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.

Disclaimer

The views, opinions and content of this publication are those of the National Assessment participants, authors, and other referenced sources, and do not necessarily reflect the views, opinions, or policies of CSAT, SAMHSA, or any other part of the U.S. Department of Health and Human Services (DHHS).

Public Domain Notice

Material appearing in this document – except quoted passages, tables, graphs, or figures from copyrighted sources – is in the public domain and may be reproduced or copied without permission from SAMHSA or the authors. Citation of the source is appreciated. However, this publication may not be reproduced or distributed *for a fee* without the specific, written authorization of the Office of Communications, SAMHSA, DHHS.

Electronic Access and Copies of Publication

This publication may be accessed electronically through the following Internet World Wide Web connection: www.samhsa.gov. For additional free copies of this document please call SAMHSA's National Clearinghouse for Alcohol and Drug Information at 1-800-729-6686 or 1-800-487-4889 (TDD).

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.

Originating Office

Division of Pharmacologic Therapies, Center for Substance Abuse Treatment, SAMHSA, DHHS, 5600 Fishers Lane, Rockville, MD 20857.

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.

Charles G. Curie, MA, A.C.S.W., Administrator, Substance Abuse and Mental Health Services Administration

H. Westley Clark, MD, JD, MPH, CAS, FASAM, Director, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration

Contents

(This document also is available in HTML format at www.samhsa.gov.)

Contents: Conference Papers

(These documents, in HTML format, are available at www.samhsa.gov.)

Part 15. State-Level Data: Washington and Virginia: Ann Marie Gordon, MS, State of Washington Toxicology Laboratory

Part 16. State-Level Data: Texas: Jane C. Maxwell, PhD, Gulf Coast Addiction Technology Transfer Center, University of Texas at Austin

Part 17. National Violent Death Reporting System (NVDRS): Randy L. Hanzlick, MD, Chief Medical Examiner for Fulton County, Georgia

Part 18. National Association of Medical Examiners (NAME) Pediatric Toxicology Registry: John D. Howard, MD, Chief Medical Examiner for Pierce County, Washington

Part 19. Consumer Product Safety Commission's Use of Death Certificates: Tom Schroeder, MS, Consumer Product Safety Commission

Part 20. Electronic Prescription Monitoring Programs: Dana Droz, JD, Kentucky

Part 21. Review of Methadone Related Deaths in Ontario: Douglas Gourlay, MD, Anesthesiologist and Medical Consultant, Toronto, Ontario

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 from1990 through 1999; this number doubled again in 2002 (Ouelette-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,

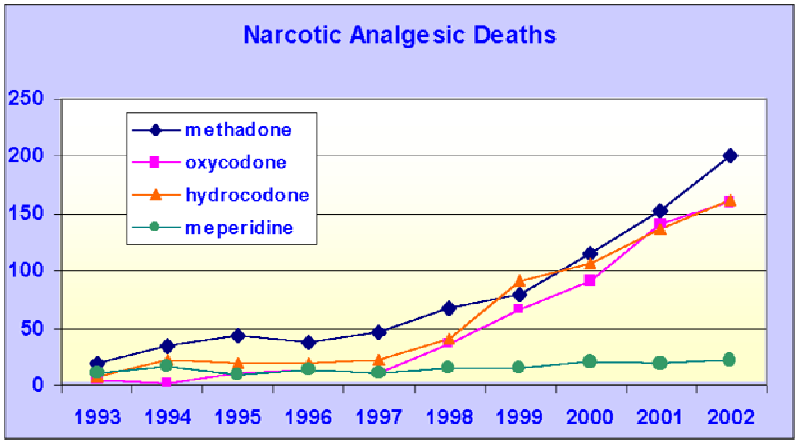
oxycodone, and methadone – were present in 71 percent of the deaths reported in the State and were identified as causative in 53 percent (Sorg and Greenwald, 2002). The number of deaths in which methadone was detected doubled between 1999 and 2000, leveled off in 2001, then increased again in 2002 (Sorg, 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

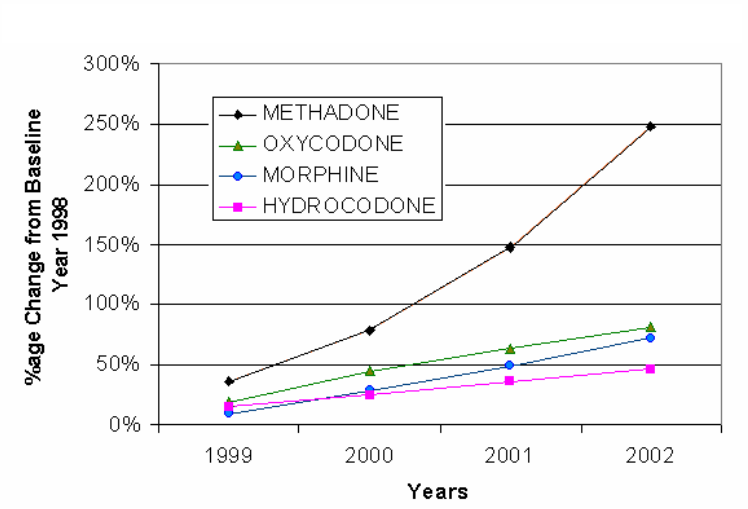
Concern over methadone-associated mortality is not new. Extensive surveillance data have documented such deaths ever since methadone's introduction as an analgesic and its subsequent use in the treatment of opioid addiction. This has occurred within the context of increased abuse of all opioid drugs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

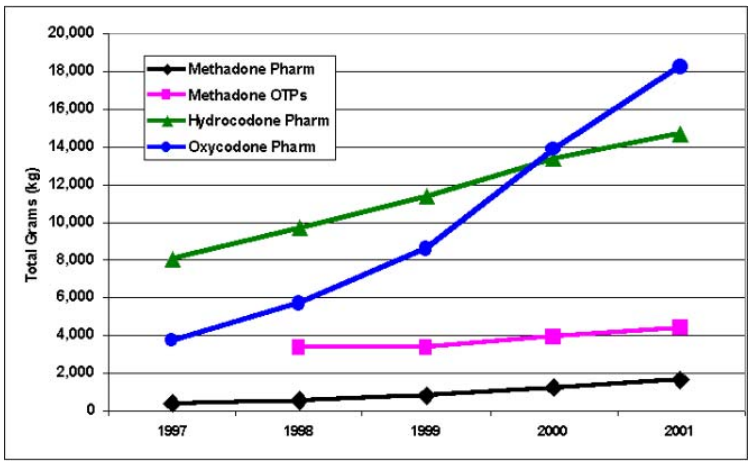
Figure 2. Percent Change in Distribution of Methadone and Three Comparison Drugs, from Baseline Year 1998 through 2002



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).

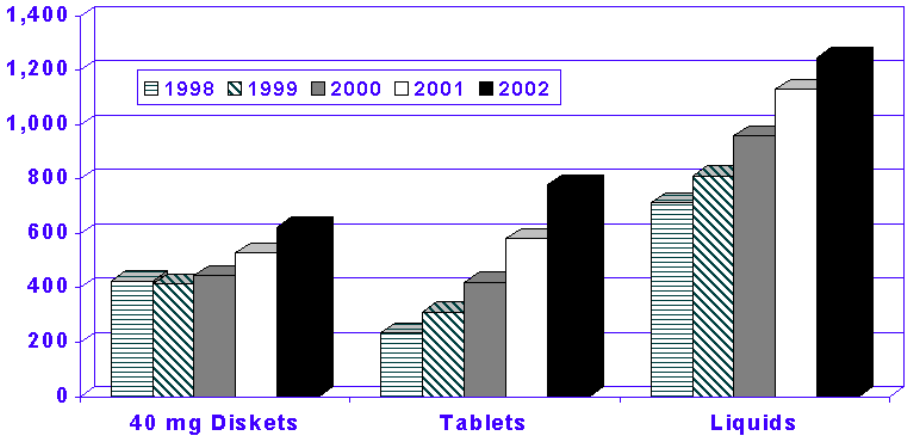
Figure 3. Distribution of Methadone through OTPs and Pharmacies, Compared



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.

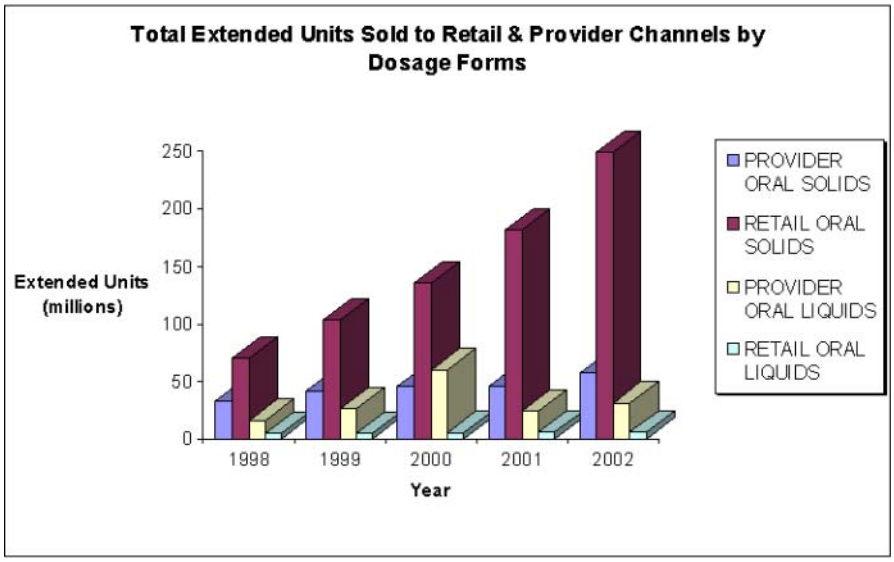
- **First**, recent years have seen documented increases in abuse of heroin and all opioid analgesics. When their preferred drugs are not available, some individuals turn to abuse of methadone.
- **Second**, over the same period, methadone (primarily in tablet form) has become more accessible as physicians 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.

Part 7. References and Bibliography

Appel PW. Joseph H, Richman BL. Causes and rates of death among methadone maintenance patients before and after the onset of the HIV/AIDS epidemic. Mt Sinai J Med. **2000**;67(5-6):444-451.

Associated Press. Overdose increases linked to methadone. Stuart News (Stuart, Florida). October 4, **2002**.

Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. Hepatology. **2001**;34(1):188-193.

Backmund M, Meyer K, Zwehl W, Nagengast O, Eichenlaub D. Myocardial infarction associated with methadone and/or dihydrocodeine. Eur Addict Res. **2001a**;7(1):37-39.

Baden MM. Evaluation of deaths in methadone users. Leg Med Annu. **1978**;127–31.

Baden MM. Methadone related deaths in New York City. Int J Addict. **1970**;5(3):489-498.

Ballesteros MF, Budnitz DS, Sanford CP, Gilchrist J, Agyekum GA, Butts J. Increase in deaths due to methadone in North Carolina [research letter]. JAMA. **2003**;290(1):40.

Barrett DH, Luk AJ, Parrish RG, Jones TS. An investigation of medical examiners cases in which methadone was detected, Harris County, Texas, 1987-1992. J Forensic Sci, JFSCA. **1996**;41(3):442-448.

Barton WI. Deaths involving methadone: A statistician's view. Drug Forum. **1975**;4(2):139-158.

Bartu EE, Popescu A, Heutt KF, Hansson R, Plumley N. Methadone-related deaths in Western Australia 1993-99. Aust NZ J Pub Health. 2002;26(4):364-370.

Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. **2000**;22(3)179-190.

Belluck P. Methadone, once the way out, suddenly grows as killer drug. New York Times (National Edition). New York Times. February 9, **2003A**: 1,20.

Belluck P. Overdoses and deaths from abuse of drug methadone are up. New York Times. February 2, **2003B**.

Belluck P. Recently for drug abusers, methadone has become a double-edged sword. New York Times (National Edition). February 9, **2003C**: 20.

Bendavid, N. Survey of drugs in Cook County: 333,000 labeled hard-core users. Chicago Tribune. December 12, **1997**;sec 1:1.

Bittar P, Piguet V, Kondo-Oestreicher J, et al. Methadone induced long QTc and "torsade de pointe." Swiss Medical Forum (Forum Med Suisse). **2002**(Apr 10, Suppl 8):36S. [Abstract P244.]

Borron SW, Monier C, Risede P, Baud FJ. Interaction of opiates with benzodiazepines in overdoses. J Toxicology:Clin Toxicology. **2001**;39(3):212.

Bowler GM, Galloway DW, Meiklejohn BH, and Macintyre CC. Sharp fall in blood pressure after injections of heparin containing chlorbutanol. Lancet. **1986**;1:848-849.

Brown FM, Griffiths PS. P450 Guide: Comprehensive Enzymatic Drug Metabolism Reference. 2nd ed. Montgomery, AL: P450Guide.com; **2000**.

Bruera E. Opioid rotation, methadone urged for hard-to-treat cancer pain. Presentation at 14th international meeting of MASCC. In: Oncology News International. **2002**;11(12):55.

Cairns A, Roberts IS, Benbow EW. Characteristics of fatal methadone overdose in Manchester, 1985–94. BMJ. **1996**;313(7052):264–265.

Caplan YH, Ottinger WE, Crooks CR. Therapeutic and toxic drug concentrations in post mortem blood: A six year study in the State of Maryland. J Anal Toxicol. **1983**;7(5):225-230.

Caplehorn JRM. Deaths in the first two weeks of maintenance treatment in NSW in 1994: Identifying cases of iatrogenic methadone toxicity. Drug and Alcohol Review. **1998**;17:9-18.

Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: Lives lost and saved. Med J Aust. **1999**;170(3):104-109.

CDHAG (Commonwealth Department of Health and Aged Care). Induction and Stabilisation of Patients Onto Methadone. Monograph Series No. 39. Canberra: Commonwealth of Australia; **2000**. Available at http://www.health.gov.au.

Chang A, Emmel DW, Rossi GC, Pasternak GW. Methadone analgesia in morphine-insensitive CXBK mice. Eur J Pharm. **1988**;351:189-191.

Codd E, Shank R, Schupsky J, Raffia R. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. J Pharmacol Exp Ther. **1995**;274:1263-1270.

Clark JC, Milroy CM, Forrest ARW. Deaths from methadone use. J Clin For Med. **1995**;2:143-144.

COMPA (New York State Committee of Methadone Program Administrators). Regarding Methadone Treatment and Other Pharmacotherapies: A Review. New York, NY: COMPA; revised **1999**. See also: http:www.compa-ny.org.

Concool B, Smith H, Stimmel B. Mortality rates of persons entering methadone maintenance: A seven–year study. Am J Drug Alcohol Abuse. **1979**;6(3):345-353.

Cone EJ, Fant RV, Rohay JM. Oxycodone involvement in drug abuse deaths: A DAWN-base classification scheme applied to an oxycodone postmortem database containing over 1000 cases. J Analyt Tox. **2003**;27:57-67.

Cozza KL, Armstrong SC. The Cytochrome P450 System: Drug Interaction Principles for Medical Practice. Washington, DC: American Psychiatric Publishing, Inc.;**2001**.

D'Aunno T, Pollack HA. Changes in methadone treatment practices: Results from a national panel study, 1988-2000. JAMA. **2002** Aug 21;288(7):850-6.

Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-Methyl-D-Aspartate (NMDA)-induced hyperalgesia. J. Pharmacol Exp Ther. **1999**;289:1048-1053.

Davoli M, Perucci CA, Forastiere F, et al. Risk factors for overdose mortality: A case-control within a cohort of intravenous drug users. Int J Epidemiol. **1993**;22(2):273–277.

Dole VP, Foldes F, Trigg H, et al. Methadone poisoning. NYS J Med. **1971**;71:541-543.

Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA. **1988**;260:3025-3029.

Dorsey JS. Serum methadone levels and optimal dosing in methadone maintained patients. Poster presented at: American Association for the Treatment of Opioid Dependence Conference; April 13-16, **2003**; Washington, DC. Poster P9.

Drasch G, Quitterer D, Roider G, Von Meyer L. The enantioselective detection of L- and D-methadone in blood samples from living and deceased addicts [German, abstract in English]. Rechtsmedizin. **2000**;10(5):170-175.

Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. Am J Forensic Med Pathol. **1992**;13(4):346–350.

Drummer OH, Syrjanen M, Opeskin K, Cordner SM. Deaths of heroin addicts starting on a methadone maintenance programme. Lancet. **1990**;335(8681):108.

Drummer OH. The toxicology of methadone and its involvement in sudden death. In: 35th Annual TIAFT (The International Association of Forensic Toxicologists) Conference. Padua, Italy; **1997**. Abstract 020.

Eap CB, Bourquin M, Martin J-L, et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. Dru Alcohol Dep. **2000**;6(11):47-54.

Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. Clin Pharmacokin. **2002**;41(14):1153-1193.

Eap CB, Déglon J-J, Baumann P. Pharmacokinetics and pharmacogenetics of methadone: Clinical relevance. Heroin Add & Rel Clin Probl **1999**;1(1):19-34.

Eap CB, Finkbeiner T, Gastpar M, Schebaum N, Bertschy G, Baumann P. High inter-individual variability of methadone enantiomer blood levels to dose ratios [letter]. Arch Gen Psychiatry **1988**;55:89-90.

Eastwood JA. Methadone poisoning in children. SOFT-TIAFT 1998 (Society of Forensic Technologists-The International Association of Forensic Toxicologists) Albuquerque, New Mexico; October 7, **1998**. Scientific Session 1.

Editorial. Medicine or menace? The Washington Times. February 19, **2003**.

Editorial. Methadone overdoses: Abuse of drug spreading so let's restrict the amount. Portland Press Herald (Portland, Maine). September 18, **2002**.

Ehlers S. U.S. Congress ponders anti-methadone bill [press release]. Washington, DC: Drug Policy Foundation; February 19, **1999**.

English DR, Holman CDJ, Milne E, et al. The quantification of drug-caused morbidity and mortality in Australia, 1995 edition. Canberra: Commonwealth Department of Human Services and Health. AGPS. **1995**:539-542.

Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. Cancer Treat Rep. **1979**;63(3):457-459.

Federal Register. Narcotic drugs in maintenance and detoxification treatment of narcotic dependence; Repeal of current regulations and proposal to adopt new regulations. Federal Register. July 22, **1999**;64(140):39809-39857. 21 CFR Part 291; 42 CFR Part 8. Available from the Federal Register Online via GPO at: www.access.gpo.gov/su_docs. Accessed August 1, 1999.

Federal Register. Opioid drugs in maintenance and detoxification treatment of opiate addiction; Final rule. **2001** (Jan 17);66(11):4085. 42 CFR Part 8.

FDLE (Florida Department of Law Enforcement). 2002 Interim Report of Drugs Identified in Deceased Persons by Florida Medical Examiners. November **2002**. Available at: http://www.fdle.state.fl.us/publications/examiner_drug_report_2002.pdf.

Fingerhut LA, Cox CS. Poisoning Mortality, 1985-1995. Pub Health Rep. **1998**;113(3):218-233

Flanagan RJ, Rooney C. Recording acute poisoning deaths. Forensic Sci Int. **2002**;128:3-19.

Foster DJR, Somogyi AA, Bochner F. Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. Br J Clin Pharmacol **1999**;47:403-412.

Frost JL. Commentary on: Oxycodone involvement in drug abuse deaths: A DAWN-base classification scheme applied to an oxycodone postmortem database containing over 1000 cases. J Analyt Tox. **2003**;27:67.

GAO (General Accounting Office). Methadone maintenance: some treatment programs are not effective; greater Federal oversight needed. Report to the chairman, Select Committee on Narcotics Abuse and Control, House of Representatives. Washington, DC: U.S. General Accounting Office; **1990**. Pub# GAO/HRD-90-104.

Gardner R, Methadone misuse and death by overdosage. Br J Addict. **1970**; 65(2):113–118.

Gearing FR, Schweitzer MD. An epidemiologic evaluation of long–term methadone maintenance treatment for heroin addiction. Am J Epidemiology. **1974**;100:101–111.

Gfroerer J, Penne M, Pemberton M, Folsom R. Substance abuse treatment need among older adults in 2020: The impact of the aging baby-boom cohort. Drug Alcohol Depend. **2003**;69(2):127-135.

Glauser FL, Downie RL, Smith WR. Electrocardiographic abnormalities in acute heroin overdosage. Bull Narc. **1977**;29(1):85-89.

Goldstein A, Herrera J. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. Drug Alcohol Depend. **1995**;40(2):139-150.

Gordon NB. The functional potential of the methadone maintained person. CDRWG Monograph #2. Chemical Dependency Research Working Group: The New York State Office of Alcoholism and Substance Abuse Services. December **1994**:43-46.

Gorman AL, Elliott KJ, Inturrisi CE. The d- and l- isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord, Nerurosci Lett. **1997**;223: 5-8.

Gourevitch MN, Hartel D, Tenore P, et al. Three oral formulations of methadone. A clinical and pharmacodynamic comparison. J Subst Abuse Treat. **1999**;17(3):237-241.

Gottheil E, Sterling RC, Weinstein SP. Diminished illicit drug use as a consequence of long-term methadone maintenance. J Addict Dis. **1993**;12(4):45-57.

Green H, James RA, Gilbert JD, Harpas P, Byard RW. Methadone maintenance programs – A two-edged sword? Amer J For Med Path. **2000**;21(4):359-361.

Greene MH, Luke JL, DuPont RL. Opiate overdose deaths in the District of Columbia. II. Methadone-related fatalities. J Forensic Sci. **1974**;19(3):575-584.

Greenfield L, Fountain D. Influence of time in treatment and follow-up duration on methadone treatment outcomes. J Psychopath Behavioral Assess. **2000**;22(4):353-364.

Haberman PW, Noble JA, DuFour MC. Alcohol use in combination with cocaine, heroin, and methadone by medical examiner cases. J Stud Alcohol. **1995**;56:344-347.

Hampton CT. Long QT syndrome: more common than you thought. Clin Rev. **2003**;13(1):40-46.

Hanzlick R. Death registration: history, methods, and legal issues. J Forensic Sci. **1997**;42(2):265-269.

Hanzlick R, Hunsacker III JC, Davis GJ. A Guide for Manner of Death Classification. 1st Edition. St. Louis, MO: National Association of Medical Examiners; February **2002**.

Harding-Pink, D. Deaths associated with methadone. J Toxicol Clin Exp. **1991**;11(1):31-49.

Harding-Pink D. Opioid toxicity. Lancet. **1993**;341:665-666.

Heinemann A, Iwersen-Bergmann S, Stein S, Schmoldt A, Puschel K. Methadone-related fatalities in Hamburg 1990-1999: Implications for quality standards in maintenance treatment? Forensic Sci Int. **2000**;113(1-3):449-455.

Heroin abuse and addiction. National Institutes on Drug Abuse (NIDA) Research Report Series. **1997** (October). NIH Pub# 97-4165.

Horrigan FT. Methadone block of neuronal K current. Biophysical J. **1990**;57:515A. Abstract W-Pos392.

Hser Y-I, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. **2001**:58:503-508.

Huber A, Ling W, Fradis J, Charuvastra VC. Comparison of the effects of methadone and LAAM on the electrocardiogram. Poster presented at: College of Problems of Drug Dependence (CPDD) 63rd Annual Scientific Meeting, Phoenix, AZ, June 20, **2001**. Also in: Huber A, Ling W, Fradis J, Charavastra VC. Comparison of the effects of methadone and LAAM on the electrocardiogram [abstract]. Drug Alcohol Depend. 2001;63:S70.

Huidobro F, Tamayo L, Contreras E. Effects of methadone on the action of catecholamines in isolated preparations. Arch Int Pharmacodyn Ther. **1971**;192:168-178.

Inturrisi CE, Verebely K. A gas-liquid chromatographic method for the quantitative determination of methadone in human plasma and urine. J Chrmatogr. **1972a**;65:361-369.

Inturrisi CE, Verebely K. The levels of methadone in the plasma in methadone maintenance. Clin Pharm Ther. **1972b**;13(5 part 1):633-637.

Joseph H, Appel P. Historical perspectives and public health issues. In: Parrino MW, chair. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993**:11-24 DHHS Pub# (SMA) 93-1991.

Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): A review of historical and clinical issues. Mt Sinai J Med. **2000**;67(5-6):347-364.

Joseph H, Woods JS eds. Methadone Treatment Works: A Compendium for Methadone Maintenance Treatment. CDRWG Monograph Series #2. Chemical Dependency Research Working Group: The New York State Office of Alcoholism and Substance Abuse Services. December **1994**. Available at: http://users.rcn.com/nama.interport/mono2.htm. Accessed May 23, 2002.

Kallan JE. Drug abuse-related mortality in the United States: Patterns and correlates. Amer J Drug Alcohol Abuse. **1998**;24(1):103-117.

Karch SB. Stephens BG. Toxicology and the pathology of deaths related to methadone: Retrospective review. West J Med. **2000**;172:11-14.

Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, Ebert SN. Influence of opioid agonists on cardiac human *ether-a-go-go*-related gene K^+ currents. J Pharm Exp Ther. **2002**;303(3):688-694.

Kauffman JF, Woody GE. Matching Treatment to Patient Needs in Opioid Substitution Therapy. Treatment Improvement Protocol (TIP) Series 20. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1995**. DHHS Pub# (SMA) 95-3049.

Kocheril AG, Bokhari SA, Batsford WP, Sinusas AJ. Long QTc and torsades de pointes in human immunodeficiency virus disease. Pacing Clin Electrophysiol. **1997**;20(11):2810-2816.

Kramer T. Side effects and therapeutic effects. Medsacape Gen Med. **2003**;5(1). Available at http://www.medscape.com.

Krantz MJ, Lewkowiez L, Hays H, et al. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. **2002**;137:501-504.

Kreek MJ. A personal retrospective and prospective viewpoint. In: Parrino MW. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993**:133-143. DHHS Pub# (SMA) 93-1991.

Kreek MJ, Gutjahr CL, Garfield JW, Bowen DV, Field FH. Drug interactions with methadone. Ann NY Acad Sci. **1976**;281:350-370.

Kreek MJ, Hachey DL, Klein PD. Stereoselective disposition of methadone in man. Life Sci. **1979**;24:925-932.

Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. **1973a**;223:665-668.

Kreek MJ. Plasma and urine levels of methadone. NY State J Med. **1973b**;73(23):2773-2777.

Kreek MJ. Rationale for maintenance pharmacotherapy of opiate dependency. In: O'Brien CP, Jaffe JH. Addictive States. New York, NY: Raven Press, Ltd.; **1992**:205-229.

Kringsholm B. Deaths among drug addicts in Denmark in 1968-1986. Forensic Sci Int. **1988**;38(1–2):139-149.

Kringsholm B, Kaa E, Steentoft A, Worm K, Simonsen KW. Deaths among drug addicts in Denmark in 1987-1991. Forensic Sci Int. **1994**;67(3):185-195.

Kung H-C, Hanzlick R, Spitler JF. Abstracting data from medical examiner/coroner reports: Concordance among abstractors and implications for data reporting. J Forensic Sci. **2001**;46(5):1126-1131.

La Harpe R, Fryc O. Fatalities associated with methadone administration in the Geneva canton (1987–1993). Arch Kriminol. **1995**;196(1-2):24–29.

Leavitt SB. Does methadone maintenance treatment affect heart health? Addiction Treatment Forum: Special Report (peer reviewed). June **2001**. Available at: http://www.atforum.com.

Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P. When "enough" is not enough: New perspectives on optimal methadone maintenance dose. Mt Sinai J Med. **2000**;67(5-6):404-411.

Lee CH, Berkowitz BA. Calcium antagonist activity of methadone, l-acetylmethadol and l-pentazocine in the rat aortic strip. J Pharmacol Exp Ther. **1977**;202(3):646-653.

Lehder DM, Arria A, Artigiani EE, Wish ED. Alcohol and drug-related overdose deaths in Maryland: 1997-2001. College Park, MD; Center for Substance Abuse Research (CESAR), University of Maryland: November **2002**. Available at http://www.dewsonline.org.

Leshner AI. Drug abuse research helps curtail the spread of deadly infectious diseases. NIDA Notes. **1999**;14(2):3-4. NIH Pub# 99-3478.

Litovitz TL, Klein-Schwartz W, Rodgers GC, et al. 2001 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Amer J Emergency Med. **2002**;20(5):391-452.

Lobert S. Methadone may be a useful alternative for cancer pain. Oncology Nurs Forum. **2003**;30(1):21.

Loimer N, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend **1992**;30(3):241-246.

Magura S. Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. Mt Sinai J Med. **2001**;68(1):62-74.

Mallinckrodt Inc. Methadose® Oral Concentrate (Methadone hydrochloride oral concentrate USP) [package insert]. St. Louis, MO: Mallinckrodt Inc; **2000**.

Mallinckrodt Inc. Methadose® Oral Tablets (Methadone hydrochloride tablets USP; 5, 10, 40 mg) [package inserts]. St. Louis, MO: Mallinckrodt Inc; **1995**.

Manfredi PL, Foley KM, Payne R, Inturrisi CE, Houde R. Parenteral methadone: An essential medication for the treatment of pain. In progress, **2003**.

Mantelli L, Corti V, Bini R, Cerbai E, Ledda F. Effects of dl-methadone on the response to physiological transmitters and on several functional parameters of the isolated guinea-pig heart. Arch Int Pharmacodyn Ther. **1986**;282(2):298-313.

Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: A meta-analysis. Addiction. **1998**;93(4):515-532.

Martell BA, Arnstein JH, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opioid users. Poster presented at: American Association for the Treatment of Opioid Dependence Conference; April 13-16, **2003**; Washington, DC. Poster P16.

Mathot F, Kurz X, Noel C, Firket P. Long QTc and psychotropic drugs use. Int J Neuropsychopharmacology. **2002**;3(Suppl 1):S173. [Abstract P.02.18.]

McCaffrey BR. Heroin access spurs need for methadone. USA Today. January 25, **1999**.

Merrill J. Garvey T, Rosson C. Methadone concentrations taken as indicating deaths due to overdose need to be reviewed [letter]. BMJ. **1996**;313:1481.

Mikolaenko I, Robinson A, Davis GG. A review of methadone deaths in Jefferson County, Alabama. J For Med Path. **2002**;23(3):299-304.

Milroy CM, Forrest ARW. Methadone deaths: A toxicological analysis. J Clin Pathol. **2000**;53:277-281.

Moody DE, Alburges ME, Parker RJ, Collins JM, Strong JM. The involvement of cytochrome P450 3A4 in the *N*-demethylation of *L*-α-acetylmethadol (LAAM), norLAAM, and methadone. Drug Metab Disp. **1997**;25(12):1347-1353.

Nakamura K, Hachey DL, Kreek MJ, Irving CS, Klein PD. Quantitation of methadone enantiomers in humans using stable isotope-labeled [$^{2}H_{3}$]-, [$^{2}H_{5}$]-, and [$^{2}H_{8}$]methadone. J Pharm Sci. **1982**;71(1):40-43.

NCHS (National Center for Health Statistics). International Classification of Diseases, Tenth Revision (ICD-10). Available at: http://www.cdc.gov/nchs/about/major/dvs/icd10des.htm. Updated **2002**.

Neeleman J, Farrell M. Fatal methadone and heroin overdoses: time trends in England and Wales. Journal of Epidemiology and Community Health. **1997**; 51:435-437.

NIDA (National Institute on Drug Abuse). Infectious diseases and drug abuse. NIDA Notes. **1999** (August);14(2):15. NIH pub #99-3478.

NIH (National Institutes of Health). Effective Medical Treatment of Opiate Addiction. NIH Consensus Statement. Bethesda, MD: National Institutes of Health; **1997**(Nov 17-19);15(6):1-38. (See also: JAMA. 1998;280:1936-1943.)

Novick DM, Richman BL, Friedman JM, et al. The medical status of methadone maintained patients in treatment for 11-18 years. Drug Alcohol Dep. **1993**;33:235-245.

Okruhlica L, Devinsk F, Valentova J, Klempova D. Does therapeutic threshold of methadone concentration in plasma exist? Heroin Add & Rel Clin Probl. **2002**;4(1):29-36.

Oliver P, Keen J, Mathers N. Deaths from drugs of abuse in Sheffield 1997-1999: What are the implications for GPs prescribing to heroin addicts? Fam Pract. **2002**;19(1):93-94.

ONDCP (Office of National Drug Control Policy). Drug Abuse in America [slide presentation]. Washington, DC: Office of National Drug Control Policy; **2002**. Available at: http://www.whitehousedrugpolicy.gov.

ONDCP (Office of National Drug Control Policy). Policy Paper: Opioid Agonist Treatment. Washington, DC: Office of National Drug Control Policy; **1999** (March).

ONDCP (Office of National Drug Control Policy). Methadone Fact Sheet. Washington, DC: Office of National Drug Control Policy; **2000** (April). Available at: http://www.whitehousedrugpolicy.gov.

ONDCP (Office of National Drug Control Policy). President's National Drug Control Strategy 2003. Washington, DC: Office of National Drug Control Policy; **2003** (February). Available at: http://www.whitehousedrugpolicy.gov.

Parrino MW. The renaissance of methadone treatment in America. J Maintenance in the Addictions. **2003**;2(1/2):5-17.

Payte JT. A brief history of methadone in the treatment of opioid dependence: a personal perspective. J Psychoactive Drugs. **1991**;23(2):103-107.

Payte JT, Khuri ET, Joseph H, Woods J. The methadone maintained patient and the treatment of pain. CDRWG Monograph #2. Chemical Dependency Research Working Group: The New York State Office of Alcoholism and Substance Abuse Services. **1994**: 35-40.

Payte JT, Khuri ET. Principles of methadone dose determination. In: Parrino MW. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993a**:47-58 DHHS Pub# (SMA) 93-1991.

Payte JT, Khuri ET. Treatment duration and patient retention. In: Parrino MW. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993b**:119-124. DHHS Pub# (SMA) 93-1991.

Payte JT, Zweben JE. Opioid maintenance therapies. In: Graham AW, Schultz TK, eds. Principles of Addiction Medicine. 2nd ed. Chevy Chase, MD: American Society of Addiction Medicine, Inc; **1998**:557-570.

Perret G, Deglon JJ, Kreek MJ, Ho A, La Harpe R. Lethal methadone intoxications in Geneva, Switzerland, from 1994 to 1998. Addiction. **2000**;95(11):1647-1653.

Petry NM, Bickel WK, Badger GJ. A 12-year study (1975 - 1986) of mortality in methadone maintenance patients: Selected demographic characteristics and drug-use patterns of AIDS and non-AIDS-related deaths. Subst Use Misuse. **1998**; 33(12):2521-2534.

Prouty RW, Anderson WH. The forensic science implications of site and temporal influences on postmortem blood-drug concentrations. J Forensic Sci. **1990**;35(2):243-270.

Rendig SV, Amsterdam EA, Henderson GL, Mason DT. Comparative cardiac contractile actions of six narcotic analgesics: morphine, meperidine, pentazocine, fentanyl, methadone and l-alpha-acetylmethadol (LAAM). J Pharmacol Exp Ther. **1980**;215(1):259-265.

Rettig RA, Yarmolonsky A (eds). Federal Regulation of Methadone Treatment. Committee on Federal Regulation of Methadone Treatment; Division of Biobehavioral Sciences and Mental Disorders; Institute of Medicine (IOM). Washington, DC: National Academy Press; **1995**.

Robinson AE, Williams FM. The distribution of methadone in man. J Pharm Pharmac. **1971**;23:353-358.

Roizin L, Helpern M, Baden M. Methadone fatalities in heroin addicts. Psychiatric Quart. **1972**;46(3):393-410.

Rosenblum A, Magura S, Joseph H. Ambivalence toward methadone treatment among intravenous drug users. J Psychoactive Drugs. **1991**;23(1):21-

Roxane Laboratories. Dolophine® Hydrochloride (Methadone Hydrochloride Injection, USP) [package insert]. Manufactured by Eli Lilly and Company. Columbus, Ohio: Roxane Laboratories, Inc; May 26, **1995**.

Roxane Laboratories. Methadone Hydrochloride Intensol™ (Oral Concentrate, USP 10 mg/mL) [package insert]. Columbus, Ohio: Roxane Laboratories, Inc; Revised February **1998**.

Roxane Laboratories. Methadone Hydrochloride Tablets USP [package insert]. Columbus, Ohio: Roxane Laboratories, Inc; Revised December **2000**.

SAMHSA (Substance Abuse and Mental Health Services Administration). National Household Survey on Drug Abuse (NHSDA). **2001**. Available at http://www.samhsa.gov.

SAMHSA (Substance Abuse and Mental Health Services Administration). The Dawn Report. Narcotic Analgesics. January **2003**. Available at http://www.samhsa.gov.

SAMHSA (Substance Abuse and Mental Health Services Administration). Mortality Data From the Drug Abuse Warning Network, 2001. DAWN Series D-23, **2002**. DHHS Publication No. (SMA) 03-3781. Available at http://www.samhsa.gov.

Sanford C. Deaths from Unintentional Drug Overdoses in North Carolina, 1997-2001: A DHHS Investigation into Unintentional Poisoning-Related Deaths. NC Injury and Violence Prevention Unit. North Carolina Department of Health and Human Services. September 20, **2002**.

Segal RJ, Catherman RL. Methadone – A cause of death. J Forensic Sci. **1974**;19(1):64-71.

Seyler DE, Borowitz JL, Maickel RP. Calcium channel blockade by certain opioids. Fundam Appl Toxicol. **1983**;3(6):536-542.

Sorg MH. Accidental methadone deaths in Maine 1997-2002. Slide presentation and handout October 7, **2002**.

Sorg MH, Greenwald M. Maine Drug-Related Mortality Patterns:1997-2002. State of Maine; December 27, **2002**. (Report in cooperation with the Maine Office of the Attorney General and Maine Office of Substance Abuse.)

Sporer KA. Acute heroin overdose. Ann Intern Med. **1999**;130:584-590.

Squires T. National confidential enquiry into methadone related deaths (Scotland) 2000. The Scottish Executive, Health Department, Clinical Resource and Audit Group (CRAG Ref 99/05); **2000**. Available at: http://www.show.scot.nhs.uk/crag/topics/mhealth/NCEMRD.doc.

Stimmel B, Lipski J, Swartz M, Donoso E. Electrocardiographic changes in heroin, methadone and multiple drug abuse: A postulated mechanism of sudden death in narcotic addicts. Proc Natl Conf Methadone Treat. **1973**;1:706-710. Also in: Lipski J, Stimmel B, Donoso E. The effect of heroin and multiple drug abuse on the electrocardiogram. Amer Heart J. 1973;86(5):663-668 [This was an earlier analysis of the same methadone-maintained population].

Stine SM, Meandzija B, Kosten TR. Pharmacologic therapies for opioid addiction. In: Graham AW, Schultz TK, eds. Principles of Addiction Medicine. 2nd ed. Chevy Chase, MD: American Society of Addiction Medicine, Inc; **1998**:545-555.

Symanski JD, Gettes LS. Drug effects on the electrocardiogram. A review of their clinical importance. Drugs. **1993**;46(2):219-248.

Takehana H, Izumi T. Alcoholic heart disease [Japanese, English abstract]. Nippon Rinsho. **2000**;58(1):151-156.

Tomargo J. Drug-induced torsade de pointes: from molecular biology to bedside. Jpn J Pharmacol. **2000**;83:1-19.

Valmana A, Oyefeso A, Clancy C, Ghodse H. Methadone-related deaths: Data from 18 coroners' jurisdictions in England. Med Sci Law. **2000**;40(1):61-65.

van Laar M, Crutis G, Vicente J, Frost N, Hartnoll R. EMCDDA standard protocol for the EU member states to collect data and report figures for the key indicator drug-related deaths by the standard reitox tables. EMCDDA Scientific Report 20-08-2002. Lisbon Portugal: European Monitoring Centre for Drugs and Drug Addiction; **2002**. Available at http://www.emcdda.eu.int.

White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. **1999**;94(7):961-972.

Williamson PA, Foreman KJ, White JM, Anderson G. Methadone-related overdose deaths in South Australia, 1984–1994. Med J Aust. **1997**;166:302-305.

Wolff K. Characterization of methadone overdose: Clinical considerations and the scientific evidence. Ther Drug Monit. **2002**;24(4):457-470.

Wolf K, Sanderson M, Hay AWM, Ralstrick D. Methadone concentrations in plasma and their relationship to drug dosage. Clin Chem. **1991**;37(2):205-209.

Wu C, Fry CH, Henry JA. Membrane toxicity of opioids measured by protozoan motility. Toxicology. **1997a**;117:35-44.

Wu C, Fry CH, Henry JA. The mode of action of several opioids on cardiac muscle. Exp Physiol. **1997b**;82:261-272.

Wu C, Henry JA. Interaction between ethanol and opioids in a protozoan assay. Hum Exp Toxicol. **1994**;13:145-148.

Zador D, Sunjic S, Darke S. Heroin-related deaths in New South Wales, 1992: Toxicological findings and circumstances. Med J Australia. **1996**;164:204-207.

Zador D Sunjic S. Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. Addiction. **2000**;95(1):77-84.

Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. Drug Alcohol Depend. **1998**;52(3):257-260.

Zickler P. 33-year study finds lifelong, lethal consequences of heroin addiction. NIDA Notes. **2001**;16(4):1. NIH Publication No. 02-3478.

Zweben JE, Payte JT. Methadone maintenance in the treatment of opioid dependence; A current perspective. West J Med. **1990**;152:588-599.

Part 8. Appendices

Appendix 1. Participants in the National Assessment

Co-Chairs

Bruce A. Goldberger, PhD, DABFT
Associate Professor and
Director of Toxicology
Departments of Pathology and Psychiatry
College of Medicine, University of Florida
Rocky Point Labs
Gainesville, FL

Mark W. Parrino, MPA
President
American Association for the Treatment of Opioid Dependence (AATOD)
New York, NY

Seddon R. Savage, MD, FASAM
Pain Consultant, Manchester VAMC
Project Director
New Hampshire ReMOTE Project
Bradford, NH
Associate Professor of Anesthesiology
Adjunct Faculty, Dartmouth Medical School

Participants (alphabetically)

Gavin Bart, MD
Director of Clinical Research
Laboratory of the Biology of Addictive Diseases
The Rockefeller University
New York, NY

Lawrence S. Brown, Jr., MD, MPH, FASAM
President, American Society of Addiction Medicine (ASAM)
Senior Vice President
Addiction Research and Treatment Corporation
Brooklyn, NY

Yale H. Caplan, PhD
Director
National Scientific Services
Baltimore, MD

Jennifer Collier, JD
Director of National Policy and State Strategy
Legal Action Center
Washington, DC

Edward J. Cone, PhD
Pinney Associates
Bethesda, MD

Daniel S. Connolly
Director, Giuliani Partners, LLC
New York, NY

Fiona J. Couper, PhD
Chief Toxicologist
Office of the Chief Medical Examiner
Government of the District of Columbia
Washington, DC

Ed Covington, MD
Director
Chronic Pain Rehabilitation Program
Cleveland Clinic Foundation
Cleveland, OH

Gregory G. Davis, MD, MSPH
Associate Professor of Pathology, Forensic Division
University of Alabama at Birmingham
Birmingham, AL

Ken DeCerchio, MSW, CAP
Director of Substance Abuse
Department of Children and Families
Tallahassee, FL

Danna E. Droz, JD
Consultant
Frankfort, KY

Aaron M. Gilson, PhD
Assistant Director
Pain and Policy Studies Group
University of Wisconsin-Madison
Madison, WI

Ann Marie Gordon, MS
Laboratory Manager
Washington State Toxicology Laboratory
Washington State Patrol
Seattle, WA

Douglas Gourlay, MD, FRCP, FASAM
Medical Consultant
Center for Addiction and Mental Health
Toronto, Ontario; Canada

Randy L. Hanzlick, MD
Chief Medical Examiner, Fulton County, Georgia
Associate Professor, Emory School of Medicine
Atlanta, GA

Robert Heimer, PhD
Associate Professor of Epidemiology and Public Health and of Pharmacology
Yale University School of Medicine
New Haven, CT

Howard A. Heit, MD, FACP, FASAM
Assistant Clinical Professor, Georgetown University
Liaison Committee of Pain and Addiction
Fairfax, VA

Jack E. Henningfield, PhD
Vice President, Research and Health Policy
Pinney Associates
Bethesda, MD

John D. Howard, MD
Chief Medical Examiner, Pierce County Medical Examiner's Office
National Association of Medical Examiners
Tacoma, WA

Jerome H. Jaffe, MD
Clinical Professor of Psychiatry
University of Maryland School of Medicine
Baltimore, MD

Amanda Jenkins, PhD
Chief Toxicologist
The Office of the Cuyahoga County Coroner
Cleveland, OH

Herman Joseph, PhD
Social Research Scientist
National Alliance of Methadone Advocates
New York, NY

Paul T. Kersten
General Manager, Sales and Marketing
Roxane Laboratories, Inc.
Bedford, OH

Mori J. Krantz, MD
Associate Professor of Medicine and Cardiology
Denver Health
Denver, CO

Mary Jeanne Kreek, MD
Professor, Head of Laboratory, and Senior Physician
The Laboratory of the Biology of Addictive Diseases
The Rockefeller University
New York, NY

Bridget Martell, MD, MA
Medical Director
Melrose-On-Track Clinic
Albert Einstein College of Medicine
Bronx, NY

Jane C. Maxwell, PhD
Research Scientist
Gulf Coast Addiction Technology Transfer Center
The University of Texas at Austin
Austin, TX

Elinore McCance-Katz, MD, PhD
American Academy of Addiction Psychiatry
Prairie Village, KS
Professor of Psychiatry and Chair, Addiction Psychiatry
Medical College of Virginia
Richmond, VA

Michael Neely, MBA
Senior Product Manager, Addiction Therapy
Tycohealthcare, Mallinckrodt, Inc.
Hazelwood, MO

Raymond I. Pora
Sales/Marketing
VistaPharm, Inc.
Frankfort, IL

Catharine (Kay) Sanford, MSPH
Public Health Epidemiologist
Injury and Violence Prevention
Department of Health and Human Services
State of North Carolina
Raleigh, NC

Michael J. Schobelock, PharmD
Associate Director
Medical Affairs Department
Roxane Laboratories, Inc.
Columbus, OH

Mark J. Shuman, MD, MS
Associate Medical Examiner
Miami-Dade County Medical Examiner Department
Miami, FL

Marcella H. Sorg, PhD, RN
Research Associate
Margaret Chase Smith Center for Public Policy
University of Maine
Orono, ME

Flo Stein, MPH
Chief, Community Policy Management
Division of Mental Health, Developmental Disabilities, and Substance Abuse Services
North Carolina Department of Health and Human Services
Raleigh, NC

Barry Stimmel, MD
Editor, Journal of Addictive Disease
Dean, Graduate Medical Education
Mount Sinai School of Medicine
New York, NY

Royce Watkins
Chairman and Chief Executive Officer
Cebert Pharmaceuticals, Inc.
Birmingham, AL

Federal Partner Participants

(alphabetically)

Dan Budnitz, MD, MPH
EIS Officer
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention
Atlanta, GA

Silvia Calderon, PhD
Team Leader and Interdisciplinary Scientist
Controlled Substance Staff
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

H. Westley Clark, MD, JD, MPH, CAS, FASAM
Director
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Elizabeth Crane, PhD, MPH
Service Fellow
Drug Abuse Warning Network
Office of Applied Studies
Substance Abuse and Mental Health Services Administration
Rockville, MD

Denise Curry, MA, JD
Liaison Unit Chief
Office of Diversion Control
Drug Enforcement Administration
Arlington, VA

Gretchen Feussner
Pharmacologist
Drug and Chemical Evaluation Section
Office of Diversion Control
Drug Enforcement Administration
Washington, DC

Lois A. Fingerhut, MA
Special Assistant for Injury Epidemiology
National Center for Health Statistics
Centers for Disease Control and Prevention
Hyattsville, MD

Angel Gonzalez, MD
Medical Officer
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Laura A. Governale, PharmD
Drug Utilization Specialist
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Melvyn Robert Haas, MD
Associate Director for Medical Affairs
Center for Mental Health Services
Substance Abuse and Mental Health Services Administration
Rockville, MD

June E. Howard
Chief, Targeting and Analysis Unit, Drug Operations Section
Office of Diversion Control
Drug Enforcement Administration
Arlington, VA

James R. Hunter, RPh, MPH
Senior Program Manager
Controlled Substance Staff
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Kirk E. James, MD
Special Expert
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

T. Stephen Jones, MD
Associate Director for Prevention of Bloodborne Infections
Centers for Disease Control and Prevention
Atlanta, GA

Deborah B. Leiderman, MD
Director
Controlled Substance Staff
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Robert Lubran, MS, MPA
Director
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Moira O'Brien, MPhil
Program Director, Research on Emerging and Current Trends
Division of Epidemiology, Services and Prevention Research
National Institute on Drug Abuse
National Institutes of Health
Bethesda, MD

Rita Ouellet-Hellstrom, PhD
Epidemiologist
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Martin L. Pollock, PharmD
Safety Evaluator
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Robert A. Rappaport, MD
Acting Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Nicholas P. Reuter, MPH
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Barbara T. Roberts, PhD
Associate Deputy Director
Office for Demand Reduction
White House Office of National Drug Control Policy
Washington, DC

Tom Schroeder, MS
Statistician
U.S. Consumer Product Safety Commission
Bethesda, MD

Greg Skipper, MD
National Advisory Council Member
Center for Substance Abuse Treatment
Medical Director
Alabama Physician Health Program
Montgomery, AL

Arlene Stanton, PhD, NCC
Social Science Analyst
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Richard T. Suchinsky, MD
Associate Chief for Addictive Disorders
Department of Veterans Affairs
Washington, DC

Alan Trachtenberg, MD, MPH
Medical Officer
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, MD

Frank J. Vocci, PhD
Director
Division of Treatment Research and Development
National Institute on Drug Abuse
National Institutes of Health
Bethesda, MD

Celia Jaffe Winchell, MD
Medical Team Leader, Addiction Drug Products
Division of Anesthetic, Critical Care, and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

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-SATS	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.
N-SSATS (UFDS)	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).
TEDS	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	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.
DEA	U.S. Drug Enforcement Administration
ARCOS	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). 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. Available at: http://www.deadiversion.usdoj.gov/arcos/index.html.
NFLIS	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. 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. See: http://www.deadiversion.usdoj.gov/nflis/overview.htm.
ONDCP	Office of National Drug Control Policy, The White House
National Drug Control Strategy	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. See http://www.whitehousedrugpolicy.gov/index.html.
DENS	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. 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. See http://www.densonline.org/ for more information.

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
FDA	U.S. Food and Drug Administration
MedWatch	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. See: http://www.fda.gov/medwatch/index.html
NCHS - CDC	National Center for Health Statistics / Centers for Disease Control and Prevention See: http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm
NAMCS	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.
NHAMCS	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.
CDC WONDER	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. See: http://wonder.cdc.gov/
AAPCC	American Association of Poison Control Centers
TESS	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. See: http://www.aapcc.org/annual.htm
IMS	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. 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. Additional information is available at http://www.imshealth.com.

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities	
RADARS	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. 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. See: http://www.purduepharma.com.
OTHER…	
NVDRS	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.
NAME PedTox Registry	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.
CPSC/NEISS	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.
PMPs	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.
NIJ/ADAM	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/

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 iinvolve 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 in 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

μg/L – 1 μg/L = 1000 ng/1000 mL = 1 ng/mL

μg/mL – 1 μg/mL = 1000 ng/mL
(1 ng/mL = 0.001 μg/mL)

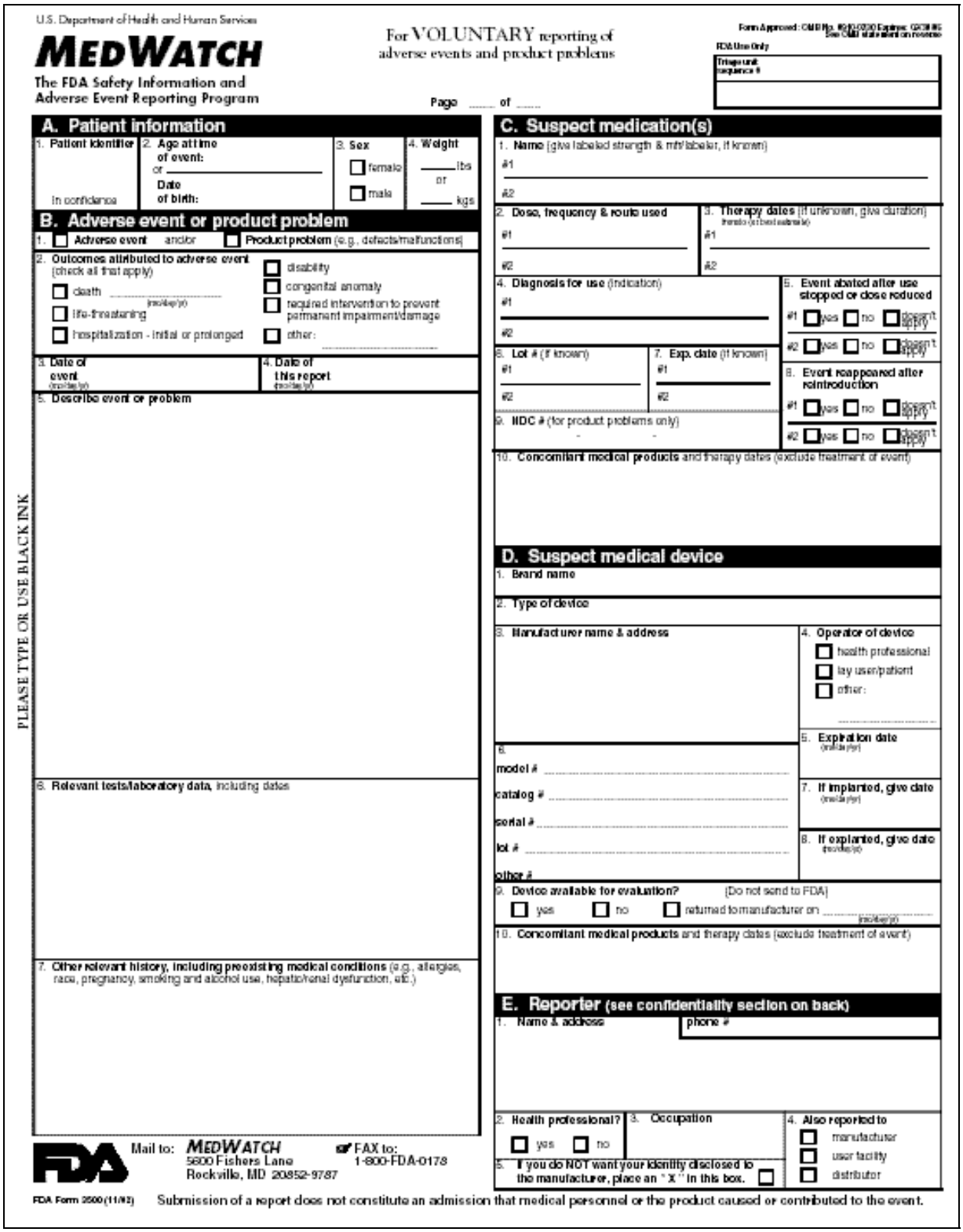
mg/L – 1 mg/L = 1000 ng/mL
(1 ng/mL = 0.001 mg/L)

mg/dL – 1 mg/dL = 10,000 ng/mL
(1 ng/mL = 0.0001 mg/dL)

mg% – 1 mg% = 1 mg/100 mL = 10,000 ng/mL
(1 ng/mL = .0001 mg%)

μmol – 1 μmol = 345 ng/mL
(1 ng/mL = 0.0029 μmol = 2.9 mmol
specific to methadone molecular weight)

Appendix 6. MedWatch Form



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Form Approved: OMB No. 0910-0291 Expires: 02/28/05
See OMB statement on reverse.

FDA Use Only

Triage unit
Sequence #

Page ____ of ____

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — female / male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death (mm/dd/yy)
   - life-threatening
   - hospitalization - initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other:
3. Date of event (mm/dd/yy)
4. Date of this report (mm/dd/yy)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) (mm/dd/yy or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 yes no doesn't apply
   #2 yes no doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 yes no doesn't apply
   #2 yes no doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - health professional
   - lay user/patient
   - other:
5. Expiration date (mm/dd/yy)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mm/dd/yy)
8. If explanted, give date (mm/dd/yy)
9. Device available for evaluation? (Do not send to FDA)
   yes no returned to manufacturer on ____ (mm/dd/yy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address
   phone #
2. Health professional? yes no
3. Occupation
4. Also reported to
   - manufacturer
   - user facility
   - distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box.

FDA

Mail to: MEDWATCH, 5600 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 _____Death Case or _____ 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

M E M O R A N D U M

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.