Highlights

- From 2003 to 2008, the national estimated number of methadone items reported in NFLIS more than doubled from 4,967 items to 10,459 items ($p < 0.05$), while buprenorphine increased more than 250-fold from 21 items to 5,627 items ($p < 0.05$).

- Significant increases in methadone items were reported between 2003 and 2008 in the West, Midwest, and South ($p < 0.05$). Reporting of methadone items increased 221% in the West, more than 100% in both the Midwest and South, and 38% in the Northeast.

- Significant increases in buprenorphine items were reported in the Northeast and South between 2003 and 2008 ($p < 0.05$). Reporting of buprenorphine items increased 155-fold in the Northeast and 539-fold in the South.

- In 2008, compared to other U.S. counties, high relative concentrations of methadone seizures occurred in counties in Eastern Kentucky; Northern Georgia and Western North Carolina; Southern Georgia and Northern Florida; the east coast of Maine; and Northern Michigan. In the Northwestern United States, higher relative percentages were reported in counties in Eastern Oregon, Western Montana, and parts of Utah.
**Introduction**

The National Forensic Laboratory Information System (NFLIS) is a Drug Enforcement Administration (DEA), Office of Diversion Control program that collects drug identification results and associated information from drug cases analyzed by federal, state, and local forensic laboratories. These laboratories analyze substances secured in law enforcement operations.

This NFLIS Special Report presents findings on methadone and buprenorphine, two synthetic opioid analgesics. Use of narcotic analgesics for pain management and opioid treatment programs continues to increase in the United States, which has contributed to increases in opioid-related overdoses and fatalities. The abuse of pain relievers is now comparable to more prominent illicit drugs such as marijuana. For example, the 2008 National Survey on Drug Use and Health (NSDUH) reported that the nonmedical use of prescription-type pain relievers by first-time users in the past year was equal to first-time users of marijuana (2.2 million).\(^1\)

In the mid-1960s, methadone was introduced as maintenance treatment for heroin addicts. In the 1990s, physicians began prescribing methadone for pain management. While pain relief from a dose of methadone lasts about 4 to 8 hours, methadone’s duration of action is from 8 to 59 hours. Users of methadone may feel the need for more pain relief before it is gone from the body. Toxic levels of methadone also may build up if it is taken too often, if the amount taken is too high, or if it is taken with certain medicines or supplements.\(^2\)

Buprenorphine, which is available in different formulations to treat pain or heroin addiction, is 20 to 30 times more potent than morphine as an analgesic. Buprenorphine, like methadone, is also used for opioid-dependence therapy.

This NFLIS Special Report presents findings on methadone and buprenorphine drug items reported to NFLIS between 2003 and 2008. National and regional estimates for methadone and buprenorphine are presented along with state- and county-level results. Information also is presented from DEA’s System To Retrieve Information from Drug Evidence II (STRIDE), DEA’s Automation of Reports and Consolidated Orders System (ARCOS), IMS Health’s National Prescription Audit Plus Retail database, Drug Abuse Warning Network (DAWN) emergency department data, and the Centers for Disease Control and Prevention (CDC) medical examiner data on opioid-related deaths.

**National and Regional Estimates**

This section presents national and regional estimates for methadone and buprenorphine items analyzed by state and local forensic laboratories from 2003 to 2008. National and regional trends also are presented. The methods used in preparing these estimates are described in Appendix A.

According to NFLIS, during 2008 nearly 1.8 million drug items were analyzed by state and local laboratories in the United States. Methadone represented 10,459 items and buprenorphine represented 5,627 items, each accounting for less than 1 percent of the overall drug caseload. However, from 2003 to 2008, the estimated number of methadone and buprenorphine items analyzed by state and local laboratories increased significantly (\(p < 0.05\)). Methadone more than doubled from 4,967 items in 2003 to 10,459 items in 2008, while buprenorphine increased more than 250-fold from 21 items in 2003 to 5,627 items in 2008 (Table 1 and Figure 1).

Significant increases in the number of methadone items were reported in the West, Midwest, and South between 2003 and 2008 (\(p < 0.05\)). In the West, the estimated number of methadone items increased 221% from 546 items in 2003 to 1,753 items in 2008 (Figure 2). Methadone increased more than 100% in both the Midwest (from 859 to 1,756 items) and South (2,036 to 4,840 items) and 38% in the Northeast (from 1,526 items to 2,110 items). Between 2007 and 2008, however, reports of methadone remained relatively stable in all regions.

Buprenorphine items increased significantly in the Northeast and South between 2003 and 2008 (\(p < 0.05\)). In the Northeast, the number of estimated buprenorphine items increased 155-fold from 17 items in 2003 to 2,631 items in 2008 (Figure 3). In the South, reports of buprenorphine increased 539-fold from 4 to 2,156 items during this same period. From 2007 to 2008, the number of reported buprenorphine items increased significantly in the Northeast and the South, with increases of more than 50% in the Northeast (1,746 to 2,631 items) and more than 100% in the South (917 to 2,156 items).

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Table 1

<table>
<thead>
<tr>
<th>TOTAL</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>National</td>
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<td>7,303</td>
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<td>546</td>
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<td>1,074</td>
<td>1,280</td>
<td>1,611</td>
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<td>Midwest</td>
<td>7,970</td>
<td>859</td>
<td>1,038</td>
<td>1,037</td>
<td>1,624</td>
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<td>Northeast</td>
<td>12,200</td>
<td>1,526</td>
<td>1,988</td>
<td>1,847</td>
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<td>2,241</td>
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<tr>
<td>South</td>
<td>22,073</td>
<td>2,036</td>
<td>2,569</td>
<td>3,345</td>
<td>4,431</td>
<td>4,852</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National</td>
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<td>21</td>
<td>262</td>
<td>540</td>
<td>1,809</td>
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<td>West</td>
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<td>*</td>
<td>540</td>
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<tr>
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<td>127</td>
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<tr>
<td>Northeast</td>
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<td>17</td>
<td>244</td>
<td>427</td>
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<tr>
<td>South</td>
<td>3,514</td>
<td>4</td>
<td>10</td>
<td>61</td>
<td>366</td>
<td>917</td>
</tr>
</tbody>
</table>

*The estimate does not meet standards of precision and reliability. See Appendix A for a description of the methodology.

Note: Numbers may not sum to totals due to suppression and rounding.

Figure 1. NFLIS national trend estimates for methadone and buprenorphine, by year, 2003–2008.

Figure 2. NFLIS regional trend estimates for methadone, by year, 2003–2008.

Figure 3. NFLIS regional trend estimates for buprenorphine, by year, 2003–2008.*

*A dashed trend line indicates that the trend estimate does not meet standards of precision and reliability. See Appendix A for a description of the methodology.
The DEA’s System to Retrieve Information from Drug Evidence II (STRIDE) collects the results of drug evidence analyzed at DEA laboratories across the country. STRIDE reflects evidence submitted by the DEA, other federal law enforcement agencies, and some local police agencies that was obtained during drug seizures, undercover drug buys, and other activities. STRIDE captures data on both domestic and international drug cases; however, the following results describe only those drugs obtained in the United States.

During 2008, a total of 51,022 drug exhibits or items were reported in STRIDE, about 3% of the estimated 1.8 million drug items analyzed by state and local laboratories during this period. In STRIDE, methadone and buprenorphine each represented less than 1% of total drug items reported in 2008. The number of methadone items reported in STRIDE increased from 97 items in 2003 to 159 in 2006, then fell to 130 in 2007 and rose to 165 in 2008. Buprenorphine items increased from 8 items in 2003 to 53 items in 2008.

### Toxic Exposures and Fatalities

According to medical examiner data obtained from death certificates compiled by the Centers for Disease Control and Prevention’s National Center for Health Statistics (CDC/NCHS), methadone-related deaths steadily increased from 2001 to 2006 (a 272% total increase).3 This was substantially higher than any other drug specifically reported on in the CDC’s National Vital Statistics System (NVSS) (Figure 4). In 2006, methadone deaths (5,416) accounted for 15% of all reported poisoning deaths (37,286), as well as 39% of all opioid analgesic poisoning deaths (13,755). CDC defined a methadone-related death as one in which methadone caused or contributed to the death. For 2006, 84% of methadone deaths were reported as unintentional poisonings, 5% as suicides, and less than 1% as homicides. Information on buprenorphine-related deaths are included in “other synthetic narcotics” and are not tracked specifically in the NVSS.

DAWN began tracking emergency department (ED) visits for the nonmedical use of methadone in 2004. From 2004 to 2006, methadone ED visits increased 23% (from 36,806 to 45,130 visits), while hydrocodone increased 44% (from 39,844 to 57,550 visits) and oxycodone increased 56% (from 41,701 to 64,888 visits).4 In 2006, methadone-related ED visits reported in DAWN represented 22% of all narcotic analgesics-related ED visits.

Methadone, along with oxycodone (32%) and hydrocodone (29%), accounted for 83% of all ED visits associated with the nonmedical use of narcotic pharmaceuticals.

One cautionary note for methadone-reported ED visits: these records frequently do not distinguish methadone used for treatment of opiate addiction from methadone that is prescribed for pain. In fact, a patient on opioid replacement therapy presenting to ED staff may have the methadone documented in the medical record, but it may or may not be related to the ED visit.

**Figure 4.** Number of U.S. poisoning deaths in which specific narcotics and psychodysleptics are mentioned, 2001–2006.

Source: CDC/NCHS NVSS.

Note: Substance-specific data are not additive because a death certificate could have multiple drugs listed. The CDC’s NVSS uses the World Health Organization’s International Classification of Diseases (ICD). ICD-10 T40 classification includes poisoning deaths by narcotics and psychodysleptics (hallucinogens). Poisoning deaths for “Other opioids” (ICD-10 T40.2) include 76 drugs, including codeine, hydrocodone, morphine, oxycodone, and oxymorphone. Poisoning deaths for “Other synthetic narcotics” (ICD-10 T40.4) include 27 drugs, including buprenorphine, fentanyl, and propoxyphene. Retrieved October 12, 2009, from http://apps.who.int/classifications/apps/icd/icd10online/index.htm?qt=36.htm
Methadone and Buprenorphine Prescriptions Dispensed

Methadone deaths may result from its abuse and diversion from hospitals, pharmacies, practitioners, and pain management physicians. Some deaths may also occur as the result of the misuse of legally prescribed methadone or methadone obtained from narcotic treatment programs (NTPs). In some instances, individuals who were legally prescribed methadone may not have been adequately educated regarding the importance of taking the drug in the manner prescribed, including not taking methadone in combination with other drugs or alcohol.

Buprenorphine, like methadone, is a chosen method for opioid dependence therapy because of its long half-life, which provides a milder withdrawal. Buprenorphine is available alone or in combination with the opioid antagonist, naloxone, to deter its abuse by intravenous injection. In the United States, the Drug Addiction Treatment Act of 2000 requires a special federal waiver to prescribe buprenorphine for opioid addiction treatment on an outpatient basis. According to SAMHSA, there are more than 10,000 physicians and 1,800 NTPs that have been authorized nationally to treat opioid addiction with buprenorphine.

IMS Health’s National Prescription Audit Plus Retail database indicates the number of methadone and buprenorphine prescriptions that have been legally dispensed for legitimate medical purposes, although it should be noted that for methadone, the IMS prescription data do not include methadone dispensed in NTPs. Nationally, methadone prescriptions increased from over 2.22 million in 2003 to nearly 4.17 million in 2008 (an increase of 88%) (Figure 5). In comparison, buprenorphine experienced more than a 37-fold increase in prescriptions over this period, from about 96,000 prescriptions in 2003 to 3.54 million in 2008.

Figure 5. Methadone and buprenorphine prescriptions dispensed nationally, 2003–2008.

Retail Distribution of Methadone and Buprenorphine

Distribution by Type of Business

Methadone is increasingly being used for pain management, which is generally associated with practitioners that prescribe the drug to individuals. DEA data from ARCOS show that, from 2003 to 2008, distribution of methadone to practitioners and pharmacies increased more than distribution to other businesses. The quantity of methadone distributed to pharmacies increased 84% from almost 3.3 million grams in 2003 to about 5.9 million grams in 2008, while distribution to practitioners increased 154% from about 15,000 grams to more than 38,000 grams (Table 2). In comparison, methadone distribution to hospitals increased 56% from about 394,000 to about 613,000 grams, while distribution to NTPs increased 42% from about 5.7 million to about 8.1 million grams.

The distribution of buprenorphine reported in ARCOS also increased sharply from 2003 to 2008. The largest increases of buprenorphine in terms of distribution were to pharmacies, which increased 66-fold, from over 11,000 grams in 2003 to about 754,000 grams in 2008. Distribution to NTPs increased from less than 100 grams to nearly 5,000 grams; distribution to


Source: IMS Health’s National Prescription Audit Plus™ retail database.
hospitals increased from about 700 grams to more than 24,000 grams; and distribution to practitioners increased from over 1,000 grams to more than 17,000 grams.

**Distribution by Formulation**

Methadone is currently marketed as oral concentrate (10 mg/mL), oral solution (5 and 10 mg/5 mL), tablets (5, 10, and 40 mg), injectable (10 mg/mL), and powder (50, 100, and 500 mg bottles for prescription compounding). Currently, pharmacies and hospitals mainly distribute 5 mg and 10 mg tablets, NTPs distribute liquids (and to a lesser degree, 40 mg tablets), and practitioners prescribe tablets.

DEA data from ARCOS demonstrate that from 2003 to 2008, the greatest increases for methadone (by grams) were for 5 mg and 10 mg tablets (Figure 6). The number of grams distributed as 5 mg and 10 mg tablets rose nearly 117% from more than 2.9 million in 2003 to 6.4 million in 2008. In comparison, the number of methadone grams distributed in liquid form increased 54% from more than 3.9 million to nearly 6.1 million. The number of methadone grams distributed by 40 mg tablets (dispersible) increased 90% from 2003 to 2007 (from about 1.9 million grams to 3.6 million grams) but then dropped 59% from 2007 to 2008. This can be attributed in large part to a voluntary agreement reached by manufacturers of methadone 40 mg tablets (dispersible), effective as of January 1, 2008. Under this agreement, 40 mg tablets are only to be available to facilities authorized for detoxification or maintenance treatment of opioid addiction and to hospitals. The 40 mg formulation is not U.S. Food and Drug Administration (FDA) approved for use in pain management.

ARCOS data for the retail distribution of buprenorphine (Figure 7) demonstrate that the drug is predominantly distributed in tablets. From 2003 to 2008, the number of buprenorphine grams distributed in tablet form increased more than 70-fold, from 11,500 grams to 815,900 grams. In contrast, the number of buprenorphine grams distributed in liquid form increased from nearly 600 grams to over 1,700 grams, while the number of buprenorphine grams distributed in powder form increased from about 500 grams to over 1,100 grams. Finally, in 2008, ARCOS reported that about 500 grams of buprenorphine were distributed in patch form. No patches were reportedly distributed for buprenorphine in prior years.

Table 2

<table>
<thead>
<tr>
<th>TYPE OF BUSINESS</th>
<th>TOTAL</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methadone (in grams)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National</td>
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<td>9,426,401</td>
<td>11,332,572</td>
<td>12,320,237</td>
<td>13,967,301</td>
<td>14,866,588</td>
<td>14,673,761</td>
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<tr>
<td>NTPs</td>
<td>42,319,532</td>
<td>5,743,272</td>
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<td>7,638,455</td>
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</tr>
<tr>
<td>Pharmacies</td>
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<td>4,246,007</td>
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<tr>
<td>Hospitals</td>
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<td>584,144</td>
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<td>237,228</td>
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<td>51,046</td>
<td>53,992</td>
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</tr>
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<td><strong>Buprenorphine (in grams)</strong></td>
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<td></td>
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</tr>
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<tr>
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<td>3,390</td>
<td>5,728</td>
<td>9,186</td>
<td>17,290</td>
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</tbody>
</table>

* Includes practitioners and mid-level practitioners. Source: DEA ARCOS.
**Figure 6.** Nationwide distribution of methadone, 2003–2008.

![Graph showing nationwide distribution of methadone from 2003 to 2008.](source)

*Available in oral solution (5 and 10 mg/5 mL) and injectables (10 mg/mL).*

![Source: DEA ARCOS.](source)

**Figure 7.** Nationwide distribution of buprenorphine, 2003–2008.

![Graph showing nationwide distribution of buprenorphine from 2003 to 2008.](source)

*Available in oral solution (5 and 10 mg/5 mL) and injectables (10 mg/mL).*

![Source: DEA ARCOS.](source)
This section presents data at the state level for the percentage of analyzed drug items identified as methadone and buprenorphine in 2005 and 2008. Data at the county level also are shown for methadone for 2008. The data presented are based on information provided to the forensic laboratories by the submitting law enforcement agencies, which includes the ZIP Code or county of origin associated with the drug seizure incident. It is important to note that these data represent only those items that were submitted and analyzed by forensic laboratories. Some laboratories within several states are not currently reporting data to NFLIS.

Figure 8 illustrates that in 2005, the highest within-state percentages of methadone (as reflected by the percentage of all drug items in the state identified as methadone) were in the West and South. In 2005, methadone accounted for 1% or more of the laboratory drug caseloads in 3 states and from 0.5% to 0.99% of the laboratory drug caseloads in 15 states. Among these states with reporting levels greater than or equal to 0.5%, 7 were in the West, 6 in the South, 4 in the Northeast, and 1 in the Midwest. By 2008, methadone reports to NFLIS increased in a number of states, particularly those in the West and South (Figure 9). In 2008, methadone accounted for 1% or more of lab caseloads in 9 states and from 0.5% to 0.99% of caseloads in 15 states. Among states that reported 0.5% or more of their caseloads as methadone in 2008, 10 were in the South, 8 in the West, 3 in the Midwest, and 3 in the Northeast.

Figure 10 shows methadone by county for 2008. Notable are the high relative percentages to other U.S. counties in counties between Eastern Kentucky and Northern Georgia, counties between Southern Georgia and Northern Florida, New York City, counties along the east coast of Maine, and counties in Northern Michigan and Eastern Wisconsin. High relative percentages also were reported in a number of counties in the Northwestern United States. This included areas of Northern Washington State, Eastern Oregon, Western Montana, and several counties in Utah.

For buprenorphine, reporting levels were generally low in 2005 (Figure 11). In only one state (Massachusetts) did buprenorphine account for 0.4% or greater of the overall laboratory drug caseload. State-level percentages of buprenorphine increased in 2008, particularly in the Northeast, and to a lesser extent in the South and West (Figure 12). In 2008, buprenorphine accounted for 0.4% or more of the laboratory caseloads in seven Northeastern states, three Southern states, and three Western states.

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8 When a ZIP Code or county of origin is not available, the drug seizure location is assigned to the same county as the submitting law enforcement agency. If the submitting agency is unknown, the seizure is assigned to the county in which the laboratory completing the analyses is located.
Note: NFLIS data for NYPD Crime Laboratory are not specific to individual counties within New York City.

Figure 10. Percent of analyzed drug items identified as methadone, by county, 2008.

Figure 11. Percent of analyzed drug items identified as buprenorphine, by state, 2005.

Figure 12. Percent of analyzed drug items identified as buprenorphine, by state, 2008.
Summary of Nationwide Trends in Methadone and Buprenorphine

The nationwide trends of methadone retail distribution, methadone reported by crime laboratories, and methadone-related fatalities have demonstrated a parallelism for several years beginning in 2002 (Figure 13). Multiple data sources that include kilogram distribution of methadone from pharmaceutical manufacturers (ARCOS), methadone items analyzed by crime laboratories (NFLIS), and confirmed methadone-related deaths (NVSS) indicated upward trends in methadone from 2002 to 2006. NVSS data for 2007 and 2008 are not yet available. During this period, methadone distribution increased between 9% and 20% annually, methadone deaths increased between 16% and 29%, and analyzed methadone items increased between 14% and 34%. From 2006 to 2008, the rate of increase for both methadone distribution and methadone analyzed by crime laboratories has stabilized considerably.

While NVSS death data for buprenorphine is currently limited, buprenorphine distribution and analysis by crime laboratories continue to rise (Figure 14). From 2002 to 2008, the retail distribution of buprenorphine increased more than 7,000-fold from 107 grams to 800,317 grams. Likewise, buprenorphine items reported to NFLIS increased more than 250-fold from 13 items in 2002 to 5,627 items in 2008. NVSS reports deaths related to buprenorphine in the category labeled “other and unknown synthetic narcotics,” which includes 27 specified drugs. As a result, these data are not displayed.

In summary, multiple sources indicate that methadone and buprenorphine use and abuse have been on the rise this decade. A number of measures taken by various federal agencies to counter the methadone-related morbidity and mortality may have contributed to the stabilization in NFLIS and ARCOS data. While methadone is still more prevalent in terms of reporting in NFLIS, buprenorphine has increased at a sharper rate, indicating the need for continued monitoring. This is especially true considering the level at which buprenorphine is being distributed and prescribed for legal medical purposes.

Moving forward, the DEA can continue to compare NFLIS data with other drug reporting systems to monitor drug-related problems in the United States. This can include utilizing the NFLIS data to help assess how drugs such as methadone and buprenorphine are being abused, illegally trafficked, and diverted throughout the United States.

Figure 13. Trends in methadone distribution, items analyzed and deaths in the United States, 2002–2008.

Figure 14. Trends in buprenorphine distribution and items analyzed in the United States, 2002–2008.
Since 2001, NFLIS reports have included national and regional estimates for the number of drug items and drug cases analyzed by state and local forensic laboratories in the United States. This appendix discusses the methods used for producing these estimates, including sample selection, weighting, and imputation and adjustment procedures. RTI International, under contract to the DEA, began implementing NFLIS in September 1997. Results from a 1998 survey (updated in 2002, 2004, and 2008) provided laboratory-specific information, including annual caseload figures, used to establish a national sampling frame of all state and local forensic laboratories that routinely perform drug analyses. A representative probability proportional to size sample was drawn on the basis of annual cases analyzed per laboratory, resulting in a NFLIS national sample of 29 state laboratory systems and 31 local or municipal laboratories, for a total of 165 individual laboratories. Only the data for those laboratories in the sample that reported drug analysis data for 6 or more months during 2008 were included in the national estimates.

**Weighting Procedures**

Data were weighted with respect to both the original sampling design and nonresponse in order to compute design-consistent, nonresponse-adjusted estimates. Weighted prevalence estimates were produced for drug cases and drug items analyzed by state and local forensic laboratories from January 2003 through December 2008.

A separate item-level and case-level weight was computed for each sample laboratory or laboratory system using caseload information obtained from an updated laboratory survey administered in 2008. These survey results allowed for the case- and item-level weights to be poststratified to reflect current levels of laboratory activity. Item-level prevalence estimates were computed using the item-level weights, and case-level estimates were computed using the case-level weights.

**Drug Report Cutoff**

For some drugs, such as cannabis/THC and cocaine, thousands of items are reported annually, allowing for reliable national prevalence estimates to be computed. For other drugs, reliable estimates cannot be computed because of a combination of low item counts and substantial variability in item counts between laboratories. Thus, a cutoff point for estimates was established.

The method for evaluating the precision and reliability of estimates was established using the relative standard error, or RSE, which is the ratio between the standard error of an estimate and the estimate itself. As a rule, drug estimates with an RSE greater than 50% were suppressed and not shown in the tables.

Earlier reports stated that the coefficient of variation, or CV, was the statistic used to evaluate the reliability of an estimate. The CV and the RSE both measure variation; however, the RSE is usually expressed as a percentage and the CV is usually expressed as a decimal.

**Imputations and Adjustments**

Due to technical and other reporting issues, several laboratories did not report data for every month during 2008. This resulted in missing monthly data, which is a concern in calculating national estimates of drug prevalence. Imputations were performed separately by drug for laboratories missing monthly data, using drug-specific proportions generated from laboratories reporting a full year of data.

Although most forensic laboratories report case-level analyses in a consistent manner, a small number of laboratories do not produce item-level counts that are comparable with those submitted by the vast majority of laboratories. Most laboratories report items in terms of the number of vials of the particular pill, yet a few laboratories report the count of the individual pills themselves as items. Because the case-level counts across laboratories are comparable, they were used to develop item-level counts for the few laboratories that count items differently. For those laboratories, it was assumed that drug-specific ratios of cases to items should be similar to laboratories serving similarly sized areas. Item-to-case ratios for each drug were produced for the similarly sized laboratories, and these drug-specific ratios were then used to adjust the drug item counts for the relevant laboratories.

**Statistical Techniques for Trend Analysis**

A trend analysis was performed on the January 2003 through December 2008 national and regional estimates. Typically, models test for mean differences; however, the national and regional estimates are totals. To work around this challenge, a bootstrapping technique was employed. (Bootstrapping is an iterative technique used to estimate variances when standard variance estimation procedures cannot be used.) All statistical tests were performed at the 95% confidence level (p < 0.05). In other words, if a linear trend was found to be statistically different, then the probability of observing a linear trend (under the assumption that no linear trend existed) was less than 5%.

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