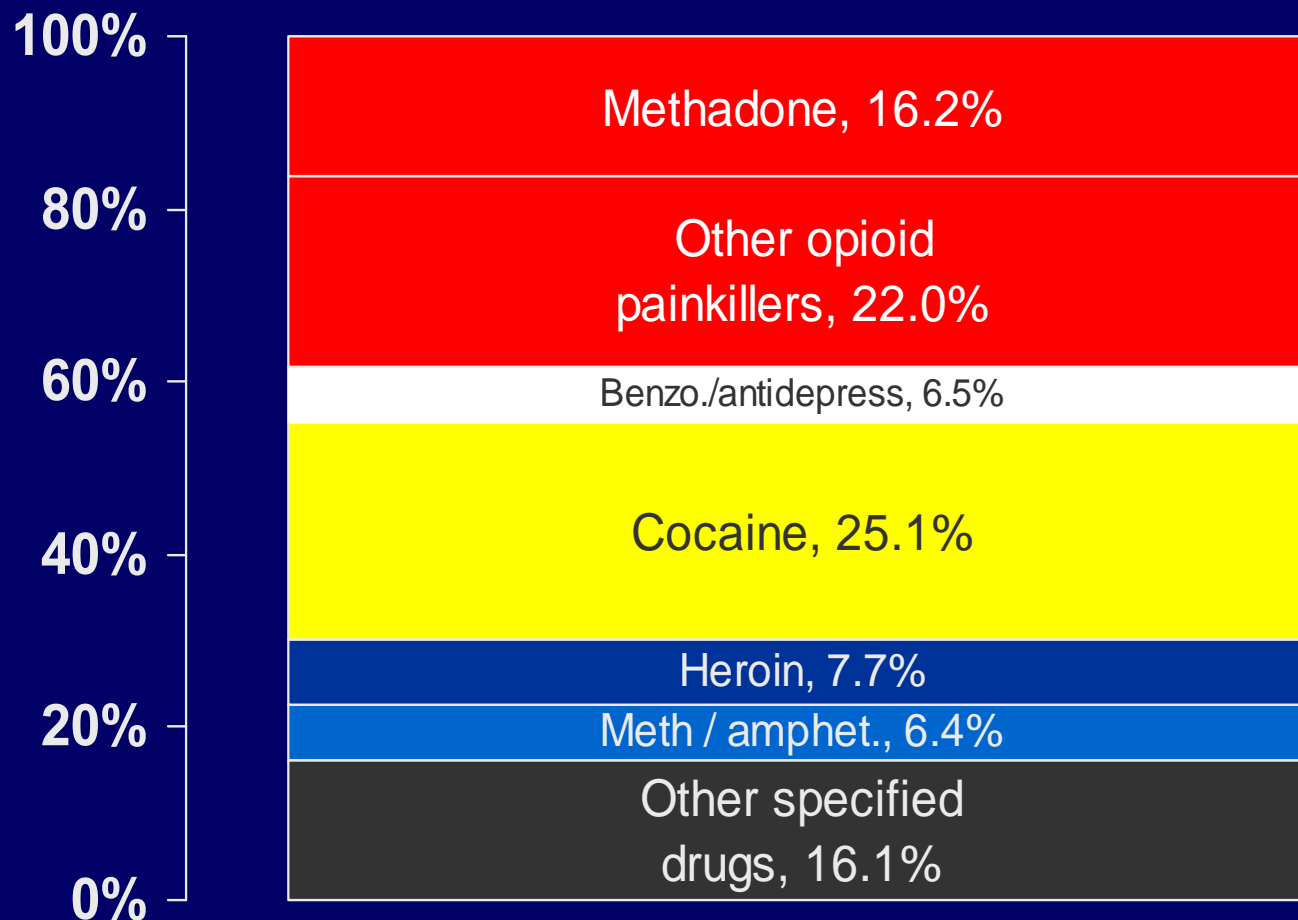
Possible Applications

- Scientific Publications
 - PMP data are invaluable
 - Help reinforce value of PMP data nationwide
- Development of Signal Detection System
- Combination of both above
- Others?

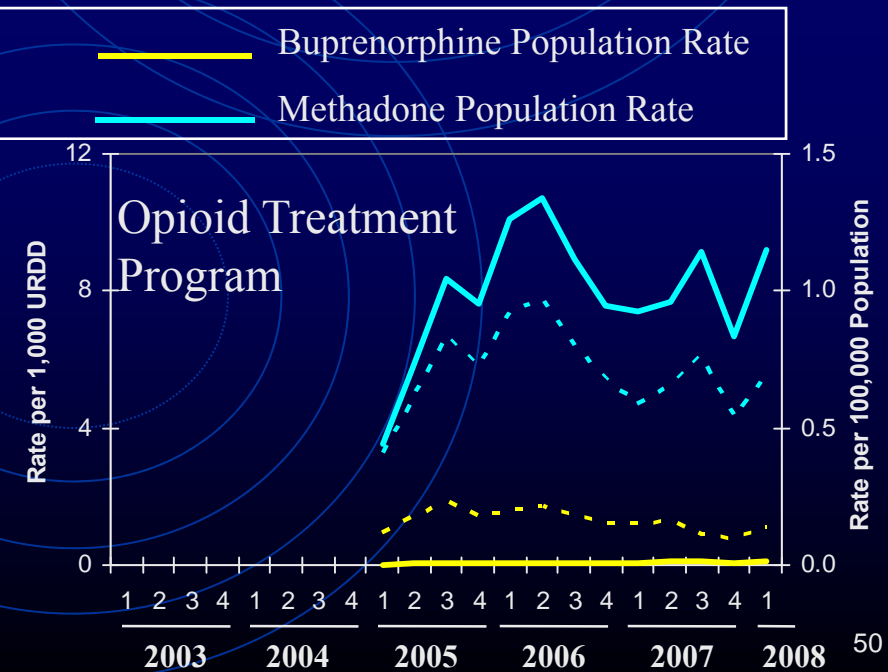
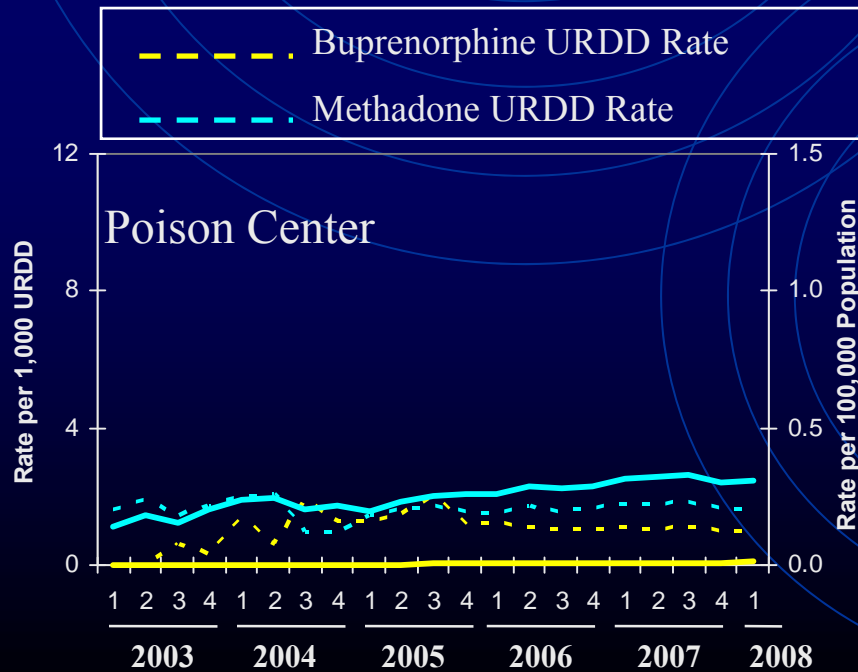
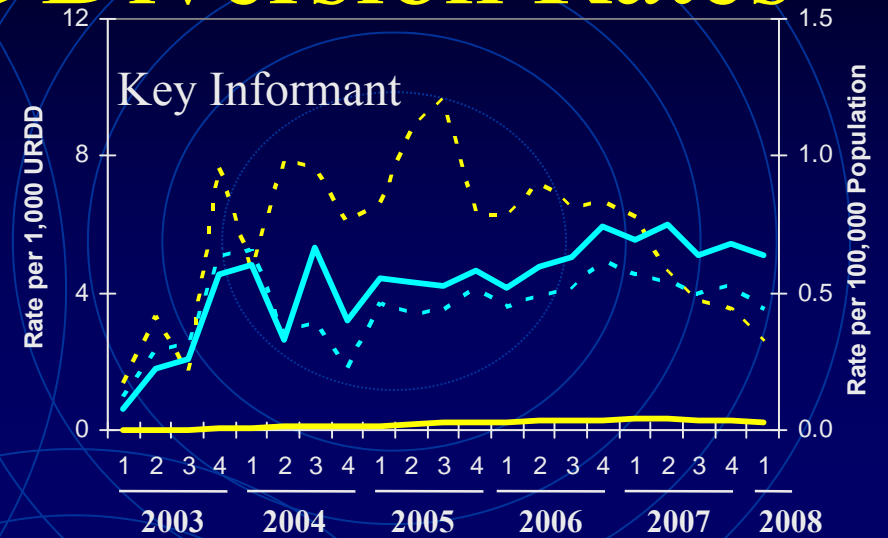
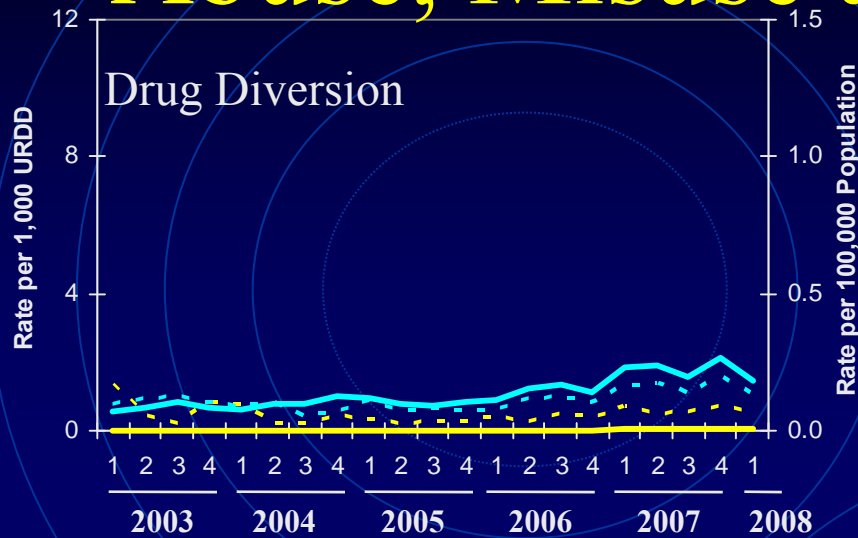
Tale of Two Denominators

- Population
 - Tried and true - Disease burden on whole population
 - Does not account for drug availability
- Unique Recipients of Dispensed Drug (URDD)
 - Number of unique people filling prescription for drug
 - Accounts for availability of drug in community
 - Relates events to corresponding patient benefit
 - Alternatives – weight of drug, number of Rx

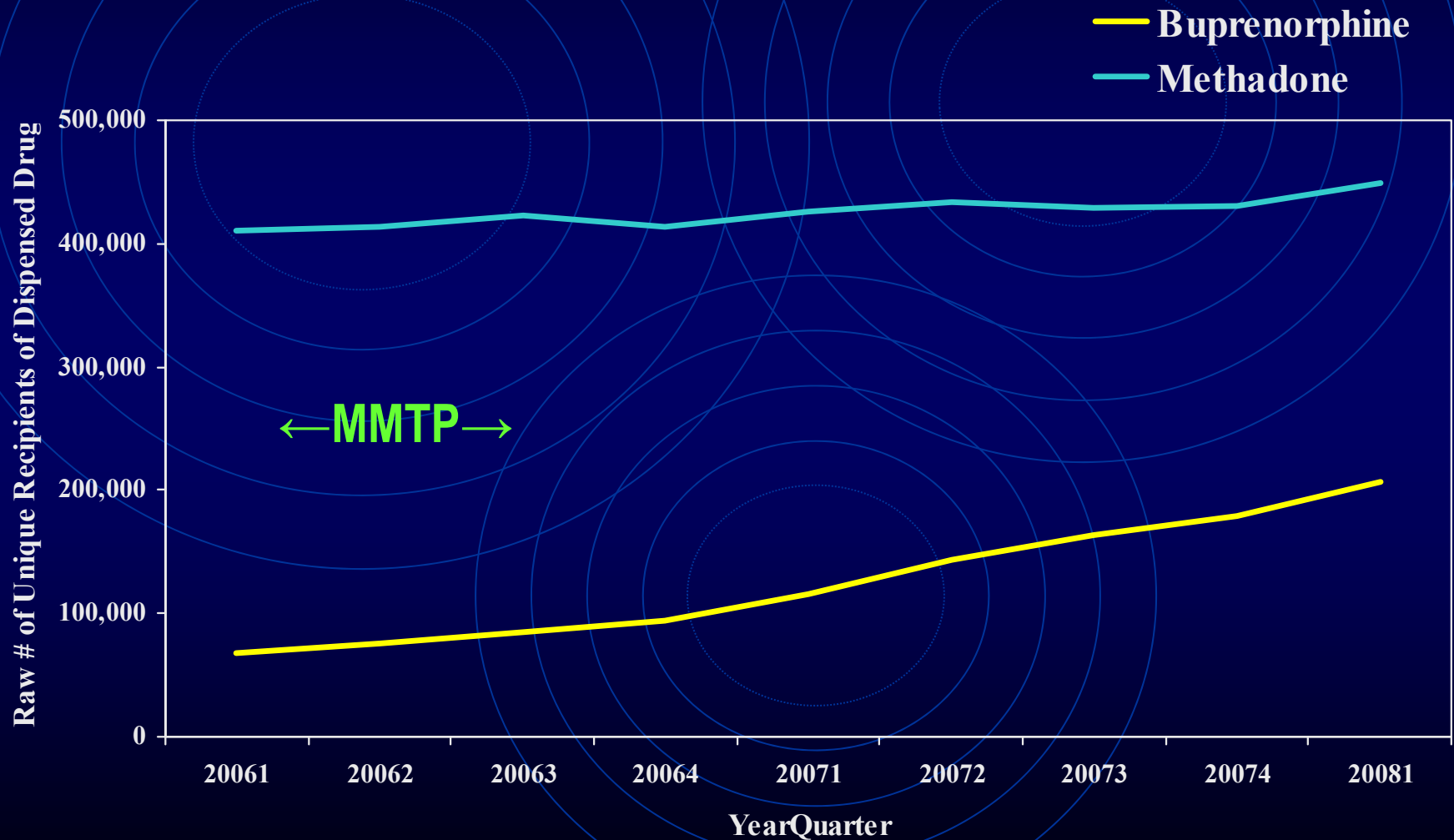
Example of Issue Evaluation Buprenorphine and Methadone



Abuse, Misuse and Diversion Rates

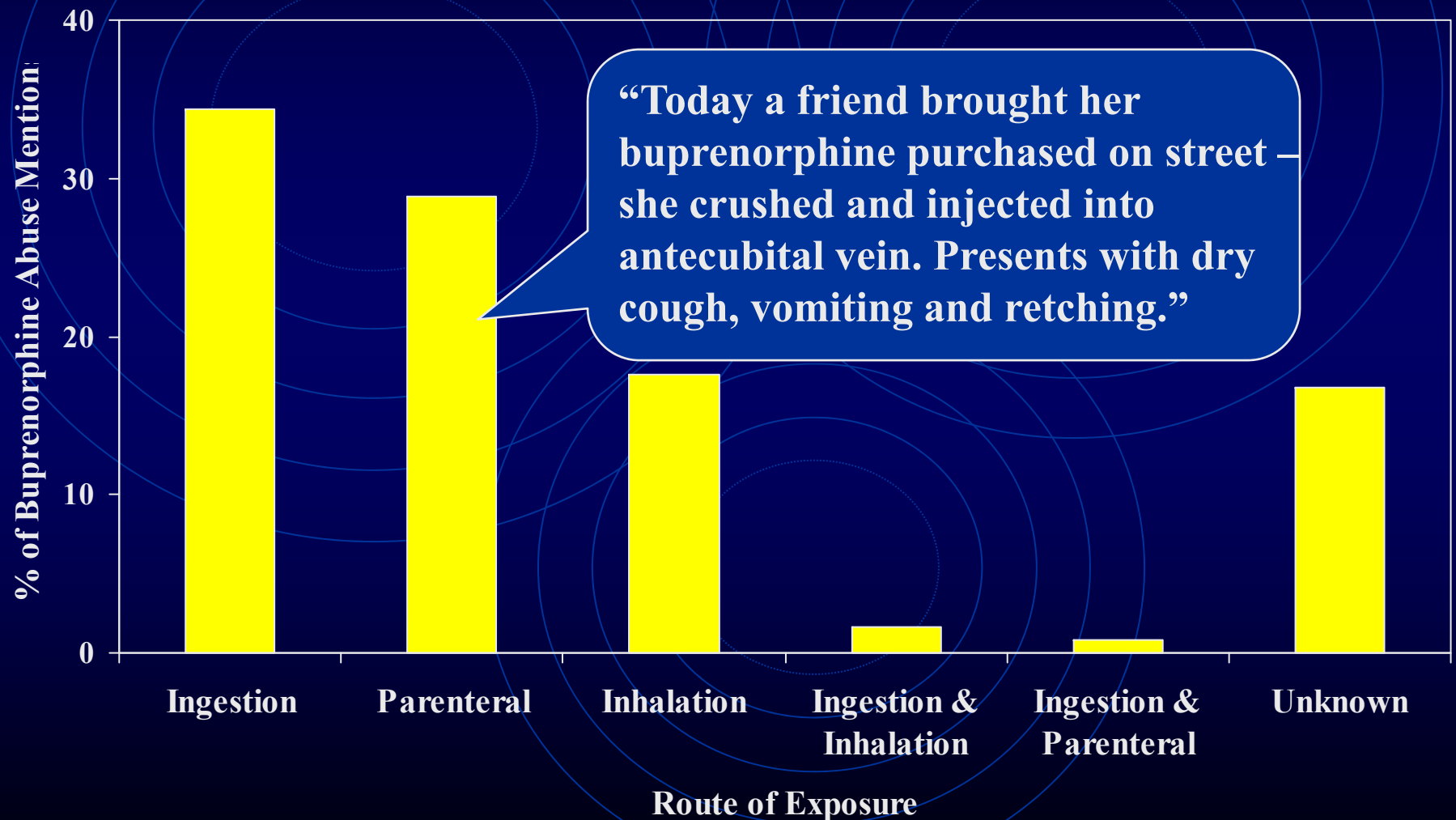


Buprenorphine and Methadone Use in United States

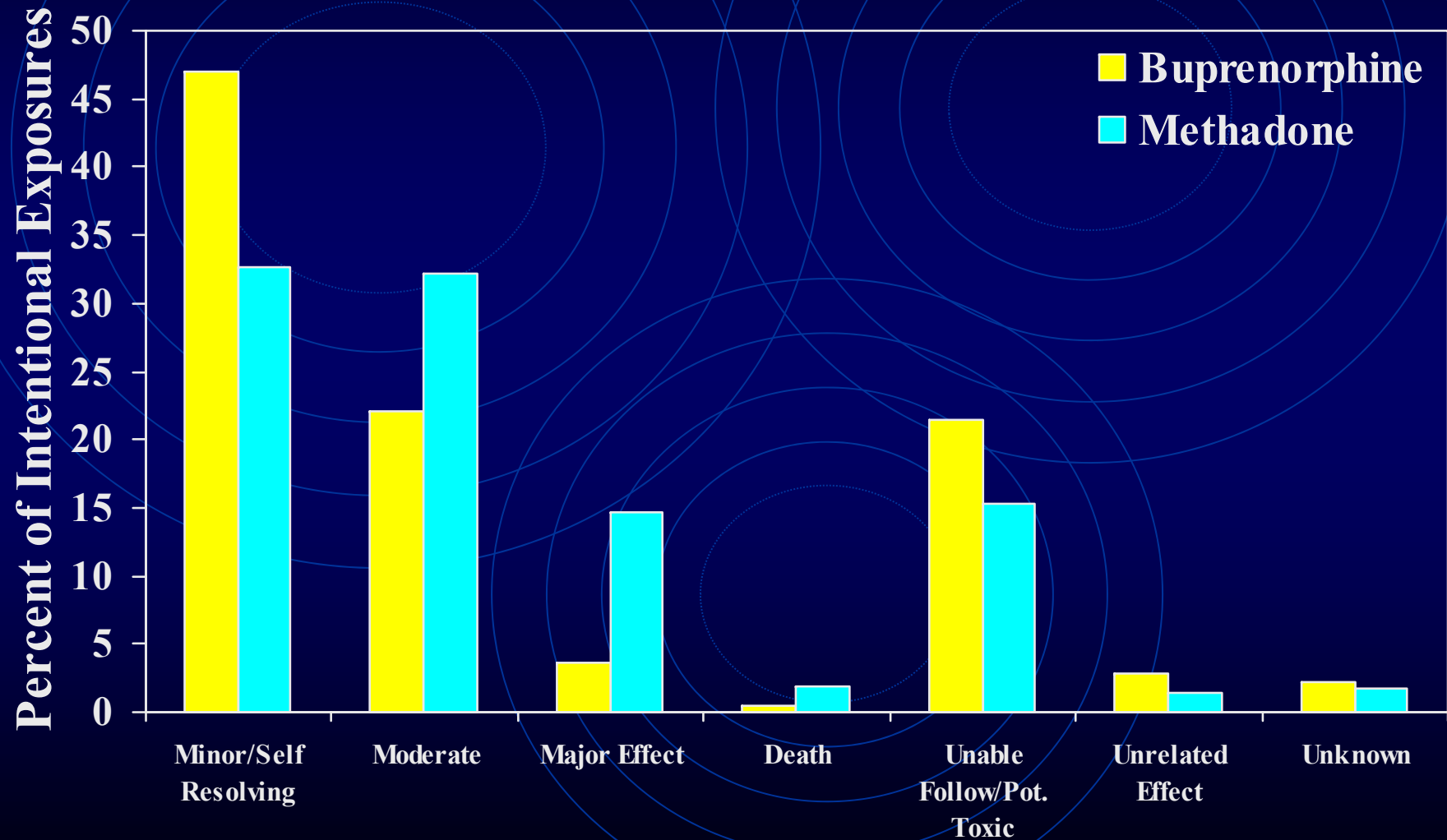


URDD data - Verispan LLC; SAMHSA, National Survey of Substance Abuse Treatment Services, 2006

Poison Center Buprenorphine Abuse Cases, Route of Exposure, 2003 – 6/2007



Poison Center Intentional Exposures by Associated Medical Outcome, 2003–2007



Limitations

- Handling of missing data/unspecified
 - Does not affect substance-specific rates
 - Additional methods being explored
- System does not benefit of drugs directly
 - URDD approximates benefit-risk
- External validity not established
 - Good concordance with parallel federal studies (NSDUH, DAWN, vital statistics)
 - Additional analyses in progress
- Signal detection

Scientific Publications: Possible Research Questions

- What is the proportion of “abusers” by drug?
 - Rx from ≥ 20 prescribers AND ≥ 16 pharmacies
 - Also referred to as “Doctor Shoppers”