

Methadone-Associated Mortality: **Report of a** **National Assessment**



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
www.samhsa.gov

Acknowledgements

Numerous people contributed to the development of the National Assessment Meeting and this report (see Appendix A). The meeting was conducted by Northrop Grumman Information Technology, Health Solutions & Services, under contract 280-99-0900 with the Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Substance Abuse Treatment (CSAT). Stewart B. Leavitt, PhD, served as researcher/writer and Alan Trachtenberg, MD, MPH, was SAMHSA's medical editor and a meeting facilitator. Johnson, Bassin & Shaw, Inc., provided assistance in the production of this document. Raymond Hylton, Jr., RN, MSN, CSAT, served as the Government project officer.

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Recommended Citation

Center for Substance Abuse Treatment, Methadone-Associated Mortality: Report of a National Assessment, May 8-9, 2003. CSAT Publication No. 28-03. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2004.

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CSAT Publication No. 28-03

Printed 2004

Preface

Methadone is a medication valued for its effectiveness in reducing the mortality associated with opioid addiction as well as the various medical and behavioral morbidities associated with addictive disorders. It also is an inexpensive and increasingly popular analgesic medication suitable for the treatment of even the most severe acute or chronic pain in well-selected patients.

In 2002 and 2003, articles appeared in prominent newspapers – including the *New York Times* – describing methadone as “widely abused and dangerous.” These alarming reports arose from an apparent increase in deaths among persons using the medication.

The reports were of grave concern to the Substance Abuse and Mental Health Services Administration (SAMHSA), the agency of the Department of Health and Human Services which in 2001 assumed from the Food and Drug Administration (FDA) the responsibility for regulation and oversight of the Nation’s opioid treatment programs (OTPs, commonly known as methadone clinics). SAMHSA’s Center for Substance Abuse Treatment (CSAT) already was working with the Centers for Disease Control and Prevention (CDC), the Drug Enforcement Administration (DEA), the National Institute on Drug Abuse (NIDA), and the FDA, as well as with some of the States most directly affected by rising methadone mortality rates. The media reports, coupled with an increase in requests for consultation and assistance from State authorities and practitioners in the field, created added urgency for SAMHSA to evaluate and address the causes of the increase.

To address these issues, SAMHSA convened a multidisciplinary group – including representatives from various Federal and State agencies, researchers, epidemiologists, pathologists, toxicologists, medical examiners, coroners, pain management specialists, addiction medicine experts, and others – to conduct a National Assessment of Methadone-Associated Mortality in May 2003.

The term “methadone-associated mortality” broadly encompasses fatalities in which methadone has been detected during postmortem analysis or is otherwise implicated in a death. Defining methadone’s role in such deaths is an unsettled area, complicated by inconsistencies in methods of determining and reporting causes of death, the presence of

other central nervous system (CNS) drugs, and the absence of information about the decedent's antemortem physical or mental condition and level of opioid tolerance. Moreover, the source, formulation, and quantity of methadone implicated in an individual's death often are difficult to determine.

Participants in the National Assessment presented and carefully reviewed the available data on methadone formulation, distribution, patterns of prescribing and dispensing, as well as the relevant data on drug toxicology and drug-associated morbidity and mortality. As a result of their deliberations, participants arrived at a number of important conclusions regarding the reports of methadone-associated mortality and formulated recommendations for reducing that mortality.

This document summarizes the data used by the Assessment experts to evaluate the nature and scope of the problem, as well as to present their findings and recommendations. Participants' slides and other presentation materials are available on SAMHSA's web site; a Background Briefing Report prepared for the Assessment also is available on the web site.

These documents provide an excellent source of information and expert analysis of both anecdotal and statistical reports of methadone-associated mortality. The conclusions of the experts assembled for the National Assessment can help inform future policy and assure that appropriate access to this important medication is preserved.

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Part 1. Purpose of the National Assessment

Methadone has a long, successful history as a potent analgesic and a highly effective medication for reducing the morbidity and mortality associated with opioid addiction (Joseph and Woods, 1994; Joseph, et al., 2000). However, recent reports of methadone-associated deaths have stirred public concern. Diversion, abuse, and deaths associated with many opioid medications, including methadone, have been the subject of front-page news. Articles appearing in prominent newspapers, including the *New York Times*, have described methadone as a “killer drug” that is “widely abused and dangerous” (Belluck, 2003a, 2003b, 2003c; Associated Press, 2002; *Washington Times*, 2003).

While these articles focused on the dangerous consequences of opioid medications when misused, the articles often did not balance that negative perspective with positive information about how the drugs provide vital relief to persons suffering from serious pain and, in the case of methadone, opioid addiction. The articles tended to perpetuate long-standing myths and misconceptions about opioid-based medications. Such misinformation has the potential to discourage the appropriate use of these medications even though, properly administered, they have demonstrated efficacy and safety in millions of patients worldwide.

The news reports were and remain of grave concern to the Substance Abuse and Mental Health Services Administration (SAMHSA), within the U.S. Department of Health and Human Services. In 2001, SAMHSA assumed responsibility from the Food and Drug Administration (FDA) for the regulation and oversight of the Nation’s opioid treatment programs (OTPs, commonly referred to as “methadone clinics”). SAMHSA’s Center for Substance Abuse Treatment (CSAT) already had been working with the Centers for Disease Control and Prevention (CDC), the Drug Enforcement Administration (DEA), the National Institute on Drug Abuse (NIDA), and the FDA, as well as with some of the affected States, to assess the issue of opioid overdose deaths. However, the media reports, combined with increasing requests for consultation and assistance from State authorities and practitioners in the field, added urgency to SAMHSA’s efforts to address the causes of methadone-associated mortality in a focused and expeditious manner.

Thus, on May 8-9, 2003, SAMHSA's CSAT convened a multidisciplinary group of more than 70 experts – including representatives of various Federal and State agencies, researchers, epidemiologists, pathologists, toxicologists, medical examiners, coroners, pain management specialists, addiction medicine experts, and others (see Appendix 1 for a complete list of participants) – to conduct a National Assessment of Methadone-Associated Mortality.

The experts who participated in the National Assessment sought to determine whether opioid treatment programs (OTPs) that use methadone in the treatment of opioid addiction and the revised Federal regulations governing the manner in which OTPs administer methadone could be contributing to methadone-associated mortality.

Participants presented and carefully reviewed the available data on methadone formulation, distribution, patterns of prescribing and dispensing, as well as the relevant data on drug toxicology and drug-associated morbidity and mortality. Based on their assessments, participants arrived at a number of important conclusions regarding the reports of methadone-associated mortality and formulated recommendations for reducing that mortality.

Part 2. Background

Methadone has a number of unique pharmacologic properties, such as its slow onset and long duration of action, its relatively low need for dose escalation because of tolerance, its antagonism of the glutamate receptor N-methyl-D-aspartate (NMDA), its inhibition of serotonin/norepinephrine reuptake, and its very modest cost – all of which make it an appropriate choice for opioid therapy of pain and addiction (Savage, meeting presentation, 2003 [see www.samhsa.gov]; Lobert, 2003; Bruera, 2002; Payte, et al., 1994; Joseph and Woods, 1994; Kreek, 1992; Ettinger, et al., 1979).

Methadone's Pharmacology and Mechanisms of Action

A synthetic opioid, methadone is among the most thoroughly studied drugs in modern medicine. Approved by the FDA in 1947 as an analgesic, by 1950 methadone was being used to treat the painful symptoms of withdrawal from heroin and other opioids. In 1964, researchers discovered that continuous, daily maintenance doses of oral methadone allowed opioid-addicted patients to function more normally in recovery (Payte, 1991; Zweben and Payte, 1990; Dole, 1988; Gearing and Schweitzer, 1974).

Oral methadone, whether used for addiction treatment or pain relief, is available as a solid tablet, a rapidly dissolving wafer (diskette), and a premixed liquid, all of which are essentially bioequivalent (Mallinckrodt, 1995, 2000; Roxane, 1995, 1998, 2000). Each of the formulations is 80 to 95 percent bioavailable (compared with only 30 percent for oral morphine) and readily absorbed (Eap, et al., 2000; Inturrisi, 1972b).

Methadone is stored extensively in the liver and secondarily in other body tissues. Its elimination half-life averages 24 to 36 hours at steady state, but may range from 4 to 91 hours. Because of this long half-life, achieving steady-state serum methadone levels (SMLs) – in which drug elimination is in balance with the amount of drug remaining in the body – requires, on average, from 4 to 5 days, although it can take much longer in some individuals. When methadone is initiated, before a steady state is achieved, a rule of thumb is that half of each day's dose remains in the body to be added to the next day's new dose, producing rising SMLs (which can reach dangerous levels if doses are excessive). After each dose, the SML typically reaches a peak in 3 to 4 hours (with a range of 1 to 5 hours), although individual physiologic responses differ for a variety of reasons (Eap, et al., 2002, 1988).

Largely as a function of liver enzyme activity, methadone is broken down to form a number of inactive metabolites (Foster, et al., 1999; Kreek, et al., 1979). Drugs that *induce* activity of these enzymes can accelerate methadone metabolism, abbreviate the duration of its effects, lower the SML, and precipitate abstinence (withdrawal) syndrome. Conversely, drugs that *inhibit* these enzymes can slow methadone metabolism, raise the SML, and extend the duration of drug effects (Eap, et al., 1999). When interactions with other substances occur, changes in SMLs can result in under- or over-medication. Genetic and environmental factors also act on the enzymes, leading to considerable individual variation in methadone potency (Nakamura, et al., 1982; Robinson and Williams, 1971). Equally important to this kinetic variability, however, is the wide inter-individual and intra-individual variation in opioid tolerance, which is highly dependent on dosing history and even can reflect external stimuli and environment (Eap, et al., 2002, 1988).

Methadone's Safety Profile

Through many years of clinical trials and experience, methadone has been shown to have a favorable safety profile when used as indicated (Stine, et al., 1998; Payte and Zweben, 1988; Zweben and Payte, 1990). Few serious adverse reactions and no cumulative organ damage have been associated with daily administration of appropriate doses over more than 20 years in some patients. Mortality from all causes is many-fold lower in methadone-treated patients than in untreated opioid addicts. Studies consistently have shown that the risk of communicable diseases (such as HIV and hepatitis C) is significantly reduced by participation in methadone maintenance therapy, even in patients who do not achieve total abstinence from illicit drug use (Appel, et al., 2000; Backmund, et al., 2001; Bell and Zador, 2000). Moreover, research shows that patients in whom methadone therapy is discontinued have mortality rates three to four times higher than patients in whom methadone therapy is continued (Goldstein and Herrera, 1995; Concool, et al., 1979; Gearing and Schweitzer, 1974).

Still, methadone is a potent drug; fatal overdoses have been reported over the years (Baden, 1970; Gardner, 1970; Clark, et al., 1995; Drummer, et al., 1992). As with most other opioids, the primary toxic effect of excessive methadone is respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia (White and Irvine, 1999; Harding-Pink, 1993). Among patients in addiction treatment, the largest proportion of methadone-associated deaths have occurred during the drug's

induction phase, usually when (1) treatment personnel overestimate a patient's degree of tolerance to opioids, or (2) a patient uses opioids or other central nervous system (CNS) depressant drugs in addition to the prescribed methadone (Karch and Stephens, 2000; Caplehorn, 1998; Harding-Pink, 1991; Davoli, et al., 1993). In fact, when deaths occur during later stages of treatment, other drugs usually are detected at postmortem examination (Appel, et al., 2000). In particular, researchers have called attention to the "poison cocktail" resulting from the intake of multiple psychotropic drugs (Borron, et al., 2001; Haberman, et al., 1995) such as alcohol, benzodiazepines, and other opioids. When used alone, many of these substances are relatively moderate respiratory depressants; however, when combined with methadone, their additive or synergistic effects can be lethal (Kramer, 2003; Payte and Zweben, 1998).

It is important to note that postmortem blood concentrations of methadone do not appear to reliably distinguish between individuals who have died from methadone toxicity and those in whom the presence of methadone is purely coincidental (Drummer, 1997; Caplan, et al., 1983). This poses challenges for efforts to achieve more accurate forensic determinations of cause of death in such cases, and underscores the need for appropriate case definitions, as well as for improved systems to gather and classify premortem and other data for surveillance and prevention purposes (Hanzlick, 1997; Baden, 1978).

National Data on Methadone Use and Associated Mortality

Data from MedWatch – the FDA's Safety Information and Adverse Event Reporting Program – indicate that, from 1970 through 2002, 1,114 cases of methadone-associated deaths in adults were reported. Critically, a greater number of methadone-associated deaths were reported in 2001 alone than during the entire period from 1990 through 1999; this number doubled again in 2002 (Ouellette-Hellstrom, et al., meeting presentation, 2003).

Reports from U.S. poison control centers also show that the overall number of opioid-related deaths has been on the rise, with many cases involving oxycodone and hydrocodone (Budnitz, meeting presentation, 2003; Litovitz, et al., 2002; Fingerhut and Cox, 1998; Cone, et al., 2003; Florida Department of Law Enforcement, 2002; Eastwood, 1998). Similarly, data from the Drug Enforcement Administration (DEA) National Forensic Laboratory System (NFLS) indicate that seizures by law enforcement agencies

of illicitly obtained opioid analgesics such as hydrocodone and oxycodone have outpaced seizures of methadone; nevertheless, methadone seizures have been increasing as well (Howard, meeting presentation, 2003). Methadone tablet seizures increased 133 percent between 2001 and 2002; in contrast, seizures of liquid methadone increased only 11 percent during the same period (Howard, meeting presentation, 2003).

Recently, the availability of low-cost, high-purity heroin in some parts of the U.S. has fostered increased rates of abuse, since such heroin can be smoked or ingested intranasally by new users, eliminating the need for injection and thus fostering experimentation (SAMHSA, 2001; McCaffrey, 1999). In such cases, miscalculations of drug purity have led to fatal overdoses. As a result, death rates among IV heroin users are 13 times greater than those for the population as a whole (Zickler, 2001; SAMHSA, 2002).

The abuse of opioids other than heroin also is of concern. According to SAMHSA's 2001 National Household Survey on Drug Abuse, the number of new non-medical users of prescription drugs has increased steadily since the mid-1980s. The greatest part of this increase involves non-medical use of opioid analgesics, which increased from 400,000 persons in the mid-1980s to about 2 million in 2000 (Crane, meeting presentation, 2003; SAMHSA, 2001). Data from SAMHSA's Drug Abuse Warning Network (DAWN) indicate that, in 2002, heroin/morphine, cocaine, and alcohol in combination with other drugs – such as opioid analgesics or marijuana – were the substances most often mentioned in national data on drug-related deaths reported through DAWN (SAMHSA, 2003).

From 1994 to 2001, DAWN recorded an increasing number of opioid analgesic mentions in drug-related emergency department visits, with the largest increases reported for oxycodone (352 percent), methadone (230 percent), and hydrocodone (131 percent). In 2001, “opioid dependence” (presumed to involve addiction rather than solely physical dependence) was the most frequently mentioned motive for abuse of opioid analgesics, followed by “suicide attempts,” “psychotropic effects” and “unknown” or “other” motives (SAMHSA, 2003).

State-Level Data on Methadone Use and Associated Mortality

In 2002 and 2003, concerns were heightened by news reports of methadone-associated deaths in Maine, Florida, and North Carolina – all States in which per capita distribution of methadone tablets through pharmacies exceeds the national average (Associated Press, 2002; Ballesteros, et al., 2003; Sanford, 2002; Sorg, 2002, Sorg and Greenwald, 2002). These data suggest a correlation between increased pharmacy distribution of methadone tablets for pain management and increased problems with methadone, including methadone-associated deaths.

In Maine, surveillance data depict an increase in methadone-associated fatalities that roughly parallels the increase in all drug deaths between 1997 and 2002 (Sorg, meeting presentation, 2003; Sorg, 2002). Opioid analgesics – most often heroin/morphine, oxycodone, and methadone – were present in 71 percent of the deaths reported in the State and were identified as causative in 53 percent (Sorg and Greenwald, 2002). The number of deaths in which methadone was detected doubled between 1999 and 2000, leveled off in 2001, then increased again in 2002 (Sorg, 2002). A high rate of mental illness and physical disorders (such as heart, lung, and liver disease), along with concomitant use of psychiatric medications and benzodiazepines, also were found in decedents (Sorg and Greenwald, 2002).

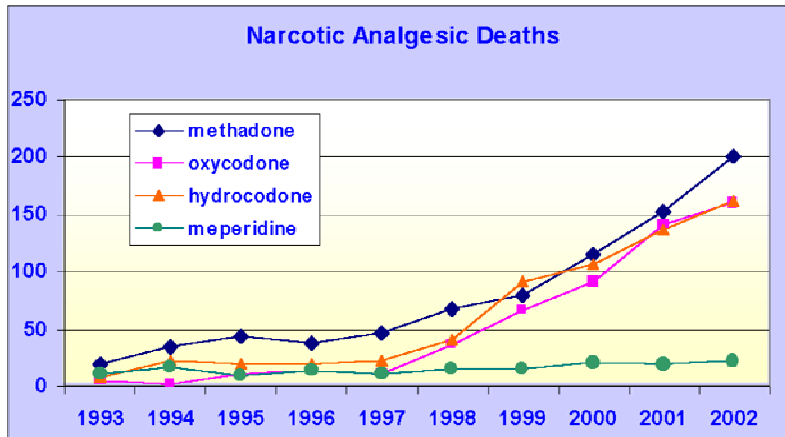
In Florida, cases of methadone-associated mortality showed a large increase from 2001 to 2002. Although in the first six months of 2002 most deaths (83 percent) were attributed to use of multiple drugs, the number in which methadone was deemed to be causative roughly equaled those in which it was merely “present” (FDLE, 2002).

In North Carolina, the number of deaths associated with methadone increased five-fold from 1997 through May 2001, for a total of 198 cases over that five-year period (Sanford, meeting presentation, 2003). When the source of the methadone could be determined (in about half the cases), physician prescription orders were identified in 75 percent, with the rest obtained from non-medical sources (e.g., prescribed to a relative/friend, obtained at a party, or “street purchase”). Only four percent of the decedents were participating in addiction treatment at or near the time of death, and OTPs were considered an unlikely source of the methadone involved in the fatal cases (Ballesteros, et al., 2003; Sanford, 2002). During the time period examined, the amount of methadone dispensed through retail outlets (primarily pharmacies) in North Carolina

increased four-fold; the amount distributed through OTPs increased only two and a half times (Sanford, meeting presentation, 2003; Sanford, 2002).

In Washington State, methadone-associated deaths during the period 1993 through 2002 roughly paralleled those associated with oxycodone and hydrocodone (Figure 1). Concomitant use of multiple drugs was reported in 92 percent of deaths involving methadone (Gordon, meeting presentation, 2003).

Figure 1. Deaths Associated With Opioid Analgesics in Washington State



Source: Washington State data courtesy of Ann Marie Gordon, MS.

In Texas, which experienced an increase in methadone-associated fatalities during the early 1990s (Barrett, et al., 1996), cases of overdose involving persons being treated in OTPs actually declined between 1999 and 2002 (Maxwell, meeting presentation, 2003). Over the same period, the number of death certificates that included mention of methadone increased three-fold. Thus, while overdose mortality was declining among OTP patients, such fatalities were rising in the overall population (Maxwell, meeting presentation, 2003).

In States that have collected, analyzed, and reported relevant data, methadone-associated mortality appears to be increasing, although the absolute number of cases remains a relatively modest portion of the total number of drug-related deaths (SAMHSA, 2002). Methadone seldom is reported as the sole cause of death. In those relatively rare cases, the drug often was ingested accidentally. The majority of methadone-associated deaths involved at least one other drug, often another opioid or

central nervous system depressant such as alcohol or a benzodiazepine (Borron, et al., 2001; Haberman, et al., 1995).

Part 3. Deliberations

As part of the National Assessment, SAMHSA commissioned a Background Briefing Report containing research data and other information to help establish a common understanding of the problem. This briefing report was distributed to participants in advance of the May meeting and is available on SAMHSA's web site (www.samhsa.gov).

Opening the meeting, CSAT Director H. Westley Clark, MD, JD, MPH, CAS, FASAM, reaffirmed SAMHSA's concerns about methadone-associated mortality and the importance of a response to the problem. He noted that, if OTPs or their clinical practices were responsible for any part of the increase in methadone-associated mortality, SAMHSA, as the Federal agency that regulates such programs, would work actively to rectify the problem. If, on the other hand, OTPs were not a significant source of methadone in overdose cases, that finding should be documented and communicated widely.

Next, SAMHSA's Alan Trachtenberg, MD, MPH, described the policy context surrounding reports of opioid-associated deaths, particularly fatalities involving methadone. Dr. Trachtenberg defined the meeting's objectives as:

- Determining whether OTPs' use of methadone in the treatment of opioid addiction and the revised Federal regulations governing the manner in which OTPs administer methadone could be contributing to methadone-associated mortality;
- Assessing the need for improved nationwide surveillance of opioid-associated deaths, particularly methadone-associated mortality;
- Assessing the adequacy of case definitions used by coroners and medical examiners (MEs) in the attribution of opioids' specific role in drug-associated deaths; and
- Recommending preventive measures for implementation by health care professionals and educators, regulators, and law enforcement agencies at all levels of government.

Dr. Trachtenberg's remarks were followed by participants' presentations of the epidemiologic data; problems involved in surveillance; definitions and patterns of opioid misuse, abuse and addiction; and case definitions of methadone-related fatalities. (Summaries of the presentations and slide handouts are found online at www.samhsa.gov.)

Each day's presentations were followed by action planning sessions that focused on specific questions. Based on their review of background information, speaker presentations, and the action planning sessions, meeting participants reached consensus on a set of findings and recommendations.

Part 4. Findings

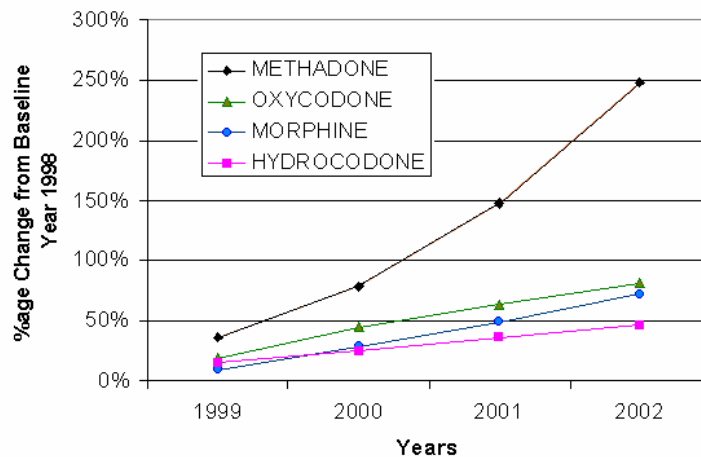
Concern over methadone-associated mortality is not new. Extensive surveillance data have documented such deaths ever since methadone's introduction as an analgesic and its subsequent use in the treatment of opioid addiction. This has occurred within the context of increased abuse of all opioid drugs (Crane, meeting presentation, 2003; ONDCP, 2002; SAMHSA, 2001).

The current analysis has prompted a number of important findings, described in the following pages.

Recent Increases in Methadone Use Are Related to Its Use as an Analgesic

The greatest incremental growth in methadone distribution in recent years is associated with use of the drug as an analgesic and its distribution through pharmacies rather than through OTPs (Governale, meeting presentation, 2003; DEA, 2003) (Figure 2). However, the growth in distribution of methadone through pharmacies has been overshadowed by the increase in distribution of oxycodone and hydrocodone.

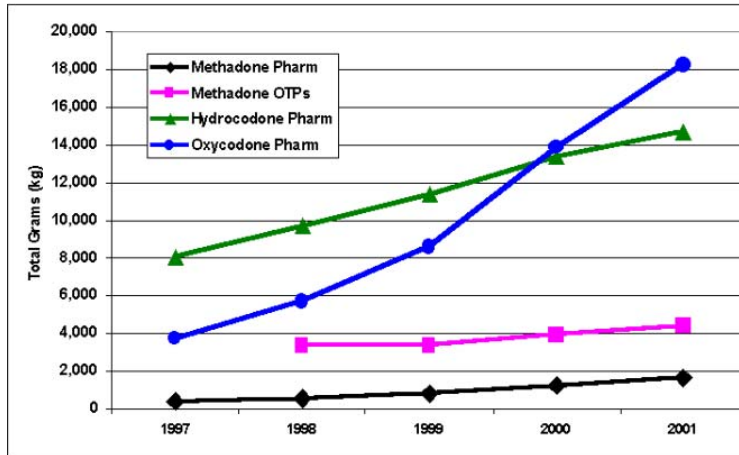
Figure 2. Percent Change in Distribution of Methadone and Three Comparison Drugs, from Baseline Year 1998 through 2002



Source: Data from IMS Health, National Prescription Audit Plus, courtesy of Laura A. Governale, PharmD.

By comparison, distribution of methadone through OTPs remained relatively flat during the period measured (Howard, meeting presentation, 2003) (Figure 3).

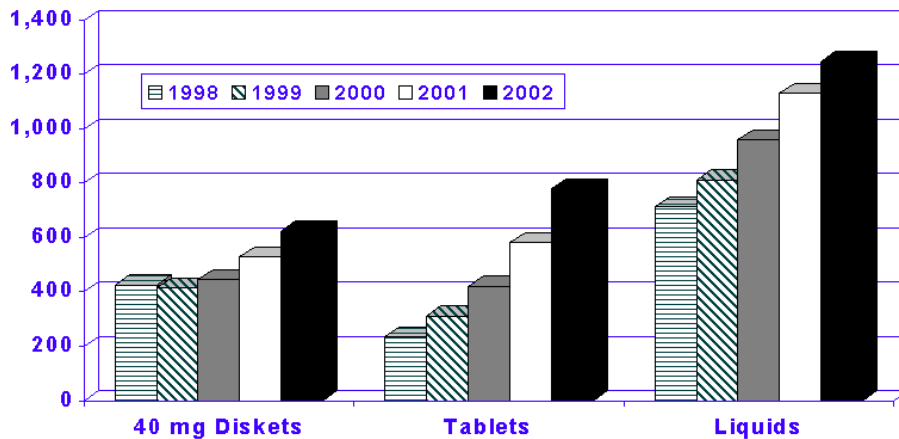
Figure 3. Distribution of Methadone through OTPs and Pharmacies, Compared



Source: Data derived from DEA ARCOS-2; methadone pharmacy 2000 data are an interpolated estimate.

Although use of all formulations of methadone has shown steady, incremental growth over the past several years (Figure 4), the distribution of tablets (most often used in pain management) and diskettes has surpassed that of liquid formulations (most often used by OTPs). For example, the rate of increase from 1999 to 2002 was far greater for tablets (331 percent) than for either diskettes (147 percent) or liquids (175 percent). In 2002, about 55 percent of all methadone distributed nationwide was in the form of tablets or diskettes (Howard, meeting presentation, 2003).

Figure 4. Methadone Distribution, by Formulation, 1998 – 2002 (grams per 100,000 population)



Source: Adapted from DEA ARCOS-2 data provided by June E. Howard.

In 2002, OTPs accounted for the largest amount of methadone products purchased (68 percent), followed by pharmacies (29 percent). However, whereas OTPs purchased 98 percent of all the methadone sold in liquid form and 79 percent of all the methadone sold in diskette form in the U.S., pharmacies accounted for 88 percent of all purchases of the tablet form (OTPs purchased only 1.75 percent of the tablets). Within OTPs nationwide during 2002, 65 percent of methadone was distributed as liquids, 26 percent as diskettes, and less than one percent as tablets (Howard, meeting presentation, 2003).

***Increases in Methadone-Associated Mortality
Also Are Related to Its Use as an Analgesic***

The greatest incremental growth in methadone distribution in recent years is associated with use of the drug as an analgesic and its distribution through pharmacies. In fact, distribution of solid methadone formulations (tablets and diskettes), primarily through pharmacies, has surpassed distribution of the liquid formulations that are the mainstay of dispensing in OTPs. From 1998 through 2002, the volume of methadone distributed through pharmacies increased five-fold, whereas the volume distributed through OTPs increased only 1.5-fold. In 2002 alone, pharmacies accounted for 88 percent of all purchases of methadone tablets (DEA, 2003). Data from the DEA's ARCOS system indicate that the growth in methadone distribution overall has lagged far behind the increases seen for other opioid analgesics, such as oxycodone and hydrocodone products (DEA, 2003).

The DEA data are supported by independent information from IMS Health, which tracks drug prescriptions and sales through selected channels of distribution (Governale, meeting presentation, 2003). From 1998 to 2002, the number of retail prescriptions filled each year for oxycodone, hydrocodone, morphine, and methadone all increased. While fewer prescriptions were written for methadone than for the other three opioids, the number of prescriptions for methadone increased three-fold between 1998 and 2003 (from 0.5 to 1.8 million prescriptions) – a rate of increase larger than that for the other three drugs. The number of units of methadone in solid form distributed through retail channels averaged a 38 percent annual increase, whereas comparatively minor growth was seen for solid formulations distributed through OTP channels.

Taken together, the data confirm a correlation between increased methadone distribution through pharmacy channels and the rise in methadone-associated mortality.

This supports the hypothesis that the growing use of oral methadone, prescribed and dispensed for the outpatient management of chronic pain, explains the dramatic increases in methadone consumption and the growing availability of the drug for diversion to abuse.

OTPs and the Revised Federal Regulations Are Not Significant Contributors to Methadone-Associated Mortality

A major concern of the National Assessment participants was whether OTPs and the revised SAMHSA regulations governing the manner in which OTPs administer and dispense methadone have contributed to recent increases in methadone-associated mortality. The SAMHSA regulations effective in 2001 (42 CFR Part 8) allow patients – especially those who are relatively advanced in the course of treatment – to take home doses of methadone on an increased number of days.

Examination of the data available to the National Assessment participants indicates that OTPs and the 2001 regulatory changes *did not* have a significant effect on rates of methadone-associated mortality. As already noted, the upward trend in fatalities involving methadone appeared prior to 2001 and, thus, preceded SAMHSA’s regulatory changes (Kallan, 1998). The trend in methadone-associated deaths parallels death rates associated with other opioid agents (SAMHSA, 2003). In the cases in which the sources of methadone associated with deaths could be traced, OTPs did not appear to be involved. Within OTPs, patient deaths during the start-up (induction) phase – the period of highest risk for in-treatment mortality – are rare due to Federal regulations that impose specific requirements on the induction (“loading”) dose, as well as improvements in patient care that resulted from the SAMHSA requirement that OTPs must be accredited.

Further, the growth in the number of OTPs administering methadone and in the number of persons receiving methadone treatment has been modest and does not parallel the rate of increase in methadone-associated deaths. Although the data remain incomplete, National Assessment participants concurred that methadone tablets and/or diskettes that have become available through channels *other than OTPs* are most likely the central factor in recent increases in methadone-associated mortality.

Part 5. Recommendations

Available databases and other evidence support many valid and important observations. However, participants in the National Assessment also recognized that certain information deficits will require further consideration as efforts to assess and address methadone-associated mortality move forward.

Uniform Case Definitions Should Be Established

Comparisons of data from various epidemiologic databases or studies of methadone-associated mortality are difficult, because they often do not employ common terminology or definitions (Kung, et al., 2001). It would be helpful to develop uniform medical examiner/coroner case definitions and reporting methods, as well as a data-collection system sufficiently comprehensive and flexible to handle new problems as they arise.

Scientifically concise and universally accepted case definitions can address the critical distinction between deaths *caused* by methadone and deaths in which methadone is a contributing factor or merely present.

Professional organizations need to agree on a uniform nomenclature that clearly distinguishes between the expected consequences of physiologic dependence and drug tolerance (which occur with many commonly used opioid medications) and the phenomenon of addiction (which is a chronic, relapsing, neurobiological disorder with behavioral manifestations).

Development of a central repository for opioid-related medical examiner/coroner cases – that is, a National Opioid Death Registry – would facilitate the necessary data compilations and analyses. National Assessment participants concluded that Federal support and involvement would be needed to ensure that comprehensive toxicologic analyses are conducted in all local jurisdictions and reported to such a national registry.

Standards for Toxicologic Testing Are Needed

Standards should be developed to guide toxicologic testing in cases of suspected drug-induced deaths (Milroy and Forrest, 2000; Merrill, 1996; Prouty and Anderson, 1990). National Assessment participants suggested that the Food and Drug Administration might provide reference standards for such toxicologic tests, with relevant professional organizations providing input and assistance. Once standard case definitions are

determined, investigative techniques for medical examiners and coroners should be enhanced and standardized.

More Useful Data Are Needed

Overall, more flexibility is needed in the design of data sets and the performance of data analyses, as are better methods of integrating data from different collection systems. Procedures for accessing new and existing data also should be simplified.

Better information is needed to describe how methadone-associated deaths occur. For example, data could inform whether the drug's potential for lethality may be the result of a slow onset of action, leading to repeated dosing – and, ultimately, overdose – as an individual attempts to achieve the desired drug effect. Today, such a conclusion requires additional information.

More information is needed about the particular formulations of methadone – tablets, diskettes, liquids, or injectables – involved in specific cases of mortality (natural, accidental, suicide, homicide, or undetermined).

Accurate information is needed to determine the sources of methadone associated with fatalities (e.g., thefts, robberies or diversion from medical practices, pharmacies, or OTP clinics). For example, current data indicate that most methadone-associated deaths, where dosage form information is available, involve 5 and 10 mg tablets. However, it is not clear whether those tablets are obtained through legal prescriptions, prescription forgeries, other diversion tactics, or pharmacy thefts or robberies. Future reviews will benefit from improvements to DEA's Drug Theft System over the past year. These changes will permit the extraction and review of data for specific drugs in a more reliable manner. While more timely information will be available, some limitations will remain, since the accuracy of the system is totally dependent on pharmacies and other registrants submitting acceptable reports. In addition, unlike other DEA systems, the Drug Theft System is not completely automated and relies instead on the manual inputting of data.

More information is needed about the population being legitimately prescribed methadone – their health history, concomitant use of other medications, and current or past involvement with alcohol or other drugs. This information would be useful in assessing factors that may be contributing to mortality and why so many fatalities involve individuals using multiple drugs.

It would be helpful to know what information individuals are receiving from their physicians when methadone is prescribed, and whether patients and prescribers fully understand the potential dangers of methadone misuse and abuse.

It also would be useful to compare data from IMS Health, ARCOS, or State prescription monitoring programs (PMPs) with medical examiner data to estimate how much methadone is being prescribed in regions that report increased cases of methadone-associated deaths. The group endorsed the expansion of PMPs, including creation of a uniform system for reporting and compiling data, leading to a national database. However, participants also recognized that PMPs have limitations and need to be improved, and that further assessment of possible adverse effects on patient confidentiality and access to care is needed (Droz, meeting presentation, 2003).

Better information is needed about the nature of education and prevention messages currently being communicated to and by the public, patients, practitioners, and the media. Given inaccurate or incomplete information, patients may be deterred from seeking treatment using methadone or other opioid drugs for legitimate medical problems, including addiction. Anecdotal information contributed by meeting participants suggests an urgent need to clarify popular misperceptions and to correct misinformation at all levels.

In identifying data needs, participants concluded that it would be helpful to know of any specific national and local concerns. Whatever research occurs should be interdisciplinary, involving stakeholders from various fields. It would be helpful if the Federal government developed a special work group to focus on this issue.

Health Professionals Need Better Training in Addressing Pain and Addiction

Today, pain and addiction are recognized as pervasive medical disorders for which health professionals have an ethical obligation to provide the best available treatment. All FDA-approved opioid medications, including methadone, are powerful and useful drugs in this treatment. On the other hand, inappropriate prescribing, misuse, and abuse of prescription opioids (including methadone) are serious public health problems attended by substantial morbidity and mortality. The medical community and government agencies are responsible both for ensuring that such medications continue to be available for therapeutic use and for preventing their misuse or abuse.

Thus, physicians and other health professionals must become well-grounded in their knowledge of how to treat both pain and addiction. Accordingly, the diagnosis and treatment of addiction, and appropriate pharmacotherapies for pain and addiction, should be part of core educational curricula for all health care professionals. In particular, physicians need to understand methadone's pharmacology and appropriate use, as well as specific indications and cautions to consider when deciding whether to use this medication in the treatment of pain or addiction. While this recommendation is relevant to the educational needs of the medical community as a whole, it has particular resonance for staff of OTPs and physicians who provide pain treatment.

Public Misperceptions About Methadone Must Be Addressed

There is an immediate need for professional organizations and regulatory agencies to present scientific evidence and credible data to counter misinformation about methadone and “methadone clinics” (OTPs) presented in the mass media. The public needs to know that methadone-associated mortality is being addressed, and that when methadone is prescribed, dispensed, and used appropriately, related mortality is virtually eliminated. To this end, National Assessment participants agreed that professional associations, provider organizations, and advocacy groups need to be engaged in these educational activities.

Participants also agreed that a special evidence-based “White Paper” on methadone should be developed to communicate vital information to policymakers, health professionals, and the public. Such a White Paper would incorporate information from the meeting deliberations and Background Briefing Report prepared for the National Assessment, in addition to other information that may be required to address a range of issues.

The contents of the White Paper could be made available in relevant form to various stakeholder groups, including: addiction treatment providers (physicians, nurses, counselors) and administrators, pain management specialists, psychiatrists, pharmacists, and others. Patient advocacy groups also could play a significant role in disseminating this vital information.

National Assessment participants viewed the White Paper as an organizing tool and as a way to initiate a process that could become more far-reaching in its objectives.

Public Policies Must Respond to Multiple Needs

More than 50 years of clinical experience have shown that methadone is a fundamentally safe and effective medication. Accordingly, neither policy nor regulatory concerns should impede patients' access to medically indicated use of methadone and other medications vital to the treatment of pain and addiction.

Any comprehensive framework affecting health care policy and medical practice regarding opioid medications should address the needs of law enforcement and regulatory agencies, professional education, pain management, and addiction treatment providers. For example, National Assessment participants agreed that broad regulatory actions directed toward all OTPs, such as State-imposed restrictions on prescribing methadone, are unlikely to be effective. The exception would be actions focusing on particular programs or geographic areas where problems are identified. In the absence of such specific problems, generalized actions against OTPs would have no effect on the overall mortality problem at best and, at worst, could have damaging effects on the availability of a vital treatment modality.

Part 6. Conclusions

From the data examined during this National Assessment, it appears that the recent upsurge in public concern over methadone abuse and fatalities is linked to several factors, some of which may be an appropriate impetus to new health policy.

- **First**, recent years have seen documented increases in abuse of heroin and all opioid analgesics. When their preferred drugs are not available, some individuals turn to abuse of methadone.
- **Second**, over the same period, methadone (primarily in tablet form) has become more accessible as physicians increasingly have prescribed it for pain relief.
- **Third**, press reports in some States have suggested that methadone has become more available to unauthorized users following the adoption of new Federal regulations that enabled OTPs to relax their policies regarding take-home doses of methadone. However, these allegations are not supported by the data reviewed during the National Assessment. In fact, the perception that OTPs are contributing to the problem of overdose deaths appears to be highly exaggerated. An argument can be made that Federal requirements for dosing during the start-up (induction) phase of methadone maintenance treatment actually may have helped to minimize methadone-associated fatalities. It also should be noted that OTPs provide demonstrably effective treatment for opioid addiction.

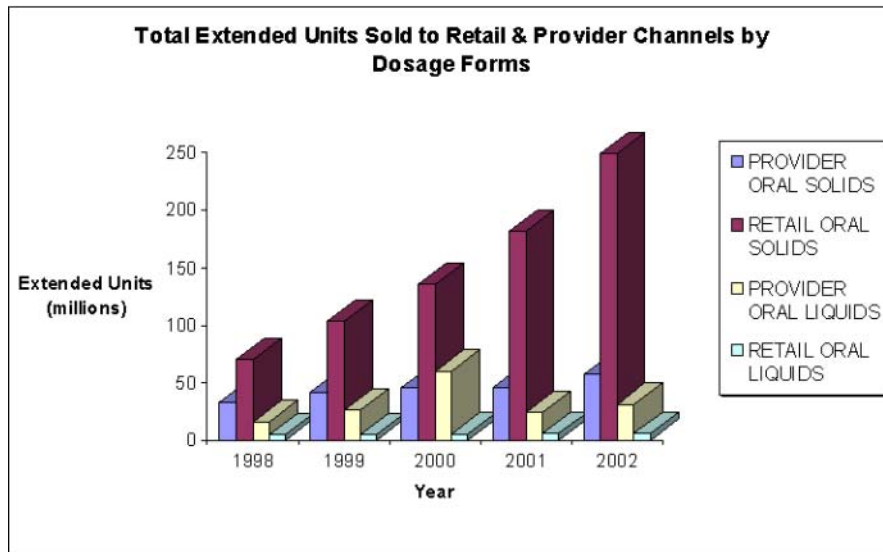
Three primary scenarios characterize current reports of methadone-associated mortality:

1. In the context of legitimate patient care, methadone accumulates to harmful serum levels during the first few days of treatment for addiction or pain (that is, the induction period before methadone steady state is achieved or tolerance develops).
2. Illicitly obtained methadone is used by some individuals who have diminished or no tolerance to opioids and who may use excessive and/or repetitive doses in an attempt to achieve euphoric effects.

3. Methadone – either licitly administered or illicitly obtained – is used in combination with other CNS depressant agents (such as benzodiazepines, alcohol, or other opioids).

The data reviewed for this National Assessment show that the greatest incremental growth in methadone distribution in recent years is associated with use of the drug as an analgesic and its distribution through pharmacies. In fact, the rate of increase in distribution of solid methadone formulations (tablets and diskettes), primarily through pharmacies, has surpassed the rate of increase in distribution of the liquid formulations that are the mainstay of dispensing in OTPs (Figure 5).

Figure 5. Number of Units of Methadone Distributed Through Retail and Other Channels, by Dosage Form



Data from IMS Health, Retail and Provider Perspective, courtesy of Laura A. Governale, PharmD.

Taken together, the data confirm a correlation between increased methadone distribution through pharmacy channels and the rise in methadone-associated mortality. The data, thus, support the hypothesis that the growing use of oral methadone, prescribed and dispensed for the outpatient management of pain, explains the dramatic increases in methadone consumption and the growing availability of the drug for diversion to illicit use. Although the data remain incomplete, National Assessment meeting participants concurred that methadone tablets and/or diskettes distributed through channels *other than OTPs most likely are the central factor in methadone-associated mortality.*

With the release of this National Assessment Report, it is hoped that action will be initiated at the Federal and State levels, and in the public and private sectors, to implement the recommendations offered here. Additionally, SAMHSA must continue its current vigilance and ongoing efforts to improve the quality, safety, efficacy, and reliability of addiction treatment, as well as enhancing patient satisfaction and community understanding and acceptance of methadone treatment. This will ensure that OTPs continue to make an important contribution to solving the problem of methadone-associated mortality.

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Part 8. Appendices

Appendix 1. Participants in the National Assessment

Appendix 2. Agenda

Appendix 3. Epidemiologic Databases Consulted

Appendix 4. Past Investigations of Methadone-Associated Mortality

Appendix 5. Methadone Serum Level Conversion Factors

Appendix 6. MedWatch Form

Appendix 7. PedTox Case Report Form (from NAME)

Appendix 8. Methadone Identified in Laboratory Testing

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Appendix 2. Agenda

Thursday, May 8, 2003

Introductions:

Alan Trachtenberg, MD, MPH; Medical Officer, DPT/CSAT/SAMHSA

Opening Remarks: The CSAT Perspective:

H. Westley Clark, MD, JD, MPH, CAS, FASAM; Director, CSAT

The Opioid Treatment Program (OTP) Perspective:

Mark W. Parrino, MPA, President, AATOD (OTP Co-Chair)

Clinical Importance of Methadone in Opioid Agonist Therapy (OAT)
and Pain Management:

Seddon R. Savage, MD, FASAM (Pain Co-Chair)

Challenges to the Forensic Community:

Bruce Goldberger, PhD (Toxicology Co-Chair)

Drug Abuse Warning Network (DAWN) and other SAMHSA Office of Applied
Studies (OAS) Data:

Elizabeth Crane, PhD, MPH

Opioid Utilization (Denominator) Data:

ARCOS: June Howard, DEA, & Alan Trachtenberg, CSAT

NCHS Outpatient Utilization Data: Catharine Burt, EdD, NCHS

IMS: Laura Governale, PharmD, FDA

Methadone Mortality Data from MedWatch (Passive National Surveillance):

Martin L. Pollock, PharmD, FDA

Surveillance of Medication-Related Mortality and Morbidity (Current efforts of the
National Center for Injury Prevention and Control):

Dan Budnitz, MD, MPH

Cardiac Questions (QT prolongation, TdP):

Background: *Mori Krantz, MD*

New Population-based Data: *Bridget Martell, MD*

Discussion: *Barry Stimmel, MD*

Trends in Fatal Opioid Poisoning - National Numerator and Death Certificate Data:

Lois Fingerhut, MA, NCHSR

State-Level Data:

Florida: *Bruce Goldberger, PhD*

North Carolina: *Kay Sanford, MSPH*

Maine: *Marcella Sorg, RN, PhD*

Washington & Virginia: *Ann Marie Gordon, BA, MS*

Texas: *Jane Maxwell*

Discussion Breakout Meetings (3 Interdisciplinary Groups):

Questions for resolution:

- What are the problems?
- Which drugs and persons are involved?
- What further data are needed? Why?
- Where should data come from?
- How should the data be organized?
- How can the data help in developing action plans?

Group Reports & Discussion

Friday, May 9, 2003

Overview:

H. Westley Clark, MD, JD, MPH, CAS, FASAM; Director, CSAT

The Challenge for the Morning:

Seddon R. Savage, MD, FASAM

Relevant New Efforts at Data Collection:

National Violent Death Reporting System (NVDRS): *Randy Hanzlick, MD*

NAME Pediatric Toxicology Registry: *John Howard, MD*

Consumer Product Safety Commission: *Tom Schroeder, MS*

Electronic Prescription Monitoring Systems: *Danna Droz*

Developing Relationships Between Medical Examiner & Medical Practitioner – A report from Canada:

Doug Gourlay, MD

Action Planning Breakout Sessions (3 Intra-disciplinary Groups): Forensics (Pathology & Toxicology), Addiction Treatment, Pain Treatment:

General questions for resolution:

- Are there actions that could/should be taken immediately?
- What are longer-range goals?
- How can each “community”/ disciplinary group contribute?
- What resources, programs, or services (RPS) already exist?
- What new RPSs can/should be developed? Why?
- Who are the target audiences?
- How should outcomes be monitored?

Group Reports from Breakout Sessions

Brief Statements from Organization representatives (NAME, AAFS, SOFT, ASAM, AAAP, AAPM, etc.):

Open invitation for voluntary additions to the record (proceedings) from the national organizations represented at the meeting.

Closing: Where do we go from here?

Mark W. Parrino, MPA

Appendix 3. Epidemiologic Databases Consulted

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
SAMHSA - OAS	The Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies (OAS) is a source of information on the prevalence and incidence of substance abuse and mental health problems in the U.S. and the characteristics of those who suffer from these problems. SAMHSA's OAS is also the national source of information on the location, organization, and capacity of providers which offer services to prevent and treat substance abuse and the cost, quality, and effectiveness of the services of these providers. For more information on the various surveys and reports see: http://www.samhsa.gov .
NSDUH (NHSDA)	The National Survey on Drug Use and Health (NSDUH) has been conducted since 1971 and serves as the primary source of information on the prevalence and incidence of illicit drug, alcohol, and tobacco use, as well as the non-medical use of licit drugs, in the civilian, noninstitutionalized population aged 12 or older in the U.S. Information about substance abuse and dependence, mental health problems, and receipt of substance abuse and mental health treatment also is included. Since 1999, about 70,000 interviews are conducted each year. Before 2002, the name of the survey was the National Household Survey on Drug Abuse (NHSDA).
DAWN	The Drug Abuse Warning Network (DAWN) provides semiannual estimates of the number of drug-related visits to hospital emergency departments based on a nationally representative sample of short-stay general hospitals located throughout the coterminous United States. DAWN also collects information on drug-related deaths from selected medical examiner offices. Emergency room estimates are produced for 21 large metropolitan areas and for the nation, while drug-related death data are produced for more than 40 metropolitan areas.
DASIS	The Drug and Alcohol Services Information System (DASIS) is the primary source of national data on substance abuse treatment and has three components:
<i>I-SATS</i>	The Inventory of Substance Abuse Treatment Services (I-SATS) is a listing of all known public and private substance abuse treatment facilities in the United States and its territories. Before 2000, the I-SATS was known as the National Master Facility Inventory.
<i>N-SSATS (UFDS)</i>	The National Survey of Substance Abuse Treatment Services (N-SSATS) is an annual survey of all facilities in the I-SATS that collects information on location, characteristics, services offered and utilization. Information from the N-SSATS is used to compile and update the National Directory of Drug and Alcohol Abuse Treatment Programs and the on-line Substance Abuse Treatment Facility Locator. The N-SSATS includes a periodic survey of substance abuse treatment in adult and juvenile correctional facilities. Before 2000, the N-SSATS was known as the Uniform Facility Data Set (UFDS).
<i>TEDS</i>	The Treatment Episode Data Set (TEDS) is a compilation of data on the demographic and substance abuse characteristics of admissions to substance abuse treatment. Information on treatment admissions is routinely collected by State administrative systems and then submitted to SAMHSA in a standard format.
DSRS	The Drug Services Research Survey (DSRS) is a national survey which obtained information on drug treatment providers and patients in 1990. The survey consisted of several components, a facility-based telephone interview with a sample of 1,183 drug treatment providers followed by a patient record-based survey of 2,200 patients discharged from treatment in a sub-sample of the programs. Follow-up of the patients to assess post-treatment status was conducted in the Services Research Outcomes Study (SROS).
SROS	The Services Research Outcome Study (SROS) is a follow-on to the 1990 Drug Services Research Survey (DSRS). The SROS provided for a five-year post-discharge follow-up of a broadly representative sample of approximately 3,000 drug abuse patients treated during 1989 to 1990. The study ascertained their behavior up to five years after the 1989-1990 treatment episode, and analyzes treatment results in light of the type and cost of treatment services the patients received.

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
ADSS	<p>The Alcohol and Drug Services Study (ADSS) is a nationally representative survey of substance abuse treatment facilities and patients. The data were collected to estimate the patient length of stay and the costs of treatment as well as to describe the post-treatment status of patients. ADSS builds upon the 1990 Drug Services Research Survey (DSRS) and the Services Research Outcome Study (SROS) with a more complete sampling frame, an enhanced sampling design, and more detailed measures of the level of treatment services provided, the costs of treatment, and patients in treatment.</p>
DEA ARCOS	<p>U.S. Drug Enforcement Administration</p> <p>The Automation of Reports and Consolidated Orders System (ARCOS) is an automated, comprehensive drug reporting system that monitors the flow of controlled substances from their point of manufacture through commercial distribution channels to point of sale or distribution at the dispensing/retail level by hospitals, retail pharmacies, practitioners, mid-level practitioners, and teaching institutions. Included in the list of controlled substance transactions tracked by ARCOS are the following: All Schedules I and II materials (manufacturers and distributors); Schedule III narcotic materials (manufacturers and distributors); and selected Schedule III and IV psychotropic drugs (manufacturers only).</p> <p>ARCOS accumulates these transactions which are then summarized into reports which give investigators in Federal and State government agencies information which can then be used to identify the diversion of controlled substances into illicit channels of distribution.</p> <p>Available at: http://www.deadiversion.usdoj.gov/arcos/index.html.</p>
NFLIS	<p>The National Forensics Laboratory Information System (NFLIS) from the DEA systematically collects results from drug analyses conducted by State and local forensic laboratories, and reflects drug evidence seized by law enforcement agencies. Results in this report are presented for both drug items and drug cases.</p> <p>Approximately 300 State and local forensic laboratories in the United States analyze nearly 2 million drug items each year. The Drug Enforcement Administration (DEA) has long recognized that these analyses represent valuable information. The current partnership includes 34 State lab systems and 49 local or municipal labs, a total of 179 individual labs.</p> <p>See: http://www.deadiversion.usdoj.gov/nflis/overview.htm.</p>
ONDCP National Drug Control Strategy	<p>Office of National Drug Control Policy, The White House</p> <p>An annual report to Congress compiles data from a variety of sources relating to drug misuse and abuse in the U.S., as well as Administration strategies and budgets to address the problem.</p> <p>See http://www.whitehousedrugpolicy.gov/index.html.</p>
DENS	<p>The Drug Evaluation Network System (DENS) is an electronic information system to track national trends in substance abuse treatment sponsored by the White House Office of National Drug Control Policy (ONDCP) and the Center for Substance Abuse Treatment (CSAT). It is a collaborative effort between the Treatment Research Institute (TRI) at the University of Pennsylvania and the National Center on Addiction and Substance Abuse (CASA) at Columbia University. The goal of the project is to provide practical and current clinical and administrative information on patients entering into substance abuse treatment throughout the nation.</p> <p>Through the RADARS System (see below), Purdue Pharma provided funding in 2002 to add questions to the DENS questionnaire about prescription drugs identified by individuals entering addiction treatment programs.</p> <p>See http://www.densonline.org/ for more information.</p>

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
FDA MedWatch	<p>U.S. Food and Drug Administration</p> <p>MedWatch, the FDA's Safety Information and Adverse Event Reporting Program, serves both health care professionals and the public. It provides clinical information about safety issues involving medical products, including prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products. MedWatch allows healthcare professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.</p> <p>See: http://www.fda.gov/medwatch/index.html</p>
NCHS - CDC NAMCS	<p>National Center for Health Statistics / Centers for Disease Control and Prevention See: http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm</p> <p>The National Ambulatory Medical Care Survey (NAMCS) is designed to meet the need for objective, reliable information about the use of ambulatory medical care services in the United States. Findings are based on a sample of visits to nonfederally employed office-based physicians who are primarily engaged in direct patient care. The survey was conducted annually from 1973 to 1981, in 1985, and annually since 1989.</p>
NHAMCS	<p>The National Hospital Ambulatory Medical Care Survey (NHAMCS) collects data on the utilization and provision of ambulatory care services in hospital emergency and outpatient departments. Findings are based on a national sample of visits to the emergency departments and outpatient departments of noninstitutional general and short-stay hospitals, exclusive of Federal, military, and Veterans Administration hospitals, located in the 50 States and the District of Columbia. Annual data collection began in 1992.</p>
CDC WONDER	<p>CDC's WONDER is an easy-to-use system that provides a single point of access to a wide variety of CDC reports, guidelines, and numeric public health data, including: mortality, hospital discharges, behavioral risk factors, and many other topics.</p> <p>See: http://wonder.cdc.gov/</p>
AAPCC TESS	<p>American Association of Poison Control Centers</p> <p>Toxic Exposure Surveillance Systems (TESS) data are compiled by the AAPCC. From its inception in 1983, TESS has grown dramatically, with the cumulative database in 2001 containing 31.4 million human poison exposure cases, including about 2.3 million for 2001 alone reported by 64 participating poison centers covering 48 States and the District of Columbia.</p> <p>See: http://www.aapcc.org/annual.htm</p>
IMS	<p>Operating in more than 100 countries, IMS Health, a leading provider of information to the pharmaceutical and healthcare industries, offers marketing data on prescription and over-the-counter pharmaceutical products.</p> <p>IMS tracks and measures prescriptions dispensed along with sales volumes, pricing and market share – by product, company, region and distribution channel. Customized measures of market performance include: Daily, weekly and monthly prescription tracking; key physician prescribing patterns.</p> <p>Additional information is available at http://www.imshealth.com.</p>

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
RADARS	<p>Purdue Pharma established the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System in 2002 to study the prevalence of abuse and diversion of controlled prescription medications. The system is designed to obtain quantitative and qualitative information on the relative rates of abuse, addiction, and diversion of commonly prescribed prescription pain medicines.</p> <p>Initially, the RADARS System was to monitor six types of prescription opioid pain medications with recognized abuse potential: morphine, buprenorphine, fentanyl, hydrocodone, hydromorphone, and oxycodone. As experience with the system accumulates, other types of medications, such as benzodiazepines (alprazolam and diazepam), are to be added. This database is not open to the public.</p> <p>See: http://www.purduepharma.com.</p>
OTHER...	
NVDRS	<p>The National Violent Death Reporting System (NVDRS) is a State-based initiative, funded by the CDC, which tracks violent deaths resulting from the use of physical force, either intentional or unintentional: homicide, suicide, firearm accidents, legal interventions, terrorism, etc. Within that, there is a Medical Examiner/Coroner Death Investigation Data Set (MECDIDS) providing standard fields for data collection. Another component – BLURBS – is a coding scheme allowing searches for specific toxicology data.</p>
NAME PedTox Registry	<p>The National Association of Medical Examiners' (NAME) Pediatric Toxicology (PedTox) Registry represents jurisdictions from around the U.S. and contains detailed case description information beyond what can be found in death certificate data. Reporting is voluntary and toxicologic data are not standardized.</p>
CPSC/NEISS	<p>The Consumer Product Safety Commission (CPSC) uses death certificate data for a National Electronic Injury Surveillance System (NEISS). The Commission also used NCHS (National Center for Health Statistics) data to estimate causes of death for specific product-related accidents. This includes drug-related accidents, and specific studies can be done on request to evaluate specific agents.</p>
PMPs	<p>Prescription Monitoring Programs (PMPs) have been implemented by a number of States to collect data for public health initiatives, law enforcement, and early intervention and prevention of problems related to diversion and abuse of prescription drugs. PMPs rely on pharmacies and other drug dispensers to send data electronically to central state-managed repositories.</p>
NIJ/ADAM	<p>The National Institute of Justice's (NIJ) Arrestee Drug Abuse Monitoring (ADAM) program tracks trends in the prevalence and types of drug use among booked arrestees in urban areas. The data play an important role in assembling a national picture of drug abuse in the arrestee population and have been a central component in studying the links between drug use and criminal behavior. See: http://www.adam-nij.net/</p>

Appendix 4. Past Investigations of Methadone-Associated Mortality

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality			
Reference	Location/Date	Subjects/Design	Comments
Dole et al., 1971	New York, 1960s	Series of 2 cases in a methadone program.	Accidental overdose not otherwise specified.
Gardner, 1970	London, 1965-1969	Descriptive study of 12 methadone deaths.	Concludes that at least 7 deaths occurred due to lack of opioid tolerance, while 8 resulted from too high a starting dose (greater than 70 mg).
Baden, 1970	New York, 1967-1970	Report on 24 deaths in a methadone program and 8 not in OTP.	Half of the methadone deaths were related to abuse of alcohol and other drugs. Of 8 methadone-associated deaths outside OTP, 5 involved oral overdoses (2 in opioid-naïve subjects), 3 involved IV abuse of methadone.
Gearing and Schweitzer, 1974	New York, 1964-1971	Long-term descriptive study on outcomes of subjects in OAT.	Causes of death in 153 subjects are not detailed, but at least 30 percent were polydrug-related.
Roizin et al., 1972	New York, 1972	Series of 14 deaths, 57 percent of whom were receiving methadone.	Methadone doses ranged from 40-180 mg/d. Polydrug abuse was implicated in most cases, including morphine (4) and quinine (2).
Greene et al., 1974	District of Columbia, 1970-1973	Descriptive study of methadone death rate.	Methadone deaths increased sharply following diversion to illicit markets – 46.2 percent of decedents were not opioid-tolerant – and were curtailed sharply by restricting dispensing to licensed clinics rather than private physicians.
Appel et al., 2000	New York, 1966-1976	176 deaths among 1,544 patients in and out of OAT program.	Overall, 93 deaths occurred during methadone treatment and 83 after leaving treatment. Only 2 deaths during treatment were opioid-related.
Concool et al., 1979	East Harlem, NY, 1969-1976	Review of deaths in patients enrolled in OAT, with risk assessment.	The mortality rate was 20 per 1000 patients, with deaths largely due to alcoholism and violence. None of the deaths were directly attributed to methadone.
Caplan et al., 1983	Maryland, 1975-1980	77 deaths in which methadone was present.	Methadone was the sole agent in 18 deaths. There was an overlap in serum methadone levels across sole-agent deaths, polydrug deaths, and non-drug-related deaths with methadone present.
Kringsholm et al., 1988	Denmark, 1968-1986	Descriptive study of drug deaths.	20 percent of drug deaths during abstinence were due to methadone. No details of circumstances were provided.
Petry et al., 1998	New York, 1975-1986	Review of 325 deaths among OAT patients receiving methadone.	During a 12-year period, deaths attributed to medical causes (especially AIDS) dramatically increased, while drug overdose deaths held fairly constant at low levels.
Harding-Pink, 1991	Geneva, Switzerland, 1981-1986	Description of 25 deaths associated with methadone.	14 deaths were caused by methadone, of which 3 occurred in the first two weeks of treatment and 6 less than two weeks after leaving treatment; 9 were caused by a combination of opioids and methadone. 15 deaths were associated with concurrent benzodiazepine use.

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality			
Reference	Location/Date	Subjects/Design	Comments
Davoli et al., 1993	Italy, 1980-1988	Matched case control analysis of IV drug abusers in OAT.	The risk of overdose death was higher for subjects who had left methadone treatment, particularly within the first year (odds ratio: 7.98).
Drummer et al., 1990, 1992	Victoria, Australia, 1990	10 deaths in methadone-treated patients.	Deaths occurred in the early stages of OAT, at doses ranging from 45-70 mg (mean: 53 mg). Six subjects had additional CNS-active drugs present; all had chronic hepatitis; 5 had bronchopneumonia.
Kringsholm, et al. 1994	Denmark, 1987-1991	Descriptive study of drug deaths.	Against a background of increasing fatalities, with most also involving IV heroin, methadone poisoning cases increased significantly in 1991. About half the victims were on methadone maintenance at the time of death.
Neeleman and Farrell, 1997	England and Wales, 1974-1992	Retrospective longitudinal survey.	Poisoning deaths involving methadone (alone or in combination) rose 80 percent over a 3-year period. However, there was no evidence that this was disproportionate to the increase in heroin deaths.
Barrett et al., 1996	Harris County, Texas, 1987-1992	Investigation of 91 deaths involving methadone.	A team of CDC investigators found that 85 percent of deaths involved polydrug abuse and only 20 percent of decedents were in OAT at the time of death. Only 11 cases were attributed directly to methadone toxicity.
La Harpe and Fryc, 1995	Geneva, Switzerland, 1987-1993	Description of 24 deaths associated with methadone.	No deaths occurred in first two weeks of methadone treatment, 3 occurred less than 2 weeks after leaving OAT, 11 involved concurrent use of benzodiazepines, 8 involved concurrent use of alcohol, and 11 involve concurrent use of heroin.
Goldstein and Herrera, 1995	Albuquerque, 1971-1993	Long-term follow-up of 1,019 patients registered in methadone OAT.	34 percent of patients died in the 22 years since starting methadone therapy. More than a third of the deaths were related to drug abuse. Subjects were 4-6 times more likely to die than non-addicts.
Clark et al., 1995	Sheffield, England, 1991-1994	18 subjects; case study.	7 subjects died in the early stages of methadone treatment (and had received doses in the range of 30-100 mg). 3 died after long-term use and 8 died from non-prescribed drug use. Multiple drug use was common but was not judged to have played a major role in most deaths.
Cairns et al., 1996	Manchester, England, 1985-1994	90 subjects; case study.	The number of methadone deaths increased during the study period. Methadone was the sole cause of death in 52 cases, while 36 died from other drug use. Methadone cases represented 15 percent of total fatal drug overdoses during the study period.
Williamson et al., 1997	South Australia, 1984-1994	47 fatalities, with risk assessment.	Widespread use of methadone tablets for chronic pain led to a disproportionate increase in deaths. The death rate increased sharply in 1993-94 concurrent with the opening of private methadone clinics.
Caplehorn, 1998	Sydney, Australia, 1994	13 subjects; case study.	Of 13 patient deaths, 10 died in the first two weeks of treatment, during methadone induction; doses ranged from 25-110 mg (median: 40 mg).

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality			
Reference	Location/Date	Subjects/Design	Comments
Caplehorn and Drummer, 1999	Sydney, Australia, 1994	Review of 86 methadone-associated deaths; risk assessment.	Of 89 deaths, 29 involved diversion of methadone syrup and 18 the use of methadone tablets. 38 patients died during OAT. The risk of death in the first 2 weeks was 6.7 times that of addicts outside OAT, but was reduced 98-fold later during methadone maintenance treatment.
Zador and Sunjic, 2000	New South Wales, Australia, 1990-1995	238 methadone-associated deaths examined.	44 percent of deaths were drug-related, with most (92 percent) involving polydrug abuse; 42 percent occurred during the first week of methadone treatment.
Drummer, 1997	Victoria, Australia, 1994-1997	89 deaths in which methadone was detected.	Toxic methadone concentrations overlapped those in non-drug-related deaths in which methadone was present. Those starting OAT or who used the drug occasionally were at the greatest risk of death.
Valmana et al., 2000	London, England, 1997	Review of 40 methadone-associated deaths.	Of 40 methadone-related deaths, 72 percent did not involve prescribed methadone. These decedents were younger (median age: 22 years) than those who died of prescribed methadone (median age: 37 years), suggesting more chaotic abuse patterns in younger persons.
Perret et al., 2000	Geneva, Switzerland, 1994-1998	36 methadone cases, out of 106 total drug abuse fatalities.	35 of 36 decedents used illicit drugs in combination with methadone. Of 21 deaths attributed to methadone, only a third of those decedents were in OAT. Methadone-attributed deaths remained constant at 3-5 per year throughout the study period, while overall drug abuse deaths declined markedly.
Eastwood, 1998	London, England, 1998	Description of 13 childhood deaths.	Of 13 children poisoned with methadone syrup prescribed to a parent, five died. Methadone serum concentrations in children who died overlapped that in children who survived.
Karch and Stephens, 2000	San Francisco, 1997-1998	38 cases involving methadone (out of 3,317 examined).	Methadone was cited as a cause of death in 21 cases, although blood methadone concentrations were identical in this group and in the group in whom methadone was an incidental finding.
Buster et al., 2002	Amsterdam, The Netherlands, 1986-1998	5,200 methadone-maintained patients observed.	68 overdose deaths were recorded in a group of 5,200 methadone patients, with a modest increase during first 2 weeks of treatment. The overall death rate was 2.3 per 1000 patient-years.
Heinemann et al., 2000	Hamburg, Germany, 1990-1999	Surveillance of drug-related poisonings.	An increase in methadone-related fatalities coincided with declines in heroin deaths. 65 percent of methadone decedents were not enrolled in an OTP.
Bartu et al., 2002	Western Australia, 1993-1999	84 methadone-related deaths evaluated.	74 percent of deaths were caused by a combination of drug effects, with benzodiazepines present in 75 percent of those cases. 57 percent were not in an OTP at the time of death. Methadone-associated mortality peaked in 1998 at 7.7 per 1000 patients treated, one year after expansion into the private sector.

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality			
Reference	Location/Date	Subjects/Design	Comments
Green et al., 2000	South Australia, 1996-1999	35 cases of methadone causing or contributing to death.	Of 10 patients receiving methadone maintenance treatment, 4 died within the first week. Eight non-OAT cases involved diverted methadone, while 7 involved other drugs as well. Mean age of the decedents was 25 years.
Oliver et al., 2002	Sheffield, England, 1997-1999	82 drug-abuse related deaths.	Deaths attributed wholly or partially to methadone declined from 37 percent to 18 percent during the study period, against a background of increased methadone prescribing.
Squires, 2000	Scotland, 1994-2000	Surveillance report on methadone-related deaths.	Methadone deaths peaked in 1996 and then declined, while methadone prescriptions increased by 18 percent. 45 percent of deaths involved persons not prescribed methadone, all but 2 involved drug abuse-related causes, and there were no deaths within one month of starting methadone maintenance. Of decedents who were prescribed methadone, 60 percent were on observed dosing at the time of death.

Appendix 5. Methadone Serum Level Conversion Factors

In the literature, there does not appear to be a universally accepted standard for expressing the concentration of methadone (or other agents) detected in the blood of living or deceased subjects, and authors have used diverse measures of notation. Nanograms per milliliter (ng/mL) seems to be the accepted convention in the United States addiction treatment literature; therefore, all values noted in this report have been converted to that measure using the following factors:

Unit			1.0
deci-	d	1×10^{-1}	0.1
centi-	c	1×10^{-2}	0.01
milli-	m	1×10^{-3}	0.001
micro-	μ	1×10^{-6}	0.000001
nano-	n	1×10^{-9}	0.000000001

$\mu\text{g/L}$ – $1 \mu\text{g/L} = 1000 \text{ ng}/1000 \text{ mL} = 1 \text{ ng/mL}$

$\mu\text{g/mL}$ – $1 \mu\text{g/mL} = 1000 \text{ ng/mL}$
 $(1 \text{ ng/mL} = 0.001 \mu\text{g/mL})$

mg/L – $1 \text{ mg/L} = 1000 \text{ ng/mL}$
 $(1 \text{ ng/mL} = 0.001 \text{ mg/L})$

mg/dL – $1 \text{ mg/dL} = 10,000 \text{ ng/mL}$
 $(1 \text{ ng/mL} = 0.0001 \text{ mg/dL})$

$\text{mg}\%$ – $1 \text{ mg}\% = 1 \text{ mg}/100 \text{ mL} = 10,000 \text{ ng/mL}$
 $(1 \text{ ng/mL} = .0001 \text{ mg}\%)$

μmol – $1 \mu\text{mol} = 345 \text{ ng/mL}$
 $(1 \text{ ng/mL} = 0.0029 \mu\text{mol} = 2.9 \text{ mmol}$
 specific to methadone molecular weight)

Appendix 6. MedWatch Form

U.S. Department of Health and Human Services		Form Approved: OMB No. 0910-0001 Expires 02/28/06 See OMB instructions on reverse	
MEDWATCH		For VOLUNTARY reporting of adverse events and product problems	
The FDA Safety Information and Adverse Event Reporting Program		Page ____ of ____	
A. Patient information		C. Suspect medication(s)	
1. Patient identifier <small>In confidence</small>	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
B. Adverse event or product problem		D. Suspect medical device	
1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)		1. Brand name	
2. Outcomes attributed to adverse event (check all that apply) <input type="checkbox"/> death (include yr) <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization - initial or prolonged		2. Type of device	
<input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other: _____		3. Manufacturer name & address	
3. Date of event (month/yr)	4. Date of this report (month/yr)	4. Operator of device <input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other: _____	
5. Describe event or problem		5. Expiration date (month/yr)	
		7. If implanted, give date (month/yr)	
6. Relevant tests/laboratory data, including dates		8. If explanted, give date (month/yr)	
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatohepatic dysfunction, etc.)		9. Device available for evaluation? (Do not send to FDA) <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on _____ (month/yr)	
		10. Concomitant medical products and therapy dates (exclude treatment of event)	
8. Concomitant medical products and therapy dates (exclude treatment of event)		E. Reporter (see confidentiality section on back)	
		1. Name & address _____ phone # _____	
9. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no		3. Occupation _____	
10. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. <input type="checkbox"/>		4. Also reported to <input type="checkbox"/> manufacturer <input type="checkbox"/> user facility <input type="checkbox"/> distributor	

PLEASE TYPE OR USE BLACK INK

Mail to: **MEDWATCH**
5800 Fishers Lane
Rockville, MD 20852-9787
FAX to:
1-800-FDA-0178

FDA Form 3500 (11/02) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Appendix 7. PedTox Case Report Form (from NAME)

The following case report form is from the Pediatric Toxicology (PedTox) Registry at the National Association of Medical Examiners (NAME) web site – http://www.thename.org/pedtox_index.htm.

National Association of Medical Examiners Pediatric Toxicology Registry (PedTox) Case Report Form			
Instructions: Copy this form to report any case in which a substance was detected and quantified in an infant or a child. Toxicologists or others may also report non-fatal cases meeting the same criteria. Indicate if this is a <input type="checkbox"/> Death Case or <input type="checkbox"/> Living Child.			
Your case number: _____ Age _____ Race _____ Sex _____ Weight _____			
Specimen type (include site)	Substance name	Concentration (include units)	Role*
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
* (Role=) A= Caused or contributed to death (or morbidity) by direct toxic effect. B= Caused or contributed by mechanism such as drug-induced disease, hypersensitivity, idiosyncrasy etc. C= Possibly contributed to the incident, but not directly to death (fall while intoxicated, drunk driver etc.). D= Presence of drug or substance is incidental and did not cause or contribute to death or morbidity. E= Undetermined or unknown role: presence of drug or substance may have played a role.			
Manner of death: _____ Cause of death: _____			
Do you feel that the reported concentrations are indicative of concentrations that existed at the time of the incident that led to death (or initial toxicity/illness)?			
_____ Yes _____ No, because: _____			

Your name, office, phone, e-mail _____			

IN SPACE BELOW, PLEASE PROVIDE A NARRATIVE DESCRIPTION OF CASE CIRCUMSTANCES:			

Note: The examples for item C under "Role" – e.g., "fall while intoxicated, drunk driver" – do not appear applicable for this population of children and require reinterpretation by the reporter.

Appendix 8. Methadone Identified in Laboratory Testing

MEMORANDUM

To: Alan Trachtenberg
 From: Jane C. Maxwell
 Date: April 22, 2003

Subject: Data on Methadone Identified in Laboratory Tests

In preparing for the upcoming Methadone Associated Mortality: A National Assessment Meeting, I went to the data in the National Forensic Laboratory Information System (NFLIS) to see what information might be available on methadone in that dataset. NFLIS, which is sponsored by the Drug Enforcement Administration, collects results from drug analyses conducted by State and local forensic laboratories. It reflects drug evidence seized by law enforcement agencies and analyzed by forensic laboratories. NFLIS started in 1997 and the number of laboratories participating in the system in 2002 has grown to 35 State lab systems and 52 local or municipal labs for a total of 184 individual labs. The NFLIS system is continuing to grow, as the tables below show.

Table 1 shows the number of items which were examined and identified as hydrocodone, oxycodone, methadone, and then the total number of all items identified by NFLIS for 1999-2002 in all labs reporting nationwide.

Table 1. Number of Items Examined and Reported to NFLIS*

	1999	2000	2001	2002
Hydrocodone	2,153	4,157	6,665	8,944
Oxycodone	839	2,799	5,752	8,313
Methadone	249	461	1,002	2,221
All Items	437,059	615,165	810,045	927,484

Table 2 shows the percent increase for each group of drugs year by year. Notice that while the number of cases is increasing each year, the difference in growth between years is lessening for hydrocodone and oxycodone, while the difference is increasing for methadone, which could mean that methadone is becoming more available and replacing these other drugs as their availability becomes more restricted.

Table 2. Percent Increase in Items Examined and Reported to NFLIS*

	1999-2000	2000-2001	2001-2002
Hydrocodone	93%	60%	34%
Oxycodone	234%	106%	45%
Methadone	85%	117%	122%
All Items	41%	32%	14%

Table 3 shows the forms of methadone which were identified by the laboratories reporting to NFLIS. "No form specified" means that when the data were sent to NFLIS, the field was blank, and most of these items come from laboratories that do not record

this type of information in their databases. “Unspecified” means the laboratory reported to NFLIS that the form was unspecified, and these items come from laboratories that normally record the form of the materials, but for some reason, it was not specified for these items.

Note that the increase for liquid methadone was only 11 percent from 2001 to 2002, which probably reflects the growth in the NFLIS system, since the total number of exhibits increased 14 percent in this time frame. However, the increase in solid tablets was 133 percent, which could reflect increased availability of the 5mg and 10mg pain pills.

Table 3. Form of Methadone Examined and Reported to NFLIS**

	1999	2000	2001	2002	% Change 2001-2002
No Form Specified	111	208	431	662	54%
Liquid	34	70	111	123	11%
Other	2	2	12	28	133%
Residue	5	10	13	40	208%
Solid-Powder	3		21	24	14%
Solid-Resin	1		2	2	0%
Solid-Tablet	66	143	325	756	133%
Solid-Caplet			13	16	23%
Solid-Capsule			3	2	-33%
Solid-Rock			1	2	100%
Solid-Unspecified	5	7	26	62	138%
Unspecified		5	11	20	82%
Unknown				3	

*NFLIS “Specific Drug Counts for Methadone” and “25 Most Frequently Identified Substances” for 1999-2002 downloaded by Jane Maxwell from NFLIS website, April 21, 2003.

**Email from Albert Bethke to Jane Maxwell, Friday, April 18, 2003.